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A facile synthesis of 1,2,3-triazolyl indole hybrids via $SbCl_3$-catalysed Michael addition of indoles to 1,2,3-triazolyl chalcones

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Abstract. An efficient, facile and environmentally benign synthesis of a library of 1,2,3-triazolyl chalcone hybrids (3a–u) has been accomplished by grinding the reactants at room temperature in excellent yields in very short reaction time. Subsequently, $SbCl_3$ catalysed Michael addition of indoles to the chalcones afford 1,2,3-triazolyl indole hybrids (5a–l) in excellent yields.

Keywords. Environmentally benign; 1,2,3-triazolyl chalcone; Michael addition; $SbCl_3$ catalysed; 1,2,3-triazolyl indole.

1. Introduction

Chalcones represent an important group of natural products belonging to the flavonoids family.[1,2] Compounds with the backbone of chalcones possess interesting biological activities such as cytotoxic,[3] antimalarial,[4] antileishmanial,[5] antiinflammatory,[6] antiHIV,[7] antifungal[8] and tyrosine kinase inhibitors.[9]

On the other hand, 1,2,3-triazoles have received much attention due to their interesting pharmacological activity profile such as antibiotic, antifungal, antehelmintic,[10] anticancer activity,[11] and antiHIV.[12] They also serve as potential chemotherapeutic agents for various diseases.[13]

Indole derivatives continue to receive much attention in organic synthesis because of their biological activities.[14,15] Among them, 3-substituted indoles are important building blocks for the synthesis of biologically active compounds and natural products.[16]

Keeping in view of the potential importance of the above said individual bioactive compounds, it was envisaged that synthesis of molecules containing two of the above said moieties in a single framework is worth the attempt. In this regard, we report here for the first time the synthesis of the hybrid molecules containing the triazole–enone and triazole–indole skeletons.

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2. Experimental

All chemicals, reagents and solvents were of commercially high purity grade purchased from Avra Synthesis Pvt. Ltd. and Merck Pvt. Ltd. India. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Avance 300 MHz spectrometer and the chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane, with coupling constant (J) values in Hertz (Hz). In ^{1}H NMR, the abbreviation of splitting refers as s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublet and bs=broad singlet. ^{13}C NMR data are reported with the solvent peak ($CDCl_3$ = 77.00 MHz) as the internal standard. Elemental analyses of all the compounds were performed which were in agreement with the calculated values within ± 0.4%.

2.1 *Synthesis of 4-acetyl-1-benzyl-5-methyl-1,2,3-triazole* ***(1)***[17]

A mixture of benzyl azide (3.00 g, 1.0 equiv), acetyl acetone (2.25 g, 1.0 equiv), potassium carbonate (6.23 g, 2.0 equiv) and absolute ethanol (95%, 15 ml) was taken in a round bottomed flask equipped with stirrer. The reaction mixture was stirred at 75°C for 30 min. The progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was removed under vacuum and to the residual mass, excess of ice-water was added and neutralized with 10% HCl (20 ml). The product was extracted

with diethyl ether (20 ml) and the extract was dried over anhydrous sodium sulphate. Evaporation of the solvent gave the crude product, which was purified by column chromatography using petroleum ether: ethylacetate (98:3) as eluent and recrystallized from absolute ethanol. Yield: 3.97g (82%), Mp. 148°C.

2.2 *General procedure for the synthesis of 1,2,3-triazolyl chalcone hybrids (**3**)*

A mixture of 4-acetyl-1-benzyl-5-methyl-1,2,3-triazole, **1** (0.2 g, 1.0 equiv) and aromatic/heteroaromatic aldehydes, **2** (1.0 equiv) and 50% aqueous sodium hydroxide solution (1 ml) was ground for 4–7 min at room temperature and poured onto excess of crushed ice and neutralized with dilute hydrochloric acid. The chalcone derivatives (**3**) which precipitated as solids were filtered and recrystallized from ethanol. Yield: 97–99%.

2.2a *(E)-1-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-3-phenylprop-2-en-1-one (**3a**)*: Yield 0.27 g (97%), white solid, mp.157–158°C. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 2.55 s (3H, CH_3); 5.57 s (2H, N-CH_2), 7.20–7.72 m (10H, ArH), 7.87 d (1H, =CH, J = 15.9 Hz), 8.05 d (1H, =CH, J = 15.9 Hz). ^{13}C NMR spectrum ($CDCl_3$, 75 MHz), δ, ppm: 9.31, 51.75, 123.16, 127.25, 128.60, 128.71, 128.85, 129.14, 130.41, 134.07, 135.09, 137.95, 143.53, 144.36, 184.40. Found, %: C 75.27, H 5.65, N 13.84. $C_{19}H_{17}N_3O$. Calculated, %: C 75.23, H 5.65, N 13.85.

2.3 *General procedure for the synthesis of 1,2,3-triazolyl indole hybrids (**5**)*

To a solution of 1-benzyl-5-methyl-1,2,3-triazol-4-yl-3-arylprop-2-en-1-one, **3** (0.2 g, 1.0 equiv) and indole/2-methylindole, **4** (1.0 equiv) in CH_3CN (3–5ml) was added $SbCl_3$ (10 mol%) and the mixture was refluxed for 3–4 h. After completion of reaction as indicated by TLC, the catalyst was filtered and the filtrate was concentrated under reduced pressure to give the crude product, which was triturated with petroleum ether. The triazolyl indole hybrids (**5**) which precipitated as solids were filtered recrystallized from ethanol. Yield: 95–98%.

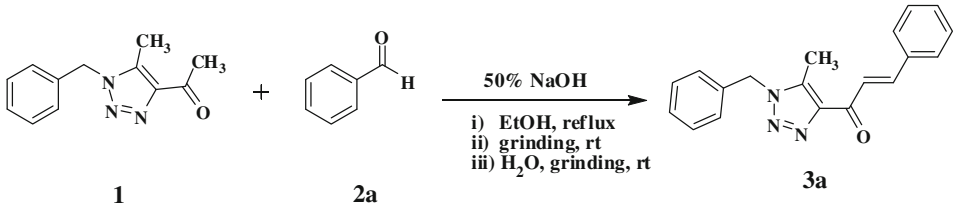
2.3a *1-(1-Benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-3-(1H-indol-3-yl)-3-phenylpropan-1-one (**5a**)*: Yield: 0.37 g (96%), colourless solid, mp.138–139°C. ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), δ, ppm, 2.32 s (3H, CH_3), 3.88 dd (1H, CH_2, J = 7.8 and 16.2 Hz), 4.01 dd (1H, CH_2, J = 7.5 and 16.2 Hz), 5.09 t (1H, CH, J = 7.8 Hz), 5.53 s (2H, N-CH_2), 6.97–7.50 m (14H, ArH), 8.02 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$, 75 MHz), δ, ppm, 9.08, 38.23, 46.29, 51.66, 110.94, 119.34, 119.49, 119.61, 121.55, 122.03, 126.11, 126.94, 127.26, 128.29, 128.58, 129.12, 134.00, 136.61, 137.09, 143.93, 144.51, 194.85. Found, %: C 77.09, H 5.76, N 13.31. $C_{27}H_{24}N_4O$. Calculated, %: C 77.12, H 5.75, N 13.32.

The analytical data of all the synthesized compounds are presented in the supplementary information.

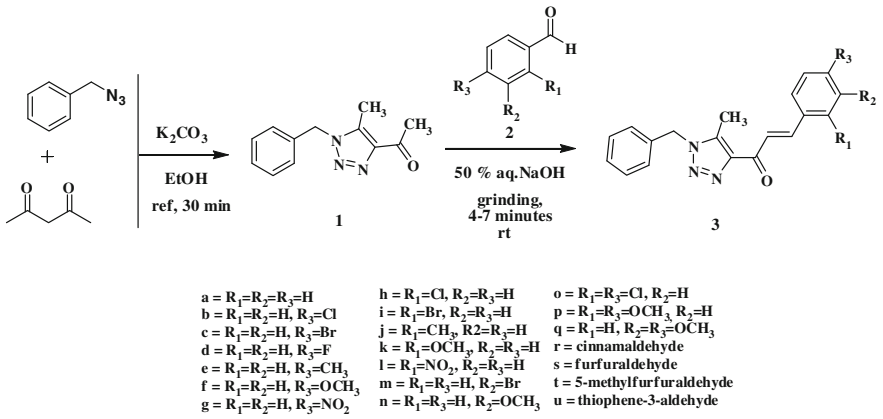
3. Results and discussion

Traditionally, chalcones could be obtained via Claisen–Schmidt condensation carried out in acidic or basic media under homogeneous conditions, with many drawbacks, such as catalyst recovery and waste disposal problems.[18] As a potential alternative, heterogeneous catalysts have also been used for Claisen–Schmidt condensation, including Lewis acids,[19] Bronsted acids,[20] solid acids,[21] and solid bases.[22] In addition, ionic liquids[23] and microwave[24] have also been tried to enhance the yields of the chalcones. But all these reported methods make use of organic solvents during condensation and during isolation of products by way of extraction. These organic solvents have been considered to be hazardous to human health and the environment due to their volatile nature. Hence, development of organic reactions under solvent-free conditions being eco-friendly has attained much importance. In particular, organic reactions in water medium are of current interest.

To the best of our knowledge, though there are very few reports on triazolyl chalcone synthesis in organic



Scheme 1. Reaction optimization for the synthesis of 1,2,3-triazolyl chalcone hybrid (**3a**).



Scheme 2. Synthesis of 1,2,3-triazolyl chalcone hybrids **(3a–u)**.

solvents,[25] perusal of literature suggests the lack of any report on the synthesis of 1,2,3-triazolyl chalcone hybrids in water which forms the first part of the present study. Here, it is notable that the yield of the hybrids in the organic solvent *viz*. ethanol and in water medium is comparable.

At the outset, a mixture of 1,2,3-triazolylketone (**1a**, 1.0 equiv), benzaldehyde (**2a**, 1.1 equiv) and 50% NaOH in ethanol (5 ml) was stirred at room temperature (scheme 1). The reaction was completed in 5 min affording the 1,2,3-triazolyl chalcone hybrid (**3a**) in 97% yield. On the other hand, grinding the heterogenous reaction mixture in minimum amount of water at room temperature gave identical yield of **3a** in comparable reaction time, i.e., 4 min. The later protocol avoiding the organic solvent viz. ethanol is greener.

The broad scope of the above said protocol involving water as media was established via the synthesis of a library of 1,2,3-triazolyl chalcone hybrids (**3a–u**, scheme 2) in excellent yields (97–99%, table 1).

Table 1. Synthesis of 1,2,3-triazolyl chalcone hybrids **(3a–u)**.

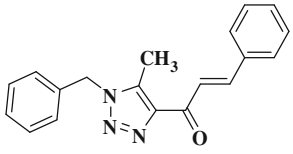
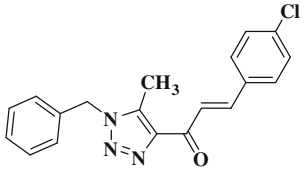
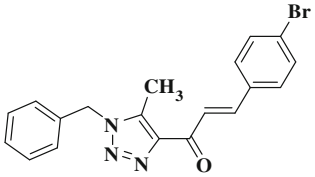
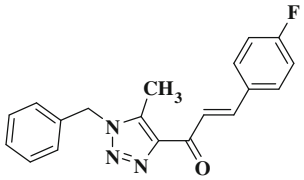
Entry	Aldehydes (**2a–u**)	1,2,3-triazolyl chalcones (**3a–u**)	Solvent (ethanol) Time (min)	Solvent (ethanol) Yield (%)	Water (grinding) Time (min)	Water (grinding) Yield (%)
1	**2a**	 **3a**	3	97	4	97
2	**2b**	 **3b**	2	97	4	98
3	**2c**	 **3c**	2	98	4	98
4	**2d**	 **3d**	2	99	4	98

Table 1. (continued)

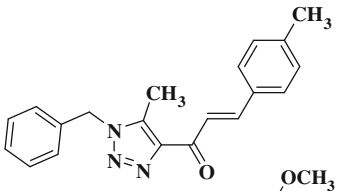
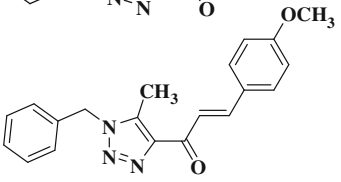
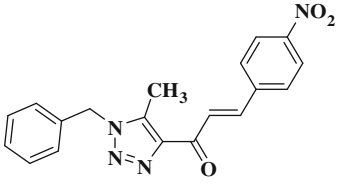
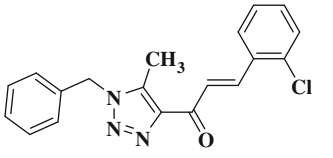
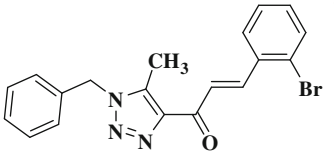
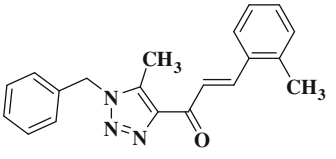
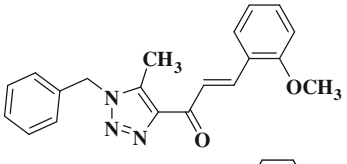
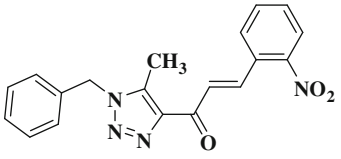
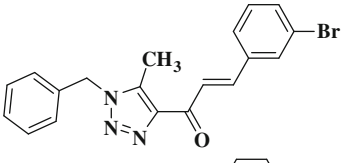
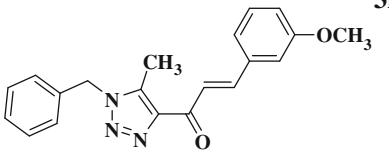
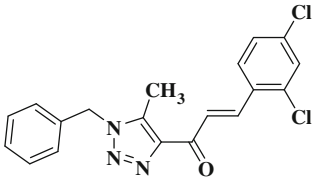
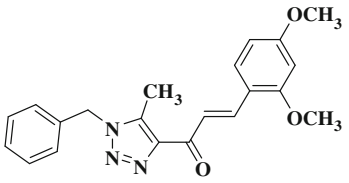
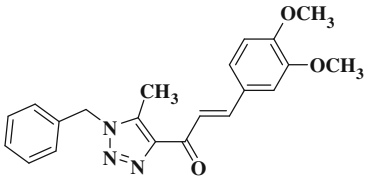
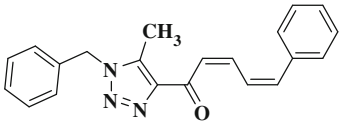
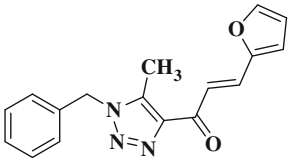
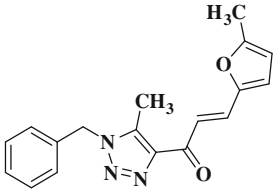
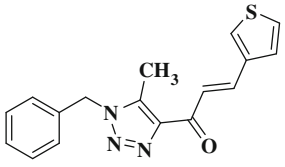
Entry	Aldehydes (**2a–u**)	1,2,3-triazolyl chalcones (**3a–u**)	Solvent (ethanol) Time (min)	Solvent (ethanol) Yield (%)	Water (grinding) Time (min)	Water (grinding) Yield (%)
5	**2e**	 **3e**	3	98	5	99
6	**2f**	 **3f**	3	96	4	97
7	**2g**	 **3g**	4	98	6	97
8	**2h**	 **3h**	4	98	7	98
9	**2i**	 **3i**	4	97	7	98
10	**2j**	 **3j**	4	97	7	97
11	**2k**	 **3k**	3	98	7	97
12	**2l**	 **3l**	4	98	7	97
13	**2m**	 **3m**	3	98	6	98
14	**2n**	 **3n**	3	97	6	97

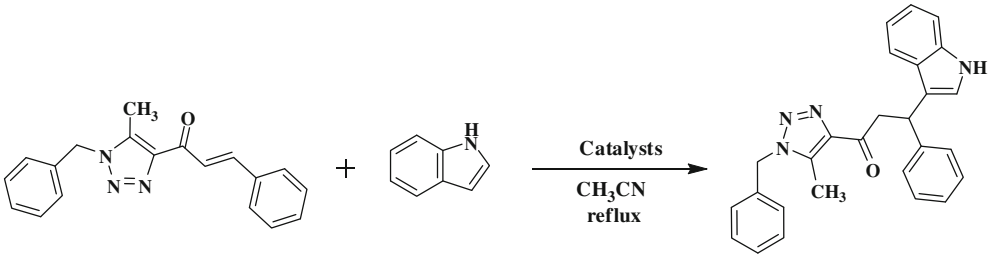
Table 1. (continued)

Entry	Aldehydes (**2a–u**)	1,2,3-triazolyl chalcones (**3a–u**)	Solvent (ethanol) Time (min)	Solvent (ethanol) Yield (%)	Water (grinding) Time (min)	Water (grinding) Yield (%)
15	**2o**	 **3o**	4	98	7	98
16	**2p**	 **3p**	4	97	7	97
17	**2q**	 **3q**	4	96	7	97
18	**2r**	 **3r**	4	97	7	97
19	**2s**	 **3s**	2	98	5	98
20	**2t**	 **3t**	2	97	5	97
21	**2u**	 **3u**	2	97	5	97

The X-ray crystal structure of compounds, **3a**[26] and **3d**[27] proved their structures unequivocally.

3.1 *Micheal addition of indoles to 1,2,3-triazolyl chalcone hybrids*

Three substituted indoles exhibit numerous biological activities[28] and are also used as building blocks for the synthesis of natural products and therapeutic agents.[29] Among the various approaches for preparing three-substituted indoles,[30,31] Michael addition[32,33] of indoles to electron-deficient olefins or α,β-unsaturated ketones being direct method is very elegant. This conjugate addition is facilitated in the presence of various catalysts,[34] protic[30] and/or Lewis acid.[31] As the strong acid catalysed Michael addition is associated with the side reactions resulting in dimerization and polymerization, utility of efficient catalysts in the conjugate addition has attained importance.

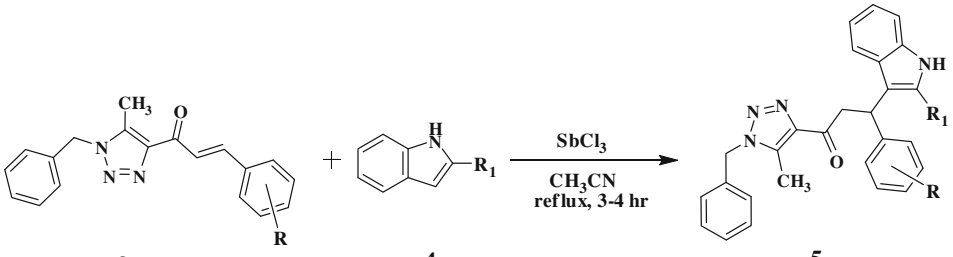


3a **4** **5a**

Scheme 3. Catalyst screening in the synthesis of 1,2,3-triazolyl indole hybrid **(5a)**.

Table 2. Catalyst screening in the synthesis of 1,2,3-triazolyl indole hybrid **(5a)**.

	Reaction condition		
Entry	Catalyst	Reaction time (h)	Yield (%)
1	$FeCl_3$	10	70
2	$AlCl_3$	12	60
3	$SbCl_3$	3	96
4	$SnCl_3$	>12	–
5	PTSA	>12	–



3 **4** **5**

R
a = H; b = 4-CH_3; c = 4-NO_2; d = 4-Br; e = 2,4-di-Cl; f = furan-2

R^1 = H, CH_3

Scheme 4. Synthesis of 1,2,3-triazolyl indole hybrids **(5a–l)**.

Here, we report for the first tme the synthesis of hybrid compounds containing 1,2,3-triazole and indole skeleton via. $SbCl_3$ catalysed conjugate addition of indoles to 1,2,3-triazolyl chalcones, the details of which are presented *vide infra*.

In the preliminary study, for the purpose of screening of the catalyst, $FeCl_3$ (10 mol%) was used as catalyst in the Michael addition of indole (**4**, 1.0 equiv) to the chalcone (**3a**, 1.0 equiv) which gave the product (**5a**) in 60% yield in 10 h (scheme 3). The reaction was then performed by varying the catalysts (table 2, entry 1–5). This screening study indicated that $SbCl_3$ (table 2, entry 3) is the best catalyst affording 96% of **5a** in short reaction time (3 h).

Further, to establish the broad scope of the catalyst, synthesis of a series of 1,2,3-triazole-indole hybrids (**5**) has been accomplished via the Michael addition of indole/2-methylindole (**4**) with 1,2,3-triazolyl chalcones (**3**) in the presence of $SbCl_3$(10 mol%) in CH_3CN (scheme 4). Generally, after completion of the reaction as indicated by TLC, the catalyst was filtered and the filtrate concentrated under reduced pressure to give the crude product, which on triturating with petroleum ether afford the 1,2,3-triazolyl indole hybrids (**5a–l**) as solids in excellent yields (95–98%, table 3). The products were recrystallized from ethanol.

The synthesized compounds were characterized by NMR (1D and 2D), IR and mass spectral techniques.

Table 3. Synthesis of 1,2,3-triazolyl indole hybrids (**5a–l**).

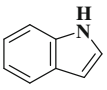
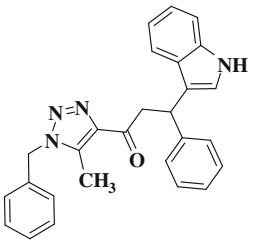
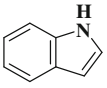
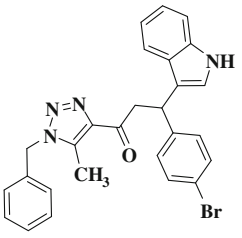
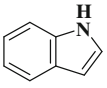
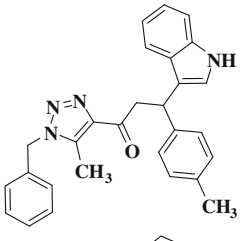
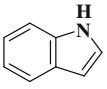
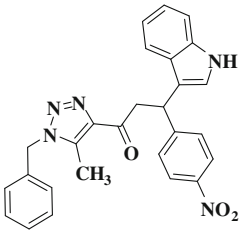
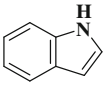
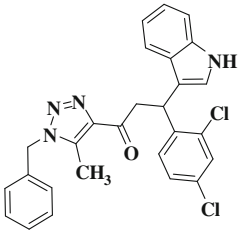
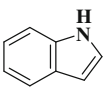
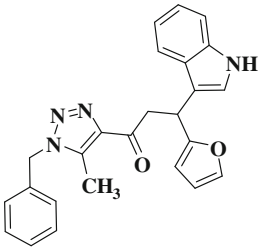
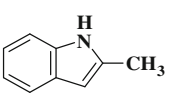
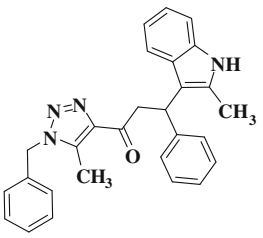
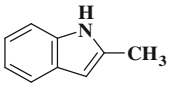
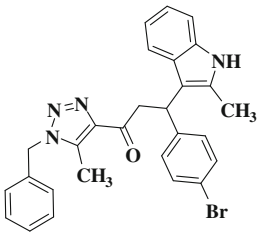
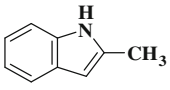
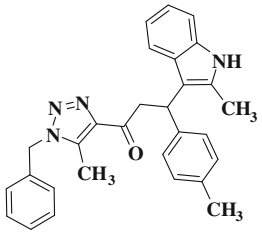
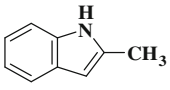
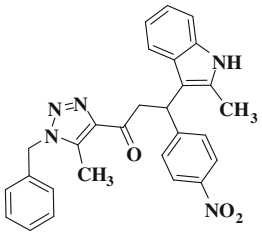
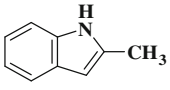
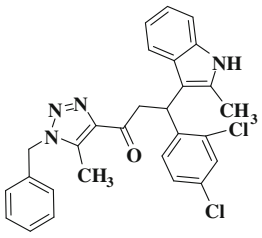
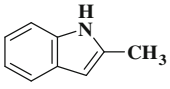
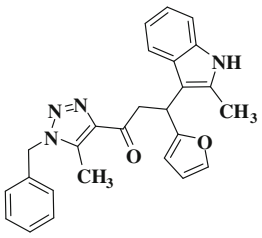
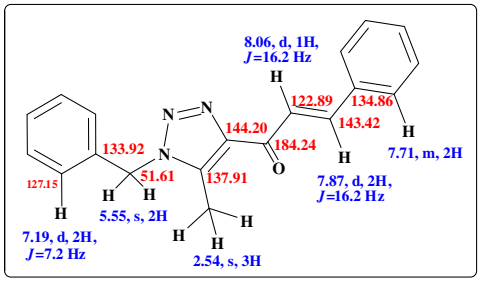
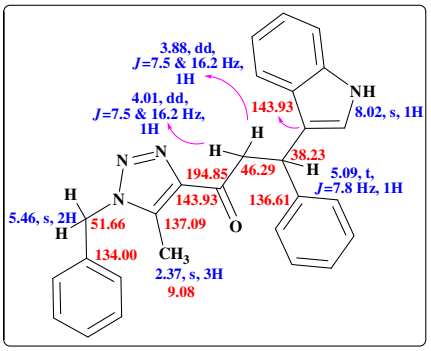
Entry	Chalcone (**3**)	Indole (**4**)	1,2,3-triazolyl indole hybrid (**5a–l**)	Time (h)	Yield (%)
1	**3a**		 **5a**	3	96
4	**3c**		 **5b**	3.5	95
2	**3e**		 **5c**	3	98
3	**3g**		 **5d**	3.5	95
5	**3o**		 **5e**	4	95
6	**3s**		 **5f**	4	97
7	**3a**		 **5g**	3.5	97

Table 3. (continued)

Entry	Chalcone (**3**)	Indole (**4**)	1,2,3-triazolyl indole hybrid (**5a–l**)	Time (h)	Yield (%)
10	**3c**		 **5h**	3.5	96
8	**3e**		 **5i**	3	98
9	**3g**		 **5j**	3.5	95
11	**3o**		 **5k**	4	95
12	**3s**		 **5l**	4	95



(3a)



(5a)

Figure 1. Selected ^{1}H and ^{13}C NMR chemical shift values.

Selected ^{1}H and ^{13}C NMR chemical shift values of representative compounds **3a** and **5a** are presented *vide infra* (figure 1).

4. Conclusion

In conclusion, we have reported for the first time a facile, rapid, mild and environmentally benign, green protocol for the synthesis of a library of 1,2,3-triazolyl chalcone hybrids by just grinding the reactants and $SbCl_3$ catalysed synthesis of a series of 1,2,3-triazolyl indole hybrids via Michael addition in excellent yields.

Supplementary information

The supplementary information can be seen in www.ias.ac.in/chemsci.

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