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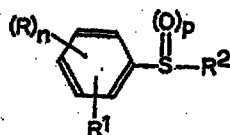


(54) PHARMACEUTICAL COMPOSITIONS

(71) We, RECKITT & COLMAN PRODUCTS LIMITED, a British Company, of Dansom Lane, Hull, Yorkshire, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pharmaceutical compositions and in particular to pharmaceutical compositions which may be used in the treatment of disorders of the cardiovascular system.

According to this invention there are provided pharmaceutical compositions comprising a compound of the formula:—



in which n is an integer 2,

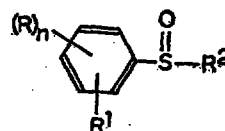
p is an integer 1 or 2,
 (R)n represents alkoxy groups having 1 to 3 carbon atoms; or when attached to adjacent carbon atoms of the benzene ring the group —O(CH2)mO— where m is an integer 1, 2 or 3,

R1 represents a hydrogen atom or when (R)n represents alkoxy groups R1 may also represent an alkoxy or alkyl group having 1 to 3 carbon atoms,

R2 represents an alkyl group having 1 to 7 carbon atoms, an alkenyl or alkynyl group having 3 to 5 carbon atoms or a hydroxy-alkyl group having 2 or 3 carbon atoms; together with one or more pharmaceutically acceptable solid diluents or carriers, or saline.

[Price 25p]

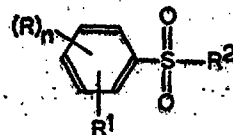
In particular the present invention provides pharmaceutical compositions comprising sulfoxides of the formula



in which R, R1, R2 and n are as hereinbefore defined together with one or more pharmaceutically acceptable diluents or carriers.

Some of the sulfoxides are described in the Specification of and claimed in our co-pending Patents Application No. 1872/73 (Serial No. 1,337,576).

In particular the present invention provides pharmaceutical compositions comprising sulphones of the formula



in which R, R1, R2 and n are as hereinbefore defined together with one or more pharmaceutically acceptable diluents or carriers.

These compositions produce a significant reduction in blood pressure when administered to normotensive, DOCA or renal rats and also cats and dogs and have utility in the treatment of those conditions in man for which an anti-hypertensive or vasodilator drug is employed. By DOCA rats is meant rats rendered hypertensive by the administration

of deoxycorticosterone acetate (DOCA) following unilateral nephrectomy.

5 The pharmaceutical compositions may be in a form suitable for oral administration or in a form suitable for parenteral administration. Compositions intended for oral use may be in the form of tablets, packaged powder or granules, or hard or soft capsules.

10 Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more sweetening, flavouring, colouring or preserving agents in order to provide pharmaceutically elegant and palatable preparations.

Tablets contain the compound of said formula in admixture with excipients which are suitable for manufacture of tablets. These excipients may be inert diluents, such as, calcium phosphate, lactose, sucrose or dextrose; granulating and disintegrating agents, such as starch or alginic acid; binding agents such as starch, gelatine or acacia; and lubricating agents such as magnesium stearate, stearic acid or talc.

30 Compositions for oral use in the form of hard gelatine capsules contain the compound of said formula mixed with an inert solid diluent such as calcium phosphate, lactose or kaolin, or as soft gelatine capsules in which the compound of said formula is mixed with an oily medium such as arachis oil, liquid paraffin or olive oil.

35 Compositions intended for parenteral administration may be in the form of sterile injectable preparations such as solutions or suspensions in saline. The preparations may also contain suitable wetting agents and suspending agents.

40 For the purposes of convenience and accuracy of dosing the compositions are advantageously employed in a unit dosage form. For oral administration the unit dosage form contains from 1mg to 500mg, preferable from 10mg to 100mg, of the compound of said formula. Parenteral unit dosage forms contain from 1mg to 10mg of the compound of said formula per 1ml of the preparation. The compounds of said formula may be prepared by oxidising the corresponding thioethers. The oxidation may be carried out employing as the oxidising agent hydrogen peroxide, N-halosuccinimides, 1-chlorobenzotriazole and other known chemical equivalents.

50 In the preparation of compounds of said formula in which $p=1$ (sulphoxides) suitable methods for carrying out this oxidation include the use of hydrogen peroxide in acetic acid, N-bromosuccinimide or N-chlorosuccinimide in methanol, and 1-chlorobenzotriazole in methanol or methylenechloride. In order to minimise the formation of a further oxidation product, namely the sulphone ($p=2$) an equi-

molar proportion of the oxidising agent should be employed, and the oxidation conducted at 0—20°C.

In the preparation of compounds of said formula in which $p=2$ (sulphones) a convenient process for carrying out the oxidation is in acetic acid using a 2—3 fold excess of hydrogen peroxide and heating the mixture on a steam bath.

75 The thioethers used as starting materials may be readily prepared from thiols for example by treatment with an organo-halide or sulphate.

The following examples illustrate the preparation of compounds which may be used in the preparation of the pharmaceutical compositions of the invention:—

Example 1.

3,4-Dimethoxyphenylmethyl sulfoxide
3,4 - Dimethoxythiophenol (28.3g, 0.17 mole; A. A. Levi and S. Smiles. J. Chem. Soc. 520 (1931)) was added to sodium (3.83g, 0.17 mole) in absolute ethanol. Dimethyl sulphate (20.8g, 0.17 mole) was slowly added to the mixture which was then refluxed for two hours. The solvent was removed under reduced pressure. The residue was extracted with chloroform. The extracts were washed with water, dried over magnesium sulphate and evaporated to give 3,4-dimethoxyphenylmethyl sulphide (28.6g) b.p. 110°C/0.8 mm.

Anal. Calcd. for $C_9H_{12}O_2S$: C, 58.7 : H, 6.6 : S, 17.4

Found: C, 58.5 : H, 6.4 : S, 17.2%

30% Hydrogen peroxide (11.3ml, 0.1 mole) was added to the 3,4-dimethoxyphenylmethyl sulphide (18.4g, 0.1 mole) in glacial acetic acid (100 ml.) with cooling. The mixture after remaining at room temperature for 24 hours was made alkaline by the slow addition of ice-cold aqueous sodium hydroxide. The mixture was extracted with chloroform. The extracts were washed with water, dried over magnesium sulphate and evaporated to dryness under reduced pressure to give white crystalline 3,4-dimethoxyphenylmethyl sulphoxide (15.1g). A sample recrystallised from diisopropyl ether had m.p. 82—84°C.

Anal. Calcd. for $C_9H_{12}O_3S$: C, 54.1 : H, 6.1 : S, 16.0

Found: C, 53.9 : H, 6.3 : S, 15.7%

Example 2.

3,4-Dimethoxyphenylethyl sulfoxide
3,4-Dimethoxythiophenol (8.6g, 0.05 mole), sodium (1.15g, 0.05 mole), ethanol (50ml.) and ethyl iodide (7.8g, 0.05 mole) were reacted according to the manner of Example 1 to give 3,4-dimethoxyphenylethyl sulphide (7.3g.) b.p. 100—108°C/0.2 mm.

Anal. $C_{10}H_{14}O_2S$ requires : C, 60.7 : H, 7.1 : S, 16.2
 Found: C, 60.7 : H, 7.0 : S, 15.9%

5 The 3,4-dimethoxyphenylethyl sulphide (1.98g.) was oxidised, according to the manner of Example 1, to give 3,4-dimethoxyphenylethyl sulphoxide (1.6g.).

Anal. Calcd. for $C_{10}H_{14}O_3S$: C, 56.1 : H, 6.6
 10 Found: C, 56.0 : H, 6.4%

Example 3.

2,5-Dimethoxyphenylmethyl sulphoxide
 2,5 - Dimethoxythiophenol (2.8g., 0.017 mole: Suter and Hansen J. Am. Chem. Soc. 54, 4102, (1932)) was added to sodium (0.4g., 0.017 mole) in absolute ethanol. Dimethyl sulphate (2.1g., 0.017 mole) was slowly added to the mixture which was then refluxed for two hours. The solvent was removed under reduced pressure. The residue was extracted with chloroform. The extracts were washed with water, dried over magnesium sulphate and evaporated to give 2,5-dimethoxyphenylmethyl sulphide (2.8g.) b.p. 92—96°C/0.3 mm.

Anal. Calcd. for $C_9H_{12}O_2S$: C, 58.7 : H, 6.6 : S, 17.4
 Found: C, 59.0 : H, 6.5 : S, 17.5%

The 2,5-dimethoxyphenylmethyl sulphide (2.3g.) was oxidised according to the manner of Example 1 to give 2,5-dimethoxyphenylmethyl sulphoxide (1.8g.) m.p. 70—72°C. 30

Anal. Calcd. for $C_9H_{12}O_3S$: C, 54.1 : H, 6.1 : S, 16.0
 Found: C, 53.5 : H, 6.0 : S, 16.5% 35

Example 4.

3,4-Dimethoxyphenylmethyl sulphone
 3,4 - Dimethoxyphenylmethyl sulphide (6.1g., 0.03 mole) and 30% hydrogen peroxide (11.3ml., 0.1 mole) were heated on a steam bath for 2 hours in glacial acetic acid (100ml.) The mixture was poured on to ice (300g.) and the resulting white precipitate filtered, washed well with water and recrystallised from ethanol to give 3,4-dimethoxyphenylmethyl sulphone (5.7g.) m.p. 115—117°C. 40

Anal. Calcd. for $C_9H_{12}O_4S$: C, 50.0 : H, 5.6 : S, 14.8
 Found: C, 49.8 : H, 5.8 : S, 14.7 45

The Table below sets out details of further examples of compounds of said formula. The compounds in which $p=1$ (sulphoxides) were prepared by the method of Example 1, and those in which $p=2$ (sulphones) were prepared by the method of Example 5. 55

TABLE

Ex- ample	Substituent on Benzene Ring						R ²	p	m.p. °C	Formula	% Calcd.			% Found		
	2	3	4	5	6						C	H	S	C	H	S
5		MeO	MeO				<i>n</i> -Pr	1	—	C ₁₁ H ₁₆ O ₃ S	57.9	7.1	14.1	57.7	7.0	13.6
6		MeO	MeO				<i>i</i> -Pr	1	68—70	C ₁₁ H ₁₆ O ₃ S	57.9	7.1	14.1	57.9	6.9	14.1
7		MeO	MeO				<i>n</i> -Bu	1	—	C ₁₂ H ₁₈ O ₃ S	59.5	7.5		59.5	7.6	
8		MeO	MeO				<i>i</i> -Bu	1	—	C ₁₂ H ₁₈ O ₃ S	59.5	7.5		58.9	7.4	
9		MeO	MeO				CH ₂ CH=CH ₂	1	—	C ₁₁ H ₁₄ O ₃ S	58.5	6.2		58.5	6.3	
10		MeO	MeO				CH ₂ CH ₂ OH	1	125—6	C ₁₀ H ₁₄ O ₄ S	52.2	6.1	13.9	51.8	6.1	13.8
11	MeO		MeO				Me	1	—	C ₉ H ₁₂ O ₃ S	54.1	6.1		53.7	6.0	
12	MeO					MeO	<i>n</i> -Pr	1	—	C ₁₁ H ₁₆ O ₃ S	57.9	7.1		57.9	7.3	
13	MeO					MeO	<i>i</i> -Pr	1	—	C ₁₁ H ₁₆ O ₃ S	57.9	7.1		57.7	6.9	
14	MeO					MeO	<i>n</i> -Bu	1	—	C ₁₂ H ₁₈ O ₃ S	59.5	7.5	13.3	59.3	7.2	12.8
15	MeO					MeO	<i>i</i> -Bu	1	—	C ₁₂ H ₁₈ O ₃ S	59.5	7.5		59.3	7.2	
16	MeO					MeO	CH ₂ CH=CH ₂	1	—	C ₁₁ H ₁₄ O ₃ S	58.5	6.2		58.8	6.3	
17	MeO					MeO	CH ₂ CH ₂ OH	1	108—110	C ₁₀ H ₁₄ O ₄ S	52.2	6.1	13.9	52.4	6.1	14.1

TABLE (Continued)

Ex- ample	Substituent on Benzene Ring					R ²	P	m.p. °C	Formula	% Calcd.			% Found		
	2	3	4	5	6					C	H	S	C	H	S
18		MeO	MeO	MeO		Me	1	74-6	C ₁₀ H ₁₄ O ₄ S	52.2	6.1	13.9	52.2	6.1	13.9
19		EtO	EtO			Me	1	61-2	C ₁₁ H ₁₆ O ₃ S	57.9	7.1	14.1	57.6	6.9	14.0
20		OCH ₃ , CH ₃ O				Me	1	—	C ₉ H ₁₀ O ₃ S	54.6	5.1	16.2	53.8	5.0	16.1
21	MeO	MeO				Me	1	—	C ₉ H ₁₂ O ₃ S	54.1	6.1	16.0	54.1	6.0	16.2
22	MeO				MeO	Me	1	97-8	C ₉ H ₁₂ O ₃ S	54.1	6.1	16.0	53.6	6.2	15.7
23		MeO		MeO		Me	1	74-6	C ₈ H ₁₂ O ₃ S	54.1	6.1	16.0	54.3	6.2	16.0
24		EtO	EtO			n-Pr	1	—	C ₁₃ H ₂₀ O ₃ S	61.0	7.9	12.5	60.7	8.2	12.0
25		MeO	MeO			n-Am	1	—	C ₁₃ H ₂₀ O ₃ S	61.0	7.9	12.5	60.6	8.0	12.0
26		MeO	MeO			n-C ₇ H ₁₅	1	—	C ₁₅ H ₂₄ O ₃ S	63.4	8.5	11.3	63.4	8.5	11.4
27		MeO	MeO		Me	Me	1	92-3	C ₁₀ H ₁₄ O ₃ S	56.1	6.6	15.0	56.0	6.5	14.9
28		MeO	MeO		MeO	Me	1	117-9	C ₁₀ H ₁₄ O ₃ S	52.2	6.1	13.9	51.7	6.2	12.5

TABLE (Continued)

Ex- ample	Substituent on Benzene Ring					R ²	p	m.p. °C.	Formula	% Calcd.			% Found		
	2	3	4	5	6					C	H	S	C	H	S
29		MeO	MeO		Me	Me	2	141—142	C ₁₀ H ₁₄ O ₄ S	52.2	6.1	13.9	52.0	6.2	14.1
30		MeO	MeO		MeO	Me	2	193—4	C ₁₀ H ₁₄ O ₆ S	48.8	5.7	13.0	48.6	5.6	12.6
31	MeO			MeO		Me	2	77—8	C ₁₀ H ₁₄ O ₆ S	48.8	5.7	13.0	49.7	5.7	14.6
32	MeO		MeO			Me	2	104—6	C ₉ H ₁₂ O ₄ S	50.0	5.6	14.9	49.7	5.6	15.2
33	MeO	MeO				Me	2	84—5	C ₉ H ₁₂ O ₄ S	50.0	5.6	14.9	49.8	5.5	15.1
34		MeO		MeO		Me	2	115—6	C ₉ H ₁₂ O ₄ S	50.0	5.6	14.9	49.9	5.6	15.0

The invention is further illustrated by the following examples of compositions in which all parts and percentages are by weight.

5

Example I.

A mixture of 1 part of 3,4-dimethoxyphenylmethyl sulphoxide, 5 parts of lactose and 5 parts of starch, together with 1% of magnesium stearate was compressed into tablets. Conveniently the tablets are of such a size as to contain 10 or 25mg of 3,4-dimethoxyphenylmethyl sulphoxide. Similarly tablets containing 50mg of 3,4-dimethoxyphenylmethyl sulphoxide were prepared from a mixture of 2 parts of the sulphoxide, 5 parts of lactose, 5 parts of starch together with 1% of magnesium stearate.

15

Example II.

A mixture of 1 part of 3,4-dimethoxyphenylmethyl sulphoxide, and 9 parts of a tablet base comprising starch with the addition of 1% magnesium stearate was compressed into tablets.

20

Conveniently the tablets are of such a size as to contain 10 or 25mg of 3,4-dimethoxyphenylmethyl sulphoxide. Similarly tablets containing 50mg of 3,4-dimethoxyphenylmethyl sulphoxide were prepared from a mixture of 2 parts of the sulphoxide, 9 parts of starch together with 1% magnesium stearate.

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Example III.

Various strength capsules are prepared containing 3,4-dimethoxyphenylmethyl sulphoxide and the following ingredients (amounts are in mg):—

35

	Sulphoxide	Magnesium stearate	Calcium phosphate	Lactose
	10	2	—	190
	25	2	—	175
5	50	3	—	150
	100	3	—	100
	10	—	20	170
	25	—	20	155
	50	—	20	130
10	100	—	20	80

The above ingredients may be screened through a 40 B.S.S. mesh screen before being mixed and filled into hard gelatine capsules.

Example IV.

- 15 Ampoules were prepared containing 5 mls of an isotonic solution prepared from 1 gm 3,4-dimethoxyphenylmethyl sulphoxide and 0.735 gm sodium chloride in 100 mls distilled water. The solution was stable to steam autoclaving at 10 psi for 35 minutes.

Example V.

- 25 The 3,4-dimethoxyphenylmethyl sulphoxide in each of the foregoing Examples I—IV may be replaced by 2,4-dimethoxyphenylmethyl sulphoxide, 3,4-dimethoxyphenylethyl sulphoxide, 2,5-dimethoxyphenylmethyl sulphoxide, 3,4-dimethoxyphenylmethyl sulphone, 2,5-dimethoxyphenylmethyl sulphone, 3,4-dimethoxyphenylpropyl sulphoxide, 3,4,6-trimethoxyphenylmethyl sulphoxide, or 3,5-dimethoxyphenylmethyl sulphoxide.

	Compound of Example No.	% Fall in Blood pressure
65	1	65
	2	50
	3	46
	4	59
	5	30
70	23	50
	28	51

The following are some of the results when compounds were administered orally to groups of DOCA hypertensive rats at dosage levels of 20, 50 and 100 mg/kg. At each dose level a group of 6 rats was employed for each compound. The figures are for the maximum percentage fall in the blood pressure.

- 75 It is expected that the likely human oral dose of a composition of the invention will be 200—500 mg of active ingredient per day for the relief of hypertension.

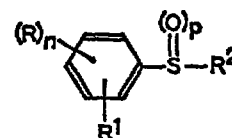
- 80 It has been shown that these compounds possess interesting and prolonged vasodilator actions which are exerted on the smooth muscle fibres of the blood vessels of the peripheral circulation. There is no action on the autonomic nervous system. That the vasodilator activity is of peripheral origin is demonstrated by the following findings:—

- 85 1. The compounds have hypotensive activity in spinalised cats and pithed rats.
2. The compounds are active against vasoconstriction produced by noradrenaline and vasopressin in a variety of isolated perfused blood vessel preparation, e.g. rabbit ear, rat mesenteric vessels.

Further the compounds antagonise the pressor effects of noradrenaline, tyramine and angiotensin in the anaesthetised cat and dog at 3 to 10 mg/Kg. Nictitating membrane contractions were also antagonised.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a compound of the formula:—



in which n is an integer 2,
p is an integer 1 or 2,

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60

95

100

	Sulphoxide	Magnesium stearate	Calcium phosphate	Lactose
	10	2	—	190
	25	2	—	175
5	50	3	—	150
	100	3	—	100
	10	—	20	170
	25	—	20	155
	50	—	20	130
10	100	—	20	80

The above ingredients may be screened through a 40 B.S.S. mesh screen before being mixed and filled into hard gelatine capsules.

Example IV.

- 15 Ampoules were prepared containing 5 mls of an isotonic solution prepared from 1 gm 3,4-dimethoxyphenylmethyl sulphoxide and 0.735 gm sodium chloride in 100 mls distilled water. The solution was stable to steam auto-
- 20 claving at 10 psi for 35 minutes.

Example V.

- 25 The 3,4-dimethoxyphenylmethyl sulphoxide in each of the foregoing Examples I—IV may be replaced by 2,4-dimethoxyphenylmethyl sulphoxide, 3,4-dimethoxyphenylethyl sulphoxide, 2,5-dimethoxyphenylmethyl sulphoxide, 3,4-dimethoxyphenylmethyl sulphone, 2,5-dimethoxyphenylmethyl sulphone, 3,4-dimethoxyphenylpropyl sulphoxide, 3,4,6-trimethoxyphenylmethyl sulphoxide, or 3,5-dimethoxyphenylmethyl sulphoxide.
- 30

	Compound of Example No.
65	1
	2
	3
	4
70	5
	11
	19

- 75 It is expected that the likely human oral dose of a composition of the invention will be 200—500 mg of active ingredient per day for the relief of hypertension.

- 80 It has been shown that these compounds possess interesting and prolonged vasodilator actions which are exerted on the smooth muscle fibres of the blood vessels of the peripheral circulation. There is no action on the autonomic nervous system. That the vasodilator activity is of peripheral origin is demonstrated by the following findings:—

- 85 1. The compounds have hypotensive activity in spinalised cats and pithed rats.
2. The compounds are active against vasoconstriction produced by noradrenaline and vasopressin in a variety of isolated perfused blood vessel preparation, e.g. rabbit
- 90 ear, rat mesenteric vessels.

Screening for antihypertensive activity has been carried out employing known pharmacological tests such as those using normotensive, DOCA and renal hypertensive rats according to the method of Stanton H. C. and White J. B., *Archs. Int. Pharmacodyn. Ther.* 154, No. 2, 351 (1966) and Weeks J. R. and Jones J. A., *Proc. Exper. Biol. & Med.* 104, No. 4, 646 (1960).

The following are some of the test results obtained with compounds of said formula. The compounds were administered intraperitoneally at a dose of 100mg/kg to groups of DOCA hypertensive rats, and the figures are for the maximum percentage fall in the blood pressure.

Compound of Example No.	% Fall in Blood Pressure.	
1	65	50
2	50	
3	46	
4	59	
5	30	
23	50	55
28	51	

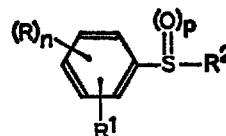
The following are some of the results when compounds were administered orally to groups of DOCA hypertensive rats at dosage levels of 20, 50 and 100 mg/kg. At each dose level a group of 6 rats was employed for each compound. The figures are for the maximum percentage fall in the blood pressure.

% Fall in Blood pressure		
	20	50
100 mg/kg dose		
30	36	53
21	34	50
5	14	21
33	41	50
16	28	42
18	18	26
24	28	44

Further the compounds antagonise the pressor effects of noradrenaline, tyramine and angiotensin in the anaesthetised cat and dog at 3 to 10 mg/Kg. Nictitating membrane contractions were also antagonised.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a compound of the formula:—



in which n is an integer 2,
p is an integer 1 or 2,



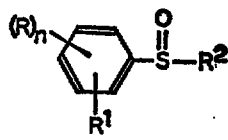


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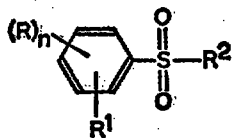
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- (R)_n represents alkoxy groups having 1 to 3 carbon atoms, or when attached to adjacent carbon atoms of the benzene ring the group —O(CH₂)_mO— where m is an integer 1, 2 or 3, R¹ represents a hydrogen atom or when (R)_n represents alkoxy groups R¹ may also represent an alkoxy or alkyl group having 1 to 3 carbon atoms, R₂ represents an alkyl group having 1 to 7 carbon atoms, an alkenyl or alkynyl group having 3 to 5 carbon atoms or a hydroxy-alkyl group having 2 or 3 carbon atoms; together with one or more pharmaceutically acceptable solid diluents or carriers, or saline.
2. A pharmaceutical composition according to Claim 1 in which the compound is a sulphoxide of the formula



- in which R, R¹, R² and n are as defined in Claim 1.
3. A pharmaceutical composition according to Claim 1 in which the compound is a sulphone of the formula



in which R, R¹, R² and n are as defined in Claim 1.

4. A pharmaceutical composition as claimed in Claim 1 or 2 in which the compound is 3,4-dimethoxyphenylmethyl sulphoxide, 3,4-dimethoxyphenylpropyl sulphoxide, 3,4-dimethoxyphenylethyl sulphoxide, 2,5-dimethoxyphenylmethyl sulphoxide, 3,5-dimethoxyphenylmethyl sulphoxide, or 3,4,6-trimethoxyphenylmethyl sulphoxide.

5. A pharmaceutical composition as claimed in Claim 1 or 3 in which the compound is 3,4-dimethoxyphenylmethyl sulphone.

6. A pharmaceutical composition as claimed in any one of the preceding Claims in unit dosage form for oral administration comprising from 1 to 500 mg of said compound.

7. A pharmaceutical composition as claimed in Claim 6 wherein the unit dosage form comprising from 10 to 100 mg of said compound.

8. A pharmaceutical composition as claimed in any one of Claims 1 to 5 in unit dosage form for parenteral administration comprising from 1 to 10 mg of said compound per 1 ml of the composition.

9. A pharmaceutical composition as claimed in any one of Claims 1 to 3 and substantially as hereinbefore described with reference to any one of Examples I to V.

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