Original Article

Novel Chroman Analogs as Promising Heterocyclic Compounds: Their Synthesis and Antiepileptic Activity

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ABSTRACT

Aim: New series of novel chroman analogs was designed and synthesized using appropriate synthetic route. **Materials and Methods:** Structures of synthesized chroman hydrazides fused with different anhydrides were supported by spectral data. After the neurotoxicity, assessed by rotarod motor impairment method, antiepileptic activities of twenty synthesized compounds were evaluated by both Pentylenetetrazole Seizure (PTZ) and Maximal electroshock seizure (MES) methods on mice. Administration at the suitable dose level of 30 mg/kg, 100 mg/kg and 300 mg/kg body weight of compounds and standards was done for PTZ and MES methods and for neurotoxicity. **Results:** Compound 5j (30 mg/kg) showed highest and advanced antiepileptic activity than reference drugs. None of the compounds showed neurotoxicity at 30 mg/kg and 100 mg/kg, as determined by the rotarod test. Whereas compounds 5m and 5p exhibited neurotoxicity at higher dose of 300 mg/kg after 4 hr. **Conclusion:** The results of the present study prove that the compounds have significant antiepileptic potential and are suitable candidates for further exploration.

Key words: Anhydride, Antiepileptic, Chroman, Neurotoxicity, Synthesis.

INTRODUCTION

A large section of the population around 45-100 million people is affected globally with epilepsy.[1,2] It is a common neurological disorder associated with the tendency to have repeated seizures and convulsions. A seizure is characterized by a disturbance in the electrical activity of the brain. Convulsion is a symptom of an epileptic seizure associated with contraction and relaxation of body muscles rapidly and repeatedly. It can start at any age but, generally young people are more affected than old age people.[3] More than 40 different Antiepileptic Drugs (AEDs) are available in clinical use, but in about one-third of patients these drugs fail to provide adequate control of epileptic seizures.[4] However, dose related neurotoxicity and distinctive adverse effects limit their clinical use.[5,6] About 30-40% patients are resistant to current epileptic pharmacotherapy despite availability of many different AEDs and despite understanding epileptic seizure pathogenesis.[7]

The different chemical classes of available AEDs include barbiturates, carbamates, hydantoin, carboxamides, succinimides, etc. The SAR of active drugs like Phenobarbital (2), Promidone, Phenytoin (3), Ethosuximide (4), Felbamate (5), Carbamazepine (6) and Clonazepam, clearly reveals the presence of amide as well as anhydride group in their structures.[8,9] Some newer antiepileptic drugs which are currently under clinical trial eg, Oxcarbazine (7), Brivaracetam, Seletracetamand (1-(4-phenylpiperazin-1-yl)-3-(2-(trifluoromethyl) phenyl) pyrrolidine-2, 5-dione, 8) have shown to possess amide group.[10]

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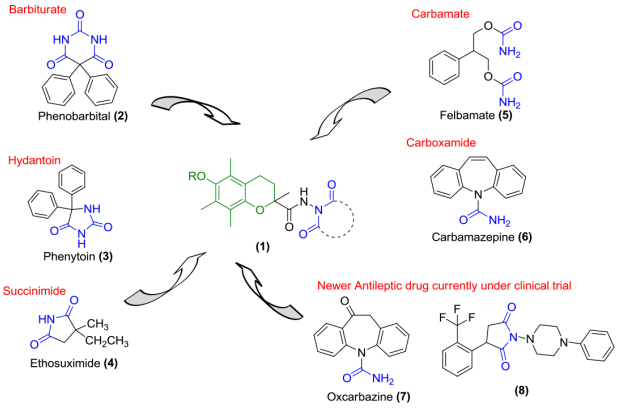
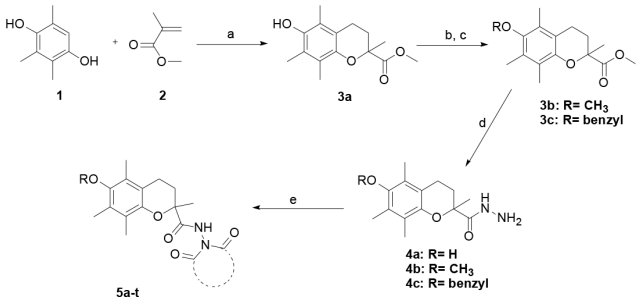


Figure 1: Pharmacophoric pattern of antiepileptic drugs and model compound.



Scheme 1: Synthetic pathway for compounds 5a-t. (a) (HCHO)n, $[CH_3(CH_2)_3]_2NH$, CH_3COOH, reflux, 20 hr; (b) dimethyl sulfate, K_2CO_3, CH_3COCH_3, 50°C, 24 hr (3b); (c) benzyl bromide, DMF, K_2CO_3, RT, 12 hr (3c); (d) $NH_2NH_2.H_2O$, C_2H_5OH, reflux, 10 hr (e) Different anhydrides, CH_3COOH, reflux, 2-4 hr.

Benzopyrans including chromans and flavonoids, due to their physico-chemical properties, have wide ranging biological applications. Review of literature reveals several pharmacological activities of chroman derivatives including anticancer,[11,12] insulin release process inhibitor,[13] human rhinovirus (HRV) capsid-binding inhibitor,[14] anti-HIV,[15] antimicrobial,[16] etc. Considering the antiepileptic potential of chroman and its derivatives, the design of the chroman analogs based on AEDs pharmacophoric pattern is presented in Figure 1.

In the present study, we report the synthesis, characterization of twenty new chroman anhydride derivatives (5a-t) and report their antiepileptic activity by PTZ and MES methods along with their neurotoxicity by rotarod test.

RESULTS AND DISCUSSION

Chemistry

Synthetic strategies adopted for the synthesis of the target compounds (5a-t) described in this study has been depicted in Scheme1. Trolox (3a), conveniently synthesized by known procedure[17] undergoes methylation[18] and benzylation[19] to give 3b and 3c, respectively. The ester group of carboxylate present in 3a, 3b and 3c undergoes nucleophilie attack by hydrazine moiety resulting in 4a, 4b and 4c, respectively.[20] Conversion of chroman hydracids (4a-c) to the corresponding chroman-anhydride derivatives (5a-t) by condensation reaction with different anhydrides has been carried out. The properties of synthesized compounds (5a-t) are shown in Table 1.

The structures of all the newly synthesized compounds were confirmed on the basis of melting point analysis, FT-IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopy. The obtained data were in consistency with the proposed structures.

The final products (5a-t) were identified by its IR spectra which showed characteristic strong absorption band at 1685-1757 of amide (-CO, stretch). Compounds 5a-i displayed a broad absorption band at 3349-3500 of hydroxy group (-OH, stretch). In ^{1}H NMR, the amide group ($-CONH_2$) was observed as a singlet at δ 8.08-10.44 ppm which was further confirmed by the disappearance of this sharp absorption peak in D_2O exchange spectrum. The hydroxy group (-OH) in compounds (5a-i) was confirmed by the sharp singlet at around δ7.49-7.51 ppm except in compounds 5d, 5g and 5i (singlet at δ4.32-4.39 ppm) due to $CDCl_3$.The presence of singlet peak at δ 3.49-3.61 ppm due to a methoxy group ($-OCH_3$)of 5j-n clearly indicated methylation. A singlet peak at δ4.60-4.70ppm was assigned to benzylic methyl ($-CH_2-$)in compounds 5o-t. All of the other aromatic and aliphatic protons were present at their distinct place. In ^{13}C NMR, the signal due to carbonyl group of amide (C=O) appeared at δ160.3 173.6 ppm. Other signals were found corresponding to their established structures. The mass spectra of almost all compounds showed $(M+H)^+$(m/z) peaks according to their molecular weight. However, in some cases, $(M+Na^+)^+$and $(M-H)^+$(m/z) peaks were also observed. Complete details are provided in the Experimental section.

Antiepileptic activity

All twenty compounds were evaluated for antiepileptic and neurological toxicity studies (e.g., ataxia, sedation, hyper-excitability) in mice using rotarod test at the doses of 30 mg/kg, 100 mg/kg and 300 mg/kg.[21] Data relative to the neurological toxicity (NT) and antiepileptic properties of synthesized compounds (5a-t) are shown in Table 2.

All compounds (5a-t) were devoid of toxicity upon rotarod neurotoxicity screening at the dose of 30 mg/kg

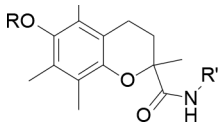
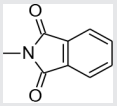
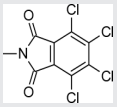
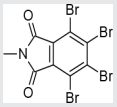
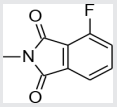
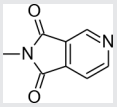
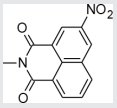
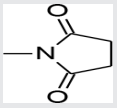
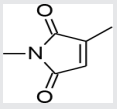
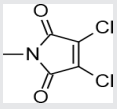
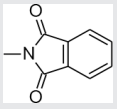
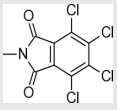
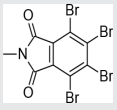
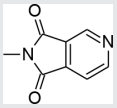
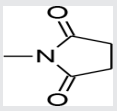
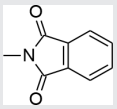
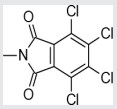
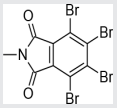
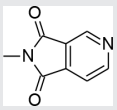
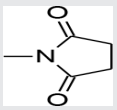
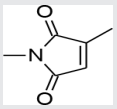


Table 1: Compounds (5a-t) differing in the substitution at R'.

Compd.[a,b]	Entry	R'	ReactionTime (hours)	Mol. formula	Mol. weight	Yield (%)[c]	MP (°C)	R_f[d]
5a	**4a**		2	$C_{22}H_{22}N_2O_5$	394.42	91	230	0.6
5b	**4a**		2	$C_{22}H_{18}Cl_4N_2O_5$	532.20	90	283	0.5
5c	**4a**		2	$C_{22}H_{18}Br_4N_2O_5$	710.00	91	270	0.5
5d	**4a**		2	$C_{22}H_{21}FN_2O_5$	412.41	68	218	0.4
5e	**4a**		4	$C_{21}H_{21}N_3O_5$	395.41	70	220	0.6
5f	**4a**		4	$C_{26}H_{23}N_3O_7$	489.48	72	140	0.7
5g	**4a**		2	$C_{18}H_{22}N_2O_5$	346.38	85	236	0.6
5h	**4a**		3	$C_{19}H_{22}N_2O_5$	358.39	86	218	0.5
5i	**4a**		3	$C_{18}H_{18}Cl_2N_2O_5$	413.25	71	170	0.4
5j	**4b**		2	$C_{23}H_{24}N_2O_5$	408.45	88	210	0.6
5k	**4b**		2	$C_{23}H_{20}Cl_4N_2O_5$	546.22	81	228	0.4
5l	**4b**		2	$C_{23}H_{20}Br_4N_2O_5$	724.03	80	258	0.5

Continued...

Table 1: Cont'd								
5m	**4b**		3	$C_{22}H_{23}N_3O_5$	409.45	78	185	0.4
5n	**4b**		3	$C_{19}H_{24}N_2O_5$	360.40	75	170	0.6
5o	**4c**		4	$C_{29}H_{28}N_2O_5$	484.58	69	190	0.5
5p	**4c**		3	$C_{29}H_{24}Cl_4N_2O_5$	622.32	64	190	0.5
5q	**4c**		3	$C_{29}H_{24}Br_4N_2O_5$	800.13	66	220	0.5
5r	**4c**		4	$C_{28}H_{27}N_3O_5$	485.53	63	168	0.4
5s	**4c**		3	$C_{25}H_{28}N_2O_5$	436.50	61	120	0.6
5t	**4c**		3	$C_{26}H_{28}N_2O_5$	448.51	62	140	0.7

[a] Reagents and conditions: 5a-q (0.001 mol), 4a-c (0.001 mol), acetic acid (10 ml)
[b] Ratio of the product was determined by the analysis of crude FT-IR, ^{1}H NMR, ^{13}C NMR and Mass spectra
[c] Yield refers to pure products after chromatography.
[d] R*f*= EtOAc/Hexane (40:60)

and 100 mg/kg at 0.5 hr. While as compounds 5m and 5p were toxic at the dose of 300 mg/kg after 4 h. However, all the compounds were less toxic than standard drug, phenytoin (100 mg/kg).

The results of antiepileptic study of compounds (5a-t) by PTZ method showed that all compounds displayed significant activity. Most active compounds 5e, 5f and 5hr presented protection at the dose level of 30 mg/kg after both the time intervals 0.5 h and 4 hr. Whereas compounds 5a, 5b, 5j, 5k and 5p showed protection at 100 mg/kg dose level after 4 hr. Compounds 5c, 5d, 5i, 5l, 5m, 5o and 5s exhibited protection at 100 mg/kg dose level after 0.5 h and 4 hr time intervals while compounds 5n, 5q and 5r showed protection at 300 mg/kg dose level after 4 hr. The remaining compounds (5g and 5t) had activity at the dose level of 300 mg/kg at both the time intervals. Compound 5f showed good activity which may be due to increase in the ring size as other compounds (5g, 5i, 5n and 5s) having smaller ring system possessed less activity. It seemed that substitution of 6-OH group resulted in more active compounds (5a, 5b, 5e, 5f and 5hr). Amongst the electronegative groups (chloro, bromo and fluoro) in tested compounds, chloro derivatives (5b, 5k and 5p) showed better activity.

All compounds (5a-t) displayed protection in PTZ model (Table 2). Therefore compounds may have inhibited or attained PTZ-induced seizure in mice by increasing GABAergic neurotransmission.[22]

Maximal Electroshock Seizure (MES) method when applied on mice showed reasonable activity by several compounds. Most potent compounds 5j and 5t were comparable in activity with result to standard drug, phenytoin at dose level of 30 mg/kg after the time periods of 0.5 h and 4 h. Furthermore, compounds 5f,

Table 2: Effect of compounds (5a-t) administered orally at the dose of 30 mg/kg, 100 mg/kg and 300 mg/kg on convulsions induced by PTZ and MES andon neurotoxicity (NT).

Compounds	Intraperitoneal injection in mice (mg/kg)					
	NT		PTZ		MES	
	0.5 hr	4 hr	0.5 h	4 hr	0.5 hr	4 hr
5a	-	-	30	100	-	-
5b	-	-	30	100	-	-
5c	-	-	100	100	-	-
5d	-	-	100	100	-	-
5e	-	-	30	30	300	-
5f	-	-	30	30	100	-
5g	-	-	300	300	-	-
5h	-	-	30	30	-	-
5i	-	-	100	100	100	100
5j	-	-	30	100	30	30
5k	-	-	30	100	-	300
5l	-	-	100	100	-	100
5m	-	300	100	100	300	300
5n	-	-	100	300	100	100
5o	-	-	100	100	100	100
5p	-	300	30	100	-	300
5q	-	-	100	300	-	-
5r	-	-	100	300	300	-
5s	-	-	100	100	-	-
5t	-	-	300	300	30	30
Phenytoin	100	100			30	30
Sodium Valproate			200	200		

[a] The figure in the table indicates minimum dose required for bioactivity in half or more of the mice examined at 0.5 hr and 4 hr.
[b] Dash indicates the absence of antiepileptic activity and neurotoxicity at the maximum dose administered (300 mg/kg).

5n and 5o had protection of seizures in mice at the dose level of 100 mg/kg after both time periods except for the compound 5f which showed protection only after 0.5 hr. However, in case of compounds 5k, 5m and 5p protection of seizures was observed at higher dose of 300 mg/kg. It had been found that compounds with hydroxyl group at position 6 of the envisaged compounds possessed less activity in comparison to other groups (methoxy and benzyl) at the same position. The occupancy of electron withdrawing groups (chloro, bromo and fluoro) might not had significant effect on activity as compounds 5b, 5c, 5d, 5k, 5l, 5p and 5q were less active or inactive.

MATERIALS AND METHODS

Melting points were checked in open glass capillaries and are uncorrected. The TLC of the compound used E Merck silica gel GF-254 precoated plates (Merck, Darmstadt, Germany). NMR spectra were determined on JEOL ECX-500 spectrometer in DMSO-*d6* and $CDCl_3$ (400 and 500 MHz) for ^1H and 125 MHz for ^{13}C. The chemical shifts were recorded in (δ, ppm) relative to TMS as an internal standard. The mass spectra were determined by Waters-Q-T of Premier-HAB213 spectrometer and Microscopic II triple Quadrupole mass spectrometer using EI and the m/z values are indicated in Dalton. Infrared spectra (KBr) were recorded by using Bruker FT/IR Vector 22 spectrophotometer.

Synthesis of 3a-c

The compounds were prepared by a literature procedure[11] which involved methylation and benzylation. The material was recrystallized from methanol and purification was done by column chromatography (pet. ether/EtOAc 90/10).

Synthesis of 4a-c

The compounds were prepared by a literature procedure.[11] It includes nucleophillic addition by hydrazine.

(a) 6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide (4a)

Yield: White solid **(**60%); ^{1}HNMR (500MHz, DMSO-d_6, ppm): 8.47 (s,1H,OH), 7.43 (s,1H,-NH), 4.19 (s,2H,NH_2), 2.52-2.49 (m,1H), 2.40-2.37 (m,1H), 2.20-2.15 (m,1H), 2.04 (s,3H), 2.02 (s,3H), 1.94 (s,3H), 1.68-1.63 (m,1H), 1.35 (s,3H).

(b) 6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide (4b)

Yield: White solid (90%); ^{1}H NMR (400MHz, $CDCl_3$, ppm): 7.51 (s,1H,-NH), 3.81-3.80 (d,2H,-NH_2), 3.60 (s,3H), 2.63-2.56 (m,1H), 2.52-2.45 (m,1H), 2.37-2.31 (m,1H), 2.18 (s,3H), 2.12 (s,3H), 1.90-1.85 (m,1H), 1.52 (s,3H).

(c) 6-(Benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbohydrazide (4c)

Yield: White solid (71%); ^{1}H NMR (400MHz, $CDCl_3$, ppm): 7.53 (s,1H,-NH), 7.48-7.37 (m,5H, Ph), 4.67 (s,2H), 3.82-3.81 (d,2H,-NH_2), 2.64-2.58 (m,1H), 2.54-2.46 (m,1H), 2.39-2.33 (m,1H), 2.21 (s,3H), 2.14 (s,3H), 2.13 (s,3H), 1.91-1.87 (m,1H), 1.53 (s,3H).

General procedure for the synthesis of final compounds (5a-t)

A mixture of selected chroman-hydrazides (4a-c, 100 mmol) and different anhydrides (0.1mol) in glacial acetic acid was refluxed for 2-4hr to complete the reaction and lead to final compounds 5a-t.

(a) *N*-(1,3-dioxoisoindolin-2-yl)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide (5a)

Yellow solid; IR (KBr, ν, cm^{-1}): 3379 (>NH), 1687 (>CO strech);^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.23 (s, -CONH-, exchangeable with D_2O), 7.94-7.88 (m, 4H), 7.49 (s, -OH, exchangeable with D_2O), 2.61-2.53 (m, 2H, >CH_2), 2.26-2.20 (m, 1H, >CH_2), 2.07 (s, 3H, -CH_3), 2.04 (s, 3H, -CH_3), 2.00 (s, 3H, -CH_3), 1.83-1.77 (m, 1H, >CH_2), 1.46 (s, 3H, -CH_3); HR-MS: 395.1607 $(M+H)^+$, calcd. 395.1609.

(b) 6-hydroxy-2,5,7,8-tetramethyl-*N*-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)chroman-2-carboxamide (5b)

Red solid; IR (KBr, ν, cm^{-1}): 3473 (-OH),3393 (>NH), 2937 (aliphatic C-H), 1699 (>CO strech); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.44 (s, -CONH), 7.51 (s, -OH-), 2.62-2.49 (m, 2H, >CH_2), 2.28-2.22 (m, 1H), 2.06 (s, 3H, -CH_3), 2.03 (s, 3H, -CH_3), 1.99 (s, 3H, -CH_3), 1.82-1.75 (m, 1H), 1.47 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): 173.4 (-CONH-), 161.2 (>C=O, >C=O), 146.5, 144.2, 139.9, 129.5, 126.4, 123.3, 121.9, 120.6, 117.5, 77.9 (>C<), 30.4 (-CH_2), 24.4 (-CH_3), 20.3 (-CH_2), 13.3 (-CH_3), 12.7 (-CH_3), 12.3 (-CH_3); HR-MS: 528.9888 $(M+H)^+$, calcd. 528.9891.

(c) 6-hydroxy-2,5,7,8-tetramethyl-*N*-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)chroman-2-carboxamide (5c)

Red solid; IR (KBr, ν, cm^{-1}): 3479 (-OH),3377 (>NH), 2941 (aliphatic C-H), 1699 (>CO strech); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.39 (s, -CONH), 7.50 (s, -OH-), 2.60-2.49 (m, 2H, >CH_2), 2.28-2.22 (m, 1H), 2.06 (s, 3H, -CH_3) , 2.03 (s, 3H, -CH_3), 1.99 (s, 3H, -CH_3), 1.82-1.75 (m, 1H), 1.47 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): 173.4 (-CONH-), 161.6 (>C=0,>C=0), 146.4, 144.2, 138.2, 129.2, 123.3, 121.9, 120.6, 117.5, 77.9 (>C<), 30.4 (-CH_2), 24.5 (-CH_3), 20.3 (-CH_2), 13.3 (-CH_3), 12.7 (-CH_3), 12.4 (-CH_3); HR-MS: 704.7870 $(M+H)^+$,calcd. 704.7880.

(d) *N*-(4-fluoro-1,3-dioxoisoindolin-2-yl)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide (5d)

Light green solid; IR (KBr, ν, cm^{-1}): 3369 (-OH stretch), 2926 (aliphatic C-H), 1686 (>CO stretch); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.17 (s, -CONH-), 7.79-7.74 (m, 1H), 7.70 (d, *J=7.3 Hz*, 1H), 7.42 (t, *J=8.4 Hz*, 1H), 4.34 (s, -OH), 2.76-2.65 (m, 2H, >CH2), 2.43-2.36 (m, 1H), 2.19 (s, 3H, -CH_3), 2.16 (s, 3H, -CH_3), 2.12 (s, 3H, -CH_3), 1.97-1.90 (m, 1H), 1.63 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 173.5 (-CONH-),163.8 (>C=0), 161.5 (>C=0), 145.9, 143.7, 137.4, 137.3, 132.1, 123.2, 123.0, 122.1, 121.6, 120.2, 119.0, 118.1, 78.9 (>C<), 30.1 (-CH_2), 24.0 (-CH_3), 20.2 (-CH_2), 12.3 (-CH_3), 12.2 (-CH_3), 11.4 (-CH_3); HR-MS: 413.1512 $(M+H)^+$, calcd. 413.1511.

(e) *N*-(1,3-dioxo-1*H*-pyrrolo[3,4-c]pyridin-2(3*H*)-yl)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide (5e)

Orange solid; IR (KBr, ν, cm^{-1}): 3379 (-OH stretch), 2930 (aliphatic C-H), 1715 (>CO stretch); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.37 (s, -CONH-), 9.19-9.16 (m, 2H), 7.96-7.95 (m, 1H), 7.50 (s, -OH), 2.61-2.53 (m, 2H, >CH_2), 2.28-2.21 (m, 1H, >CH_2), 2.07 (s, 3H, -CH_3), 2.03 (s, 3H, -CH_3), 1.99 (s, 3H, -CH_3), 1.83-1.76 (m, 1H, >CH_2), 1.47 (s, 3H, -CH_3); HR-MS: 396.1559 $(M+H)^+$, calcd. 396.1559.

(f) 6-hydroxy-2,5,7,8-tetramethyl-N-(5-nitro-1,3-dioxo-1*H*-benzo[de]isoquinolin-2(3*H*)-yl)chroman-2-carboxamide (5f)

Orange solid; IR (KBr, ν, cm^{-1}):3403 (-OH stretch), 2926 (aliphatic C-H), 1698 (>CO stretch); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.34 (s, -CONH), 9.52(s, 1H), 8.97 (d, *J=12.8 Hz*, 1H), 8.82 (d, *J=8.2 Hz*, 1H), 8.70 (dd, *J=7.4 Hz*, *J=12.2 Hz*, 1H), 8.06 (dd, *J=7.4 Hz*,

J=13.7 Hz, 1H), 7.51 (s, -OH-), 2.63-2.61 (m, 2H), 2.36-2.30 (m, 1H), 2.09 (s, 3H, $-CH_3$), 2.04 (s, 3H, $-CH_3$), 2.02 (s, 3H, $-CH_3$), 1.86-1.80 (s, 1H), 1.52 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 172.9 (-CONH-), 161.3 (>C=0), 161.2 (>C=0), 146.5, 146.4, 146.4, 137.8, 135.3, 131.7, 131.2, 129.9, 129.7, 124.5, 123.7, 123.2, 122.3, 121.8, 120.6, 117.7, 78.1 (>C<), 30.5 ($-CH_2$), 24.4 ($-CH_3$), 20.3 ($-CH_2$), 13.3 ($-CH_3$), 12.7 ($-CH_3$), 12.4 ($-CH_3$); HR-MS: 512.1433 $(M+Na)^+$,calcd. 512.1439.

(g) *N*-(2,5-dioxopyrrolidin-1-yl)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide (5g)

White solid; IR (KBr, ν, cm^{-1}): 3500 (-OH stretch), 2933 (aliphatic C-H), 1707 (>CO stretch);^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.08 (s, -CONH-), 4.39 (s, 1H, -OH), 2.78 (s, 4H, $>CH_2$), 2.70-2.65 (m, 2H, $>CH_2$), 2.38-2.30 (m, 1H, $>CH_2$), 2.14 (s, 6H, $-CH_3$), 2.10 (s, 3H, $-CH_3$), 1.59 (s, 3H, $-CH_3$); HR-MS: 347.1600 $(M+H)^+$, calcd. 347.1600.

(h) 6-hydroxy-2,5,7,8-tetramethyl-*N*-(3-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)chroman-2-carboxamide (5h)

Yellowish-orange solid; IR (KBr, ν, cm^{-1}): 3349 (-OH stretch), 2923 (aliphatic C-H), 1685 (>CO stretch); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.01 (s, -CONH), 7.50 (s, -OH-), 6.75 (d, *J=1.8 Hz, 1H*), 2.56-2.43 (m, 2H, $>CH_2$), 2.20-2.14 (m, 1H), 2.04 (s, 3H, $-CH_3$), 2.02 (s, 3H, $-CH_3$), 1.99 (d, 3H, $-CH_3$), 1.97 (s, 3H, $-CH_3$), 1.78-1.71 (m, 1H), 1.40 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 173.5 (-CONH-), 169.4 (>C=0), 168.3 (>C=0), 146.4, 145.3, 144.2 (>C<), 127.3 (>C<), 123.2, 121.9, 120.6, 117.5, 77.7 (>C<), 30.4 ($-CH_2$), 24.3 ($-CH_3$), 20.2 ($-CH_2$), 13.2 ($-CH_3$), 12.7 ($-CH_3$), 12.3 ($-CH_3$), 11.5 ($-CH_3$); HR-MS: 381.1421$(M+Na)^+$, calcd. 381.1420.

(i) *N*-(3,4-dichloro-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide (5i)

Brown solid; IR (KBr, ν, cm^{-1}): 3382 (-OH stretch), 2929 (aliphatic C-H), 1757 (>CO stretch); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.07 (s, -CONH-), 4.32 (s,-OH) , 2.66 (t, *J=6.4 Hz*, 2H, $>CH_2$), 2.39-2.32 (m, 1H, $>CH_2$), 2.17 (s, 3H, $-CH_3$), 2.15 (s,3H, $-CH_3$), 2.11 (s, 3H, $-CH_3$), 1.95-1.88 (m, 1H, $>CH_2$), 1.59 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 173.6 (>C=O), 160.3 (>C=O), 146.0, 143.6, 133.2, 122.1, 121.7, 119.1, 118.0, 78.8 (>C<), 30.0 ($-CH_2$), 23.9 ($-CH_3$), 20.1 ($-CH_2$), 14.2, 12.3, 12.2, 11.3; HR-MS: 413.0671 $(M+H)^+$, calcd. 413.0656.

(j) *N*-(1,3-dioxoisoindolin-2-yl)-6-methoxy-2,5,7,8-tetramethylchroman-2-carboxamide (5j)

White solid; IR (KBr, ν, cm^{-1}): 3409 (>NH stretch), 2932 (aliphatic C-H), 1707 (>CO stretch); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.31 (s, -CONH-), 7.94-7.88 (m, 4H), 3.50 (s, 3H, $-OCH_3$), 2.63-2.54 (m, 2H, $>CH_2$), 2.30-2.24 (m, 1H, $>CH_2$), 2.08 (s, 3H, $-CH_3$), 2.07 (s, 3H, $-CH_3$), 2.04 (s, 3H, $-CH_3$), 1.84-1.77 (m, 1H, $>CH_2$), 1.49 (s, 3H, $-CH_3$); HR-MS: 409.1763 $(M+H)^+$, calcd. 409.1761.

(k) 6-methoxy-2,5,7,8-tetramethyl-*N*-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)chroman-2-carboxamide (5k)

Light yellow solid; IR (KBr, ν, cm^{-1}): 3397 (>NH stretch), 2937 (aliphatic C-H), 1705 (>CO stretch); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.53 (s, -CONH-), 3.49 (s, 3H, $-OCH_3$), 2.63-2.49 (m, 2H, $>CH_2$), 2.31-2.25 (m, 1H, $>CH_2$), 2.07 (s, 6H, $-CH_3$), 2.03(s, 3H, $-CH_3$), 1.85-1.76 (m, 1H, $>CH_2$), 1.50 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 173.2 (-CONH-), 161.2 (>C=0,>C=0), 150.2, 146.9, 139.9, 129.5, 127.8, 126.4, 125.7, 122.8, 118.2, 78.3 (>C<), 60.3 ($-OCH_3$), 30.2 ($>CH_2$), 24.6 ($-CH_3$), 20.1 ($>CH_2$), 12.9 ($-CH_3$), 12.6 ($-CH_3$), 12.0 ($-CH_3$); HR-MS: 545.0209 $(M+H)^+$, calcd. 545.0209.

(l) 6-methoxy-2,5,7,8-tetramethyl-*N*-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)chroman-2-carboxamide (5l)

White solid; IR (KBr, ν, cm^{-1}): 3384 (>NH stretch), 2932 (aliphatic C-H), 1709 (>CO stretch); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.49 (s, -CONH-), 3.49 (s, 3H, $-OCH_3$), 2.63-2.49 (m, 2H, $>CH_2$), 2.31-2.25 (m, 1H, $>CH_2$), 2.07 (s, 6H, $-CH_3$), 2.03 (s, 3H, $-CH_3$), 1.83-1.76 (m, 1H, $>CH_2$), 1.50 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6):173.2 (-CONH-), 161.6 (>C=0,>C=0), 150.2, 146.9, 138.2, 129.2, 127.8, 125.7, 122.8, 121.9, 118.2, 78.3 (>C<), 60.3 ($-OCH_3$), 30.2 ($>CH_2$), 24.6 ($-CH_3$), 20.1 ($>CH_2$), 12.9 ($-CH_3$), 12.6 ($-CH_3$), 12.0 ($-CH_3$). HR-MS: 718.8027 $(M+H)^+$, calcd. 718.8025.

(m) *N*-(1,3-dioxo-1*H*-pyrrolo[3,4-c]pyridin-2(3*H*)-yl)-6-methoxy-2,5,7,8-tetramethylchroman-2-carboxamide (5m)

Off-white solid; IR (KBr, ν, cm^{-1}): 3395 (>NH stretch), 2934 (aliphatic C-H), 1706 (>CO stretch); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.46 (s, -CONH-), 9.19-9.16 (m, 2H), 7.96-7.95 (m, 2H), 3.49 (s, 3H, $-OCH_3$), 2.64-2.54 (m, 2H, $>CH_2$), 2.31-2.25 (m, 1H, $>CH_2$), 2.08 (s, 3H, $-CH_3$), 2.07 (s, 3H, $-CH_3$), 2.04 (s, 3H, $-CH_3$),

1.84-1.78 (m, 1H, >CH_2), 1.50 (s, 3H, -CH_3); HR-MS: 410.1715 $(M+H)^+$, calcd. 410.1715.

(n) *N*-(2,5-dioxopyrrolidin-1-yl)-6-methoxy-2,5,7,8-tetramethylchroman-2-carboxamide (5n)

White solid; IR (KBr, ν, cm^{-1}): 3370 (>NH stretch), 2938 (aliphatic C-H), 1701 (>CO stretch); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.07 (s, -CONH-), 3.61 (s, 3H, -OCH_3), 2.79 (s, 4H, -CH_3), 2.68-2.63 (m, 2H, >CH_2), 2.38-2.31 (m, 1H, >CH_2), 2.18 (s, 3H, -CH_3), 2.15 (s, 3H, -CH_3), 2.14 (s, 3H, -CH_3), 1.98-1.91 (m, 1H, >CH_2), 1.60 (s, 3H, -CH_3); HR-MS: 361.4043 $(M+H)^+$, calcd. 361.1764.

(o) 6-(benzyloxy)-*N*-(1,3-dioxoisoindolin-2-yl)-2,5,7,8-tetramethylchroman-2-carboxamide (5o)

White solid;IR (KBr, ν, cm^{-1}): 3400 (>NH stretch), 2925 (aliphatic C-H), 1731 (>CO stretch) ; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.35 (s, -CONH-), 7.94-7.88 (m, 4H), 7.45 (d, *J=7.0 Hz*, 2H), 7.38 (t, *J=8.0 Hz*, 2H), 7.34-7.30 (m, 1H), 4.60 (s, 2H), 2.65-2.52 (m, 2H, >CH_2), 2.31-2.25 (m, 1H, >CH_2), 2.12 (s, 3H, -CH_3), 2.10 (s, 3H, -CH_3), 2.09 (s, 3H, -CH_3), 1.86-1.77 (m, 1H, >CH_2), 1.51 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 173.3 (-CONH-), 165.5 (>C=0,>C=0), 149.0, 147.1, 138.1, 135.9, 129.8, 128.8, 128.4, 128.1, 126.0, 124.3, 122.9, 118.4, 78.3 (>C<), 74.7 (>CH_2), 30.2 (>CH_2), 24.6 (>CH_3), 20.1 (>CH_2), 13.2 (>CH_3), 12.7 (>CH_3), 12.3 (>CH_3); HR-MS: 507.1896 $(M+Na)^+$, calcd. 507.1916.

(p) 6-(benzyloxy)-2,5,7,8-tetramethyl-*N*-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)chroman-2-carboxamide (5p)

White solid; IR (KBr, ν, cm^{-1}): 3414 (>NH stretch), 2931 (aliphatic C-H), 1739 (>CO stretch); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.57 (s, -CONH-), 7.46 (d, *J=7.1 Hz*, 2H), 7.38 (t, *J=7.0 Hz*, *J=7.8 Hz*, 3H), 7.33-7.30 (m, 1H), 4.60 (s, 2H), 2.65-2.50 (m, 2H, >CH_2), 2.34-2.30 (m, 1H, >CH_2), 2.12 (s, 3H, -CH_3), 2.10 (m, 3H, -CH_3), 2.08 (s, 3H, -CH_3), 1.84-1.79 (m, 1H, >CH_2), 1.52 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): 173.2 (-CONH-), 161.2 (>C=0,>C=0), 149.0, 147.1, 139.9, 138.1, 129.5, 128.9, 128.4, 128.1, 126.4, 126.0, 122.8, 118.3, 78.3 (>C<), 74.7 (>CH_2), 30.2 (>CH_2), 24.6 (>CH_3), 20.1 (>CH_2), 13.2 (>CH_3), 12.7 (>CH_3), 12.3 (>CH_3); HR-MS: 619.0361$(M-H)^+$, calcd. 619.0361.

(q) 6-(benzyloxy)-2,5,7,8-tetramethyl-*N*-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)chroman-2-carboxamide (5q)

White solid; IR (KBr, ν, cm^{-1}): 3409 (>NH stretch), 2928 (aliphatic C-H), 1728 (>CO stretch); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.52 (s, -CONH-), 7.46 (d, *J=7.0 Hz*, 2H), 7.38 (t, *J=7.2 Hz*, 2H), 7.34-7.30 (m, 1H), 4.60 (s, 2H), 2.65-2.50 (m, 2H, >CH_2), 2.34-2.28 (m, 1H, >CH_2), 2.12 (s, 3H, -CH_3), 2.10 (s, 3H, -CH_3),2.09 (s, 3H, -CH_3) 1.86-1.78 (m,1H, >CH_2), 1.52 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): 173.1 (-CONH-), 161.6 (>C=0,>C=0),149.0, 147.1, 149.0, 47.1, 138.2, 138.1, 129.2, 128.9, 128.4, 128.1, 126.0, 122.8, 121.9, 118.3, 78.3 (>C<),74.7 (>CH_2), 30.2 (>CH_2), 24.7 (>CH_3), 20.1 (>CH_2), 13.2 (>CH_3), 12.7 (>CH_3), 12.3 (>CH_3); HR-MS: 794.8340 $(M-H)^+$, calcd. 794.8341.

(r) 6-(benzyloxy)-*N*-(1,3-dioxo-1*H*-pyrrolo[3,4-c]pyridin-2(3*H*)-yl)-2,5,7,8-tetramethylchroman-2-carboxamide (5r)

White solid; IR (KBr, ν, cm^{-1}): 3375 (>NH stretch), 2926 (aliphatic C-H), 1736 (>CO stretch); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.49 (s, -CONH-), 9.20 (s, 1H), 9.17 (d, *J=4.6 Hz*, 1H), 7.96 (d, *J=5.0 Hz*, 1H), 7.46 (d, *J=6.8 Hz*, 2H), 7.38 (t, *J=6.8 Hz*, 2H), 7.33-7.30 (m, 1H), 4.60 (s, 2H), 2.65-2.49 (m, 2H, >CH_2), 2.33-2.27 (m, 1H, >CH_2), 2.12 (s, 3H, -CH_3), 2.10 (s, 3H, -CH_3), 2.09 (s, 3H, -CH_3), 1.86-1.80 (m, 1H, >CH_2), 1.52 (s, 3H, -CH_3); HR-MS: 508.1848 $(M+Na)^+$, calcd. 508.1848.

(s) 6-(benzyloxy)-*N*-(2,5-dioxopyrrolidin-1-yl)-2,5,7,8-tetramethylchroman-2-carboxamide (5s)

White solid; IR (KBr, ν, cm^{-1}): 3370 (>NH stretch), 2927 (aliphatic C-H), 1732 (>CO stretch); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.10 (s, -CONH-), 7.48 (d, *J=7.4 Hz*, 2H), 7.40 (t, *J=7.0 Hz*, 2H), 7.35-7.31 (m, 1H), 4.68 (s, 2H), 2.79 (s, 4H, >CH_2), 2.70-2.63 (m, 2H, >CH_2), 2.39-2.29 (m, 1H, >CH_2), 2.21 (s, 3H, -CH_3), 2.17 (s, 3H, -CH_3), 2.15 (s, 3H, -CH_3), 2.02-1.93 (m, 1H, >CH_2), 1.61 (s, 3H, -CH_3); HR-MS: 459.1896 $(M+Na)^+$, calcd. 459.1894.

(t) 6-(benzyloxy)-2,5,7,8-tetramethyl-*N*-(3-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)chroman-2-carboxamide (5t)

Light yellow solid;IR (KBr, ν, cm^{-1}): 3375 (>NH stretch), 2926 (aliphatic C-H), 1736 (>CO stretch); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.02 (s, -CONH-), 7.48 (d, *J=7.0 Hz*, 2H), 7.40 (t, *J=7.0 Hz*, 2H), 7.35-7.32 (m, 1H), 6.42 (d, *J=1.8 Hz*, 1H), 4.70 (s, 2H), 2.66 (t, *J=6.6 Hz*, 2H, >CH_2), 2.39-2.33 (m, 1H, >CH_2), 2.22 (s, 3H, -CH_3), 2.18 (s, 3H, -CH_3), 2.17 (s, 3H, -CH_3), 2.11 (d, *J=1.8 Hz*, 3H, -CH_3), 1.98-1.91 (m, 1H, >CH_2), 1.61 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$):173.4

(-CONH-), 168.4 (>C=0), 167.1 (>C=0), 149.4, 146.1, 145.3 (>C<), 137.7, 128.8, 128.6, 128.0, 127.8, 126.9, 122.5, 118.4, 79.0 (>C<), 74.8 ($>CH_2$), 29.9 ($>CH_2$), 23.9 ($-CH_3$), 20.1 ($-CH_3$), 13.0 ($>CH_2$), 12.3 ($-CH_3$), 12.1 ($-CH_3$), 11.6 ($-CH_3$); HR-MS: 449.2076 $(M+H)^+$, calcd. 449.2080.

Antiepileptic Activity

The antiepileptic evaluation of the synthesized compounds was performed using reported procedures.[23,24] Male albino mice (CF-1 strain, 18-25 g) were used. Test compounds were dissolved in polyethyleneglycol (PEG-400) and were administered intraperitoneally (i.p.). The MES convulsion was measured using Ugo Basile Convulsiometer. Sodium valproate and phenytoin were used as standards in antiepileptic tests.

Neurotoxicity screening

Neurotoxicity induced by compounds (5a-t) was measured in mice by the rotarod test.[21] The mice (n=6) were trained to stay on rotating rotarod (3.2 cm diameter) that rotated at six revolutions per minute. Trained mice were given IP injection of compounds at doses (30 mg/kg, 100 mg/kg and 300 mg/kg). After 30 min the mice were allowed to place on the rotating rod. The mice fail to manage equilibrium on rod for 1 min were noted for neurotoxicity.[25]

Pentylenetetrazole seizure (PTZ) method

The mice (n=6) were administered by compounds intraperitonealy. After 30 min, mice were treated with subcutaneous injection of pentylenetetrazole (PTZ, 60 mg/kg). Then mice were placed singly in isolated-plastic cagesand were observed for 60 min. The failure to detect an episode of clonic spasms of at least 5 secis termed as protection. These results were compared with standard drug, sodium valproate (200 mg/kg, i.p).

Maximal electroshock seizure (MES) method

Antiepileptic activity of compounds (5a-t) was measured by maximal electroshock seizure (MES) method.[23] Albino mice were divided into group of 6 animals each. Maximal electroshock seizure were elicited with a 60 Hz (50 mA) for 0.2 sec via corneal electrodes. Compounds were intraperitonealy injected (0.01 mL/kg body weight) at 30 mg/kg, 100 mg/kg and 300 mg/kg doses and activity was evaluated after 0.5 hr and 4 hr. Abolishment of the hind limb tonic extensor spasm was noted.

CONCLUSION

The success of the proposed scheme is depicted as a series of chromanan hydride analogs (5a-t) was synthesized in good yield and purity by the condensation reaction of chroman hydrazides and different anhydrides. The antiepileptic activity of these analogs was determined by PTZ and MES and compared with standard drugs, sodium vaproate and phenytoin, respectively. All compounds were found to be active by applying PTZ method which supports the inhibition of PTZ-induced seizure in mice by enhancing GABAergic neurotransmission. Whereas by MES method some, not all, of the compounds were found to have good activity. At low dose of 30 mg/kg, compound 5j possessed similar or better activity as compare to standard drugs and considered as the most potent antiepileptic among the series. Most of the compounds of the series displayed lack of neurotoxicity except for compounds 5m and 5p which were toxic at the dose of 300 mg/kg after4 h. Thus, a platform for further development of related compounds into promising antiepileptic agents is suggested with lesser neurotoxicity.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

PTZ: Pentylenetetrazole Seizure; **MES:** Maximal electroshock seizure; **NT:** Neurological toxicity; **AEDs:** Antiepileptic Drugs; **SAR:** Structure Activity Relationship; **FT-IR:** Fourier-transform infrared spectroscopy; **^{1}H-NMR:** Proton nuclear magnetic resonance; **^{13}C-NMR:** Carbon-13 nuclear magnetic resonance; **GABA:** Gamma aminobutyric acid; **TMS:** Tertramethyl Silane; **IP:** Intraperitoneal.

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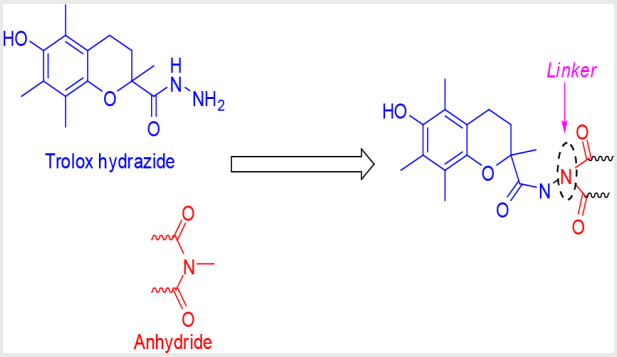
PICTORIAL ABSTRACT



SUMMARY

Chromans are considered to be an important chemical synthon, associated with a broad range of biological effects including antiepileptic activity. Antiepileptic study of test compounds (5a-t) in male albino mice by Maximal electroshock seizure (MES) and pentylenetrazole induced convulsion (PTZ) methods was carried out. Compound 5j (30 mg/kg) showed highest and advanced antiepileptic activity than reference drugs in both the methods. Moreover, none of the compounds showed neurotoxicity at 30 mg/kg and 100 mg/kg, as determined by the rotarod test.

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