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Effect of Aminoethylpyrroles on Carrageenan-induced Inflammation and on Lipid Peroxidation in Rats: Some Structural Aspects

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Abstract—Nine 3-(2-aminoethyl)pyrrole derivatives were investigated as anti-inflammatory agents in the carrageenan-induced rat paw oedema model and as antioxidants in the non-enzymatic lipid peroxidation assay. It was found that the derivatives which were substituted with a *p*-toluenesulphonyl group exhibited considerable anti-inflammatory activity and some also showed antioxidant properties. However, the presence of a *p*-toluenesulphonyl group did not invariably lead to activity. A structural feature which was essential for both activities was the aminoethyl side chain. Although a relationship between the anti-inflammatory and the antioxidant activities was not apparent, the combination of these properties could be useful.

The acidic non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for their anti-inflammatory, analgesic and antipyretic properties. However, their therapeutic potential is limited due to the frequent development of gastrointestinal side-effects. The gastrointestinal lesions produced by the NSAIDs are the result, at least in part, of a direct contact mechanism which is a combination of the local irritation produced by the acidic group in the molecule and the local inhibition of the cytoprotective actions of prostaglandins on the gastric mucosa (Shanbhag et al 1992). Acidic drugs have a higher tendency to accumulate in the stomach wall soon after oral absorption (Shen 1981), while certain anti-inflammatory amines have been shown to accumulate in inflammatory exudates (Bird et al 1983). Thus, basic anti-inflammatory compounds are gaining increasing attention due to their potentially favourable physicochemical properties (Shen 1981; Schlegel et al 1984; Ronsisvalle et al 1988; Andreadou et al 1992).

Recently, it has been reported that pergolide exerts potent anti-inflammatory activity in the carrageenan-paw oedema assay and in the lipoidal amine-induced arthritis model in rats (Bendele et al 1991). Pergolide is a basic compound based on 3-(2-di-*n*-propylaminoethyl)pyrrole. Therefore, we considered it of interest to evaluate the anti-inflammatory properties of the aminoethylpyrrole derivatives *1–9* shown in Scheme 1. In these compounds, the amino side chain was kept unchanged while various substituents were introduced on the pyrrole ring in an attempt to identify suitable structural features for optimal activity.

Reactive oxygen species are implicated in the induction and prolongation of the inflammatory process, while a number of commercially available NSAIDs have been shown to possess radical scavenging properties (Roberfroid et al 1987; Halliwell & Gutteridge 1989) and it has been suggested that the presence of a pyrrole moiety in a compound increases its antioxidant potential, because the scavenged radical may be stabilized by delocalization over the pyrrole ring (Pierrefiche et al 1993). Consequently, in the present study we also investigated the antioxidant properties of the pyrrole derivatives *1–9* and related them to their anti-inflammatory activities.

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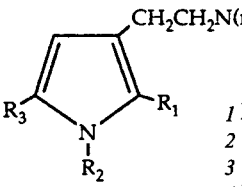

1 R_1:H, R_2:H, R_3:H
2 R_1:H, R_2:p-$CH_3C_6H_4SO_2$, R_3:H
3 R_1:H, R_2:H, R_3:CH_3C=O
4 R_1: CH_3C=O, R_2:p-$CH_3C_6H_4SO_2$, R_3:H
5 R_1:H, R_2:p-$CH_3C_6H_4SO_2$, R_3:CH_3C=O
6 R_1:C_6H_5C=O, R_2:H, R_3:H
7 R_1:H, R_2:H, R_3:C_6H_5C=O
8 R_1:C_6H_5C=O, R_2:p-$CH_3C_6H_4SO_2$, R_3:H
9 R_1:H, R_2:p-$CH_3C_6H_4SO_2$, R_3:C_6H_5C=O

SCHEME 1. Structures of compounds *1–9*.

Materials and Methods

Preparation of the aminoethylpyrroles 1–9

3-(2-Di-*n*-propylaminoethyl)pyrrole (*1*), 1-*p*-toluenesulphonyl-3-(2-di-*n*-propylaminoethyl)pyrrole (*2*), 3-(2-di-*n*-propylaminoethyl)-5-acetylpyrrole (*3*), 1-*p*-toluenesulphonyl-3-(2-di-*n*-propylaminoethyl)-2- and 5-acetylpyrroles (*4* and *5*), 3-(2-di-*n*-propylaminoethyl)-5-benzoylpyrrole (*7*) and 1-*p*-toluenesulphonyl-3-(2-di-*n*-propylaminoethyl)-5-benzoylpyrrole (*9*) were synthesized as previously described (Demopoulos 1988; Demopoulos et al 1989).

1-*p*-Toluenesulphonyl-2-benzoyl-3-(2-di-*n*-propylaminoethyl)pyrrole (*8*) was prepared, in a better yield, by a modification of the previously described method. Specifically, instead of introducing the benzoyl group under the reported Vilsmeir-Haack conditions (Demopoulos et al 1989), this was attained by refluxing *1* (1·1 g, 5·64 mmol),

benzoyl chloride (1 mL, 8·6 mmol) and triethylamine (1·5 mL, 10·8 mmol) in xylene (15 mL) for 24 h. The overall yield of *8* was 16%.

2-Benzoyl-3-(2-di-*n*-propylaminoethyl)pyrrole (*6*) was synthesized according to the following procedure. A mixture of *8* (0·75 g, 1·6 mmol), methanol (80 mL) and 5% NaOH (30 mL) was stirred at room temperature for 48 h. After this period, the mixture was poured into saturated NaCl and extracted with ethyl acetate. Evaporation of the organic solvent afforded *6* which was converted to its salt with fumaric acid (1 : 0·5) and recrystallized from 2-propanol/diethyl ether, 0·51 g (87%); mp 153–155°C. Anal. Calcd for $C_{21}H_{28}O_3N$: C, 70·76; H, 7·92; N, 7·86. Found: C, 71·06; H, 7·96; N, 7·75.

Inhibition of the carrageenan-induced oedema

Oedema was induced in the right hind paw of male Fischer-344 rats, 200 ± 20 g, by the subplantar injection of 0·1 mL 2% carrageenan in water. The test compound, suspended in physiological saline with the addition of Tween 80, or vehicle, was given intraperitoneally immediately after carrageenan injection. The rats were killed 3·5 h after carrageenan injection, and the hind paws were both excised and weighed separately. The difference between the weight of the injected and uninjected paws was calculated for each animal. The change in paw weight was compared with that in vehicle-treated control animals and expressed as a percent inhibition of the control oedema (Andreadou et al 1992).

In-vitro lipid peroxidation

Hepatic microsomal fractions were prepared from untreated male Fischer-344 rats. Fractions were heat-inactivated (90°C for 90 s) and suspended in Tris-HCl/KCl buffer (50 mM/150 mM, pH 7·4). The incubation mixtures contained the microsomal fraction, corresponding to 0·125 g liver mL^{-1}, ascorbic acid (0·2 mM) in Tris buffer, and various concentrations (0·25–1 mM) of the tested compounds dissolved in dimethylsulphoxide. An equal volume of the solvent (0·1 mL) was added to the control incubate. The reaction was started by the addition of freshly-prepared $FeSO_4$ solution (10 μM). The mixture was incubated at 37°C for 45 min. Aliquots (0·3 mL) of the incubation mixture (final volume 4 mL) were taken at various time intervals. Lipid peroxidation was assayed spectrophotometrically (535 nm against 600 nm) by determination of the 2-thiobarbituric acid-reactive material (Rekka et al 1989a). Each experiment was performed at least in duplicate.

Determination of R_M values from reversed-phase thin-layer chromatography

Silica gel normal-phase plates, impregnated with 5% (v/v) liquid paraffin in light petroleum ether, were used. As a mobile phase, a methanol/water mixture (70/30, v/v) containing 1% aqueous ammonia (27%) was used. The plates were developed in closed chromatography tanks, saturated with the polar phase. Spots were detected under UV light or by iodine vapour. R_f values were determined from at least eight individual measurements. R_M values were calculated from the corresponding R_f values (Rekka et al 1989b), applying the equation: $R_M = \log[(1/R_F) - 1]$.

Results

The anti-inflammatory effects of the synthesized aminoethylpyrroles in the carrageenan-induced rat oedema assay are presented in Table 1. All the compounds were administered intraperitoneally at a dose of 0·128 mmol kg^{-1}. Compounds *2*, *4*, *5*, *8* and *9* produced an approximately 40% oedema reduction. Compounds *1*, *3* and *7* were inactive at this dose while *6* was toxic. Indomethacin, used as a reference compound, exhibited 52% oedema reduction at an intraperitoneal dose of 4 mg kg^{-1} (11 μmol kg^{-1}).

The antioxidant potential of the aminoethylpyrroles *1–9* was studied in the non-enzymatic lipid peroxidation assay. Table 1 shows the percent inhibition of lipid peroxidation of these compounds at a concentration of 1 mM after 45 min incubation. Compound *1* was found to interfere with the assay. Compounds *3*, *5*, *7* and *8* did not show any significant effect on lipid peroxidation. The order of decreasing antioxidant activity of the rest of the compounds was *2* > *4* > *6* > *9*. The time course of lipid peroxidation, as affected by various concentrations of compounds *2*, *4*, *6* and *9* is shown in Fig. 1. DL-α-Tocopherol acetate was used as a positive control and at a concentration of 0·5 mM was found to inhibit lipid peroxidation by 100, 75, 19 and 9% after 5, 15, 30 and 45 min incubation, respectively.

The lipophilicity of the compounds was determined from reversed-phase thin-layer chromatography and expressed as

Table 1. Anti-inflammatory and antioxidant activity and R_M values of the examined aminoethylpyrroles.

Compound	Paw weight increase (%) ± s.d.[a]	Oedema reduction (%) compared with controls	Inhibition (%) of lipid peroxidation compared with controls	R_M ± s.d.
Control	76·8 ± 8·0	—	—	—
1	79·9 ± 9·6	0	Assay interference	0·305 ± 0·035
2	43·4 ± 8·1*	43	69	0·378 ± 0·028
3	74·2 ± 5·5	3	1	0·095 ± 0·020
4	49·1 ± 5·2*	36	66	0·183 ± 0·022
5	47·0 ± 9·1*	39	0	0·231 ± 0·028
6	Toxic	—	52	0·245 ± 0·031
7	77·8 ± 11·1	0	13	0·315 ± 0·038
8	41·5 ± 6·5*	46	2	0·327 ± 0·029
9	43·2 ± 8·3*	44	41	0·537 ± 0·021

[a] All compounds were administered intraperitoneally to rats (n = 5–10) at the same molar dose of 0·128 mmol kg^{-1}; *$P < 0·001$ compared with control value.

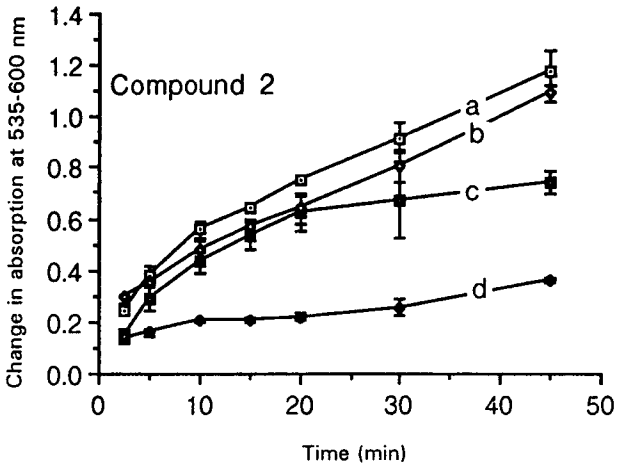

FIG. 1. Time course of lipid peroxidation, as affected by various concentrations of compounds *2*, *4*, *6* and *9*. □, 0; ○, 0·25; ■, 0·5; ●, 1 mM.

the R_M values shown in Table 1. The order of decreasing lipophilicity in this series of compounds was *9* > *2* > *8* > *7* > *1* > *6* > *5* > *4* > *3*.

Discussion

The in-vivo anti-inflammatory efficacy of the synthesized aminoethylpyrroles was assessed by using the functional model of carrageenan footpad in the rat (Winter et al 1962; VanArman 1979). This model represents the responses of clinically observed inflammatory diseases and reliably predicts the anti-inflammatory efficacy of the NSAIDs.

Concerning the structures of the tested compounds, the main difference between the active and the inactive aminoethylpyrrole anti-inflammatory agents is the presence on the former of a toluenesulphonyl functionality. Further introduction of acyl substituents at positions 2- and 5- on the pyrrole ring does not significantly influence the anti-inflammatory activity. Thus, compound *2* is equipotent with its acetyl (*4* and *5*) and benzoyl (*8* and *9*) derivatives. Also, it is worth noting that the pairs of isomers (*4* and *5*, *8* and *9*) induced similar oedema reduction.

To examine the role of the amino side chain for the observed anti-inflammatory activity in this series of pyrrole derivatives, 1-(*p*-toluenesulphonyl)pyrrole was also tested. This compound, at a dose of 0·128 mmol kg^{-1}, produced no significant oedema reduction. Thus, our data indicate that the minimal structural requirements for anti-inflammatory activity in this type of compound are both amino and arylosulphonyl functionalities.

The carrageenan oedema assay in rats, during its second phase, is particularly effective in detecting compounds that are anti-inflammatory as a result of inhibition of prostaglandin amplification (Vinegar et al 1976; Kuroda et al 1992). Recently, it has been reported that certain 3-aroyl-1-(2-aminoethyl)indoles inhibited prostaglandin synthesis and exhibited antinociceptive activity (Bell et al 1991). Taking into account that a nonclassical bioisosteric relationship exists between a carbonyl and a sulphonyl group (Silverman 1992), we suggest that there are common structural features between the anti-inflammatory pyrroles and the antinociceptive indoles which could account for their activity. These are an aminoethyl side chain and an aroyl or arylosulphonyl group introduced to a pyrrole ring at positions 1 and 3.

A significant event associated with the appearance of phagocytic cells in the injured tissue is the superoxide anion radical-dependent, ferrous ion-promoted peroxidation of membrane lipids. Lipid peroxides are in this way released and are highly pro-inflammatory (Bragt et al 1980; Hertz & Cloarec 1984; Kasama et al 1988). It has been reported that some products of lipid peroxidation are potent chemotactic factors (Petrone et al 1980; Curzio et al 1982; Hertz & Cloarec 1984) and that lipid peroxidation enhances the release of arachidonic acid (Fujimoto & Fujita 1982) and histamine (Masini et al 1990). Also, low levels of lipid peroxides can activate both cyclo-oxygenase and lipoxygenase enzymes and thereby increase eicosanoid formation (Lands & Marshall 1985; Riendeau et al 1989). A number of anti-inflammatory agents have been shown to inhibit lipid peroxidation, and this has been proposed as a part of the mechanism of their anti-inflammatory activity (Cheeseman & Forni 1988; Cynshi et al 1990; Komeshima et al 1992; Andreadou et al 1992). Furthermore, compounds which react with lipid peroxyls may suppress the enzymatic oxygenation of arachidonic acid to form bioactive lipid peroxides (Reddana et al 1985; Seeger et al 1988). Therefore, we investigated the possible interrelationship between the anti-inflammatory activity and the antioxidant properties of the synthesized aminoethylpyrroles. The antioxidant potential of these compounds was expressed as their ability to inhibit non-enzymatic microsomal lipid peroxidation in-vitro.

Concerning the structural features of the active antioxidants, we observe that the toluenesulphonyl group is present in all the aminoethylpyrrole derivatives that exhibited similar time- and concentration-dependent effects on lipid peroxidation (i.e. compounds *2*, *4* and *9*). However, its presence is not invariably connected with activity. Thus, introduction of an acetyl group at position 5 (compound *5*) or a benzoyl group at position 2 (compound *8*) leads to a loss of activity. Compound *6*, which lacks the toluenesulphonyl group, also showed some antioxidant activity. However, this was apparent only at the concentration of 1 mM. Furthermore, *6* showed a lag period in the lipid peroxidation time-course which was not observed with the other aminoethylpyrrole antioxidants containing the toluenesulphonyl functionality (Fig. 1). It has been suggested that compounds which possess easily donatable hydrogen atoms and introduce a lag period into the peroxidation time-course, are chain-breaking antioxidants (Halliwell 1990). Compound *6* contains an acidic pyrrole-NH hydrogen and, unlike *2*, *4* and *9*, may act as a chain-breaking antioxidant, scavenging intermediate radicals such as peroxy or alkoxy.

To ascertain the contribution of the amino side chain to the observed antioxidant activities in this series of pyrrole derivatives, we also tested 1-(*p*-toluenesulphonyl)pyrrole, 2-acetylpyrrole, 2-benzoylpyrrole, 1-(*p*-toluenesulphonyl)-2-acetylpyrrole and 1-(*p*-toluenesulphonyl)-2-benzoylpyrrole. These compounds showed no inhibition of lipid

peroxidation concentrations of 1 mM. A possible explanation of this could be the greater ability of the basic pyrrole derivatives, compared with their non-basic counterparts, to partition in lipid bilayers by interacting with the phosphate groups of microsomal phospholipids.

A number of experimental results indicate that a linear (Ohkawa et al 1991; Yu et al 1993) or a parabolic (Nihro et al 1991) correlation could exist between lipophilicity and activity in a series of antioxidant compounds. However, our attempts to correlate the lipophilicity (expressed as R_M values) and the antioxidant activity of the examined aminoethylpyrroles was unsuccessful. It is noteworthy that while for the pair of the benzoyl isomers (*8* and *9*) the most active antioxidant was also the most hydrophobic (i.e. *9*), the reverse occurs in the pair of the acetyl isomers (*4* and *5*) where the most active antioxidant was the least hydrophobic (i.e. *4*). Therefore, in addition to lipophilicity, other properties, such as favourable electronic distribution for reacting rapidly with radicals, or the ability to affect membrane fluidity (Nagatsuka & Nakazawa 1982; Mowri et al 1984), contribute to the observed variations in the antioxidant activity in this series of compounds.

The present study has shown that certain derivatives of aminoethylpyrrole, structurally related to pergolide, possess anti-inflammatory properties. A number of these are also antioxidants inhibiting in-vitro lipid peroxidation. Although a relationship between the anti-inflammatory and the antioxidant activities is not apparent, the ability of these anti-inflammatory compounds to inhibit lipid peroxidation is a desirable property, since it could prevent further tissue damage during the inflammatory process. Compound *2* exerts considerable anti-inflammatory as well as antioxidant activity; its preparation is simple and, therefore, it may serve as a useful lead structure.

Finally, it has been suggested that oxygen-derived free radicals are directly implicated in the mechanism of the induction of acute gastric mucosal injury by NSAIDs and that scavenging these radicals protects against injury by maintaining the integrity of the gastric mucosa (Rainsford 1989; Salim 1992). Thus, compounds which combine anti-inflammatory and antioxidant properties may have a reduced tendency to cause gastrointestinal side-effects.

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