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Paper

One pot synthesis of highly functionalized pyrimido[1, 2-*b*]indazoles *via* 6-*endo-dig* cyclization

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An efficient synthesis of nitrogen ring junction pyrimido-indazoles have been developed. This is an metal catalyzed transformation proceeds *via* A^3 coupling reaction between 1*H*-indazol-3-amine, aromatic aldehydes and alkynes, which undergoes 6-*endo-dig* cyclization leading to the highly functionalized pyrimido [1, 2-*b*]indazoles. Response surface methodology (RSM) was used to investigate the effect of catalyst (A_1), reaction temperature (B_1) and time (C_1). The fluorescence quantum yield of the pyrimido[1,2-*b*]indazoles were calculated.

Introduction

Ring junction nitrogen heterocyclic compounds are valuable for obtaining biological leads and exploring drug discovery programs.[1] In addition, the nitrogen fused heterocyclic fragments are important in pharmaceutical and biomedical research since these systems occur in several natural and biologically active molecules.[2] They exhibit promising biological profile such as anti-cancer,[3,4] anti-inflammation,[5,6] anti-bacterial,[7-9] analgesia,[10] anti-virus,[11] anti-cytotoxin,[12] anti-spasm,[13] anti-tuberculosis,[14] anti-oxidation,[15] antimalarial,[16] anti-hypertension,[17] anti-obesity ,[18] anti-psychotic,[19] anti-diabetes,[20] etc. They also constitutes the core ring junction structure of several currently marketed drugs.[21-24]

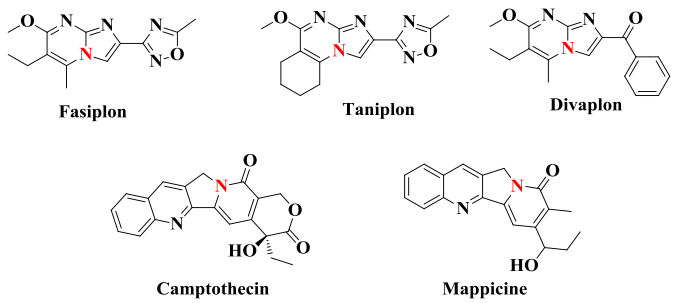

Figure 1. Clinical and FDA approved drugs with ring junctioned nitrogen heterocycles as core structure

These compounds have immense importance in pharmaceutical industry owing to their wide range of interesting biological activity. The anxiolytic drugs such as fasiplon, taniplon and divaplon having nitrogen ring junction core motifs are currently used in clinics (**Fig 1**).[25] Camptothecin and mappicine are recently approved by FDA (Food and Drug Administration), USA having nitrogen ring junction structure. These two drugs have possible uses in antimicrobial, anticancer, antibiotic and antiparasitic action. Therefore, there is a demand for the efficient and practical synthetic pathway to generate heterocyclic units for the synthesis of natural and biomimetic compounds.[26, 27]

Current researchers in organic synthesis focus on the discovery of the methods that taken into the account of sustainable chemistry. The Multi Component Assembly reactions (MCARs) are considered as rapid assembling of more than two reactants into higher mass compounds in a single pot. It became very interesting in the discovery of biologically active compounds due to their atom economy, ease to handle and higher yield.[28-30] A^3 coupling is a type of MCARs involves an aldehyde, alkyne and amine as reactants which give propargylamine as product.[31] This reaction was described as a direct dehydrative condensation. It requires a transition metal catalyst like ruthenium, copper, silver or gold to get a desired product. Domino reactions also fall under the category of MCARs which allow the formation of complex compounds starting from simple reactants.[32] **R**ecently, copper mediated organic transformation had an important role for the product formation. Naresh et al. reported a microwave assisted one pot multi component transformation to synthesis furoquinoxalines in good to excellent yields *via* copper catalysed A^3 coupling. The reactions proceeds *via* 5-*endo-dig* cyclization[33]. Similarly, the A^3 coupling through 5-*endo-dig* cyclization to synthesized N-fused heterocycles were described by Chernyak et al.[34] and Guchhait et al.[35] In earlier report, we have reported an overview of synthetic arylation *via* transition metal catalyst.[36] Now, our intent to offer an one pot synthesis of highly functionalized pyrimido [1, 2-*b*]indazoles *via* 6-*endo-dig* cyclization from simple reaction conditions, easy to access, low cost starting materials

Response surface methodology (RSM) is a collection of mathematical and statistical techniques for empirical model building. By careful design of experiments, the objective is to optimize a response (output variables) which is influenced by several independent variables (input variables). An experiment series of tests, runs, in which changes are made in the output variables in order to identify the reasons for changes in the output response. [37-42]

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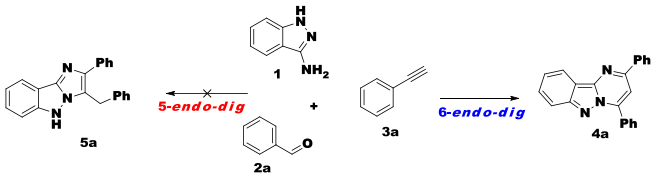
Results & Discussion

As part of our on-going effort in the synthesis of nitrogen ring junction heterocyclic compounds, [43, 44] for the first time here in, we have described a simple, easy to handle and highly efficient approach for the synthesis of functionalized pyrimido [1,2-*b*]indazole derivatives *via* A^3 coupling reaction. RSM coupled with Box-Behnken design (BBD) was employed for both reaction conditions to optimize the operational parameter. Levels of selection for each variable based on the preliminary results (**Table 2)**.



Scheme 1. Regiospecific synthesis of 2,4-diphenylpyrimido[1,2-*b*]indazole *via* 6-*endo-dig* cyclization

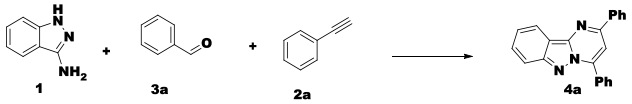
The general reaction pathway was mentioned in **Scheme 1** which implies, two possible product formation of 2,4-diphenylpyrimido[1,2-*b*]indazole **4a** and 3-benzyl-2-phenyl-5*H*-imidazo[1,2-*b*]indazole **5a.** Here we intent to report the synthesis of 2,4-diphenylpyrimido[1,2-*b*]indazole *via* multicomponent assembly reaction through 6-*endo-dig* cyclization. In optimization, we have set up this scheme by investigating the reaction of 1*H*-indazol-3-amine **1**, phenyl acetylene **2a** and benzaldehyde **3a** in the absence of catalyst and solvent at 120 ^{o}C for 16 h, but the desired compound **4a** was not achieved (**Table 1, entry 1 and 2**).

When this reaction was carried out in the presence of copper catalyst such as CuI, CuBr, CuCl, CuO, $CuSO_4.5H_2O$ and $Cu(OAC)_2$ (10 mol %) along with TFA (10 mol %) at 85 ^{o}C, the desired product **4a** was observed with reasonable yield (**Table 1, entry 7**). Further, the reaction conditions were fine-tuned by changing the solvents, acid catalysts, and reaction time (**Table 1, entry 8-22**). While we used DMSO (**Table 1, entry 11**) and DMF (**Table 1, entry 12**) as a solvent the temperature maintained at 120 ^{o}C. After the optimization, we have found that 20 mol % $CuSO_4.5H_2O$ and 10 mol % *p*-toluenesulfonic acid (PTSA) in the presence of toluene at 120 ^{o}C for 8h has been considered as an optimized condition for synthesis of 2,4-diphenylpyrimido[1,2-*b*]indazole **4a** (**Table 1, entry 21**). The synthesized product was fully characterized by its melting point, ^{1}H NMR, ^{13}C NMR and HRMS data.

A Box-Behnken design (BBD) center-united design was employed to design the experiments and the results obtained after running the seventeen experiments are represented in **Table 3**.[38,39] The three components such as the catalyst loading (A_1), reaction temperature (B_1) and response time (C_1) were utilized for metal mediated reaction The best – fitting models were determined by multiregression and backward elimination. The experimental yield (actual) was obtained as an average of triplicate determinations. The yield was increased from 22 to 91 %, depending on the reaction conditions.

On the basis of the BBD analysis, the quadratic polynomial model relationship between the experimental yield ($\mathbf{Y_1}$) and the process variables in coded units is obtained from **equation 1.**

Table 1. Optimization to the synthesis of 2,4-diphenyl pyrimido[1,2-*b*]indazole **4a**



Entry	Metal Catalyst (mol %)	Acid Catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1	-	-	Neat[a]	16	NR
2	-	-	ACN	16	NR
3	CuI (10)	TFA(10)	ACN	4	15
4	CuBr (10)	TFA(10)	ACN	4	20
5	CuCl (10)	TFA(10)	ACN	4	Traces
6	CuO (10)	TFA(10)	ACN	4	45
7	$CuSO_4.5H_2O$ (10)	TFA(10)	ACN	4	65
8	$Cu(OAC)_2$ (10)	TFA(10)	ACN	4	30
9	$CuSO_4.5H_2O$ (10)	Iodine(10)	ACN	16	50
10	$CuSO_4.5H_2O$ (10)	PTSA(10)	THF	16	73
11	$CuSO_4.5H_2O$ (10)	PTSA(10)	DMSO[a]	16	45
12	$CuSO_4.5H_2O$ (10)	PTSA(10)	DMF[a]	16	25
13	$CuSO_4.5H_2O$ (10)	PTSA(10)	1,4-Dioxane	16	70
14	$CuSO_4.5H_2O$ (10)	PTSA(10)	Toluene	16	80
15	$CuSO_4.5H_2O$ (10)	PTSA(10)	Benzene	16	70
16	$CuSO_4.5H_2O$ (5)	PTSA(10)	Toluene	16	63
17	$CuSO_4.5H_2O$ (15)	PTSA(10)	Toluene	16	77
18	$CuSO_4.5H_2O$ (20)	PTSA(10)	Toluene	16	87
19	$CuSO_4.5H_2O$ (30)	PTSA(10)	Toluene	16	84
20	$CuSO_4.5H_2O$ (20)	PTSA(10)	Toluene	4	70
21	$CuSO_4.5H_2O$ (20)	PTSA(10)	Toluene	8	90
22	$CuSO_4.5H_2O$ (20)	PTSA(5)	Toluene	8	78
23	$CuSO_4.5H_2O$ (20)	PTSA(15)	Toluene	8	83
22	$CuSO_4.5H_2O$ (20)	PTSA(10)	Toluene	12	88

Note: Reactions were carried out with 1mmol of **1**, **2a** and **3a** in 5mL of solvent at the reflux temperature of the solvents (except neat, DMSO or DMF reactions). NR - No reaction. [a]Reaction temperature – 120 ^{o}C. [b]Isolated yield. The optimized condition was mentioned in bold letter.

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$$Y_1 = 89.60 + 6.87A_1 + 1.75B_1 + 23.63C_1 - 2.25A_1B_1 - 2.50\ A_1C_1 + 0.75B_1C_1 - 8.30A_1^{\ 2} - 3.05B_1^{\ 2} - 27.80C_1^{\ 2} \quad (1)$$

Where Y_1 represents the experimental yield of the reaction, then A_1, B_1 and C_1 are the coded variables in the reaction. **Figure 2** shows the good linear correlation between the predicted and actual yield. From this, we can understand, the predicted yield is consistent with the experimental yield. This means that the accuracy of the forecast values is sufficient and the model successfully describes the predicted and actual yield.

Table 2. Selected variables and levels used in the BBD

Reaction	Variables	Code	Units	Levels		
				-1	0	+1
Metal reaction	Catalyst used (mol %)	A_1	mg	10	20	30
	Reaction temperature	B_1	^oC	110	120	130
	Reaction time	C_1	h	4	8	12

Table 3. Design and matrix response for BBD

Run	Metal Condition				
	A_1	B_1	C_1	Y_1 (%)	X_1 (%)
1.	30	120	12	80.10	81.50
2.	20	110	12	81.40	79.88
3.	10	120	12	72.31	72.75
4.	30	130	8	85.22	84.63
5.	30	120	4	40.11	39.25
6.	20	120	8	90.33	89.60
7.	20	110	4	33.13	34.13
8.	20	120	8	88.01	89.60
9.	20	130	4	35.03	36.13
10.	10	120	4	22.05	20.50
11.	20	130	12	86.32	84.88
12.	10	130	8	75.03	75.38
13.	20	120	8	91.22	89.60
14.	20	120	8	89.11	89.60
15.	20	120	8	90.10	89.60
16.	10	110	8	67.08	67.38
17.	30	110	8	86.00	85.63

Where Y_1 – Experimental Yield, X_1 – Predicted Yield

Analysis of variance (ANOVA) for the response surface quadratic model was used to investigate the fitness, signification of the mannequin, precision of the mannequin, result of the private variables and interactive effect on the answer. The ANOVA for response surface quadratic models are presented in **Table 4**. The Model F-value of 410.40 implies the model is significant. There may be an increase in F value of about 0.01 %, which may be due to noise. If the values of "prob" is less than 0.050 of "F" then the model terms are significant. From the **Table 2**, A_1, B_1, C_1, A_1B_1, A_1C_1, A_1^2, B_1^2, C_1^2 are significant model terms. If the values greater than 0.1000 then the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy) and model reduction it may improve your model. In case "Lack of Fit F-value" is 2.88 then it implies the Lack of Fit is not significant relative to the pure error. Around 16.63% probability that a "Lack of Fit F-value" this large could occur due to interference. Non-significant lack of fit is good and we want the model to fit. The "Pred R-Squared" of 0.9784 is in reasonable agreement with the "Adj R-Squared" of 0.9957; i.e., the deviation is less than 0.2."Adeq Precision" measures the signal to interference ratio (**Figure 2**). A ratio greater than 4 is desirable. The ratio of 58.772 indicates an adequate signal. This model can be used to navigate the design space.

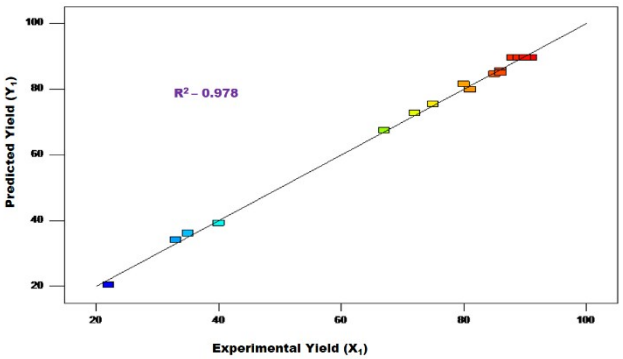

Figure 2. Predicted and Experimental values of yield

The results in **Table 4** shows that the interaction between variables has a significant effect on the yield of the product. The interaction between the relevant variables would be less when the contour of the response surface is circular.[45-47] On the other hand, the interaction between the corresponding variables would be higher when the contour of the response surface is elliptical.[48,49] The effect of interaction between catalyst loading (A_1) and reaction temperature (B_1) on constant reaction time (C_1) of 8 h is shown in **Figure 3A**. The combined effect of A_1 and C_1 on B_1 of 120 ^oC is shown in **Figure 3B.** The effect of interaction between B_1 and C_1 on A_1 of 20 mol % is shown in **Figure 3C**. The contour plots of A_1 and B_1 (**Figure 3Ab**) are almost circular, which indicates that there is less interaction between A_1 and B_1. The contour plots of A_1 and C_1 (**Figure 3Bb**), B_1 and C_1 (**Figure 3Cb**) are elliptical, which indicates a perfect interaction between A_1, $C_1$and B_1, C_1.

Table 4. ANOVA for response surface quadratic model

Source	Sum of Squares	DF	Mean Square	F Value	p-value Prob > F	
Model	8680.02	9	964.45	410.40	< 0.0001	S
A_1	378.13	1	378.13	160.90	< 0.0001	
B_1	24.50	1	24.50	10.43	0.0145	
C_1	4465.13	1	4465.13	1900.05	< 0.0001	
A_1B_1	20.25	1	20.25	8.62	0.0219	
A_1C_1	25.00	1	25.00	10.64	0.0138	
B_1C_1	2.25	1	2.25	0.96	0.3604	
A_1^2	290.06	1	290.06	123.43	< 0.0001	
B_1^2	39.17	1	39.17	16.67	0.0047	
C_1^2	3254.06	1	3254.06	1384.71	< 0.0001	
Residual	16.45	7	2.35			
Lack of Fit	11.25	3	3.75	2.88	0.1663	NS
Pure Error	5.20	4	1.30			
Correlation Total	8696.47	16				

Where S – Significant, NS – Non-significant, DF – Degree of freedom

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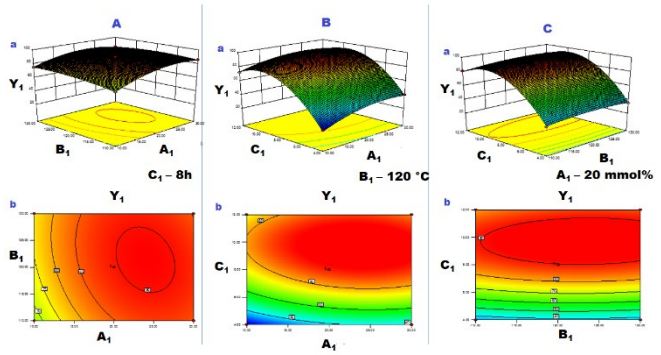
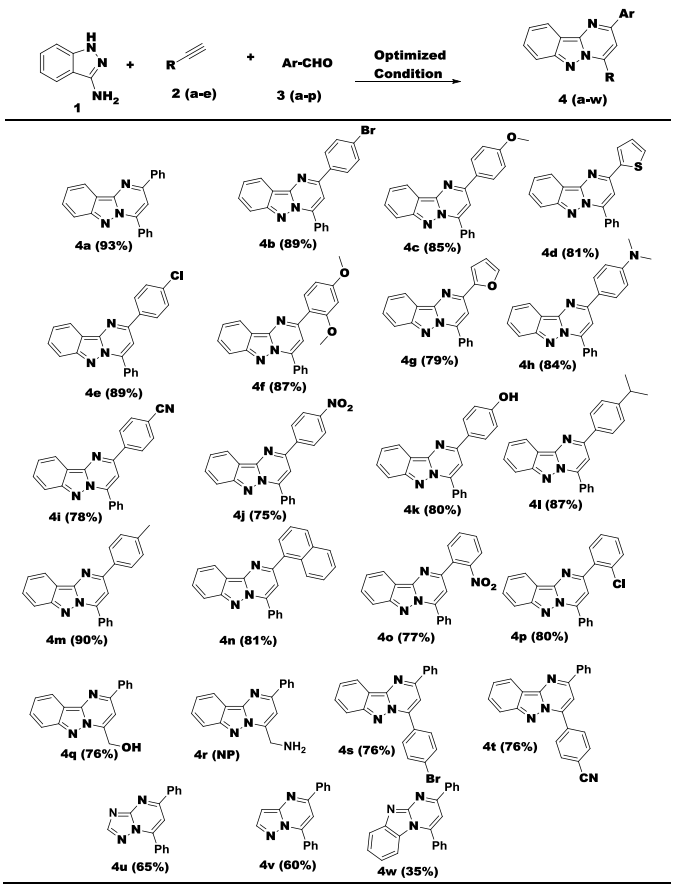


Figure 3. Combined effect of different parameters on the yield for metal mediated reaction. (A) Effect of temperature and catalyst. (B) Effect of time and catalyst. (C) Effect of time and temperature.

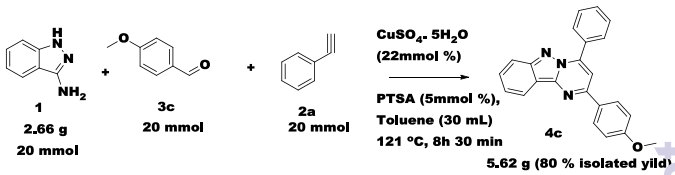
Table 5. Model validation for the compound **4a**

Parameter	Catalyst mol % (A_1)	Reaction Temperature °C (B_1)	Reaction Time h (C_1)	Yield (%)
Predicted	21.33	121.33	8.53	93.1
Experimental	20.00	120.00	8.00	90.0

Table 6. Synthesis of pyrimido[1,2-*b*]indazole derivatives **4(a-w)** through A^3 coupling

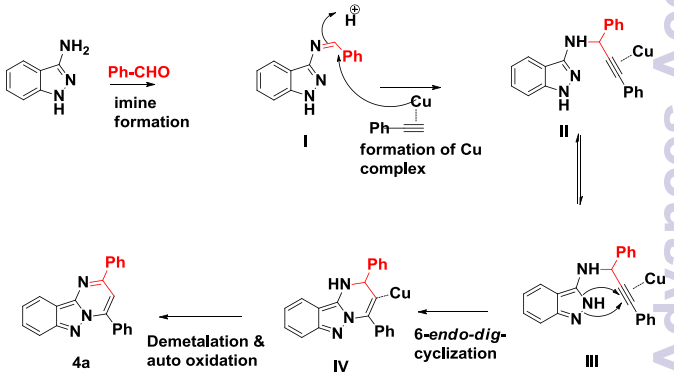


From these experiments, the optimum conditions for predicted and experimental yields are shown in **Table 5.** To confirm the adequacy of the model for predicting the maximum yield, three confirmation runs was performed using optimized condition; The results are 93.1 %, 91.2 % and 91.7 % isolated yields for the compound **4a**. The good agreement between the experimental and predicted yield has been tested by RSM with the statistical design of experiments. It has been effectively used to optimize parameters which has been involved in the reaction.



Scheme 2. Gram scale preparation of the compound **4c**

To demonstrate the positive impact of this reaction, the scope of the reaction substrate was explored under optimized conditions. A wide range of substituted aromatic aldehydes **3(a-p)** which includes electron neutral, electron releasing and electron withdrawing groups could be reacted with 1*H*-indazol-3-amine **1(a-d)** and alkynes **2 (a-e)** to get corresponding pyrimido [1,2-*b*]indazoles **4(a-w)** in moderate to good yields (**Table 6**). All aromatic aldehydes including hetero aldehydes were easily converted into the desired products which showed that steric nature did not affect the reactivity. We have explored the gram scale preparation of 5.69 g (85 % yield) of the compound **4c** (**Scheme 2**) from 20 mmol of 1*H*-indazol-3-amine **1**, 20 mmol of phenyl acetylene **2a**, and 20 mmol of 4-methoxybenzaldehyde **3c.**



Scheme 3. A plausible mechanism for formation of compound **4a** *via* metal catalyzed A^3 coupling.

The plausible mechanism for the formation 2,4-diphenylpyrimido[1,2-*b*]indazole **4a** *via* A^3 coupling reaction was illustrated in **scheme 3**. The first step involved the formation of imine with the elimination of one water molecule from amine and aldehyde. The formed imine **I** *insitu* was attacked by copper acetylide (Cu-A) resulting in copper complex intermediate **II** followed by isomerization to form intermediate **III (Scheme 3)**. Then it undertook intramolecular N-H bond activation and regioselective attack at the electron deficiency center of the triple *via* 6-*endo-dig*- cyclization offering the intermediate **IV**. The intermediate **IV** consequently undergoes demetalation and autoxidation leading to the formation of 2,4-diphenylpyrimido[1,2-*b*]indazole **4a**

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The synthesized ring junction compounds **4(a-t)** are yellow to red powder with good solubility in most common organic solvents. The compounds are showing higher fluorescence properties in ethyl acetate medium.

The solvatochromism spectra of the 2,4-diphenylpyrimido[1,2-*b*] indazole **4a,** was studied with 15 different solvents (**Figure S1**). Among all the solvents, ethyl acetate exhibits good UV/Vis absorbance. Similarly, we have utilized ethyl acetate for remaining synthesized compounds **4(a-t).** The UV/Vis absorbance and fluorescence emission spectra of the synthesized ring junction compounds **4(a-t)** were recorded (**Figure S2**) in ethyl acetate (10^{-5} M). Among these compounds, compound **4h** shows the maximum fluorescence intensity (**Figure S3**).

Table 7. Photo physical parameter of the synthesized compounds **4(a-t)**

Entry	λmax (abs, nm)	λmax (em, nm)	Stokes shift (nm)	OD	I	Φ_F
Tryptophan	280	355	75	0.384	158517	0.130
4a	306	533	227	0.774	46182	0.019
4b	308	535	227	0.540	38524	0.023
4c	306	499	193	1.176	59599	0.016
	268(Sh)	499	231	0.827	59599	0.023
4d	270	543	273	1.761	29458	0.005
4e	308	535	227	1.794	70535	0.013
4f	272	530	258	0.449	54760	0.040
	322(Sh)	530	208	0.439	54760	0.041
4g	322	536	214	1.562	42560	0.008
4h	362	527	165	1.019	79531	0.025
	260(Sh)	527	267	0.703	79531	0.036
4i	308	542	234	0.440	47543	0.035
	242(Sh)	542	300	0.210	47543	0.073
4j	310	553	223	0.612	51780	0.027
4k	302	530	228	1.132	79947	0.023
4l	310	532	222	1.712	27454	0.005
4m	310	533	233	1.973	71400	0.012
4n	296	531	235	0.870	39377	0.014
4o	296	528	232	0.566	26728	0.015
4p	296	532	236	0.678	65789	0.031
4q	284	532	248	0.272	75413	0.090
	270	532	262	0.209	75413	0.117
4s	306	534	228	1.883	73195	0.013
	270(Sh)	534	264	1.251	73195	0.019
4t	308	553	245	1.064	31279	0.010
	270(Sh)	553	283	0.838	31279	0.012

Sh - shoulder; abs - absorbance; em - emission; OD - excited absorbance; I - integral area; Φ_F - Fluorescence quantum yield

We have calculated the Fluorescence quantum yield[50] (Φ_F) of the fluorescence active compounds. The Φ_F was calculated by using following formula **2**,

$$\Phi_F = (\Phi_R * I_S * OD_R * \eta_s) / (I_R * OD_S * \eta_R) \quad (2)$$

Where Φ_R = Fluorescence quantum yield of reference, I_S and I_R = integral area of reference and sample, respectively, OD_S and OD_R = excited absorbance of sample and reference respectively, $\eta_{s \text{ and } R}$ = refractive index of sample solvent and reference solvent respectively. We have used tryptophan[51,52] as a standard for calculating emission of quantum yield **(Table 7)**.

Conclusion

In conclusion, we have delivered a pathway for the synthesis of pyrimido[1,2-*b*]indazoles *via* MCARs. The Cu/PTSA catalyzed three component cascade coupling reaction which proceeds *via* regioselective 6-*endo*-dig cyclo isomerization sequence to afford pyrimido[1,2-*b*]indazole derivatives in moderate to good yields. The compounds produced herein tolerate functional groups viable for subsequent derivatization. RSM coupled with Box-Behnken design (BBD) was employed for this reaction conditions. The results showed the significance of the quadratic model and provided optimized conditions for the synthesis of **4(a-w)**. The levels of selection for each variable based on the preliminary results. The synthesized pyrimido[1,2-*b*]indazole derivatives showed good fluorescent properties. In future, we have planned for application oriented studies from the photo physical data.

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Notes and references

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† Electronic Supplementary Information (ESI) available.

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