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Synthesis and antioxidant properties of substituted 3-benzylidene-7-alkoxychroman-4-ones

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Abstract—A series of 3-benzylidene-7-alkoxychroman-4-one derivatives were synthesized and evaluated for their antioxidant activities. The antioxidant activity was assessed using three methods, namely, 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging, ferric reducing antioxidant power (FRAP), and thiobarbituric acid reactive substances (TBARS) assays. 3-Benzylidene-7-alkoxychroman-4-one derivatives bearing catecholic group on benzylidene moiety exhibited excellent antioxidant activity. Compounds having catechol moiety exhibited potent antioxidant activities in all tested methods and they were more active than the reference drug, Trolox.

Generation of reactive oxygen species (ROS) and free radicals in vivo is involved in a wide range of human diseases.[1] ROS, including superoxide anion, hydrogen peroxide, and hydroxyl radical, are by-products of a variety of pathways of aerobic metabolism. They are unstable and react readily with a wide range of biological substrates, such as lipids, DNA, and proteins, resulting in cell damage.[2–4] The human body possesses innate defense mechanisms to counter free radicals in the form of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. The unbalance between formation and detoxification of free radical species results in the progression of oxidative stress and leads to the development of a wide spectrum of serious diseases, for example, cancer, atherosclerosis, aging, immunosuppression, inflammation, ischemic heart disease, diabetes, hair loss, and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.[5–7] Many studies have suggested that agents with the ability to protect against ROS may be therapeutically useful in these diseases. Vitamin C, vitamin E, selenium, β-carotene, lycopene, lutein and other carotenoids have been used as supplementary antioxidants. Apart from these, polyphenolic plant secondary metabolites such as flavonoids play an important role in the defense against free radicals.[8–10] These compounds show antiviral, antibacterial, vasoactive, antiatherogenic, antiproliferative, and antiinflammatory properties, and preventing role in cancer, Alzheimer's, Parkinson's, and cardiovascular diseases.[11–13] Some of these activities are at least partially related to their antioxidant properties. Chalcones (1,3-diaryl-2-propen-1-ones) are flavonoids lacking a heterocyclic C ring. Various chalcones were assessed for their inhibitory effects on lipid peroxidation and radical scavenging activities. Among those tested, naturally occurring butein **1**, sappanchalcone **2**, and licochalcones B and D (**3** and **4**, respectively) showed potent scavenging activity on 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radicals.[14,15] On the other hand, homoisoflavonoids (3-benzylidenechroman-4-ones) are related to flavonoids and occur as natural products and exhibit biological activity. Also, among this category of flavonoids, compounds, for example, sappanone A (**5**) and intricatinol **6** displayed high antioxidant activity (Fig. 1).[16,17]

Keywords: Alkoxychroman-4-ones; Synthesis; Antioxidant activity.
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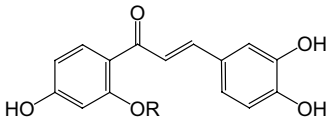
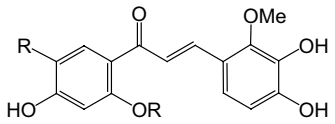
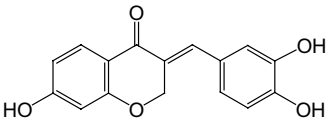


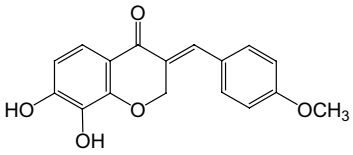
1, Butein; R= H
2, Sappanchalcone; R= Me



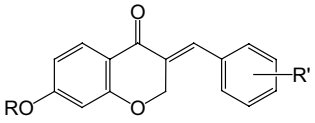
3, Licochalcone B; R= H
4, Licochalcone D; R= $CH_2CH=C(CH_3)_2$



5, Sappanone A



6, Intricatinol



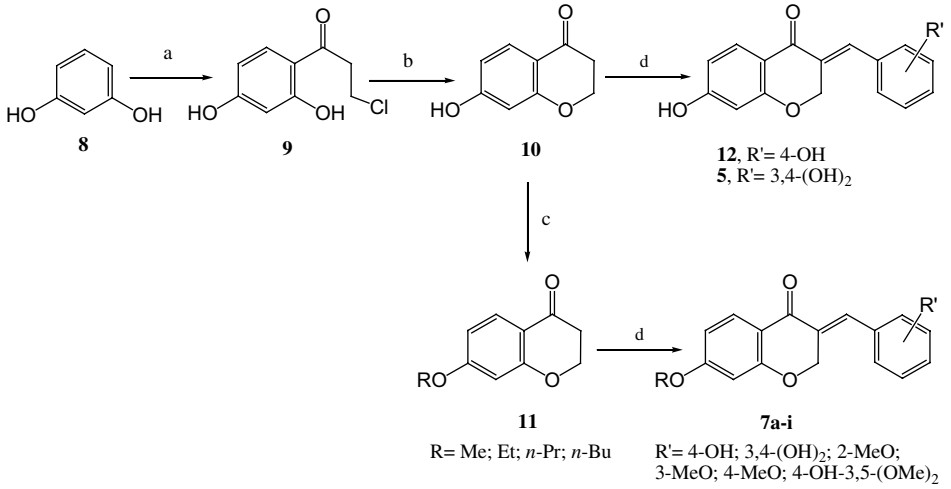
7a-i, R= Me; Et; *n*-Pr; *n*-Bu
R'= 4-OH; 3,4-$(OH)_2$; 2-MeO;
4-MeO; 4-OH-3,5-$(OMe)_2$

Figure 1.

In an effort to develop a novel antioxidant, we synthesized a series of 3-benzylidene-7-alkoxychroman-4-one derivatives **7** and evaluated their antioxidant activities (Fig. 1). Indeed, the target compounds **7** can be considered as *O*-alkyl analog of sappanone A (**5**), also possessing same basic structure in respect to intricatinol **6** but with different hydroxylation and *O*-methyl substitution pattern (alkoxy moiety on chroman ring instead on benzylidene residue).

The synthesis of 3-benzylidene-7-alkoxychroman-4-one derivatives **7** was achieved through the route outlined in Scheme 1. The reaction of resorcinol **8** with 3-chloropropionic acid using trifluoromethane sulfonic acid furnished 2′,4′-dihydroxy-3-chloro propiophenone **9** which was cyclized using 2 M NaOH to give 7-hydroxy-4-chromanone **10**, in 61% yield.[18] Alkylation of 7-hydroxy-4-chromanone **10** with appropriate alkyl iodide in the presence of K_2CO_3 gave 7-alkoxy chroman-4-one **11**.[19] Acid catalyzed condensation of 7-hydroxy-4-chromanone **10** with 4-hydroxybenzaldehyde or 3,4-dihydroxybenzaldehyde afforded 3-benzylidene-7-hydroxy-chromanones **12** and **5**, respectively.[16,20,21] Similarly, condensation of 7-alkoxy chroman-4-one **11** with different aryl aldehydes afforded 3-benzylidene-7-alkoxychroman-4-one derivatives **7** in good yields (Scheme 1).[20,21]

Antioxidants may be classified according to their mode of action as being free radical scavenger, chelators of metal ions involved in catalyzing lipid oxidation or oxy-



Scheme 1. Synthesis of 3-benzylidene-4-chromanones **5**, **7a**–**i**, and **12**. Reagents and conditions: (a) 3-chloropropionic acid, CF_3SO_3H (3 equiv) at 80 °C for 30 min; (b) 2.0 M NaOH; (c) appropriate alkyl iodide, K_2CO_3, DMF; (d) HCl (gas), CH_3COOH, appropriate aldehyde.

gen scavengers that react with oxygen in closed systems.[22] Several different methods are available and have been used to assess the total antioxidant capacity of numerous molecules. In the present study, three commonly used antioxidant evaluation methods, the DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging, ferric reducing antioxidant power (FRAP) methods, and thiobarbituric acid reactive substances (TBARS) assay were chosen to determine the antioxidant potential of the target compounds in comparison with Trolox.

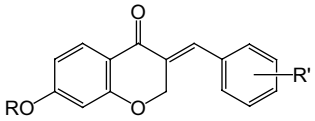
DPPH radical scavenging activity. The DPPH radical scavenging model is extensively used to evaluate antioxidant activities in less time than other methods. DPPH is a stable free radical that can accept an electron or hydrogen radical and thus be converted into a stable, diamagnetic molecule. DPPH has an odd electron and so has a strong absorption band at 517 nm. When this electron becomes paired, the absorption decreases with respect to the number of electrons taken up. The scavenging effect of the synthesized compounds on the DPPH radical was evaluated according to the method reported previously.[23,24] The IC_{50} values of these compounds are presented in Table 1. Among 3-benzylidene-7-alkoxychroman-4-ones, compounds **7f–i** (IC_{50}: 24.30 ± 0.51 to 27.15 ± 0.52 μM), having catechol moieties, showed good DPPH free radical scavenging activity, superior in respect to sappanone A (**5**, *O*-desalkyl analog) and Trolox. The same order of activity was followed by compound **7e**, the 4′-hydroxy-3′,5′-dimethoxybenzylidene analog. In fact, all monohydroxy (or methoxy) benzylidene derivatives (**7a–d** and **12**) did not show significant DPPH free radical scavenging activity at concentrations ⩽100 μg/mL.

Lipid peroxidation inhibitory activity. The effects on lipid peroxidation in rat brain homogenates were examined using thiobarbituric acid reactive substances (TBARS) assay according to the method reported previously.[25,26] The lipid peroxidation inhibitory activity of each compound was expressed as IC_{50} value, that is, the concentration in μM necessary to inhibit TBARS formation by 50%, and was calculated from the corresponding log-dose inhibition curve. While monohydroxy (or methoxy) benzylidene derivatives (**7a–d** and **12**) showed insignificant activity ($IC_{50} > 100$ μM), catecholic compounds **7f–i** and 4′-hydroxy-3′, 5′-dimethoxybenzylidene analog **7e** exhibited potent inhibition of lipid peroxidation ($IC_{50} < 15$ μM). They were more potent than the reference compound Trolox. However, no significant difference was observed between the active compounds **7e–i**.

Ferric reducing antioxidant power (FRAP) assay. The FRAP assay measures the ability of a compound to reduce the ferric 2,4,6-tripyridyl-*s*-triazine complex to the colored ferrous complex. FRAP values are obtained by comparing the absorbance change at 593 nm in test reaction mixtures with those containing ferrous ions in known concentration.[27,28] According to the data presented in Table 1, compound **7f** having catechol and 7-methoxy substituents showed the most antioxidant power in FRAP assay. Generally, all *ortho*-hydroxy or methoxy phenolic compounds exhibited comparable or more potent antioxidant potential in FRAP assay in respect to reference drug Trolox.

Overall, the result of DPPH assay was relatively consistent with those of the FRAP and TBARS assays. In other words, a glance at Table 1 shows that compounds **7a–d** and **12** which showed no activity toward DPPH radicals were inactive also in TBARS and FRAP assays, while compounds **7e–i** and **5** that exhibited antioxidant activity based on TBARS and FRAP assays showed good activity in DPPH method as well. The present

Table 1. Antioxidant activities of 3-benzylidene-7-alkoxychroman-4-ones **7a–i** and related compounds **5** and **12** in comparison with Trolox



Compound	R	R′	DPPH radical scavenging activity (IC_{50}, μM)	Inhibition of lipid peroxidation (IC_{50}, μM)	FRAP value (Fe^{2+} μM) (100 μg)
7a	Me	4-OH	>100	>100	NA[a]
7b	Me	4-MeO	>100	>100	NA
7c	Me	3-MeO	>100	>100	NA
7d	Me	2-MeO	>100	>100	NA
7e	Me	4-OH-3,5-$(OMe)_2$	30.76 ± 0.62	10.96 ± 0.34	61.61 ± 0.58
7f	Me	3,4-$(OH)_2$	27.15 ± 0.52	12.11 ± 0.42	71.64 ± 0.47
7g	Et	3,4-$(OH)_2$	24.30 ± 0.51	11.88 ± 0.39	62.73 ± 0.48
7h	*n*-Pr	3,4-$(OH)_2$	25.44 ± 0.53	11.36 ± 0.48	53.82 ± 0.54
7i	*n*-Bu	3,4-$(OH)_2$	24.50 ± 0.58	10.96 ± 0.51	44.62 ± 0.48
5	H	3,4-$(OH)_2$	35 ± 0.47	14.33 ± 0.52	49.3 ± 0.27
12	H	4-OH	>100	>100	NA
Trolox			36.27 ± 0.49	41.57 ± 0.39	41.93 ± 0.45

[a] NA, no activity.

results demonstrate that catecholic 3-benzylidene-7-alkoxychroman-4-ones were more effective, as antioxidants in the three assays, than other monooxygenated benzylidenechroman-4-ones and well-defined antioxidant, Trolox. The antioxidative activity of these compounds lends further support to the fact that the catechol system is more important for antioxidative activity. Among catecholic compounds, comparison between antioxidant activities of compound **5** and *O*-alkyl analogs **7f–i** revealed that *O*-alkyl groups are well tolerated in terms of different type of antioxidative properties and in some cases, the compounds had superior activity with respect to their parent compound **5**. We conclude, therefore, that selected analogs of benzylidenechroman-4-ones that are devoid of phenolic groups on chroman ring (by O-alkylation of 7-hydroxy group) and bearing catecholic benzylidene moiety are excellent antioxidant agents in three different antioxidant assays (DPPH, TBARS, and FRAP).

Perusal of the literature also revealed a promising agreement between our results and the reported activities of a number of flavonoids. Indeed, 3-benzylidenechroman-4-ones (homoisoflavonoids) are related to flavonoids and occur as natural products and exhibit antioxidant activity. It has been reported that in other group of flavonoids, the required structural criteria for high antioxidant activity included the *ortho*-dihydroxy groups (catechol structure) in the B-ring or in the A-ring. For instance, quercetin, quercetin 3,5-di-*O*-glucoside, luteolin, (+)-catechin, (−)-epicatechin and fisetin are all highly active against DPPH radicals having $IC_{50} = 10.89$, 14.41, 11.04, 18.19, 16.09, and 14.06 μM, respectively.[29] All of them have 3′, 4′-di-OH in common, yet noticeable differences exist among their A and B rings. Other structural features, for example, the methoxy group (methoxylation) might play a certain role in reducing or increasing the activity of the flavonoids. For example, hesperetin was more

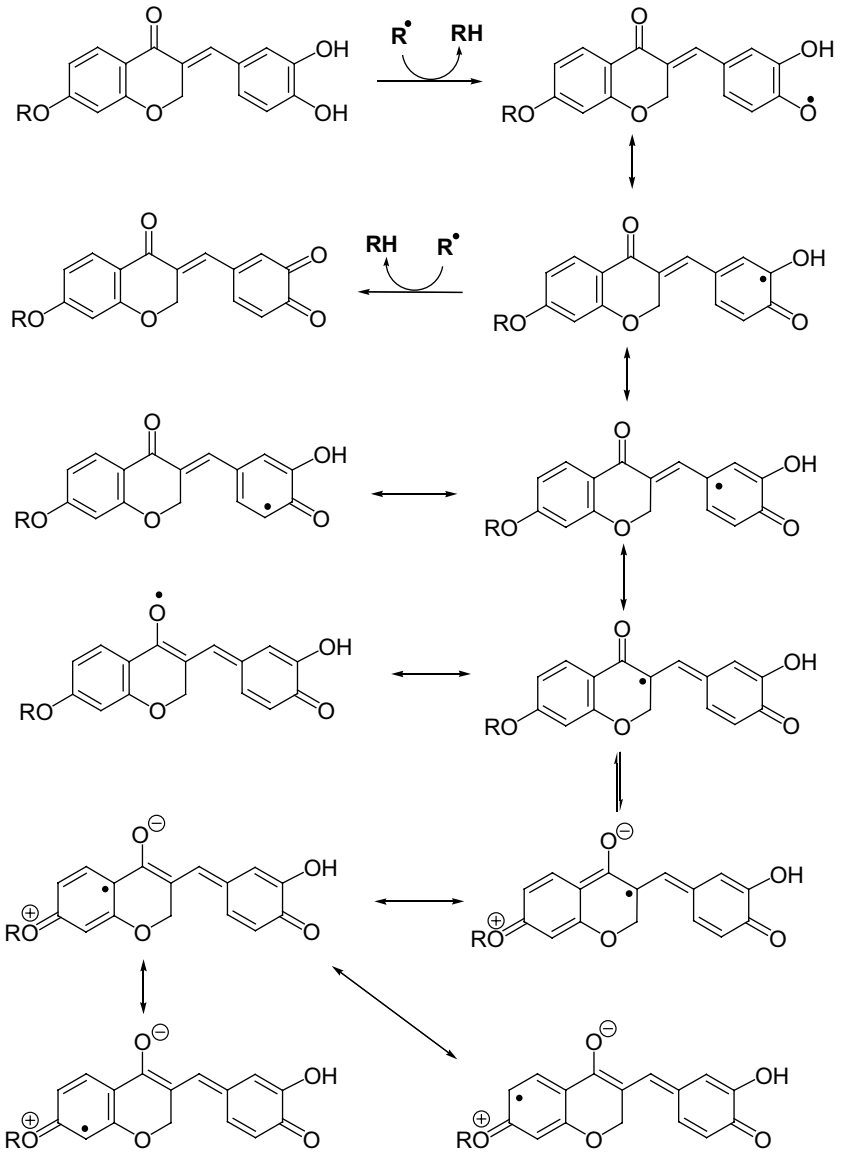


Figure 2. The proposed mechanism for the antioxidant activity of 3-benzylidene-7-alkoxychroman-4-one derivatives **7f–i**.

effective than the corresponding flavanone (naringenin) without the methoxy group, but glycitein was close to the corresponding isoflavone (daidzein) without the methoxy group.[30,31] Similarly, our observation with catecholic 3-benzylidenechroman-4-ones **7f–i** indicated that these compounds showed relatively high and close IC_{50} values ranging from 24.5 to 27.15 μM in DPPH radical scavenging method and also alkoxy substituent on the chroman ring could modulate lipophilicity and physicochemical properties. In addition, *O*-alkyl groups are well tolerated in the terms of different types of antioxidative properties and in some cases, the compounds had superior activity with respect to their parent compound **5**.

Antioxidative activity is a multifactorial potential. Propensity of radical formation and stabilization, ability of metal complexation, and lipophilicity are important factors for the antioxidant activity. The presence of *ortho*-electron donating hydroxy or methoxy substituent of the phenolic compounds is known to increase the stability of the radical and hence, the antioxidative activity.[32] This would also contribute to the formation of the complex with transition metal ions. In addition, the formation of an internal hydrogen-bond in catechol moieties and presence of *para*-substituted conjugated side chains result in a high propensity to electron transfer and stabilization of radical species. Considering these possibilities, an explanation for the potent antioxidant activity of 3-benzylidene-7-alkoxychroman-4-one derivatives **7f–i** might be found in the possible stabilization of the radical that is formed after hydrogen abstraction. As shown in Figure 2, the free electron that is generated due to hydrogen abstraction of one of the catecholic hydroxyl groups can be delocalized over the 3-benzylidene moiety and chromanone ring. This involves a keto–enol transformation of the carbonyl group, and the extension of conjugation to chroman ring. In this way the unpaired electron is transferred to the carbonyl group. The unpaired electron can then be transferred to the other aromatic group in chroman ring. As could be seen from Figure 2, in some of these structures, the positive charge is located on the 7-oxygen atom to which alkyl is attached. The electron releasing character of alkyl attached to oxygen particularly stabilized the latter species. This indicated that the presence of the *O*-alkyl groups at C-7 position of 3-benzylidenechroman-4-one could be beneficial for radical stabilization and strengthen the activity of the catecholic 3-benzylidene-7-alkoxychroman-4-one analogs.

In summary, 3-benzylidene-7-alkoxychroman-4-one derivatives bearing catecholic group on benzylidene moiety exhibited excellent antioxidant activity.

Acknowledgments

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19. *General procedure for synthesis of 7-alkoxychroman-4-ones (**11**):* To a solution of compound **10** (1 mmol), potassium carbonate (1 mmol) in dimethyl formamide (3 mL) was added appropriate alkyl iodide (1.2 mmol). The mixture was heated in 80 °C for 1 h, the cooled reaction mixture was diluted with water (7 mL) and the product was extracted with $CHCl_3$ (3× 10 mL). The combined organic layer was washed with water, dried, and evaporated to give crude **11**. The compound was purified with a short column (silica gel) using chloroform as eluent.
Compound **11c**: yield 81%; mp 40–41 °C, light cream powder; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, 1H, H_5, J = 8.7 Hz), 6.56 (dd, 1H, H_6, J = 8.7 and 2.3 Hz), 6.38 (d, 1H, H_8, J = 2.3 Hz), 4.5 (t, 2H, H_2, J = 6.4 Hz), 3.94 (t, 2H, OCH_2, J = 6.5 Hz), 2.74 (t, 2H, H_3, J = 6.4 Hz), 1.77 (sixtet, 2H, CH_2, J = 6.5 Hz), 1.03 (t, 3H, CH_3, J = 6.5 Hz); IR (KBr, cm^{-1}) 1685 (C=O); EIMS (*m*/*z*, %) 207 (M^++1, 83), 134 (100), 106 (98), 78 (47), 50 (73). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.62; H, 6.98.
Compound **11d**: yield 82%; mp 34–36 °C, white powder; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, 1H, H_5, J = 8.9 Hz), 6.56 (dd, 1H, H_6, J = 8.9 and 2.3 Hz), 6.38 (d, 1H, H_8, J = 2.3 Hz), 4.50 (t, 2H, H_2, J = 6.3 Hz), 3.98 (t, 2H, OCH_2, J = 6.2 Hz), 2.73 (t, 2H, H_3, J = 6.3 Hz), 1.98–1.23 (m, 4H, CH_2–CH_2), 0.97 (t, 3H, CH_3, J = 6.2 Hz); IR (KBr, cm^{-1}) 1685 (C=O); EIMS (*m*/*z*, %) 221 (M^++1, 40), 165 (60), 137 (100), 109 (24), 92 (12), 64 (17). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.23. Found: C, 71.06; H, 7.45.

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21. *General procedure for synthesis of substituted 3-benzylidenechroman-4-ones:* Dry hydrogen chloride gas was passed through an ice-cold solution of 7-alkoxychroman-4-ones (**11**) (0.08 mol) and substituted benzaldehyde (0.1 mol) in acetic acid (6 mL) for 3 min. The reaction mixture was allowed to stand at room temperature for 24 h. The precipitate was filtered, dried, and crystallized from ethanol. Representative spectral data for compounds **7e**, **7g**, **7h**, and **7i** are given.
Compound **7e**: yield 76%; mp 98–100 °C, orange powder; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1H, H_5-chroman, J = 8.8 Hz), 7.75 (t, 1H, CH, J = 1.7 Hz), 6.72–6.35 (m, 4H, aromatic), 5.8 (s, 1H, OH), 5.43 (d, 2H, H_2-chroman, J = 1.7 Hz), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); IR (KBr, cm^{-1}) 3477 (OH), 1658 (C=O); EIMS (*m*/*z*, %) 342 (M^+, 30), 341 (80), 309 (25), 202 (25), 174 (18), 150 (100), 90 (18), 77 (32). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.87; H, 5.53.
Compound **7g**: Yield 82%; mp 207–209 °C, brown powder; ^{1}H NMR ($CDCl_3$) δ 7.84 (d, 1H, H_5-chroman, J = 8.8 Hz), 7.62 (t, 1H, CH, J = 1.7 Hz), 7.45 (br s, 2H, OH), 6.96–6.67 (m, 3H, aromatic), 6.58 (dd, 1H, H_6-chroman, J = 8.8 and 2.3 Hz), 6.38 (d, 1H, H_8-chroman, J = 2.3 Hz), 5.36 (d, 2H, H_2-chroman, J = 1.7 Hz), 4.07 (q, 2H, OCH_2, J = 6.9 Hz), 1.41 (t, 3H, CH_3, J = 6.9 Hz); IR (KBr, cm^{-1}) 3513 (OH), 1608 (C=O); EIMS (*m*/*z*, %) 312 (M^+, 100), 283 (25), 255 (18), 181 (12), 178 (18), 165 (98), 102 (46), 69 (18), 55 (25). Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.01; H, 5.37.
Compound **7h**: yield 67%; mp 184–186 °C, brown powder; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 1H, H_5-chroman, J = 8.6 Hz), 7.67 (t, 1H, CH, J = 1.7 Hz), 7.57 (s, 1H, OH), 7.08 (br s, 1H, OH), 7.01–6.69 (m, 3H, aromatic), 6.59 (dd, 1H, H_6-chroman, J = 8.6 and 2.3 Hz), 6.39 (d, 1H, H_8-chroman, J = 2.3 Hz), 5.37 (d, 2H, H_2-chroman, J = 1.7 Hz), 3.97 (t, 2H, OCH_2, J = 7.1 Hz), 1.82 (sextet, 2H, CH_2, J = 7.1 Hz), 1.04 (t, 3H, CH_3, J = 7.1 Hz); IR (KBr, cm^{-1}) 3452 (OH), 1608(C=O); EIMS (*m*/*z*, %) 326 (M^+, 100), 282 (13), 255 (11), 179 (18), 137 (18), 102 (13). Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.72; H, 5.37.
Compound **7i**: yield 70%; mp 165–167 °C, yellow powder; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, 1H, H_5-chroman, J = 8.8 Hz), 7.66 (t, 1H, CH, J = 1.7 Hz), 7.60 (s, 2H, OH), 6.98 (m, 3H, aromatic), 6.58 (dd, 1H, H_6-chroman, J = 8.8 and 2.3 Hz), 6.47 (d, 1H, H_8-chroman, J = 2.3 Hz), 5.38 (d, 2H, H_2-chroman, J = 1.7 Hz), 4.05 (t, 2H, OCH_2, J = 6.6 Hz), 2.52 (m, 4H, CH_2–CH_2), 0.95 (t, 3H, CH_3, J = 6.7 Hz); IR (KBr, cm^{-1}) 3513 (OH), 1603 (C=O); EIMS (*m*/*z*, %) 340 (M^+, 100), 312 (13), 283 (18), 255 (17), 220 (12), 193 (31), 147 (18), 137 (25), 102 (39), 63 (18). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.74; H, 6.05.
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24. *DPPH radical scavenging assay.* The reaction mixture containing various concentrations of the compounds and methanolic solution of DPPH (150 μM) was incubated at 37 °C for 30 min and absorbance was measured at 517 nm. The percent scavenging activity was calculated using the following formula: Inhibition (%) = $100 \times (Abs_{control} - Abs_{compound})/Abs_{control}$. The DPPH radical scavenging activity of compounds was expressed in terms of IC_{50}, which was obtained from linear regression plot between concentrations of test compound and percent inhibitions.
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26. *Thiobarbituric acid reactive substances (TBARS) assay.* Brain homogenate from young adult male Wistar rats was prepared in 0.15 M KCl (10% w/v) and centrifuged at 800*g* for 10 min, and the supernatant was used for in vitro lipid peroxidation assays. The incubation mixture in a final volume of 1 mL contained brain homogenate (0.5 mL), 0.15 M KCl, and varying amounts of synthetic agents in DMSO. Lipid peroxidation was initiated by addition of ferric chloride (200 mM) in combination with ascorbic acid (200 mM). After incubation for 20 min at 37 °C the reaction was terminated by addition of 0.5 mL cold phosphotangestic acid (10%) and equal volume of thiobarbituric acid (2×0.05 M), followed by heating at 100 °C for 10 min. Then *n*-butanol (2 mL) was added to the mixture and centrifuged at 3000 rpm, emission of supernatant organic phase being measured by spectrofluroimetry method (ex: 515 nm and em: 555 nm).
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28. *Ferric reducing antioxidant power (FRAP) assay.* The FRAP assay reagent was prepared by adding 10 vol of 300 mM acetate buffer, pH 3.6 (3.1 g sodium acetate and 16 mL glacial acetic acid), 1 vol of 10 mM 2,4,6-tripyridyl-*s*-triazine prepared in 40 mM HCl and 1 vol of 20 mM $FeCl_3$. The mixture was diluted to 1/3 with methanol and pre-warmed at 37 °C. This reagent (3 mL) was mixed with 0.1 mL diluted test compounds. The mixture was shaken and incubated at 37 °C for 8 min and the absorbance was read at 593 nm. A blank with only 0.1 mL methanol was used for calibration. The difference in absorbance between the tested sample and the blank reading was calculated and the data were expressed as μM of ferric reduced to ferrous form.
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