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Full Paper

# Synthesis and Evaluation of 5-(*o*-Tolyl)-1*H*-tetrazole Derivatives as Potent Anticonvulsant Agents

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A series of 5-(*o*-tolyl)-1*H*-tetrazole derivatives were synthesized and evaluated for their anticonvulsant activities. 1-(2-Methylbenzyl)-5-(*o*-tolyl)-1*H*-tetrazole (**3h**) showed important anticonvulsant activity against the MES-induced seizures, as well as lower neurotoxicity with an $ED_{50}$ value of 12.7 mg/kg and a $TD_{50}$ value of over 500 mg/kg after intraperitoneal injection into mice, providing **3h** with a high protective index ($TD_{50}/ED_{50}$) of over 39.4. The achieved results prove that the distinctive compounds could be valuable as a model for future development, adaptation, and investigation to construct more active analogues.

**Keywords:** 5-(*o*-Tolyl)-1*H*-tetrazole derivatives / Anticonvulsant / Synthesis

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## Introduction

The derivatives of tetrazoles exhibit a variety of biological activities, such as antibiotic [1], anti-allergic [2], anti-inflammatory [2], antihypertensive [3], and antiviral activities [4]. So far, many tetrazole-based derivatives have been successfully developed and prevalently used as clinical drugs such as antihypertensive losartan [5], antibacterial ceforanide [6], anticoagulant cilostazol [7], anti-asthmatic pranlukast [8], diuretic azosemide [9], and antinociceptive alfentanil [10, 11].

Quite recently, Siddiqui et al. designed a series of triazole-based anticonvulsant agents [12], which have shown considerable anticonvulsant activities. Especially, compound **I** (Fig. 1) with 1-(*o*-tolyl)-1*H*-1,2,4-triazole moiety, which showed promising anticonvulsant activities with $ED_{50}$ values of 13.9 mg/kg in MES screen and 81.6 mg/kg in scPTZ test, respectively. The substitution in the *ortho*-position of the phenyl ring with electron-donating groups was generally beneficial to activity [13], and the importance of the *ortho*-methyl group for anticonvulsant activity had been depicted in many studies [14–17] including the recently marketed drug tiagabine.

Based on the above structural characteristics, it was assumed that the compound containing *ortho*-methylphenyl group moiety in a single molecule could be beneficial to anticonvulsant activity. In view of this structural estimation and the important biological activity of tetrazole-based derivatives, it has been planned to synthesize and evaluate a series of 5-(*o*-tolyl)-1*H*-tetrazole derivatives as anticonvulsant agents. The structures of designed compounds along with compound **I** are shown in Fig. 1.

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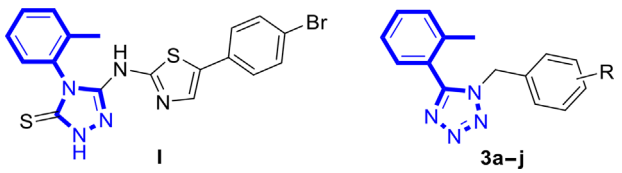



**Figure 1.** The modification of 5-(*o*-tolyl)-1*H*-tetrazole.

## Results and discussion

### Chemistry

Target compounds **3a–j** were prepared according to Scheme 1. *o*-Tolunitrile **1** was reacted with sodium azide ($NaN_3$) in dry toluene in the presence of triethylamine hydrochloride at 100°C to afford quantitative yield of 5-(*o*-tolyl)-1*H*-tetrazole (**2**), which was treated with different substituted benzyl chlorides in acetonitrile at 60°C to furnish target compounds **3a–j** in a good yield.

### Pharmacology

The anticonvulsant activity of the synthesized compounds (**3a–j**) was determined using two animal models of seizure according to the standard protocols within the Antiepileptic Drug Development (ADD) Program at National Institute of Neurological Disorders and Stroke, National Institutes of Health, Rockville, USA which included maximal electroshock seizure (MES) [18] and subcutaneous pentylenetetrazole (scPTZ) [19]. Almost all clinically significant AEDs are protective in at least one of these two models [20–23]. In addition to the initial anticonvulsant screen, acute neurotoxicity (NT) was evaluated in the rotarod test [24]. The results of anticonvulsant activity and NT studies are summarized in Table 1.

As seen in Table 1, **3e**, **3f**, and **3h–j** compounds among the tested compounds exhibited considerable anticonvulsant activities in the MES test. The most active of these compounds were **3f** and **3h** which showed 100% protection at a dose of 30 mg/kg at 0.5 and 4 h post administration. In the scPTZ screen, a test used to identify compounds that elevate seizure threshold, **3d**, **3f**, **3g**, **3i**, and **3j** showed protection at 300 mg/kg after 0.5 h and only **3f** among these compounds continued to show activity after 4.0 h at 300 mg/kg dose.

In addition, all the compounds of the *in vivo* screening were evaluated against the minimal motor impairment in the rotarod test, and showed low toxicity. Especially, **3b**, **3d**, and **3f–h** showed non-toxic behavior at the maximum dose of 300 mg/kg after both the time durations. The compounds **3a, 3c, 3e, 3i**, and **3j** elucidated neurotoxicity at 300 mg/kg at 0.5 h followed by an increase in non-toxic potential except **3a** and **3e** after delayed absorption at 4 h by preventing minimal motor impairment.

As a result of preliminary screening, the most active compounds **3f** and **3h** were subjected to further investigations at different doses for quantification of their anticonvulsant activity (indicated by $ED_{50}$) and neurotoxicity (indicated by $TD_{50}$) in mice (Table 2). The selected compounds **3f** and **3h** displayed anticonvulsant activity against MES-induced seizure with $ED_{50}$ values of 39.9 and 12.7 mg/kg and $TD_{50}$ values of 449.8 and over 500 mg/kg, respectively.

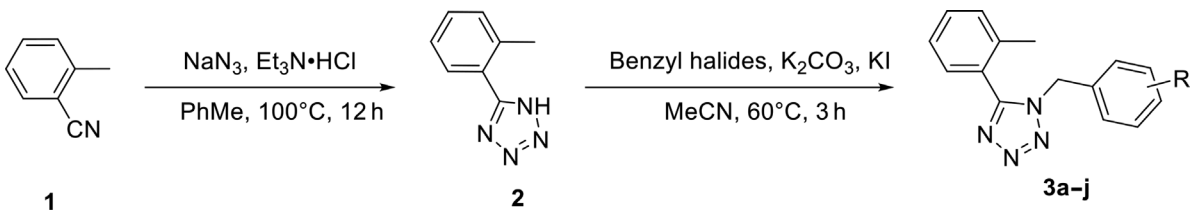
## Conclusion

In summary, a series of 5-(*o*-tolyl)-1*H*-tetrazole derivatives were synthesized and evaluated in *in vivo* animal models of epilepsy. The results of this study demonstrated that some 5-(*o*-tolyl)-1*H*-tetrazole derivatives possess a good anticonvulsant activity. Specially, **3f** and **3h** possess a good anticonvulsant activity and low toxicity in MES model. The obtained results showed that certain compounds could be useful as a template for future design, modification, and investigation to produce more active analogues.

## Experimental

### Chemistry

Melting points were determined in open capillary tubes and were uncorrected. $^1$H-NMR spectra were measured on a Bruker Avance 600 MHz NMR spectrometer, with all chemical shifts given in ppm relative to tetramethylsilane. Chemical shift values are in hertz. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; td, triplet of doublets; for $^1$H-NMR data. High resolution mass spectra were recorded on an AB SCIEX Triple TOF™ 5600 equipped with an electrospray ionization source. Ethyl




**Scheme 1.** The synthesis route of target compounds **3a–j**.

**Table 1.** Phase I anticonvulsant activity and neurotoxocity of compounds 3a–j administered intraperitoneally to mice.

| Compounds | R | Intraperitoneal injection in mice[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | MES screening[b] | | scPTZ screening[c] | | NT screening[d] | |
| | | 0.5 h | 4 h | 0.5 h | 4 h | 0.5 h | 4 h |
| **3a** | 4-$CH_3$ | – | 100 | – | – | 300 | 300 |
| **3b** | 4-$C(CH_3)_3$ | – | – | – | – | – | – |
| **3c** | 4-$CF_3$ | – | – | – | – | 300 | – |
| **3d** | 4-$NO_2$ | – | 100 | 300 | – | – | – |
| **3e** | 4-F | 300 | 300 | – | – | 300 | 300 |
| **3f** | 3-F | 30 | 30 | 300 | 300 | – | – |
| **3g** | 2-F | – | – | 300 | – | – | – |
| **3h** | 2-$CH_3$ | 30 | 30 | – | – | – | – |
| **3i** | 2-Cl | 100 | 30 | 300 | – | 300 | – |
| **3j** | 2,6-di-F | 300 | 300 | 300 | – | 300 | – |
| Phenytoin | | 30 | 30 | – | – | 100 | 100 |

[a] Doses of 30, 100, and 300 mg/kg were administered. The animals were examined 0.5 and 4.0 h after injection were made. The dash (–) indicates the absence of activity at maximum dose administered (300 mg/kg).
[b] Maximal electroshock test.
[c] Subcutaneous pentylenetetrazole test.
[d] Neurotoxocity screening (rotarod test).

acetate/*n*-hexane (1:3) (**2**) and ethyl acetate/*n*-hexane (1:9) (**3a–j**) were used as developing solvent for TLC. The major chemicals were purchased from Xiya Reagent Co., Ltd (China).

The $^1$H and MS spectra and the InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

*Synthesis of 5-(o-tolyl)-1H-tetrazole (**2**)*

$NaN_3$ (0.30 g, 4.5 mmol) was added to a mixture of 2-methylbenzonitrile **1** (0.36 g, 3 mmol) and $Et_3N \cdot HCl$ (0.62 g, 4.5 mmol) in toluene (10 mL) with stirring at room temperature. The reaction temperature was raised up to 100°C for about 13 h. After completion of reaction (monitored by thin-layer chromatography, TLC), the reaction mixture was cooled and extracted with water (3 × 30 mL). The water layers were combined. A total of 20% HCl was added dropwise to the aqueous phase to precipitate the crude product. After filtration, the crude solid was recrystallized from ethyl acetate/hexane to give white crystals. Yield: 64.1%; Rf = 0.52; white solid; mp: 153–155°C. FT-IR: 3200–2300 (w, $\nu$(N–H)), 3029 (w, $\nu$(C–H)), 2970 (w, $\nu(CH_3)$), 1900–1600 (w, overtones $\delta$ (C–H, Ph)), 1607 (s, $\nu$(C=C)), 1562 (s, $\delta$(N–H)), 1485 (s, $\nu$(C=C)), 1463 (s, $\delta(CH_3)$), 744 (s, $\delta$(C–H, Ph)) $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$, 600 MHz) $\delta$: 7.69 (d, 1H, ArH, $J$ = 7.8 Hz), 7.49 (td, 1H, ArH, $J$ = 1.2, 7.2 Hz), 7.44 (d, 1H, ArH, $J$ = 7.8 Hz), 7.40 (dt, 1H, ArH, $J$ = 1.2, 7.2 Hz), 2.48 (s, 3H, $CH_3$). ESI–HRMS calcd. for $C_8H_8N_4$ ($[M+H]^+$): 161.0749; found: 161.0825.

*General procedure for the synthesis of **3a–j***

A mixture of 5-(*o*-tolyl)-1*H*-tetrazole **2** (0.161 g, 1 mmol), halides (1.2 mmol), $K_2CO_3$ (0.276 g, 2 mmol), and catalytic amounts of KI in 10 mL acetonitrile was heated to 60°C for about 3 h. After completion of reaction (monitored by TLC), the mixture was poured into water and extracted with ethyl

**Table 2.** Phase II quantitative anticonvulsant evaluation in MES model in mice (test drug administered i.p.).

| Compounds | TPE (h)[a] | $ED_{50}$[b] | $TD_{50}$[c] | PI[d] |
|---|---|---|---|---|
| **3f** | 0.8 | 39.9 (18.6–63.8)[e] | 449.8 (390.1–796.9) | 11.3 |
| **3h** | 0.8 | 12.7 (2.9–21.0) | >500 | >39.4 |
| Phenytoin | 2 | 9.5 (8.1–10.4) | 65.5 (52.5–72.9) | 6.9 |
| Phenobarbital | 1 | 21.8 (21.8–25.5) | 69 (62.8–72.9) | 3.2 |

[a] Time to peak effect.
[b] $ED_{50}$: median effective dose affording anticonvulsant protection in 50% of animals; the dose is measured in mg/kg.
[c] $TD_{50}$: median toxic dose eliciting minimal neurological toxicity in 50% of animals; the dose is measured in mg/kg.
[d] PI: protective index ($TD_{50}/ED_{50}$).
[e] 95% confidence intervals given in parentheses.

acetate. The organic layer was dried ($MgSO_4$), concentrated and purified by silica gel column.

*1-(4-Methylbenzyl)-5-(o-tolyl)-1H-tetrazole (**3a**)*
Yield: 50.2%; Rf = 0.53; white solid; mp: 89–91°C; $^1$H-NMR ($CDCl_3$, 600 MHz): $\delta$ 2.37 (s, 3H, $Ar_2$–$CH_3$), 2.63 (s, 3H, $Ar_1$–$CH_3$), 5.80 (s, 2H, $CH_2$), 7.21 (d, 2H, $J$ = 7.8 Hz, $Ar_2H$), 7.30–7.33 (m, 2H, ArH), 7.35–7.38 (m, 3H, ArH), 8.01 (d, 1H, $J$ = 7.8 Hz, ArH). ESI–HRMS calcd. for $C_{16}H_{16}N_4$ ($[M+H]^+$): 265.1375; found: 265.1452.

*1-(4-(tert-Butyl)benzyl)-5-(o-tolyl)-1H-tetrazole (**3b**)*
Yield: 65.3%; Rf = 0.62; colorless oily liquid; $^1$H-NMR ($CDCl_3$, 600 MHz): $\delta$ 1.35 (s, 9H, $CH_3$), 2.68 (s, 3H, $CH_3$), 5.83 (s, 2H, $CH_2$), 7.32–7.35 (m, 2H, ArH), 7.37–7.40 (m, 1H, ArH), 7.42–7.46 (m, 4H, ArH), 8.06 (d, 1H, $J$ = 7.2 Hz, ArH). ESI–HRMS calcd. for $C_{19}H_{22}N_4$ ($[M+H]^+$): 307.1844; found: 307.1915.

*1-(4-(Trifluoromethyl)benzyl)5-(o-tolyl)-1H-tetrazole (**3c**)*
Yield: 25.2%; Rf = 0.48; colorless oily liquid; $^1$H-NMR ($CDCl_3$, 600 MHz): $\delta$ 2.64 (s, 3H, $CH_3$), 5.90 (s, 2H, $CH_2$), 7.32–7.34 (m, 2H, ArH), 7.37–7.40 (m, 1H, ArH), 7.54 (t, 1H, $J$ = 7.8, 15.6 Hz, ArH), 7.63–7.67 (m, 2H, ArH), 7.76 (s, 1H, ArH), 8.05 (d, 1H, $J$ = 7.8 Hz, ArH). ESI–HRMS calcd. for $C_{16}H_{13}F_3N_4$ ($[M+H]^+$): 319.0192; found: 319.1164.

*1-(4-Nitrobenzyl)-5-(o-tolyl)-1H-tetrazole (**3d**)*
Yield: 41.4%; Rf = 0.26; white solid; mp:101–103°C; $^1$H-NMR ($CDCl_3$, 600 MHz): $\delta$ 2.63 (s, 3H, $CH_3$), 5.96 (s, 2H, $CH_2$), 7.34 (d, 2H, $J$ = 7.8 Hz, ArH), 7.39 (t, 1H, $J$ = 7.8 Hz, ArH), 7.60 (d, 2H, $J$ = 7.8 Hz, ArH), 8.02 (d, 1H, $J$ = 7.2 Hz, ArH), 8.28 (d, 2H, $J$ = 8.4 Hz, ArH). ESI–HRMS calcd. for $C_{15}H_{12}N_5O_2$ ($[M+H]^+$): 296.1069; found: 296.1154.

*1-(4-Fluorobenzyl)-5-(o-tolyl)-1H-tetrazole (**3e**)*
Yield: 37.3%; Rf = 0.41; white solid; mp: 45–47°C; $^1$H-NMR ($CDCl_3$, 600 MHz): $\delta$ 2.63 (s, 3H, $CH_3$), 5.81 (s, 2H, $CH_2$), 7.08–7.11 (m, 2H, ArH), 7.31–7.34 (m, 2H, ArH), 7.37–7.39 (m, 1H, $Ar_1H$), 7.45–7.47 (m, 2H, ArH), 8.02 (d, 1H, $J$ = 8.4 Hz, ArH). ESI–HRMS calcd. for $C_{15}H_{13}FN_4$ ($[M+H]^+$): 269.1124; found: 269.1188.

*1-(3-Fluorobenzyl)-5-(o-tolyl)-1H-tetrazole (**3f**)*
Yield: 47.8%; Rf = 0.47; white solid; mp: 34–35°C; $^1$H-NMR ($CDCl_3$, 600 MHz): $\delta$ 2.65 (s, 3H, $CH_3$), 5.83 (s, 2H, $CH_2$), 7.08 (td, 1H, $J$ = 2.4, 8.4 Hz, ArH), 7.16 (d, 1H, $J$ = 9.6 Hz, ArH), 7.22 (d, 1H, $J$ = 7.8 Hz, $Ar_1H$), 7.32–7.35 (m, 2H, ArH), 7.36–7.40 (m, 2H, ArH), 8.05 (d, 1H, $J$ = 7.8 Hz, ArH). ESI–HRMS calcd. for $C_{15}H_{13}FN_4$ ($[M+H]^+$): 269.1124; found: 269.1189.

*1-(2-Fluorobenzyl)-5-(o-tolyl)-1H-tetrazole (**3g**)*
Yield: 37.8%; Rf = 0.61; white solid; mp: 66–68°C; $^1$H-NMR ($CDCl_3$, 600 MHz): $\delta$ 2.64 (s, 3H, $CH_3$), 5.92 (s, 2H, $CH_2$), 7.13–7.18 (m, 2H, $Ar_2H$), 7.30–7.33 (m, 2H, ArH), 7.35–7.40 (m, 3H, $Ar_1H$), 8.06 (d, 1H, $J$ = 7.2 Hz, ArH). ESI–HRMS calcd. for $C_{15}H_{13}FN_4$ ($[M+H]^+$): 269.1124; found: 269.1196.

*1-(2-Methylbenzyl)-5-(o-tolyl)-1H-tetrazole (**3h**)*
Yield: 41.6%; Rf = 0.65; white solid; mp: 63–65°C; $^1$H-NMR ($CDCl_3$, 600 MHz): $\delta$ 2.53 (s, 3H, $Ar_2$–$CH_3$), 2.64 (s, 3H, $Ar_1$–$CH_3$), 5.86 (s, 2H, $CH_2$), 7.24–7.27 (m, 2H, ArH), 7.30–7.35 (m, 4H, ArH), 7.36–7.39 (m, 1H, ArH), 8.05 (d, 1H, $J$ = 7.8 Hz, ArH). ESI–HRMS calcd. for $C_{16}H_{16}N_4$ ($[M+H]^+$): 265.1375; found: 265.1450.

*1-(2-Chlorobenzylbenzyl)-5-(o-tolyl)-1H-tetrazole (**3i**)*
Yield: 45.3%; Rf = 0.61; white solid; mp: 54–56°C; $^1$H-NMR ($CDCl_3$, 600 MHz): $\delta$ 2.64 (s, 3H, $CH_3$), 6.00 (s, 2H, $CH_2$), 7.23 (dd, 1H, $J$ = 1.2, 7.2 Hz, ArH), 7.29 (td, 1H, $J$ = 1.2, 7.8 Hz, ArH), 7.32–7.35 (m, 3H, ArH), 7.37–7.39 (m, 1H, ArH), 7.47 (dd, 1H, $J$ = 1.2, 7.8 Hz, ArH), 8.02 (d, 1H, $J$ = 7.2 Hz, $Ar_1H$). ESI–HRMS calcd. for $C_{15}H_{13}ClN_4$ ($[M+H]^+$): 285.0829; found: 285.0899.

*1-(2,6-Difluorobenzyl)-5-(o-tolyl)-1H-tetrazole (**3j**)*
Yield: 53.1%; Rf = 0.44; white solid; mp: 80–82°C; $^1$H-NMR ($CDCl_3$, 600 MHz): $\delta$ 2.61 (s, 3H, $CH_3$), 5.94 (s, 2H, $CH_2$), 7.01 (t, 2H, $J$ = 7.8 Hz, ArH), 7.29–7.32 (m, 2H, $J$ = 7.8 Hz, ArH), 7.35–7.38 (m, 1H, ArH), 7.40–7.42 (m, 1H, ArH), 8.01 (d, 1H, $J$ = 7.8 Hz, ArH). ESI–HRMS calcd. for $C_{15}H_{12}F_2N_4$ ($[M+H]^+$): 287.1030; found: 287.1102.

## Pharmacology

*Maximal electroshock test (MES)*
The maximal electroshock seizure test was carried out according to the standard protocol [18, 19]. Male mice (Kunming, China), weighing 20–25 g, were used as experimental animals. Mice were housed under temperature-controlled conditions (25–30°C) and a 12-h light/dark cycle. They were allowed to acclimatize with free access to food and water for a 24-h period before testing except during the experiment. Abolition of hind limb tonic extension spasm was recorded as anticonvulsant activity. The test compounds were dissolved in an aqueous solution of 50% polyethylene glycol. In preliminary screening, each compound was administered as an *ip* injection at three dose levels (30, 100, 300 mg/kg body mass) and the anticonvulsant activity was assessed after 0.5 and 4 h intervals of administration.

*Subcutaneous pentylenetetrazole seizure test (scPTZ)*
This test involved treating the mice with metrazol (pentylenetetrazole, 85 mg/kg in mice). This produced clonic seizures lasting for a period of at least 5 s in 97% of the animals tested. At the anticipated time of testing, the convulsant was subcutaneously administered. The test compound was intraperitoneally administered in mice and the animals were observed over a 30-min period. Mice were tested 30 min and 4 h after doses of 100 and 300 mg/kg of the test compound were administered. The absence of clonic spasms over the period of observation indicated the compound's ability to abolish the effect of pentylenetetrazol on the seizure threshold.

*Neurotoxicity screening*

The rotarod test was used to evaluate neurotoxicity. The mice were trained to stay on an accelerating rotarod that rotated at six revolutions per minute. The rod diameter was 3.2 cm. Trained animals were given *ip* injection of the test compounds in doses of 100 and 300 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials.

*Quantification studies*

The $ED_{50}$ was calculated using the Bliss method [25, 26]. The $ED_{50}$ values were presented as the mean with 95% confidence intervals. Neurotoxicity was indicated by the inability of the animals to maintain equilibrium on the rod for at least 1 min in each of the three trials. Neurotoxicity was expressed as the median toxic dose ($TD_{50}$ in mg/kg) eliciting minimal neurological toxicity in 50% of animals. The quantitative determination of $ED_{50}$ and $TD_{50}$ values were performed at the previously estimated time of peak effect after *ip* injection into mice.

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*The authors have declared no conflict of interest.*

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