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The study of catalyst free and copper catalyzed reactions of cyanochromenes and sodium azide

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ABSTRACT

Two different roles of sodium azide under two different conditions are described here along with the plausible mechanisms. When sodium azide was treated with cyanochromenes under catalyst free conditions, the azide anion acted as a base. Hence, a base mediated rearrangement of cyanochromenes was resulted in formation of benzofuran derivatives. However, in the presence of catalytic amount of CuI the azide anion acted as a diene to produce chromenotetrazoles.

1. Introduction

Synthetic, medicinal and pharmaceutical applications of chromenes are well explored in a plethora of literature.[1–3] In different occasions, these derivatives are utilized as anti-HIV, antitumour, antimicrobial, fungicidal, insecticidal agents, photochromic materials and ingredients of antioxidants.[2a] Especially, the chromenes with an electron withdrawing functionality at C-3 are known as good Michael acceptors.[2,3] By applying the same concept, recently, we have disclosed protocols for the indole and azide addition on 3-nitrochromenes.[3] However, as per the electron withdrawing functionalities at the C-3 of the chromene derivatives are concerned, the reactivity of the cyanochromenes is less explored than the nitrochromenes.

Beside chromenes, Benzofuran derivatives are also important motifs, which are widely occurred in natural products and exhibit significant biological activities.[4,5] Hence, a great effort has been paid towards the synthesis of these heterocycles. Several attempts have been made to achieve, particularly, the 3-cyanobenzofurans due to the huge synthetic utility of the nitrile functionality.[5] However, most of the protocols towards the synthesis of 3-cyanobenzofurans involve multistep reactions, application of toxic metal catalysts or complex combination of reagents.[5] Hence, the chemists are in search of more convenient and easy methods to synthesize 3-cyanobenzofuran derivatives.

Over the last few decades, transition metal catalysts have been drawing the attention of the chemists due to their wide spectrum of utilities in numerous chemical transformations.[6] These catalytic activities are mainly originated from the activation of a particular functionality towards a certain type of reaction via coordination.[7] This type of activation promotes the other reagents to react with that functional group and thus the reaction achieve an added selectivity. As an example, in the present report, we wish to disclose our finding, which involve the activation of nitrile functionality of cyanochromenes by a Cu catalyst. This activation promotes the azide anion to react with the nitrile functionality selectively, as a 1,3-dipole, to produce chromenotetrazoles. In absence of the catalyst, the azide anion acts as a base and the cyanochromene undergo base mediated rearrangement to produce 3-cyanobenzofuran derivative.

2. Results and discussions

In a recent publication, we reported a protocol for the synthesis of chromenotriazoles from nitrochromenes (Scheme 1).[3a] The triazoles were formed via the elimination of the nitro functionality of the nitrochromenes, when the nitrochromenes were treated with sodium azide in DMSO under catalyst-free conditions. Prompted by this success, we planned to use cyanochromenes, in the place of

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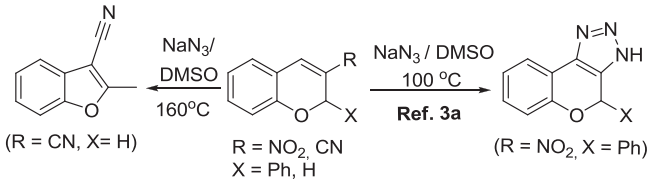
nitrochromenes, to synthesize triazole derivatives by the elimination of the cyano functionality. However, on heating cyanochromene (entry 2, Table 1) with sodium azide at 160 °C in DMSO, 2-methyl-3-cyanobenzofuran derivative was formed. The structure was verified by ^{1}H NMR, ^{13}C NMR, LRMS, HRMS and single crystal X-ray analysis data (Fig. 1 and Supplementary data). This result demonstrates an unprecedented type of transformation, which leads to the synthesis of 3-cyanobenzofuran derivatives directly from 3-cyanochromenes.



Scheme 1. Reactivity of sodium azide towards nitro and cyanochromene.

Table 1
Effect of different bases

Entry[a,b]	Base	Temp (°C)	Solvent	Time	Yield (%)[c]
1	NaN_3	130	DMSO	2 h	56
2	NaN_3	160	DMSO	20 min	76
3	TEA	130	DMSO	24 h	10
4	TEA	160	DMSO	1 h	15
5	DBU	160	DMSO	30 min	65
6	DIPA	160	DMSO	24 h	—
7	DABCO	160	DMSO	55 min	30
8	K_2CO_3	160	DMSO	20 min	67
9	Na_2CO_3	160	DMSO	40 min	56
10	Cs_2CO_3	160	DMSO	1 h	55
11	KO^{t}Bu	rt	DMSO	—	dec
12	NaOMe	160	DMSO	25 min	45
13	*N*,*N*-Diethylethane-1,2-diamine	160	DMSO	2 h	—
14	$NaHCO_3$	160	DMSO	2 h	59
15	NaN_3	130	DMF	5 h	40

[a] All reactions were carried out on 0.5 mmol scale.
[b] Base (1.2 equiv) in DMSO at mentioned temp.
[c] Yields refers to isolated and purified compound.

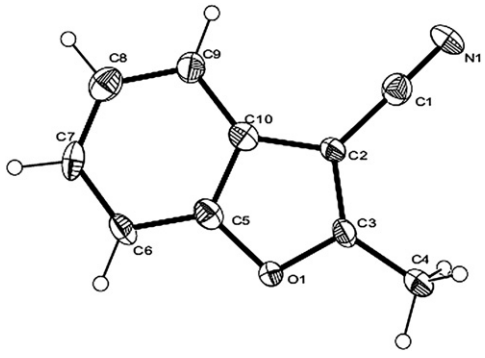
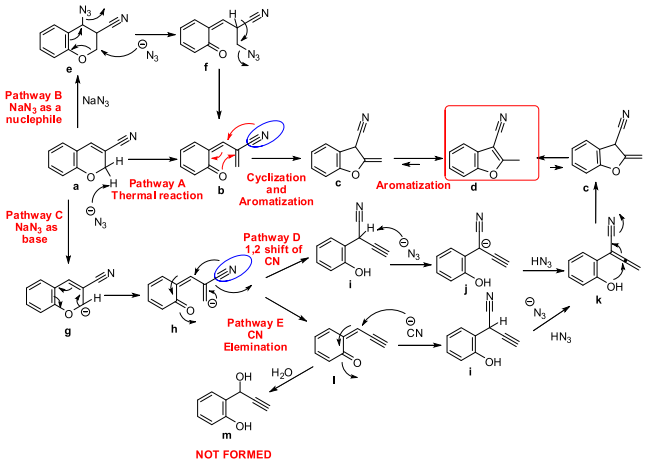


Fig. 1. X-ray crystal structure of **1a** (ORTEP diagram).

In this reaction, the cyanide functionality was shifted to the benzylic position and a six membered pyran ring was rearranged to a five membered furan ring. As the reaction was occurred only at high temperature, we first assumed a thermal reaction. Hence, our initial assumption was a thermal cleavage of the pyran ring, followed by the 1,2-shift of the cyano functionality and cyclization to produce intermediate **c** (Pathway **A**, Scheme 2). Aromatization of the intermediate **c** produces the final product. However, when we performed a reaction in the absence of sodium azide, no product was formed and the starting material was recovered. This experimental observation rules out the possibility, which is described in pathway **A**. Then we assumed a nucleophilic attack by azide anion to form intermediate **e** (Pathway **B**), which is followed by the ring opening via the cleavage of C–O bond in S_N2 manner to form intermediate **f**. A base mediated E2 reaction on intermediate **f**, may produce intermediate **b**, which would be converted into final product as described earlier. To clarify this assumption, we screened the reaction with bases, like DIPA, NaOMe and *N*,*N*-diethylethane-1,2-diamine as they may act as nucleophile as well as base (Table 1). However, the reactions were either failed (entries 6 and 13) or produced the desired product in poor yields (entry 12).



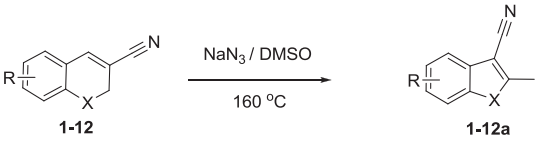
Scheme 2. Plausible mechanism for the conversion.

On the other hand, bases like DBU, K_2CO_3, Na_2CO_3 and Cs_2CO_3 produced better yields of the desired product. Among the different bases, K_2CO_3 produced better yields than the others. This fact tells more about a base mediated mechanism, which happened via the abstraction of a proton by a base at high temperature to produce the unstable anion **g**. This anion undergoes ring cleavage to produce the intermediate **h**. The 1,2-shift of the cyano functionality was occurred either via pathway **D** or **E** to produce the intermediate **k** (allene intermediate). Intermediate **k** undergoes cyclization and followed by the aromatization to produce the desired product. It is not clear whether the reaction was occurred via pathway **D** or **E**. However, in the crude ^{1}H NMR, we did not observe the formation of product **m** under air and moisture, we prefer the pathway **D** as the most favourable route for the formation of the product **d**. From our studies with different bases, we found that a base of moderate strength, like sodium azide, was more suitable than other strong or weak bases. Hence, we evaluated the scope of our methodology by using sodium azide in DMSO (entry 2).

After determining the best conditions for the conversion, we utilized different cyanochromene derivatives, to evaluate the scope of this methodology (Table 2). With unsubstituted cyanochromene, the reaction produced the expected benzofuran derivative in good yield (entry 1). A comparable result was observed with 6-methyl-3-cyanochromene (entry 2). However, the yields of the desired products were decreased in the case of methoxy substituted cyanochromenes (entries 3 and 4). The yield of the product was further decreased when the dimethoxy substituted cyanochromene

derivative was used as substrate (entry 5). Moreover, the desired products were obtained in moderate yields from the 6-halo cyanochromene derivatives (entries 6, 7). However, the yield of the desired product was poor in case of 6-iododerivative (entry 8).

Table 2
Synthesis of benzofuran and benzothiophene derivatives



1-12

X: O, S

1-12a

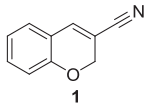
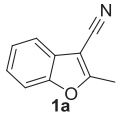
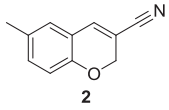
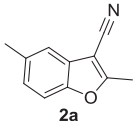
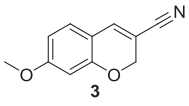
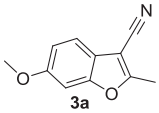
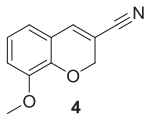
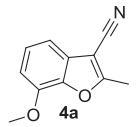
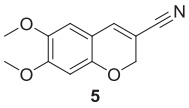
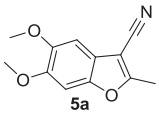
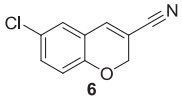
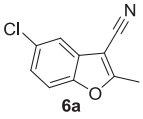
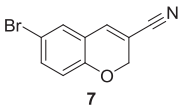
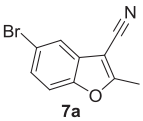
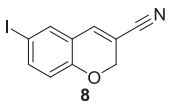
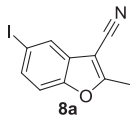
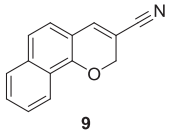
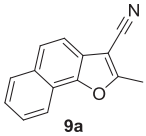
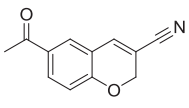
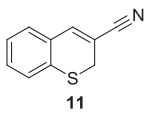
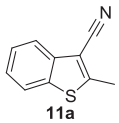
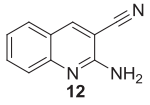
Entry[a,b]	Cyanochromene	Product	Time (min)	Yield[c] (%)
1	 **1**	 **1a**	20	76
2	 **2**	 **2a**	24	74
3	 **3**	 **3a**	28	59
4	 **4**	 **4a**	25	54
5	 **5**	 **5a**	50	35
6	 **6**	 **6a**	30	53
7	 **7**	 **7a**	28	60
8	 **8**	 **8a**	40	24
9	 **9**	 **9a**	35	70
10	 **10**	—	—	—[d]

Table 2 (*continued*)

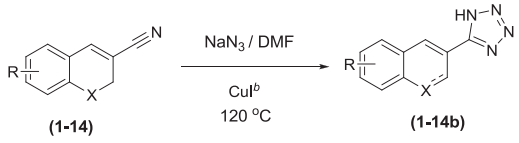
Entry[a,b]	Cyanochromene	Product	Time (min)	Yield[c] (%)
11	 **11**	 **11a**	20	25
12	 **12**	—	—	—[e]

[a] All reactions were carried out on 0.5 mmol scale.
[b] NaN_3 (1.2 equiv) in DMSO at 160 °C.
[c] Yields refer to isolated and purified compounds.
[d] Inseparable mixture of compounds.
[e] NR: reaction was not occurred and only starting material was recovered.

Interestingly, when the benzene ring of the cyanochromene was replaced with naphthalene moiety (entry 9) the reaction furnished the corresponding product in good yield. On the other hand, the reaction of 6-acetyl-2*H*-chromene-3-carbonitrile in the present reaction conditions resulted in the formation of an inseparable mixture of products even at lower temperature (entry 10). The crude ^{1}H NMR did not show a trace amount of the desired product, although, all the starting materials were consumed. The present reaction conditions were found to be suitable even for the preparation of benzothiophene derivative (entry 11). However, in this case, the desired product was obtained in poor yield. When the stable aromatic heterocycle, like 2-amino-3-cyanoquinoline (entry 12), was treated with sodium azide under catalyst free conditions, no product was observed and the starting material was recovered.

On the other hand, the result was completely different when the reaction of sodium azide and cyanochromene (**1**) was carried out in the presence of catalytic amount of CuI. In this case, the reaction was occurred at lower temperature and the resulting product was chromenotetrazole (**1b**, Table 3), which was confirmed by ^{1}H NMR, ^{13}C NMR, LRMS, HRMS and single crystal X-ray analysis data (Fig. 2).

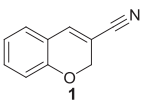
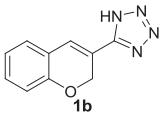
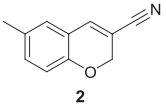
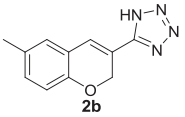
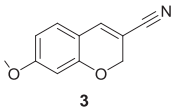
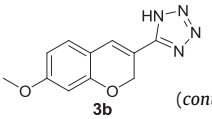
Table 3
Synthesis of chromenotetrazoles



(1-14)

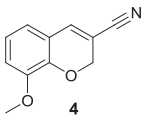
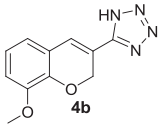
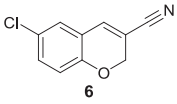
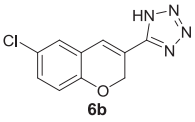
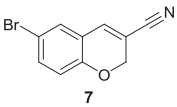
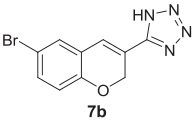
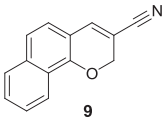
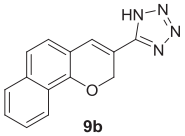
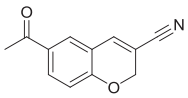
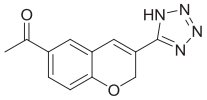
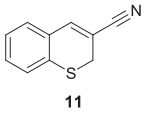
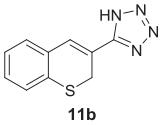
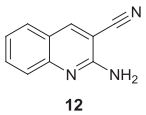
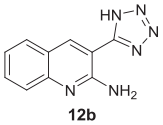
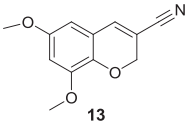
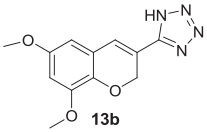
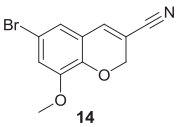
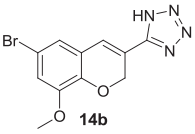
X: O, S, N

(1-14b)

Entry[a,b]	Cyanochromene	Product	Time (h)	Yield[c] (%)
1	 **1**	 **1b**	4	89
2	 **2**	 **2b**	4.5	89
3	 **3**	 **3b**	5	81

(*continued on next page*)

Table 3 (*continued*)

Entry[a,b]	Cyanochromene	Product	Time (h)	Yield[c] (%)
4	 4	 4b	5	80
5	 6	 6b	4	86
6	 7	 7b	5	85
7	 9	 9b	5	87
8	 10	 10b	3	88
9	 11	 11b	3.5	66
10	 12	 12b	3	89
11	 13	 13b	7	84
12	 14	 14b	5	84

[a] All reactions were carried out on 0.5 mmol scale.
[b] NaN_3 (1.2 equiv)/CuI (20 mol %) in DMF at 120 °C.
[c] Yields refers to isolated and purified compounds.

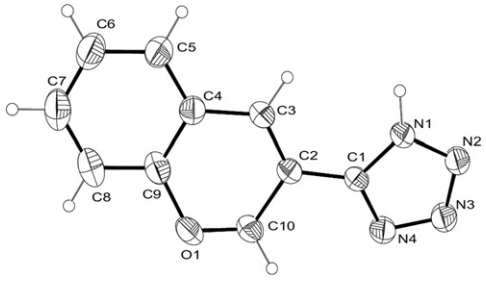
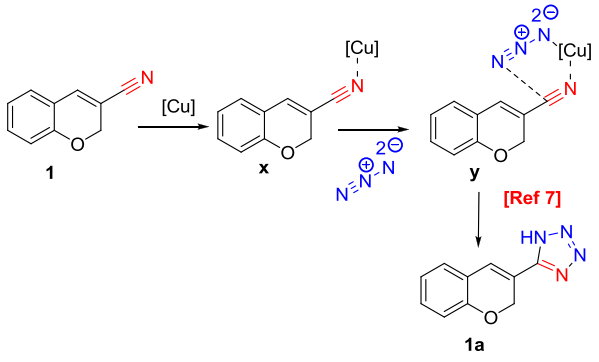


Fig. 2. X-ray crystal structure of **1b** (ORTEP diagram).

With this exciting experimental outcome in hand, we focused our attention towards exploring the most favourable conditions for the reaction. On screening with different solvents, we found that the reaction produced better result in DMF than DMSO. Next, we screened different catalysts to find a better alternative of CuI. However, Cu_2O, $Cu(OAc)_2$, $TiCl_4$, $AlCl_3$ and $ZnBr_2$ produced the desired product in lower yields. Iodine was found to be ineffective for the conversion (see Supplementary data). Hence, we used DMF as solvent and CuI as catalyst for evaluating the scopes of this protocol.

Under the present reaction conditions, several cyanochromenes underwent cycloaddition to form chromenotetrazoles as shown in Table 3. The use of unsubstituted and methyl substituted cyanochromenes resulted in excellent yields of the product (entries 1 and 2). Moreover, comparable yields were obtained with methoxy substituted cyanochromenes (entries 3, 4, 11 and 12). The expected tetrazoles were obtained in excellent yields from cyanochromenes with electron withdrawing groups (entries 5, 6 and 8). Interestingly, the cyanobenzochromene (entry 9) is also produced the expected tetrazole in excellent yield under the present reaction conditions. From Table 2, it is evident that the reaction of cyanochromene possessing an electron donating group took longer time compared with unsubstituted cyano chromene and a cyanochromene with an electron withdrawing substituent to form their corresponding tetrazoles. It is worthy to note that the present reaction conditions were utilized for the nitrogen and sulfur analogues of cyanochromenes like cyanothiochromene (**11**) and cyanoquinoline (**12**). Under these conditions the reaction furnished their corresponding products, i.e., thiochromenotetrazole (**11b**) and 2-aminoquinolinotetrazole (**12b**) in moderate and excellent yields, respectively.

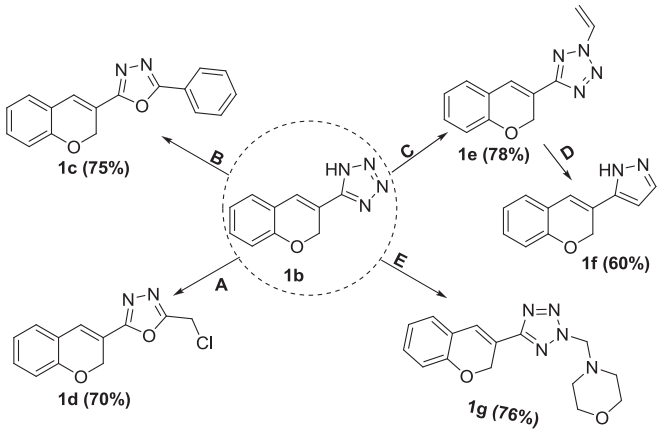
The most notable point is that under these reaction conditions the chromene ring remained unaffected and the product formation was occurred via selective transformation of the cyano functionality into tetrazoles. The plausible mechanism is similar to the Zn^{2+} catalyzed transformation of nitriles into tetrazole, which was proposed earlier by Sharpless (Scheme 3).[8] We assume a similar type of activation of nitrile functionality by the coordination of Cu(I) with the nitrogen (intermediate **x**, Scheme 3) and hence, the azide anion attacked at the nitrile functionality selectively as outlined in Scheme 3. To the best of our knowledge, these chromenotetrazole derivatives are new in the literature.



Scheme 3. Plausible mechanism for the formation of chromenotetrazole.

After exploring the scope of this protocol, we attempted to evaluate the synthetic applicability of the tetrazole derivatives (Scheme 4). To pursue this goal, we transformed the tetrazole ring into oxadiazole and pyrazole rings. The chromeno oxadiazole derivatives (**1c** and **1d**) were obtained by treating **1b** with benzoyl chloride and 2-chloroacetyl chloride.

To prepare the pyrazole (**1f**) derivative, the chromenotetrazole derivative (**1b**) was refluxed with dibromoethane in acetonitrile in the presence of triethylamine as a base to obtain **1e** in good yield. The compound **1e** was heated at 150 °C in xylene to obtain the desired pyrazole (**1f**). Next, in order to evaluate further utility of the



Conditions:
A: 2-chloroacetyl chloride (1.2 equiv.)/ Toluene / Reflux (12 h)
B: Benzoyl chloride (1.2 equiv.)/ Toluene / Reflux (14 h)
C: 1, 2-Dibromo ethane (2 equiv.)/ TEA (4 equiv.)/ Acetonitrile/ Reflux
D: Xylene/ 150°C (36 h)
E: Morpholine (1.1 equiv.)/ Formline (1.5 equiv.)/ MeOH/ rt (24 h)

Scheme 4. Synthetic utilities of chromenotetrazole.

chromenotetrazoles, compound **1b** was treated with morpholine and formaline in methanol at room temperature and the 3-methylmorpholine substituted chromenotetrazole (**1g**) was selectively produced in moderate yield. The structure of the compound **1g** was confirmed by single crystal X-ray analysis (Fig. 3). It is noteworthy that pyrazoles, oxadiazoles and morpholines are very important due to their synthetic and medicinal utilities as described in several literature.[9] More studies on the biological activities of the tetrazole, oxadiazole and pyrazole derivatives are currently underway in our laboratory.

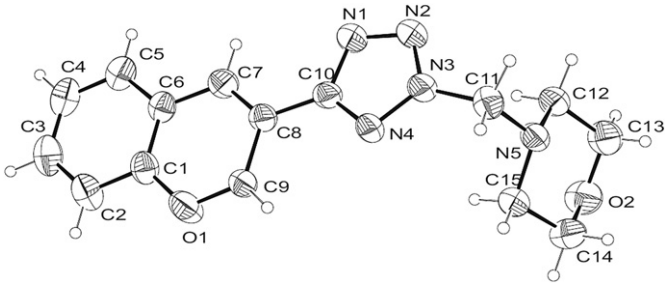


Fig. 3. X-ray crystal structure of **1g** (ORTEP diagram).

Further, when we placed the solutions of different tetrazole derivatives in front of UV lamp, compound **12b** displayed fluorescent properties. In this context, it is noteworthy to mention that the fluorescence sensing activities of quinoline derivatives are reported in the literature.[10] Hence, we focused our attention towards exploring the metal sensing activity of the tetrazole derivative (Fig. 4). To pursue this goal, we prepared a 0.1 M solution of ligand (**12b**, Table 3) in DMF. A 0.1 M solution of the metal ion in DMF was then added to 3 mL of a 0.1 M solution of the ligand (compound **12b**) and the fluorescence enhancement was measured. With Zn^{2+}, the maximum fluorescence enhancement was observed when 200 μL of the metal ion solution was added to the ligand solution. Later, we measured the fluorescence enhancement with other metal ions, including Na^{+}, K^{+}, Mn^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Hg^{2+} and Ni^{2+} (Fig. 4). With Ni^{2+}, the fluorescence was quenched abruptly.

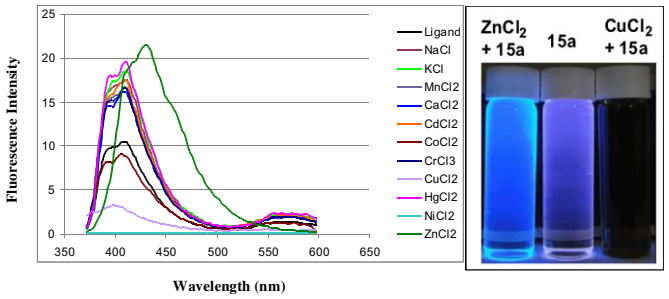


Fig. 4. Change of fluorescence intensity of **12b** with different metal salts. 200 μL solution of the metal ion in DMF was added to 3 mL 0.1 M solution of the ligand (compound **12b**) and the fluorescence enhancement was measured.

Co^{2+} and Cu^{2+} also showed fluorescence quenching properties. On the other hand, Na^{+}, K^{+}, Mn^{2+}, Ca^{2+}, Cd^{2+}, Cr^{3+} and Hg^{2+} showed comparable enhancement of fluorescence. However, with Hg^{2+}, the enhancement is greater than Na^{+}, K^{+}, Mn^{2+}, Ca^{2+}, Cd^{2+} and Cr^{3+}. As shown in Fig. 3, compound **12b** showed the highest fluorescence enhancement to Zn^{2+} ions, which was quite distinct from all the others. This selectivity of **12b** towards Zn^{2+} is very important as Zn^{2+} is the second most abundant transition metal ion in the human body after iron.[10a]

3. Conclusion

In conclusion, we have demonstrated a novel method for the synthesis of 3-cyanobenzofuran derivatives from cyanochromenes under catalyst free conditions. The reaction was occurred via a sodium azide mediated rearrangement of the pyran ring into furan ring and a 1,2-shift of the nitrile functionality. The mechanism was supported by the experimental outcomes. In the presence of CuI, a chromenotetrazole was formed due to the selective activation of the nitrile functionality. In addition, this report demonstrates the utilities of the tetrazole derivative as potential Zn^{2+} ion sensor as well as synthetic intermediate. Studies aimed at exploring more utilities of benzofurans and chromenotetrazoles in biological and synthetic fields are currently underway in our laboratory.

4. Experimental section

4.1. General

General remarks: all reactions were carried out under nitrogen atmosphere and in glassware, which had been oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography by use of E. Merck silica gel 60 (230–400 mesh). MS were measured by JEOL JMS-HX110 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Advance EX 400. Chemical shifts were reported in parts per million (δ) using DMSO-d_6 and $CDCl_3$ as internal standard and coupling constants were expressed in hertz. UV study was done on Agilent HP8453 spectrophotometer and the Fluorescence study was performed on Varian Carry Eclipse Fluorescence spectrophotometer. All the substrates were prepared by following reported procedures.[11]

*4.1.1. General procedure for the synthesis of 2-methylbenzofuran-3-carbonitrile (**1a**).* To a stirred solution of cyanochromene (1 mmol) in DMSO (2 mL) in a 50 mL round bottom flask was added NaN_3 (1.1 equiv). The reaction mixture was then heated to 160 °C. The progress of reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was quenched with ice water

(25 mL) and extracted with ethyl acetate. Organic layer was dried over $MgSO_4$ then filtered and evaporated. The crude compound was then column purified to yield corresponding pure compound.

*4.1.2. General procedure for the synthesis of chromene tetrazole by using NaN_3/CuI (**1b**).* To a stirred solution of cyanochromene (0.5 mmol) in DMF (2 mL) in a 50 mL round bottom flask was added NaN_3 (1.1 equiv) and CuI (20 mol %). The reaction mixture was then heated to 120 °C. The progress of reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was quenched with ice water (25 mL) and acidified (pH=3.5) by aq HCl (4 M). The precipitate was filtered and washed with ice water (25 mL) to obtain the pure product.

*4.1.3. Synthesis of 2-(2H-chromen-3-yl)-5-phenyl-1,3,4-oxadiazole (**1c**).* A mixture of **1b** (1 mmol) and benzoyl chloride (1.1 mmol) in toluene (10 mL) in a 50 mL round bottom flask was refluxed overnight. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude compound was then purified by column chromatography to afford yellow solid.

Compound **1d** was prepared by following a similar procedure and by using chloroacetylchloride (1.1 mmol) in place of benzoyl chloride.

*4.1.4. Synthesis of 5-(2H-chromen-3-yl)-1-vinyl-1H-tetrazole (**1e**).* To a stirred solution of dibromoethane (2 mmol) and **1b** (1 mmol) in 5 mL acetonitrile in a 25 mL round bottom flask was added solution of Et_3N (4 mmol) in acetonitrile (3 mL) dropwise. The reaction mixture was then refluxed and the progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled to room temperature and acetonitrile was removed under reduced pressure. The residue was dissolved in dichloromethane (30 mL) and washed with H_2O (25 mL). The organic solution was dried over $MgSO_4$ and the solvent was evaporated. The product was purified by column chromatography.

*4.1.5. Synthesis of 5-(2H-chromen-3-yl)-1H-pyrazole (**1f**).* A stirred solution of compound **1e** (1 mmol) in xylene (15 mL) was heated at 140 °C and the progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was evaporated under reduced pressure. The product was purified by column chromatography to yield yellow solid.

*4.1.6. Synthesis of 4-((5-(2H-chromen-3-yl)-1H-tetrazol-1-yl)methyl) morpholine (**1g**).* To an ice cold solution of **1a** (1 mmol) in methanol (2 mL) was added formalin (1.6 equiv) and stirred at room temperature for 15 min. Then morpholine (1 equiv) was added dropwise. The progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was evaporated under reduced pressure. The compound was purified by column chromatography to yield off white solid.

4.2. Spectral data

*4.2.1. 2-Methylbenzofuran-3-carbonitrile (**1a**).* White solid; mp: 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61–7.63 (m, 1H), 7.47–7.49 (m, 1H), 7.35–7.37 (m, 2H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 153.9, 126.2, 125.8, 124.6, 119.7, 113.6, 111.7, 91.6, 14.1; LRMS (EI) (*m*/*z*) (relative intensity) 157 (100) $[M]^+$; HRMS calcd for $C_{10}H_7NO$ $[M]^+$: 157.0528, found 157.0532.

*4.2.2. 2,5-Dimethylbenzofuran-3-carbonitrile (**2a**).* White solid; mp: 137–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39 (s, 1H), 7.35 (d, *J*=8.44 Hz, 1H), 7.15 (d, *J*=8.44 Hz, 1H), 2.64 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 152.4, 134.4, 126.9, 126.3, 119.5, 113.7, 111.2, 91.2, 21.5, 14.1; LRMS (EI) (*m*/*z*) (relative intensity) 171 (100) $[M]^+$, 156 (30), 115 (55); HRMS calcd for $C_{11}H_9NO$ $[M]^+$: 171.0684, found 171.0683.

*4.2.3. 6-Methoxy-2-methylbenzofuran-3-carbonitrile (**3a**).* Yellow solid; mp: 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (d, *J*=8.56 Hz, 1H), 6.99 (d, *J*=2.0 Hz, 1H), 6.95 (dd, *J*=2.16, 11.44 Hz, 1H), 3.85 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 159.0, 154.9, 119.7, 119.2, 113.7, 113.2, 96.5, 91.2, 55.9, 13.9; LRMS (EI) (*m*/*z*) (relative intensity) 187 (97) $[M]^+$, 172 (100); HRMS calcd for $C_{11}H_9NO_2$ $[M]^+$: 187.0633, found 187.0636.

*4.2.4. 7-Methoxy-2-methylbenzofuran-3-carbonitrile (**4a**).* Yellow solid; mp: 151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25–7.29 (m, 1H), 7.20 (d, *J*=8 Hz, 1H), 6.87 (d, *J*=7.92 Hz, 1H), 4.02 (s, 3H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 145.4, 143.2, 127.8, 125.5, 113.5, 111.8, 107.8, 92.0, 56.4, 14.1; LRMS (EI) (*m*/*z*) (relative intensity) 187 (100) $[M]^+$, 144 (15); HRMS calcd for $C_{11}H_9NO_2$ $[M]^+$: 187.0629, found 187.0633.

*4.2.5. 5,6-Dimethoxy-2-methylbenzofuran-3-carbonitrile (**5a**).* Off white solid; mp: 171–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.02 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 149.1, 148.6, 148.1, 118.2, 113.9, 100.9, 95.8, 91.4, 56.7, 56.6, 14.1; LRMS (EI) (*m*/*z*) (relative intensity) 217 (100) $[M]^+$, 202 (40); HRMS calcd for $C_{12}H_{11}NO_3$ $[M]^+$: 217.0739, found 217.0741.

*4.2.6. 5-Chloro-2-methylbenzofuran-3-carbonitrile (**6a**).* White solid; mp: 166–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (d, *J*=1.96 Hz, 1H), 7.41 (d, *J*=8.64 Hz, 1H), 7.28–7.34 (m, 1H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 152.3, 130.5, 127.5, 126.1, 119.4, 112.7, 91.4, 14.1; LRMS (EI) (*m*/*z*) (relative intensity) 191 (100) $[M]^+$, 165 (5); HRMS calcd for $C_{10}H_6ONCl$ $[M]^+$: 191.0138, found 191.0133.

*4.2.7. 5-Bromo-2-methylbenzofuran-3-carbonitrile (**7a**).* White solid; mp: 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.76 (d, *J*=1.96 Hz, 1H), 7.47 (dd, *J*=1.80, 8.72 Hz, 1H), 7.37 (d, *J*=8.76 Hz, 1H) 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 152.8, 128.9, 128.0, 122.6, 117.9, 113.2, 112.8, 91.4, 14.1; LRMS (EI) (*m*/*z*) (relative intensity) 235 (100) $[M]^+$, 156 (20); HRMS calcd for $C_{10}H_6NOBr$ $[M]^+$: 234.9633, found 234.9634.

*4.2.8. 5-Iodo-2-methylbenzofuran-3-carbonitrile (**8a**).* Yellow solid; mp: 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.98 (d, *J*=1.56 Hz, 1H), 7.67 (dd, *J*=1.64, 8.60 Hz, 1H), 7.29 (d, *J*=2.0 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 153.4, 134.6, 128.6, 113.6, 112.8, 111.9, 90.9, 88.1, 14.1; LRMS (EI) (*m*/*z*) (relative intensity) 283 (100) $[M]^+$, 156 (20); HRMS calcd for $C_{10}H_7INO$ $[M]^+$: 282.9494, found 282.9494.

*4.2.9. 2-Methylnaphtho[1,2-b]furan-3-carbonitrile (**9a**).* Off white solid; mp: 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.61 (d, *J*=8.28 Hz, 1H), 7.97 (s, *J*=8.20 Hz, 1H), 7.78 (d, *J*=9.0 Hz, 1H), 7.67 (t, *J*=7.72 Hz, 1H), 7.61 (d, *J*=9.04 Hz, 1H), 7.67 (t, *J*=7.32 Hz, 1H) 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 151.6, 131.1, 129.1, 127.5, 126.9, 126.8, 125.8, 122.7, 120.2, 115.0, 111.9, 91.5, 14.0; LRMS (EI) (*m*/*z*) (relative intensity) 207 (100) $[M]^+$ HRMS calcd for $C_{14}H_9NO$ $[M]^+$: 207.0684, found 207.0683.

*4.2.10. 2-Methylbenzo[b]thiophene-3-carbonitrile (**11a**).* White solid; mp: 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85 (d, *J*=7.92 Hz, 1H), 7.78 (d, *J*=8.0 Hz, 1H), 7.46–7.50 (m, 1H), 7.38–7.42 (m, 1H), 2.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 138.1, 137.7,

126.0, 125.7, 122.5, 122.1, 114.4, 105.7, 15.9; LRMS (EI) (*m*/*z*) (relative intensity) 173 (100) $[M]^+$, 172 (85); HRMS calcd for $C_{10}H_7NS$ $[M]^+$: 173.0299, found 173.0298.

*4.2.11. 5-(2H-Chromen-3-yl)-1H-tetrazole (**1b**).* White solid; mp: 208–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.44 (s, 1H), 7.22–7.28 (m, 2H), 6.96 (t, *J*=7.4 Hz, 1H), 6.87 (d, *J*=8.0 Hz, 1H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.7, 153.0, 131.0, 128.2, 126.1, 121.9, 120.9, 116.9, 115.7, 64.3; LRMS (EI) (*m*/*z*) (relative intensity) 201 (100) $[M+1]^+$, 172 (15); HRMS calcd for $C_{10}H_8N_4O$ $[M+1]^+$: 201.0776, found 201.0780.

*4.2.12. 5-(6-Methyl-2H-chromen-3-yl)-1H-tetrazole (**2b**).* Off white solid; mp: 235–237 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.39 (s, 1H), 7.03–7.06 (m, 2H), 6.77 (d, *J*=8.0 Hz, 1H), 5.14 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.0, 151.6, 131.4, 130.8, 128.4, 126.3, 120.8, 116.9, 115.5, 64.3, 20.0; LRMS (EI) (*m*/*z*) (relative intensity) 214 (55) $[M]^+$, 185 (100), 170 (38); HRMS calcd for $C_{11}H_{10}N_4O$ $[M]^+$: 214.0855, found 214.0848.

*4.2.13. 5-(7-Methoxy-2H-chromen-3-yl)-1H-tetrazole (**3b**).* Off white solid; mp: 235–237 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.40 (s, 1H), 7.20 (d, *J*=8.4 Hz, 1H), 6.56 (dd, *J*=2.4, 8.4 Hz, 1H), 6.49 (s, 1H), 5.16 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 155.2, 152.9, 129.2, 126.2, 114.1, 113.4, 108.1, 101.5, 64.4, 55.4; LRMS (EI) (*m*/*z*) (relative intensity) 230 (67) $[M]^+$, 201 (100), 186 (40); HRMS calcd for $C_{11}H_{10}N_4O_2$ $[M]^+$: 230.0804, found 230.0798.

*4.2.14. 5-(8-Methoxy-2H-chromen-3-yl)-1H-tetrazole (**4b**).* Light yellow solid; mp: 203–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.43 (s, 1H), 6.99 (d, *J*=6.9 Hz, 1H), 6.88–6.93 (m, 2H), 5.17 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.9, 147.6, 142.7, 126.3, 121.7, 121.6, 120.0, 116.9, 114.5, 64.2, 55.7; LRMS (EI) (*m*/*z*) (relative intensity) 230 (100) $[M]^+$; HRMS calcd for $C_{11}H_{10}N_4O_2$ $[M]^+$: 230.0804, found 230.0802.

*4.2.15. 5-(6-Chloro-2H-chromen-3-yl)-1H-tetrazole (**6b**).* Off white solid; mp: 237–239 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.34 (d, *J*=2.5 Hz, 1H), 7.24 (s, 1H), 7.17 (dd, *J*=8.5, 2.5 Hz, 1H), 6.86 (d, *J*=8.6 Hz, 1H), 5.22 (d, *J*=0.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.8, 152.1, 128.8, 126.6, 125.2, 123.9, 122.9, 119.9, 117.1, 65.5; LRMS (EI) (*m*/*z*) (relative intensity) 234 (100) $[M]^+$, HRMS calcd for $C_{10}H_7N_4OCl$ $[M]^+$: 234.0304, found 234.0308.

*4.2.16. 5-(6-Bromo-2H-chromen-3-yl)-1H-tetrazole (**7b**).* Off white solid; mp: 229–231 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.40 (d, *J*=2.4 Hz, 1H), 7.22 (dd, *J*=8.9, 2.5 Hz, 1H), 7.10 (br s, 2H), 6.76 (d, *J*=8.5 Hz, 1H), 5.21 (d, *J*=1.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.4, 152.3, 130.5, 128.8, 125.8, 125.3, 117.2, 116.2, 112.7, 66.0; LRMS (EI) (*m*/*z*) (relative intensity) 278 (46) $[M]^+$, 251 (100); HRMS calcd for $C_{10}H_7N_4OBr$ $[M+H]^+$: 278.9803, found 278.9804.

*4.2.17. 5-(2H-Benzo[h]chromen-3-yl)-1H-tetrazole (**9b**).* Yellow solid; mp: 230–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.12 (d, *J*=8.44 Hz, 1H), 7.94 (s, 1H), 7.85 (d, *J*=8.04 Hz, 1H), 7.78 (d, *J*=8.84 Hz, 1H), 7.52–7.57 (m, 1H), 7.39 (t, *J*=7.28 Hz, 1H), 7.16 (d, *J*=8.8 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.2, 151.6, 129.6, 129.3, 129.2, 128.9, 128.5, 127.0, 123.9, 121.8, 121.4, 117.3, 115.5, 65.6; LRMS (EI) (*m*/*z*) (relative intensity) 250 (50.5) $[M]^+$, 221 (100); HRMS calcd for $C_{14}H_{10}N_4O$ $[M]^+$: 250.0855, found 250.0852.

*4.2.18. 1-(3-(1H-Tetrazol-5-yl)-2H-chromen-6-yl)ethanone (**10b**).* Yellow solid; mp: 228–230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.82–7.87 (m, 2H), 7.46 (s, 1H), 6.96 (d, *J*=8.3 Hz, 1H), 5.31 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.5, 157.6, 153.8, 131.5, 131.2, 128.6, 124.4, 120.8, 118.7, 115.9, 65.3, 26.5; LRMS (EI) (*m*/*z*) (relative intensity) 242 (12) $[M]^+$, 241 (100), 185.2 (16); HRMS calcd for $C_{12}H_{10}N_4O_2$ $[M]^+$: 242.0804, Found 242.0760.

*4.2.19. 5-(2H-Thiochromen-3-yl)-1H-tetrazole (**11b**).* Yellow solid; mp: 191–193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.52 (s, 1H), 7.31–7.37 (m, 2H), 7.20–7.27 (m, 2H), 4.02 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 131.7, 131.4, 129.6, 129.3, 129.2, 126.8, 126.0, 118.7, 24.8; LRMS (EI) (*m*/*z*) (relative intensity) 216 (55) $[M]^+$, 188 (68), 172 (100); HRMS calcd for $C_{10}H_8N_4S$ $[M]^+$: 216.0470, found 216.0472.

*4.2.20. 3-(1H-Tetrazol-5-yl)quinolin-2-amine (**12b**).* Green solid; mp: 239–241 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.65 (s, 1H), 7.74 (d, *J*=8.0 Hz, 1H), 7.65 (t, *J*=7.4 Hz, 1H), 7.51 (d, *J*=8.5 Hz, 1H), 7.26 (t, *J*=7.6 Hz, 1H), 6.92 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 149.2, 145.5, 133.0, 128.7, 125.6, 123.0, 121.1, 116.6, 94.7; LRMS (EI) (*m*/*z*) (relative intensity) 212 (100) $[M]^+$, 184. HRMS Calcd for $C_{10}H_8N_6$ $[M]^+$: 212.0810, found 212.0804.

*4.2.21. 5-(6,8-Dimethoxy-2H-chromen-3-yl)-1H-tetrazole (**13b**).* Light brown solid; mp: 206–208 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.43 (s, 1H), 7.03 (d, *J*=8.5 Hz, 1H), 6.69 (d, *J*=8.6 Hz, 1H), 5.18 (d, *J*=1.1 Hz, 2H), 3.81 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.8, 152.9, 147.1, 136.6, 126.5, 123.2, 115.6, 114.2, 105.7, 64.3, 60.3, 55.9; LRMS (EI) (*m*/*z*) (relative intensity) 260 (77) $[M]^+$, 232 (100); HRMS calcd for $C_{12}H_{12}N_4O_3$ $[M]^+$: 260.0909, found 260.0911.

*4.2.22. 5-(6-Bromo-8-methoxy-2H-chromen-3-yl)-1H-tetrazole (**14b**).* Yellow solid; mp: 196–198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.33 (s, 1H), 7.12 (s, 2H), 5.19 (d, *J*=1.1 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.3, 148.5, 141.8, 123.7, 122.7, 121.7, 120.3, 116.3, 112.6, 64.8, 56.1; LRMS (EI) (*m*/*z*) (relative intensity) 308 (62) $[M]^+$, 281 (100); HRMS calcd for $C_{11}H_9N_4O_2Br$ $[M]^+$: 307.9909, found 307.9902.

*4.2.23. 2-(2H-Chromen-3-yl)-5-phenyl-1,3,4-oxadiazole (**1c**).* White solid; mp: 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (d, *J*=7.9 Hz, 2H), 7.51–7.58 (m, 3H), 7.38 (s, 1H), 7.18–7.27 (m, 2H), 6.97 (t, *J*=7.5 Hz, 1H), 6.91 (d, *J*=8.0 Hz, 1H), 5.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 162.0, 154.9, 132.1, 131.7, 129.3, 128.5, 127.9, 127.3, 123.9, 122.2, 121.3, 116.5, 116.2, 64.3; LRMS (EI) (*m*/*z*) (relative intensity) 276 (100) $[M]^+$; HRMS calcd for $C_{17}H_{12}N_2O_2$ $[M]^+$: 276.0899, found 276.0899.

*4.2.24. 2-(Chloromethyl)-5-(2H-chromen-3-yl)-1,3,4-oxadiazole (**1d**).* White solid; mp: 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33 (s, 1H), 7.24 (t, *J*=8.0 Hz, 1H), 7.16 (d, *J*=7.4 Hz, 1H), 6.95 (t, *J*=7.4 Hz, 1H), 6.88 (d, *J*=8.1 Hz, 1H), 5.20 (s, 2H), 4.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 161.9, 154.9, 132.0, 129.3, 128.7, 122.3, 120.9, 116.5, 115.4, 63.9, 33.1; LRMS (EI) (*m*/*z*) (relative intensity) 248 (100) $[M]^+$; HRMS calcd for $C_{12}H_9N_2O_2Cl$ $[M]^+$: 248.0353, found 248.0359.

*4.2.25. 5-(2H-Chromen-3-yl)-1-vinyl-1H-tetrazole (**1e**).* Yellow solid; mp: 159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 (s, 1H), 7.53 (dd, *J*=15.6, 8.7 Hz, 1H), 7.17–7.24 (m, 2H), 6.95 (m, 1H), 6.89 (d, *J*=8.0 Hz, 1H), 6.22 (dd, *J*=15.6, 1.4 Hz, 1H), 5.39 (dd, *J*=8.7, 1.4 Hz, 1H), 5.29 (d, *J*=1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 154.4, 130.6, 129.6, 127.9, 126.1, 121.8, 121.5, 118.9, 115.9, 108.4, 64.9; LRMS (EI) (*m*/*z*) (relative intensity) 226 (100) $[M]^+$, 200 (60); HRMS calcd for $C_{12}H_{10}N_4O$ $[M]^+$: 226.0855, found 226.0850.

*4.2.26. 5-(2H-Chromen-3-yl)-1H-pyrazole (**1f**).* Yellow solid; mp: 144–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.90 (br s, 1H),

7.78 (s, 1H), 7.08–7.14 (m, 2H), 6.98 (s, 1H), 6.90 (t, J=7.2 Hz, 1H), 6.81 (d, J=7.8 Hz, 1H), 6.66 (s, 1H), 5.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 147.5, 129.8, 128.6, 126.7, 122.8, 121.5, 117.9, 115.2, 102.9, 101.5, 65.3; LRMS (EI) (m/z) (relative intensity) 198 (100) $[M]^+$, 197 (62), 169 (20); HRMS calcd for $C_{12}H_{10}N_2O$ $[M]^+$: 198.0793, found 198.0795.

*4.2.27. 4-((5-(2H-Chromen-3-yl)-1H-tetrazol-1-yl)methyl)morpholine (**1g**).* White solid; mp: 132–134 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.51 (s, 1H), 7.34 (d, 1H) 7.15–7.22 (m, 1H), 6.94 (t, J=7.4 Hz, 1H), 6.88 (d, J=8.1 Hz, 1H), 5.60 (s, 2H), 5.22 (d, J=0.96 Hz, 2H), 3.58 (t, J=4.8 Hz, 4H), 2.57 (t, J=4.7 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.6, 130.6, 128.1, 124.6, 124.5, 121.8, 121.3, 119.1, 115.6, 73.8, 65.9, 64.4, 49.2; LRMS (EI) (m/z) (relative intensity) 299 (100) $[M]^+$; HRMS calcd for $C_{15}H_{17}N_5O_2$ $[M]^+$: 299.1382, found 299.1380.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.12.062.

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