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Original article

Synthesis of 3-aryl-5-decapentyl-1,2,4-oxadiazoles possessing antiinflammatory and antitumor properties

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Abstract

A simple, convenient and straightforward synthesis of 3-aryl-1,2,4-oxadiazoles **4a–f** from arylamidoximes **1a–f** and palmitic acid **2** is described. Compounds **4a–f** are non-lethal in mice at four times the therapeutic dose (i.p., $LD_{50} > 1$ g kg^{-1} of the animals' body weight). These heterocycles have been found to possess antiinflammatory property similar to aspirin and ibuprofen. Three compounds, viz., **4a**, **d**, **e** have also been evaluated for antitumor activity, where **4d** exhibited an excellent activity comparable to lapachol.

Keywords: Arylamidoximes; 1,2,4-Oxadiazoles; Spectroscopy; Antiinflammatory activity; Antitumor property

1. Introduction

A search of literature revealed that several 1,3,4-oxadiazoles containing long hydrocarbon chains have been synthesized [1]. These heterocyclic fatty acid derivatives were prepared with a view to enlarge the variety of new fatty compounds with possible biological activity. However, no biological activity tests of these fatty heterocyclic compounds have been described. To the best of our awareness, 1,2,4-oxadiazoles having long fatty acid chain at C-5 have not been reported. Therefore, it appeared attractive to undertake the synthesis of 1,2,4-oxadiazoles carrying a 15-carbon side-chain at C-5. In fact, these new heterocycles may be considered as isosters of palmitic acid esters and amides which possess interesting pharmacological properties. For example, *N*-(2-hydroxyethyl)palmitamide (PEA) helps to prevent acute respiratory diseases (ARD) in men [2,3]. It has also been shown that administration of PEA does not have any influence on the formation of antibodies [4]. The production of palmitic acid ethyl ester (PAEE) in pregnant rat and its offspring was explored with interesting findings [5]. PEA is gaining more importance as evident in the following paragraphs.

In 2001, Ueda et al. [6] purified and characterized an acid amide which selectively hydrolyzed *N*-palmitoylethanolamine. These authors also cited the previous work related to the antiinflammatory behavior of PEA [7–10]. They concluded that the mechanism of action of PEA was not clear.

In another work, Petrocellis et al. [11] tried to explain the mechanism of action of PEA and suggested that PEA might act as a positive modulator of vaniloid VR receptors or inhibit the degradation of anandamide (AEA) by inhibiting either the activity or the expression of fatty acid amide hydrolase (FAAH). Actually, PEA increases the biological activity of AEA. Here also, the exact mechanism of action for inflammation reduction was not dealt with. In the same year, Costa et al. [12] described the therapeutic effect of palmitoylethanolamide (PEA) and demonstrated its curative effect in acute inflammation. They concluded that the inhibition of COX activity and of NO and free-radical formation at the inflammation sight might be responsible for the activity. Lambert et al. [13], revising their work on PEA considered this compound as a new class of antiinflammatory agent and thought that PEA (an endogenous compound) is accumulated at the inflammation site and helps to suppress it. Very recently,

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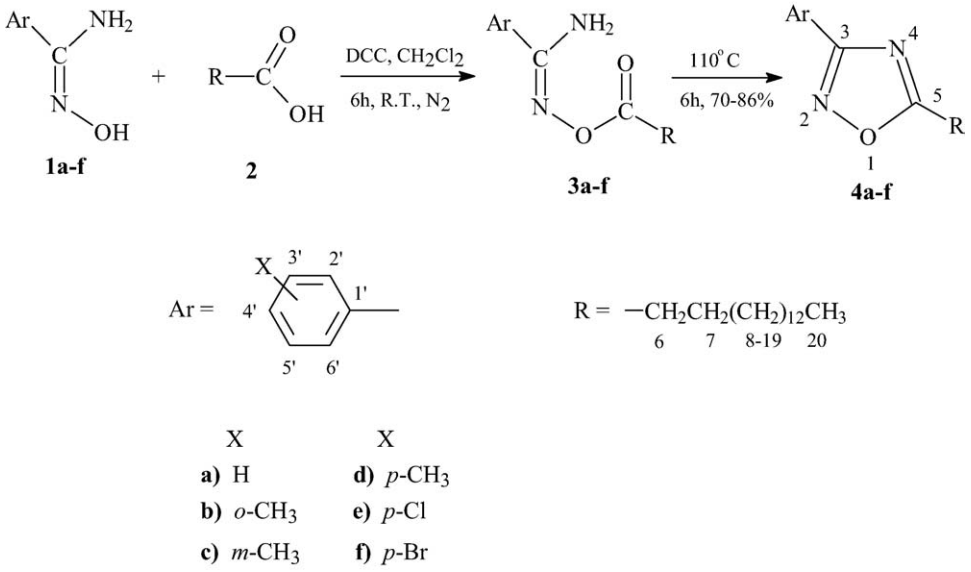
Verme et al. [14] identified the nuclear receptor peroxisome proliferator-activated receptor-α (PPAR) which secures the fatty acid amide (PEA) and causes the inflammation reduction. A recent publication also reports the antiinflammatory activity of triterpene-fatty acid esters and free fatty acids [15].

1,2,4-Oxadiazoles themselves are significant in terms of their pharmacological properties. Several such activities have been cited by Kaboudin and Navaee [16]. 1,2,4-Oxadiazoles with propyl and isopropyl functions at C-5 have been found to possess antiinflammatory activity [17,18]. The title compounds **4a–f** exhibited antiinflammatory activity closely resembling to aspirin and ibuprofen. Further, compounds **4a**, **d**, **e** were tested for antitumor activity where **4d** has demonstrated the growth inhibition of carcinoma cells by 75%. Thus, it is clear that the 1,2,4-oxadiazole nucleus is quite interesting and might disclose more undiscovered biological activities. Therefore, this contribution reports for the first time a simple and straightforward synthesis of six 1,2,4-oxadiazoles having a long hydrocarbon chain attached at C-5 (Scheme 1) possessing antiinflammatory and antitumor properties.



Scheme 1.

2. Chemistry

The title 1,2,4-oxadiazoles **4a–f** have been prepared by reacting arylamidoximes **1a–f** with palmitic acid **2** in the presence of dicyclohexylcarbodiimide. The formation of the intermediates **3a–f** were visualized on the thin-layer chromatogram. Filtration and work-up left crude **3a–f** in almost quantitative yield. No effort was made to purify them because even slight heating causes some ring closure hence the product remains as a mixture of **3a–f** and **4a–f**. These were heated individually for about 6 h at 110 °C for complete cyclization. The structures of **4a–f** were verified by the spectroscopic data period. The infrared spectra (KBr pellets) and the ^{1}H NMR chemical shift data agreed with the proposed structures.

Two of these compounds, **4b** is a thick oil while **4c** is a paste, but the others could be recrystallized from chloroform/n-hexane.

3. Experimental

3.1. General

Melting points were determined with a digital Melting Point Apparatus, series 1A-9100, Electrothermal Engineering Ltd., UK, and are uncorrected. Elemental analyses of all compounds were carried out by Eliete de Fátima V. Barros of our Department. Infrared spectra were recorded on a Bruker spectrophotometer Model IF S66 using KBr pellets, and the ^{1}H NMR spectra were measured with a 300 MHz Varian Unity Plus Instrument in $CDCl_3$ employing tetramethylsilane (TMS) as an internal standard. Low resolution mass spectra of all compounds were obtained on a Finnigan MATGCQ ion trap instrument, having electron energy of 70 eV. Thin-layer chromatography (TLC) was done on plates coated with silica gel g (Merck) containing fluorescent indicator (F_{254}). The plates were developed with chloroform/n-hexane (4:1) and the spots were visualized under ultraviolet light. Commercially available solvents and reagents were used for the experiments described in this paper.

3.2. Synthesis

3.2.1. Benzamidoximes *1a–f*

Benzamidoxime and ring substituted benzamidoximes were synthesized by the method reported earlier [19,20].

3.2.2. 3-Aryl-5-decapentyl-1,2,4-oxadiazoles *4a–f*

An appropriate arylamidoxime **1** (1.0 mmol), palmitic acid **2** (1.0 mmol) and dicyclohexylcarbodiimide (1.25 mmol) were

dissolved in dichloromethane (5.0 ml) and left under stirring for 6 h at room temperature under nitrogen atmosphere. TLC (cyclohexane/ethyl acetate, 9:1) confirmed the consumption of all arylamidoxime. Filtration of dicyclohexylurea and washing the solid with a little dichloromethane gave a transparent solution which contained largely the intermediate *O*-palmitoylbenzamidoxine **3a–f**. Each intermediate was heated individually at 110 °C for about 6 h for complete cyclization. Further purification was achieved by passing the crude 1,2,4-oxadiazole through a column containing silica gel. The pure compound could be eluted with cyclohexane/ethyl acetate (9.9:0.1). Thus, all oxadiazoles **4a–f** have been obtained in the pure form. The yields furnished below are of chromatographically pure compounds. Oxadiazoles **4a**, **d–f** were crystallized and recrystallized from chloroform–*n*-hexane. The details of each compound are given below:

*3.2.2.1. 5-Decapentyl-3-phenyl-1,2,4-oxadiazole (**4a**).* M.p. 44.5–45.0 °C (86%), R_f = 0.50; IR (KBr): 3060 (ν C–H, aromatic), 2947 (ν CH_3), 2920 (ν_{as} CH_2), 2839 (ν_s CH_2), 1598 (ν C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.05–8.09 (m, 2H, Ar-H), 7.45–7.51 (m, 3H, Ar-H), 2.94 (t, 2H, H-6, H-6′), 1.87 (p, 2H, H-7, H-7′), 1.18–1.45 (m, 24H, H-8, H-8′ to H-19, H-19′), 0.88 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 180.1 (C-5); 168.2 (C-3), 131.0 (C-4'), 128.8 (C-3′ and C-5′), 127.4 (C-2′ and C-6′), 126.9 (C-1′), 31.9 (C-6), 29.66, 29.64, 29.61, 29.5, 29.4, 29.3, 29.1, 29.0, 26.7, 26.6, 22.7 (C-7 to C-19), 14.1 (C-20); MS (EI): *m/z* (M^+, 356); Anal. Calcd. for $C_{23}H_{36}N_2O$ (356.5194): C, 77.47; H, 10.17; N, 7.85. Found: C, 77.61; H, 10.17; N, 8.16%.

*3.2.2.2. 5-Decapentyl-3-(o-tolyl)-1,2,4-oxadiazole (**4b**).* Colorless oil (70.3%), R_f = 0.49; IR (KBr): 3063 (ν C–H, aromatic), 2928 (ν_{as} CH_2), 2853 (ν_s CH_2), 1592 (ν C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.94–8.00 (dd, 1H, *J* = 7.5 Hz, *J* = 1.8 Hz, Ar-H), 7.26–7.42 (m, 3H, Ar-H), 2.95 (t, 2H, H-6, H-6′), 1.88 (p, 2H, H-7, H-7′), 1.19–1.50 (m, 24H, H-8, H-8′ to H-19, H-19′), 0.88 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 178.9 (C-5), 168.8 (C-3), 138.1 (C-2′), 131.3 (C-4′), 130.4 (C-6′), 129.9 (C-3′), 126.2 (C-1′), 125.9 (C-5′), 29.66, 29.64, 29.61, 29.5, 29.4, 29.3, 29.1, 29.0, 26.6, 26.5, 22.7 (C-7 to C-19), 14.1 (C-20); MS (EI): *m/z* (M^+, 370); Anal. Calcd. for $C_{24}H_{38}N_2O$ (370.5492): C, 77.79; H, 10.34; N, 7.56. Found: C, 77.97; H, 10.42; N, 7.87%.

*3.2.2.3. 5-Decapentyl-3-(m-tolyl)-1,2,4-oxadiazole (**4c**).* Paste (70%), R_f = 0.54; IR (KBr): ~3050 (ν C–H, aromatic), 2926 (ν_{as} CH_2), 2854 (ν_s CH_2), 1576 (ν C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.84–7.92 (m, 2H, Ar-H), 7.28–7.40 (m, 2H, Ar-H), 2.94 (t, 2H, H-6, H-6′), 2.42 (s, 3H, Ar-CH_3), 1.87 (p, 2H, H-7, H-7′), 1.20–1.48 (m, 24H, H-8, H-8′ to H-19, H-19′), 0.88 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 179.9 (C-5), 168.3 (C-3), 138.6,9 (C-3′), 131.8 (C-4′), 128.7 (C-5′), 127.9 (C-2′), 126.8 (C-1′), 124.5 (C-6′), 31.9 (C-6), 29.66, 29.64, 29.61, 29.5, 29.4, 29.3, 29.1, 29.0, 26.68, 26.64, 22.7 (C-7 to C-19), 21.3 (Ar-CH_3), 14.1 (C-20); MS (EI): *m/z* (M^+, 370); Anal. Calcd. for $C_{24}H_{38}N_2O$ (370.5492): C, 77.79; H, 10.34; N, 7.56. Found: C, 77.59; H, 10.36; N, 7.59%.

*3.2.2.4. 5-Decapentyl-3-(p-tolyl)-1,2,4-oxadiazole (**4d**).* M.p. 57.1 °C (74.4%), R_f = 0.52; IR (KBr): 3063 (ν C–H, aromatic), 2954 (ν CH_3), 2917 (ν_{as} CH_2), 2848 (ν_s CH_2), 1588 (ν C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.96 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.28 (d, 2H, *J* = 8.7 Hz, Ar-H), 2.93 (t, 2H, H-6, H-6′), 2.41 (s, 3H, Ar-CH_3), 1.86 (p, 2H, H-7, H-7′), 1.18–1.48 (m, 24H, H-8, H-8′ to H-19, H-19′), 0.88 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 179.9 (C-5), 168.2 (C-3), 141.3 (C-4′), 129.5 (C-3′ and C-5′), 127.3 (C-2′ and C-6′), 124.1 (C-1′), 31.9 (C-6), 29.6, 29.5, 29.3, 29.1, 29.0, 26.7, 22.7 (C-7 to C-19), 21.5 (Ar-CH_3), 14.1 (C-20); MS (EI): *m/z* (M^+, 370); Anal. Calcd. for $C_{24}H_{38}N_2O$ (370.5492): C, 77.79; H, 10.34; N, 7.56. Found: C, 77.50; H, 10.36; N, 7.12%.

*3.2.2.5. 5-Decapentyl-3-(p-Chlorophenyl)-5-decapentyl-1,2,4-oxadiazole (**4e**).* M.p. 60.2 °C (85%), R_f = 0.56; IR (KBr): 2955 (ν CH_3), 2918 (ν_{as} CH_2), 2847 (ν_s CH_2), 1591 (ν C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 2H, *J* = 9.0 Hz, Ar-H), 7.45 (d, 2H, *J* = 8.7 Hz, Ar-H), 2.93 (t, 2H, H-6, H-6′), 1.86 (p, 2H, H-7, H-7′), 1.18–1.48 (m, 24H, H-8, H-8′ to H-19, H-19′), 0.87 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 180.3 (C-5), 167.4 (C-3), 137.1 (C-4′), 129.1 (C-3′ and C-5′), 128.7 (C-2′ and C-6′), 125.4 (C-1′), 29.64, 29.60, 29.5, 29.3, 29.1, 29.0, 26.6, 22.7 (C-7 to C-19), 31.9 (C-6), 14.1 (C-20); MS (EI): *m/z* (M^+, 390); Anal. Calcd. for $C_{23}H_{35}N_2OCl$ (390.9658): C, 70.65; H, 9.02; N, 7.17. Found: C, 70.77; H, 8.80; N, 7.36%.

*3.2.2.6. 5-Decapentyl-3-(p-bromophenyl)-5-decapentyl-1,2,4-oxadiazole (**4f**).* M.p. 63.4 °C (81%), R_f = 0.57; IR (KBr): 3081 (ν C–H aromatic), 2949 (ν CH_3), 2917 ($\nu_{as}CH_2$), 2846 (ν_sCH_2), 1593 (ν C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.61 (d, 2H, *J* = 8.7 Hz, Ar-H), 2.93 (t, 2H, H-6, H-6′), 1.86 (p, 2H, H-7, H-7′), 1.18–1.52 (m, 24H, H-8, H-8′ through H-19, H-19′), 0.88 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 180.3 (C-5), 167.5 (C-3), 132.1 (C-3′ and C-5′), 128.9 (C-2′ and C-6′), 125.9 (C-4′), 125.6 (C-1′), 29.6, 29.5, 29.3, 29.1, 29.0, 26.6, 22.7 (C-7 to C-19), 31.9 (C-6), 14.1 (C-20); MS (EI): *m/z* ($M^{+\bullet}$, 434); Anal. Calcd. for $C_{23}H_{35}N_2OBr$ (435.4198): C, 63.43; H, 8.10; N, 6.43. Found: C, 63.79; H, 8.39; N, 6.18%.

4. Biological evaluation of compounds 4a–f

4.1. Determination of acute antiinflammatory activity

Three-month-old Swiss white mice with 25–30 g body weight were maintained with water and food (Labina-Agribands of Brazil, Ltd.) ad libitum. Ten groups, each containing 10 animals, were used separately for each experiment. Saline solution (0.9%) was administered to the control group. The drugs used for comparison purposes were aspirin

Table 1
Acute antiinflammatory activity test results of compounds **4a–f**

Compound	Dose (mg kg^{-1})	Average paw weight (g)	Edema inhibition (%)
Control	–	0.155	–
Aspirin	250	0.049***	68
Ibuprofen	250	0.042***	73
CMC	–	0.147*	5
4a	250	0.109*	29
4b	250	0.070**	55
4c	250	0.051***	67
4d	250	0.051***	67
4e	250	0.103**	33
4f	250	0.102**	34

Significant differences: *$P < 0.05$ **$P < 0.005$ and ***$P < 0.001$.

and ibuprofen. All compounds were suspended in 1% carboxymethylcellulose (CMC) dissolved in water and a single dose of 250 mg kg^{-1} was administered intraperitoneally in the morning. Other animal group received 1% CMC only. Two positive and one negative antiinflammatory tests were done in three animal groups by intraperitoneal administration of 250 mg kg^{-1} of aspirin (standard for pharmacological comparative tests [21] in the first group, 250 mg kg^{-1} of ibuprofen (Brazilian Teuto Laboratory Ltd., Brazil) in the second group and 0.9% of aqueous saline solution in the third group, respectively. The antiinflammatory activity was determined by Levy and Kerley [22] method. A 0.1 ml of 1% carrageenin (Sigma, St. Louis, USA) in 0.9% aqueous NaCl solution was injected through the plantar tissue of the right hind paw of each mouse to produce inflammation. The test compounds were injected intraperitoneally 30 min later. After 4 h, their paws were cut and weighed. The results were analyzed according to the percentage of inflammation reduction as described earlier [23]. Table 1 represents the results obtained.

4.2. Determination of dose–response for antiinflammatory activity

Compounds with the best antiinflammatory activity (**4c and 4d**) and ibuprofen (obtained from Bristol-Myers Squibb, Brazil) were administrated in single doses of 50, 150, 250 and 350 mg kg^{-1}, in separate animal groups having inflammation induced by carrageenan. The reduction of inflammation was recorded after 4 h in each animal group (Fig. 1).

*4.3. Determination of acute toxicity of **4a–f***

Graded doses (50–1000 mg kg^{-1}) of the compounds were administered intraperitoneally to various groups each containing five mice [24]. On the first day, the animals were evaluated every 10 min for 4 h followed by 24, 48 and 72 h for changes in spontaneous motor activity, reactivity, gait, respiration, appearance of writhing, piloerection, etc., plus mortality. This shows that the compounds employed in these experiments did not show any abnormal phenomenon.

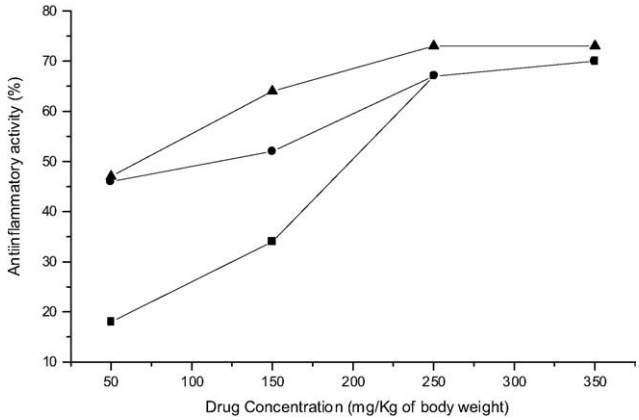


Fig. 1. Dose–response for **4c** (■), **4d** (●) and ibuprofen (▲). For introducing inflammation, 1.0% of carrageenin in 0.9% aqueous NaCl solution was used.

4.4. Statistics

The antiinflammatory activity differences between the control and test groups of various drugs were analyzed by the Student's *t*-test for independent samples. $P < 0.05$ was used as the criterion of statistical significance, which is the test standard.

*4.5. Determination of antitumor activity of **4a, d, e***

Five groups of Swiss white mice (each containing six animals) were used for carrying out the tests. The Stock et al.'s method [25] was used for pharmacological tests. The animals were disinfected, and anesthetized and subjected to a surgical intervention with one incision in the axial region where a tumor fragment was inserted subcutaneously. The treatment was started 48 h after surgical intervention. The compounds **4a**, **d**, **e** were administered intraperitoneally for 8 days in only one dose of 200 mg kg^{-1} day^{-1}. All compounds were suspended in 1% CMC solution. After completing the treatment, the animals were weighed again to observe the change in weight. The tumoral mass was removed and put in the sterilized petridish, separated by the group and finally weighed. The tumor inhibition percentage was determined by the equation: TWI = [C − T/C] × 100, where TWI = percentage of tumor growth inhibition, C = average tumor weight of control group and T = average tumor weight of the treated group [26].

5. Results and discussion

*5.1. Preliminary acute toxicity and antiinflammatory activity test of 3-aryl-5-decapentyl-1,2,4-oxadiazoles **4a–f***

All six compounds **4a–f** are non-lethal in mice at four times the therapeutic dose (i.p., $LD_{50} > 1$ g kg^{-1}). Preliminary antiinflammatory activity tests for compounds **4a–f** exhibited positive results. Oxadiazoles **4a**, **4e** and **4f** reduced carrageenan-induced edema in mice by 29, 33 and 34%,

respectively. This result is significant ($P < 0.05$) (see Table 1) compared to the control group treated with saline solution. However, compounds **4b**, **4c** and **4d**, which have a *ortho*-, *meta*- and *para*-substituent in the phenyl ring did show a significant decrease in edema (55, 67 and 67%; $P < 0.001$) greater than the control animals treated with 0.9% saline or 1% CMC solution. Furthermore, the antiinflammatory effect of compounds **4c** and **4d** were comparable with aspirin (68%) and ibuprofen (73%). These results are compiled in Table 1. Since compounds **4c** and **4d** gave the best acute antiinflammatory activity, its dose–response curve was compared with ibuprofen (see Fig. 1), which clearly shows that administration of 250 mg of compound **4c** per kg of animal's body weight reduces the inflammation by 67%. This is closer to the value obtained by ibuprofen. Increasing the dose of **4c** and **4d** to 350 mg kg^{-1} of the animal's weight slightly improves the performance of these heterocycles and brings the activity very close to ibuprofen (70 and 73%, Fig. 1). A comparison of the antiinflammatory activity of 3-(*m*-tolyl)-5-decapentyl-3-(*m*-tolyl)-1,2,4-oxadiazole **4c** and 5-decapentyl-3-(*p*-tolyl)-1,2,4-oxadiazole **4d** with oxadiazoles containing isopropyl chain at C-5 clearly shows the better performance of **4c** and **4d**, respectively [18]. We observed that all compounds with decapentyl group at C-5 of 1,2,4-oxadiazoles increased the antiinflammatory activity. This observation might be explained by postulating that the compounds with longer hydrocarbon chains are able to enter the cells more quickly and leave the cells more slowly than those with shorter chains due to their increased hydrophobicity, or perhaps the shorter molecules are excreted more quickly.

In order to get more insight especially for compounds **4c** and **4d**, we wished to compare these oxadiazoles with *N*-(2-hydroxyethyl)palmitamide (PEA). For this purpose, we synthesized PEA by the known procedure [27]. Its antiinflammatory property was determined and compared with oxadiazoles **4c** and **4d**. Carrageenan-induced edema in a group of five animals showed quite interesting results. Compound **4c** reduced inflammation by 44% in 2 h whereas PEA behaved somewhat similarly. After 4 h, the diminution was approximately 67% for **4c** and 60% for PEA. This effect gradually decreased and after 24 h, the observed decrease was only 56% which means that the drug started losing its effect after some time. However, both oxadiazole **4d** and PEA kept on decreasing the inflammation and after 30 h, a reduction of 74 and 80% were observed (Fig. 2). This clearly indicates that **4d** and PEA behave similarly.

As far as compounds **4c** and **4d** are concerned, we feel that the 1,2,4-oxadiazole moiety gets attached at PPAR-α also in a similar manner as PEA. This attachment should be through the hydrogen bonding where the hydrogen donor is from the receptor and acceptor is either PEA or 1,2,4-oxadiazole part. Both molecules have some similarity. Shorter chains due to their increased hydrophobicity, or perhaps the shorter molecules are excreted more rapidly.

Although the mechanism of inflammation reduction either by PEA or by 1,2,4-oxadiazole derivatives has not been established, it appears that both class of compounds presumably have something in common when they approach the enzyme site. Possibly PEA and oxadiazoles form hydrogen bonds with one or more amino acid residues present in the enzyme cavity.

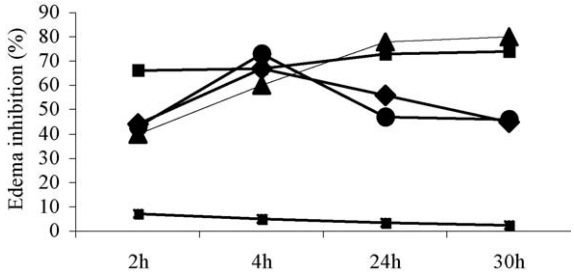


Fig. 2. Effect of PEA on edema (10 mg kg^{-1} of the animal's body weight) [▲], ibuprofen (250 mg kg^{-1}) [●], **4c** (250 mg kg^{-1}) [♦], **4 d** (250 mg kg^{-1}) [■] and CMC (1% w/v in saline) [■], after 2, 4, 24 and 30 h injection of carrageenan (1% w/v in saline solution). Each point represents the percentage of edema reduction of five animals per group.

*5.2. Preliminary antitumor activity test of 3-aryl-5-decapentyl-1,2,4-oxadiazoles **4a–f***

Tumors were created in the epithelial cells (see Section 4). Compounds **4a**, **d**, **e** showed the inhibition of 75, 55 and 23%, respectively, in descending order **4d** > **4a** > **4e**. These results were compared with lapachol which inhibited Ehrlich's carcinoma cells' growth by 80%. According to the standard of National Cancer Institute, a substance is considered active if it inhibits the tumor growth by 50% [28]. The tumor appearance of the control group gradually became intensely red with normal growth which was not limited to the surface only but started penetrating into the tissues. With the exception of **4e**, the other two compounds **4a**, **d** exhibited significant reduction in red color and turning slowly to whitish color. No tissue penetrating effects were observed. Although we tested only three compounds for this activity, it is quite clear that electron donating group at *para* position on the phenyl ring have profound influence in reducing the tumor size whereas the electron-withdrawing group diminishes such effect.

In conclusion, we have achieved the synthesis of six 3-aryl-5-decapentyl-1,2,4-oxadiazoles **4a–f** in an efficient manner. Pharmacological evaluation of these compounds revealed them to possess antiinflammatory and antitumor activities. None of the tested compounds presented any toxicity in doses ranging from 50 to 1000 mg kg^{-1} of the animals' bodyweight.

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