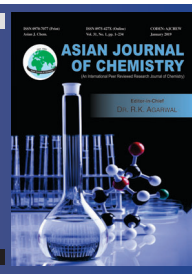
Asian Journal of Chemistry; Vol. 31, No. 6 (2019), 1389-1397

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2019.22061



Synthesis, Characterization and Anticonvulsant Potential of 2,5-Disubstituted 1,3,4-Oxadiazole Analogues

RAJNISH KUMAR[1,*] and MOHD. MUSTAQEEM ABDULLAH[2]

[1]Department of Pharmaceutical Chemistry, Noida institute of Engineering and Technology (Pharmacy Institute), Plot No. 19, Knowledge Park 2, Greater Noida-201306, India
[2]Department of Pharmaceutical Chemistry, ANA Institute of Pharmaceutical Sciences and Research, Agras Road, Near Rubber Factory, National Highway 24, P.O. Bhitaura, Bareilly-243501, India

*Corresponding author: E-mail: mpharm.rajnish@gmail.com

Received: 9 March 2019; *Accepted*: 3 April 2019; *Published online*: 29 April 2019; AJC-19385

A new series of compounds in which benzimidazole, oxadiazole and quinoline were incorporated, was synthesized and investigated for their anticonvulsant activity. Some of the newly synthesized compounds have shown good anticonvulsant activity. Significant anticonvulsant potency of the prepared derivatives has been evaluated by minimal electroshock and subcutaneous pentylenetetrazole animal model methods. The structure of synthesized compounds indicated that the introduction of strong electron donating groups like methoxy, amino and hydroxyl group and weak electron withdrawing halogen at phenyl ring attached to 1,3,4-oxadiazole moiety causes improvement in anticonvulsant activity. Locomotor behaviour was evaluated by actophotometer and toxicology study was also performed to evaluate their significance as required anticonvulsant compounds.

Keywords: Benzimidazole, Quinoline, 1,3,4-Oxadiazoles, Anticonvulsant, Locomotor activity.

INTRODUCTION

The epilepsies are normal and every now and again obliterating neurological confusion with several distinct forms. Spontaneous epileptic seizures frequently cause flashing incapacitate of cognizance, leaving the persons in danger of impedance in their well being and also public activity. If there is any occurrence of seizures, neither successful prophylaxis nor fix is accessible till now as treatment is symptomatic [1,2]. About 75-80 % of epileptic patients might be given satisfactory seizure control with the assistance of regular antiepileptic drugs. Regardless of the advancement of a few new anticonvulsants, the medications of epilepsy still stay insufficient. Be that as it may, over 30 % of individuals with epilepsy don't have seizure control even with the best accessible medicine [3]. Compliance with medicine is the big problem because epilepsy needs long-term treatment with unwanted effects of many drugs [4,5]. Defiance of continuous discovery of new molecules, epilepsy cannot be treated unambiguously. Albeit older, first generation and newer, second generation antiepileptic medications have showed up in the market, the improvement of novel specialists, especially compounds powerful against complex partial seizures, remains a noteworthy focal point of antiepileptic medicate inquire about epilepsy [6,7]. Nitrogen-containing heterocyclic compounds possess the variety of pharmacological activities , among them 1,3,4-oxadiazoles, benzimidazole and quinoline derivatives are associated with diverse biological activities, such as antibacterial [8-10], antimalarial [11-13], anti-inflammatory [14-16] and antifungal [17-19]. Several investigations have also revealed that compounds consisting 1,3,4-oxadiazole, benzimidazole and quinoline pharmacophores in their structure, constitute vary good anticonvulsant potential [20-26]. In this study, hybrid phamacophore approach has been used as rational drug design process to design the new antiepileptic compounds [27]. The hybrid pharmacophores approach aims the utilization of more than one pharmacophores (each of them has potential pharmacological activity) in single molecule to produce compounds with better pharmacological activity. Therefore, in this context to increase the efficacy of the compounds as well as find out the drugs which are effective in both MES and PTZ seizure model,

we clubbed three dynamic pharmacophores 1,3,4-oxadiazole, benzimidazole and quinoline which are required to yield synergistic impacts to the subsequent compounds by synthesizing 2-chloro-3-(1-(5-substituted-1,3,4-oxadiazaol-2-yl)methyl)-1*H*-benzo[*d*]imidazole-2-yl)quinoline (**6a-m**), 5-{[2-(2-chloroquinolin-3-yl)-1*H*-benzimidazole-1-yl]methyl)-2,5-dihydro-1,3,4-oxadiazole-2-thiol (**7**), 1,2-dihydro-1-((5-substituted 1,3,4-oxadiazaol-2-yl)methyl)-2-oxoquinoline-3-carbaldehyde (**11a-e**) and 1,2-dihydro-1-((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)-2-oxoquinoline-3-carbaldehyde (**12**) from acetanilide.

EXPERIMENTAL

2-Chloroquinoline-3-carbaldehyde (2): Compound **2** was synthesized from Vilsmeier-Haack reaction as described [28]. Yield 66 %, m.p. 147 ºC.

3-(1*H*-benzimidazole-2-yl)-2-chloroquinoline (3): It was prepared as described [29]. Yield 79 %, m.p. 219-223 ºC.

Ethyl-[2-(2-chloroquinoline-3-yl)-1*H*-benzimidazole-1-yl)acetate (4): Ethyl chloroacetate (0.12 mol) and K_2CO_3 (0.20 mol) were added to a 60 mL acetone solution of 3-(1*H*-benzimidazole-2-yl)-2-chloroquinoline (**3**) (0.1 mol), then the solution was refluxed for 8h. After cooling to room temperature, the reaction mixture was filtered. Excess acetone was removed from the clear filtrate by distillation, and then was added to water. The residue was washed with water, and then dried under air. Further purification was done by recrystallization from ethyl acetate to give ethyl-[2-(2-chloroquinoline-3-yl)-1*H* benzimidazole-1-yl]acetate (**4**): Yield 75 %, m.p. 231-234 ºC; IR (KBr, ν_{max}, cm^{-1}): 3098.42 (C-H, Ar), 1743 (C=O), 1494.95 (C=C, Ar), 1347 (C-N), 1292, 1163 (C-O); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.68-8.63 (d, 2H, Ar), 8.28-8.24 (m, 4H, Ar), 8.18 (s, 1H, Ar), 7.50-7.40 (t, 4H, Ar), 3.49-3.47 (q, 2H, CH_2), 2.21-2.03 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.3 (C-2, C=O), 153.3 (C-2, benzimidazole), 151.6 (C-2, quinoline), 146.4 (C-9, quinoline), 138.9 (C-4, benzimidazole), 136.4 (C-10, quinoline), 134.3 (C-5, benzimidazole), 130.1 (C-1,6, quinoline), 128.1 (C-8, quinoline), 126.7 (C-5,7, quinoline), 126.8 (C-4, quinoline), 123 (C-7,8, benzimidazole), 115.3 (C-6,9, benzimidazole), 64.4 (CH_2), 50.8 (CH_2), 14.1 (CH_3); EI-MS (*m/z*): 365.09 (M^+); Anal. calcd. (found) % for $C_{20}H_{16}N_3O_2Cl$ (m.w. 365.81): C, 65.67 (65.47); H, 4.41 (4.24); N, 11.49 (11.18).

2-[2-(2-Chloroquinolin-3-yl)-1*H*-benzimidazole-1-yl]-acetohydrazide (5): Mixture of ethyl [2-(2-chloroquinoline-3-yl)-1*H*-benzimidazole-1-yl]acetate (**4**) and hydrazine hydrate was refluxed in the presence of ethanol (10-15 mL) for 10-14 h at 110-120 ºC. After completion of reaction, mixture was cooled at room temperature and poured into crushed ice. A white solid precipitate was obtained which was washed with water and recrystallized from ethanol. Yield 62 %; m.p. 226-230 ºC; IR (KBr, ν_{max}, cm^{-1}): 3248.69 (N-H), 3125.40 (C-H, Ar), 1650.95 (C=O), 1497.99 (C=C, Ar), 1293.06, 1184.86 (C-O); ^{1}H NMR (300MHz, DMSO-d_6) δ ppm: 8.94 (s, 1H, CONH); 8.75-8.71 (t, 4H, Ar), 8.45 (s, 1H, Ar), 7.55-7.41 (m, 4H, Ar), 4.03 (s, 2H, NH_2), 3.86-3.85 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 161.7 ($CONH_2$), 151.8 (C-2, benzimidazole), 147.2 (C-2, quinoline), 145.9 (C-4, quinoline), 138.9 (C-4, benzimidazole), 135.9 (C-10, quinoline), 133.2 (C-5, benzimidazole), 131.4 (C-1, quinoline), 129.4 (C-6, quinoline), 128.1 (C-5,8, quinoline), 127.2 (C-7, quinoline), 126.8 (C-9, quinoline), 119.4 (C-7,8, benzimidazole), 114.2 (C-6,9, benzimidazole), 32.9 (CH_2); EI-MS (*m/z*): 351.08 (M^+); Anal. calcd. (found) % for $C_{18}H_{14}N_5OCl$ (m.w. 351.78): C, 61.46 (61.22); H, 4.01 (3.83); N, 19.91 (19.78).

General method for the synthesis of 2-chloro-3-(1-(5-substituted-1,3,4-oxadiazaol-2-yl)methyl)-1*H*-benzo[*d*]-imidazole-2-yl)quinoline (6a-m): A mixture of 2-[2-(2-chloroquinolin-3-yl)-1*H*-benzimidazole-1-yl]acetohydrazide (**5**) (0.025 mol) and different substituted benzoic acid (0.025 mol) was refluxed in the presence of $POCl_3$ (10-15 mL) for 6-10 h at 110-120 ºC. After completion of reaction, mixture was cooled at room temperature and poured into crushed ice. On basification of sodium bicarbonate (5 %) a solid mass was so separated was washed with water and crystallized from ethanol.

2-Chloro-3-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}quinoline (6a): Yield 81 %, m.p. 215-217 ºC; IR (KBr, ν_{max}, cm^{-1}): 3098 (C-H, Ar), 1494 (C=C, Ar), 1347 (C-N), 1292 (C-O); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.76-8.74 (m, 3H, Ar), 8.24-8.20 (m, 3H, Ar), 7.78-7.75 (t, 1H, Ar), 7.64-7.60 (t, 2H, Ar), 7.56-7.53 (t, 2H, Ar), 7.50-7.47 (t, 2H, Ar), 4.63 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.3, (C-5, oxadiazole), 161.6 (C-2, oxadiazole), 154.2 (C-2, benzimidazole), 147.4 (C-2, quinoline), 142.2 (C-4, quinoline), 137.6 (C-4, benzimidazole), 136.4 (C-10, quinoline), 134.3 (C-5, benzimidazole), 131.4 (C-1, quinoline), 130.8 (C-6, quinoline), 129.3 (C-3, 5, phenyl), 128.8 (C-4, phenyl), 128.1 (C-8, quinoline), 127.9 (C-5, quinoline), 127.5 (C-2,6, phenyl), 127.2 (C-7, quinoline), 126.8 (C-9, quinoline), 126.2 (C-1, phenyl), 118.9 (C-7,8, benzimidazole), 113.8 (C-6,9, benzimidazole), 45.8 (CH_2); EI-MS (*m/z*): 437.10 (M^+); Anal. calcd. (found) % for $C_{25}H_{16}N_5OCl$ (m.w. 437.88): C, 68.57 (68.32); H, 3.68 (3.43); N, 15.99 (15.74).

2-Chloro-3-(1-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]-methyl}-1*H*-benzimidazol-2-yl)quinoline (6b): Yield 87 %, m.p. 102-104 ºC; IR (KBr, ν_{max}, cm^{-1}): 3187 (C-H, Ar), 1610 ($C-NO_2$), 1490 (C=C), 1315 (C-N), 1196 (C-O), 1044 (N-N); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.49 (s, 1H, Ar), 7.56-7.53 (d, 6H, Ar), 7.55-7.47 (t, 4H, Ar), 6.57-6.53 (d, 2H, Ar), 4.52 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.2 (C-5, oxadiazole), 164.6 (C-2, oxadiazole), 152.6 (C-2, benzimidazole), 148.4 (C-2, quinoline), 147.7 (C-4, phenyl), 136.4 (C-4, quinoline), 132.7 (C-3, quinoline), 131.3 (C-1, phenyl), 130.8 (C-7, quinoline), 130.9 (C-7, benzimidazole), 127.4 (C-2,6, phenyl), 127.2 (C-5, quinoline), 126.9 (C-8, quinoline), 125.8 (C-6, quinoline), 121.2 (C-5,6, benzimidazole), 120.4 (C-3,5, phenyl), 115.7 (C-4, benzimidazole), 43.2 (CH_2); EI-MS (*m/z*): 482.08 (M^+); Anal. calcd. (found) % for $C_{25}H_{16}N_5OCl$ (m.w. 482.87): C, 62.18 (61.88); H, 3.13 (3.07); N, 17.40 (17.18).

2-Chloro-3-(1-((5-(4-methoxyphenyl)-1,3,4-oxadiazaol-2-yl)methyl)-1*H*-benzo[*d*]imidazole-2-yl)quinoline (6c): Yield 92 %, m.p. 176-178 6C; IR (KBr, ν_{max}, cm^{-1}): 3085 (C-H, Ar), 1748 (C=O), 1485 (C=C, Ar), 1341 (C-N), 1282 (C-O); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.51 (s, 1H, Ar), 7.78-7.75 (d, 2H, Ar), 7.64-7.60 (d, 2H, Ar), 7.57-7.53 (t, 4H, Ar), 6.50-6.48 (d, 4H, Ar), 4.53 (s, 2H, CH_2), 3.52 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.6 (C-5, oxadiazole), 164.7

(C-2, oxadiazole), 160.4 (C-4, phenyl), 152.7 (C-2, benzimidazole), 150.8 (C-2, quinoline), 134.6 (C-4, quinoline), 131.2 (C-7, quinoline), 128.5 (C-2,6, phenyl), 127.6 (C-6,8, quinoline), 126.8 (C-3, quinoline), 125.9 (C-5, quinoline), 121.7 (C-5,6 benzimidazole), 118.6 (C-1, phenyl), 117.5 (C-7, benzimidazole), 116.2 (C-4, benzimidazole), 114.3 (C-3,5, phenyl), 53.5 (CH_2); EI-MS (*m/z*): 467.11 (M^+); Anal. calcd. (found) % for $C_{26}H_{18}N_5O_2Cl$ (m.w. 467.9): C, 66.74 (66.67); H, 3.88 (3.71); N, 14.97 (14.62).

2-Chloro-3-(1-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-methyl}-1*H*-benzimidazol-2-yl)quinoline (6d): Yield 89 %, m.p. 156-158 ºC; IR (KBr, ν_{max}, cm^{-1}): 3064 (C-H, Ar), 1492 (C=C), 1350 (C-N), 1268 (C-O), 1068 (N-N), 678 (C-Cl); ^{1}H NMR (300MHz, DMSO-d_6) δ ppm: 8.39 (s, 1H, Ar), 8.24-8.20 (m, 4H, Ar), 7.60 (s, 1H, Ar), 7.58-7.56 (t, 2H, Ar), 7.56-7.53 (q, 4H, Ar), 7.50-7.48 (t, 2H, Ar), 3.95 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.3 (C-5, oxadiazole), 163.4 (C-2, oxadiazole), 151.6 (C-2, benzimidazole), 151.4 (C-2, quinoline), 137.6 (C-4, quinoline), 135.7 (C-4, phenyl), 134.8 (C-7, benzimidazole), 132.4 (C-3, quinoline), 131.6 (C-8, quinoline), 129.3 (C-3,5, phenyl), 128.8 (C-12, 13, phenyl), 128.1 (C-6, quinoline), 127.2 (C-7, 9, quinoline), 124.1 (C-1, phenyl), 122.4 (C-5,6 benzimidazole), 115.5 (C-4, benzimidazole), 45.6 (CH_2); EI-MS (*m/z*): 471.06 (M^+); Anal. calcd. (found) % for $C_{25}H_{15}N_5OCl_2$ (m.w. 472.32): C, 63.57 (63.17); H, 3.20 (3.01); N, 14.83 (14.42).

2-Chloro-3-(1-{[5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazol-2-yl)quinoline (6e): Yield 48 %, m.p. 234-236 ºC; IR (KBr, ν_{max}, cm^{-1}): 3069 (C-H, Ar), 1490 (C=C), 1350 (C-N), 1280 (C-O), 1061 (N-N), 670 (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.39 (s, 1H, Ar), 8.18-8.16 (m, 2H, Ar), 7.60 (s, 1H, Ar), 7.57-7.54 (t, 2H, Ar), 7.52-7.47 (t, 2H, Ar), 4.57-4.53 (q, 4H, Ar), 1.27 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 164.7 (C-2, oxadiazole), 163.2 (C-5, oxadiazole), 153.3 (C-2, benzimidazole), 150.9 (C-2, quinoline), 136.4 (C-4, quinoline), 135.7 (C-4, phenyl), 135.3 (C-1, phenyl), 133.7 (C-2, phenyl), 131.4 (C-3, quinoline), 131.0 (C-7, quinoline), 130.3 (C-6, phenyl), 128.1 (C-5, quinoline), 127.9 (C-8, quinoline), 127.6 (C-5, phenyl), 125.1 (C-6, quinoline), 123.8 (C-5,6, benzimidazole), 113.5 (C-4,7, benzimidazole), 46.8 (CH_2); EI-MS (*m/z*): 505.02 (M^+); Anal. calcd. (found) % for $C_{25}H_{14}N_5OCl_3$ (m.w. 506.77): C, 59.25 (59.09); H, 2.78 (2.56); N, 13.82 (13.57).

2-(5-((2-(2-Chloroquinolin-3yl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-yl)phenol (6f): Yield 48 %, m.p. 84 ºC; IR (KBr, ν_{max}, cm^{-1}): 3578 (O-H), 3056 (C-H, Ar), 2945 (C-H), 1487 (C=C), 1340 (C-N), 1254 (C-O), 1058 (N-N); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.31(s, 1H, Ar), 7.98-7.68 (d, 4H, Ar), 7.54-7.43 (t, 2H, Ar), 7.29-7.22 (m, 3H, Ar), 7.01-6.79 (m, 3H, Ar), 4.85 (s, 1H, OH), 3.89 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 164.5 (C-2, oxadiazole), 161.7 (C-5, oxadiazole), 155.3 (C-1, phenyl), 153.3 (C-2, benzimidazole), 148.6 (C-2, quinoline), 143.9 (C-1, quinoline), 136.7 (C-4, benzimidazole), 136.2 (C-10, quinoline), 132.3 (C-5, benzimidazole), 131.4 (C-4, quinoline), 128.4 (C-6, quinoline), 130.2 (C-4, phenyl), 128.9 (C-6, phenyl), 128.1 (C-8, quinoline), 127.9 (C-5,7, quinoline), 126.8 (C-9, quinoline), 123.2 (C-7,8, benzimidazole), 121.9 (C-5, phenyl), 116.4 (C-3, phenyl), 115.3 (C-6,9, benzimidazole), 112.2 (C-2, phenyl), 45.8 (CH_2); EI-MS (*m/z*): 453.09 (M^+); Anal. calcd. (found) % for $C_{25}H_{16}N_5O_2Cl$ (m.w. 453.87): C, 66.16 (66.27); H, 3.55 (3.59); N, 15.43 (15.61).

2-Chloro-3-(1-((5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[d]imidazol-2-yl)quinoline (6g): Yield 63 %, m.p. 123-124 ºC; IR (KBr, ν_{max}, cm^{-1}): 3039 (C-H, Ar), 2918 (C-H), 1447 (C=C), 1354 (C-N), 1291 (C-O), 1128 (N-N); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.48 (s, 1H, Ar), 8.15-7.63 (d, 4H, Ar), 7.51-7.39 (t, 2H, Ar), 7.32-7.26 (d, 2H, Ar), 7.21-7.13 (t, 4H, Ar), 4.62 (s, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 164.5 (C-2, oxadiazole), 162.6 (C-5, oxadiazole), 153.3 (C-2, benzimidazole), 149.8 (C-2, quinoline), 143.6 (C-1, quinoline), 138.9 (C-4, benzimidazole), 137.2 (C-1, phenyl), 136.4 (C-10, quinoline), 134.3 (C-5, benzimidazole), 132.3 (C-1, phenyl), 131.4 (C-4, quinoline), 129.9 (C-6, quinoline), 130.2 (C-4, phenyl), 129.4 (C-3, phenyl), 128.9 (C-6, phenyl), 128.1 (C-8, quinoline), 127.9 (C-5, quinoline), 127.4 (C-5, phenyl), 127.2 (C-7,9, quinoline), 121.7 (C-7,8, benzimidazole), 117.4 (C-6,9, benzimidazole), 45.8 (CH_2); EI-MS (*m/z*): 471.06 (M^+); Anal. calcd. (found) % for $C_{25}H_{15}N_5OCl_2$ (m.w. 472.32): C, 63.57 (63.32); H, 3.20 (3.04); N, 14.83 (14.72).

2-Chloro-3-(1-((5-(pyridine-3-yl)-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-2-yl)quinoline (6h): Yield 87 %, m.p. 112-123 ºC; IR (KBr, ν_{max}, cm^{-1}): 3142 (C-H, Ar), 3037 (C-H), 1417 (C=C), 1364 (C-N), 1268 (C-O), 1047 (N-N); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.81 (s, 1H, Ar), 8.55 (s, 1H, Ar), 8.52-7.68 (m, 5H, Ar), 7.61 (t, 3H, Ar), 7.34 (t, 2H, Ar), 4.99 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.7 (C-2, oxadiazole), 164.2 (C-5, oxadiazole), 153.3 (C-2, benzimidazole), 151.3 (C-2, quinoline), 149.1 (C-2, pyridine), 148 (C-4, pyridine), 143.8 (C-4, quinoline), 138.9 (C-4, benzimidazole), 136.4 (C-10, quinoline), 134.3 (C-5, benzimidazole), 134.1 (C-6, pyridine), 131.4 (C-1, 6, quinoline), 128.1 (C-5, 8, quinoline), 127.5 (C-7, quinoline), 125.9 (C-9 quinoline), 124.5 (C-1, 5, pyridine), 122.4 (C-7,8, benzimidazole), 113.8 (C-6, 9, benzimidazole), 54.4 (CH_2); EI-MS (*m/z*): 438.09 (M^+); Anal. calcd. (found) % for $C_{24}H_{15}N_6OCl$ (m.w. 438.86): C, 65.68 (65.47); H, 3.45 (3.21); N, 19.15 (19.19).

2-(5-((2-(2-Chloroquinolin-3-yl)-1*H*-benzo[*d*]imidazol-1-yl)methy)-1,3,4-oxadiazol-2-yl)benzamine (6i): Yield 42 %, m.p. 85-87 ºC; IR (KBr, ν_{max}, cm^{-1}): 3176 (N-H), 3050 (C-H, Ar), 2948 (C-H), 1609 (C=N), 1430 (C=C), 1342 (C-N), 1291 (C-O), 1076 (N-N); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.62 (s, 1H, Ar), 7.85-7.68 (m, 4H, Ar), 7.42-7.24 (t, 4H, Ar), 7.13-6.52 (m, 4H, Ar), 5.09 (s, 2H, CH_2), 3.86 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.2 (C-2, oxadiazole), 162.9 (C-5, oxadiazole), 151.8 (C-2, benzimidazole), 147.9 (C-2, quinoline), 144.2 (C-4, quinoline), 142.1 (C-1, phenyl), 137.4 (C-4, benzimidazole), 136.4 (C-10, quinoline), 134.3 (C-5, benzimidazole), 131.4 (C-6,9, quinoline), 129.6 (C-4, phenyl), 128.3 (C-6, phenyl), 128.1 (C-5, 8, quinoline), 127.2 (C-1,7, quinoline) , 124.4 (C-2, phenyl), 119.4 (C-7,8, benzimidazole), 117.4 C-3, 5, phenyl), 112.6 (C-6,9, benzimidazole), 52.1 (CH_2); EI-MS (*m/z*): 452.11 (M^+); Anal. calcd. (found) % for $C_{25}H_{17}N_6OCl$ (m.w. 452.89): C, 66.30 (66.12); H, 3.78 (3.52); N, 18.56 (18.47).

2-Chloro-3-(1-((5-2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-2-yl)quinolone (6j): Yield 57 %, m.p. 187-189 ºC; IR (KBr, ν_{max}, cm^{-1}): 3063 (C-H,

Ar), 2959 (C-H), 1395 (C=C), 1335 (C-N), 1286 (C-O), 1064 (N-N); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.48-7.68 (m, 5H, Ar), 7.61-7.43 (t, 2H, Ar), 7.37 (d, 1H, Ar), 7.24-6.83 (m, 5H, Ar), 5.19 (s, 2H, CH_2), 3.73 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 163.7 (C-2, oxadiazole), 159.4 (C-5, oxadiazole), 154.6 (C-1, phenyl), 151.8 (C-2, benzimidazole), 148.2 (C-2, quinoline), 143.9 (C-1, quinoline), 137.4 (C-4, benzimidazole), 135.4 (C-10, quinoline), 133.6 (C-5, benzimidazole), 131.4 (C-4,6, quinoline), 129.8 (C-4, phenyl), 128.5 (C-6, phenyl), 128.0 (C-8, quinoline), 127.5 (C-5,7, quinoline), 125.5 (C-9, quinoline), 124.1 (C-7,8, benzimidazole), 120.1 (C-5, phenyl), 111.2 (C-6,9, benzimidazole), 114.8 (C-3, phenyl), 110.6 (C-2, phenyl), 56.2 (CH_3), 48.4 (CH_2); EI-MS (*m/z*): 467.11 (M^+); Anal. calcd. (found) % for $C_{26}H_{18}N_5O_2Cl$ (m.w. 467.90): C, 66.74 (66.81); H, 3.88 (3.63); N, 14.97 (14.58).

4-(5-((2-(2-Chloroquinolin-3-yl)-1*H*-benzo[*d*]imidazol-1-yl)methy)-1,3,4-oxadiazol-2-yl)benzenamine (6k): Yield 83 %, m.p. 153-154 ºC; IR (KBr, ν_{max}, cm^{-1}): 3317 (N-H), 2950 (C-H, Ar), 2875 (C-H), 1623 (C=N), 1410 (C=C), 1354 (C-N), 1312 (C-O), 1092 (N-N); ^{1}H NMR (300MHz, DMSO-d_6) δ ppm: 8.39 (s, 1H, Ar), 7.86-7.65 (m, 4H, Ar), 7.51-7.35 (t, 2H, Ar), 7.21-6.57 (m, 6H, Ar), 4.89 (s, 2H, CH_2), 3.48 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 163.7 (C-2, oxadiazole), 159.4 (C-5, oxadiazole), 152.6 (C-2, benzimidazole), 149.4 (C-2, quinoline), 148.4 (C-4, phenyl), 144.5 (C-4, quinoline), 138.9 (C-4, benzimidazole), 136.4 (C-10, quinoline), 134.3 (C-5, benzimidazole), 131.4 (C-1, 6, quinoline), 128.3 (C-2,6, phenyl), 128.1 (C-5,8, quinoline), 126.8 (C-7,9, quinoline), 119.4 (C-7,8, benzimidazole), 116.8 (C-3,5, phenyl), 116.2 (C-1, phenyl), 112.7 (C-6, 9, benzimidazole), 43.8 (CH_2); EI-MS (*m/z*): 452.11 (M^+); Anal. calcd. (found) % for $C_{25}H_{17}N_6OCl$ (452.89): C, 66.30 (66.11); H, 3.78 (3.58); N, 18.56 (18.41).

3-(5-((5-Benzyl-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-2-yl)-2-chloroquinoline (6l): Yield 93 %, m.p. 213-215 ºC; IR (KBr, ν_{max}, cm^{-1}): 3110 (C-H, Ar), 2898 (C-H), 1459 (C=C), 1360 (C-N), 1263 (C-O), 1026 (N-N); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.64-7.48 (m, 7H, Ar), 7.32-7.07 (t, 5H, Ar), 7.06- 6.97 (d, 2H, Ar), 4.85 (s, 2H, CH_2), 3.68(s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 167.7 (C-2, oxadiazole), 165.8 (C-5, oxadiazole), 153.3 (C-2, benzimidazole), 152.1 (C-2, quinoline), 147.6 (C-1, quinoline), 137.9 (C-4, benzimidazole), 136.8 (C-10, quinoline), 136.3 (C-1, phenyl), 134.3 (C-5, benzimidazole), 131.4 (C-4, quinoline), 131 (C-6, quinoline), 129.1 (C-2,6, phenyl), 128.7 (C-3,5, phenyl), 128.1 (C-8, quinoline), 127.9 (C-5, quinoline), 127.2 (C-7, quinoline), 126.8 (C-9, quinoline), 125.8 (C-4, phenyl), 122.2 (C-7,8, benzimidazole), 115.3 (C-6,9, benzimidazole), 47.2 (CH_2), 30.9 (CH_2); EI-MS (*m/z*): 451.11 (M^+); Anal. calcd. (found) % for $C_{26}H_{18}N_5OCl$ (m.w. 451.90): C, 69.10 (69.25); H, 4.01 (4.32); N, 15.50 (15.20).

2-Chloro-3-(1-((5-((naphthalene-2-yloxy)methyl)-1,3,4-oxadizol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-2-yl)quinoline (6m): Yield 74%, m.p. 242-245 ºC; IR (KBr, ν_{max}, cm^{-1}): 3076 (C-H, Ar), 2888 (C-H), 1403 (C=C), 1355 (C-N), 1291 (C-O), 1056 (N-N); ^{1}H NMR (300MHz, DMSO-d_6) δ ppm: 8.37-7.67 (m, 9H, Ar), 7.43-7.26 (t, 4H, Ar), 7.11-6.93 (m, 3H, Ar), 5.27 (s, 2H, OCH_2), 4.59 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 161.4 (C-2, oxadiazole), 158.6 (C-5, oxadiazole), 157.9 (C-1, naphthalene), 151.5 (C-2, benzimidazole), 148.2 (C-2, quinoline), 145.9 (C-4, quinoline), 138.9 (C-4, benzimidazole), 135.7 (C-10, quinoline), 134.8 (C-9, naphthalene), 134.3 (C-5, benzimidazole), 131.4 (C-1, quinoline), 130.4 (C-6, quinoline), 129.6 (C-3,4, naphthalene), 128.1 (C-8, quinoline), 127.9 (C-5, quinoline), 127.4 (C-5, naphthalene), 127.2 (C-7, quinoline), 126.9 (C-3,7,8, naphthalene), 124 (C-6, naphthalene), 120.1 (C-7,8, benzimidazole), 118.8 (C-2, naphthalene), 112.4 (C-6,9, benzimidazole), 105.9 (C-10, naphthalene), 72.3 (CH_2O), 42.7 (CH_2); EI-MS (*m/z*): 517.13 (M^+); Anal. calcd. (found) % for $C_{30}H_{20}N_5O_2Cl$ (m.w. 517.96): C, 69.56 (69.35); H, 3.89 (3.75); N, 13.52 (13.43).

5-{[2-(2-Chloroquinolin-3-yl)-1*H*-benzimidazole-1-yl]-methyl)-2,5-dihydro-1,3,4-oxadiazole-2-thiol (7): A mixture of 2-[2-(2-choloroquinolin-3-yl)-1*H*-benzimidazole-1-yl]-acetohydrazide (**5**) (0.01 mol), KOH (0.01 mol), CS_2 (4 mL) and ethanol (15 mL) was heated under reflux until the evaluation of hydrogen sulphide gas stoped. The resultant product was recrystallized from methanol. Yield 67 %, m.p. 136-138 ºC; IR(KBr, ν_{max}, cm^{-1}): 3191 (C-H, Ar), 2700 (S-H), 1493 (C=C), 1318 (C-N), 1282 (C-O), 1022(N-N), 750 (C-S); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.46-8.47 (s, 1H, Ar), 8.29-8.32 (t, 2H, Ar), 7.90-7.93 (t, 2H, Ar), 7.56-7.61 (m, 4H, Ar), 4.52 (s, 2H, CH_2), 3.21 (s, 1H, SH); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 163.2 (C-2, oxadiazole), 158.4 (C-5, oxadiazole), 151.7 (C-2, benzimidazole), 148.3 (C-2, quinoline), 141.6 (C-4, quinoline), 137.9 (C-4, benzimidazole), 135.8 (C-10, quinoline), 132.1 (C- 5, benzimidazole), 130.8 (C-1, 6, quinoline), 128.7 (C-5,8, quinoline), 121.5 (C-7,8, benzimidazole), 116.8 (C-6,9, benzimidazole), 45.1 (CH_2); EI-MS (*m/z*): 393.04 (M^+); Anal. calcd. (found) % for $C_{19}H_{12}N_5OSCl$ (m.w. 393.84): C, 57.94 (57.81); H, 3.07 (3.01); N, 17.78 (17.68).

1,2-Dihydro-2-oxoquinoline-3-carbaldehyde (8): 2-Oxo-1,2-dihydroquinoline-3-carbaldehyde was synthesized from a suspension of 2-chloroquinoline-3-carbaldehyde in 70 % acetic acid [29].

Ethyl-2-(3-formyl-2-oxoquinolin-1(2*H*)-yl)acetate (9): In a mixture of 2-oxo-quinoline-3-carbaldehyde (0.01 mol) in dry acetone (100 mL) and K_2CO_3 (2 g), ethyl chloroacetate 1.2 mL was added dropwise at room temperature for a period of 20-30 min. The reaction mixture was stirred at room temperature for 10-15 h. The solid thus obtained was filtered off and filtrate was concentrated under reduced pressure. Yield 89 %, m.p. 184-186 ºC; IR (KBr, ν_{max}, cm^{-1}): 3098 (N-H), 1748 (C=O), 1494 (C=C), 1347 (C-N), 1292 (C-O); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.74-8.70 (d, 1H, Ar); 8.39 (s, 1H, Ar); 8.24-8.20 (m, 3H, Ar); 7.56-7.53 (d, 2H, Ar); 7.50-7.47 (t, 1H, Ar); 4.57-4.53 (s, 2H, CH_2); 1.52-1.21 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 177.6 (C, carbonyl), 166.4 (C, carboxyl), 154.7 (C, amide), 139.2 (C-4, quinoline), 131.3 (C-6, quinoline), 129.8 (C-5, quinoline), 128.2 (C-2, quinoline), 126.6 (C-10, quinoline), 124.9 (C-3, quinoline), 124.3 (C-9, quinoline), 121.5 (C-7, quinoline), 54.2 (2C, CH_2), 24.1 (CH_3); EI-MS (*m/z*): 259.08 (M^+); Anal. calcd. (found) % for $C_{14}H_{13}NO_4$ (m.w. 259.25): C, 64.86 (64.81); H, 5.05 (5.01); N, 5.40 (5.34).

2-(3-Formyl-2-oxoquinolin-1(2*H*)-yl)acetohydrazide (10): To a mixture of 2-chloro-3-formyl-3, 4-dihydro-2*H*-

quinolin-1-yl)acetic acid ethyl ester (0.01 mol) and hydrazine hydrate 98 % (0.01 mol; 0.49 mL) was added in ethanolic solution. The reaction mixture was refluxed for 3 h. The reaction mixture was cooled and the solid mixture thus obtained and filtered off. Washed with cold water and recrystallized with methanol. Yield 73 %, m.p. 213-215 ºC; IR (KBr, ν_{max}, cm^{-1}): 3248 (N-H), 3125 (C-H, Ar),1650 (C=O), 1497 (C=C, Ar), 1293 (C-O); ^{1}H NMR (DMSO-d_6) δ ppm: 9.64 (s, 1H, CONH), 8.64-8.60 (s, 1H, Ar), 8.45 (s, 1H, Ar), 8.39-8.30 (d, 2H, Ar), 7.62-7.50 (m, 2H, Ar), 4.62 (s, 2H, CH_2), 3.31 (s, 3H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 174.4 (1C, carbonyl), 169.2, 154.7 (2C, amide), 141.4 (C-4, quinoline), 135.4 (C-6, quinoline), 130.1 (C-5, quinoline), 127.7 (C-2, quinoline), 124.5 (C10, quinoline), 122.2 (C-3, quinoline), 117.6 (C-9, quinoline), 115.5 (C-7, quinoline), 51.5 (CH_2); EI-MS (*m/z*): 245.07 (M^+); Anal. calcd. (found) % for $C_{12}H_{11}N_3O_3$ (m.w. 245.23): C, 58.77 (58.70); H, 4.52 (4.33); N, 17.13 (17.10).

General procedure for the synthesis of 1,2-dihydro-1-((5-(substituted)-1,3,4-oxadiazol-2-yl)methyl)-2-oxoquinoline-3-carbaldehyde (11a-e): An equimolar mixture of 2-(3-formyl-2-oxoquinolin-1(2*H*)-yl)acetohydrazide and different substituted benzoic acid was refluxed in the presence of $POCl_3$ (10-15 mL) for 6-10 h at 110-120 ºC. After completion of reaction, mixture was cooled at room temperature and poured into crushed ice. On basification of sodium bicarbonate (5 %), solid mass was so separated was washed with water and crystallized from ethanol.

1,2-Dihydro-1-((5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methyl)-2-oxoquinoline-3-carbaldehyde (11a): Yield 93 %, m.p. 213-215 ºC; IR (KBr, ν_{max}, cm^{-1}): 3028 (C-H, Ar), 2843 (C-H), 1670 (C=O), 1605 (C=N), 1491 (C=C), 1280 (C-O), 1072 (N-N); ^{1}H NMR (DMSO-d_6) δ ppm: 9.12 (s, 1H, CHO), 7.81-7.59 (m, 2H, Ar), 6.84-7.63 (m, 6H, Ar), 6.41 (s, 1H, Ar), 3.99 (s, 3H, OCH_3), 2.60 (s, 2H, CH_2); 13C NMR (100 MHz, DMSO-d_6) δ ppm: 181.5 (C, carbonyl), 167.2 (C, amide), 163.4 (C-5, oxadiazole), 159.7 (C-2, oxadiazole), 160.7 (C-4, phenyl), 143.3 (C-4, quinoline), 135.3 (C-6, quinoline), 131.8 (C-5, quinoline), 128.5 (C-2,6, phenyl), 127 (C-8, quinoline), 126.6 (C-10, quinoline), 124.9 (C-3,9, quinoline), 121.5 (C-7, quinoline), 118.5 (C-1, phenyl), 114.8 (C-3, 5, phenyl), 114.8 (C-5, phenyl), 65.8 (CH_3), 48.2 (CH_2); EI-MS (*m/z*): 361.10 (M^+); Anal. calcd. (found) % for $C_{20}H_{15}N_3O_4$ (m.w. 361.35): C, 66.48 (66.26); H, 4.18 (4.12); N, 11.63 (11.43).

1,2-Dihydro-1-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-methyl)-2-oxoquinoline-3-carbaldehyde (11b): Yield 93 %, m.p. 213-215 ºC; IR (KBr, ν_{max}, cm^{-1}): 3092 (C-H, Ar), 2905 (C-H), 1655 (C=O), 1615 (C=N), 1475 (C=C), 1276 (C-O), 1035 (N-N); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.80 (s, 1H, CHO), 7.68-6.42 (m, 8H, aromatic), 6.14 (s, 1H, aromatic), 4.14 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 176.2 (1C, carbonyl), 168.4 (1C, amide), 162.2 (C-2, oxadiazole), 160.6 (C-5, oxadiazole), 151.2 (C-4, phenyl), 141.4 (C-4, quinoline), 136.8 (C-6, quinoline), 133.5 (C-1, phenyl), 132.8 (C-5, quinoline), 129.5 (C-2,6, phenyl), 127.3 (C-8, quinoline), 125.9 (C-10, quinoline), 122.4 (C-3,9, quinoline), 121.5 (C-7, quinoline), 111.5 (C-3,5, phenyl), 53.5 (CH_2); EI-MS (*m/z*): 376.08 (M^+); Anal. calcd. (found) % for $C_{19}H_{12}N_4O_5$ (m.w. 376.32): C, 60.64 (60.38); H, 3.21 (3.04); N, 14.89 (14.81).

1,2-Dihydro-1-((5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl)methyl)-2-oxoquinoline-3-carbaldehyde (11c): Yield 93 %, m.p. 213-215 ºC; IR (KBr, ν_{max}, cm^{-1}): 3010 (C-H, Ar), 2850 (C-H), 1678 (C=O), 1605 (C=N), 1468 (C=C), 1410 (C-NO_2), 1285 (C-O), 1052 (N-N); ^{1}H NMR (DMSO-d_6) δ ppm: 8.71 (s, 1H, CHO), 7.80-6.20 (m, 7H, Ar), 6.04 (s, 1H, Ar), 3.14 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 176.2 (1C, carbonyl), 166.4 (1C, amide), 161.8 (C-2, oxadiazole), 158.4 (C-5, oxadiazole), 151.2 (C-4, phenyl), 141.4 (C-4, quinoline), 136.8 (C-6, quinoline), 133.5 (C-1, phenyl), 132.8 (C-5, quinoline), 129.5 (C-2,6, phenyl), 127.3 (C-8, quinoline), 125.9 (C-10, quinoline), 122.4 (C-3,9, quinoline), 121.5 (C-7, quinoline), 111.5 (C-3,5, phenyl), 53.5 (CH_2); EI-MS (*m/z*): 421.06 (M^+); Anal. calcd. (found) % for $C_{19}H_{11}N_5O_7$ (m.w. 421.31): C, 54.16; H, 2.63; N, 16.62. Found: C, 53.88; H, 2.33; N, 16.42.

1-((5-(3,5-Dichlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1,2-dihydro-2-oxoquinoline-3-carbaldehyde (11d): Yield 93 %, m.p. 203-212 ºC; IR (KBr, ν_{max}, cm^{-1}): 2982 (C-H, Ar), 2764 (C-H), 1705 (C=O), 1585 (C=N), 1491 (C=C), 1280 (C-O), 1072 (N-N), 740 (C-Cl); ^{1}H NMR (DMSO-d_6) δ ppm: 8.91 (s, 1H, CHO), 7.89-6.21 (m, 7H, Ar), 6.06 (s, 1H, Ar), 3.99 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 182.6 (1C, carbonyl), 166.5 (1C, amide), 164.2 (C-2, oxadiazole), 160.4 (C-5, oxadiazole), 145.3 (C-4, quinoline), 136.2 (C-3,5, phenyl), 134.5 (C-6, quinoline), 132.5 (C-5, quinoline), 131.1 (C-4, phenyl), 128.1 (C-1, phenyl), 128.2 (C-8, quinoline), 126.6 (C-10, quinoline), 123.9 (C-2,5, phenyl), 122.5 (C-3, quinoline), 120.3 (C-9, quinoline), 118.9 (C-7, quinoline), 56.0 (CH_2); EI-MS (*m/z*): 399.01 (M^+); Anal. calcd. (found) % for $C_{19}H_{11}N_3O_3Cl_2$ (m.w. 400.21): C, 57.02 (56.79); H, 2.77 (2.38); N, 10.50 (10.15).

1-((5-(2-Chloro-4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-methyl)-1,2-dihydro-2-oxoquinoline-3-carbaldehyde (11e): Yield 93 %, m.p. 145-148 ºC; IR (KBr, ν_{max}, cm^{-1}): 3080 (C-H, Ar), 2955 (C-H), 1670 (C=O), 1652 (C=N), 1522 (C=C), 1040 (N-N), 753 (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.05 (s, 1H, CHO), 7.81-6.26 (m, 6H, Ar), 6.10 (s, 2H, Ar), 3.45 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 191.2 (C, carbonyl), 165.1 (C-2, oxadiazole), 162.8 (C-5, oxadiazole), 161.5 (C-4, phenyl), 158.1 (C, amide), 140.5 (C-4, quinoline), 132.6 (C-6, quinoline), 130.9 (C-2, phenyl), 128.1 (C-1, phenyl), 127.7 (C-6, phenyl), 126.9 (C-5, quinoline), 125.2 (C-8, quinoline), 123.6 (C-10, quinoline), 121.8 (C-3, quinoline), 119.3 (C-9, quinoline), 118.5 (C-7, quinoline), 116.1 (C-3, phenyl), 114.5 (C-5, phenyl), 43.2 (CH_2); EI-MS (*m/z*): 383.04 (M^+); Anal. calcd. (found) % for $C_{19}H_{11}N_3O_3$ ClF (m.w. 383.76): C, 59.47 (59.10); H, 2.89 (2.75); N, 10.95 (10.68).

1,2-Dihydro-1-((5-mercapto-1,3,4-oxadiazol-2-yl)-methyl)-2-oxoquinoline-3-carbaldehyde (12): A mixture of 2-(3-formyl-2-oxoquinolin-1(2*H*)-yl)acetohydrazide (**10**), (0.01 mol), KOH (0.01 mol), CS_2 (4 mL) and ethanol (15 mL) was heated under reflux until the evaluation of H_2S gas stoped. The resultant product was recrystallized from methanol. Yield 93 %, m.p. 145-148 ºC; IR (KBr, ν_{max}, cm^{-1}): 3191 (C-H, Ar), 2700 (S-H), 1492 (C=C), 1318 (C-N), 1282 (C-O), 1022 (N-N), 750 (C-S); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.55 (s, 1H, CHO), 7.71-6.16 (m, 4H, Ar), 6.18 (s, 2H, Ar), 2.85 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 187.7 (CHO), 164.1 (CONH), 162.4 (C-2, oxadiazole), 159.3 (C-5, oxadiazole),

143.3 (C-4, quinoline), 135.3 (C-6, quinoline), 129.7 (C-5, quinoline), 128.2 (C-8, quinoline), 126.6 (C-10, quinoline), 122.2 (C-3,9, quinoline), 117.5 (C-7, quinoline), 51.2 (CH_2); EI-MS (*m/z*): 287.03 (M^+); Anal. calcd. (found) % for $C_{13}H_9N_3O_3S$ (m.w. 287.29): C, 54.35 (54.31); H, 3.16 (3.10); N, 14.63 (14.36).

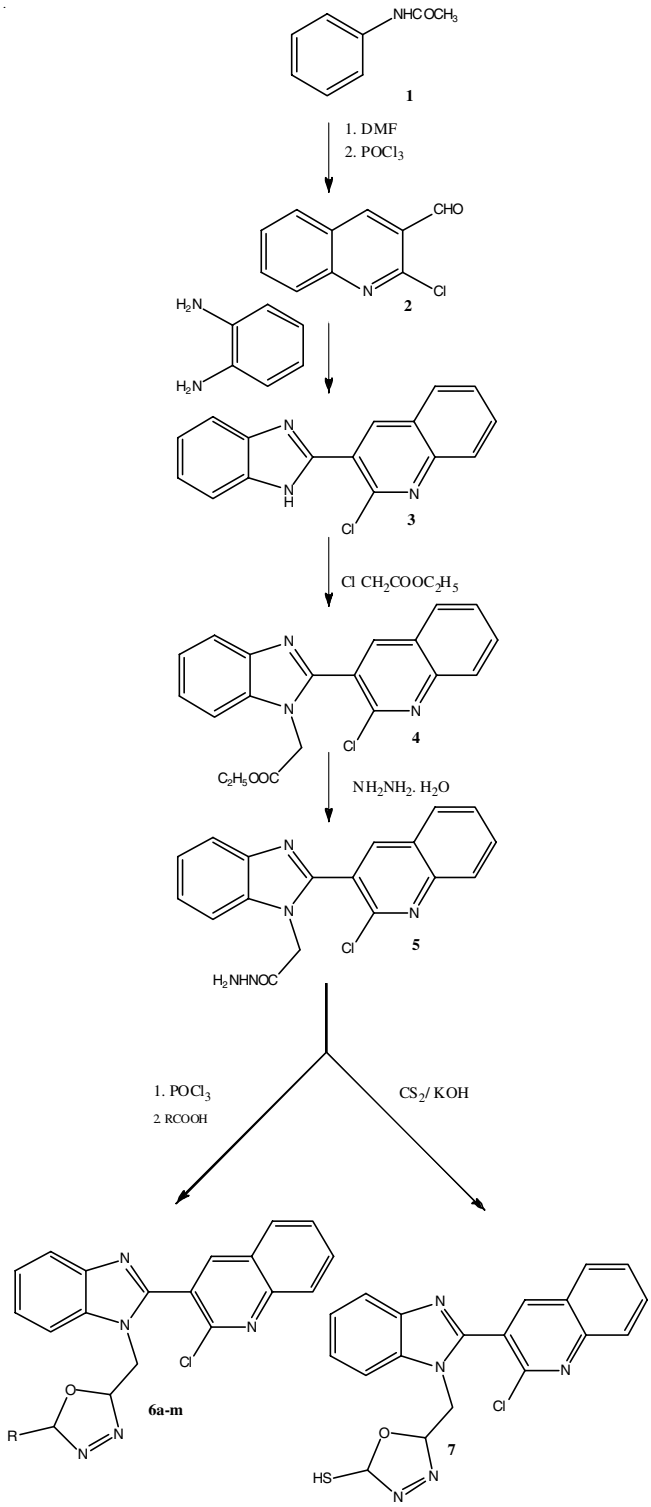
Biological activity: All the synthesized compounds were evaluated for their anticonvulsant effect using male albino mice (Swiss, 18-25 g). The qualitative evaluations were performed in mice involved two animal model for convulsion *i.e.* maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ).

Maximal electroshock seizure (MES) design test: The conduct of the animals and electrographic seizures produced in this model were steady with the human issue as revealed before. Animals were checked for affectability to electric stimuli 24 h preceding administration of test compounds and those animals which neglect to indicate hind limb tonic extension were rejected. Animals were assigned into control, standard and test groups. The control group received polyethylene glycol (30 % v/v, i.p.), standard group animals were given phenytoin (25 mg/kg, i.p.) [30] and test groups were injected with compounds **6a-m**, **7**, **11a-e** and **12** at previously selected doses. A 60 Hz cyclic current of 50 mA intensity for 0.2 s utilizing corneal terminals evoked maximal seizures. A drop of electrolyte solution (0.9 % NaCl) was applied to the corneal electrodes which ensure better contact to the animal [31]. The animal were observed for hind limb tonic extension and duration was noted *i.e.*, prevention or decline in the duration of hind limb extension was considered as defensive activity.

Subcutaneous pentylenetetrazole (scPTZ) design test: The subcutaneous pentylenetetrazole test was performed according to the known protocol [32]. This strategy utilizes pentylenetetrazole (75 mg/kg) that produces seizures in > 95 % of animals as 0.5 % solution subcutaneously in the back midline. Animals were assigned into control, standard and test groups. The control group received polyethylene glycol (30 % v/v) i.p., standard group animals were given phenytoin (25 mg/kg, i.p.) and test groups were injected with **6a-m**, **7**, **11a-e** and **12** at previously selected doses. After 1 h, the administration of these substances to the respective groups, all the animals of assigned groups were administered with pentylenetetrazole. Each animal was observed onset of clonus and tonic convulsions after definite period of time. Prevention or decline in the duration of onset of convulsions was considered as defensive activity.

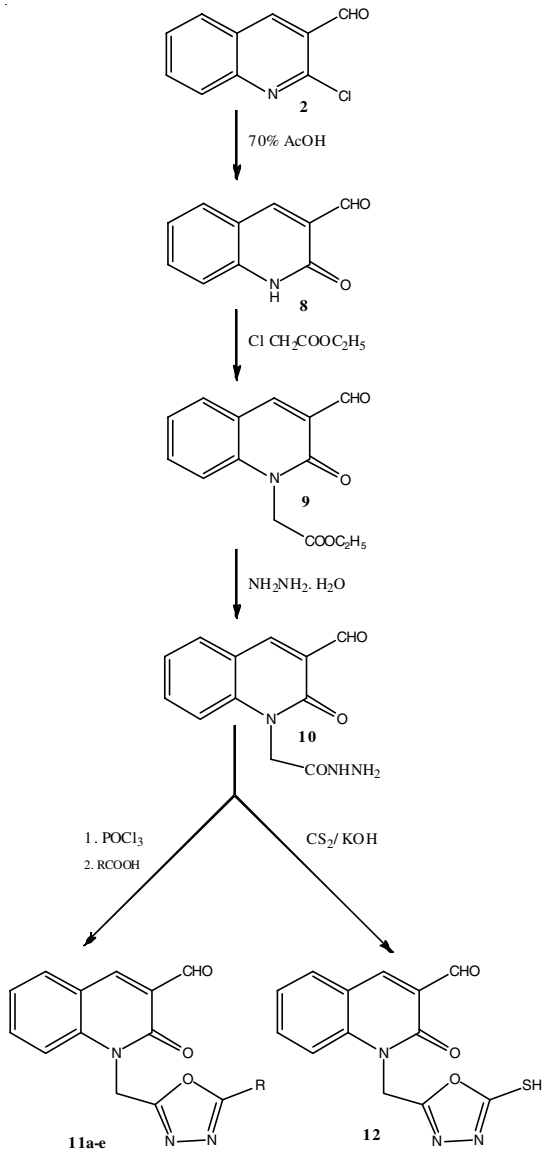
RESULTS AND DISCUSSION

In the present work, the synthesis route involved for the preparation of the compounds **6a-m** and **7** is depicted in **Scheme-I** and for compounds **11a-e** and **12**, it is depicted in **Scheme-II**. Vilsmeier-Haack reaction [28] was used which involve acetamide to synthesize 2-chloroquinoline-3-carbaldehyde (**2**). Reaction of compound **2** with *o*-phenylene diamine yielded 3-(1*H*-benzimidazole-2-yl)-2-chloroquinoline (**3**) and reaction with 70 % acetic acid afforded 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**8**) in the conditions as described earlier [29]. Compounds **3** and **8** were refluxed with chloroacetic acid to get ethyl [2-(2-chloroquinoline-3-yl)-1*H*-benzimidazole-1-yl)-acetate (**4**) and ethyl 2-(3-formyl-2-oxoquinolin-1(2*H*)-yl)-acetate (**9**), respectively. Compounds **4** and **9** were refluxed with hydrazine hydrate to give 2-[2-(2-choloroquinolin-3-yl)-1*H*-benzimidazole-1-yl]acetohydrazide (**5**) and 2-(3-formyl-2-oxoquinolin-1(2*H*)-yl)acetohydrazide (**10**), which on reaction with various substituted benzoic acids in the presence of $POCl_3$, gives 2-chloro-3-{1-[(5-substituted-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}quinolines (**6a-m**) and 1,2-dihydro-1-



R = Methoxyphenyl, 4-chlorophenyl, 2, 4-dichlorophenyl, 2 –OH phenyl, 2-chlorophenyl, pyridine-3-yl, 2- aminophenyl, 2-methoxyphenyl, 4- aminophenyl, benzyl, naphthalene-2-yloxy)methyl

Scheme-I



R = 4-methoxyphenyl, 4-nitrophenyl 3,5-dinitrophenyl, 3,5-dichlorophenyl, 2-chloro-4-fluorophenyl

Scheme-II

((5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methyl)-2-oxoquinoline-3-carbaldehydes (**11a-e**). On the other hand, refluxing compounds **5** and **10** in the presence of CS_2 and KOH yielded thiazole derivatives **7** and **12**, respectively.

All the newly synthesized compounds were isolated in moderate to good yield and the structures of all the compounds were established through spectroscopic (IR, ^{1}H NMR and mass) as well as elemental analyses data. In general, IR spectra of newly synthesized compounds **6a-m** revealed C-H Ar, C=C, C-N, C-O (oxadiazole) and N-N peaks near 3050, 1450, 1350, 1260 and 1050 cm^{-1}, respectively. In ^{1}H NMR spectra, signals of respective protons of newly synthesized compounds showed the peaks for aromatic protons in between δ 8.7-6.5 and presence of -OCH_2, -OH, -CH_2, -NH_2 and -OCH_3 were confirmed by the presence of singlets at δ 5.27, 4.85, 4.5, 3.8 and 3.73, respectively.

The appeared signals of IR spectra for compounds **11a-e** were 3050, 1670, 1600, 1470 and 1050 for C-H Ar, C=O, C=N, C=C and N-N str. vibrations while in ^{1}H NMR spectra, signals appeared for aromatic protons in between 7.89-6.04 which also consisting singlet of proton present on C-4 of quinoline. The presence of -CH_2 and -OCH_3 was confirmed by peaks in between 3.14- 4.14 and 3.99, respectively. ^{13}C NMR information additionally bolstered the structures of synthesized derivatives. So, both analytical and spectral data (IR, ^{1}H, ^{13}C NMR and mass) of all the synthesized compounds were in full agreement with the proposed structures.

On associating the structures of all synthesized compounds with their anticonvulsant action, it has been seen that compounds bearing the gatherings like methoxybenzene, aminobenzene, 2-pyridyl, 2-ethoxynaphthalene, benzyl, toluidine and cresol on oxadiazole ring have high potency in MES and scPTZ tests. Then again, supplanting of these gatherings with nitrobenzene, halobenzene and phenyl group on oxadiazole ring has brought about compounds with lesser anticonvulsant potential.

Anticonvulsant activity: The evaluation of synthesized compounds 2-chloro-3-{1-[(5-substituted-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}quinolines (**6a-m**), 5-{[2-(2-choloroquinolin-3-yl)-1*H*-benzimidazole-1-yl]methyl)-2,5-dihydro-1,3,4-oxadiazole-2-thiol (**7**), 1,2-dihydro-1-((5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methyl)-2-oxoquinoline-3-carbaldehydes (**11a-e**) and 1,2-dihydro-1-((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)-2-oxoquinoline-3-carbaldehyde (**12**) for anticonvulsant activity was done by the use of two most accepted animal models, MES [33,34] and scPTZ [35]. All the orchestrated compounds were administered intraperitoneally into mice utilizing dosages of 30, 100, 200 and 300 mg/kg. The perceptions were taken into account at two diverse time interims (0.5 and 4.0 h) and data is compiled in Table-1. Effect on locomotor activity of the entire synthesized compounds was determined against diazepam as reference by actophotometer and the data is shown in Table-2. Acute toxicity study (LD_{50}) was carried out to access any chance of toxic effect of synthesized derivatives towards increment of dose according to the OECD Guidelines No. 423 and the data is compiled in Table-3.

In maximal electroshock seizure (MES) test, among all the synthesized compounds **6h**, **6k**, **6l**, **6m** and **11a** had been found with very good anticonvulsant potential as all had shown protection at the dose level of 30 mg/kg against the seizure spread at both the time intervals 0.5 and 4 h while in scPTZ test, protection was shown at 100 mg/kg after 4 h. Compounds **6c**, **6f**, **6i**, **6j**, **7** and **12** had shown moderate activity in which compounds **6c** and **6f** had started showing protection at the dose level of 30 mg/kg after 0.5 h, but 100 mg/kg and 300 mg/kg were required after 4 h in MES and scPTZ, respectively which indicated rapid onset but shorter duration of action. Compounds **6I**, **6j**, **7** and **12** shown protection at the dose level of 100 mg/kg after 0.5 h and at 300 mg/kg after 4 h in both the animal models which indicated about longer onset and shorter duration of action. Compounds **6a**, **6b**, **6d**, **6g**, **11a**, **11d** and **11e** have shown very little activity as they shown protection at the dose level of 300 mg/kg in both the time interim in MES and in scPTZ test, they don't show protection after 4 h. Compounds **6e** and **11c** were found inactive due to heavy presence of electronegative substitute on phenyl ring.

Locomotor activity: Every animal was kept in actophotometer for 5 min and basal movement score was recorded for

TABLE-1
ANTICONVULSANT ACTIVITY OF SYNTHESIZED COMPOUNDS **6a-m**, **7, 11a-e** AND **12**

Compounds	Intraperitoneal injection in mice[a]					
	MES screen		ScPTZ			
	HLTE (s)		Onset of clonus(s)		Onset of tonic(s)	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
6a	300	300	300	–	300	–
6b	300	300	300	–	300	–
6c	30	100	30	300	30	300
6d	100	300	300	–	300	–
6e	–	–	–	–	–	–
6f	30	100	30	300	30	300
6g	300	–	300	–	300	–
6h	30	30	30	100	30	100
6i	100	300	100	300	100	300
6j	100	300	100	300	100	300
6k	30	30	30	100	30	100
6l	30	30	30	100	30	100
6m	30	30	30	100	30	100
7	100	300	100	300	100	300
11a	30	30	30	100	30	100
11b	300	–	300		300	
11c	–	–	–	–	–	–
11d	300	–	300	–	300	–
11e	300	–	300		300	
12	100	300	100	300	100	300
Phenytoin	30	30	–	–	–	–
Carbamazepine	–	–	100	100	100	100

[a]Administered doses were 30, 100, 200 and 300 mg/kg and above data indicate the minimum dose whereby bioactivity was exhibited down the middle or a greater amount of the mice. The tested mice were examined at 0.5 and 4 h. The (–) indicates an absence of activity at maximum dose administered (300 mg/kg).

TABLE-2
LOCOMOTOR ACTIVITY DATA OF SYNTHESIZED COMPOUNDS **6a-m**, **7**, **11a-e** AND **12**

Compd. No.	Basal Mean ± SEM	After treatment Mean ± SEM	% Reduction in locomotor activity
6a	404.6 ± 2.31	389.0 ± 1.73^{ns}	3.85
6b	400 ± 2.022	387.0 ± 0.77**	3.25
6c	399.6 ± 2.50	383.4 ± 1.16**	4.05
6d	396.2±2.24	384.2 ± 2.08**	3.02
6e	404 ± 3.05	389.0 ± 0.70*	3.71
6f	407.2 ± 2.47	386.6 ± 1.43*	5.05
6g	397.6 ± 1.20	390.0 ± 0.70^{ns}	1.91
6h	398.8 ± 2.57	387.8 ± 1.82*	2.25
6i	407.2 ± 2.15	380.0 ± 0.70**	6.67
6j	406.6 ± 2.31	387.8 ± 1.28*	4.62
6k	405.2 ± 2.22	389.0 ± 0.70*	3.99
6l	399 ± 1.51	389.0 ± 1.73^{ns}	2.50
6m	407.4 ± 2.08	390.2 ± 1.39^{ns}	4.22
7	401.4 ± 0.92	388.0 ± 1.14*	3.33
11a	408 ± 1.64	386.6 ± 1.43*	5.24
11b	411.8 ± 1.98	386.2 ± 1.06**	6.21
11c	398 ± 2.34	388.8 ± 0.48*	2.31
11d	406 ± 0.83	379.8 ± 0.80*	6.45
11e	398 ± 2.09	380.0 ± 0.70**	4.52
12	397 ± 2.60	389.0 ± 1.73^{ns}	2.01
PEG-400	384.4 ± 2.58	378.4 ± 3.64	1.56
Diazepam	382.2 ± 4.76	76.0 ± 2.58**	80.10

n = 5; Time span 5 min; The percent inhibition for each group was calculated by comparison with the control group. Dose = 30 mg/kg (p.o); All values expressed as mean ± SEM (n = 5). *P ≤ 0.05, **P ≤ 0.01 as compared with control. Data was analyzed by one-way ANOVA followed by Dunnett's test).

TABLE-3
ACUTE TOXICITY DATA OF SYNTHESIZED COMPOUNDS **6a-m, 7, 11a-e** AND **12**

Compounds	Number of animals dead/total number of animals tested				
	Dose (mg/kg), i.p.				
	20	50	100	200	400
Control	0/3	0/3	0/3	0/3	0/3
6a	0/3	0/3	0/3	0/3	0/3
6b	0/3	0/3	0/3	0/3	0/3
6c	0/3	0/3	0/3	1/3	2/3
6d	0/3	0/3	0/3	0/3	1/3
6e	0/3	0/3	0/3	0/3	1/3
6f	0/3	0/3	0/3	0/3	0/3
6g	0/3	0/3	0/3	0/3	1/3
6h	0/3	0/3	0/3	0/3	1/3
6i	0/3	0/3	0/3	0/3	1/3
6j	0/3	0/3	0/3	0/3	0/3
6k	0/3	0/3	0/3	0/3	1/3
6l	0/3	0/3	0/3	0/3	1/3
6m	0/3	0/3	0/3	0/3	0/3
7	0/3	0/3	0/3	1/3	2/3
11a	0/3	0/3	0/3	0/3	1/3
11b	0/3	0/3	0/3	1/3	2/3
11c	0/3	0/3	0/3	1/3	2/3
11d	0/3	0/3	0/3	0/3	1/3
11e	0/3	0/3	0/3	0/3	1/3
12	0/3	0/3	0/3	1/3	2/3
Phenytoin	0/3	0/3	0/3	0/3	2/3
Carbamazepine	0/3	0/3	0/3	0/3	2/3

all. After 0.5 h of the various administered doses, animal's locomotor conduct was checked utilizing same actophotometer [36]. Deceased action score was taken as file of CNS dejection and percentage reduction in locomotor activity was compiled in Table-2. It was found that no significant reduction caused by active synthesized compounds.

Acute toxicity study: The diverse dosages of most active compounds were dissolved in PEG-400 and intraperitoneally administered into mice and the changes in conducts were seen and contrasted with phenytoin and carbamazepine. Unlike the standard drugs, it was found that the among the active compounds **6h**, **6k**, **6l**, **6m** and **11a** shown no mortality (0/3) at any of the dosage levels *i.e*., 20, 50 and 100 mg/kg. Be that as it may, the animals have appeared few unsafe signs, for instance, gnawing, licking, and salivation after brief time of sedation. Compounds **6c**, **7**, **11b**, **11c** and **12** exhibited mortality at the dose dimension of 200 mg/kg (1/3) and at the dose dimension of 400 mg/kg (2/3). There was not hurtfulness found in PEG-400 as vehicle alone as clear in the control event of animals (Table-3).

Conclusion

The present results have revealed that synthesized 2-chloro-3-(1-(5-substituted-1,3,4-oxadiazaol-2-yl)methyl)-1*H*-benzo[*d*]imidazole-2-yl)quinoline (**6a-m**) and 1,2-dihydro-1-((5-substituted-1,3,4-oxadiazaol-2-yl)methyl)-2- oxoquinoline-3-carbaldehyde (**11a-e**) exhibit a range of activity in anticonvulsant screening in dose dependent manner. Compounds **6h**, **6k**, **6l**, **6m** and **11a** are found to be most prominent as they cause abolition of the hind limb tonic extensor component in MES test and increased both onset of clonus and onset of tonic convulsions in scPTZ test. These compounds can be tools for ligand-based drug design purposes, which can further explore the chances of discovery of more potent molecule for the treatment of convulsion in human in near future.

ACKNOWLEDGEMENTS

The authors are highly thankful to Prof. Dr. O.P. Agarwal, Managing Director, Noida Institute of Engineering & Technology, Greater Noida, India, for providing the necessary research facilities. The authors are also grateful to Dr. Avijit Mazumder, Director, NIET Pharmacy Institute, Greater Noida, India for his continuous motivation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. J. Lopes Lima, *Curr. Pharm. Des.*, **6**, 873 (2000); https://doi.org/10.2174/1381612003400308.
2. M. Berk, J. Segal, L. Janet and M. Vorster, *Drugs*, **61**, 1407 (2001); https://doi.org/10.2165/00003495-200161100-00004.
3. P. Czapin'ski, B. Blaszczyk and S.J. Czuczwar, *Curr. Top. Med. Chem.*, **5**, 3 (2005); https://doi.org/10.2174/1568026053386962.
4. J.O. McNamara, Pharmacotherapy of the Epilepsies, In: Goodman and Gilman's: The Pharmacological Basis of Therapeutics, Chap. 21, 521 (2001).
5. P.K. Kadaba and Z. Lin, Hydrazones, Hydrazines, Semicarbazones and Thiosemicarbazones Derived from Pyridyl Ketones as Anticonvulsant Drugs and Excitatory Amino Acid Antagonists, US Patent 5942527 (1999).
6. B.N. Prasanna Kumar, K.N. Mohana and L. Mallesha, *J. Chem.*, **2013**, 1 (2013); https://doi.org/10.1155/2013/121029.
7. C.W. Bazil and T.A. Pedley, *Annu. Rev. Med.*, **49**, 135 (1998); https://doi.org/10.1146/annurev.med.49.1.135.
8. C.S. Andotra and B.S. Manhas, *Acta Cienc. Indica Chem.*, **18**, 99 (1992).
9. Y. Özkay, Y. Tunal, H. Karaca and l. Isikdag, *Arch. Pharm. Res.*, **34**, 1427 (2011); https://doi.org/10.1007/s12272-011-0903-8.
10. D. Kaminsky and R.I. Meltzer, *J. Med. Chem.*, **11**, 160 (1968); https://doi.org/10.1021/jm00307a041.
11. M.P. Hutt, E.F. Elslager and L.M. Werbel, *J. Heterocycl. Chem.*, **7**, 511 (1970); https://doi.org/10.1002/jhet.5570070308.
12. A. Kamil, S. Akhter, M. Ahmed, G.H. Rizwani, S. Hassan, S. Naeem, S. Jahan, R. Khursheed and H. Zahid, *Pak. J. Pharm. Sci.*, **28**, 2179 (2015).
13. M. Foley and L. Tilley, *Pharmacol. Ther.*, **79**, 55 (1998); https://doi.org/10.1016/S0163-7258(98)00012-6.
14. B. Silvestrini and C. Pozzatti, *Br. J. Pharmacol.*, **16**, 209 (1961); https://doi.org/10.1111/j.1476-5381.1961.tb01080.x.
15. S.N.A. Bukhari, G. Lauro, I. Jantan, C. Fei Chee, M.W. Amjad, G. Bifulco, H. Sher, I. Abdullah and N.A. Rahman, *Future Med. Chem.*, **8**, 1953 (2016); https://doi.org/10.4155/fmc-2016-0062.
16. S. Mukherjee and M. Pal, *Curr. Med. Chem.*, **20**, 4386 (2013); https://doi.org/10.2174/09298673113209990170.
17. P. Sengupta, M. Mal, S. Mandal and J. Singh and T.K. Maity, *Iran. J. Pharmacol. Therap.*, **7**, 165 (2008).
18. R.S. Kankate, P.S. Gide and D.P. Belsare, *Arab. J. Chem.*, (2015) (in press); https://doi.org/10.1016/j.arabjc.2015.02.002.
19. R. Musiol, M. Serda, S. Hensel-Bielowka and J. Polanski, *Curr. Med. Chem.*, **17**, 1960 (2010); https://doi.org/10.2174/092986710791163966.
20. A.-M.M.E. Omar and O.M. Aboulwafa, *J. Heterocycl. Chem.*, **21**, 1415 (1984); https://doi.org/10.1002/jhet.5570210538.
21. A. Zarghi, M. Faizi, B. Shafaghi, A. Ahadian, H.R. Khojastehpoor, V. Zanganeh, S.A. Tabatabai and A. Shafiee, *Bioorg. Med. Chem. Lett.*, **15**, 3126 (2005); https://doi.org/10.1016/j.bmcl.2005.04.018.
22. A. Almasirad, S.A. Tabatabai, M. Faizi, A. Kebriaeezadeh, N. Mehrabi, A. Dalvandi and A. Shafiee, *Bioorg. Med. Chem. Lett.*, **14**, 6057 (2004); https://doi.org/10.1016/j.bmcl.2004.09.072.
23. B. Bhrigu, N. Siddiqui and D. Pathak, *Acta Pol. Pharm. Drug Res.*, **69**, 53 (2012).
24. L.-J. Guo, C.-X. Wei, J.-H. Jia, L.-M. Zhao and Z.-S. Quan, *Eur. J. Med. Chem.*, **44**, 954 (2009); https://doi.org/10.1016/j.ejmech.2008.07.010.
25. H.-G. Jin, X.-Y. Sun, K.-Y. Chai, H.-R. Piao and Z.-S. Quan, *Bioorg. Med. Chem.*, **14**, 6868 (2006); https://doi.org/10.1016/j.bmc.2006.06.044.
26. L.-P. Guan, Q.-H. Jin, G.-R. Tian, K.-Y. Chai and Z.-S. Quan, *J. Pharm. Pharm. Sci.*, **10**, 254 (2007).
27. R. Morphy and Z. Rankovic, *J. Med. Chem.*, **48**, 6523 (2005); https://doi.org/10.1021/jm058225d.
28. A. Srivastawa and R.M. Singh, *Indian J. Chem.*, **44B**, 1868 (2005).
29. P. Balvantrao Sattur, N. Bhanumathi and K. Rama Rao, *Heterocycles*, **24**, 1683 (1986); https://doi.org/10.3987/R-1986-06-1683.
30. E.A. Swinyard, W.C. Brown and L.S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952).
31. W. Löscher and D. Schmidt, *Epilepsy Res.*, **2**, 145 (1988); https://doi.org/10.1016/0920-1211(88)90054-X.
32. C.R. Clark, M.J.M. Wells, R.T. Sansom, G.N. Norris, R.C. Dockens and W.R. Ravis, *J. Med. Chem.*, **27**, 779 (1984); https://doi.org/10.1021/jm00372a013.
33. R.L. Krall, J.K. Penry, B.G. White, H.J. Kupferberg and E.A. Swinyard, *Epilepsia*, **19**, 409 (1978); https://doi.org/10.1111/j.1528-1157.1978.tb04507.x.
34. S.M. Tasso, S.C. Moon, L.E. Bruno-Blanch and G.L. Estiú, *Bioorg. Med. Chem.*, **12**, 3857 (2004); https://doi.org/10.1016/j.bmc.2004.05.003.
35. R.J. Porter, J.J. Cereghino, G.D. Gladding, B. Hessie, H.J. Kupferberg, B. Scoville and B.G. White, *Cleve. Clin. Q.*, **51**, 293 (1984); https://doi.org/10.3949/ccjm.51.2.293.
36. P.B. Dews, *Br. J. Pharmacol. Chemother.*, **8**, 46 (1953); https://doi.org/10.1111/j.1476-5381.1953.tb00749.x.