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## A REVIEW ON CHROMEN DERIVATIVES AS ANTIPILEPTICS

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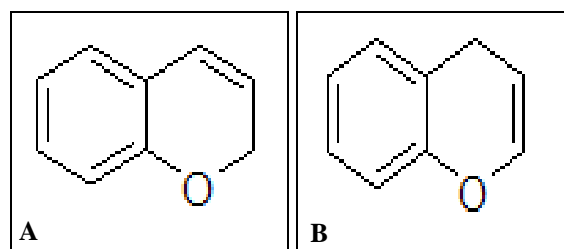
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**ABSTRACT:** Chromens are oxygen-containing heterocycles, abundantly found in nature in the form of flavone, is flavones, flavanones, catechins, anthocyanins and collectively known as flavonoids and isoflavonoids. Being a polar and ionizable aromatic compound, it improves the pharmacokinetic characteristics of lead molecules. Imidazole derivatives have occupied a unique place in the field of medicinal chemistry. Therefore, the incorporation of the chromen nucleus is an important synthetic strategy in drug discovery. The high therapeutic properties of the chromen related drugs have encouraged the researchers to synthesize new chemotherapeutic agents. A variety of cellular targets are interacting with the derivatives of chromen and that can be responsible for their wide-ranging epileptic activities. The substitution of chromen nucleus is a crucial step in the drug discovery process. In the present review, chromen derivatives having antiepileptic activity is described using a structural substitution pattern. The interest in chromen is ever-growing since they offer a fairly diverse chemical space for exploration of medicinal potential.

**INTRODUCTION:** Chromen or 2H-1-benzopyran is a polycyclic organic compound that results from the fusion of a benzene ring to a heterocyclic pyran ring **Fig. 1**<sup>1</sup>. Chromen unit is present in many natural products as found in polyphenols and widely found in natural alkaloids, tocopherols, flavonoids and anthocyanins<sup>2</sup>. Chromen derivatives are reported for many useful biological activities such as anticancer<sup>3, 4</sup>, antimicrobial<sup>5</sup>, antioxidant<sup>6</sup>, antihistamine<sup>7</sup>, antidiabetic<sup>8</sup>, antiproliferative<sup>9</sup>, anti-inflammatory<sup>10</sup>, antidepressant<sup>11</sup>, etc. They are useful and important pharmacophores and special structures in medicinal chemistry.

It has found in many recent research works that chromen derivatives have a broad spectrum of activities as antiepileptic<sup>12</sup>. This review mainly enlightens the pharmaceutical importance of the chromen and its derivatives as antiepileptic.

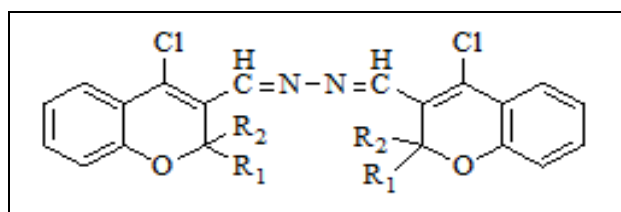


**FIG. 1: (A) 2H-CHROMEN, (B) 4H-CHROMEN**

**Chromen and Epilepsy:** Epilepsy is one of the prevalent neurological disorders which affect around 45-100 million people globally. Although many antiepileptic drugs are currently available in clinical practice, but neurotoxicity and characteristic side effects restrict their clinical use. Thus, it becomes a task for researchers to discover new chemical entities as more effective

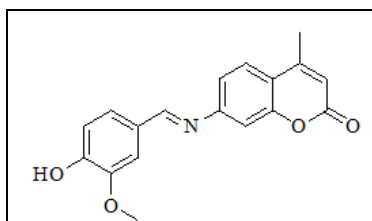
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antiepileptic with less neurotoxicity<sup>13</sup>, wherein the potential of chromen derivatives has been exploited. The study of antiepileptic activity revealed the importance of substitutions on the benzene ring and onto the pyran ring of the chromen ring system. The fact that these analogs are either 2-alkyl or 2-aryl substituted is particularly noticeable by Hegab *et al.* Compounds having 2-substitution showed higher antiepileptic activities than that of carbamazepine. The highest activities were recorded for compounds 1a and 1b (322% and 300% of the potency of carbamazepine, respectively)<sup>14</sup>.

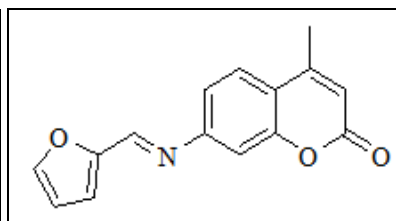


1: A: R<sub>1</sub> = R<sub>2</sub> = CH<sub>3</sub> B: R<sub>1</sub> = R<sub>2</sub> (CH<sub>2</sub>)<sub>5</sub>

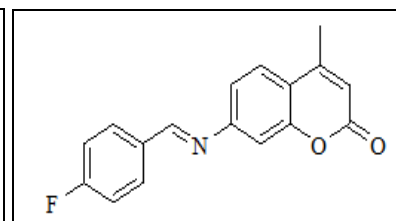
Some novel 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-3-



3

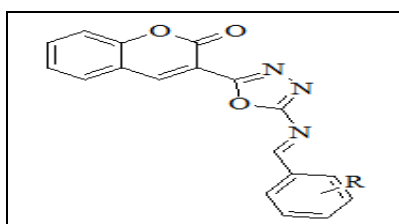


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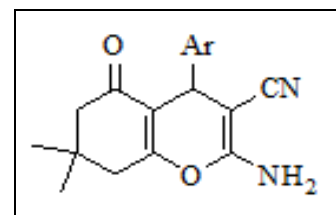
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Coumarin incorporated Schiff bases of 1, 3, 4 oxadiazoles (6) were synthesized and evaluated for antiepileptic activity. Substitutions of NO<sub>2</sub>, Cl, and OCH<sub>3</sub> at the distal phenyl ring showed potent activity against MES (maximal electroshock-induced) test. Whereas substitution of OH, F, and 3,4-(OCH<sub>3</sub>)<sub>2</sub> at distal phenyl ring displayed moderate activity against MES test. The presence of N(CH<sub>3</sub>)<sub>2</sub> showed protection against MES test at such a higher dose of 300 mg/kg. It resembled that the presence of a double bond in the structure provided the additional feature of rigidity<sup>17</sup>.



6: R = 3-NO<sub>2</sub>, 4-OH, 2-OH, 2-NO<sub>2</sub>, 4-F, 3-Cl, H

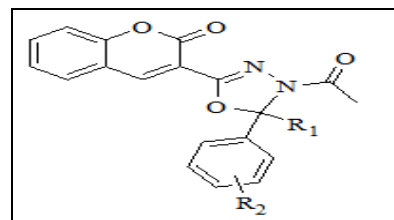
carbonitriles compounds (2) were synthesized and possessed potent inhibitory activity against  $\alpha$  glycosidase, the cytosolic carbonic anhydrase I and II form (H CA I and II) for the treatment of many neurological disorders like epilepsy<sup>15</sup>.



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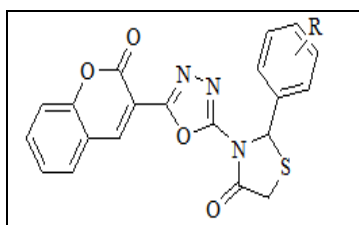
Compounds having 2-substitution with C=O (coumarin) presented a wide range of applications in the field of medicine. Such of these compounds were also reported for their antiepileptic activity in PTZ (subcutaneous pentyle-netetrazol test) induced seizure model in mice. Compound 3 was found to be more potent than compound 4 whereas, compound 5 was less potent than compound 4<sup>16</sup>.

3-(4-acetyl-5H/methyl-5-substituted phenyl-4,5 dihydro-1,3,4-oxadiazol-2-yl)-2 Hchromene-2 ones (7) were synthesized and tested for its anticonvulsant activity. All compounds possessed potent anticonvulsant activity in the MES test. It had been found that compounds having m-nitrophenyl and p-nitrophenyl substituents at position 5 of ox diazole ring exhibited activity at 100 mg/kg after 0.5 h. whereas compound with p-nitrophenyl substitution displayed activity at a lower dose of 30 mg/kg after 4 h<sup>18</sup>.



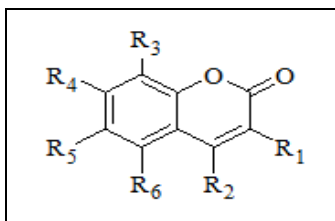
7: R<sub>1</sub> = H, CH<sub>3</sub> R<sub>2</sub> = H, OH, CH<sub>3</sub> OCH<sub>3</sub>, NO<sub>2</sub>

2-(substituted phenyl) - 3- [5'-(2'-oxo-2H chromen 3'-yl) - 1, 3, 4-oxadiazol-2-yl] - 1, 3-thiazolidin-4-ones (8) were synthesized and were screened for MES test. All compounds were found active in the MES test at a dose of 300 mg/kg. It was found that substitutions with OCH<sub>3</sub>, Cl and NO<sub>2</sub> group at distal aryl ring showed potent activity considered to other substituents having a bigger hydrophobic domain. Compounds having substituents like OH and F at distal phenyl ring displayed moderate activity though compounds with substituents like N(CH<sub>3</sub>)<sub>2</sub>, 3, 4-(OCH<sub>3</sub>)<sub>2</sub> and H showed protection at such a higher dose of 300 mg/kg<sup>19</sup>.



8: R = Cl, F, NO<sub>2</sub>, OH, CH<sub>3</sub>, OCH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>

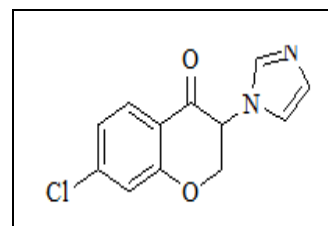
Certain chromenones (9) were Group I mGluR modulators. Hence, these substances may be useful in the treatment of diseases which followed abnormal glutamate neurotransmission or in which modulation of group I MGR receptors outcomes in a therapeutic benefit in different CNS disorders like epilepsy, Parkinson, etc.<sup>20</sup>.



9: R<sub>1</sub> = Hydrogen, Alkyl, Aryl, Heteroaryl, R<sub>2</sub> = Hydrogen, Alkyl, Aryl, Heteroaryl, Cyano, Nitro, Halogen, R<sub>3</sub> = R<sub>4</sub> = R<sub>5</sub> = R<sub>6</sub> = Hydrogen, Alkyl, Aryl, Heteroaryl, Nitro, Amino, Alkoxy, Hydroxyl

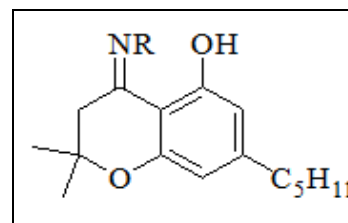
Chromanol-type compounds also act as antiepileptics. Kebriaeezadeh *et al.*, designed and synthesized some azolylchroman derivatives and investigated anticonvulsive and antiepileptogenic properties by lithiumepilocarpine induced seizure and PTZ-induced kindling models.

7-chloro-3-(1H-imidazol-1-yl) chroman-4-one (10) showed delaying in the onset of a seizure and decreasing duration of seizures in a model of epilepsy<sup>21</sup>.



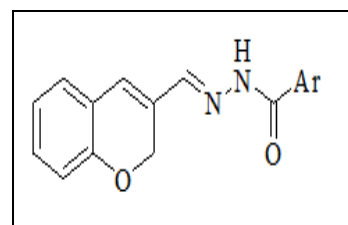
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Arnoldi *et al.* synthesized a series of 4-(alkylimino) - 5-hydroxyl - 7-alkyl - 2,3-dihydro-4H-benzopyrans (11) and evaluated against MES and PTZ (pentylene-tetrazole) induced seizures in mice. 2,2-dimethyl-4-[(2-hydroxyalkyl)imino]-5-hydroxy-7-pentyl-2,3-dihydro-4H-1-benzopyrans were found as most active among the series and showed potent activity against MES and PTZ induced seizures<sup>22</sup>.



11: R = Me, Cyclohexyl, CH<sub>2</sub>CH<sub>2</sub>SH, CH<sub>2</sub>CH<sub>2</sub>NHMe, CH<sub>2</sub>CH<sub>2</sub>OH

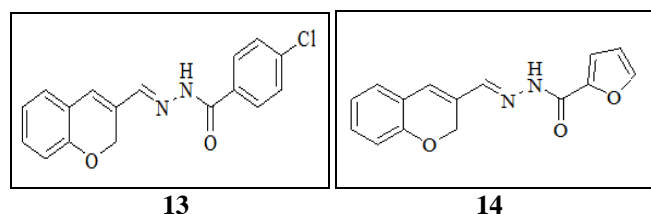
2H-chromene based hydrazones with 3-substitution at pyran ring were designed, synthesized and tested for their antiepileptic activity. The compound 12 showed higher protections against the MES test, suggested its higher ability to suppress the seizure spread. The compound 12 exhibited higher activity in scPTZ test, used to find compounds that heighten seizure threshold<sup>23</sup>.



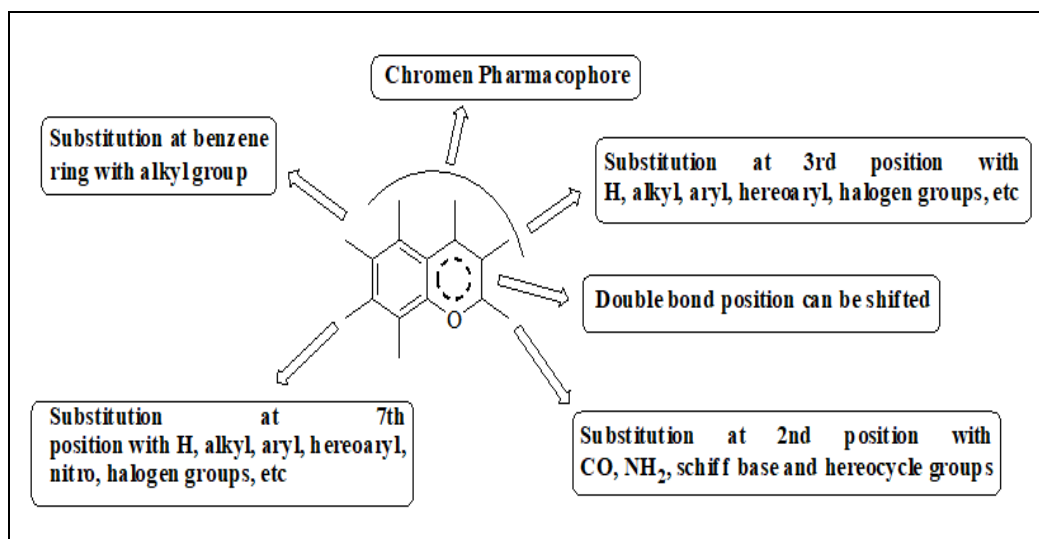
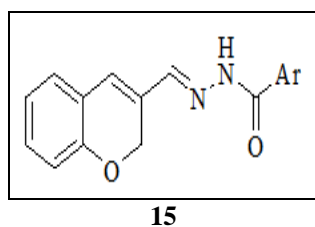
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Several 2H-chromene and coumarin based hydrazones were synthesized and evaluated for their anticonvulsant activity by maximal electroshock induced seizure tests (MES) and the subcutaneous pentylene-tetrazol (scPTZ) test in ICR mice. Compound 13 displayed activity at such a lowest dose of 30 mg/kg that was equally effective as reference drug phenytoin.

Whereas compound 14 was effective at the highest dose of 300 mg/kg against tonic-clonic seizures in the MES test. These compounds exhibited an anticonvulsant effect at 0.5 h<sup>24</sup>.



A series of aroyl hydrazones of 2H-chromene and coumarin carbaldehydes were synthesized and their anticonvulsant activity was evaluated. The 2-furyl substituted 2H-chromene (15) ranked the most potent compound among the other tested compounds from the series in the MES test and scPTZ test. These results suggested that 2H chromene aroyl hydrazones scaffold can be explored for further evaluation in models of epilepsy and derivatization<sup>25</sup>.

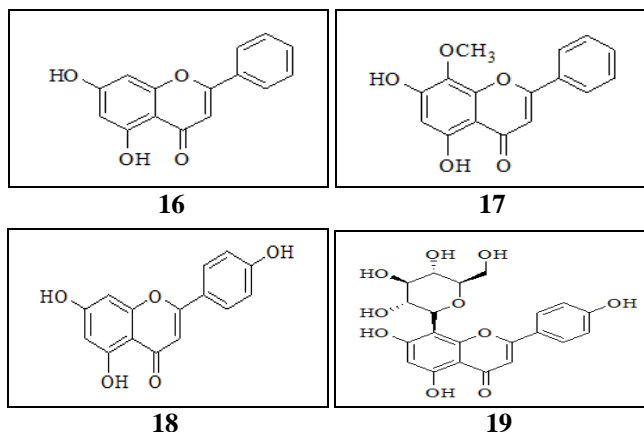


**FIG. 3: DESIGN STRATEGY OF CHROMEN DERIVATIVES FOR ANTIEPILEPTIC ACTIVITY**

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Some natural compounds such as flavonoid glycosides had possessed anticonvulsant or antiepileptic effects in different manners<sup>26</sup>.



**FIG. 2: SOME NATURAL FLAVONOIDS WITH ANTIEPILEPTIC ACTIVITIES**

**CONCLUSION:** Chromens have been most frequently studied; many of its derivatives are active against various pathological conditions. The antiepileptic potential of chromen and their derivatives are discussed in brief in this article. The substitution at benzene and pyran ring system in chromen found to be effective for its antiepileptic activity. It may help the researchers to find out its use in the treatment of epilepsy and other incurable CNS disorders.

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