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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-Benzodioxle 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].

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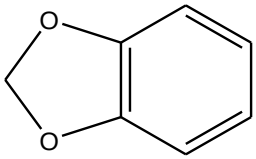


FIG. 1.1: STURCTURE OF 1, 3– BENZODIOXOLE RING SYSTEM

Literature review on Anticonvulsant Activity: Mori *et al.* [15], evaluated the effects of Piperine (1-[5-(1, 3-benzodioxol-5yl)-1-oxo-2, 4-penta dienyl]piperidine) (**Fig. 1.2**) on convulsions and on brain levels of serotonin and catecholamine in E_1 mice. Piperine completely suppressed the convulsions of E_1 mice at a dose of 60 mg/kg after intraperitoneal administration. The levels of 5-HT and dopamine found significantly higher in the cereberal 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.

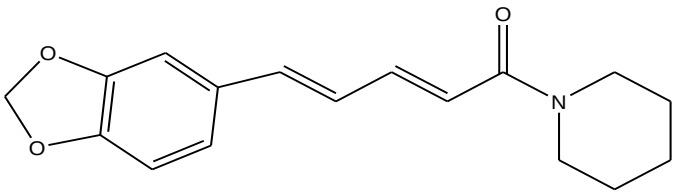
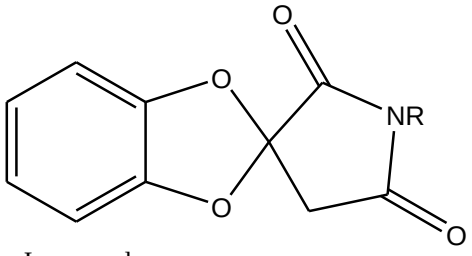


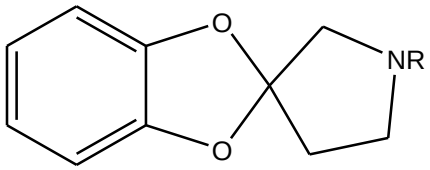
FIG. 1.2: PIPERINE

Vartayan *et al* [16], 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) and1'-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.



R: (1.3a) - Iso propyl

FIG. 1.3: N-SUBSTITUTED IMIDES OF 1, 3-BENZODIOXOLE-2-CARBOXY-2-ACETIC ACID

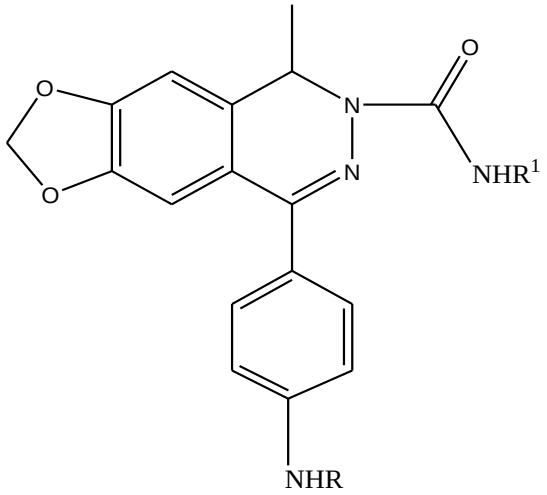


R: (1.4a) - Butyl

FIG. 1.4: N-SUBSTITUTED DERIVATIVES OF SPIRO (1, 3- BENZODIOXOLE-2, 3'-PYRROLIDINE)

Pelletier *et al* [17], synthesized a series of substituted 1,2 Dihydrophthalazines (**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(5*H*)-carboxamide (1.5a) was found most potent in the screening with IC_{50} value of 1.8µM.

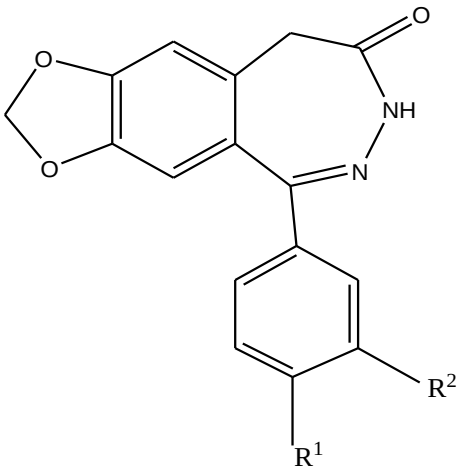
Compound named 8-(4-aminophenyl)-5-methyl-*N*-butyll [1,3] dioxolo[4,5-*g*]phthalazine-6(5*H*)-carboxamide (1.5b) was also tested against seizures induced by MES in mice and found active with ED_{50} (30mg/kg) after intraperitoneal administration.



R	**R[1]**
(1.5a) – H	n C_3H_7
(1.5b) – H	n C_4H_9

FIG. 1.5: SUBSTITUTED 1,2 DIHYDROPHTHAL AZINES

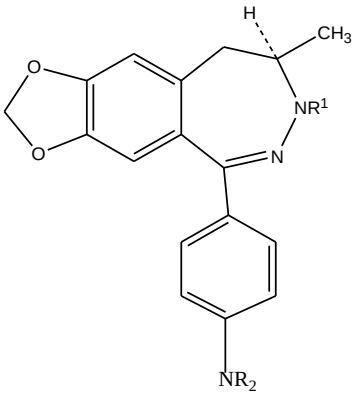
Sarro *et al* [18] synthesized a series of novel 7, 8-methylenedioxy- 4 H -2, 3- benzodiazepin- 4-ones (**Fig. 1.6**) and evaluated the series for anticonvulsant activity against audiogenic seizures in DBA/2 mice initially. Most active derivatives 5-phenyl-7,9-dihydro-8*H*-[1,3]dioxolo[4,5-*h*][2,3] benzodiazepin-8-one (1.6a), 5-(3-aminophenyl)-7,9-dihydro-8*H*-[1,3]dioxolo[4,5-*h*][2,3] benzodi azepin-8-one (1.6b) and 5-(4-aminophenyl)-7,9-dihydro-8*H*-[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.



R[1]	**R[2]**
(1.6a) – H	H
(1.6b) – H	NH_2
(1.6C) – NH_2	H

FIG. 1.6: 7, 8- METHYLENEDIOXY- 4 H -2,3- BENZO DIAZEPIN- 4-ONES

Anderson *et al* [19] 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-[(8*R*)-8-methyl-7-(pyridin-2-yl)-8, 9-dihydro-7*H*-[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 .



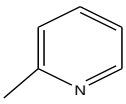
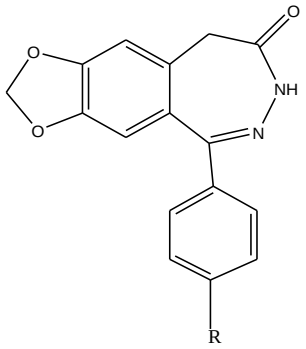
R	R^1
(1.7a) - H	

FIG.1.7: 3-ARYL-5H-2, 3-BENZODIAZEPINES

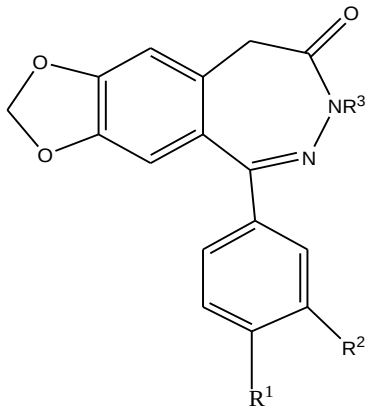
Wang *et al.* [20], synthesized a series of 7,8-(methylenedioxy)-1-phenyl-3,5-dihydro-4H- 2,3-benzodiazepin- 4- ones (**Fig. 1.8**) and assayed for antagonism of rat brain AMPA receptors. Compound named 1-(4-Aminophenyl)-7,8-(methylenedioxy)- 3,5- dihydro- 4H-2,3 – benzodiazepine- 4- one (1.8a) exhibited 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 a ED_{50} value of 2.8 mg/kg after intravenous administration.



R
(1.8a) – NH_2

FIG. 1.8: 7, 8- (METYLENEDIOXY)-1-PHENYL-3, 5-DIHYDRO-4H- 2,3- BENZODIAZEPIN- 4- ONES

Sarro *et al* [21] synthesized a series of novel 1-aryl-3, 5-dihydro-7, 8-methylenedioxy-4H-2, 3-benzo diazepin-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-8*H*-[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-8*H*-[1, 3]dioxolo[4,5-*h*][2,3] benzo diazepin-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).

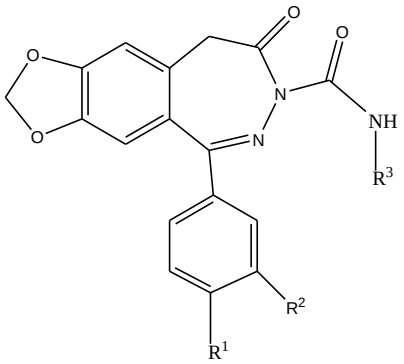


R^1	R^2	R^3
(1.9a) – NH_2	H	H
(1.9b) – H	NH_2	H

FIG. 1.9: 1-ARYL-3, 5-DIHYDRO-7, 8-METHYLENE DIOXY-4H-2, 3- BENZODIAZEPIN-4-ONES

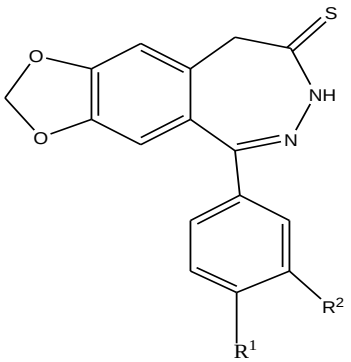
Grasso *et al* [22] synthesized a series of 3-(N-alkylcarbamoyl)-1-aryl-3,5- dihydro-7,8-methylenedioxy- 4H- 2,3-benzodiazepin-4 ones (**Fig. 1.10**) and 1-aryl- 3,5-dihydro-7,8-methylene dioxy-4H-2,3-benzodiazepine-4-thiones (**Fig. 1.11**) and screened for anticonvulsant against audiogenic seizures 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-metylcarbamoyl- 7, 8-methylenedioxy- 4H benzodiazepine- 4- one (1.10a) and 1-(4-Aminophenyl)-3,5-dihydro-7,8-methylenedioxy- 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 and25.2µmol/kg respectively in scPTZ test model after intraperitoneal administration.



	R^1	R^2	R^3
(1.10a) –	NH_2	H	CH_3

FIG. 1.10: 3-(N-ALKYLCARBAMOYL)-1-ARYL-3,5-DIHYDRO-7, 8-METHYLENEDIOXY- 4H- 2,3-BENZODIAZEPIN-4 ONES



	R^1	R^2
(1.11a) -	NH_2	H

FIG. 1.11: 1-ARYL-3, 5-DIHYDRO-7, 8-METHYLENE DIOXY-4H-2,3-BENZODIAZEPINE-4-THIONES

Grasso *et al* [23] synthesized a group of novel substituted 4-aryl-6, 7 methylenedioxyphthalazin-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-methylenedi oxyphthalazine-1(2H)-thiones (**Fig. 1.14**).

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-methylenedioxyphthalazin-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.

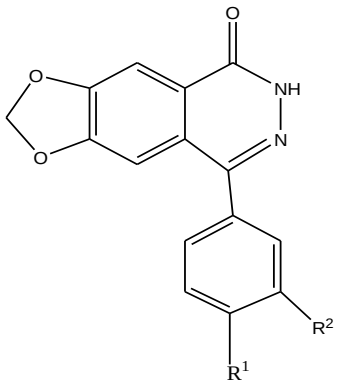
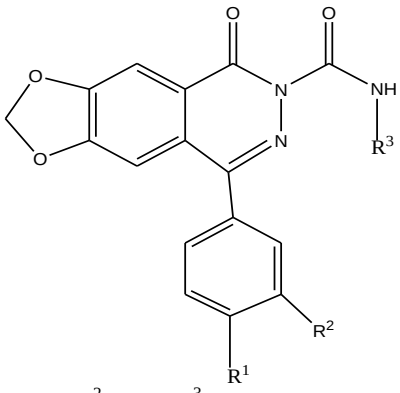


FIG. 1.12: SUBSTITUTED 4-ARYL-6, 7-METHYLENE DIOXYPHTHALAZIN-1(2H)-ONES



	R^1	R^2	R^3
(1.13a) -	NH_2	H	C_6H_{11}

FIG. 1.13: 2-(N-ALKYLCARBAMOYL)-4-ARYL-6, 7-METHYLENEDI OXYPHTHALAZIN-1(2H)-ONES

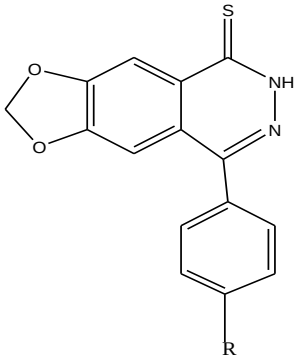
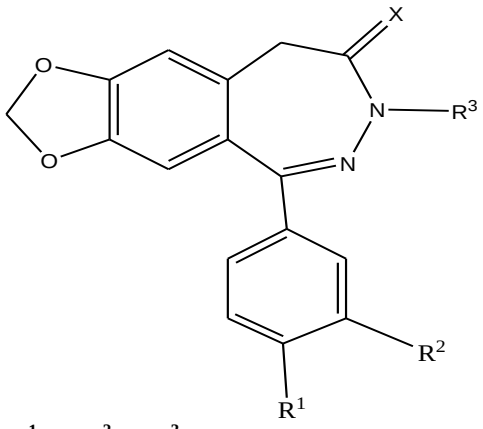


FIG. 1.14: 4-ARYL-6, 7-METHYLENEDIOXYPHTHALAZINE-1(2H)-THIONES

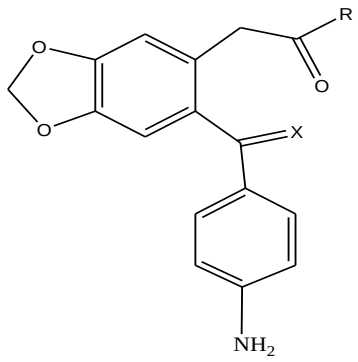
Grasso *et al* [24] synthesized a series of novel 1-aryl-7, 8-methylenedioxy-1, 2, 3, 5-tetrahydro-4H-2, 3-benzodiazepin-4-ones (**Fig. 1.15**) with their 3-N-alkyl carbamoyl derivatives and screened for anticonvulsant activity against audiogenic seizures in DBA/2mice. Most of the synthesized compounds showed a remarkable anticonvulsant activity but compound named 5-(4-aminophenyl)-7,9-dihydro-8*H*-[1,3]dioxolo[4,5-*h*][2,3] benzodi azepin-8-one (1.15a) emerged as most promising compound. Compound (1.15a) further tested against seizures induced by MES, scPTZ and found protective with ED_{50} 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 ED_{50} 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.



	R^1	R^2	R^3	X
(1.15a) -	NH_2	H	H	O

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

Micale *et al* [25] synthesized a series of novel 2-[(4-alkylsemicarbazono)-(4-amino phenyl methyl)]-4, 5-methylenedioxyphenyl acetic esters (**Fig. 1.16**). All the compounds were screened for anti-convulsant activity against audiogenic seizures in DBA/2 mice. Compound named (Z)-2-[(4-amino phenyl)-(4-methyl semicarbazono)-methyl]-4, 5-methylene dioxyphenylacetic acid methyl ester (1.16a) emerged as most promising compound with ED_{50} value 7.87µmol/kg (clonic phase) and 4.62µmol/kg (tonic phase).Compound (1.16a) was also found protective against MES and scPTZ induced seizures with ED_{50} value 15.7µmol/kg and 14.7µmol/kg respectively. Compound (1.16a) also antagonized *in vivo* seizures induced by ICV administration of AMPA or KA at ED_{50} value 13.9µmol/kg (tonic), 8.9µmol/kg (clonic) and 16.6µmol/kg respectively. Compound (1.16a) also reduced currents evoked by KA and ATPA in primary cultures of granule neurons by 60% and 54% respectively.



	R	X
(1.16a) -	OCH_3	$NHCONHCH_3$

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

Zappal *et al* [26] 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 (1.18) exhibited weak anticonvulsant activity against audiogenic induced seizures at ED_{50} 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 ED_{50} 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.

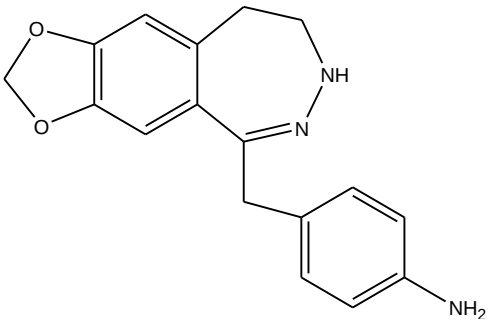


FIG.1.17. 5 -(4-AMINO BENZYL)- 7,9- DIHYDRO- 8 H-[1,3]DIOXOLO[4,5-H][2,3]BENZODIAZEPINE-8-ONE

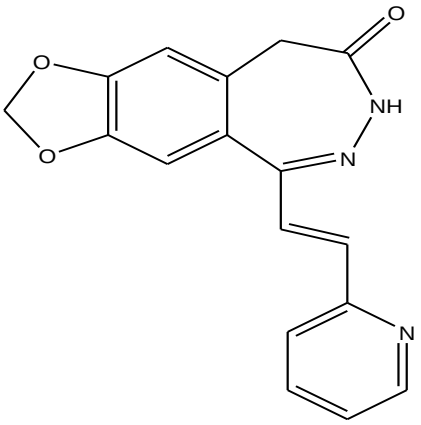
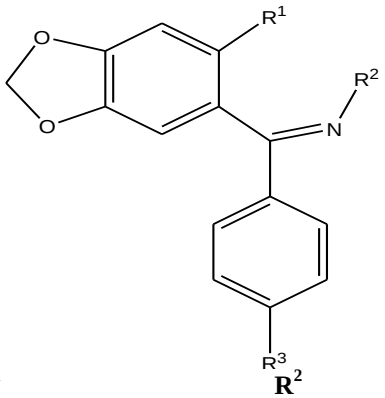


FIG. 1.18: 7, 9-DIHYDRO-5-[2-(PYRIDINE-2-YL)-VINYL]-8H-[1, 3]DIOXOLO[4, 5-H][2, 3] BENZODI AZEPINE-8-ONE

Micale *et al* [27] 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 wih ED_{50} value of 24.7µmol/kg (clonic phase) and 19.6µmol/kg (tonic phase).

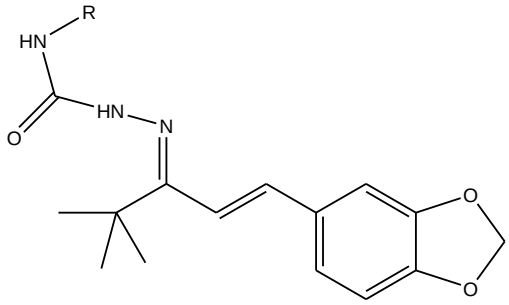


R^1	**R^2**	**R^3**
(1.19a) - CH_2COOCH_3	$NHCSNHCH_3$	Cl

FIG.1.19. 1-SUBSTITUTED 2-[(4-ARYL)-METHYL]-4, 5-METHYLENEDIOXYBENZENE DERIVATIVES

Enein *et al* [6b] synthesized series of stiripentol analogues namely 2-[(1E)-1-(1,3-benzodioxol-5-yl)-4,4-di-methyl pent-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-bezodioxol-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 ED_{50} 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 ED_{50} value of 110mg/kg.



R
(1.20a) - H

FIG. 1.20: 2-[(1E)-1-(1,3-BENZODIOXOL-5-YL)-4,4-DI-METHYL PENT-1-EN-3-YLIDENE]-N-(ARYL/H) HYDRAZINE- CARBOXAMIDES

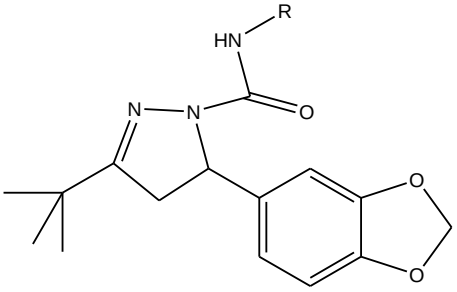
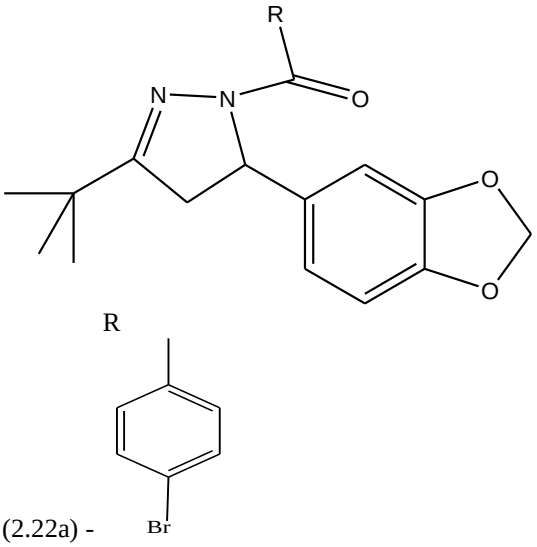


FIG. 1.21: (±)-5(RS)-N-(ARYL/H)-(1,3-BENZODIOXOL-5-YL)-3-TERT-BUTYL-4,5-DIHYDRO-1H-PYRAZOLE-1-CARBOXAMIDES



R
(2.22a) - Br

FIG. 1.22: (±)-[(5RS)-(1,3-BEZODIOXOL-5 YL)-3-TERT-BUTYL-4,5-DIHYDRO-1H-PYRAZOL-1-YL](ARYL)METHANONES

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 anti-convulsant activity of 1, 3-Benzodioxle ring system based compounds. After studying various derivatives it is concluded that compounds based on the 1, 3-Benzodioxle ring system have gain popularity in recent years and seems promising for the development of newer and effective antiepileptic drugs.

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