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Practical synthesis, anticonvulsant, and antimicrobial activity of *N*-allyl and *N*-propargyl di(indolyl)indolin-2-ones

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ABSTRACT

An operation friendly protocol for the synthesis of novel di(indolyl)indolin-2-ones via $Cu(OTf)_2$ catalyzed bis-addition of *N*-allyl and *N*-propargyl indole with isatin was developed. This methodology allowed us to achieve the products in excellent yields without requiring purification technique like column chromatography. All the synthesized compounds were evaluated for their in vivo anticonvulsant activity against maximal electroshock test. Six compounds showed maximum activity compared to the standard drug phenytoin. The scope of the new molecules as antimicrobial agents were tested against two bacterial strains (*Staphylococcus* aureus and *Escherichia coli*) and one fungal strain (*Candida albicans*).

Epilepsy is a chronic disease that is characterized by paroxysmal attacks caused by pathologic excitation of cerebral neurons. The mechanism of action of antiepileptic drugs (AEDs) consist in the blockade of voltage-dependent Na^+ channels or T-type Ca^{2+} channels, inhibition of glutamatergic transmission and facilitation of γ-aminobutyric acid (GABA) inhibitory neurotransmission.[1] On the other hand, di(indolyl)indolin-2-ones are of considerable importance due to their wide spectrum of biological activities like antiproliferative, antibacterial, antiprotozoal and anti-inflammatory.[2] They have also been used as laxatives[3] and lead molecules for inhibition of translation initiation.[4] Typical catalytic approach to construct this class of molecules involve 3-indolylation of isatins by $FeCl_3$,[5a] ionic liquids,[5b] TfOH,[5c] CAN,[5d] $Bi(OTf)_3$,[5e] silica–sulfuric acid,[5f] I_2,[5g] and $KAl(SO_4)_2$.[5h,i] As part of our current interest in the synthesis of novel heterocyclic compounds,[6] we attempted to avoid expensive precursors and produce a scalable reaction for the production of multi-gram quantities of the target di(indolyl)indolin-2-ones with a reactive moiety at the indolyl N-position (preferably allyl and propargyl). The method investigated involves N-allylation or propargylation of indoles, followed by bis-addition with isatin to form the desired *N*-allyl and *N*-propargyl di(indolyl)indolin-2-ones. The specific use of *N*-allyl or *N*-propargyl indoles as precursors was based on the following considerations: (i) In order to study the effect of spacer between the heterocyclic nitrogen and the allyl/propargyl chain of various substituents. (ii) This structural modification, suitable for further substitutions, in view of controlled pharmacodynamic and pharmacokinetic testing, will be useful for more detailed SAR information about this class of molecules. Furthermore, N–CO linkage is well recognized as pharmacophoric requirements in some of the commercial anticonvulsant drugs with varied mechanism of action, a significant anticonvulsant activity was also hypothesized (Fig. 1).

This letter reports the $Cu(OTf)_2$ catalyzed efficient synthesis of new di(indolyl)indolin-2-ones, characterized by the oxindole nucleus bearing *N*-allyl(propargyl)indole rings in the third position. The potential of these compounds was tested to evaluate the in vivo anticonvulsant activity.

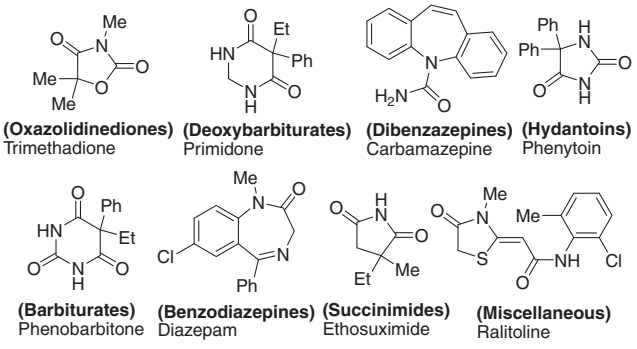

Figure 1. Chemical class and examples of anticonvulsant drugs representing –N–CO– moiety.

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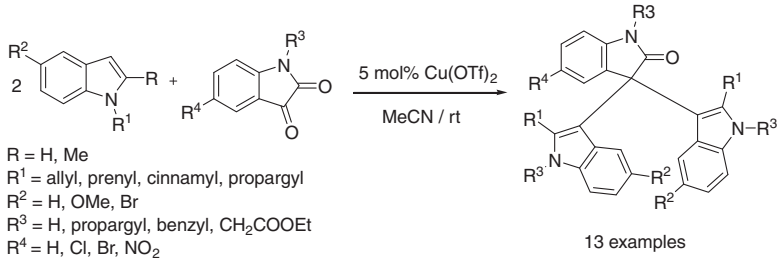
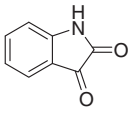
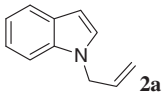
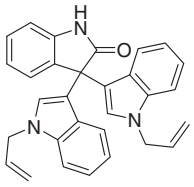
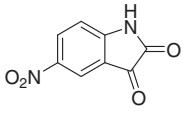
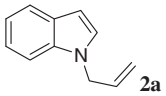
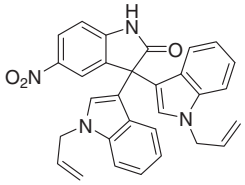
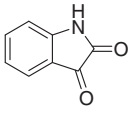
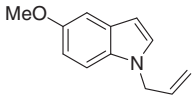
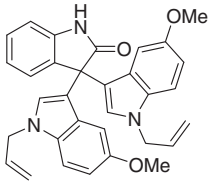
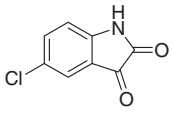
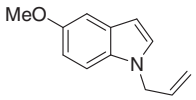
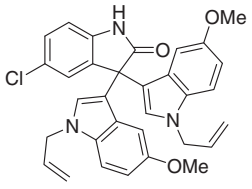
The requisite *N*-allyindoles[7] and *N*-propargylindoles[8] were prepared by standard procedures. Because of the economic attractiveness and stimulated by the growing interest in the development of copper(II) based methods[9] (and hence of their potential in large scale reactions), we became interested in $Cu(OTf)_2$ catalyzed synthesis of di(indolyl)indolin-2-ones.[10] To begin our study, indole **1a** and isatin **2a** was allowed to react using 5 mol % of $Cu(OTf)_2$ in acetonitrile. The reaction went into completion within 30 min to afford the di(indolyl)indolin-2-one **3a** in 90% yield. In order to fully examine the scope of this chemistry, various substituted isatins and indoles were introduced and tested as substrates (Scheme 1, Table 1).[11]

The corresponding di(indolyl)indolin-2-ones (**3a**–**3m**) were formed in excellent yields, when isatins bearing electron withdrawing group (entries 2 and 4–6) and indoles bearing electron releasing group (entries 3–6) are used. It is worthy to mention that we did not observe any isomerization product, when (*E*)-1-cinnamyl indole **2c** was reacted with isatin **1a**, the corresponding di(indolyl)indolin-2-one (**3g**) was provided in 85% yield with complete transfer of stereochemistry (as evidenced by the coupling constant value, $J = 16.0$ Hz). We next examined the possibility of preparing *N*-propargyl di(indolyl)indolin-2-ones by this same methodology. Delightfully, the desired products were obtained in good yields (entries 10–13). Note that these substrates possessing alkynes did not undergo isomerization to the corresponding allenyl product.[12] The structures of compounds **3a**–**m** were confirmed by IR, ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. All the compounds exhibited an IR peak between 1700 and 1725 cm^{-1} which corresponds to the stretching frequency of amide carbonyl of the oxindole ring. All the compounds showed a ^{13}C peak at $\delta_C = 52.5$–53.2 ppm and 175.0–179.1 ppm ascertained the presence of quaternary and amide carbons, respectively. These findings, confirmed the formation of di(indolyl)indolin-2-one products **3a**–**m**.



Scheme 1. $Cu(OTf)_2$ catalyzed synthesis of di(indolyl)indolin-2-ones.

Table 1
Copper(II) triflate catalyzed synthesis of *N*-allyl and *N*-propargyl (indolyl)indolin-2-ones[a]

Entry	Isatin	Indole	Di(indolyl)indolin-2-ones[b]	Time (min)	Yield[c] (%)
1	 **1a**	 **2a**	 **3a**	30	90
2	 **1b**	 **2a**	 **3b**	15	95
3	 **1a**	 **2b**	 **3c**	15	95
4	 **1c**	 **2b**	 **3d**	15	93

(*continued on next page*)

Table 1 (*continued*)

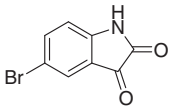
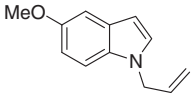
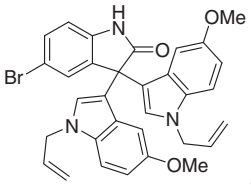
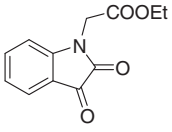
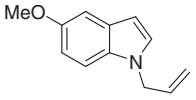
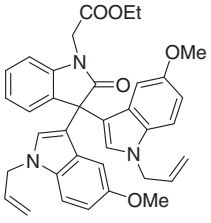
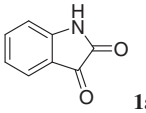
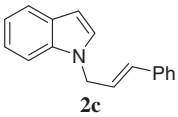
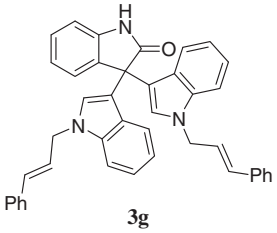
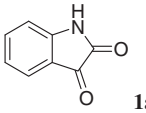
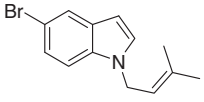
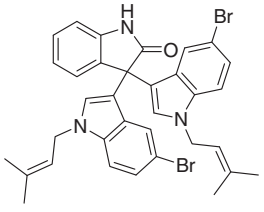
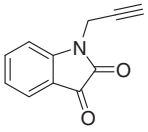
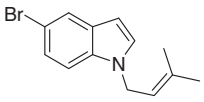
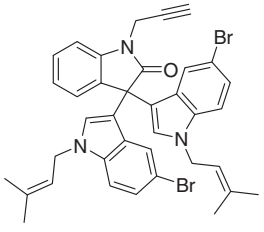
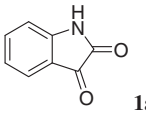
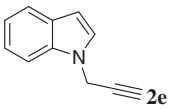
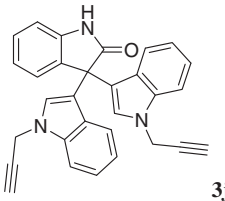
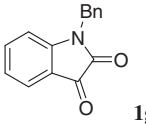
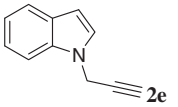
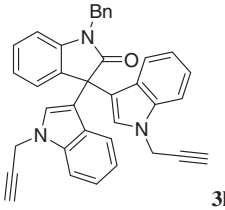
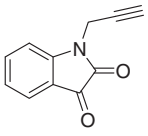
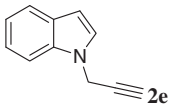
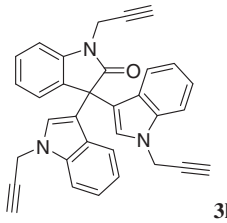
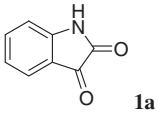
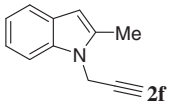
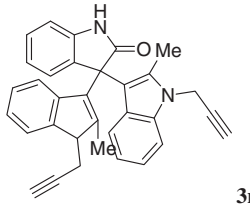
Entry	Isatin	Indole	Di(indolyl)indolin-2-ones[b]	Time (min)	Yield[c] (%)
5	 **1d**	 **2b**	 **3e**	15	92
6	 **1e**	 **2b**	 **3f**	15	94
7	 **1a**	 **2c**	 **3g**	40	85
8	 **1a**	 **2d**	 **3h**	45	88
9	 **1f**	 **2d**	 **3i**	45	86
10	 **1a**	 **2e**	 **3j**	25	89
11	 **1g**	 **2e**	 **3k**	40	88

Table 1 (*continued*)

Entry	Isatin	Indole	Di(indolyl)indolin-2-ones[b]	Time (min)	Yield[c] (%)
12	 **1h**	 **2e**	 **3l**	45	87
13	 **1a**	 **2f**	 **3m**	20	90

[a] All reactions were performed at 30 °C in acetonitrile using 5 mol % $Cu(OTf)_2$.
[b] Isolated yield without column chromatography.
[c] All products were characterized by IR, ^1H, ^{13}C NMR and mass spectroscopy.

Table 2
The effect of compounds **3a–m** on seizures induced by MES in mice[a]

Entry	Treatment group	Dose level	Time (s) in various phases of convulsion (mean ± SEM)		
			Flexion	Extensor	Clonus
1	**3a**^{ns}	20 mg/kg	5.80 ± 0.20	48.00 ± 0.32	3.60 ± 0.20
2	**3b***	20 mg/kg	4.80 ± 0.20	39.20 ± 0.40	3.40 ± 0.24
3	**3c****	20 mg/kg	4.80 ± 0.18	**31.80 ± 0.40**	3.20 ± 0.24
4	**3d****	20 mg/kg	5.80 ± 0.20	**31.60 ± 0.37**	3.40 ± 0.20
5	**3e***	20 mg/kg	4.80 ± 0.20	39.20 ± 0.40	3.40 ± 0.24
6	**3f****	20 mg/kg	4.80 ± 0.20	**31.60 ± 0.37**	3.40 ± 0.24
7	**3g***	20 mg/kg	4.80 ± 0.20	39.60 ± 0.40	3.60 ± 0.20
8	**3h***	20 mg/kg	4.80 ± 0.20	39.60 ± 0.40	3.40 ± 0.24
9	**3i****	20 mg/kg	5.40 ± 0.24	**31.60 ± 0.37**	2.80 ± 0.24
10	**3j***	20 mg/kg	4.80 ± 0.20	39.20 ± 0.40	3.20 ± 0.24
11	**3k***	20 mg/kg	4.80 ± 0.18	39.20 ± 0.40	3.20 ± 0.24
12	**3l****	20 mg/kg	5.40 ± 0.20	**31.80 ± 0.32**	3.60 ± 0.20
13	**3m****	20 mg/kg	5.40 ± 0.24	**31.60 ± 0.37**	2.80 ± 0.24
14	Phenytoin[b]	20 mg/kg	5.60 ± 0.20	43.00 ± 0.40	3.40 ± 0.24
15	Tween 80[c]	0.5% w/v	11.20 ± 0.40	55.20 ± 0.63	7.60 ± 0.32

Data were analyzed by one way ANNOVA followed by Dunnet's test.
ns: not significant, *P* value >0.05; *significant, *P* value <0.05; **highly significant, *P* value <0.001.
SEM: Standard error of means.
Bold values indicate the superior activity compared to the standard and other compounds.
[a] Mortality = recovery.
[b] Standard.
[c] Control.

All the synthesized compounds were screened for their anticonvulsant activity against Maximal Electroshock[13] (MES) induced seizure through in vivo rodent models.[14] Results of anticonvulsant activity with reference drug phenytoin are discussed in Table 2. All the compounds were active at a dose level of 20 mg/kg which is an indicative of their ability to prevent convulsion spread. The MES-convulsions are divided into three phases such as (a) tonic flexion, (b) tonic extensor and (c) clonic convulsions. The time (s) spent by the animal in each phase of the convulsions is noted down. A substance is known to possess anticonvulsant property if it reduces or abolishes the extensor phase of MES-convulsion. Analysis of Table 2 revealed that six compounds (**3c**, **3d**, **3f**, **3i**, **3l**, and **3m**) showed excellent activity and six compounds (**3b**, **3e**, **3g**, **3h**, **3j**, and **3k**) showed good anticonvulsant activity. However, these compounds were found to be more potent than the reference drug phenytoin. Compound **3a** emerged as the less attractive compound in this series showing poor anticonvulsant activity as evidenced by high extensor time than phenytoin.

Attempts to understand the SAR of the molecules started with the indole moiety. Replacement of *N*-allyl group (**3a**) with a propargyl group (**3j**) increased the anticonvulsant potency significantly, indicating the importance of propargyl group. Replacement of C5-hydrogen (**3a**) by 5-MeO group (**3c**) enhanced the activity. A markedly improved potency was observed when a small substituent like methyl was placed at the C-2 position (**3m**). The presence of hydrophobic groups like cinnamyl (**3g**) and prenyl (**3h**) offered only moderate activity. Among the substituents placed C-5 on the oxindole moiety, a chloro group (**3d**) was well tolerated and offers enhanced activity over the bromo counterpart (**3e**). Of the other substituents placed on the C-5 position, nitro group (**3b**) was found to exhibit higher potency than the unsubstituted analogue (**3a**). The presence of *N*-propargyl (**3i**) and ester (**3f**) groups on the oxindole ring renders the

Table 3
Antibacterial[a] and antifungal[b] activity of compounds **3a–m** by cup plate method[c]

Entry	Compounds	Zone of inhibition[d] (mm)		
		S. aureus	*E. coli*	*C. albicans*
1	**3a**	12	12	11
2	**3b**	10	10	**15**
3	**3c**	12	10	14
4	**3d**	10	11	10
5	**3e**	**15**	14	14
6	**3f**	12	14	10
7	**3g**	10	14	13
8	**3h**	14	12	12
9	**3i**	**15**	15	10
10	**3j**	11	10	12
11	**3k**	**15**	**17**	13
12	**3l**	10	10	12
13	**3m**	**15**	15	**15**
14	*Amikacin*[e]	17	18	NA
15	*Ketoconazole*[f]	NA	NA	16

NA: not applicable.
[a] Muller-Hinton agar was employed as culture media.
[b] Sabouraud Dextrose Agar was employed as culture media.
[c] Test concentration of 20 μg/mL was used with methanol as solvent control.
[d] Bold value indicates the maximum antimicrobial activity among the screened compounds.
[e] Standard antibacterial drug.
[f] Standard antifungal activity.

molecule more active than their respective unsubstituted oxindoles (**3h** and **3c**). The tris-propargyl pattern also led to the significant improvement in potency (**3l**).

Considering the extensive applications of di(indolyl)indolin-2-ones in medicinal chemistry and in continuation of our ongoing project on bio-active heterocycles,[6i] an attempt has been made to evaluate the antimicrobial properties of the synthesized compounds.

The representative compounds **3a–m** were tested for their antibacterial activity[16] against Gram(+)ve and Gram(−)ve bacterial strains namely *Staphylococcus aureus* (MSSA 22) and *Escherichia coli* (K 12), respectively, by employing cup-plate method[15] at a concentration of 20 μg/mL of methanol in Muller-Hinton agar media. The standard antibacterial drug *Amikacin* was screened under similar conditions. Twenty microliters of these solutions were added to each well. One of the wells was used as control by adding 20 μL of methanol. The zone of inhibition, if any, produced by diffusion of the compounds from the cup into the surrounding medium, was measured after incubation at 37 °C for 24 h (Table 3). Out of thirteen compounds, **3e**, **3i**, **3k**, and **3m** showed maximum activity (15 mm inhibition) against *S. aureus*. Compound **3k** showed maximum activity (17 mm inhibition) against *E. coli*. The in vitro antifungal activities[17] of the synthesized compounds were evaluated against *Candida albicans* (ATCC 10231) by cup plate method at a concentration of 20 μg/mL of methanol in Sabouraud Dextrose Agar Media. The standard antifungal drug *Ketoconazole* was screened under similar conditions. The same procedure employed for the evaluation of antibacterial activities was followed for antifungal evaluation also. The screening data (Table 3) revealed that compounds **3b** and **3m** showed maximum antifungal activity (15 mm inhibition).

In summary, we have synthesized *N*-allyl and *N*-propargyl di(indolyl)indolin-2-ones via $Cu(OTf)_2$ catalyzed 3-indolylation of isatin. From chemical perspective this method is simple, practical to perform and no column chromatography required for purification. All the synthesized compounds were screened for their anticonvulsant and antimicrobial activity. Among the screened compounds six compounds (**3c**, **3d**, **3f**, **3i**, **3l**, and **3m**) exhibited maximum anticonvulsant activity. The anticonvulsant potency of these compounds could be attributed to the favorable structural combination of the indole and oxindole frameworks and their substituents. The antibacterial activity study revealed that four compounds (**3e**, **3i**, **3k**, and **3m**) showed maximum activity against *S. aureus* and one compound (**3k**) showed maximum activity against *E. coli*. Antifungal activity study revealed that two compounds (**3b** and **3m**) showed maximum activity against *C. albicans*. However, the effect of compounds on the host cell and their mode of action remain to be studied.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.04.117.

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10. We have previously reported $Cu(OTf)_2$ catalyzed regioselective synthesis of phthalans, see Ref. 5h.

11. Representative procedure for the synthesis of 3,3-bis(1-allyl-1*H*-indol-3-yl)-indolin-2-one: To a stirred solution of *N*-allylindole **2a** (1.0 mmoL) in acetonitrile (2 mL) was added isatin **1a** (0.5 mmoL) and $Cu(OTf)_2$ (0.05 mmoL). The resulting reaction mixture was stirred at room temperature for 30 min. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford pure product of 3,3-bis(1-allyl-1*H*-indol-3-yl)-indolin-2-one **3a** (90%) as yellow solid; mp 269–271 °C; IR (KBr): 3848, 3431, 2511, 2331, 2028, 1700, 1365 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ_H 4.72 (s, 4H); 4.92 (d, 2H, *J* = 16.8 Hz); 5.06 (d, 2H, *J* = 9.9 Hz); 5.85–5.94 (m, 2H); 6.79 (t, 2H, *J* = 7.6 Hz); 6.87 (s, 2H); 6.89–6.90 (m, 3H); 7.02 (t, 2H, *J* = 7.6 Hz); 7.22 (d, 3H, *J* = 8.4 Hz); 7.33 (d, 2H, *J* = 8.4 Hz); 10.64 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 48.3, 52.9, 103.6, 110.6, 111.6, 114.4, 117.0, 118.2, 119.0, 121.7, 126.7, 128.0, 134.8, 134.9, 137.2, 138.9, 151.2, 159.9, 179.0. Anal. Calcd for $C_{30}H_{25}N_3O$: C, 81.24; H, 5.68; N, 9.47. Found: C, 80.98; H, 5.75; N, 9.55%.
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14. Typical experimental procedure for the evaluation of anticonvulsant activity of the synthesized compounds by MES induced convulsion method: (a) *Animals and experimental conditions*: Inbred albino mice (Swiss strain) of both genders weighing 25–30 g were used for the study. The mice were kept in clean polypropylene cages with free access to standard pellet diet and water (ab libitum), under standardized housing conditions (natural light–dark cycle, temperature 25 ± 1 °C, relative humidity 55 ± 5%). After 7 days of adaptation to laboratory conditions, the animals were randomly assigned to 12 experimental groups of 5 mice each. Each mouse was used only once. All tests were performed between 10:00 and 16:00. All efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data. The experimental protocols and procedures listed below conformed to the Guide for the Care and Use of Laboratory Animals and approved by the Institutional Ethics Committee.
(b) *MES induced seizure*: Group-I was treated with 0.5% aqueous solution of Tween 80 (polyoxyethylene sorbitan mononucleate) and served as control. Phenytoin was suspended in a 0.5% Tween 80 solution and administered intraperitoneally (ip) to group-II (20 mg/kg) and served as standard. All the test compounds were suspended in a 0.5% Tween 80 solution and administered intraperitoneally (ip) to group-III (20 mg/kg) 30 min before seizure induction. Maximum electroshock seizure was elicited using electroconvulsiometer with an altering current of 150 mA for 0.2 s via ear clip electrode. Each mouse was administered the drug or control 30 min prior to receiving an electroshock. The time (seconds) spent by the animal in different convulsion phases is noted down.
(c) *Statistical analysis*: The obtained data were analyzed using one-way analysis of variance (ANOVA) followed by Dunnet's multiple comparison test. The results are presented as mean ± standard error of means (SEM). Differences between data sets were considered as significant when P <0.001.
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16. Experimental for antibacterial activity of compounds **3a**–**m**: The beef extract (30 g), casein hydrolysate (17.5 g), soluble starch (1.5 g), agar (20 g) were taken in the above proportions and dissolved up to 1000 mL of distilled water. The constituents were heated gently at 100 °C with agitation. The pH of the medium was adjusted to 7.4 using sodium hydroxide. The pH was tested using a universal indicator paper, which showed green colour at pH 7.4. Then it was transferred to boiling tubes in hot condition and sealed with non-absorbent cotton and sterilized by autoclaving at 121 °C (15 lbs pressure) for 15 min. Then poured aseptically into sterile Petri dishes. The sterilized Muller-Hinton agar media was heated on a water bath to melt the media. When the media was lukewarm, the organism (*E. coli* or *S. aureus*) were inoculated separately and poured aseptically into sterile Petri dishes and allowed to solidify. The standard drug *Amikacin* disc was placed on the media. These vials were kept in hot air oven at 160 °C for 30 min for sterilization using methanol as solvent control. The synthesized compounds (20 μg/mL) were then added by sterile micro pipette into each cup. Initially it was kept in the refrigerator for 1 h to facilitate uniform diffusion of the drug and later kept in the incubator for a period of 24 h at 37 °C. Observations were made for the zone of inhibition around the test compounds and compared with that of standard.
17. Experimental for antifungal activity of compounds **3a**–**m**: Glucose (40 g), peptone (10 g) and agar (15 g) were taken in the above proportions at 100 °C with agitation. The pH of the medium was adjusted to 5.4. Then it was transferred to boiling tubes in hot condition and sealed with non-absorbent cotton and sterilized by autoclaving at 121 °C (15 lbs pressure) for 15 min. Then it was poured aseptically into sterile Petri dishes. The sterilized Sabouraud dextrose agar was heated on a water bath to melt the media. When the media was lukewarm, the *C. albicans* spores were inoculated separately and poured aseptically into sterile Petri dishes and allowed to solidify. The standard drug *Ketoconazole* was placed on the media. These vials were kept in hot air oven at 160 °C for 30 min for sterilization using methanol as solvent control. The synthesized compounds (20 μg/mL) were then added by sterile micro pipette into each cup. Initially it was kept in the refrigerator for 1 h to facilitate uniform diffusion of the drug and later kept in the incubator for a period of 24 h at 28 °C. Observations were made for the zone of inhibition around the test compounds and compared with that of standard.