Click chemistry approach for the regioselective synthesis of iso-indoline-1,3-dione linked 1,4 and 1,5 coumarinyl 1,2,3-triazoles and their photophysical properties

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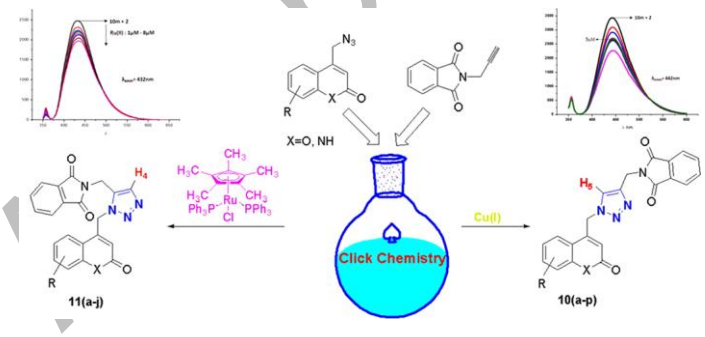
Abstract

Copper catalyzed reaction of *N*-propargyl isoindoline-1,3-dione and 4-azidomethyl coumarins and 4-azidomethyl-1-*aza* coumarins under click chemistry conditions afforded 1,4-disubstituted 1,2,3-triazoles, whereas Ruthenium catalysis yielded isomeric 1,5-disubstituted 1,2,3-triazoles. The two isomers have been distinguished by nOe studies. UV Absorption for a given pair of isomers exhibited similar trend, whereas fluorescence showed considerable differences. Photo physical studies on the interaction of azides with Copper and Ruthenium have also been carried out.

GRAPHICAL ABSTRACT



KEYWORDS: Click reaction, 1,2,3 triazoles, 2*H*-chromene-2-one, isoindoline-1,3-dione, photophysical property

INTRODUCTION

Classical 1, 3-dipolar cycloadditions were discovered by Huisgen and co-workers [1]. Absence of selectivity in the reaction of azides and unsymmetrical alkynes was reflected in the formation of regioisomeric mixture of 1,4 and 1,5-substituted 1,2,3-triazoles which required elevated temperatures and also suffered low reaction rates [2,3]. An excellent modification, effectively and independently developed by Sharpless [4] and Meldal [5] led to renaissance of Huisgen cycloaddition, manifested in the form of Click chemistry.

Copper catalyzed reaction of azides and alkynes (CuAAc) has resulted in selective formation of 1,4-disubstituted 1,2,3 triazoles at room temperature with enhanced rates even under aqueous conditions [6]. Till date, CuAAc reaction is considered as the most robust and versatile example of click chemistry which has found application in the fields of polymers and biochemistry [7-18], designing of fluorescent biochemical markers [19], synthesis of macrocycles [20], and in chemotherapy of tuberculosis [21]. Catalysis in these reactions was extended to analogous metal salts of Ag(I), Pd(0/II), Pt(II), Au(I/III) and Hg(II), which were found to be less effective [22]. Subsequently, Fokin *et.al* found that Ruthenium complexes effectively catalyze the selective formation of 1,5 disubstituted 1,2,3-triazoles [23]. Among the various Ruthenium complexes employed in this reaction, Pentamethylcyclopentadienylbis(triphenylphosphine)ruthenium(II) chloride proved to be most effective [24]. This reaction has been applied for the synthesis of 1,5-disubstituted-1,2,3-triazole benzenesulfonamides as glycoconjugate carbonic anhydrase inhibitors with good selectivity over cancer cell lines [25] and in designing polymer anchored catalyst in azide alkyne cycloaddition [26]. Podophyllotoxin triazole conjugates

have been reported to exhibit antitubulin activity [27]. Ruthenium catalysis has also been employed in the synthesis of 4-trifluoromethyl-1,4,5-trisubstituted-1,2,3-triazoles [28] and in the synthesis of trifunctional thiourea catalysts [29].

Mechanistic studies supported by DFT calculations [30,31], has revealed that in Azide-Alkyne cycloaddition with terminal alkynes, copper catalysis favors N_1-C_2 and N_3-C_1 bond formation [32] whereas Ruthenium complexes favor N_1-C_1 and N_3-C_2 bond formation via a metallocycle intermediate [24]. (**Fig.1**)

N-alkyl *iso* indoline 1,3-dione linked1,2,3-triazoles have been useful as anti-inflammatory agents[33], and have been synthesized under sonochemical conditions [34]. *Bis*-coumarinyl 1,2,3-triazole**s** have shown anti-tubercular activity with low MIC values[35] (**Fig.2**).

It is pertinent to mention the applications of coumarins and isoindoline-1,3-dione as switchable fluorescent molecular probes for intracellular tracking [36], thiol detection [37], and fluorescent liver receptor antagonists [38]. Water-soluble coumarin-triazole conjugates have been employed as fluorescent probes for hydrogen peroxide [39]. Fluorescent chemosensors for DNA, RNA, and proteins have been derived from coumarins [40]. Lockable, fluorescent molecular switch [41] is based on coumarin/phenanthridine-fused heterocyclic systems.

In view of the cleavage of C-O and C-N bonds, complex formation by Ruthenium salts

[42,43] and very few reports on the synthesis of both the regioisomers [44], it was of a considerable interest to make an appropriate choice of azide and alkyne which under optimized conditions would lead to both 1,4 and 1,5 di-substituted triazoles.

In the present paper, we describe our results on the reactions of 4-azidomethyl coumarins and their 1-*aza* analogues with *N*-propargyl isoindoline-1,3-dione (*N*-propargyl phthalimide) using both Copper and Ruthenium under click chemistry conditions.

RESULTS AND DISCUSSION

Acetylenic dipolarophile **2** was synthesized (Scheme-1) by the reaction of potassium phthalimide **1** with 3-bromoprop-1-yne employing potassium carbonate in acetone. Ethyl-4-bromoacetoacetate was prepared by bromination of ethylacetoacetate at 0-5 °C [45], which was further treated with substituted phenols **3(a-l)**, in presence of neat sulphuric acid to obtain 4-(bromomethyl)-2*H*-chromen-2-ones **4(a-l)**, *via* Pechmann cyclization [46]. Coumarinyl azides **5(a-l)** were prepared by treating **4** with sodium azide in aqueous acetone at room temperature and the compounds showed stability even above 100 °C. Substituted 4-(bromomethyl)quinolin-2(1*H*)-ones were synthesized from substituted acetoacetanilides **6(a-d)**. ω-bromoacetoacetanilides **7(a-d)** obtained by bromination, were converted into substituted 4-(bromomethyl)quinolin-2(1*H*)-ones **8(a-d)** by heating with concentrated sulphuric acid at 90 °C [47]. Azides **9(a-d)** were obtained by the reaction of **8(a-d)** with sodium azide in aqueous DMF at room temperature.

The so obtained acetylenic dipolarophile and dipolar azides were made to undergo Azide-Alkyne cycloaddition in presence of copper ascorbate in THF/water, (1:1) under reflux for 8h to obtain exclusively 1,4 substituted 1,2,3-triazole hybrids **10(a-p)** (**Scheme-2**) in excellent yields and purity.

$Cp^*RuCl(PPh_3)_2$ was employed as catalyst in the reaction of 6-methyl 4-azidomethyl coumarin **5** (X=O, R=6-CH_3) with *N*-propargyl isoindoline-1,3-dione **2**. Initial optimization of reaction condition in DCM at room temperature resulted in very low yields of the product (**Entry 1, Table 1**). Attempted reaction in THF at 65 °C resulted in better yields (**Entry 2**). In polar solvent like methanol, under reflux conditions did not give any product even when the catalyst loading was doubled (**Entry 3**). Catalysis under polar aprotic solvent like THF and dry dioxane at 65 °C showed drastic increase in yields and lesser by-products (**Entry 4**). With a view to enhance the yield, DMF was employed at higher temperatures, which resulted in reduced yields (**Entry 5**). Hence all the Ruthenium catalyzed reactions were carried out by employing dry dioxane at 65 °C. Under these conditions the 1,5 regioisomeric compounds were obtained **11(a-j)** in 60-80% yield (**Scheme-3**).

Formation of regioisomeric 1,2,3-triazoles **10** and **11** is supported by spectroscopic data. In the case of 1,4 substituted triazole, compound **10a**, (X=O, R=6-CH_3) IR spectrum showed a band at 1770 cm^{-1} due to the CO stretching of cyclic imide moiety and a band at 1719 cm^{-1} due to lactone carbonyl stretching. Formation of triazole was further confirmed by the ^{1}H-NMR wherein the C_5-H of the triazole ring appeared as a singlet at

8.23 ppm and C_4-CH_2 of coumarin resonated as a singlet at 5.86 ppm. C_3-H of coumarin appeared as a singlet at 5.74 ppm. Methylene protons linked to nitrogen of isoindoline-1,3-dione resonated as a singlet at 4.80 ppm. Further the C_5-H of coumarin was observed as a singlet at 7.58 ppm whereas C_7 and C_8 of coumarin moiety resonated as doublets at 7.43 and 7.28 ppm respectively with a J_{ortho}= 8.6 Hz. Isoindoline-1,3-dione protons appeared as a multiplet at 7.89-7.81 ppm. C_6-CH_3 of coumarin resonated as a singlet at 2.31 ppm. In ^{13}C-NMR, the C_6-CH_3 carbon resonated at 20.8 ppm, methylene carbon linked to nitrogen of isoindoline-1,3-dione appeared at 33.3 ppm whereas the methylene carbon linked to C_4 of coumarin appeared at 49.5 ppm. C_3 carbon of coumarin appeared at 114.1 ppm whereas carbonyl carbon of the cyclic imide and lactone resonated at 167.9 and 160.1 ppm respectively. Other aromatic carbons appeared in the range 117-150.7 ppm. In EI-MS, molecular ion peak was observed at *m/z* 400 which confirmed the formation of product.

Compound **11a** (X=O, R=6-CH_3) IR spectrum showed a band at 1770 cm^{-1} due to the CO stretching of cyclic imide moiety and a band at 1724 cm^{-1} due to lactone carbonyl stretching. Formation of triazole was further confirmed by the ^{1}H-NMR wherein the C_5-H of the triazole ring appears as a singlet at 7.94 ppm and C_4-CH_2 of coumarin resonated as a singlet at 6.02 ppm. The C_3-H of coumarin appeared as a singlet at 5.01 ppm. Methylene protons linked to nitrogen of isoindoline-1,3-dione resonated as a singlet at 4.98 ppm. Further the C_5-H of coumarin appeared as a singlet at 7.62 ppm whereas C_7 and C_8 of coumarin moiety resonated as doublets at 7.48 and 7.20 ppm respectively with a J_{ortho}= 8.4 Hz. Isoindoline-1,3-dione protons appeared as a multiplet at 7.64-7.77 ppm.

C_6-CH_3 of coumarin resonated as a singlet at 2.42 ppm. In ^{13}C-NMR, the C_6-CH_3 carbon resonated at 20.4 ppm, methylene carbon linked to nitrogen of isoindoline-1,3-dione appeared at 29.8 ppm whereas the methylene carbon linked to C_4 of coumarin appeared at 47.4 ppm. C_3 carbon of coumarin appeared at 111.3 ppm. Carbonyl carbon of the cyclic imide and lactone resonated at 167 and 158.8 ppm respectively. Other aromatic carbons appeared in the range 116.3-150.9 ppm. In EI-MS, molecular ion peak was observed at *m/z* 400 which confirmed the formation of product.

nOe STUDIES

Spatial orientation of the two regioisomers and the appropriate assignment the two methylene protons was studied using nOe. In 1,4 disubstituted isomer **10a** (R=6-CH_3) (Structure-I), irradiation of assigned –NCH_2- protons at 4.8 ppm showed increase in the intensity of H_5', whereas, irradiation of assigned C_4-CH_2- at 5.8 ppm exhibited increase in the intensity of H_3, H_5 and H_5'. Similarly, in the case of 1,5 disubstituted isomer **11b** (R = 6-CH_3) (Structure-II), irradiation of assigned –NCH_2- protons at 4.9 ppm showed increase in the intensity of H_4' and C_4-CH_2- whereas, irradiation of assigned C_4-CH_2- at 6.0 ppm exhibited increase in the intensity of H_3, H_5 and –NCH_2- protons. In light of the above nOe data, the assignment and the proposed structure has been confirmed, (**Fig. 3**) which is in agreement with recent literature reports [44].

PHOTOPHYSICAL STUDIES

UV absorption spectra (**Table 2**) of 1,4-isomers **10a-10j** in *N*,*N*-dimethylformamide (DMF) are characterized by the presence of an intense absorption maxima in the range of

290–336 nm except in the case of 5,6-benzo substitution **10e** which showed bathochromic shift with λ_{max} at 350 nm. The emission spectra showed considerable differences, when compared with the 1,5-isomers **11a-11j**.

UV absorption spectra of the pair of isomers **10a**(R = 6-CH_3) and **11a**(R = 6-CH_3) showed similar λ_{max} at 320 nm with nearly same absorbance (**Fig.4**), whereas in the emission spectra, the 1,5-isomer **11a** exhibited a four-fold enhancement in the intensity when compared with the corresponding 1,4-isomer **10a** (**Fig.5**). Similar higher intensity was observed with pairs of **10b-11b**, **10c-11c** and **10d-11d** (**Table 2**). In the case of 7-OCH_3 and 5,6-benzo groups, reverse trend was observed which is clear from the intensity values of **10e-11e** and **10f-11f** isomeric pairs. Similar lowering in intensity was also observed in 1,5-isomers when X=NH, irrespective of the substituents, as can be seen in pairs of **10h-11h**, **10i-11i** and **10j-11j**.

Variation of fluorescence intensity is probably due to steric effect of the two bulky phthalimido and coumarin/1-azacoumarin moieties which favors a non-planar arrangement for the 1,5-isomer. Similar steric effects have been observed in bi-phenyls [48] and other aromatic compounds [49].

Comparative study on the UV- Fluorescence measurement on Cu(I) and Ru(II) catalyzed systems have shown significant differences in their photophysical behavior.

UV-fluorescence behavior in presence of Cu(I) and Ru(II) for the same set of azide and

alkyne was measured. Initially, UV spectra of the mixture of **10m** (azide) and **2** (alkyne) were separately recorded in two solvents *viz.* tetrahydrofuran and 1,4-dioxane which showed absorbance at λ_{abs} = 356 nm and 359 nm respectively. Choice of solvents used for CuAAC and RuAAC were identical to those which had been used for the actual reaction.

Cu (I) CATALYZED SYSTEM

The solutions of **10m** (1×10^{-4} mol/L) and **2** (1×10^{-4} mol/L) were prepared in tetrahydrofuran:water (1:1) mixture and the fluorescence was observed at λ_{emm} = 442 nm.

Fluorescence spectrum was recorded serially after the addition of 1 µM – 9 µM solution of Cu(I), which was in turn was obtained by mixing copper sulphate pentahydrate and sodium ascorbate followed by the addition to the mixture of **10m** and **2** in tetrahydrofuran:water (1:1) mixture. From the fluorescence plot we observed that initially after the addition of 1 µM solution of Cu(I), a fluorescence quenching was observed. Similar trend was observed from the addition of Cu(I) from 1-4 µM. Further increase in the concentration of Cu(I) from 5 µM -9 µM, an increase in the intensity has been observed. [**Fig. 6**] Fluorescence quenching by Cu(I) on Dansyl azide have been employed for ligand acceleration studies and bio-conjugation applications [50]

Ru (II) CATALYZED SYSTEM

Solutions of **10m** (1×10^{-4} mol/L) and **2** (1×10^{-4} mol/L) were prepared in 1,4 dioxane and the fluorescence was observed at λ_{emm} = 432 nm.

Fluorescence was recorded serially after the addition of 1 µM -8 µM solution of Ru(II) to the mixture of **10m** and **2** in 1,4 dioxane. From the fluorescence plot we observed that, after the addition of 1 µM solution of Ru(II), there is a fluorescence quenching. [Fig.7] Similar trend was observed from the addition of Ru(II) from 2 µM – 8 µM and λ_{emm} was shifted to 433 nm.

Our studies have shown that increasing concentrations of Cp*RuCl$(PPh_3)_2$ resulted in quenching of azide fluorescence whereas with Cu(I) there was an initial decrease, followed by an increase in fluorescence intensity. This deviation in fluorescence quenching may be attributed to *in situ* formation of *bis* (copper intermediates) forming a dinuclear copper complex. [51, 52]

EXPERIMENTAL

Typical procedure for the synthesis of 2-(prop-2-ynyl)isoindoline-1,3-dione (2).

The synthesis is as per the literature report [53].

Typical procedure for the synthesis of 2-((1-((6-methyl-2-oxo-2h-chromen-4-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)isoindoline-1,3-dione (10a).

To a solution of compound **9** (1.0 mmol) in THF/H_2O, 1: 1(v/v), $CuSO_4 \cdot 5H_2O$ (0.15 mmol), sodium carbonate (0.15 mmol), ascorbic acid (0.3 mmol) were added. The mixture was stirred at room temperature for 15 min. then, 6-methyl-4-azidomethyl coumarin **5a** (1.0 mmol) was added, and the resulting reaction mixture was refluxed on water bath until the starting material was consumed as judged by TLC. Then, the reaction

mixture was cooled, separated solid was filtered, washed with water and recrystallised from DMF. White; Yield 82%; m.p: 198-200 °C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS) (ppm): 8.23(s, 1H, Tri-H), 7.80-7.27(m, 7H, Ar-H), 5.86(s, 2H, -C_4-CH_2), 5.74(s, 1H, C_3-H), 4.80(s, 2H, -N-CH_2), 2.31(s, 3H, -CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) (ppm): 20.8, 33.3, 49.5, 114.1, 117.0, 117.1, 123.7, 125.2, 131.9, 133.9, 134.1, 135.1, 143.2, 149.9, 150.4, 150.7, 160.1, 167.9; EI-MS *m/z* 400($M^{\cdot+}$, 13%); Anal. Calcd. for $C_{22}H_{16}N_4O_4$ (%), Calcd: C, 66.00; H, 4.03; N, 13.99; found: C, 65.95; H, 4.00; N, 13.95

Typical procedure for the synthesis of 2-((3-((6-methyl-2-oxo-2H-chromen-4-yl)methyl)-3H-1,2,3-triazol-4-yl)methyl)isoindoline-1,3-dione (11a).

To a solution of alkyne **9** (1.0 mM) in dry dioxane (5 mL), 18 mg (22 µM) of Cp*RuCl(PPh_3)$_2$ was added and the R.B flask was purged with nitrogen gas. The reaction mixture was warmed to 50 °C and stirred for 30 minutes. Azide **5** (1.0 mM) was dissolved in 5 mL of dry dioxane and added to the reaction mixture which was stirred at 60 °C for 18 hrs. Progress of the reaction was checked using T.L.C. The separated silky maroon-purple precipitate was filtered, washed with cold dioxane and dried. Dark brown solid; Yield 75 %; m.p: 256-258 °C; ^{1}H-NMR (400 MHz, DMSO-d_6, TMS) (ppm): 7.94(s, 1H, Tri-H), 7.77-7.19(m, 7H, Ar-H), 6.02(s, 2H, -C_4-CH_2), 5.01(s, 1H, C_3-H), 4.98(s, 2H, -N-CH_2), 2.42(s, 3H, -CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) (ppm): 20.4, 29.9, 47.4, 111.3, 116.3, 116.3, 122.9, 124.4, 130.9, 133.4, 133.6, 133.7, 134.5, 134.6, 150.4, 150.9, 158.8, 167.0; EI-MS *m/z* 400($M^{\cdot+}$,100%); Anal. Calcd. for $C_{22}H_{16}N_4O_4$ (%), Calcd: C, 66.00; H, 4.03; N, 13.99; found: C, 65.98; H, 4.00; N, 13.95

CONCLUSION

Regioselectivity associated with CuAAC and RuAAC under Click Chemistry conditions has been confirmed using coumarinyl azides and 2-(prop-2-ynyl) isoindoline-1, 3-dione.

UV spectra for a pair of isomers were similar while Fluorescence spectra showed a fourfold increase in intensity for the 1,5 isomer. Significant difference in fluorescence quenching of azide was observed under CuAAC and RuAAC reaction conditions. This observation may be useful for the study of HOMO-LUMO interactions of metal centers with azides.

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Table 1: Optimization of conditions for the synthesis of $Cp^*RuCl(PPh_3)_2$ catalysed 1,5-disubstituted 1,2,3-triazoles.

Entry	**Catalyst (in moles)**	**Solvent**	**Temperature (°C)**	**Time (hrs)**	**Yield (%)**
1.	1.1×10^{-5}	DCM	25	10	5
2.	1.1×10^{-5}	THF	65	12	20^a
3.	2.2×10^{-5}	MeOH	60	10	Trace
4.	**2.2×10^{-5}**	**Dry Dioxane**	**60**	**12**	**75^a**
5.	2.2×10^{-5}	DMF	110	10	10^a

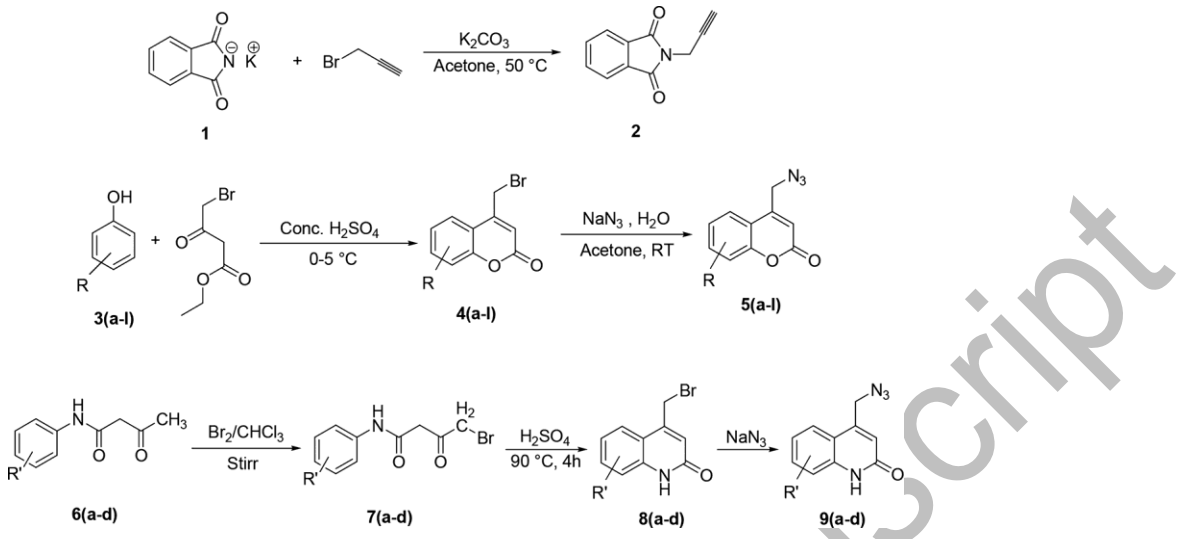
a= isolated yields

Table 2: UV-visible and fluorescence spectral data of compounds **10(a-j)** and **11(a-j)**

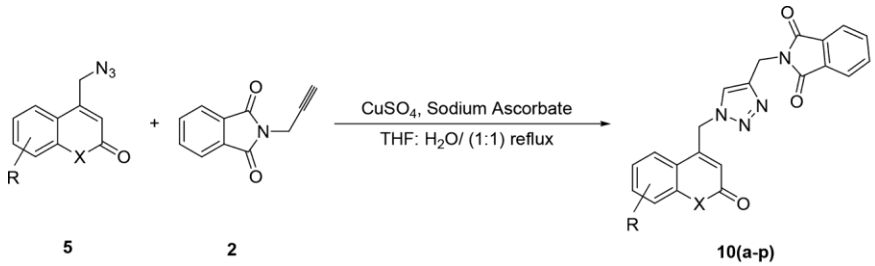
Compound	**λ_{abs} (nm)**	**ε**	**λ_{em} (nm)**	**Fluorescence intensity (a.u)**	**Stokes shift (υ_{abs} - υ_{em})**
10a (R= 6-CH_3, X=O)	320	5,490	422	21	7,554
10b (R= 7, 8-CH_3, X=O)	290	13,570	412	05	10,211
10c (R= 7-CH_3, X=O)	312	8,090	398	11	6,926
10d (R= 5,7-CH_3, X=O)	290	13,430	410	05	9,792
10e (R= 5,6 Benzo, X=O)	350	8,930	427	1023	5,152
10f (R= 7-OCH_3, X=O)	322	16,290	396	365	5,803
10g (R= 7-Cl, X=O)	305	12,560	440	35	10,059
10h (R= 6-Cl, X=NH)	343	6,300	425	151	7,721
10i (R= H, X=NH)	332	7,090	391	158	4,545
10j (R= 8-CH_3, X=NH)	336	5,900	399	129	4,699
11a (R= 6-CH_3, X=O)	320	4,680	452	77	9,127
11b (R= 7, 8-CH_3, X=O)	292	14,010	453	76	12,171
11c (R= 7-CH_3, X=O)	315	7,370	448	170	9,425
11d (R= 5,7-CH_3, X=O)	294	11,360	449	54	11,742
11e (R= 5,6 Benzo, X=O)	352	11,940	458	600	6,575

11f (R= 7-OCH_3, X=O)	322	15,030	399	115	5,993
11g (R= 7-Cl, X=O)	305	9,900	435	60	9,798
11h (R= 6-Cl, X=NH)	342	5,270	402	49	4,364
11i (R= H, X=NH)	334	5,160	392	57	4,430
11j (R= 8-CH_3, X=NH)	336	4,270	400	35	4,762

Scheme 1. Synthesis of 4-azidomethyl coumarin **5** and their 1-*aza* analogues **9**.



Scheme 2. Synthesis of Copper(I) catalyzed 1,2,3-triazoles.

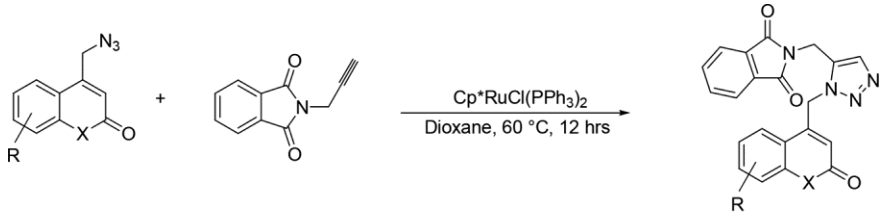


5 **2** **10(a-p)**

X=O, R= 6-CH_3, 7-CH_3, benzo[f], benzo[h], 5,7 Di-CH_3, 7,8 Di-CH_3, 6-OCH_3, 7-OCH_3, 6-Cl, 7-Cl, 6-Br, 7-OH

X=NH, R= H, 8-CH_3, 6-Cl, 7-Cl

Scheme 3. Synthesis of Cp*RuCl(PPh_3)$_2$ catalyzed 1,2,3-triazoles.



5 **2** **11(a-j)**

X=O, R= 6-CH_3, 7,8 Di-CH_3, 7-CH_3, 5,7 Di-CH_3, benzo[f], 7-OCH_3, 7-Cl

X=NH, R= H, 6-Cl, 8-CH_3

Figure1. Preferred C-N bond formations in CuAAc and RuAAC catalysed reactions.

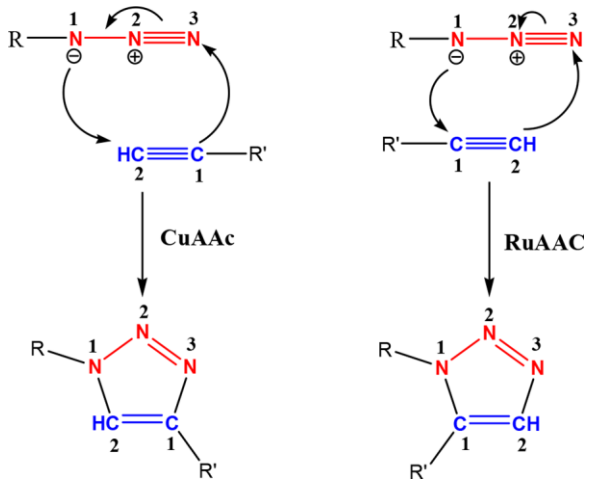
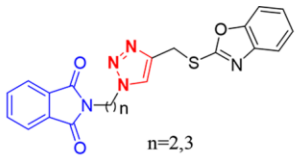
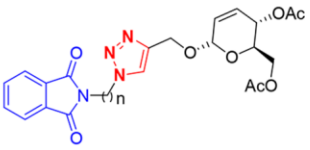


Figure 2. Structurally related 1,2,3-triazoles



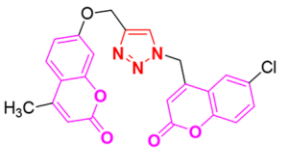
A

Ultrasound assisted synthesis of 1,2,3-triazole



B

Anti-inflammatory agent



C

Anti-tubercular agent
MIC = 6.25 µg/mL

Figure 3. NOE effects for regioisomers **10a** and **11a**

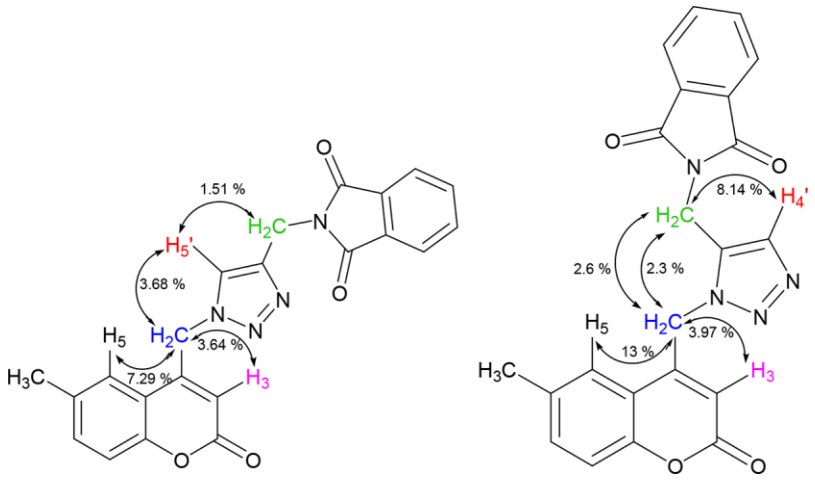


Figure 4. UV overlay spectrum of the isomers **10a** and **11a;** (R=6-CH_3, X=O)

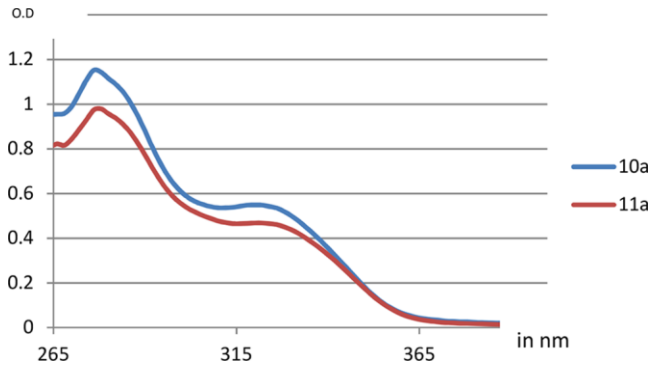


Figure 5. Fluorescence overlay spectrum of the isomers **10a** and **11a;** (R=6-CH_3, X=O)

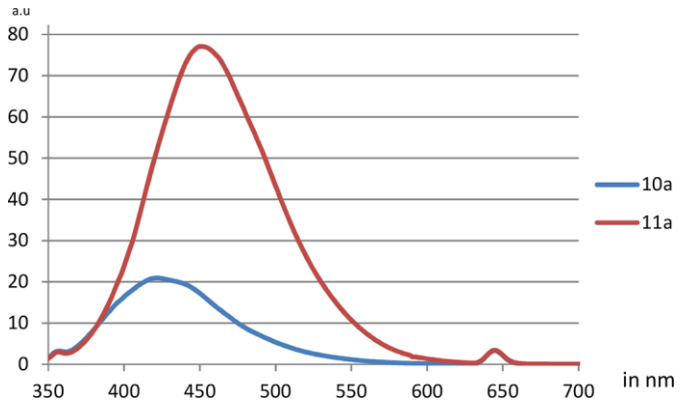


Figure 6. Fluorescence quenching on addition of Cu(I) from 1µM -9µM

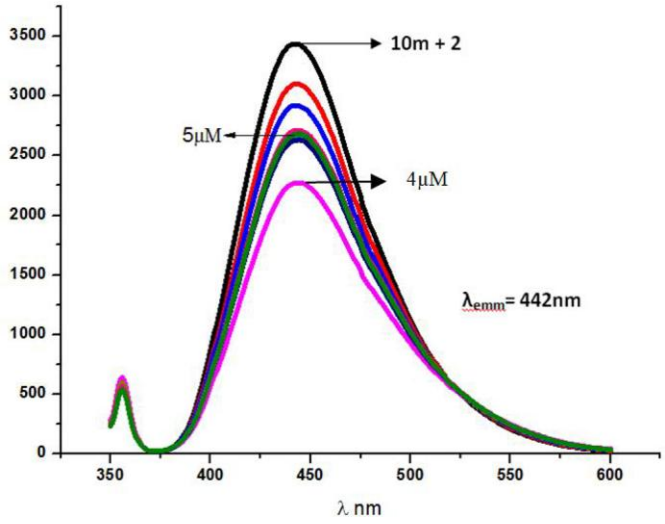


Figure 7. Fluorescence quenching on addition of Ru(II) from 1µM -8µM.