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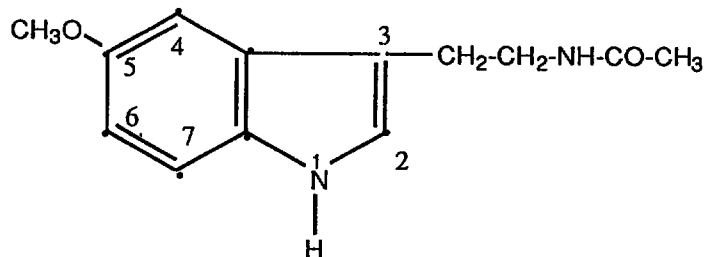
MELATONIN DERIVATIVES FOR USE
IN TREATING SLEEP DISORDERS

5

The present invention relates to a novel method of treating sleep disorders in mammals as well as pharmaceutical formulations suitable therefor.

Melatonin, represented by the structure below:

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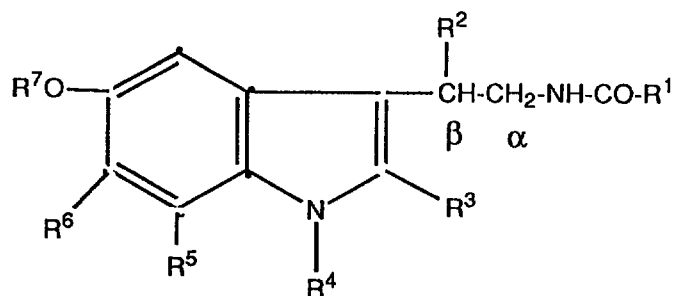
is named systematically as N-[2-(5-methoxy-3-indolyl)ethyl]acetamide. Trivial names for the compound include N-acetyl-5-methoxytryptamine and N-acetyl-O-methylserotonin. Melatonin is a pineal gland hormone which has ovulation inhibitory activity, Chu *et al.*, *Endocrinology*, **75**, 238 (1964), as well as some activity against MCF-7 human breast cancer cells, Blask *et al.* *J. Neural. Transm.* [Supp.], **21**, 433 (1986) and for the treatment of mammalian breast carcinoma, Blask *et al.*, *Neuroendocrinol. Lett.*, **9(2)**, 63 (1987). Furthermore, melatonin has been known to expedite recovery from "jet lag syndrome", Arendt *et al.*, *Ergonomics*, **30**, 1379 (1987), to cause sleep, Waldhauser *et al.*, *Psychopharmacology*, **100**, 222 (1990) and to minimize disturbances in circadian rhythms of bodily performance and function, U.S. Patent Nos. 4,600,723 and 5,242,941.

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Several melatonin analogues of the formula

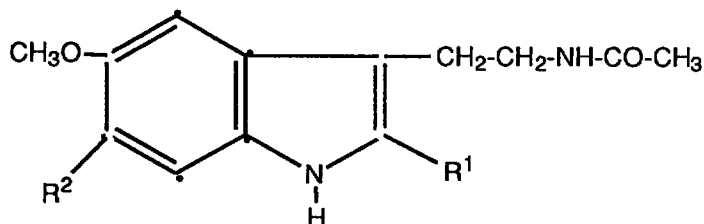


wherein

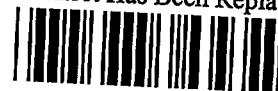
5 R^1 is hydrogen, C_1 - C_4 alkyl or C_1 - C_4 alkoxy;
 R^2 is hydrogen or C_1 - C_4 alkyl;
 R^3 is hydrogen or methyl;
 R^4 is hydrogen, haloacetyl, C_1 - C_5 alkanoyl, benzoyl or
 10 benzoyl substituted with halo or methyl;

R^5 and R^6 are individually hydrogen or halo; and
 R^7 is hydrogen or C_1 - C_4 alkyl;
 provided that when R^2 is hydrogen, at least one of R^5
 15 and R^6 is halo, have also been prepared and shown to possess
 ovulation inhibition activity (see U.S. Patent Nos. 4,997,845 and
 4,614,807). Such analogues are also stated to be active in
 treating hormonally dependent breast carcinomas in U.S. Patent
 No. 5,196,435. However, none of these references discloses the
 utility of such analogs in treating sleep disorders.

20 Finally, European Patent Application 513,702 discloses
 that melatonin and its analogues of the formula



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25 wherein R^1 and R^2 are the same or different and are hydrogen or
 halogen can be used in treating sleep disorders and in pre-
 anesthetic medication. Again, such disclosure does not teach
 the instantly claimed method of treating sleep disorders.

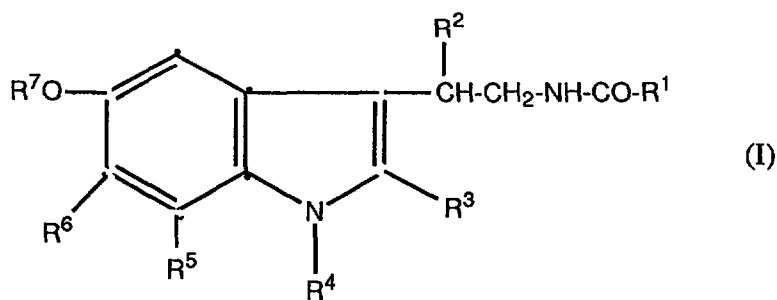
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It is an object of this invention to provide a new method for treating sleep disorders by employing certain known melatonin analogs. The instant method is believed to provide a more efficacious (in terms of bioavailability, activity, side effect profile and duration of action) means for treating such disorders than previously known. Further, the melatonin analogues used in the instant method are believed to be completely devoid of toxicity at the dosages required for treatment and, as such, a further object of the present invention is to provide a safe, efficacious, method of treating sleep disorders.

Since the present invention provides a new method for treating sleep disorders in mammals, pharmaceutical formulations suitable for such new method will be required. Accordingly, a further object of the invention is to provide pharmaceutical formulations suitable for use in the instantly claimed method.

Other objects, features and advantages of the present invention will become apparent from the subsequent description and the appended claims.

As noted above, the present invention provides a method of treating sleep disorders in a mammal suffering from such disorders which comprises administering to said mammal an effective amount of a compound of Formula (I)



wherein

R¹ is hydrogen, C₁-C₄ alkyl or C₁-C₄ alkoxy;

R² is hydrogen or C₁-C₄ alkyl;

R³ is hydrogen, C₁-C₄ alkyl, phenyl or substituted phenyl;

R⁴ is hydrogen, haloacetyl, C₁-C₅ alkanoyl, benzoyl or benzoyl substituted with halo or methyl;

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R^4 is hydrogen, haloacetyl, C_1 - C_5 alkanoyl, benzoyl or benzoyl substituted with halo or methyl;

R^5 and R^6 are each individually hydrogen or halo; and

R^7 is hydrogen or C_1 - C_4 alkyl;

provided that when R^3 , R^4 and R^5 are each hydrogen then R^2 must be C_1 - C_4 alkyl.

The following definitions refer to the various terms used above and throughout the disclosure.

The term "halo" refers to fluoro, chloro, bromo and iodo.

The term " C_1 - C_4 alkyl" refers to the straight and branched aliphatic radicals of 1-4 carbon atoms including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

The term " C_1 - C_4 alkoxy" includes the straight and branched aliphatic ether radicals of 1-4 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy.

The term "halocetyl" refers to chloroacetyl, bromoacetyl, fluoroacetyl and iodoacetyl.

The term " C_1 - C_5 alkanoyl" includes formyl, acetyl, propionyl, butyryl, α -methylpropionyl, valeryl, α -methylbutyryl, β -methylbutyryl and pivaloyl.

The term "benzoyl substituted with halo" defines mono- and di-halo benzoyl groups. Specific mono-halo benzoyl groups are chlorobenzoyl, bromobenzoyl, fluorobenzoyl and iodobenzoyl.

Di-halo benzoyl groups include those in which both halo substituents are the same. Typical di-halo benzoyl groups include 2,4-dichlorobenzoyl, 2,4-dibromobenzoyl, 2,4-difluorobenzoyl and 2,4-diiodobenzoyl.

The term "benzoyl substituted with methyl" contemplates methylbenzoyl, dimethylbenzoyl and trimethylbenzoyl.

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The term "substituted phenyl" refers to a phenyl ring which is substituted with one or two substituents selected from the group consisting of halo, C_1 - C_4 alkyl or C_1 - C_4 alkoxy. Examples of such term, therefore, include 4-chlorophenyl, 2-

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fluorophenyl, 3-iodophenyl, 4-bromophenyl, 3,4-dibromophenyl, 4-methylphenyl, 2-ethylphenyl, 3-n-propylphenyl, 4-isopropylphenyl, 4-n-butylphenyl, 3-t-butylphenyl, 4-sec-butylphenyl, 3,4-dimethylphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 2-n-propylphenyl, 4-isopropoxyphenyl, 3-isobutoxyphenyl, 4-t-butoxyphenyl, 3-ethoxy-4-methoxyphenyl and the like.

While all of the compounds of Formula 1 are believed to be useful for the method of treating sleep disorders presented herein, certain of such compounds are preferred for such use. Preferred compounds of Formula I for use in the instantly claimed method include those compounds wherein R^1 is C_1 - C_4 alkyl (especially methyl), R^3 is hydrogen or C_1 - C_4 alkyl (especially methyl) and R^4 is hydrogen.

Of such preferred compounds, particularly preferred compounds include those wherein R^2 and R^7 are each independently C_1 - C_4 alkyl (preferably methyl). The most preferred compounds for use in the method of the present invention include N-[2-methyl-2-(5-methoxy-6-fluoroindol-3-yl)ethyl]acetamide, N-[2-ethyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]acetamide, N-[2-methyl-2-(5-methoxy-6,7-dichloroindol-3-yl)ethyl]acetamide and N-[2-methyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]acetamide. The later compound is especially preferred for purposes of the present invention.

Those compounds employed in the method of the present invention wherein R^2 is C_1 - C_4 alkyl have an asymmetric center at the carbon atom to which such R^2 substituent is attached (i.e., the β -carbon atom). As such, such R^2 substituted compounds can exist as either a racemic mixture or as individual stereoisomers. All such types of compounds are contemplated for use in the method of the present invention.

The following list illustrates representative compounds suitable for use in the present invention.

N-[2-methyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]acetamide

N-[2-methyl-2-(5-methoxy-6-fluoroindol-3-yl)ethyl]-acetamide

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acetamide N-[2-ethyl-2-(5-methoxy-6-fluoroindol-3-yl)ethyl]-
acetamide N-[2-ethyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]-
5 acetamide N-[2-isopropyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]-
acetamide N-[2-isopropyl-2-(5-methoxy-6-fluoroindol-3-yl)ethyl]-
10 formamide N-[2-methyl-2-(5-methoxy-6-bromoindol-3-yl)ethyl]-
formamide N-[2-butyl-2-(5-methoxy-6-bromoindol-3-yl)ethyl]-
formamide N-[2-ethyl-2-(5-propoxy-6-chloroindol-3-yl)ethyl]-
15 formamide N-[2-propyl-2-(5-isopropoxy-6-iodoindol-3-yl)ethyl]-
propionamide N-[2-methyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]-
20 propionamide N-[2-ethyl-2-(5-methoxy-6-fluoroindol-3-yl)ethyl]-
propionamide N-[2-methyl-2-(5-ethoxy-6-bromoindol-3-yl)ethyl]-
butyramide N-[2-methyl-2-(5-ethoxy-6-fluoroindol-3-yl)ethyl]-
25 butyramide N-[2-propyl-2-(5-butoxy-6-chloroindol-3-yl)ethyl]-
butyramide N-[2-methyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]-
30 acetamide N-[2-methyl-2-(5-methoxy-7-chloroindol-3-yl)ethyl]-
acetamide N-[2-methyl-2-(5-methoxy-7-fluoroindol-3-yl)ethyl]-
acetamide N-[2-ethyl-2-(5-methoxy-7-chloroindol-3-yl)ethyl]-
35 acetamide N-[2-propyl-2-(5-methoxy-7-bromoindol-3-yl)ethyl]-
formamide N-[2-ethyl-2-(5-t-butoxy-7-chloroindol-3-yl)ethyl]-

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N-[2-ethyl-2-(5-ethoxy-7-iodoindol-3-yl)ethyl]-
formamide

N-[2-methyl-2-(5-isopropoxy-7-chloroindol-3-yl)ethyl]-
formamide

5 N-[2-methyl-2-(5-methoxy-7-bromoindol-3-yl)ethyl]-
propionamide

N-[2-ethyl-2-(5-propoxy-7-chloroindol-3-yl)ethyl]-
propionamide

10 N-[2-methyl-2-(5-s-butoxy-7-fluoroindol-3-yl)ethyl]-
propionamide

N-[2-methyl-2-(5-methoxy-7-chloroindol-3-yl)ethyl]-
butyramide

N-[2-butyl-2-(5-ethoxy-7-chloroindol-3-yl)ethyl]-
butyramide

15 N-[2-ethyl-2-(5-methoxy-7-fluoroindol-3-yl)ethyl]-
butyramide

N-[2-methyl-2-(5-methoxy-6,7-dichloroindol-3-
yl)ethyl]acetamide

20 N-[2-ethyl-2-(5-methoxy-6,7-dichloroindol-3-
yl)ethyl]acetamide

N-[2-isopropyl-2-(5-methoxy-6,7-dichloroindol-3-
yl)ethyl]acetamide

N-[2-methyl-2-(5-isopropoxy-6,7-dichloroindol-3-
yl)ethyl]acetamide

25 N-[2-methyl-2-(5-methoxy-6,7-difluoroindol-3-
yl)ethyl]acetamide

N-[2-propyl-2-(5-methoxy-6,7-difluoroindol-3-
yl)ethyl]acetamide

30 N-[2-ethyl-2-(5-butoxy-6,7-difluoroindol-3-
yl)ethyl]acetamide

N-[2-methyl-2-(5-methoxy-6-chloro-7-fluoroindol-3-
yl)ethyl]acetamide

N-[2-methyl-2-(5-methoxy-6-chloro-7-bromoindol-3-
yl)ethyl]acetamide

35 N-[2-methyl-2-(5-methoxy-6-fluoro-7-chloroindol-3-
yl)ethyl]acetamide

N-[2-methyl-2-(5-ethoxy-6-bromo-7-iodoindol-3-
yl)ethyl]acetamide

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N-[2-ethyl-2-(5-ethoxy-6-chloro-7-fluoroindol-3-yl)ethyl]acetamide

N-[2-isopropyl-2-(5-t-butoxy-6-chloro-7-fluoro-indol-3-yl)ethyl]acetamide

5 N-[2-ethyl-2-(5-butoxy-6-bromo-7-chloroindol-3-yl)ethyl]acetamide

N-[2-methyl-2-(5-methoxy-6,7-dichloroindol-3-yl)ethyl]formamide

10 N-[2-methyl-2-(5-methoxy-6,7-dibromoindol-3-yl)ethyl]formamide

N-[2-t-butyl-2-(5-methoxy-6-chloro-7-fluoroindol-3-yl)ethyl]formamide

N-[2-ethyl-2-(5-ethoxy-6-fluoro-7-bromoindol-3-yl)ethyl]formamide

15 N-[2-ethyl-2-(5-s-butoxy-6-fluoro-7-chloroindol-3-yl)ethyl]formamide

N-[2-methyl-2-(5-methoxy-6,7-dichloroindol-3-yl)ethyl]propionamide

20 N-[2-ethyl-2-(5-methoxy-6,7-dichloroindol-3-yl)ethyl]propionamide

N-[2-propyl-2-(5-isopropoxy-6-chloro-7-fluoroindol-3-yl)ethyl]propionamide

N-[2-methyl-2-(5-methoxy-6-bromo-7-iodoindol-3-yl)ethyl]propionamide

25 N-[2-methyl-2-(5-ethoxy-6-bromo-7-chloroindol-3-yl)ethyl]propionamide

N-[2-methyl-2-(5-methoxy-6,7-difluoroindol-3-yl)ethyl]butyramide

30 N-[2-ethyl-2-(5-methoxy-6-fluoro-7-chloroindol-3-yl)ethyl]butyramide

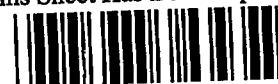
N-[2-isopropyl-2-(5-methoxy-6,7-dibromoindol-3-yl)ethyl]butyramide

N-[2-isopropyl-2-(5-butoxy-6-bromo-7-chloroindol-3-yl)ethyl]butyramide

35 N-[2-ethyl-2-(5-methoxy-6,7-dichloro-3-yl)ethyl]-butyramide

N-[2-methyl-2-(1-acetyl-5-methoxy-6-chloroindol-3-yl)ethyl]acetamide

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-9-

N-[2-butyl-2-(1-acetyl-5-methoxy-6-fluoroindol-3-yl)ethyl]acetamide

N-[2-ethyl-2-(1-acetyl-5-isopropoxy-6-chloro-7-fluoroindol-3-yl)ethyl]acetamide

5 N-[2-methyl-2-(1-propionyl-5-methoxy-6-fluoroindol-3-yl)ethyl]acetamide

N-[2-methyl-2-(1-propionyl-5-ethoxy-6,7-dichloroindol-3-yl)ethyl]acetamide

10 N-[2-ethyl-2-(1-propionyl-5-butoxy-7-chloroindol-3-yl)ethyl]acetamide

N-[2-methyl-2-(1-pivaloyl-5-ethoxy-6-bromoindol-3-yl)ethyl]formamide

N-[2-propyl-2-(1-chloroacetyl-5-methoxy-6-bromo-7-fluoroindol-3-yl)ethyl]propionamide

15 N-[2-methyl-2-(1-bromoacetyl-5-ethoxy-7-chloroindol-3-yl)ethyl]butyramide

N-[2-ethyl-2-(1-valeryl-5-isopropoxy-6,7-dichloroindol-3-yl)ethyl]acetamide

20 N-[2-methyl-2-(1-butyryl-5-methoxy-6-chloroindol-3-yl)ethyl]acetamide

N-[2-ethyl-2-(1-benzoyl-5-t-butoxy-7-bromoindol-3-yl)ethyl]formamide

N-[[2-isopropyl-2-[1-(4-chlorobenzoyl)-5-methoxy-7-fluoroindol-3-yl]ethyl]]formamide

25 N-[[2-methyl-2-[1-(4-bromobenzoyl)-5-ethoxy-6,7-dichloroindol-3-yl]ethyl]]propionamide

N-[[2-ethyl-2-[1-(2,4-dichlorobenzoyl)-5-methoxy-7-bromoindol-3-yl]ethyl]]propionamide

30 N-[[2-methyl-2-[1-(2,4-difluorobenzoyl)-5-propoxy-6-chloroindol-3-yl]ethyl]]formamide

N-[[2-methyl-2-[1-(4-iodobenzoyl)-5-ethoxy-6-fluoro-7-chloroindol-3-yl]ethyl]]acetamide

N-[[2-ethyl-2-[1-(2-methylbenzoyl)-5-methoxyindol-3-yl]ethyl]]propionamide

35 N-[[2-methyl-2-[1-(4-fluorobenzoyl)-5-ethoxyindol-3-yl]ethyl]]formamide

N-[[2-methyl-2-[1-(2,6-dimethylbenzoyl)-5-methoxy-7-fluoroindol-3-yl]ethyl]]formamide

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N-[[2-ethyl-2-[1-(2,6-dimethylbenzoyl)-5-ethoxyindol-3-yl]ethyl]]acetamide

N-[[2-ethyl-2-[1-(2,4,6-trimethoxybenzoyl)-5-methoxy-6-chloroindol-3-yl]ethyl]]propionamide

5 N-[[2-methyl-2-[1-(2,4,6-trimethoxybenzoyl)-5-methoxyindol-3-yl]ethyl]]formamide

N-[2-ethyl-2-(1-pivaloyl-5-isopropoxyindol-3-yl)ethyl]acetamide

10 N-[2-methyl-2-(1-chloroacetyl-5-methoxyindol-3-yl)ethyl]butyramide

N-[2-methyl-2-(5-methoxyindol-3-yl)ethyl]acetamide

N-[2-ethyl-2-(5-methoxyindol-3-yl)ethyl]acetamide

N-[2-ethyl-2-(5-methoxyindol-3-yl)ethyl]propionamide

N-[2-methyl-2-(5-propoxyindol-3-yl)ethyl]formamide

15 N-[2-methyl-2-(5-s-butoxyindol-3-yl)ethyl]butyramide

N-[2-ethyl-2-(5-ethoxyindol-3-yl)ethyl]propionamide

N-[2-methyl-2-(5-ethoxyindol-3-yl)ethyl]formamide

N-[2-isopropyl-2-(5-methoxyindol-3-yl)ethyl]acetamide

N-[2-ethyl-2-(5-methoxyindol-3-yl)ethyl]formamide

20 N-[2-(2-methyl-5-methoxy-6-bromoindol-3-yl)ethyl]-acetamide

N-[2-(2-ethyl-5-methoxy-6-chloroindol-3-yl)ethyl]-acetamide

25 N-[2-(2-n-propyl-5-methoxy-6-chloroindol-3-yl)ethyl]-formamide

N-[2-(2-n-butyl-5-methoxy-6-chloroindol-3-yl)ethyl]-formamide

N-[2-(2-ethyl-5-methoxy-6-iodoindol-3-yl)ethyl]-propionamide

30 N-[2-(2-isopropyl-5-methoxy-6-fluoroindol-3-yl)ethyl]- α -methylpropionamide

N-[2-(2-phenyl-5-methoxy-6-chloroindol-3-yl)ethyl]-formamide

35 N-[2-(2-phenyl-5-methoxy-6-bromoindol-3-yl)ethyl]-acetamide

N-[2-(2-phenyl-5-methoxy-6-iodoindol-3-yl)ethyl]-propionamide

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N-[2-((2-(4-chlorophenyl)-5-methoxy-6-chloroindol-3-yl))ethyl]formamide

N-[2-((2-(3-fluorophenyl)-5-methoxy-6-bromoindol-3-yl))ethyl]acetamide

5 N-[2-((2-(2-fluorophenyl)-5-methoxy-6-chloroindol-3-yl))ethyl]propionamide

N-[2-((2-(4-methylphenyl)-5-methoxy-6-bromoindol-3-yl))ethyl]formamide

10 N-[2-((2-(3-ethylphenyl)-5-methoxy-6-fluoroindol-3-yl))ethyl]butyramide

N-[2-((2-(4-n-propylphenyl)-5-methoxy-6-chloroindol-3-yl))ethyl]formamide

N-[2-((2-(3-isopropylphenyl)-5-methoxy-6-fluoroindol-3-yl))ethyl]acetamide

15 N-[2-((2-(4-methoxyphenyl)-5-methoxy-6-chloroindol-3-yl))ethyl]propionamide

N-[2-((2-(3-ethoxyphenyl)-5-methoxy-6-bromoindol-3-yl))ethyl]acetamide

20 N-[2-((2-(3-n-propoxyphenyl)-5-methoxy-6-fluoroindol-3-yl))ethyl]acetamide

N-[2-((2-(4-t-butoxyphenyl)-5-methoxy-6-chloroindol-3-yl))ethyl]formamide

N-[2-((2-(3-n-butoxyphenyl)-5-methoxy-6-chloroindol-3-yl))ethyl]acetamide

25 N-[2-(1-acetyl-5-methoxy-6-chloroindol-3-yl)ethyl]-acetamide

N-[2-(1-propionyl-5-methoxy-6-fluoroindol-3-yl)ethyl]-acetamide

30 N-[2-(1-pivaloyl-5-methoxy-6-bromoindol-3-yl)ethyl]-formamide

N-[2-(1-chloroacetyl-5-methoxy-6-iodoindol-3-yl)ethyl]propionamide

N-[2-(1-bromoacetyl-5-methoxy-6-chloroindol-3-yl)ethyl]-n-butyramide

35 N-[2-(1-valeryl-2-methyl-5-methoxy-6-bromoindol-3-yl)ethyl]acetamide

N-[2-(1-butyryl-2-ethyl-5-methoxy-6-chloroindol-3-yl)ethyl]acetamide

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N-[2-(1-benzoyl-2-n-propyl-5-methoxy-6-chloroindol-3-yl)ethyl]formamide

N-[[2-[1-(4-chlorobenzoyl)-2-n-butyl-5-methoxy-6-chloroindol-3-yl]ethyl]]formamide

5 N-[[2-[1-(4-bromobenzoyl)-2-ethyl-5-methoxy-6-iodoindol-3-yl]ethyl]]propionamide

N-[[2-[1-(2,4-dichlorobenzoyl)-2-isopropyl-5-methoxy-6-fluoroindol-3-yl]ethyl]]- α -methylpropionamide

10 N-[[2-[1-(2,4-difluorobenzoyl)-2-phenyl-5-methoxy-6-chloroindol-3-yl]ethyl]]formamide

N-[[2-[1-(4-iodobenzoyl)-2-phenyl-5-methoxy-6-bromoindol-3-yl]ethyl]]acetamide

N-[[2-[1-(2-methylbenzoyl)-2-phenyl-5-methoxy-6-iodoindol-3-yl]ethyl]]propionamide

15 N-[[2-[1-(2,6-dimethylbenzoyl)-2-(4-chloro-phenyl)-5-methoxy-6-chloroindol-3-yl]ethyl]]formamide

N-[[2-[1-(2,4,6-trimethylbenzoyl)-2-(3-fluoro-phenyl)-5-methoxy-6-bromoindol-3-yl]ethyl]]acetamide

20 N-[2-(1-pivaloyl-5-methoxy-6-chloroindol-3-yl)ethyl]acetamide

N-[2-(1-chloroacetyl-5-methoxy-6-chloroindol-3-yl)ethyl]acetamide

N-[[2-[1-(4-chlorobenzoyl)-5-methoxy-6-chloroindol-3-yl]ethyl]]acetamide

25 N-[[2-[1-(2,4-dichlorobenzoyl)-5-methoxy-6-chloroindol-3-yl]ethyl]]acetamide

N-[[2-[1-(2-methylbenzoyl)-5-methoxy-6-chloroindol-3-yl]ethyl]]acetamide

30 N-[[2-[1-(2,6-dimethylbenzoyl)-5-methoxy-6-chloroindol-3-yl]ethyl]]acetamide

N-[[2-[1-(2,4,6-trimethylbenzoyl)-5-methoxy-6-chloroindol-3-yl]ethyl]]acetamide

N-[2-(5-methoxy-6,7-dichloroindol-3-yl)ethyl]acetamide

35 N-[2-(2-methyl-5-methoxy-6,7-difluoroindol-3-yl)ethyl]acetamide

N-[2-(2-methyl-5-methoxy-6-fluoro-7-chloroindol-3-yl)ethyl]acetamide

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-13-

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N-[2-(5-methoxy-6,7-dichloroindol-3-yl)ethyl]-
propionamide

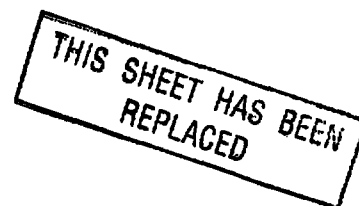
N-[2-(5-methoxy-6,7-difluoroindol-3-yl)ethyl]-
isobutyramide

5 N-[2-(2-methyl-5-methoxy-6,7-dichloroindol-3-
yl)ethyl]-n-butyramide; and the like.

10 The compounds employed in the method of this invention
are known in the art or can be made by methods described in the
art. Representative publications which teach the preparation of
compounds of Formula I include U.S. Patent Nos. 4,087,444;
4,614,807; and 4,997,845. The teaching of all such patents is
hereby incorporated by reference.

15 The compounds of Formula I, as used in this invention,
are useful in treating sleep disorders in mammals. Such
disorders, as defined for purposes of the present invention, are
characterized by difficulty in initiating or maintaining sleep
(DIMS disorders) or in obtaining restful sleep. As such, the
sleep disorders encompassed by the present invention include
insomnia, those instances where the patient is only able to
20 obtain a minimal period of sleep or where the patient is only
able to obtain a poor quality sleep in terms of patient
restfulness. A discussion of sleep disorders, the different
stages of sleep and some of the effects coming from lack of same
are reported in Goodman and Gillman, The Pharmacological Basis
25 of Therapeutics, 360 (1982), Williams et al., Sleep Disorders:
Diagnosis and Treatment, John Wiley and Sons, Chapter 2 (1988)
and European Patent Application 513,702. The teachings of such
references with respect to the scope, extent and cause of sleep
disorders is herein incorporated by reference.

30 As discussed above, the compounds of Formula I are
useful in treating sleep disorders in mammals. Such method
comprises administering to a mammal (preferably a human) in need
of such treatment a sufficient amount of one or more compounds
of Formula I so as to achieve the therapeutic intervention
35 desired. The compounds can be administered by a variety of
routes including the oral, rectal, transdermal, subcutaneous,
intravenous, intramuscular or intranasal routes. The oral and
transdermal routes are preferred. No matter what route of



X-9287

-14-

administration is chosen, such administration is accomplished by means of pharmaceutical compositions which are prepared by techniques well known in the pharmaceutical sciences.

As mentioned above, the method of the present invention utilizes pharmaceutical compositions. In making these compositions, one or more active ingredients will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, saline solution, syrup, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions may be formulated so as to provide rapid, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are formulated, preferably in a unit dosage form, such that each dosage contains from about 1 to about 500 mg, more usually about 30 to about 200 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired

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therapeutic effect, in association with one or more suitable pharmaceutical diluents, excipients or carriers.

5 The compounds employed in the method of the present invention are effective over a dosage range of about 1 mg of active ingredient per day to about 500 mg of active ingredient per day for treating sleep disorders. Thus, as used herein, the term "effective amount" refers to a dosage range of from about 1 to about 500 mg of active ingredient per day. In the treatment of adult humans, the range of about 30 to about 200 mg of active
10 ingredient per day, in single or divided doses, is preferred. However, it will be understood that the amount of compound actually administered will be determined by a physician, in light of the relevant circumstances including the choice of compound to be administered, the chosen route of administration, the age, weight, and response of the individual patient, and the
15 severity of the patient's sleep disorder symptoms.

20 The following formulation examples may employ as active ingredient any of the compounds of Formula I. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

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Example 1

Hard gelatin capsules suitable for treating a sleep disorder are prepared using the following ingredients:

5		<u>Quantity (mg/capsule)</u>
	(±)-N-[2-methyl-2-(5-methoxy)- 6-chloroindol-3-yl)ethyl]acetamide	50
10	Starch dried	200
	Magnesium stearate	10

The above ingredients are mixed and filled into hard gelatin capsules in 260 mg quantities.

Example 2

A tablet suitable for treating sleep disorders is prepared using the ingredients below:

		<u>Quantity (mg/tablet)</u>
20	(-)-N-[2-methyl-2-(5-methoxy)- 6-chloroindol-3-yl)ethyl]acetamide	100
	Cellulose, microcrystalline	400
	Silicon dioxide	10
25	Stearic acid	5

The components are blended and compressed to form tablets each weighing 515 mg.

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X-9287

-17-

Example 3

An aerosol solution suitable for treating sleep disorders is prepared containing the following components:

5		<u>Weight</u>
	(±)-N-[2-methyl-2-(5-methoxy-6-fluoroindol-3-yl)ethyl]acetamide	0.25
	Ethanol	29.75
	Propellant 22	70.00
10	(Chlorodifluoromethane)	

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. Valve units are then fitted to the container.

Example 4

Tablets suitable for a sleep disorder, each containing 60 mg of active ingredient are made up as follows:

	(+)-N-[2-methyl-2-(5-methoxy)-6-chloroindol-3-yl)ethyl]acetamide	60 mg
25	Starch	45 mg
	Microcrystalline cellulose	35 mg
	Polyvinylpyrrolidone (as 10% solution in water)	4 mg
	Sodium carboxymethyl starch	4.5 mg
30	Magnesium stearate	0.5 mg
	Talc	<u>1 mg</u>
	Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch,

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magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed by a tablet machine to yield tablets each weighing 150 mg.

5

Example 5

Capsules suitable for treating sleep disorders, each containing 80 mg of medicament, are made as follows:

10	(-)-N-[2-methyl-2-(5-methoxy)- 6,7-dichloroindol-3-yl)ethyl] acetamide	80 mg
	Starch	59 mg
	Microcrystalline cellulose	59 mg
15	Magnesium stearate	<u>2 mg</u>
	Total	200 mg

20 The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Example 6

25 Suppositories suitable for treating sleep disorders, each containing 100 mg of active ingredient, are made as follows:

	(±)-N-[2-ethyl-2-(5-methoxy-6- chloroindol-3-yl)ethyl]acetamide	100 mg
30	Saturated fatty acid glycerides to	2,000 mg

35 The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

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Example 7

Suspensions suitable for treating sleep disorders, each containing 50 mg of medicament per 5 ml dose, are made as follows:

5	(±)-N-[2-methyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]acetamide	50 mg
	Sodium carboxymethyl cellulose	50 mg
	Syrup	1.25 ml
10	Benzoic acid solution	0.10 ml
	Flavor	q.v.
	Color	q.v.
	Purified water to	5 ml

15 The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the
20 required volume.

Example 8

Capsules suitable for use in treating a sleep disorder, each containing 100 mg of medicament, are made as
25 follows:

	(±)-N-[2-methyl-2-(5-methoxy-6,7-dichloroindol-3-yl)ethyl]acetamide	100 mg
	Starch	164 mg
30	Microcrystalline cellulose	164 mg
	Magnesium stearate	<u>22 mg</u>
	Total	450 mg

35 The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 450 mg quantities.

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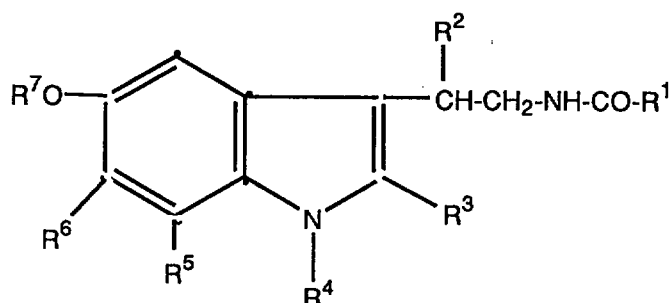
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X-9287-(EPO)

-20-

CLAIMS

1. The use of a compound of the formula



wherein

R¹ is hydrogen, C₁-C₄ alkyl or C₁-C₄ alkoxy;

R² is hydrogen or C₁-C₄ alkyl;

R³ is hydrogen, C₁-C₄ alkyl, phenyl or substituted phenyl;

R⁴ is hydrogen, haloacetyl, C₁-C₅ alkanoyl, benzoyl or benzoyl substituted with halo or methyl

R⁵ and R⁶ are each independently hydrogen or halo; and

R⁷ is hydrogen or C₁-C₄ alkyl;

provided that when R³, R⁴ and R⁵ are each hydrogen then R² must be C₁-C₄ alkyl, to prepare a medicament for treating sleep disorders.

2. The use of Claim 1 which employs a compound wherein R⁴ is hydrogen.

3. The use of Claim 1 or Claim 2 which employs a compound wherein R¹ is C₁-C₄ alkyl.

4. The use of any one of Claims 1 through 3 which employs a compound wherein R³ is hydrogen or C₁-C₄ alkyl.

5. The use of any one of Claims 1 through 4 which employs a compound wherein R⁷ is C₁-C₄ alkyl.

6. The use of any one of Claims 1 through 5 which employs a compound wherein R² is C₁-C₄ alkyl.

7. The use of any one of Claims 1 through 5 which employs a compound wherein R² is methyl.

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X-9287-(EPO)

-21-

8. The use of Claim 1 which employs a compound selected from among N-[2-methyl-2-(5-methoxy-6-fluoroindol-3-yl)ethyl]acetamide; N-[2-ethyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]acetamide; N-[2-methyl-2-(5-methoxy-6,7-dichloroindol-3-yl)ethyl]acetamide; or N-[2-methyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]acetamide.

9. The use of Claim 8 which employs N-[2-methyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]acetamide; (+)- N-[2-methyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]acetamide; or (-)- N-[2-methyl-2-(5-methoxy-6-chloroindol-3-yl)ethyl]acetamide.

10. A pharmaceutical formulation adapted for use in treating sleep disorders comprising a compound as set forth in any one of Claims 1 through 9 in combination with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

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