A REVIEW ON ANTICONVULSANT ACTIVITY OF 1, 3-BENZODIOXOLE RING SYSTEM BASED COMPOUNDS

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ABSTRACT: 1, 3-Benzodioxole ring system present in various naturally occurring molecules. Various synthetic molecules having 1, 3-Benzodioxole ring system have shown various biological activities. Stiripentol and Antiepilepserine are recently developed antiepileptic drugs which contain 1, 3-Benzodioxole rings system in core moiety. In the present work I have focused on the anticonvulsant activity of 1, 3-Benzodioxole ring system based compounds.

INTRODUCTION: 1, 3-Benzodioxole ring system present in various naturally occurring molecules like Piperonal, Sesamol, Saffrole, Myristicin etc. 1, 3-benzodioxole ring system has been considered as magic moiety (wonder nucleus), which is a core structure in various synthetic compounds displaying a broad spectrum biological activities (Fig. 1.1).

Benzodioxole moiety can be found in different well established anticancer 18, anticonvulsant 23 agents.

A large number of compounds having 1,3-benzodioxole ring system has been reported to possess different kind of biological activity like anticancer 1-5, anticonvulsant 6a,7, antidepressant 9, 10, anti-inflammatory 8, antihypertensive 14, antioxidant 4, antiprotozoal 11, anti-vitiligo 12, immunomodulatory 13.

Literature review on Anticonvulsant Activity: Mori et al. [15], evaluated the effects of Piperine (1-[5-(1, 3-benzodioxol-5yl)-1-oxo-2, 4-pentadienyl]piperidine) (Fig. 1.2) on convulsions and on brain levels of serotonin and catecholamine in E1 mice. Piperine completely suppressed the convulsions of E1 mice at a dose of 60 mg/kg after intraperitoneal administration. The levels of 5-HT and dopamine found significantly higher in the cerebral cortex and hypothalamus respectively after one hour of intraperitoneal administration of piperine at a dose of 60 mg/kg. Although level of norepinephrine found lower in the treated mice.
Vartayan et al. synthesized a series of N-substituted imides of 1, 3-benzodioxole-2-carboxy-2-acetic acid (Fig. 1.3) and N-substituted derivatives of spiro (1,3-benzodioxole-2,3’-pyrrolidine) (Fig. 1.4) from Diethyl 1,3-benzodioxole-2-carboxy-2-acetate and the corresponding diacid. Anticonvulsant activity of the series evaluated using MES test model in which compound named 1’-(propan-2-yl)-2’H,5’H-spiro[1,3-benzodioxole-2,3’-pyrrolidine]-2’,5’-dione (1.3a) and 1’-butylspiro[1,3-benzodioxole-2,3’-pyrrolidine] (1.4a) was found most protective against seizures with ED$_{50}$ value of 120 mg/kg and 74 mg/kg respectively.

Pelletier et al. synthesized a series of substituted 1,2 Dihydropthalazines (Fig. 1.5) and screened it for its ability to inhibit AMPA receptor currents using initial concentration of 10µM. Compound named 8-(4-aminophenyl)-5-methyl-N-propyl[1,3]dioxolo[4,5-g]phthalazine-6(5H)-carboxamide (1.5a) was found most potent in the screening with IC$_{50}$ value of 1.8µM.

Compound named 8-(4-aminophenyl)-5-methyl-N-butyl [1,3]dioxolo[4,5-g]phthalazine-6(5H)-carboxamide (1.5b) was also tested against seizures induced by MES in mice and found active with ED$_{50}$ (30mg/kg) after intraperitoneal administration.

Sarro et al. synthesized a series of novel 7, 8-methylenedioxy-4 H -2, 3-benzodiazepin-4-ones (Fig. 1.6) and evaluated the series for anticonvulsant activity against audiogenic seizures in DBA/2 mice initially. Most active derivatives 5-phenyl-7,9-dihydro-8H-[1,3]dioxolo[4,5-h][2,3]benzodiazepin-8-one (1.6a), 5-(3-aminophenyl)-7,9-dihydro-8H-[1,3]dioxolo[4,5-h][2,3]benzodiazepin-8-one (1.6b) and 5-(4-aminophenyl)-7,9-dihydro-8H-[1,3]dioxolo[4,5-h][2,3]benzodiazepin-8-one (1.6c) from initial screening were also tested against MES, scPTZ and AMPA induced seizures and found active.
Anderson et al. synthesized a series of 3-aryl-5H-2,3-benzodiazepines (Fig. 1.7) with N-3 aromatic substituents and screened for anticonvulsant activity using MES test in mice at a dose of 10mg/kg. Compound named 4-[(8R)-8-methyl-7-(pyridin-2-yl)-8, 9-dihydro-7H-[1, 3]dioxolo[4, 5-h][2, 3]benzodiazepin-5-yl]aniline (1.7a) found most active in the screening with ED$_{50}$ value 0.76 mg/kg.

![Fig. 1.7: 3-ARYL-5H-2, 3-BENZODIAZEPINES](image)

Wang et al. [20], synthesized a series of 7,8-(methylenedioxy)-1-phenyl-3,5-dihydro-4H-2,3-benzodiazepin-4-ones (Fig. 1.8) and assayed for antagonism of rat brain AMPA receptors. Compound named 1-(4-Aminophenyl)-7,8-(methylenedioxy)-3,5-dihydro-4H-2,3-benzodiazepine-4-one (1.8a) exhibited most potent antagonistic effect with a IC$_{50}$ value of 2.7µM. Anticonvulsant activity of compound (1.8a) was also evaluated against MES induced seizures in which it was found active with an ED$_{50}$ value of 2.8 mg/kg after intravenous administration.

![Fig. 1.8: 7, 8-(METHYLENEDIOXY)-1-PHENYL-3, 5-DIHYDRO-4H-2,3-BENZODIAZEPINE-4-ONES](image)

Sarro et al. synthesized a series of novel 1-aryl-3,5-dihydro-7, 8-methylenedioxy-4H-2, 3-benzodiazepin-4-ones (Fig. 1.9) and screened for anticonvulsant activity against sound induced seizures in DBA/2 mice, MES induced seizures and PTZ induced seizures in Swiss mice. Compound named 5-(4-aminophenyl)-7,9-dihydro-8H-[1,3]dioxolo[4,5-h][2,3]benzodiazepin-8-one (1.9a) exhibited the maximum protection against sound induced seizures in DBA/2 mice with ED$_{50}$ value 10.9 µmol/kg (tonic) and 21.8 µmol/kg (clonic). Compound named 5-(3-aminophenyl)-7,9-dihydro-8H-[1, 3]dioxolo[4,5-h][2,3]benzodiazepin-8-one (1.9b) found most protective against seizures induced by MES and scPTZ with ED$_{50}$ value 19.3µmol/kg and 40.5µmol/kg respectively. Compound (1.9b) also exhibited maximum protection against AMPA induced seizures in DBA/2 mice with ED$_{50}$ value 23.8 µmol/kg (tonic) and 29.2 µmol/kg (clonic).

![Fig. 1.9: 1-ARYL-3, 5-DIHYDRO-7, 8-METHYLENE DIOXY-4H-2, 3-BENZODIAZEPIN-4-ONES](image)

Grasso et al. synthesized a series of 3-(N-alkylcarbamoyl)-1-aryl-3,5-dihydro-7,8-methylenedioxy-4H-2,3-benzodiazepin-4 ones (Fig. 1.10) and 1-aryl-3,5-dihydro-7,8-methylene dioxo-4H-2,3-benzodiazepine-4-thiones (Fig. 1.11) and screened for anticonvulsant against audiogenic seizures in DBA/2 mice and seizures induced by MES and scPTZ in swiss mice. Compounds of series (1.10) and (1.11) were also screened against AMPA induced seizures in DBA/2 mice to correlate the anticonvulsant activity of novel
compounds with their affinity for AMPA receptors. Active compounds obtain from initial screening furthermore tested against KA induced seizures. Afterward the screening against models used by the authors, compounds named 1-(4-Aminophenyl)-3,5- dihydro-3-methylcarbamoyl-7,8-methylene dioxy-4H benzodiazepine-4-one (1.10a) and 1-(4-Aminophenyl)-3,5-dihydro-7,8- methylene dioxy-4H-2,3-benzodiazepine-4-thione (1.11a) emerged as most promising compounds with ED$_{50}$ value 18.6µmol/kg and 9.76µmol/kg respectively after intraperitoneal administration in MES test model. Compounds (1.10a) and (1.11a) exhibited the ED$_{50}$ value 16.3µmol/kg and 25.2µmol/kg respectively in scPTZ test model after intraperitoneal administration.

All the synthesized compounds screened for their anticonvulsant activity against audiogenic induced seizures in DBA/2 mice after intraperitoneal administration. Compound 4-(4-aminophenyl)-2-butylcarbamoyl-6,7-methylene dioxyphthalalazine-1(2H)-one (1.13a) was found most active with ED$_{50}$ value 3.25µmol/kg and long lasting anticonvulsant activity. Compound (1.13a) was also found active against seizures induced by MES, scPTZ, AMPA, ATPA. Compound (1.13a) also found protective against KA induced seizures with ED$_{50}$ value 38.9µmol/kg after intraperitoneal administration.

Grasso et al. $^{23}$ synthesized a group of novel substituted 4-aryl-6, 7 methylene dioxyphthalalazine-1(2H)-ones (Fig. 1.12), 2-(N-alkylcarbamoyl)-4-aryl-6,7-methylenedioxyphthalazin-1(2H)-ones (Fig. 1.13) and 4-aryl-6,7-methylenedioxyphthalazine-1(2H)-thiones (Fig. 1.14).
Grasso et al. synthesized a series of novel 1-aryl-7, 8-methylenedioxy-1, 2, 3, 5-tetrahydro-4H-2, 3-benzodiazepin-4-ones (Fig. 1.15) with their 3-N-alkyl carbamoyl derivatives and screened for anticonvulsant activity against audiogenic seizures in DBA/2 mice. Most of the synthesized compounds showed a remarkable anticonvulsant activity but compound named 5-(4-aminophenyl)-7,9-dihydro-8H-[1,3]dioxolo[4,5-h][2,3] benzodiazepin-8-one (1.15a) emerged as most promising compound. Compound (1.15a) further tested against seizures induced by MES, scPTZ and found protective with ED50 value 35.7µmol/kg and 59.7µmol/kg respectively after intraperitoneal administration. Compound (1.15a) was also found protective against AMPA and KA induced seizures with ED50 value 24.6µmol/kg (clonic phase) and 17.5µmol/kg (tonic phase) for AMPA induced seizures while 15.9µmol/kg for KA induced seizures. Compound (1.15a) also reduced the KA evoked current in cerebellar granule neurons grown in primary cultures by 38% at a dose of 100µM.

Zappal et al. synthesized 5 -(4-Amino benzyl)-7,9-dihydro-8 H-[1,3]dioxolo[4,5-h][2,3]benzodiazepine-8-one (Fig. 1.17) & 7, 9-di hydro-5-[2-(pyridine-2-yl)-vinyl]-8H-[1,3]dioxolo [4,5-h][2,3]benzodiazepine-8-one (Fig. 1.18) and screened for anticonvulsant activity in DBA/2 mice against sound induced seizures. Compound (1.17) exhibited weak anticonvulsant activity against audiogenic induced seizures at ED50 value 81.2µmol/kg (clonic phase) and 65.52µmol/kg (tonic phase). Although compound (1.17) was unable to prevent the clonic phase of audiogenic seizures but reduces the tonic phase of the audiogenic seizures at ED50 VALUE 24.1µmol/kg. Compound (1.17) also inhibited the kainate induced current in a primary culture of rat cerebellar granule cells by 20% at 100µM dose.

Fig. 1.15: 1-aryl-7,8-methylenedioxy-1,2,3,5-tetrahydro-4H-2,3- benzodiazepin-4-ones

Fig. 1.16: 2-[(4-ALKYLSEMICARBAZONO)-(4-AMINO PHENYL METHYL)]-4, 5- METHYLENEDIOXY PHENYL ACETIC ESTERS

Fig. 1.17: 5 -(4-AMINO BENZY)- 7,9- DIHYDRO- 8 H- [1,3]DIOXOLO[4,5-H][2,3]BENZODIAZEPINE-8-ONE
Micale et al. synthesized a series of 1-substituted 2-[(4-aryl)-methyl]-4, 5-methylenedioxybenzene derivatives (Fig. 1.19) and tested them for anticonvulsant activity in DBA/2 mice against sound induced seizures. Most of the new compounds found active against seizures but compound named (Z)-2-[(4-chloro phenyl)-(4-methyl thiosemicarbazono)-methyl]-4,5-methylene dioxy phenyl acetic acid methyl ester (1.19a) was most protective from the series against audiogenic seizures with ED₅₀ value of 24.7μmol/kg (clonic phase) and 19.6μmol/kg (tonic phase).

Enein et al. synthesized series of stiripentol analogues namely 2-[(1E)-1-(1,3-benzodioxol-5-yl)-4,4-di-methylpent-1-en-3-ylidene]-N-(aryl/H)hydrazine carboxamides (Fig. 1.20), (±)-5(RS)-N-(aryl/H)-(1,3-benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazole-1-carboxamides (Fig. 1.21) and (±)-(5RS)-(1,3-benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazol-1-yl)(aryl) methanones (Fig. 1.22).

All the compounds screened for anticonvulsant activity using scPTZ and MES test models. Compound named 2-[(1E)-1-(1,3-benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene] hydrazine carboxamide (1.20a) found most active in MES test with ED₅₀ value of 87mg/kg, while compound named (±)-(5RS)-(1,3-Benzodioxol-5-yl)-3-tert-butyl-4,5-dihydro-1H-pyrazol-1-yl](4-bromo phenyl) (1.22a) found most active in scPTZ test with ED₅₀ value of 110mg/kg.
CONCLUSION: Various 1, 3-Benzodioxole ring system based compounds synthesized and studied frequently in past and exhibited various biological activities. This article mainly focused on anticonvulsant activity of 1, 3-Benzodioxole ring system based compounds. After studying various derivatives it is concluded that compounds based on the 1, 3-Benzodioxole ring system have gained popularity in recent years and seems promising for the development of newer and effective antiepileptic drugs.

REFERENCES:


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