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Research Article

Synthesis of *N*-[{5-Aryl-1,3,4-oxadiazole-2-yl}methyl]-4-methoxyaniline Derivatives and Their Anticonvulsant Activity

B. N. Prasanna Kumar,[1] K. N. Mohana,[1] and L. Mallesha[2]

[1] *Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India*
[2] *PG Department of Chemistry, JSS College of Arts, Commerce and Science, Ooty Road, Mysore 25, India*

Correspondence should be addressed to K. N. Mohana; drknmohana@gmail.com

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A series of some new 2,5-disubstituted-1,3,4-oxadiazoles **4(a–i)** have been conveniently synthesized by intramolecular oxidative cyclization of (E)-2-(arylbenzylidene)-2-[(4-methoxyphenyl)amino]acetohydrazides promoted by iodobenzene diacetate as an oxidant. The structures of the synthesized compounds have been confirmed by ^{1}H and ^{13}C NMR, IR, MS, and elemental analysis. All the newly synthesized compounds were screened for their anticonvulsant activity against maximal electroshock (MES) seizure method. Compounds **4g**, **4d**, and **4a** were found to be the most potent of this series. The same compounds showed no neurotoxicity at the maximum dose administered.

1. Introduction

Epilepsy is one of the most common neurological disorders affecting a large section of people. About 50 million people worldwide have epilepsy, with almost 90% of these people being in developing countries [1]. Epilepsy also affects about 4% of individuals over their lifetime. The incidence of epilepsy is highest among children below 7 years of age and in individuals of above 55 years. Epilepsy is the third most wide spread neurological disorder found in the elderly after cerebrovascular disease and dementia. About 20–30% of patients have seizures that are resistant to available medical therapies [2]. All currently approved antiepileptic drugs have dose-related toxicity and idiosyncratic side effects [3]. Therefore, the search for a newer, more effective, and more selective agent with lesser side effects continues to be an area of investigation of medicinal chemists worldwide.

The anticonvulsant drug design is based on the major characteristics important in newly synthesized compounds which are the inclusion of a hydrophobic site and H-bond donors/acceptors in the compound which is required for the activity in MES. Although several new drugs such as vigabatrin, lamotrigine, gabapentin, tiagabine, felbamate, topiramate, fosphenytoin, and levetiracetam have appeared in the market, the development of novel agents, particularly compounds effective against complex partial seizures, remains a major focus of antiepileptic drug research.

Heterocyclic compounds containing five membered rings gained importance because of their versatile biological properties. In particular, compounds bearing 1,3,4-oxadiazoles nucleus are known have to anti-inflammatory activity [4]. Differently substituted oxadiazole molecules possess other interesting properties such as analgesic [5], antimicrobial [6], anti-HIV [7], antitumor [8], antihypertensive [9], antitumor [10], anticonvulsant [11], 5-HT-receptor antagonists [12], and glycogen phosphorylase inhibitors [13]. In the present study, new 2,5-disubstituted-1,3,4-oxadiazole derivatives **4(a–i)** have been synthesized and characterized by different spectral studies. Their anticonvulsant effects are determined through maximal electroshock (MES) seizure test.

2. Experimental

All solvents and reagents were purchased from Sigma Aldrich Chemicals Pvt. Ltd. Melting range was determined by Veego Melting Point VMP III apparatus. Elemental analyses were recorded on VarioMICRO superuser V1.3.2 Elementar.

The IR spectra were recorded using KBr discs on FT-IR Jasco 4100 infrared spectrophotometer. 1H and 13C NMR spectra were recorded on Bruker DRX-500 spectrometer at 400 MHz using DMSO-d_6 as solvent and TMS as an internal standard. The mass spectra of the samples were recorded using the instrument LC-MSD-Trap-XCT.

*2.1. Synthesis of 2-(4-Methoxyphenylamino)acetohydrazide **(2)**.* To a mixture of ethyl-(4-methoxyphenyl)glycinate **1** (0.01 mmol) and ethanol (25 mL), hydrazine hydrate (0.02 mmol) was added. The reaction mass was heated to reflux for 4 h. The reaction completion was monitored by thin layer chromatography (TLC). The reaction mixture was concentrated to half volume. The solid obtained was filtered and washed with chilled ethanol. The obtained solid was dried to get the pure product. Yield 78%; mp 116–118°C.

*2.2. General Procedure for the Synthesis of (E)-2-(Arylbenzylidene)-2-[(4-methoxyphenyl)amino]acetohydrazides **(3a–i)**.* 2-(4-Methoxyphenylamino)acetohydrazide **2** (0.001 mmol) was refluxed with different aryl aldehydes (0.001 mmol) in ethanolic solution (10 mL) for about 2 h. Completion of the reaction was confirmed by the thin layer chromatography (TLC). After completion, reaction mass was cooled to 5 to 10°C for 1 hr. Reaction mass was filtered and washed with chilled ethanol. The obtained solid was dried to get the pure product.

*2.2.1. (E)-N-(4-Chlorobenzylidene)-2-[(4-methoxyphenyl) amino]acetohydrazide **3a**.* The general experimental procedure described above afforded **3a** and the product obtained from 2-(4-methoxyphenylamino)acetohydrazide **2** and 4-chlorobenzaldehyde. Yield 92%; mp 170–172°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.87 (s, 3H, $-OCH_3$), 4.58–4.60 (d, 2H, $-CH_2$), 6.36 (s, NH), 7.03 (d, 2H, Ar-H), 7.44 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 8.14 (d, 2H, Ar-H), 8.60 (s, N=CH), 9.30 (s, NH).

*2.2.2. (E)-N-(4-Methylbenzylidene)-2-[(4-methoxyphenyl) amino]acetohydrazide **3b**.* The general experimental procedure described above afforded **3b** and the product obtained from 2-(4-methoxyphenylamino)acetohydrazide **2** and 4-methylbenzaldehyde. Yield 86%; mp 158–161°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.19 (s, 3H, Ar-CH_3), 3.88 (s, 3H, $-OCH_3$), 4.58–4.60 (d, $-CH_2$), 6.37 (s, NH), 7.55–7.76 (m, 4H, Ar-H), 8.0–8.15 (m, 4H, Ar-H), 8.55 (s, N=CH), 9.24 (s, NH).

*2.2.3. (E)-N-(4-Hydroxybenzylidene)-2-[(4-methoxyphenyl) amino]acetohydrazide **3c**.* The general experimental procedure described above afforded **3c** and the product obtained from 2-(4-methoxyphenylamino)acetohydrazide **2** and 4-hydroxybenzaldehyde. Yield 90%, Mp 170–172°C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.88 (s, 3H, $-OCH_3$), 4.58–4.60 (d, $-CH_2$), 5.20 (s, 1H, OH), 6.36 (s, NH), 6.97 (dd, 2H, Ar-H), 7.22–7.38 (m, 4H, Ar-H), 7.89 (dd, 2H, Ar-H), 8.49 (s, N=CH), 9.19 (s, NH).

*2.2.4. (E)-N-(β-Chlorobenzylidene)-2-[(4-methoxyphenyl) amino]acetohydrazide **3d**.* The general experimental procedure described above afforded **3d** and the product obtained from 2-(4-methoxyphenylamino)acetohydrazide **2** and 2-chlorobenzaldehyde. Yield 91%; mp 166–168°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.88 (s, 3H, $-OCH_3$), 4.57–4.59 (d, $-CH_2$), 6.35 (s, NH), 7.04–7.12 (d, 4H, Ar-H), 7.59-(s, 1H, Ar-H), 7.68–7.79 (m, 3H, Ar-H). 8.51 (s, N=CH), 9.32 (s, NH).

*2.2.5. (E)-N-(2-Fluoro-3-methoxybenzylidene)-2-[(4-methoxyphenyl)amino]acetohydrazide **3e**.* The general experimental procedure described above afforded **3e** and the product obtained from 2-(4-methoxyphenylamino)acetohydrazide **2** and 2-fluoro-3-methoxybenzaldehyde. Yield 87%; mp 138–140°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.86 (s, 3H, $-OCH_3$), 3.88 (s, 3H, $-OCH_3$), 4.58–4.59 (d, $-CH_2$), 6.38 (s, NH), 7.06 (dd, 2H, Ar-H), 7.31–7.34 (t, 1H, Ar-H), 7.37–7.39 (m, 4H, Ar-H), 8.48 (s, N=CH), 9.29 (s, NH).

*2.2.6. (E)-N-(4-Methoxybenzylidene)-2-[(4-methoxyphenyl) amino]acetohydrazide **3f**.* The general experimental procedure described above afforded **3f** and the product obtained from 2-(4-methoxyphenylamino)acetohydrazide **2** and 4-methoxybenzaldehyde. Yield 93%; mp 170–172°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.88 (s, 6H, $-OCH_3$), 4.57–4.59 (d, $-CH_2$), 6.36 (s, NH), 6.99 (dd, 8.26 Hz, 4H, Ar-H), 7.76–7.90 (m, 4H, Ar-H), 8.44 (s, N=CH), 9.33 (s, NH).

*2.2.7. (E)-2-[(4-Methoxyphenyl)amino]-N-[4-(trifluoromethyl)benzylidene]acetohydrazide **3g**.* The general experimental procedure described above afforded **3g** and the product obtained from 2-(4-methoxyphenylamino)acetohydrazide **2** and 3-trifluorobenzaldehyde. Yield 92%; mp 196–198°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.87 (s, 3H, $-OCH_3$), 4.58–4.60 (d, $-CH_2$), 6.36 (s, NH), 7.01 (dd, 2H, Ar-H), 7.67 (dd, 2H, Ar-H), 8.04–8.13 (m, 4H, Ar-H), 8.43 (s, N=CH), 9.31 (s, NH).

*2.2.8. (E)-2-[(4-Methoxyphenyl)amino]-N-(2-nitrobenzylidene)acetohydrazide **3h**.* The general experimental procedure described above afforded **3h** and the product obtained from 2-(4-methoxyphenylamino)acetohydrazide **2** and 2-nitrobenzaldehyde. Yield 90%; mp 179–181°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.87 (s, 3H, $-OCH_3$), 4.56–4.58 (d, $-CH_2$), 6.36 (s, NH), 7.08 (dd, 2H, Ar-H), 7.77–7.82 (m, 5H, Ar-H), 8.10–8.15 (m, 1H, Ar-H), 8.40 (s, N=CH), 9.35 (s, NH).

*2.2.9. (E)-N-(4-Bromobenzylidene)-2-[(4-methoxyphenyl) amino]acetohydrazide **3i**.* The general experimental procedure described above afforded **3i** and the product obtained from 2-(4-methoxyphenylamino)acetohydrazide **2** and 4-bro mobenzaldehyde. Yield 88%; mp 177–179°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.88 (s, 3H, $-OCH_3$), 4.58–4.60 (d, $-CH_2$), 6.35 (s, NH), 7.05–7.15 (m, 4H, Ar-H), 7.45 (d, 2H, Ar-H), 8.3 (d, 2H, Ar-H), 8.48 (s, N=CH), 9.29 (s, NH).

2.3. General Procedure for the Synthesis of 2,5-Disubstituted-1,3,4-Oxadiazoles ***(4a–i)***. (E)-2-(Arylbenzylidene)-2-[(4-methoxyphenyl)amino]acetohydrazides (**3a–i**) (0.01 mmol) was dissolved in methanol, and IBD (0.012 mmol) was added to it. The content was stirred for 2 h, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, solvent was removed under reduced pressure, and residue was taken in petroleum ether, and stirred for 30 min. The solid thus obtained was filtered, washed with petroleum ether and dried to afford (**4a–i**). The crude product was purified by recrystallization method using diethyl ether.

2.3.1. N-[{5-(4-Chlorophenyl)-1,3,4-oxadiazole-2-yl}methyl]-4-methoxyaniline ***4a***. White solid. IR (KBr, cm^{-1}): 3067 (aromatic C–H), 2924 (C–H of CH_2), 1686 (C=N), 1462 (C=C), 1376 (C–N), 1256 (C–O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.88 (s, 3H, $-OCH_3$), 4.57–4.60 (d, $-CH_2$), 6.32 (s, NH), 7.09 (d, 2H, Ar-H), 7.57 (d, 2H, Ar-H), 7.74 (d, 2H, Ar-H), 8.02 (d, 2H, Ar-H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ; 55.8, 115.7, 127.9, 130.2, 134.8, 158.9, 161.6, 164.1. MS (ESI) *m/z*: 317. Anal. Calcd. for $C_{16}H_{14}ClN_3O_2$ (in %): C, 60.86; H, 4.47; N, 13.31. Found: C, 60.84; H, 4.41; N, 13.39.

2.3.2. N-[{5-(4-Methylphenyl)-1,3,4-oxadiazole-2-yl}methyl]-4-methoxyaniline ***4b***. White solid. IR (KBr, cm^{-1}): 3076 (aromatic C–H), 2948 (C–H of CH_2), 1681 (C=N), 1469 (C=C), 1385 (C–N), 1239 (C–O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.17 (s, 3H, Ar-CH_3), 3.81 (s, 3H, $-OCH_3$), 4.58–4.60 (d, $-CH_2$), 6.34 (s, NH), 7.55 (d, 2H, Ar-H), 7.88 (d, 2H, Ar-H), 8.17 (d, 2H, Ar-H). 8.0–8.15 (m, 2H, Ar-H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ; 28.3, 55.8, 115.0, 116.0, 120.0, 124.6, 127.1, 137.4, 157.6, 163.8, 165.8. MS (ESI) *m/z*: 296. Anal. Calcd. for $C_{17}H_{17}N_3O_2$ (in %): C, 69.14; H, 5.80; N, 14.23. Found: C, 69.10; H, 5.60; N, 14.35.

2.3.3. 4-[5-{(4-Methoxyphenyl)amino}methyl]-1,3,4-oxadiazole-2-yl]phenol ***4c***. Pale brown solid. IR (KBr, cm^{-1}): 3516 (OH), 3071 (aromatic C–H), 2926 (C–H of CH_2), 1646 (C=N), 1467 (C=C), 1380 (C–N), 1253 (C–O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.86 (s, 3H, $-OCH_3$), 4.57–4.60 (d, $-CH_2$), 5.22 (s, 1H, OH), 6.33 (s, NH), 6.88 (dd, 2H, Ar-H), 7.19–7.32 (m, 4H, Ar-H), 7.82 (d, 2H, Ar-H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ; 55.4, 114.7, 116.1, 125.6 130.1, 134.2, 136.4, 157.4, 164.5, 166.0. MS (ESI) *m/z*: 399. Anal. Calcd. for $C_{16}H_{15}N_3O_3$ (in %): C, 64.64; H, 5.09; N, 14.13. Found: C, 64.42; H, 4.89; N, 14.10.

2.3.4. N-[{5-(3-Chlorophenyl)-1,3,4-oxadiazole-2-yl}methyl]-4-methoxyaniline ***4d***. Pale yellow solid. IR (KBr, cm^{-1}): 3065 (aromatic C–H), 2941 (C–H of CH_2), 1614 (C=N), 1445 (C=C), 1380 (C–N), 1241 (C–O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.87 (s, 3H, $-OCH_3$), 4.56–4.58 (d, $-CH_2$), 6.33 (s, NH), 7.04 (d, 4H, Ar-H), 7.59–7.66 (d, 1H, Ar-H), 7.76 (d, 2H, Ar-H), 7.68–7.79 (m, 1H, Ar-H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ; 55.3, 114.2, 116.7, 120.4, 124.7, 128.2, 128.8, 135.3, 158.4, 163.4, 167.8. MS (ESI) *m/z*: 317. Anal. Calcd. for $C_{16}H_{14}ClN_3O_2$ (in %): C, 60.86; H, 4.47; N, 13.31. Found: C, 60.89; H, 4.64; N, 13.51.

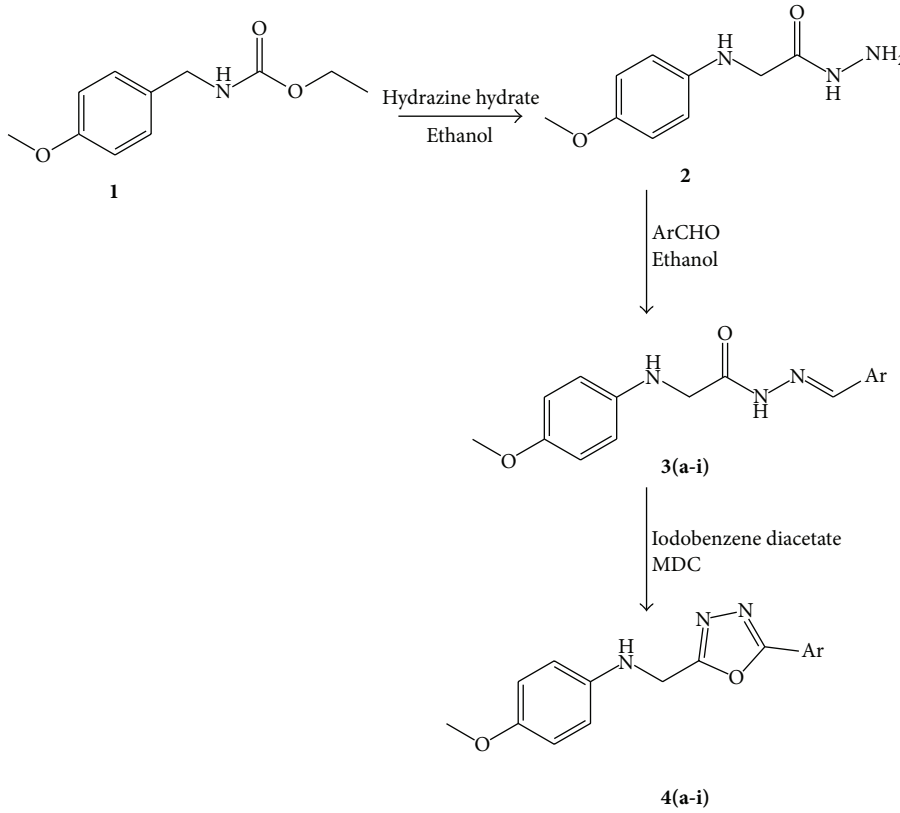
2.3.5. N-[{5-(2-Fluoro-3-methoxyphenyl)-1,3,4-oxadiazole-2-yl}methyl]-4-methoxyaniline ***4e***. White solid. FT-IR (KBr, cm^{-1}): 3069 (aromatic C–H), 2957 (C–H of CH_2), 1662 (C=N), 1484 (C=C), 1381 (C–N), 1236 (C–O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.87 (s, 3H, $-OCH_3$), 3.89 (s, 3H, $-OCH_3$), 4.57–4.59 (d, $-CH_2$), 6.36 (s, NH), 7.06 (dd, 2H, Ar-H), 7.10–7.14 (t, 1H, Ar-H), 7.37–7.39 (m, 2H, Ar-H), 7.84 (dd, 2H, Ar-H), ^{13}C NMR (DMSO-d_6, 400 MHz) δ; 55.8, 113.9, 116.0, 124.2, 126.1, 133.0, 136.0, 157.1, 162.8, 164.9. MS (ESI) *m/z*: 330. Anal. Calcd. for $C_{17}H_{16}FN_3O_3$ (in %): C, 62.00; H, 4.90; N, 12.76. Found: C, 62.10; H, 4.84; N, 12.82.

2.3.6. 4-Methoxy-N-[{4-methoxyphenyl)-1,3,4-oxadiazole-2-yl}methyl]aniline ***4f***. White solid. FT-IR (KBr, cm^{-1}): 3047 (aromatic C–H), 2941 (C–H of CH_2), 1629 (C=N), 1481 (C=C), 1386 (C–N), 1246 (C–O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.85 (s, 6H, $-OCH_3$), 4.56–4.58 (d, $-CH_2$), 6.34 (s, NH), 6.94 (dd, 4H, Ar-H), 7.76 (dd, 2H, Ar-H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ; 55.3, 114.2, 116.7, 120.4, 129.8, 136.2, 160.9, 162.5, 164.8. MS (ESI) *m/z*: 312. Anal. Calcd. for $C_{17}H_{17}N_3O_3$ (in %): C, 65.58; H, 5.50; N, 13.50. Found: C, 65.51; H, 5.46; N, 13.34.

2.3.7. 4-Methoxy-N-[{5-(4-trifluoromethyl)phenyl}-1,3,4-oxadiazole-2-yl]methyl]aniline ***4g***. White solid. FT-IR (KBr, cm^{-1}): 3069 (aromatic C–H), 2951 (C–H of CH_2), 1675 (C=N), 1469 (C=C), 1385 (C–N), 1231 (C–O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.87 (s, 3H, $-OCH_3$), 4.58–4.60 (d, $-CH_2$), 6.35 (s, NH), 7.14 (dd, 2H, Ar-H), 7.82 (dd, 2H, Ar-H), 7.96 (dd, 2H, Ar-H), 8.0–8.15 (m, 2H, Ar-H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ; 55.8, 115.6, 116.7, 124.2, 124.6, 127.6, 131.7, 132.6, 137.8, 158.0, 163.2, 165.5. MS (ESI) *m/z*: 350. Anal. Calcd. for $C_{17}H_{14}F_3N_3O_2$ (in %): C, 58.45; H, 4.04; N, 12.03. Found: C, 58.41; H, 4.12; N, 12.00.

2.3.8. 4-Methoxy-N-[{5-(2-nitrophenyl)-1,3,4-oxadiazole-2-yl}methyl]aniline ***4h***. Yellow solid. FT-IR (KBr, cm^{-1}): 3063 (aromatic C–H), 2934 (C–H of CH_2), 1688 (C=N), 1469 (C=C), 1385 (C–N), 1231 (C–O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.87 (s, 3H, $-OCH_3$), 4.54–4.59 (d, $-CH_2$), 6.33 (s, NH), 7.17 (dd, 2H, Ar-H), 7.77-7.82 (m, 2H, Ar-H), 8.10–8.15 (m, 2H, Ar-H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ; 55.7, 114.9, 116.0, 121.2, 124.2, 126.1, 133.4, 136.0, 157.4, 163.6, 165.9. MS (ESI) *m/z*: 327. Anal. Calcd. for $C_{16}H_{15}N_4O_4$ (in %): C, 58.71; H, 4.62; N, 17.12. Found: C, 58.81; H, 4.58; N, 17.21.

2.3.9. N-[{5-(4-Bromophenyl)-1,3,4-oxadiazole-2-yl}methyl]-4-methoxyaniline ***4i***. FT-IR (KBr, cm^{-1}): 3049 (aromatic C–H), 2921 (C–H of CH_2), 1680 (C=N), 1467 (C=C), 1380 (C–N), 1245 (C–O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.86 (s, 3H, $-OCH_3$), 4.57–4.60 (d, $-CH_2$), 6.33 (s, NH), 7.05 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.82 (d, 2H, Ar-H), 7.94 (d, J = 8.65 Hz, 2H, Ar-H). ^{13}C NMR (DMSO-d_6, 400 MHz) δ; 55.4, 114.7, 116.1, 126.2, 128.4, 130.1, 134.2, 136.4, 157.4, 163.2, 165.2. MS (ESI) *m/z*: 361. Anal. Calcd. for $C_{16}H_{14}BrN_3O_2$ (in %): C, 53.55; H, 3.92; N, 11.67. Found: C, 53.23; H, 3.81; N, 11.7.



Scheme 1: Synthetic route for the target compounds **4(a–i)**.

2.4. Anticonvulsant Evaluation

Animals. Male Wistar rats procured from National Institute of Nutrition, Hyderabad (190–220 g), were used in the present study. The animals were kept in individual cages for one week to acclimatize for the laboratory conditions. They were allowed to free access of water and food.

All the experimental procedures were carried out in accordance with Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. The study was reviewed and approved by the Institutional Animal Ethics Committee, G. Pulla Reddy College of Pharmacy, Hyderabad, India.

Maximal Electroshock Seizure (MES) Model. Maximal electroshock seizure model was used in the present study to evaluate the anticonvulsant activity of the compounds on male Wistar rats. Seizures were induced in rats by delivering electroshock of 150 mA for 0.2 s by means of a convulsiometer through a pair of ear clip electrodes. The test compounds (100 mg/kg) were administered by oral route in the form of solution (the compounds were dissolved in 1% sodium carboxymethyl cellulose), 30 minutes before the maximal electroshock seizure test. The animals were observed closely for 2 minutes. The percentage of inhibition of seizure relative to control was recorded and calculated [14]. Phenytoin (100 mg/kg) was used as a standard drug.

Neurotoxicity Screening. The minimal motor impairment was measured in mice by the rotarod test. Acute neurological toxicity in mice was evaluated by rotarod test [14]. The mice were trained to stay on the accelerating rotarod that rotates at 10 revolutions per minute. The rod diameter was 3.2 cm. Trained animals were administered with the test compounds at dose of 100 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least one minute in each of the three trails. Phenytoin was used as a standard drug.

Statistical Analysis. In the present study, data were analyzed by one-way analysis of variance (ANOVA) followed by dunnet test to compare difference between the groups.

3. Results and Discussion

3.1. Chemistry. The title compounds were prepared using the synthetic strategy described in Scheme 1. The 2-(4-methoxyphenylamino)acetohydrazide **2** was synthesized by the reaction of ethyl-(4-methoxyphenyl)glycinate **1** with hydrazine hydrate in ethanol as per the reported procedure [15]. The (E)-2-(arylbenzylidene)-2-[(4-methoxyphenyl)amino] acetohydrazides (**3a–i**) were synthesized by the reaction of 2-(4-methoxyphenylamino)acetohydrazide **2** which was refluxed with different substituted aldehydes in ethanolic solution for about 2 h. A series of new 2,5-disubstituted-1,3,4-oxadiazoles (**4a–i**) have been accomplished in excellent yields by the oxidation of (E)-2-(arylbenzylidene)-2-[(4-methoxyphenyl)amino] acetohydrazides (**3a–i**) of various aryl aldehydes with one equivalent of iodobenzene diacetate

Table 1: Chemical structure and physical data of 2,5-disubstituted-1,3,4-oxadiazoles **4(a–i)**.

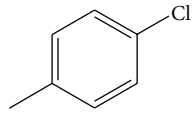
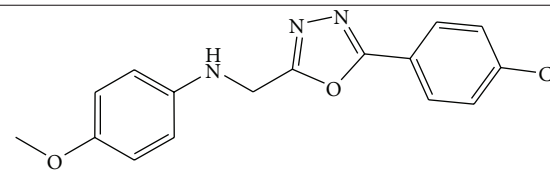
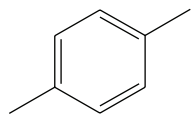
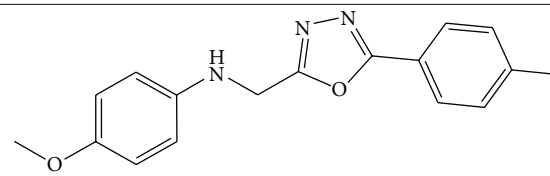
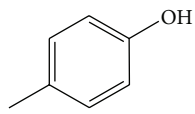
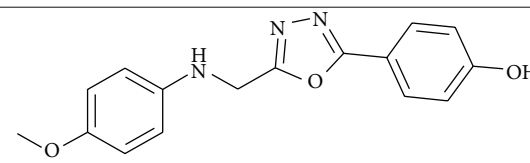
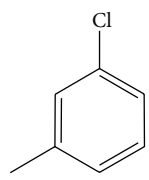
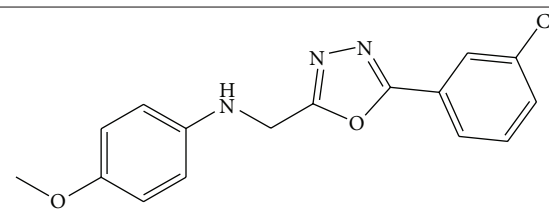
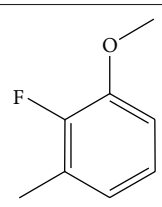
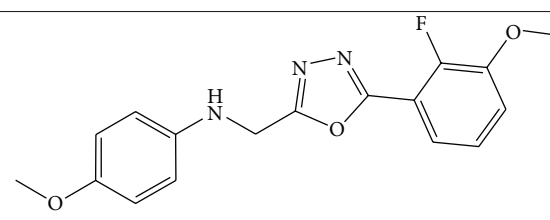
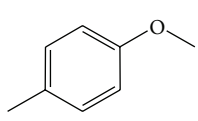
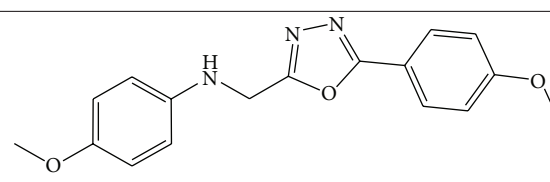
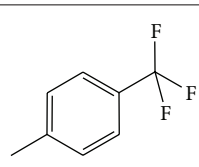
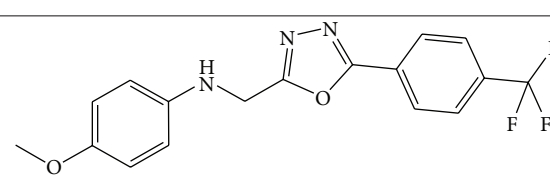
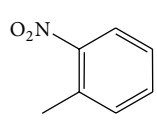
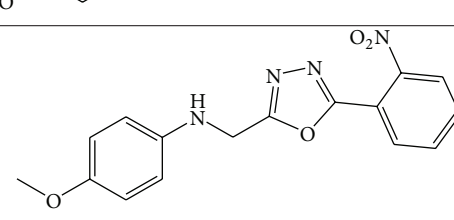
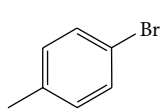
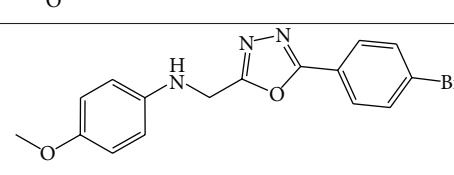
Compound	Ar	Structure	Yield (%)	M. P (°C)
4a			78.0	140–142
4b			84.0	157–159
4c			81.0	162–164
4d			85.0	148–150
4e			80.0	170–172
4f			84.0	167–169
4g			86.0	154–156
4h			85.0	182–184
4i			83.0	176–178

Table 2: Effect of the tested compounds in the maximal electroshock seizure test.

Treatment	E/F	% Protection
4a	2.25	63.21
4b	5.81	28.42
4c	5.34	30.40
4d	2.24	63.40
4e	3.79	52.31
4f	5.26	31.52
4g	2.10	67.53
4h	3.97	50.20
4i	3.84	51.62
Phenytoin	1.98	75.88
Control (vehicle)	8.21	—

Values are expressed as mean; $n = 6$ animals in each group.
E/F = extension/flexion [decrease in ratio of extension phase (in seconds)/flexion phase (in seconds). % Protection = (control − test)/(control) ∗ 100.

(IBD) in dichloromethane. Compounds **3a–i** and **4a–i** are synthesized based on reported procedure [16].

The synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectral and elemental analyses. The IR spectra of (**4a–i**) were recorded using KBr pellets in the range of 4000–400 cm^{-1}. The absorption bands around 3065 cm^{-1} are assigned to the aromatic C–H stretch. The strong bands around 2924 cm^{-1} are assigned to the C–H stretch, the appearance of a medium to strong absorption bands above 1610 cm^{-1} due to a stretching vibration of the azomethine (C=N) bond formation in synthesized compounds. The ^{1}H NMR spectrum of **4a** and **4h** showed singlet in the region of δ, 3.88 and 3.87, respectively, and doublet in the region of δ, 4.57 and 4.54, respectively. All the compounds showed singlet OCH_3 group in the region of δ, 3.81–3.88. The proton spectral data of **4a–i** shows resonance peak at δ 6.32–6.36 ppm (s, 1H, and NH). The carbon spectral data agree with respect to the number of protons and their chemical shifts with the proposed structures. ^{13}C NMR spectra present the correct number of carbon atoms at the appropriate chemical shift values. The mass spectra of **4a** showed molecular ion peak at *m/z* 317, which is in agreement with the molecular formula $C_{16}H_{14}ClN_3O_2$. The elemental analyses data showed good agreement between the experimentally determined values and the theoretically calculated values within ±0.4%. The chemical structures and physical data of all the synthesized compounds are tabulated in Table 1.

3.2. Anticonvulsant Activity. In the present study, the anticonvulsant activity of the nine newly synthesized 2,5-disubstituted-1,3,4-oxadiazoles **4**(**a–i**) was evaluated by MES induced seizure in rats at the dose of 100 mg/kg, and the results are summarized in Table 2. Compounds **4g**, **4d**, and **4a** demonstrated significant protective effect on MES induced seizure. Similarly, compounds **4e**, **4i**, and **4h** that showed moderate protective effect and a significant difference in protectiveness were observed when compared to standard group.

Table 3: Neurotoxicity screening of the compounds **4(a–i)**.

Compound	Neurotoxicity screen			
	0.5 h	1 h	2 h	4 h
4a	0/4	0/4	0/4	0/4
4b	0/4	0/4	1/4	1/4
4c	0/4	0/4	1/4	1/4
4e	0/4	0/4	0/4	0/4
4f	0/4	0/4	1/4	1/4
4g	0/4	0/4	0/4	0/4
4h	0/4	0/4	0/4	0/4
4i	0/4	0/4	0/4	0/4
Phenytoin	0/4	0/4	0/4	0/4

The data in the table represent ratio between the numbers of the animals that exhibited neurotoxicity against the number of tested animals.

Compounds **4f**, **4c**, and **4b** have relatively lower anticonvulsant potencies. All the compounds were examined for their neurotoxicity on mice using rotarod method given in the dose of 100 mg/kg. Except for compounds **4f**, **4c**, and **4b**, none of the compounds showed neurotoxicity. These compounds showed 25% toxicity compared to standard once at 2 h of oral administration (Table 3). The structure activity relationship study of these compounds indicates that the introduction of a benzene ring at position 5 of 1,3,4-oxadiazole ring; trifluoromethyl substituent at the paraposition showed the best anticonvulsant activity in **4g**. Compounds **4d** and **4a** possessing a chloro group had good anticonvulsant activity in the MES model. Both compounds did not exhibit neurotoxicity at the highest administered dose. The fluoro and methoxy groups in **4e** resulted in increased anticonvulsant activity. The presence of bromo group in **4i** and nitro group in **4h** shows moderate anticonvulsant activity. Anticonvulsant activity has increased considerably when methyl group in **4b** was replaced with tolyl variation **4c**. The presence of electron releasing methoxy group in benzene ring in **4f** has more anticonvulsant activity as compared to **4c**.

Conflict of Interests

The authors report no conflict of interests. The authors alone are responsible for the content and writing of the paper.

Acknowledgments

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