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(54) Titre : DERIVES DE BENZIMIDAZOLONE UTILES POUR LE TRAITEMENT DES TROUBLES PREMENSTRUELS ET D'AUTRES TROUBLES SEXUELS CHEZ LA FEMME

(54) Title: BENZIMIDAZOLONE DERIVATIVES FOR THE TREATMENT OF PREMENSTRUAL AND OTHER FEMALE SEXUAL DISORDERS

(57) Abrégé/Abstract:
The invention relates to the use of benzimidazolone derivatives of formula (I) for the preparation of a medicament for the treatment of premenstrual and other female sexual disorders.

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(54) Title: BENZIMIDAZOLONE DERIVATIVES FOR THE TREATMENT OF PREMENSTRUAL AND OTHER FEMALE SEXUAL DISORDERS

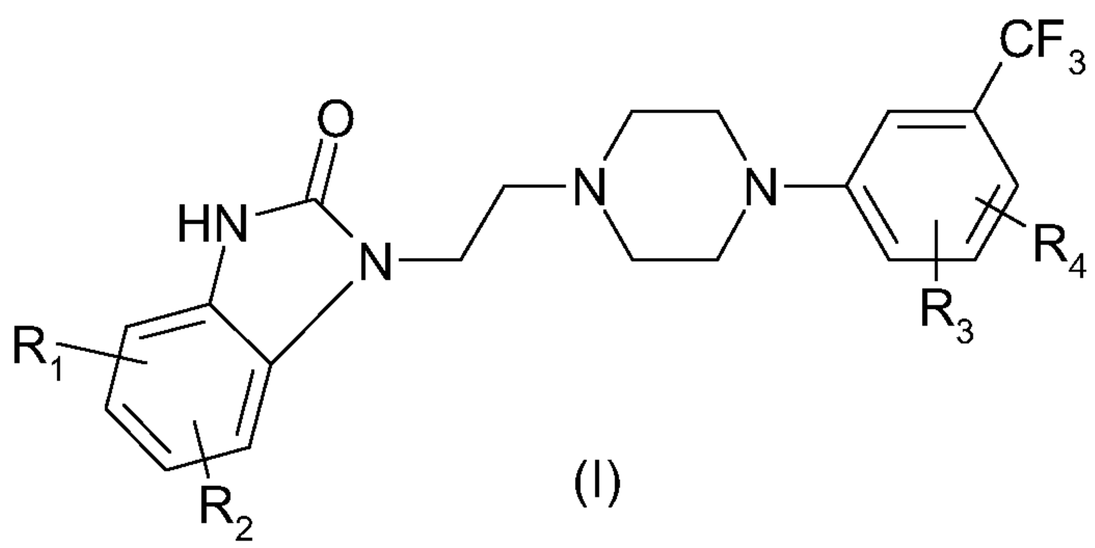
(57) Abstract: The invention relates to the use of benzimidazolone derivatives of formula (I) for the preparation of a medicament for the treatment of premenstrual and other female sexual disorders.

Benzimidazolone derivatives for the treatment of premenstrual and other female sexual disorders

The invention relates to the use of benzimidazolone derivatives of formula (I) and their acid addition salts for the preparation of a medicament for the treatment of premenstrual and other female sexual disorders.

Description of the invention

The compounds of formula (I) and their acid addition salts are disclosed in WO 01/21593 A1 and have the following chemical structure:



(I)

wherein R_1, R_2, R_3, and R_4 denote hydrogen or hydroxy with the proviso that R_1, R_2, R_3, and R_4 cannot simultaneously represent hydrogen.

Preferred compounds according to the present invention are those of general formula (I) wherein two or three of the four radicals R_1, R_2, R_3, and R_4 denote hydrogen.
Also preferred are those compounds of general formula (I) wherein one of the radicals R_1, R_2, R_3, and R_4 denotes hydroxy, whilst the other radicals represent hydrogen.

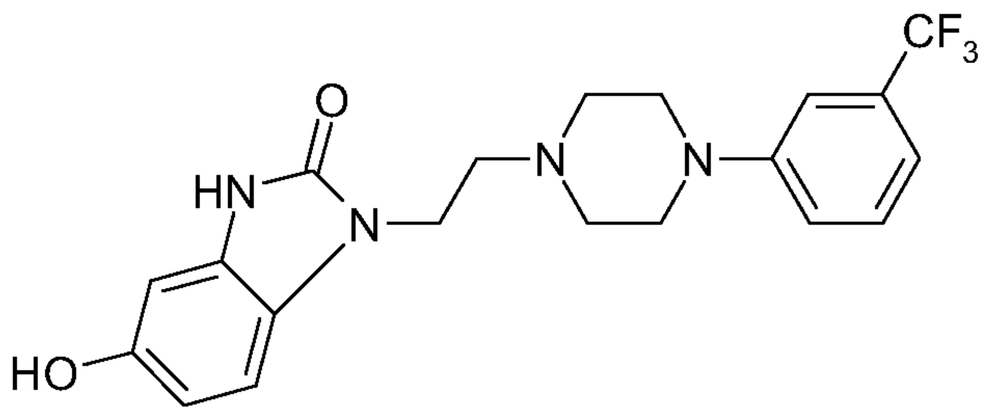
Above mentioned compounds show affinity for the 5-HT1A and 5-HT2-receptor. They may be of value in the treatment of those diseases where an altered functioning of neurosignal transmission is present. Examples of these CNS disorders include depression, schizophrenia, Parkinson, anxiety, sleep disturbances, sexual and mental disorders and age associated memory impairment (WO 01/21593 A1).

The generic term “Sexual disorders” includes Sexual Desire Disorders, Sexual Arousal Disorders, Orgasmic Disorders, Sexual Pain Disorders, Sexual Dysfunction due to a General Medical Condition, Substance-Induced Sexual Dysfunction, and Sexual Dysfunction not otherwise specified (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision. Washington DC, American Psychiatric Association, 2000).

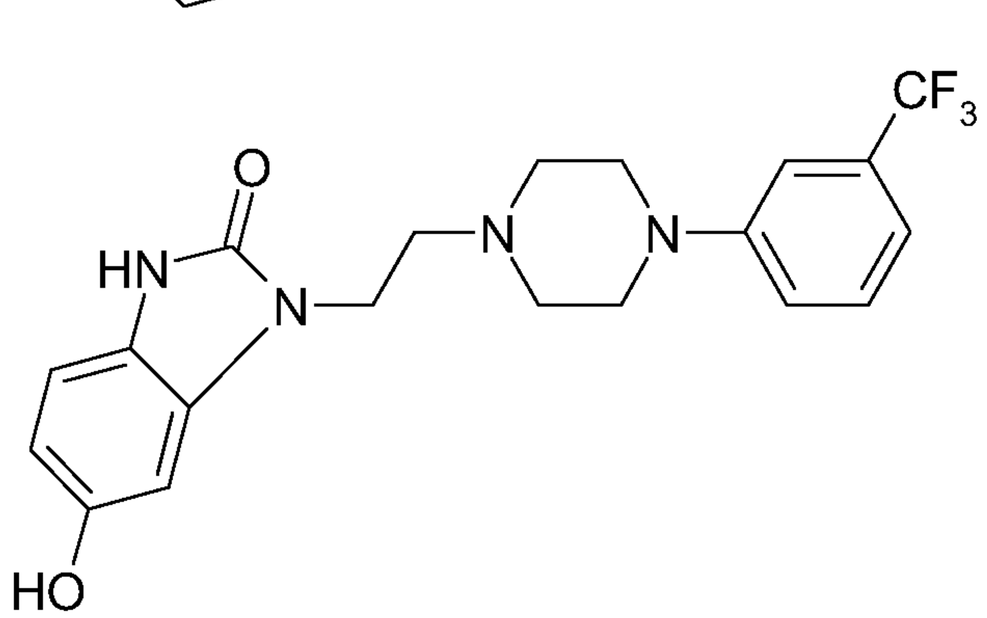
The present invention relates to the use of the compounds of formula (I), optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of premenstrual disorders.

In a preferred embodiment, the present invention relates to the use of the compounds of formula (I) selected from the group consisting of

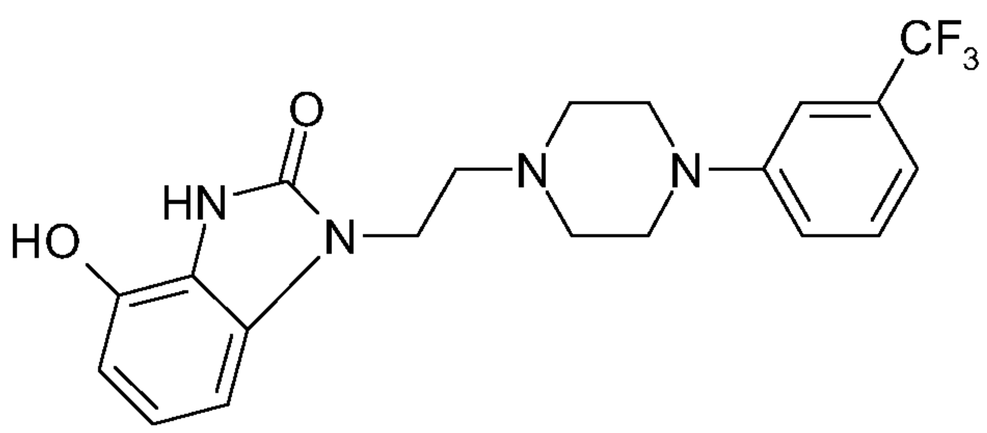
(I.a)



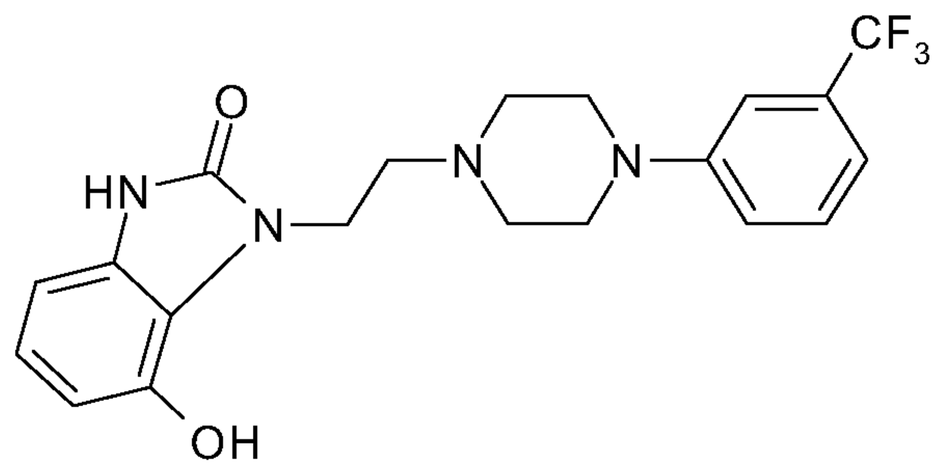
(I.b)



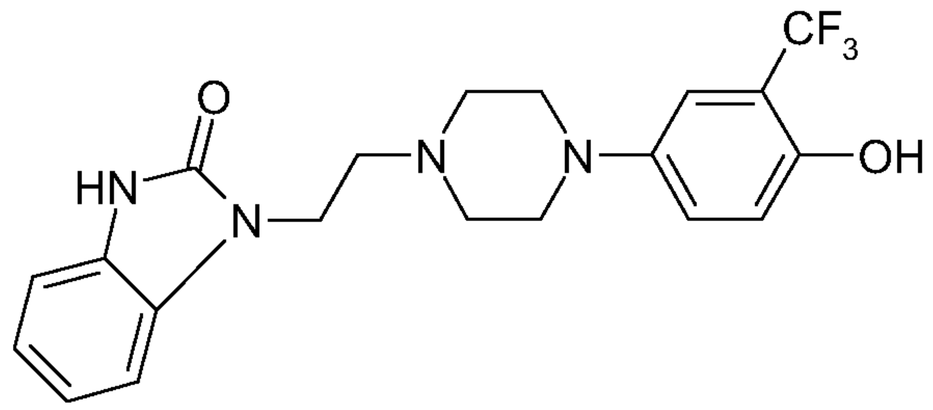
(I.c)



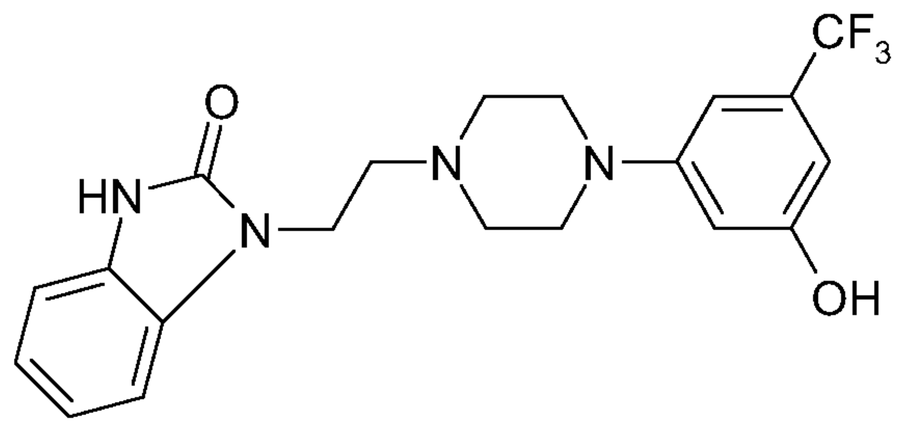
(I.d)



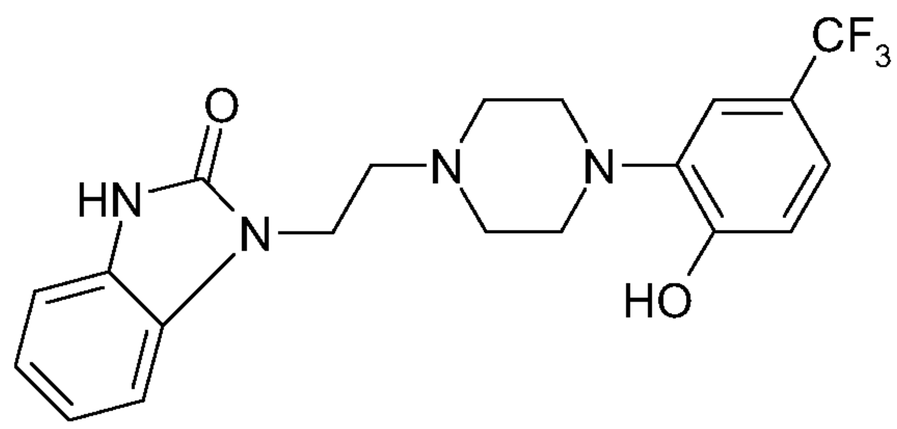
(I.e)



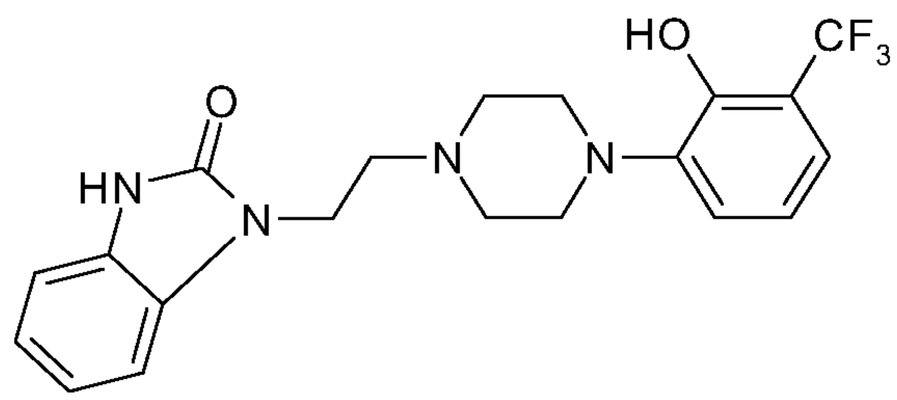
(I.f)



(I.g)



(I.h)



optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of premenstrual disorders.

In a further preferred embodiment the invention relates to the use of the compounds of formula (I), optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of premenstrual

disorders selected from the group consisting of premenstrual dysphoria, premenstrual syndrome, premenstrual dysphoric disorder.

In a further preferred embodiment, the present invention relates to the use of the compounds of formula (I) selected from the group consisting of the compounds (I.a), (I.b), (I.c), (I.d), (I.e), (I.f), (I.g) and (I.h), optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of premenstrual disorders selected from the group consisting of premenstrual dysphoria, premenstrual syndrome, premenstrual dysphoric disorder.

In another preferred embodiment the invention relates to the use of the compounds of formula (I), optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of sexual arousal disorder in females.

In a further preferred embodiment, the present invention relates to the use of the compounds of formula (I) selected from the group consisting of the compounds (I.a), (I.b), (I.c), (I.d), (I.e), (I.f), (I.g) and (I.h), optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of sexual arousal disorder in females.

In another preferred embodiment the invention relates to the use of the compounds of formula (I), optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of orgasmic disorder in females.

In a further preferred embodiment, the present invention relates to the use of the compounds of formula (I) selected from the group consisting of the compounds (I.a), (I.b), (I.c), (I.d), (I.e), (I.f), (I.g) and (I.h), optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of orgasmic disorder in females.

In another preferred embodiment the invention relates to the use of the compounds of formula (I), optionally in form of the pharmacologically acceptable acid addition

salts thereof for the preparation of a medicament for the treatment of sexual pain disorders in females.

In a further preferred embodiment, the present invention relates to the use of the compounds of formula (I) selected from the group consisting of the compounds (I.a), (I.b), (I.c), (I.d), (I.e), (I.f), (I.g) and (I.h), optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of sexual pain disorders in females.

In a particular preferred embodiment the invention relates to the use of the compounds of formula (I), optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment sexual pain disorders selected from the group consisting of dyspareunia, vaginismus, noncoital sexual pain disorder, sexual dysfunction due to a general medical condition and substance-induced sexual dysfunction.

In a further preferred embodiment, the present invention relates to the use of the compounds of formula (I) selected from the group consisting of the compounds (I.a), (I.b), (I.c), (I.d), (I.e), (I.f), (I.g) and (I.h), optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment sexual pain disorders selected from the group consisting of dyspareunia, vaginismus, noncoital sexual pain disorder, sexual dysfunction due to a general medical condition and substance-induced sexual dysfunction.

The beneficial effects of the compounds of formula (I) and the compounds (I.a), (I.b), (I.c), (I.d), (I.e), (I.f), (I.g) and (I.h), optionally in form of the pharmacologically acceptable acid addition salts thereof can be observed regardless of whether the disturbance existed lifelong or was acquired, is of the „generalized type“ or „situational type“and independent of etiologic origin (organic - both, physically and drug induced-, psychogen (due to psychological factors), a combination of organic - both, physically and drug induced-, and psychogen (due to combined factors), or unknown). The term “lifelong” refers to such sexual disorders of the present invention, which have been present since the onset of sexual functioning. The term “acquired” refers to such sexual disorders of the present invention which developed

only after a period of normal sexual functioning. The „generalized type“ refers to such sexual disorders of the present invention wherein the disorder is not limited to certain types of stimulation, situations, or partners. The „situational type“ applies to such sexual disorders of the present invention wherein the disorder is limited to certain types of stimulation, situations, or partners. The subtype due to “psychological factors” applies when psychological factors are judged to have the major role in the onset, severity, exacerbation, or maintenance of the sexual disorder, and general medical conditions and substance play no role in the etiology of the sexual disorder. Finally the subtype due to “combined factors” applies when 1) psychological factors are judged to have a role in the onset, severity, exacerbation, or maintenance of the sexual disorder, and 2) a general medical condition or substance use is also judged to be contributory but is not sufficient to account for a sexual disorder (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision. Washington DC, American Psychiatric Association, 2000).

The compounds of formula (I) and the the compounds (I.a), (I.b), (I.c), (I.d), (I.e), (I.f), (I.g) and (I.h) can be used either as free base or in form of its pharmaceutically acceptable acid addition salts. The term „acceptable acid addition salts includes both organic and inorganic acids such as maleic, citric, tartaric, methanesulphonic, acetic, benzoic, succinic, gluconic, isethionic, glycinic, lactic, malic, mucoic, glutamic, sulphamic and ascorbic acid; inorganic acids include hydrochloric, hydrobromic, nitric, sulfuric, or phosphoric acid, and mixtures thereof.

The compounds of formula (I) and the compounds (I.a), (I.b), (I.c), (I.d), (I.e), (I.f), (I.g) and (I.h), optionally used in form of its pharmaceutically acceptable acid addition salts, may be incorporated into the conventional pharmaceutical preparation in solid, liquid or spray form. The composition may, for example, be presented in a form suitable for oral, rectal, parenteral administration or for nasal inhalation: preferred forms includes for example, capsules, tablets, coated tablets, ampoules, suppositories and nasal spray.

The active ingredient may be incorporated in excipients or carriers conventionally used in pharmaceutical compositions such as, for example, talc, arabic gum, lactose, gelatine, magnesium stearate, corn starch, acqueous or non acqueous vehicles, polyvynil pyrrolidone, semisynthetic glicerides of fatty acids, benzalconium chloride, sodium phosphate, EDTA, polysorbate 80. The compositions are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose

of the active ingredient. The dosis range applicable per day is between 0.1 to 400, preferably between 1.0 to 300, more preferably between 2 to 200 mg.
Each dosage unit may conveniently contain from 0,01 mg to 100 mg, preferably from 0,1 to 50 mg.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number or layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Solutions for injection are prepared in the usual way, e.g of. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, and transferred into injection vials or ampoules.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

The Examples which follow illustrate the present invention without restricting its scope:

Examples of pharmaceutical formulations

A)	Tablets	per tablet
	compound (I.a)	100 mg
	lactose	240 mg
	corn starch	340 mg
	polyvinylpyrrolidone	45 mg
	magnesium stearate	15 mg
		740 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B)	Tablets	per tablet
	compound (I.b)	80 mg
	corn starch	190 mg
	lactose	55 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	15 mg
	sodium-carboxymethyl starch	23 mg
	magnesium stearate	2 mg
		400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-carboxymethyl starch and the magnesium

stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

C)	Coated tablets	per coated tablet
	compound (I.c)	5 mg
	corn starch	41.5 mg
	lactose	30 mg
	polyvinylpyrrolidone	3 mg
	magnesium stearate	0.5 mg
		80 mg

The active substance, corn starch, lactose and polyvinylpyrrolidone are thoroughly mixed and moistened with water. The moist mass is pushed through a screen with a 1 mm mesh size, dried at about 45°C and the granules are then passed through the same screen. After the magnesium stearate has been mixed in, convex tablet cores with a diameter of 6 mm are compressed in a tablet-making machine . The tablet cores thus produced are coated in known manner with a covering consisting essentially of sugar and talc. The finished coated tablets are polished with wax.

D)	Capsules	per capsule
	compound (I.d)	1 50 mg
	Corn starch	268.5 mg
	Magnesium stearate	1.5 mg
		420 mg

The substance and corn starch are mixed and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The finished mixture is packed into size 1 hard gelatine capsules.

E)	Ampoule solution	
	compound (I.e)	50 mg
	sodium chloride	50 mg
	water for inj.	5 ml

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion.

F) Suppositories

compound (I.f)	50 mg
solid fat	1650 mg
	1700 mg

The hard fat is melted. At 40°C the ground active substance is homogeneously dispersed. It is cooled to 38°C and poured into slightly chilled suppository moulds.

In a particular preferred embodiment of the instsnt invention, the compounds of formula (I) are administered in form of specific film coated tablets. Examples of these preferred formulations are listed below. The film coated tablets listed below can be manufactured according to procedures known in the art (see hereto WO 03/097058).

G) Film coated tablet

Core

Constituents	**mg/tablet**
compound (I.a)	25.000
Lactose monohydrate	71.720
Microcrystalline cellulose	23.905
HPMC (Methocel E5)	1.250
Carboxymethylcellulose sodium	2.500
Magnesium stearate	0.625

Coating

Constituents	**mg/ tablet**
HPMC (Methocel E5)	1.440
Polyethylene Glycol 6000	0.420
Titanium dioxide	0.600

Talc	0.514
Iron oxide red	0.026

Total Film coated tablet	**128.000**

H) Film coated tablet

Core

Constituents	**mg/tablet**
compound (I.b)	50.000
Lactose monohydrate	143.440
Microcrystalline cellulose	47.810
HPMC (e.g. Pharmacoat 606)	2.500
Carboxymethylcellulose sodium	5.000
Magnesium stearate	1.250

Coating

Constituents	**mg/ tablet**
HPMC (e.g. Pharmacoat 606)	2.400
Polyethylene Glycol 6000	0.700
Titanium dioxide	1.000
Talc	0.857
Iron oxide red	0.043

Total Film coated tablet	**255.000**

I) Film coated tablet

Core

Constituents	**mg/tablet**
compound (I.c)	100.000
Lactose monohydrate	171.080
Microcrystalline cellulose	57.020
HPMC (e.g. Methocel E5)	3.400
Carboxymethylcellulose sodium	6.800

Magnesium stearate	1.700

Coating

Constituents	**mg/ tablet**
HPMC (e.g. Methocel E5)	3.360
Polyethylene Glycol 6000	0.980
Titanium dioxide	1.400
Talc	1.200
Iron oxide red	0.060
Total Film coated tablet	**347.000**

J) Film coated tablet

Core

Constituents	**mg/tablet**
compound (I.d)	2.000
Dibasic Calciumphosphate, anhydrous	61.010
Microcrystalline cellulose	61.010
HPMC (Methocel E5)	1.950
Carboxymethylcellulose sodium	2.600
Colloidal silicon dioxide	0.650
Magnesium stearate	0.780

Coating

Constituents	**mg/ tablet**
HPMC (Methocel E5)	1.440
Polyethylene Glycol 6000	0.420
Titanium dioxide	0.600
Talc	0.514
Iron oxide red	0.026
Total Film coated tablet	**133.000**

K) Film coated tablet

Core

Constituents	**mg/tablet**
compound (I.e)	100.000
Dibasic Calciumphosphate, anhydrous	69.750
Microcrystalline cellulose	69.750
HPMC (e.g. Methocel E5)	2.750
Carboxymethylcellulose sodium	5.000
Colloidal silicon dioxide	1.250
Magnesium stearate	1.500

Coating

Constituents	**mg/ tablet**
HPMC (e.g. Methocel E5)	2.400
Polyethylene Glycol 6000	0.700
Titanium dioxide	1.043
Talc	0.857

Total Film coated tablet	**255.000**

L) Film coated tablet

Core

Constituents	**mg/tablet**
compound (I.f)	20.000
Lactose monohydrate	130.000
Microcrystalline cellulose	43.100
Hydroxypropyl Cellulose (e.g. Klucel LF)	1.900
Sodium Starch Glycolate	4.000
Magnesium stearate	1.000

Coating

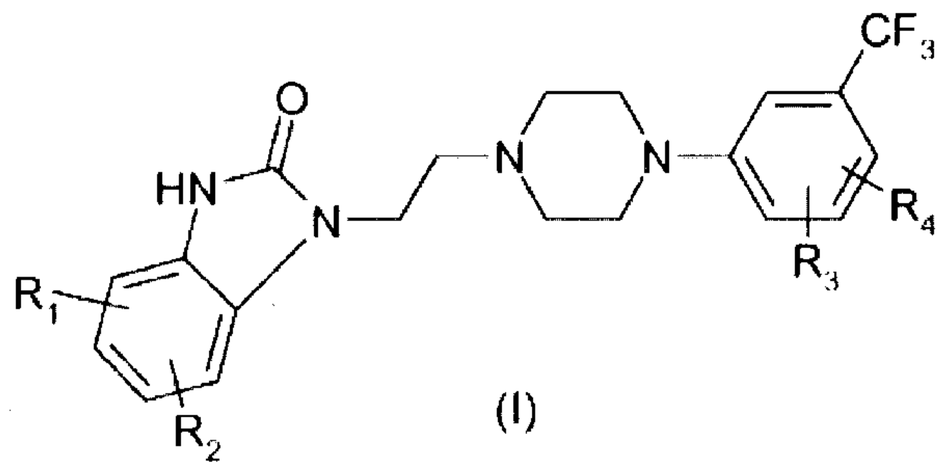
Constituents	**mg/ tablet**

HPMC (e.g. Methocel E5)	2.400
Polyethylene Glycol 6000	0.700
Titanium dioxide	1.043
Talc	0.857

Total Film coated tablet	**205.000**

CLAIMS:

1. Use of a compound of formula (I)



(I)

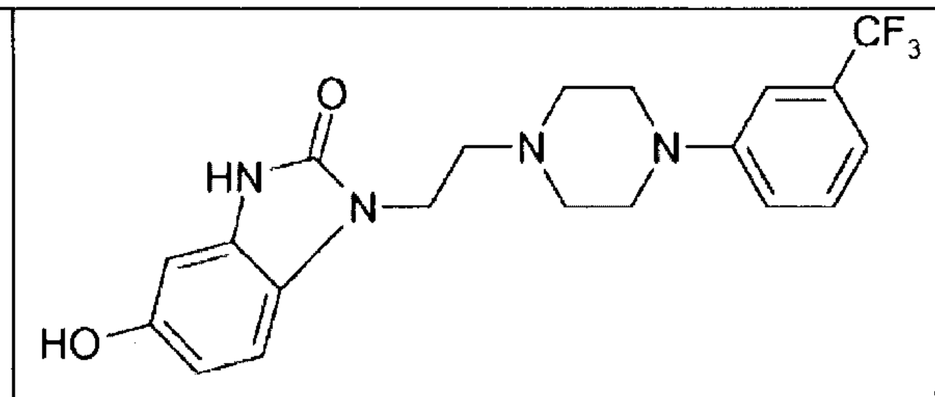
wherein R1, R2, R3, and R4 denote hydrogen or hydroxy with the proviso that R1, R2, R3, and R4 cannot simultaneously represent hydrogen, optionally in form of the pharmacologically acceptable acid addition salts thereof for the preparation of a medicament for the treatment of premenstrual disorders.

2. Use according to claim 1, wherein the premenstrual disorder is selected from the group consisting of premenstrual dysphoria, premenstrual syndrome and premenstrual dysphoric disorder.

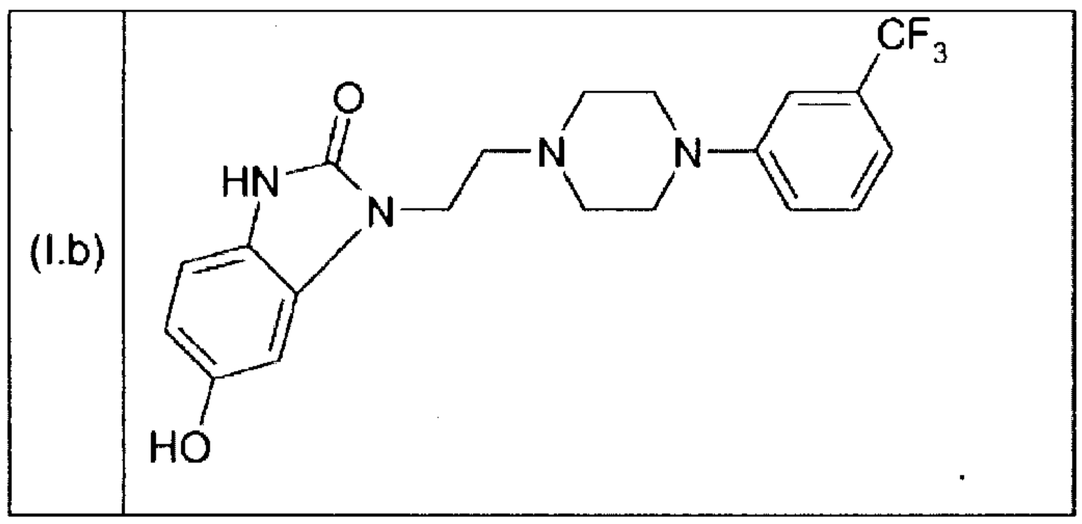
3. Use according to claim 1 or 2, wherein the compound is applied in form of a pharmaceutically acceptable acid addition salt selected from the salts formed by the acids selected from the group consisting of maleic, citric, tartaric, methanesulphonic, acetic, benzoic, succinic, gluconic, isethionic, glycinic, lactic, malic, mucoic, glutamic, sulphamic, ascorbic, hydrochloric, hydrobromic, nitric, sulfuric, phosphoric acid, and mixtures thereof.

4. Use according to any one of claims 1 to 3, wherein the compound is applied in a dosage range between 0.1 to 400 mg per day.

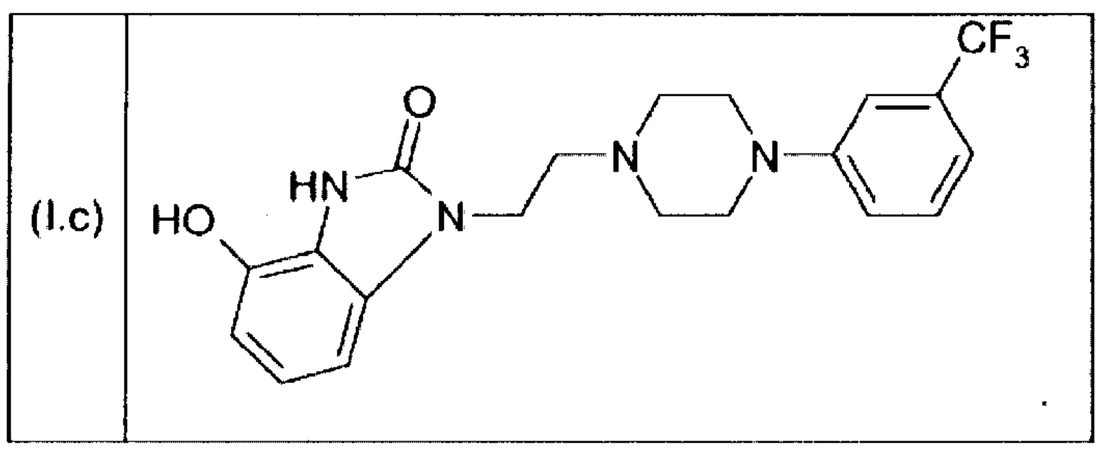
5. Use according to any one of claims 1 to 4, wherein the compound is compound (I.a)

(I.a) 

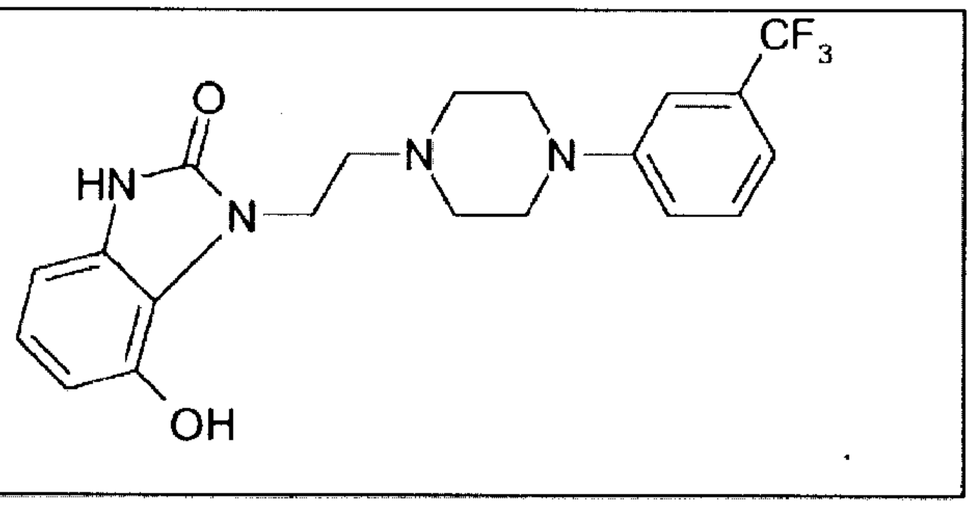
6. Use according to any one of claims 1 to 4, wherein the compound is compound (I.b)

(I.b) 

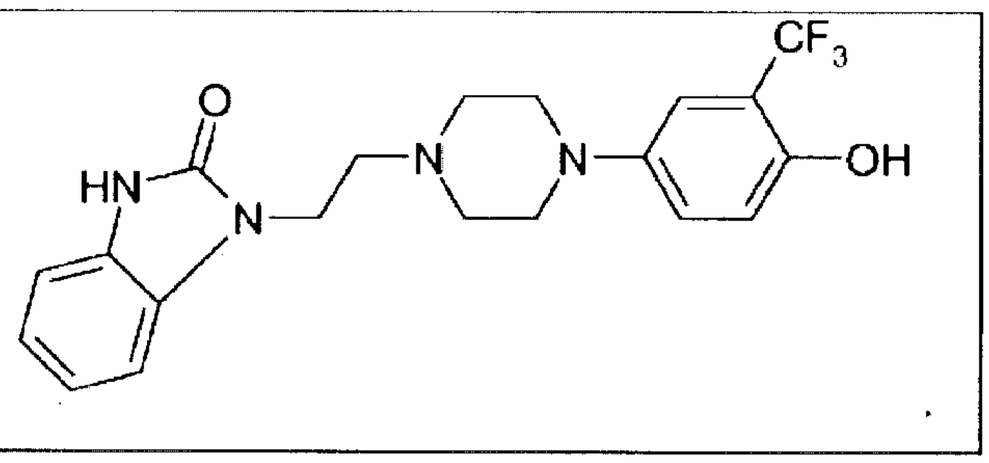
7. Use according to any one of claims 1 to 4, wherein the compound is compound (I.c)

(I.c) 

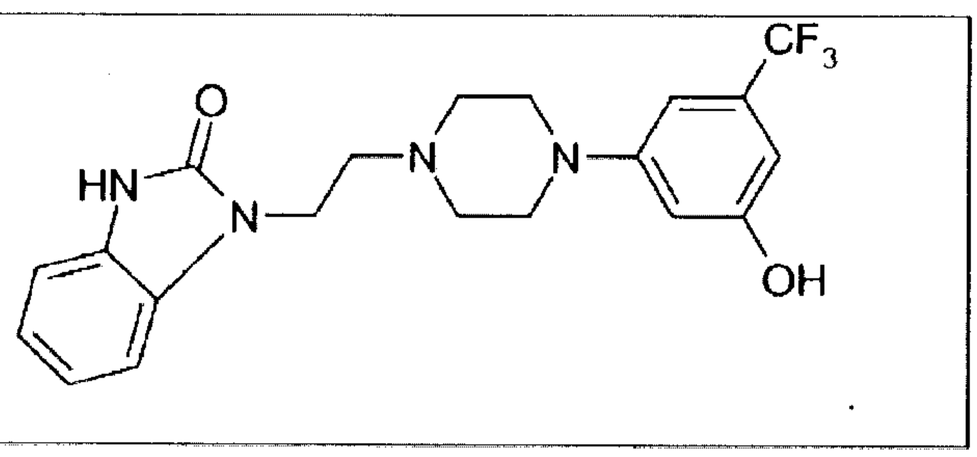
8. Use according to any one of claims 1 to 4, wherein the compound is compound (I.d)

(I.d) 

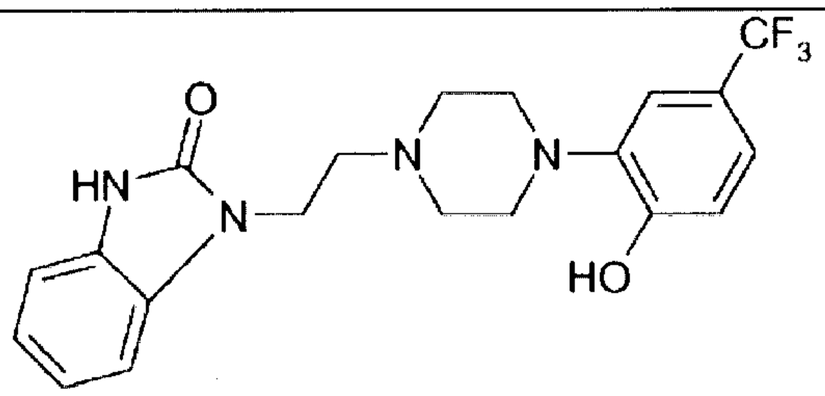
9. Use according to any one of claims 1 to 4, wherein the compound is compound (I.e)

(I.e) 

10. Use according to any one of claims 1 to 4, wherein the compound is compound (I.f)

(I.f) 

11. Use according to any one of claims 1 to 4, wherein the compound is compound (I.g)

(I.g)	

12. Use according to any one of claims 1 to 4, wherein the compound is compound (I.h)

(I.h)