Bioorganic & Medicinal Chemistry Letters 19 (2009) 5419–5422

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Prenyloxyphenylpropanoids as a novel class of anticonvulsive agents

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ARTICLE INFO

Article history:
Received 15 June 2009
Revised 22 July 2009
Accepted 23 July 2009
Available online 26 July 2009

Keywords:
Mes test
Neuroprotective activity
Prenyloxyphenylpropanoids

ABSTRACT

In this study, we synthesized some natural and semi-synthetic prenyloxyphenylpropanoids (e.g., acetophenones, benzoic and cinnamic acids, chalcones, and coumarins), and we assessed their in vivo neuroprotective activity, using the mouse maximal electroshock-induced seizure model (MES test). 7-Isopentenyloxycoumarin and (2*E*)-3-{4-[(3-methylbut-2-enyl)oxy]phenyl}prop-2-enoic acid, administered ip at a dose of 300 mg/kg, suppressed MES-induced seizures in mice in a time- and dose-dependent manner.

Neurodegenerative syndromes represent a widely differentiated group of diseases affecting the nervous system, including the brain, the spinal cord, and peripheral nerves, arising from several causes, many of which are still unknown.[1] Due to their incidence, morbidity, and mortality, neurodegenerative diseases represent nowadays a huge problem from a medical, social, and financial point of view for the human society all over the world. Pathologically, neurodegeneration result from abnormalities in the functionality of specific regions of the central and the peripheral nervous systems and/or specific populations of neurons. Depending on which cluster of cells begins to undergo pathological changes, this will lead to the clinical phenotype of that particular illness. Recent studies allowed to identify a certain number of genes responsible for several neurodegenerative diseases. Moreover, during last years, valuable animal models were developed to study factors and mechanism underlying the etiology and pathogenesis of these syndromes. Currently used therapeutic approaches are able to treat the symptoms for a limited period of time but, as progression of the disease advances, these treatments become ineffective. Different therapeutic approaches were proposed, depending on which biological target is triggered. Drugs commonly used in such situations are able to restore the imbalance in neurotransmitters functionality that characterize the most part of neurodegenerative diseases. Explicative examples to this aim are (a) the use of L-DOPA in combination with DOPA-decarboxylase inhibitors in the treatment of Parkinson's disease and (b) the use of cholinomimetics and acetylcholinesterase inhibitors in the therapy of Alzheimer's disease. Other drugs that were proposed in the therapeutic management of neurodegenerative disorders include inhibitors of key enzymes like COX-2,[2] MAO-B,[3] *i*NOS,[4] and caspase,[5] heavy metal chelators,[6] radical and reactive oxygen species scavengers,[7,8] statins,[9] and finally the most recent approaches are genetic[10] and stem-cell[11] based therapies.

In recent years natural products have been re-discovered as a valuable source of novel agents exerting positive effects in the treatment of cancer and microbial infections, against which synthetic drugs failed due to progressively increasing pharmacological resistance. In addition several natural compounds were seen in the last decade to efficiently interfere at different levels with the development and progress of many neurodegenerative disorders. These include ferulic acid,[12] oleamide,[13] polyphenols,[14] tocopherols,[15] curcumin,[16] folate,[17] and coumarins.[18]

In the last five years our research group studied extensively chemical and biological properties of secondary metabolites of phenylpropanoid biosynthetic origin, and containing a sesquiterpenyl, monoterpenyl, and semiterpenyl chains attached to a phenol group. These represent quite a rare group of natural products.[19] As a continuation of our studies aimed at evaluating pharmacological properties of prenyloxyphenylpropanoids, we wish to report herein the activity of natural compounds belonging to selected subcategories (e.g., acetophenones, benzoic and cinnamic acids, chalcones, and coumarins) as in vivo neuroprotective

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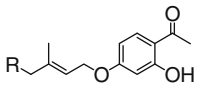
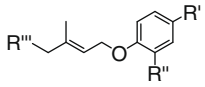
doi:10.1016/j.bmcl.2009.07.110

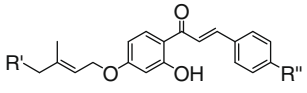
anticonvulsant agents using the mouse maximal electroshock-induced seizure model (MES test). The following secondary metabolites were synthesized and evaluated: the acetophenones 1-{2-hydroxy-4-[(3-methylbut-2-enyl)oxy]phenyl}ethanone (**1**) and 1-(4-{[(2*E*)-3,7-dimethylocta-2,6-dienyl]oxy}-2-hydroxyphenyl)-ethanone (**2**), both isolated from *Melicope* spp.[20] and *Euodia merrilli* Kanehira & Sasaki ex Kanehira[21] (Fam. Rutaceae); the vanillic acid derivatives 3-methoxy-4-[(3-methylbut-2-enyl)oxy]benzoic acid (**3**) and 4-{[(2*E*)-3,7-dimethylocta-2,6-dienyl]oxy}-3-methoxybenzoic acid (**4**), both obtained as methyl esters from the liverwort *Trichocolea lanata* (Ehrh.) Dumm. (Fam. Trichocolaceae);[22] the *p*-coumaric and ferulic acids derivatives (2*E*)-3-{4-[(3-methylbut-2-enyl)oxy]phenyl}prop-2-enoic acid (**5**), isolated from *Esenbeckia hieronymi* (Fam. Rutaceae),[23] boropinic acid (**6**), extracted from *Boronia pinnata* Sm. (Fam. Rutaceae),[24] (2*E*)-3-(4-{[(2*E*)-3,7-dimethylocta-2,6-dienyl]oxy}phenyl)prop-2-enoic acid (**7**), and (2*E*)-3-(4-{[(2*E*)-3,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)-prop-2-enoic acid (**8**), both obtained from *Acronychia baueri* Schott. (Fam. Rutaceae),[25] 3-{4-[(3-methylbut-2-enyl)oxy]phenyl}propanoic acid (**9**) and 3-(4-{[(2*E*)-3,7-dimethylocta-2,6-dienyl]oxy}phenyl)propanoic acid (**10**), both isolated as methyl esters from *Zanthoxylum pistaciiflorum* Hayata (Fam. Rutaceae);[26] the chalcones cordoin (**11**), extracted from *Millettia erythrocalyx* Gagnep.,[27] *Cordoa placa*,[28] and *Derris* spp. (Fam. Leguminosae),[29] *p*-hydroxycordoin (**12**), isolated from *C. placa*,[30] and 4′-geranyloxyisoliquiritigenin (**13**), obtained from *Millettia* spp.;[31] finally the coumarins 7-isopentenyloxycoumarin (**14**), auraptene (**15**), widespread in the genus *Citrus* (Fam. Rutaceae), collinin (**16**), isolated from *Zanthoxylum schinifolium* Siebold & Zucc. (Fam. Rutaceae), 7-hydroxy-8-isopentenyloxycoumarin (**17**), extracted from *Melampodium divaricatum* DC. (Fam Asteraceae), and lacinartin (**18**), obtained from *Z. schinifolium*, *Artemisia* and *Diosma* spp. (Fam. Rutaceae).[32]



1 R = H
2 R = isopentenyl

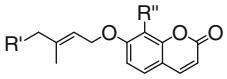


3 R′ = COOH, R″ = OCH_3, R‴ = H
4 R′ = COOH, R″ = OCH_3, R‴ = isopentenyl
5 R′ = CH=CH-COOH, R″ = H, R‴ = H
6 R′ = CH=CH-COOH, R″ = OCH_3, R‴ = H
7 R′ = CH=CH-COOH, R″ = H, R‴ = isopentenyl
8 R′ = CH=CH-COOH, R″ = OCH_3, R‴ = isopentenyl
9 R′ = CH_2CH_2-COOH, R″ = H, R‴ = H
10 R′ = CH_2CH_2-COOH, R″ = H, R‴ = isopentenyl



11 R′ = H, R″ = H
12 R′ = H, R″ = OH
13 R′ = isopentenyl, R″ = OH

Compounds **3–8** and **14–16** were synthesized as already reported.[33] Acids (**9**) and (**10**) were obtained by the same environmentally friend procedure reported for compounds **3–8** in 77% and 83% yield, respectively, and using commercially available 3-(4-hydroxyphenyl)propionic acid as the starting material. Acetophenones (**1**) and (**2**) were both synthesized in a single step procedure,



14 R′ = H, R″ = H
15 R′ = isopentenyl, R″ = H
16 R′ = isopentenyl, R″ = OCH_3
17 R′ = H, R″ = OH
18 R′ = H, R″ = OCH_3

in 76% and 68% yields, respectively, from 2,4-dihydroxyacetophenone by selective alkylation with 3,3-dimethylallyl bromide and geranyl bromide promoted by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), followed by crystallization from *n*-hexane (Fig. 1).[34]

Cordoin (**11**) was obtained in 93% yield from acetophenone (**1**) and benzaldehyde by an aldol condensation in a basic hydroalcoholic medium, followed by acidic work-up, and crystallization from *n*-hexane (Fig. 2).

The two other chalcones, *p*-hydroxycordoin (**12**), and 4′-geranyloxyisoliquiritigenin (**13**) were obtained from acetophenones (**1**) and (**2**), and *p*-hydroxybenzaldehyde in 32% and 35% yield, respectively, by a slight modification of the synthetic scheme of cordoin (**11**) (Fig. 3).[35]

Finally, coumarins (**17**) and (**18**) were obtained by the same procedure reported for compounds **14–16** in 84% and 62% yields, respectively.[34]

Compounds **1–18** were then evaluated in vivo for their neuroprotective anticonvulsant properties, using the mouse maximal electroshock-induced seizure model (MES test). Procedures involving animals and their care were carried out in accordance with current European Community and Polish legislation on animal experimentation. Additionally, all efforts were made to minimize animal suffering and to use only the number of animals necessary to record reliable scientific data. The experimental protocols and procedures described in this manuscript were approved by the Local Ethics Committee at the Medical University of Lublin (Licenses no.: 20/2008 and 26/2008), and complied with the European Communities Council Directive of 24 November 1986 (86/609/EEC). All compounds were administered intraperitoneally (ip) at a dose of 300 mg/kg. Results from the mouse MES model are reported in Table 1.

The anticonvulsant effects were considered of pivotal importance if at least 50% of the animals tested were protected against MES-induced seizures. As shown in Table 1, a well defined and distinguished pattern of results was recorded. The results partly confirm data already obtained in an in vitro study in which 7-isopentenyloxycoumarin was found to protect neuronal cells against NMDA-induced excitotoxicity.[35] Results obtained herein indicated that the compounds (**5**), (**8**), (**14**), and (**17**) considerably protected the animals against MES-induced seizures, possessing the definite anticonvulsant properties, at the respective pretreatment times in the mouse MES model. In particular for 7-isopentenyloxycoumarin (**14**) and (2*E*)-3-{4-[(3-methylbut-2-enyl)oxy]phenyl}prop-2-enoic acid (**5**) the maximum of anticonvulsant activity was reached within a very short time after ip administration, leading to a dose and time-dependent protection of all animals treated. The dose–

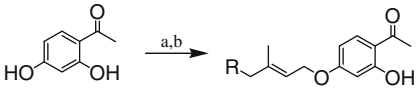


Figure 1. Reagents and conditions: (a) 3,3-dimethylallyl bromide [geranyl bromide] (1 equiv), DBU (1 equiv) acetone, rt, 24 h; (b) crystallization.

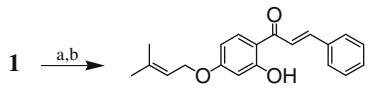


Figure 2. Reagents and conditions: (a) PhCHO (1.05 equiv), KOH (aq) 99%, EtOH, rt, 24 h; (b) crystallization.

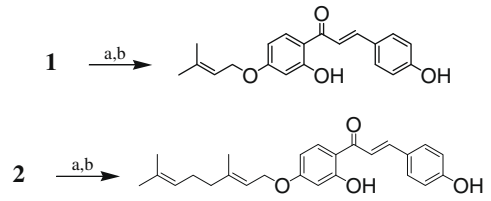


Figure 3. Reagents and conditions: (a) *p*-OHPhCHO (1.05 equiv), KOH (aq) 60%, EtOH, 100 °C→rt, 24 h; (b) crystallization.

Table 1
Time-course of anticonvulsant effects of compounds **1**–**18** against MES-induced seizures in mice

Entry	Time (min)				
	5 P/T	15 P/T	30 P/T	60 P/T	120 P/T
1	0/8	0/8	0/8	0/8	0/8
2	0/8	0/8	0/8	0/8	0/8
3	0/8	0/8	0/8	0/8	0/8
4	0/8	0/8	0/8	0/8	0/8
5	8/8	6/8	3/8	2/8	0/8
6	0/8	0/8	0/8	0/8	0/8
7	0/8	0/8	0/8	0/8	0/8
8	2/8	7/8	6/8	2/8	0/8
9	0/8	0/8	0/8	0/8	0/8
10	3/8	3/8	1/8	1/8	1/8
11	0/8	0/8	0/8	0/8	0/8
12	0/8	0/8	0/8	0/8	0/8
13	0/8	0/8	0/8	0/8	0/8
14	6/8	8/8	7/8	2/8	0/8
15	0/8	0/8	0/8	0/8	2/8
16	2/8	0/8	0/8	0/8	0/8
17	4/8	1/8	0/8	0/8	0/8
18	0/8	0/8	0/8	0/8	0/8

Data are presented as number of animals protected against maximal electroshock (MES)-induced seizures out of 8 animals per group. The MES test was performed at various pretreatment times (5, 15, 30, 60 and 120 min) after systemic (ip) administration of the investigated compounds in a fixed dose of 300 mg/kg. *P* = number of animals protected against MES-induced seizures; *T* = number of animals tested.

Table 2
Dose–response relationships of compounds **5**, **8**, and **14** against MES-induced seizures in mice

Compd	Time (min)	ED_{50} (mg/kg)	*n*[a]
5	5	228.4 ± 9.8*	16
	15	261.7 ± 20.6*	16
	30	311.5 ± 11.5*	16
	60	>> 350	–
8	5	225.1 ± 26.3*	24
	15	224.1 ± 10.7*	24
	30	223.5 ± 20.9*	24
	60	>>350	–
14	5	>>350	–
	15	238.0 ± 18.9*	16
	30	221.2 ± 21.4*	32
	60	>>350	–

* $p < 0.05$ at Student's *t* test.

[a] *n* = number of animals at those doses whose anticonvulsant effects ranged between 16% and 84%.

response relationships of the most active compounds **5**, **8**, and **14** are reported in Table 2.

All natural products taken in consideration are lipophilic, so in principle able to pass through the blood-brain barrier (BBB). The outcome that only a restricted number of compounds exhibited an appreciable anticonvulsant activity led us to hypothesize that they may trigger specific biological targets inside the CNS. From data reported in Table 1, it is evident that whole classes of compounds, like acetophenones, benzoic acid derivatives, and chalcones are totally inactive. Comparing data and structures of active and non-active products from other classes (e.g., cinnamic acids and coumarins), it arises that three structural requirements may be necessary for the observed activity: an isopentenyloxy side chain, a para-monosubstituted benzene ring, and an α,β-unsaturated carbon–carbon double bond conjugated to a carboxylate.

In fact it can be seen that both increasing the length of the O-side chain to a geranyl one, and saturating the conjugated double bond, led to a significant decrease or complete lack of activity. It seems also that the presence of a free carboxylic acid moiety or a lactone ring do not modify the anticonvulsant effect. The only notable exception to the above reported preliminary structure–activity relationship (SAR) consideration is (2*E*)-3-(4-{[(2*E*)-3,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoic acid (**8**), that, although possessing a C_{10} carbon skeleton and a disubstituted aromatic ring, is almost equal in potency to 7-isopentenyloxycoumarin (**14**) and to (2*E*)-3-{4-[(3-methylbut-2-enyl)oxy]phenyl}prop-2-enoic acid (**5**). Trying to explain this discrepancy, it could be hypothesized that these compounds exerted the observed effects acting by different mechanisms of action. Compound (**14**) is an ingredient of a patented coumarin-based pharmaceutical preparation showing a high degree of acetylcholinesterase (Ach-ase) inhibition.[39] Moreover 7-isopentenyloxycoumarin was seen to interfere on excitable cells, acting as a myorelaxant at a concentration of 100 μM on the KCl (60 mM)-induced contraction in the rat thoracic aorta, yielding a 80% inhibitory effect.[40] In addition, coumarins, structurally resembling compound (**14**), were reported to decrease spontaneous beating of cultured myocardial cells due to Ca^{+2} overload, and to be potent and selective inhibitors of key enzymes like Ach-ase and monoamino oxidase B (MAO-B). Inhibition of these enzymes was claimed to be among the main factors contributing to neuroprotection.[36–38] On the other hand (2*E*)-3-(4-{[(2*E*)-3,7-dimethylocta-2,6-dienyl]oxy}-3-methoxyphenyl)prop-2-enoic acid (**8**) was reported to be an inhibitor of COX-2 and *i*NOS.[41] Also these two enzymes were found to play a crucial role in neuroprotection.[42,43] It is also well known that natural *p*-coumaric acid derivatives structurally resembling compound (**5**), containing one or more prenyl side chains attached to the aromatic ring, exerted a valuable neuroprotective effect through the antioxidant activity.[44] Hence, it is conceivable that compounds (**5**), (**8**), and (**14**) could share the same effect but with different mechanisms of action. However the ones underlying the observed neuroprotective effects will require further efforts to be clearly depicted, and studies to this aim are currently in progress in our laboratories.

In conclusion, the findings described herein indicate that prenyloxyphenylpropanoids could be regarded as potential compounds of a novel class of anticonvulsant and in general neuroprotective agents. Considering that all tested compounds were easily synthesized from widely available and non toxic starting materials, by high-yielding, environmentally friend, and cheap synthetic routes, and that some of the active natural products are commonly extracted from edible fruits and vegetables, the present study could be considered as a topic for future studies aiming at evaluating dietary feeding chemopreventive effects on acute and chronic neurological disorders. Moreover our study may represent

a stimulus to develop a novel class of natural and semi-synthetic prenyloxyphenylpropanoids with the scope to obtain more active agents and to ameliorate the therapy of neuronal syndromes.

Acknowledgments

This study was supported by a grant (PW555/09) from the Medical University of Lublin (Lublin, Poland). The authors express their thanks to Anna Zadrozniak and Aleksandra Wlaz for their technical assistance. F.E. wish to thank Delia Pia Ravallese and Adelaide Varone for their friendly collaboration.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.07.110.

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