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(54) **UTILIZATION OF DERIVATIVES OF TETRAHYDROPYRIDINES(OR 4-HYDROXYPIPERIDINES)-BUTYLAZOLS IN THE PREPARATION OF A MEDICAMENT FOR THE TREATMENT OF PAIN**

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 546/272.7

(58) **Field of Classification Search** 514/326,
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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,731,331 A * 3/1998 Merce-Vidal et al. 514/341

FOREIGN PATENT DOCUMENTS

WO 9604287 * 2/1996
 WO 9735584 * 10/1997

OTHER PUBLICATIONS

Guitart et al. "The effect of E-5842 . . ." *European J. Pharm.* v.363, p. 127-130 (1998).*

Rossi et al. "Pharmacological characterization . . ." *CA* 127:200544 (1997).*

Kobayashi et al. "Effect o sigma ligands on the nociceptin/ . . ." *CA* 126:287948 (1997).*

Kest et al. "1,3-di-o-toylguanidin . . ." *CA* 123:140771 (1995).*

* cited by examiner

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(57) **ABSTRACT**

Derivatives of tetrahydropyridines (or 4-hydroxypiperidines)-butylazols of formula (I), wherein R₁, R₂ and R₃, which are similar or different, represent each of them hydrogen, halogen, alkyl C₁-C₄, trifluoromethyl, hydroxyl, alkoxy, or two adjacent radicals can form a ring; A is a C atom and the dotted line represents an additional bond, or A is a C atom joined to a hydroxyl group and the dotted line represents absence of additional bond; Z₁ is N or CR₄; Z₂ is N or CR₅; Z₄ is N or CR₇; and R₄, R₅, R₆ and R₇, which different, represent hydrogen, halogen, alkyl C₃-C₄, aryl or substituted aryl, or two adjacent radicals can form part of another ring. These derivatives are useful for the treatment of acute pain, neuropathic pain or nociceptive pain in mammals, including human beings.

7 Claims, No Drawings

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**UTILIZATION OF DERIVATIVES OF
TETRAHYDROPYRIDINES(OR
4-HYDROXYPIPERIDINES)-BUTYLAZOLS
IN THE PREPARATION OF A MEDICAMENT
FOR THE TREATMENT OF PAIN**

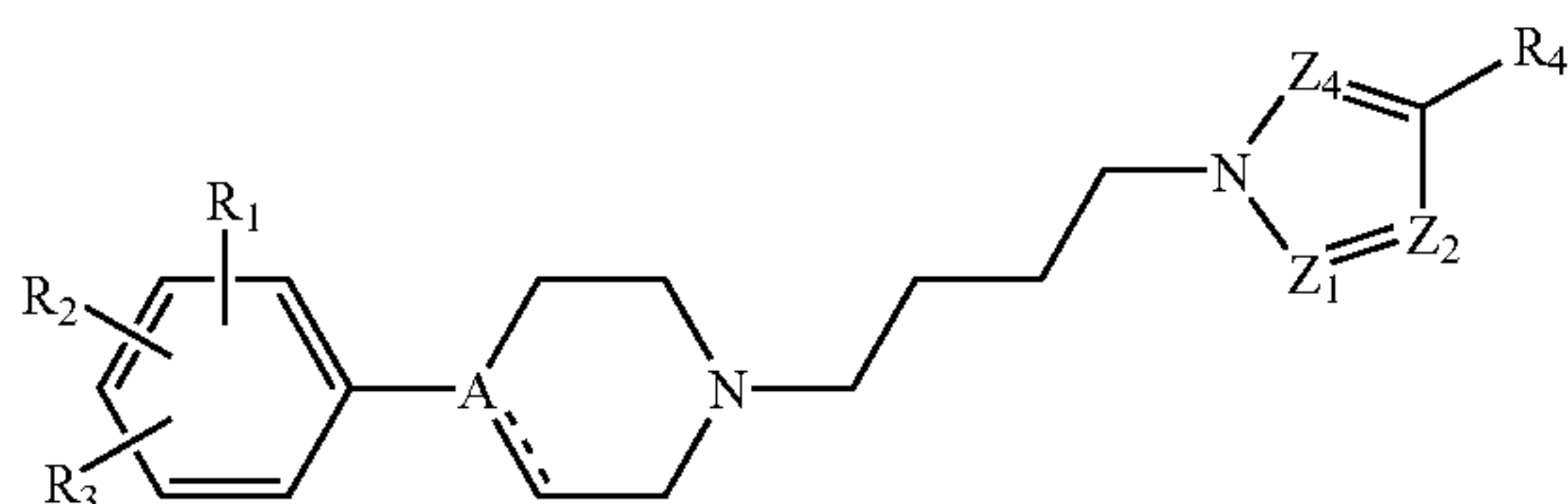
Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

FIELD OF THE INVENTION

The present invention relates to the use of derivatives of tetrahydropyridines (or 4-hydroxypiperidines)butylazoles of general formula (I), as well as their physiologically acceptable salts, in the preparation of medicaments useful in human and/or veterinary therapy for the treatment of acute pain, neuropathic pain and nociceptive pain, either alone or in combination with other analgesics, producing in this case a synergy.

BACKGROUND OF THE INVENTION

In our patent application WO 96/04287 compounds of general formula (I) are disclosed

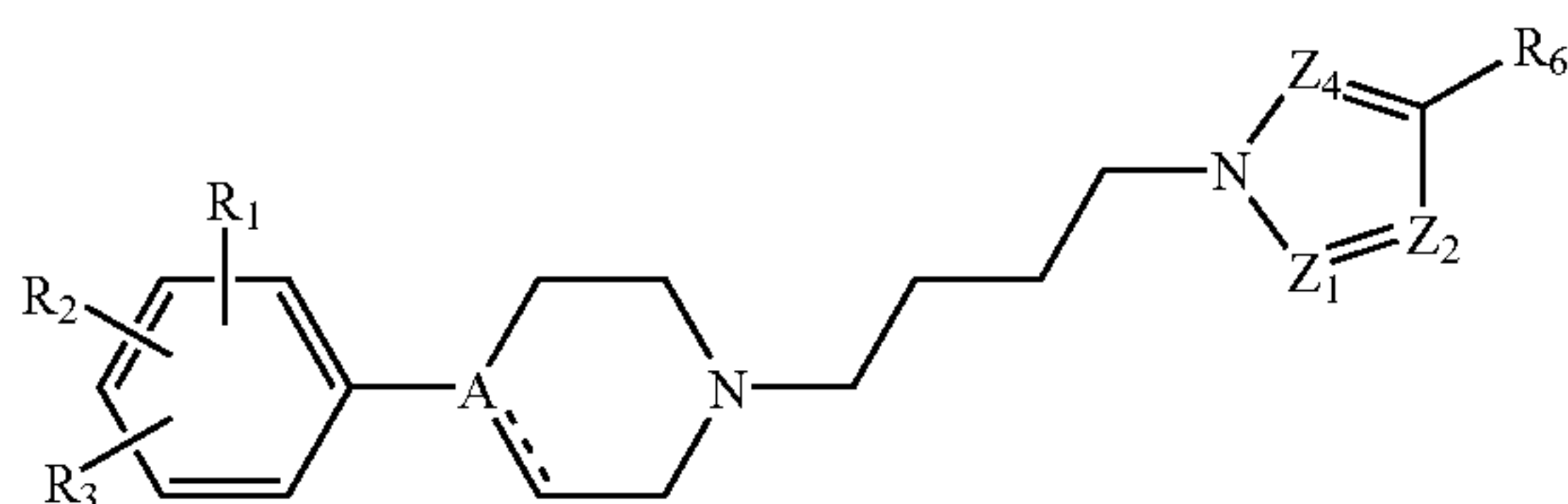


that have an affinity for the cry and 5HT_{1A} receptors, and which are claimed as medicaments useful for the treatment of anxiety, psychosis, epilepsy, convulsion, amnesia, cerebro-vascular diseases and senile dementia.

We have now discovered that the compounds of general formula (I), as well as their pharmaceutically acceptable salts, are especially useful for the preparation of medicaments, useful in human and/or veterinary therapy for the prophylaxis, alleviation or curing of acute pain, neuropathic pain and nociceptive pain, either alone or in combination with other analgesics, giving rise in this case to a synergy.

DETAILED DESCRIPTION OF THE
INVENTION

The present invention relates to the use of derivatives of tetrahydropyridines (or 4-hydroxypiperidine)butylazoles of general formula:



where

R₁, R₂ and R₃ are either identical or different and represent a hydrogen atom, a halogen atom, a C₁-C₄ alkyl group, a trifluoromethyl radical, a hydroxyl or alkoxy radical, and furthermore, two adjacent radicals can form part of an six-member aromatic ring; A represents a carbon atom and the dotted line represents an additional bond, or A represents a carbon atom bound to a hydroxyl group (C—OH) and the dotted line represents the lack of an additional bond;

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Z₁ represents a nitrogen atom or a substituted carbon atom that can be represented by C—R₄;

Z₂ represents a nitrogen atom or a substituted carbon atom that can be represented by C—R₅;

Z₄ represents a nitrogen atom or a substituted carbon atom that can be represented by C—R₇;

with the condition that Z₁, Z₂ and Z₄ taken together can represent, at most, two nitrogen atoms; and

R₄, R₅, R₆ and R₇, are identical or different and represent a hydrogen atom, a halogen atom, a C₁-C₄ alkyl group, an aryl or substituted aryl group, or two adjacent radicals can form part of a six-member aromatic ring; or one of their physiologically acceptable salts, in the elaboration of a medicament for the treatment of acute pain, neuropathic pain or nociceptive pain in mammals, including man.

The term "a halogen atom" represents a fluorine, chlorine or bromine atom.

The term "aryl or substituted aryl" represents a phenyl radical or a phenyl radical substituted by halogen.

The term "alkoxy" represents a methoxyl or ethoxyl radical.

The term "G₁-G₄ alkyl" represents a straight chain or branched radical that is based on a saturated hydrocarbon of 1 to 4 atoms of carbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl y terebutyl for example.

Physiologically acceptable salts of the compounds of general formula (I) refer both to salts formed with inorganic acids and organic acids, in particular, to salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, lactic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, benzoic acid, phenylacetic acid, cinamic acid, salicylic acid and alkyl, cycloalkyl or arylsulphonic acids.

The use of derivatives of general formula (I) for the treatment of pain refers to the use of analgesics in clinical practice. The term acute pain includes, but is not limited to, headache, arthritis, muscular tension or dysmenorrhea. The term neuropathic pain includes, but is not limited to, chronic back pains, pain associated with arthritis, herpes, pain associated with cancer, pain of a phantom limb, pain during childbirth or neuropathic pain resistant to opioids. The term nociceptive pain includes, but is not limited to, post-operation pain, dental pain, pain arising from surgery, pain caused by serious burns, post-natal pain or pain related with the genitourinary tract.

The derivatives of general formula (I) can be prepared according to the procedures disclosed in our patent application WO 96/04287.

In human therapy, the dosage administered of the compounds of the present invention varies as a function of the seriousness of the affliction to be treated. Normally the dosage will lie between 1 and 100 mg/day. The compounds of the invention can be administered as the only active ingredient or in conjunction with another analgesic in 2 proportion of one part of compound of general formula (I) with around one to ten parts of the other analgesic, with the aim of provoking a synergy. Other analgesics include, but are not limited to, non-steroid anti-inflammatory compounds such as aspirin or indomethacine, other analgesics such as paracetamol, narcotic analgesics or related compounds such as morphine, meperidine or pentazocine. The compounds of the invention, with a suitable pharmaceutical formulation, are administered by different routes, such as orally, transdermally, parenterally, subcutaneously, intranasally, intramuscularly or intravenously. Pharmaceutical compositions that contain compounds of general formula (I) are disclosed in our patent application WO 96/04287.

Illustrative examples of compounds included in the scope of the present invention include compounds that are characterised by the data indicated in tables 1 and 2.

TABLE 1

Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Z ₁	Z ₂	R ₆	Z ₄	m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
1	H	H	H	H	H	Cl	CH	CH	Cl	CH	102-103° C.	3364 (b.a., OH), 2950, 2810, 1375, 1130, 991, 969, 760, 696, 605 KBr	1.56(quin, J=7.1Hz, 2H), 1.65(b.a., 1H); 1.76 (d, J=12.4Hz, 2H); 1.90(quin, J=7.6Hz, 2H); 2.20(m, 2H); 2.40-2.55(a.c., 4H); 2.83(d, J=9.5Hz, 2H); 4.11 (t, JH=8Hz, 2H); 7.21-7.42(a.c., 5H); 7.52(d, J=8.5Hz, 2H) (CDCl ₃)
2	H	H	H	H	H	Cl	C-CH ₃	N	Cl	CCl	86-89° C.	3196 (b.a., OH), 2951, 2924, 2824, 1406, 1247, 1146 762, 703 KBr	1.59(m, J=5.3 J=6.6, 2H); 1.70-1.32(a.c., 4H); 2.16 (d, t, J=13.0Hz, J=4.4Hz, 2H); 2.37(s, 3H); 2.41-2.55 (a.c., 5H); 2.79(d, J=11.3Hz, 2H); 3.88(t, J=7.5Hz, 2H); 7.27(t, J=7.2Hz, 1H); 7.36(t, J=7.6Hz, 2H); 7.51 (d, J=7.3Hz, 2H) (CDCl ₃)
3	H	H	H	H	H	CH=CH-CH=CH-C	CH	N	CH=CH-CH=CH-C	CH	122-123° C.	3180 (b.a., OH), 2929, 2818, 1496, 1467, 1459, 1445, 1286, 1219, 1143, 769, 743, 707 KBr	1.51(quin, J=7.4Hz, 2H); 1.73(d, J=12.7Hz, 2H); 1.87 (quin, J=7.6Hz, 2H); 2.10(dt, J=12.9Hz, J=4.1Hz, 2H); 2.36-2.50(a.c., 4H); 2.70(d, J=11.2Hz, 2H); 3.25(b.a., 1H); 4.12(t, J=7.1Hz, 2H); 7.21-7.40(a.c., 6H); 7.51 (d, J=8.3Hz, 2H); 7.70-7.75(a.c., 2H) (CDCl ₃)
4	H	H	H	H	H	H	CH	N	H	N	123° C.	3180 (b.a., OH), 2949, 2919, 2838, 1276, 1145, 1135, 1006, 770, 707, 676 KBr	1.45(quin, J=7.5Hz, 2H); 1.69(d, J=12.9Hz, 2H); 1.85 quin, J=7.5Hz, 2H); 2.07(dt, J=13.0Hz, J=4.1Hz, 2H); 2.33-2.45(a.c., 4H); 2.69(d, J=11.2Hz, 2H); 2.93(b.a., 1H); 4.10(t, J=6.9Hz, 2H); 7.18(t, J=7Hz, 1H); 7.27 (t, J=7.8Hz, 2H); 7.46(d, J=8.3Hz, 2H); 7.80(s, 1H); 7.91(s, 1H) (CDCl ₃)
5	H	H	Cl	H	H	Cl	CH	CH	Cl	CH	106° C.	3145 (b.a., OH), 2947, 2918, 2834, 1318, 1147, 1083, 1112, 990, 817, 612 KBr	1.47(quin, J=7.5Hz, 2H); 1.69(d, J=11.9Hz, 2H); 1.84 (quin, J=7.6Hz, 2H); 2.05(dt, J=13Hz, J=4.4Hz, 2H); 2.34-2.50(a.c., 5H); 2.72 (d, J=11.2Hz, 2H); 4.05 (t, J=7.0Hz, 2H); 7.29(AB system, J=8.6Hz, 2H); 7.36 (s, 2H); 7.42(AB system, J=8.6Hz, 2H) (CDCl ₃)
6	H	H	Cl	H	H	Cl	C-CH ₃	N	Cl	CCl	oil	3340 (b.a., OH), 2946, 2820, 1537, 1492, 1471, 1406, 1376, 1247, 1135, 1094, 1013, 828, 755 film	1.54(m, 2H); 1.67-1.78(a.c., 4H); 2.06(dt, J=13Hz, J=4.2Hz, 2H); 2.32(s, 3H); 2.38-2.45(a.c., 5H); 2.73 (d, J=11.2Hz, 2H); 3.86(t, J=7.3Hz, 2H); 7.28(AB system, J=8.6Hz, 2H); 7.43(AB system, J=8.6Hz, 2H) (CDCl ₃)
7	H	CF ₃	H	H	H	Cl	CH	CH	Cl	CH	oil	3360 (b.a., OH), 2948, 2823, 1438, 1378, 1330, 1212, 755 film	1.48(quin, J=7.6Hz, 2H); 1.71(d, J=12.5Hz, 2H); 1.85 (quin, J=7.6Hz, 2H); 2.06-2.21(a.c., 3H); 2.36-2.43 (a.c., 4H); 2.76(d, J=11.5Hz, 2H); 4.06(t, J=7.1Hz,

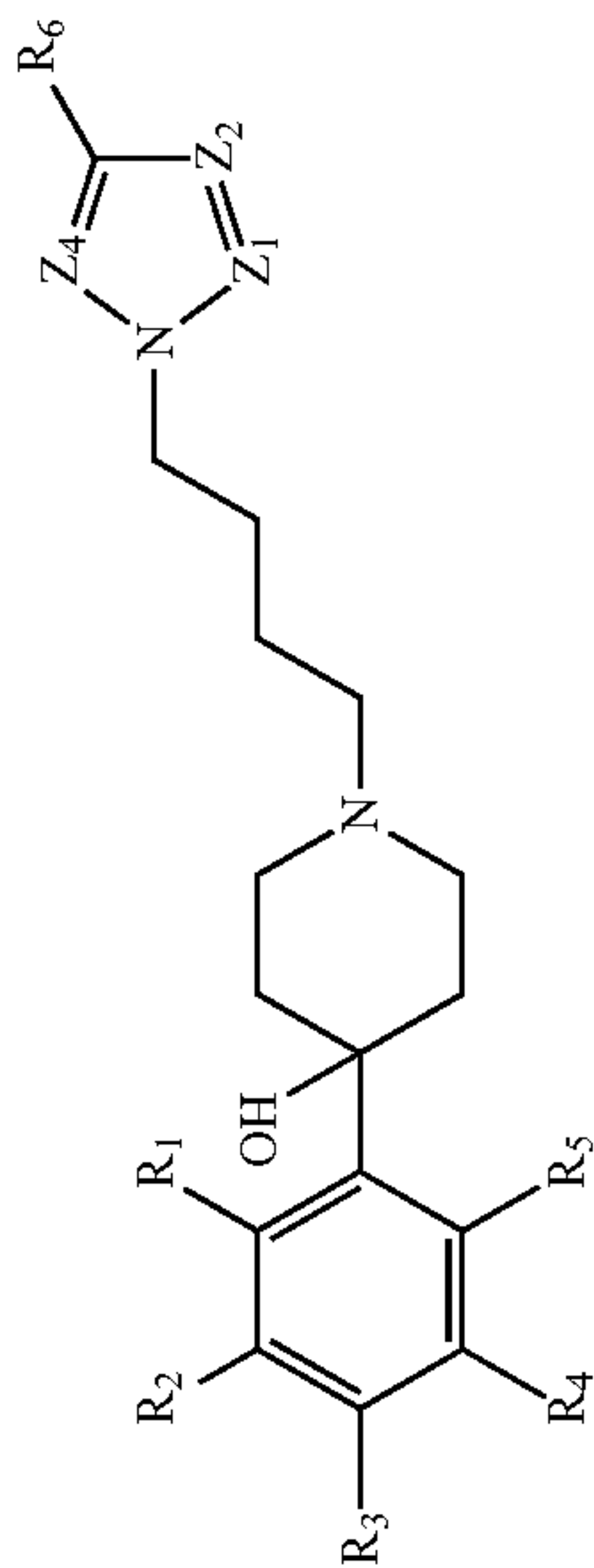


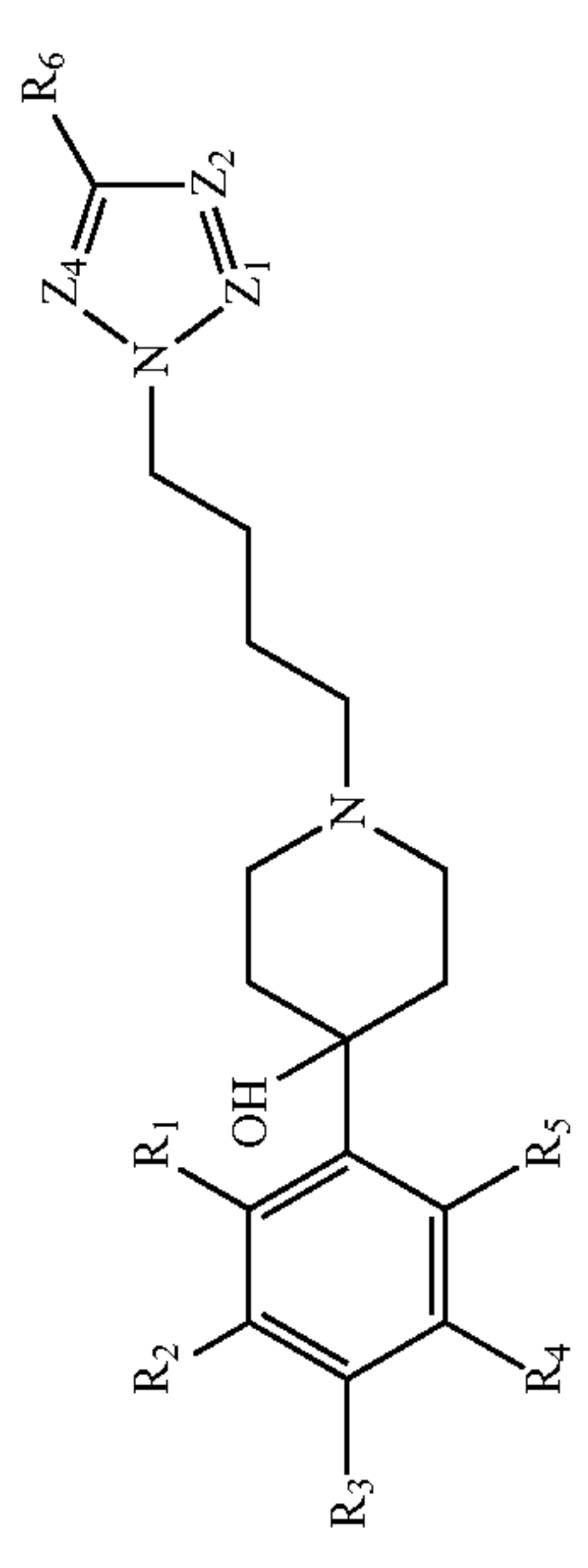
TABLE 1-continued

Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	Z ₁	Z ₂	R ₆	Z ₄	m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
8	H	CF ₃	H	H	H	C-CH ₃	N	Cl	CCl	oil	1165, 1124, 1047, 972, 804, 704 film	7.35(s, 2H); 7.43-7.51(a.c., 2H); 7.66(d, J=7.5Hz, 1H); 7.79(s, 1H) (CDCl ₃) 1.57(quin, J=7.5Hz, 2H); 1.70-1.80(a.c., 4H); 2.15(dt, J=12.9Hz J=3.6Hz, 2H); 2.35(s, 3H); 2.40-2.52(a.c., 4H); 2.80(d, J=11.7Hz, 2H); 3.88(t, J=7.0Hz, 2H); 7.42-7.57(a.c., 2H); 7.69(d, J=7.5Hz, 1H); 7.82(s, 1H) (CDCl ₃)
9	H	H	F	H	H	C-CH ₃	N	Cl	CCl	oil	3340 (b.a., OH), 2948, 2823, 1408, 1330, 1165, 1126, 1075, 789, 763, 704 film	1.58(m, 2H); 1.64-1.81(a.c., 4H); 2.14(dt, J=12.9Hz J=3.6Hz, 2H); 2.32(s, 3H); 2.43-2.60(a.c., 4H); 2.84(d, J=11Hz, 2H); 3.87(t, J=7.1Hz, 2H); 4.18(b.a., 1H), 7.01(t, J=8.8Hz, 2H); 7.46(dd, J=8.8Hz J=5.2Hz, 2H) (CDCl ₃)
10	H	H	H	H	H	CH	CH	CH=CH-CH=CH-C	109-111° C.	3190 (b.a., OH), 2956, 2823, 1461, 1446, 1319, 1303, 1218, 1142, 738, 703 film	1.57(m, 2H); 1.73(d, J=14Hz, 2H); 1.80(b.a., 1H); 1.90(m, 2H); 2.13(dt, J=13Hz J=4Hz, 2H); 2.32-2.46(a.c., 4H); 2.76(d, J=11.3Hz, 2H); 4.16(t, J=7.1Hz, 2H); 6.50(d, J=3.1Hz, 1H); 7.05-7.14(a.c., 2H); 7.18-7.40(a.c., 5H); 7.50(d, J=7.8Hz, 2H); 7.00(d, J=7.3Hz, 1H) (CDCl ₃)	
11	H	H	CH ₃	H	H	C-CH ₃	N	Cl	CCl	oil	KBr 3360 (b.a., OH), 2946, 2818, 1535, 1471, 1406, 1376, 1247, 1134, 817, 755	1.53(m, 2H); 1.66-1.84(a.c., 4H); 2.09(dt, J=12.9Hz, J=3.6Hz, 2H); 2.33(s, 3H); 2.56(s, 3H); 2.59-2.50(a.c., 4H); 2.77(d, J=11.2Hz, 2H); 3.87(t, J=7.0Hz, 2H); 7.15(AB system, J=7.8Hz, 2H); 7.33(AB system, J=7.8Hz, 2H) (CDCl ₃)
12	H	H	H	H	H	N	CH	H	CH	89-91° C.	3137 (b.a., OH), 2947, 2532, 1396, 1378, 1119, 1046, 756, 697 KBr	1.51(quin, J=7.6Hz, 2H); 1.73(d, J=12.3Hz, 2H); 1.89(quin, J=7.6Hz, 2H); 2.00-2.20(a.c., 3H); 2.35-2.45(a.c., 4H); 2.76(d, J=10.2Hz, 2H); 4.13(t, J=7.1Hz, 2H); 6.21(s, 1H); 7.21(m, 1H); 7.30-7.37(a.c., 3H); 7.44-7.52(a.c., 3H) (CDCl ₃)
13	H	H	H	H	H	N	CH	CH=CH-CH=CH-C	107-109° C.	3311 (b.a., OH), 2953, 2803, 1465, 1375, 1133, 1117, 1043, 1017, 761, 744, 704 KBr	1.53(m, 2H); 1.71(d, J=12.2Hz, 2H); 1.95(m, 2H); 2.10(m, 2H); 2.29(b.a., 1H); 2.35-2.47(a.c., 4H); 2.71(d, 2H); 4.39(t, J=7.1Hz, 2H); 7.13(t, 1H); 7.22-7.44(a.c., 5H); 7.50(d, J=8Hz, 2H); 7.71(d, J=8.3Hz, 1H); 7.95(s, 1H) (CDCl ₃)	
14	H	H	H	H	H	N	C-CH=CH-CH=CH	CH	CH	120-122° C.	3295 (b.a., OH), 2946, 2817, 1377, 1126, 786, 735, KBr	1.58(m, 2H); 1.73(d, J=13.5Hz, 2H); 1.90-2.20(a.c., 4H); 2.38-2.47(a.c., 4H); 2.75(d, J=10.5Hz, 2H); 4.42(t, J=6Hz, 2H); 7.06(t, J=7.5Hz, 1H); 7.22-7.37(a.c.,

TABLE 1-continued

Ex.											¹ H-RMN (300 MHz), δ (solvent)	
	R ₁	R ₂	R ₃	R ₄	R ₅	Z ₁	Z ₂	R ₆	Z ₄	m.p.		IR cm ⁻¹
15	H	H	CH ₃	H	H	N	CH	Cl	CH	81-82° C.	700 KBr 3122 (b.a., OH), 2936, 1475, 1434, 1378, 1319, 898, 973, 814	4H); 7.49(d, J=7.8Hz, 2H); 7.61-7.71(a.c., 2H); 7.90 (s, 1H) (CDCl ₃) 1.51(quin, J=7.6Hz, 2H); 1.73(d, J=11.7Hz, 2H); 1.87 (quin, J=7.6Hz, 2H); 2.12(dt, J=12.8Hz J=4.4Hz, 2H), 2.33(s, 3H); 2.35-2.48(a.c., 5H); 2.74(d, J=11.2Hz, 2H); 4.07(t, J=7.1Hz, 2H); 7.15(d, J=8Hz, 2H); 7.25-7.40(a.c., 4H) (CDCl ₃)
16	H	H	CH ₃ O	H	H	N	CH	Cl	CH	122-123° C.	KBr 3190 (b.a., OH), 2954, 2823, 2827, 1509, 1314, 1243, 1178, 971	1.49(quin, J=7.6Hz, 2H); 1.72(d, J=11.8Hz, 2H); 1.84 (quin J=7.4Hz, 2H); 2.00-2.14(a.c.(dt+b.a.), 3H); 2.34-2.47(a.c., 4H); 2.72(d, J=11Hz, 2H); 3.77(s, 3H); 4.05(t, J=7.1Hz, 2H); 6.85(d, J=9Hz, 2H); 7.24-7.42(a.c., 4H) (CDCl ₃)
17	H	H	H	H	H	CPh	N	H	CH	108-110° C.	KBr 3220 (b.a., OH), 2944, 2817, 1473, 1446, 1421, 1136, 1046, 787, 773, 761, 700	1.45(quin, J=7.6Hz, 2H); 1.68-1.82(a.c., 4H); 2.08 (dt, J=13.0Hz J=4.1Hz, 2H); 2.29-2.42(a.c., 4H); 2.5 (b.a., 1H); 2.67(d, J=11.2Hz, 2H); 4.01 m(t, J=7.3Hz, 2H); 7.01(s, 1H); 7.08(s, 1H); 7.20-7.56(a.c., 10H) (CDCl ₃)
18	H	H	CH ₃	H	H	CH	N	CH=CH-CH=CH-C	N	oil	KBr 3260 (b.a., OH), 2944, 2817, 1497, 1459, 1381, 1287, 1135, 1046, 817, 745	1.58(quin, J=7.6Hz, 2H); 1.74(d, J=12Hz, 2H); 1.82 (b.a., 1H); 1.95(quin, J=7.6Hz, 2H); 2.11(dt, 2H); 2.33(s, 3H); 2.40-2.50(a.c., 4H); 2.74(d, J=11.5Hz, 2H); 4.20(t, J=7.1Hz, 2H); 7.15(d, J=8.3Hz, 2H); 7.22-7.35(a.c., 3H); 7.37-7.43(a.c., 2H); 7.79(m, 1H); 7.87(s, 1H) (CDCl ₃)
19	H	H	H	H	H	CH	N	Ph	CPh	138-139° C.	film 3194 (b.a., OH), 2939, 2806, 1509, 1446, 773, 766, 758, 696	1.38(m, 2H); 1.56(m, 2H); 1.72(d, J=12.4Hz, 2H); 2.09(dt, 2H); 2.25(t, J=7.4Hz, 2H); 2.39(m, 2H); 2.66 (m, 2H); 3.10(b.a., 1H); 3.78(t, J=7.2Hz, 2H); 7.10-7.52(a.c., 16H);
20	CH=CH-CH=CH	H	H	H	H	N	CH	Cl	CH	oil	KBr 3357 (b.a., OH), 2946, 2833, 1434, 1379, 1315, 1140, 1123, 972, 781, 613	1.44(quin, J=7.3Hz, 2H); 1.77(quin, J=7.5Hz, 2H); 2.15-2.30(a.c., 5H); 2.34(t, J=7.5Hz, 2H); 2.57(m, 2H); 2.73(d, J=11.3Hz, 2H); 3.99(t, J=7.1Hz, 2H); 7.26-7.46 (a.c., 6H); 7.73(d, J=8.1Hz, 1H); 7.82(m, 1H); 8.91 (m, 1H) (CDCl ₃)
21	H	CH=CH-CH=CH	H	H	H	N	CH	Cl	CH	142-143° C.	KBr 3131 (b.a., OH), 2950, 2820, 1377, 1311, 971, 829, 761, 613	1.55(quin, J=7.5Hz, 2H); 1.70-1.97(a.c., 5H); 2.29 (dt, J=12.7Hz, J=4.1Hz, 2H); 2.41-2.55(a.c., 4H); 2.83 (d, J=11.7Hz, 2H); 4.11(t, J=7.0Hz, 2H); 7.39-7.50 (a.c., 4H); 7.64(dd, J=9.1Hz, J=1.5Hz, 1H); 7.81-7.85

TABLE 1-continued



Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	Z ₁	Z ₂	R ₆	Z ₄	m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
22	H	H	H	H	H	N	CH	C ₆ HCl	CH	137–140° C.	KBr 3347, 2944, 2810, 1562, 1492, 1376, 1127, 1094, 1002, 952, 828, 760, 699	(a.c., 3H); 7.95(s, 1H) (CDCl ₃) 1.56(m, 2H); 1.74(m, 2H); 1.80(b.a., 1H); 1.94(m, 2H); 2.40(dt, J=13.1Hz, J'=4.0Hz, 2H); 2.40–2.50(a.c., 4H); 2.77(m, 2H); 4.15(t, J=7.0Hz, 2H); 7.25–7.40 (a.c., 7H); 7.50(d, J=8.3Hz, 2H); 7.61(s, 1H); 7.72 (s, 1H) (CDCl ₃)
23	H	H	F	H	H	CH	N	CH=CH–CH=C		120–122° C.	KBr 3230, 2947, 2915, 1504, 1219, 1135, 835, 746	1.58(m, 2H); 1.70(m, 2H); 1.93(m, 2H); 2.12(m, 2H); 2.40–2.55(a.c., 4H); 2.76(m, 2H); 4.19(t, J=7.0Hz, 2H); 7.02(m, 2H); 7.26(m, 2H); 7.30–7.50(a.c., 3H); 7.74(m, 1H); 7.83(s, 1H) (CDCl ₃)
24	H	CF ₃	H	H	H	N	CH	Cl	CH	HCl 147–148° C.	KBr 3259, 2465, 2420, 2365, 1328, 1108, 1073	1.62–1.84(a.c., 6H); 2.53(m, 2H); 3.09–3.40(a.c., 6H); 4.12(t, J=6.8Hz, 2H); 5.76(s, 1H); 7.51(s, 1H); 7.52– 7.82(a.c., 4H); 8.02(s, 1H); 10.96(b.a., 1H); (DMSO-d ₆)
25	H	H	F	H	H	N	CH	CH=CH–CH=C		136–137° C.	KBr 3303, 2951, 2805, 1506, 1464, 1376, 1218, 1162, 1118, 832, 741	1.54(m, 2H); 1.60–1.80(a.c., 3H); 1.97(m, 2H); 2.06 (dt, J=13.0Hz, J'=4.3Hz, 2H); 2.30–2.43(a.c., 4H, 2.72 (m, 2H); 4.40(t, J=7.0Hz, 2H); 6.99(t, J=8.8Hz, 2H), 7.12(m, 1H); 7.32–7.47(a.c., 4H); 7.71(d, J=8.1Hz, 1H); 7.96(s, 1H) (CDCl ₃ –CD ₃ OD [1:1])
26	H	H	F	H	H	N	C–CH=CH–CH=CH		CH	148–150° C.	KBr 3325, 2950, 2923, 2812, 1509, 1377, 1218, 1131, 834, 758	1.57(m, 2H); 1.70–1.77(a.c., 3H); 1.98–2.19(a.c., 4H); 2.35–2.49(a.c., 4H); 2.77(d, J=11.2Hz, 2H); 4.45 (t, J=7.0Hz, 2H); 6.98–7.15(a.c., 3H); 7.25–7.49(a.c., 3H); 7.63(d, J=8.3Hz, 1H); 7.69(d, J=7.8Hz, 1H); 7.91 (s, 1H) (CDCl ₃ –CD ₃ OD [1:1])
27	H	H	F	H	N	N	C–CH=CH–CH=CH		N	109–110° C.	KBr 3400, 2931, 2812, 1509, 1229, 1101, 831, 745	1.47–1.80(a.c., 4H); 1.90–2.25(a.c., 5H); 2.25–2.55 (a.c., 4H); 2.70(m, 2H); 4.78(t, J=6.9Hz, 2H); 7.01 (t, J=8.7Hz, 2H); 7.26–7.54(a.c., 4H); 7.85(dd, J=6.7Hz, J=3.0Hz, 2H) (CDCl ₃ –CD ₃ OD [1:1])
28	H	H	F	H	H	N	N	CH=CH–CH=CH–C		102–103° C.	KBr 3430, 2952, 2925, 1508, 1223, 1140, 833, 744	1.45–1.80(a.c., 4H); 1.85–2.25(a.c., 5H); 2.25–2.55 (a.c., 4H); 2.77(m, 2H); 4.69(t, J=6.9Hz, 2H); 7.01 (t, J=8.7Hz, 2H); 7.26–7.53(a.c., 5H); 8.06(d, J=7.3Hz, 1H) (CDCl ₃ –CD ₃ OD [1:1])
29	H	H	F	H	H	CH	N	H	N	oil	KBr 3350 (b.a., OH), 2947, 2818, 1509, 1222, 1138, 836, 681	1.55(m, 2H); 1.74(d, J=12.6Hz, 2H); 1.94(m, 2H); 2.13(m, 2H); 2.40–2.55(a.c., 4H); 2.79(m, 2H); 4.20 (t, J=6.9Hz, 2H); 7.02(t, J=8.4Hz, 2H); 7.46(m, 2H); 7.91(s, 1H); 8.04(s, 1H) (CDCl ₃)
30	H	H	Cl	H	H	CH	N	H	N	89–91° C. film	3119 (b.a., OH), 2956, 2829, 1509,	1.46(m, 2H); 1.71(m, 2H); 1.90(quin, J=7.4Hz, 2H); 2.05(m, 2H); 2.33–2.50(a.c., 4H); 2.54(b.a., 1H); 2.72

TABLE 1-continued

Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Z ₁	Z ₂	Z ₃	Z ₄	m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
												1379, 1277, 1145, 1007, 824, 685	(m, 2H); 4.16(t, J=7.1Hz, 2H); 7.28(m, 2H); 7.42(m, 2H); 7.86(s, 1H); 7.99(s, 1H) (CDCl ₃)

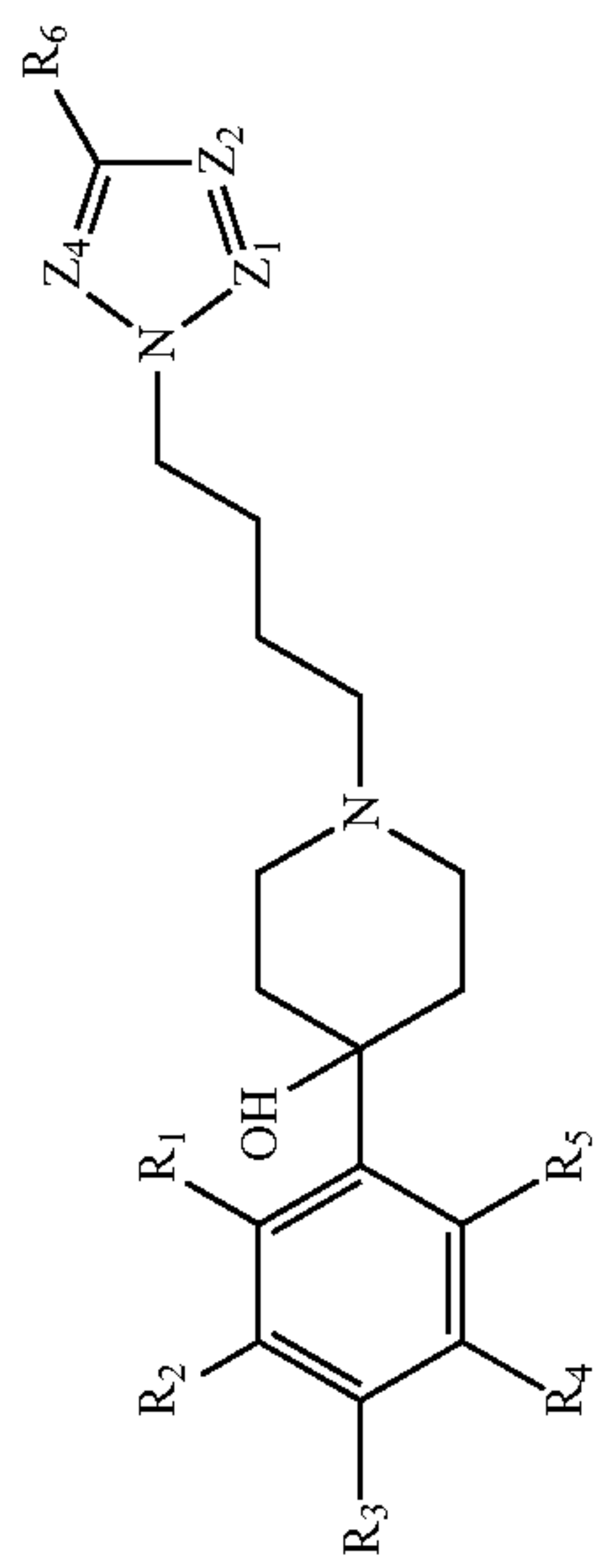
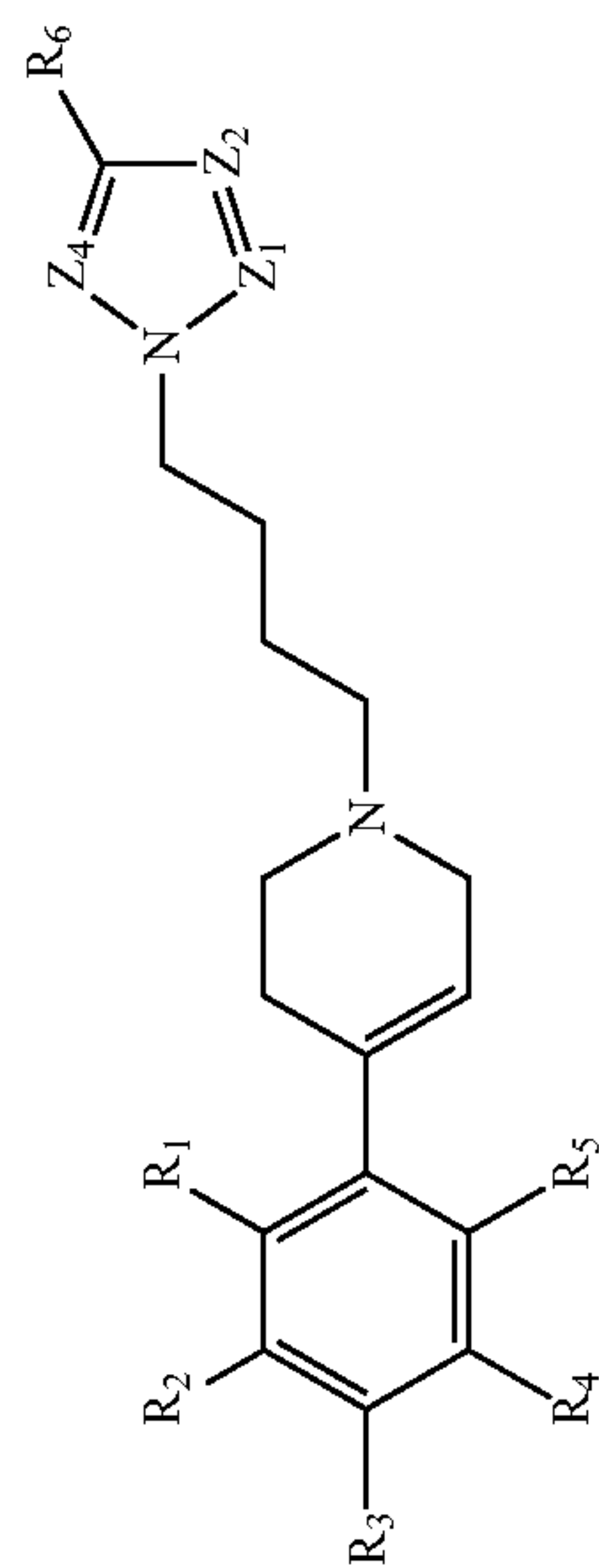


TABLE 2

Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	Z ₁	Z ₂	R ₆	Z ₄	Salt/m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
1a	H	H	H	H	H	N	CH	Cl	CH	62-64° C.	3113, 2920, 2745, 1375, 1325, 1138, 965, 837, 742, 688	1.56(quin, J=7.6Hz, 2H); 1.91(quin, J=7.6Hz, 2H); 2.47(t, J=7.4Hz, 2H); 2.58(m, 2H); 2.65(t, J=5.6Hz, 2H); 3.14(m, 2H); 4.11(t, J=7.1Hz, 2H); 6.06(m, 1H); 7.23-7.42(a.c., 7H) (CDCl ₃)
2a	H	H	H	H	H	CH	N	CH=CH-CH=CH-C		66-69° C.	2933, 1495, 745, 694, 665 film	1.55(quin, J=7.6Hz, 2H); 1.92(quin, J=7.6Hz, 2H); 2.43(t, J=7.3Hz, 2H); 2.52(m, 2H); 2.61(t, J=5.6Hz, 2H); 3.07(m, 2H); 4.14(t, J=7.1Hz, 2H); 6.02(m, 1H); 7.20-7.40(a.c., 8H); 7.80(m, 1H); 7.86(s, 1H) (CDCl ₃)
3a	H	H	H	H	H	CH	N	H	N	63-64° C.	2942, 1438, 1381, 1271, 1142, 1006, 753, 697, 681, KBr	1.56(m, 2H); 1.95(m, 2H); 2.47(t, J=7.1Hz, 2H); 2.56(m, 2H); 2.66(t, J=5.3Hz, 2H); 3.11(m, 2H); 4.19(t, J=7.0Hz, 2H); 6.05(s, 1H); 7.21(m, 1H); 7.30(t, J=7.6Hz, 2H); 7.36(d, J=7.8Hz, 2H); 7.94(s, 1H); 8.06(s, 1H) (CDCl ₃)
4a	H	H	Cl	H	H	N	CH	Cl	CH	103-104° C.	2939, 1493, 1436, 1381, 1306, 1122, 1097, 973, 843, 824, 730 KBr	1.54(m, 2H); 1.90(m, 2H); 2.45(t, J=7.4Hz, 2H); 2.51(m, 2H); 2.65(t, J=5.6Hz, 2H); 3.10(m, 2H); 4.10(t, J=7.0Hz, 2H); 6.03(m, 1H); 7.26(AB system, J=8.6Hz, 2H); 7.29(AB system, J=8.6Hz, 2H); 7.37(s, 1H); 7.41(s, 1H) (CDCl ₃)
5a	H	H	Cl	H	H	C-CH ₃	N	Cl	CCl	119-120° C.	2922, 1531, 1494, 1469, 1403, 1380, 1366, 1245, 1094, 1010 KBr	1.59(m, 2H); 1.76(m, 2H); 2.36(s, 3H); 2.42-2.53(a.c., 4H); 2.67(t, J=5.3Hz, 2H); 3.12(m, 2H); 3.88(t, J=7.4Hz, 2H); 6.04(m, 1H); 7.27(AB system, J=9.1Hz, 2H); 7.30(AB system, J=9.1Hz, 2H) (CDCl ₃)
6a	H	CF ₃	H	H	H	N	CH	Cl	CH	oil	2944, 1434, 1375, 1331, 1247, 1165, 1126, 1076, 972, 800, 698 film	1.53(quin, J=7.5Hz, 2H); 1.89(quin, J=7.7Hz, 2H); 2.45(t, J=7.3Hz, 2H); 2.54(m, 2H); 2.66(t, J=5.5Hz, 2H); 3.10(m, 2H); 4.08(t, J=7.1Hz, 2H); 6.10(m, 1H); 7.35-7.56(a.c., 5H); 7.59(s, 1H) (CDCl ₃)
7a	H	CF ₃	H	H	H	C-CH ₃	N	Cl	CCl	oil	2931, 2815, 1533, 1405, 1331, 1246, 1165, 1125, 1076, 797, 699 film	1.62(quin, J=6.6Hz, 2H); 1.77(quin, J=7.6Hz, 2H); 2.37(s, 3H); 2.51(t, J=7.2Hz, 2H); 2.60(m, 2H); 2.71(t, J=5.6Hz, 2H); 3.17(m, 2H); 3.89(t, J=7.3Hz, 2H); 6.14(m, 1H); 7.40-7.50(a.c., 2H); 7.55(d, J=7.5Hz, 1H); 7.62(s, 1H) (CDCl ₃)
8a	H	H	F	H	H	N	CH	Cl	CH	86-87° C.	2936, 1512, 1378, 1326, 1229, 988, 967	1.60(quin, J=7.5Hz, 2H); 1.91(quin, J=7.5Hz, 2H); 2.50-2.82(a.c., 4H); 2.76(t, J=5.6Hz, 2H); 3.19(m, 2H); 4.11(t, J=6.9Hz, 2H); 5.97(s, 1H);

TABLE 2-continued



Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	Z ₁	Z ₂	R ₆	Z ₄	Salt/m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
9a	H	H	F	H	H	C-CH ₃	N	Cl	CCl	79-82° C.	KBr 2934, 1531, 1512, 1408, 1247, 1225, 1167, 818	6.99(t, J=8.8Hz, 2H); 7.32(dd, J=8.8Hz, J' =5.4Hz, 2H); 7.38(s, 1H); 7.40(s, 1H) (CDCl ₃) 1.74(m, 4H); 2.35(s, 3H); 2.60-2.72(a.c., 4H); 2.90(m, 2H); 3.33(m, 2H); 3.88(m, 2H); 5.95(s, 1H); 6.99(t, J=8.6Hz, 2H); 7.31(a.c., 2H) (CDCl ₃)
10a	H	H	H	H	H	C-CH ₃	N	Cl	CCl	oil	KBr 2929, 1533, 1405, 1246, 748	1.59(m, 2H); 1.76(m, 2H); 2.37(s, 3H); 2.49(t, J=7.3Hz, 2H); 2.58(m, 2H); 2.69(t, J=5.4Hz, 2H); 3.14(m, 2H); 3.89(t, J=7.4Hz, 2H); 6.06(m, 1H); 7.22-7.40(a.c., 5H) (CDCl ₃)
11a	H	H	H	H	H	C-CH ₃	N	Cl	CCl	.HCl 203-204° C.	2930, 2576, 1407, 1376, 1245, 750	1.69(m, 2H); 1.81(m, 2H); 2.35(s, 3H); 2.71(d, J=7.2Hz, 1H); 2.91(m, 1H); 3.17(a.c., 3H); 3.56(m, 1H); 3.75(m, 1H); 3.90-3.97(a.c., 3H); 6.17(s, 1H); 7.25-7.40(a.c., 3H); 7.47(d, J=7.6Hz, 2H); 11.30(b.a., 1H) (DMSO-d ₆)
12a	H	H	H	H	H	C-CH ₃	N	Cl	CCl	.2HCl 192-194° C.	3569, 2941, 2692, 2556, 1601, 1446, 769, 753, 698	1.67(m, 2H); 1.76(m, 2H); 2.36(s, 3H); 2.69(d, J=18.0Hz, 1H); 2.88(m, 1H); 3.15(a.c., 3H); 3.54(m, 1H); 3.72(m, 1H); 3.85-398(a.c., 3H); 6.15(s, 1H); 7.22-7.38(a.c., 3H); 7.45(d, J=7.3Hz, 2H); 9.93(b.a., 1H); 11.36(b.a., 1H) (DMSO-d ₆)
13a	H	H	F	H	H	CH	CH	CH=CH-CH=CH-C	oil	2937, 1510, 1464, 1230, 1161, 816, 742	1.61(quin, J=7.7Hz, 2H); 1.93(quin, J=7.6Hz, 2H); 2.42-2.58(a.c., 4H); 2.66(t, J=5.6Hz, 2H); 3.11(m, 2H); 4.17(t, J=7.0Hz, 2H); 5.98(m, 1H); 6.51(d, J=3.9Hz, 1H); 6.95-7.39(a.c., 8H); 7.65(d, J=7.8Hz, 1H) (CDCl ₃)	
14a	H	H	H	H	H	CH	CH	CH=CH-CH=CH-C	oil	2938, 1510, 1485, 1463, 1446, 1376, 1336, 1315, 763, 740, 695	1.63(quin, J=7.4Hz, 2H); 1.949quin, J=7.4Hz, 2H); 2.49(t, J=7.6Hz, 2H); 2.60(m, 2H); 2.69(t, J=5.3Hz, 2H); 3.14(m, 2H); 4.19(t, J=7.1Hz, 2H); 6.08(m, 1H); 6.53(m, 1H); 7.08-7.44(a.c., 9H); 7.67(d, J=8.1Hz, 1H) (CDCl ₃)	
15a	H	H	CH ₃	H	H	C-CH ₃	N	Cl	CCl	87-88° C.	2939, 2916, 1529, 1404, 1378, 1243, 1166, 1131, 1016	1.59(m, 2H); 1.75(m, 2H); 2.32(s, 3H); 2.36(s, 3H); 2.47(t, J=7.2Hz, 2H); 2.54(m, 2H); 2.67(t, J=5.2Hz, 2H); 3.11(m, 2H); 3.87(t, J=7.3Hz, 2H); 6.01(s, 1H); 7.11(AB system, J=8.1Hz, 2H); 7.27(AB system, J=8.1Hz, 2H) (CDCl ₃)
16a	H	H	H	H	H	N	CH	H	CH	36-38° C.	2941, 1396, 748, 695	1.54(quin, J=7.6Hz, 2H); 1.91(quin, J=7.6Hz, 2H); 2.45(t, J=7.6Hz, 2H); 2.55(m, 2H); 2.65(t, J=5.6Hz, 2H); 3.11(m, 2H); 4.14(t, J=7.1Hz,

TABLE 2-continued

Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	Z ₁	Z ₂	R ₆	Z ₄	Salt/m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
17a	H	H	H	H	H	N	CH	CH=CH—CH=CH—C	CH	50–52° C.	2942, 1465, 1158, 832, 740, 691 film	2H); 6.03(m, 1H); 6.21(m, 1H); 7.20–7.39(a.c., 6H); 7.49(m, 1H) (CDCl ₃) 1.61(quin, 2H); 2.00(quin, J=7.5Hz, 2H); 2.43–2.58(a.c., 4H); 2.68(m, 2H); 3.14(s, 2H); 4.43(t, J=6.6Hz, 2H); 6.02(s, 1H); 7.13(t, J=7.3Hz, 1H); 7.20–7.51(a.c., 7H); 7.73(d, J=7.9Hz, 1H); 7.99(s, 1H) (CDCl ₃)
18a	H	H	H	H	H	N	C—CH=CH—CH=CH	CH	CH	73–75° C.	3049, 2940, 2778, 1467, 1371, 1158, 1143, 1131, 757, 742, 692 KBr	1.60(quin, J=7.6Hz, 2H); 2.09(quin, J=7.4Hz, 2H); 2.48(t, J=7.4Hz, 2H); 2.55(m, 2H); 2.66(t, J=5.6Hz, 2H); 3.11(d, J=2.9Hz, 2H); 4.45(t, J=7.1Hz, 2H); 6.03(s, 1H); 7.07(t, J=7.5Hz, 1H); 7.20–7.39(a.c., 6H); 7.63(d, J=4.3Hz, 1H); 7.70(d, J=8Hz, 1H); 7.91(s, 1H) (CDCl ₃)
19a	H	H	CH ₃	H	H	N	CH	Cl	CH	72–73° C.	3115, 2938, 2740, 1376, 1328, 1137, 986, 966, 844, 824, 797 KBr	1.55(quin, 2H); 1.90(quin, J=7.5Hz, 2H); 2.33(s, 3H); 2.46(t, J=7.5Hz, 2H); 2.55(m, 2H); 2.66(t, J=6.4Hz, 2H); 3.11(m, 2H); 4.10(t, J=7.0Hz, 2H); 6.01(s, 1H); 7.12(AB system, J=8Hz, 2H); 7.27(AB system, J=8Hz, 2H); 7.37(s, 1H); 7.41(s, 1H) (CDCl ₃)
20a	H	H	CH ₃ O	H	H	N	CH	Cl	CH	104–105° C.	2923, 1533, 1405, 1379, 1246, 749 KBr	1.54(quin, 2H); 1.89(quin, J=7.6Hz, 2H); 2.44(t, J=7.4Hz, 2H); 2.52(m, 2H); 2.65(t, J=5.3Hz, 2H); 3.10(m, 2H); 3.78(s, 3H); 4.09(t, J=7.0Hz, 2H); 5.95(s, 1H); 6.84(AB system, J=8.5Hz, 2H); 7.31(AB system, J=8.5Hz, 2H); 7.36(s, 1H); 7.40(s, 1H) (CDCl ₃)
21a	H	H	H	H	H	N	CH	Cl	CH	oil	2948, 223, 2811, 2774, 1446, 1382, 1316, 971, 748, 695 film	2.08(quin, J=7.0Hz, 2H); 2.42(t, J=7.0Hz, 2H); 2.58(m, 2H); 2.67(t, J=5.6Hz, 2H); 3.13(m, 2H); 4.17(t, J=6.9Hz, 2H); 6.07(m, 1H); 7.23–7.45(a.c., 7H) (CDCl ₃)
22a	H	H	H	H	H	CCH ₃	N	Cl	CCl	oil	2923, 1533, 1405, 1379, 1246, 749 film	1.95(quin, J=7.2Hz, 2H); 2.39(s, 3H); 2.46(t, J=7.0Hz, 2H); 2.58(m, 2H); 2.69(t, J=4.9Hz, 2H); 3.13(m, 2H); 3.96(t, J=7.3Hz, 2H); 6.07(m, 1H); 7.20–7.41(a.c., 5H) (CDCl ₃)
23a	H	H	H	H	H	CPh	N	H	CH	oil	2940, 1496, 1474, 1445, 1379, 1275, 774, 698 film	1.51(m, 2H); 1.81(m, 2H); 2.40(t, J=7.4Hz, 2H); 2.56(m, 2H); 2.63(t, J=4.9Hz, 2H); 3.09(m, 2H); 4.04(t, J=7.2Hz, 2H); 6.03(m, 1H); 7.03(m, 1H); 7.13(m, 1H); 7.22–7.48(a.c., 8H); 7.58(m, 2H) (CDCl ₃)

TABLE 2-continued

Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	Z ₁	Z ₂	R ₆	Z ₄	Salt/m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
24a	H	H	CH ₃	H	H	CH	N	CH=CH-CH=CH-C	Z ₄	90-91° C.	2939, 2915, 1500, 1461, 1377, 1365, 750 KBr	1.59(m, 2H); 1.95(m, 2H); 2.32(s, 3H); 2.46(t, J=7.3Hz, 2H); 2.53(m, 2H); 2.63(t, J=5.5Hz, 2H); 3.08(m, 2H); 4.20(t, J=6.95Hz, 2H); 6.00(s, 1H); 7.11(d, J=7.8Hz, 2H); 7.27(a.c., 4H); 7.40(m, 1H); 7.80(m, 1H); 7.8(s, 1H) (CDCl ₃)
25a	H	H	H	H	H	CH	N	Ph	CPh	100-101° C.	3130, 2939, 2770, 1600, 1506, 1443, 1259, 954, 780, 774, 750, 696, 649 KBr	1.46(quin, J=7.5Hz, 2H); 1.65(quin, J=7.6Hz, 2H); 2.33(t, J=7.3Hz, 2H); 2.53(m, 2H); 2.60(m, 2H); 3.05(m, 2H); 3.84(t, J=7.2Hz, 2H); 6.02(m, 1H); 7.05-7.50(a.c., 15H); 7.61(s, 1H) (CDCl ₃)
26a	CH=CH-CH=CH	CH=CH-CH=CH	H	H	H	N	CH	Cl	CH	oil	3057, 3043, 2942, 2806, 2768, 1378, 1365, 971, 801, 778 KBr	1.61(quin, J=7.5Hz, 2H); 1.95(quin, J=7.6Hz, 2H); 2.51-2.57(a.c., 4H); 2.76(t, J=5.6Hz, 2H); 3.20(m, 2H); 4.14(t, J=7.1Hz, 2H); 5.74(m, 1H); 7.26-7.50(a.c., 6H); 7.75(d, J=8Hz, 1H); 7.84(m, 1H); 8.02(m, 1H) (CDCl ₃)
27a	H	CH=CH-CH=CH	CH=CH-CH=CH	H	H	N	CH	Cl	CH	95-96° C.	3111, 2920, 2806, 1374, 1326, 966, 826, 749, 612, film KBr	1.57(m, 2H); 1.92(m, 2H); 2.48(m, 2H); 2.71(a.c., 4H); 3.18(m, 2H); 4.11(m, 2H); 6.22(m, 1H); 7.38-7.50(a.c., 4H); 7.61(m, 1H); 7.75-7.84(a.c., 4H) (CDCl ₃)
28a	H	H	F	H	H	CH	N	CH=CH-CH=CH-C	CH=CH-CH=CH-C	135-136° C.	3050, 2920, 2780, 2760, 1510, 1492, 1459, 1224, 1202, 1161, 771, 751 KBr	2.54(m, 2H); 2.74(t, J=5.6Hz, 2H); 2.92(t, J=6.7Hz, 2H); 3.24(m, 2H); 4.35(t, J=6.7Hz, 2H); 5.98(m, 1H); 7.00(t, J=8.7Hz); 7.26-7.40(a.c., 4H); 7.42(m, 1H); 7.81(m, 1H); 8.01(s, 1H) (CDCl ₃)
29a	H	H	H	H	H	CH	N	CH=CH-CH=CH-C	CH=CH-CH=CH-C	HCl 177-178° C.	2940, 2488, 1500, KBr	1.70-1.90(a.c., 4H); 2.78(m, 2H); 3.17(m, 2H); 3.20-3.50(b.a., 2H); 3.79(m, 2H); 4.30(t, J=6.6Hz, 2H); 6.15(s, 1H); 7.17-7.40(a.c., 5H); 7.45(d, J=7.3Hz, 2H); 7.65(m, 2H); 8.35(s, 1H) (DMSO-d ₆)
30a	H	H	F	H	H	CH	N	CH=CH-CH=CH-C	CH=CH-CH=CH-C	106-108° C.	2942, 1512, 1498, KBr	1.59(quin, J=7.5Hz, 2H); 1.96(quin, J=7.5Hz, 2H); 2.40-2.50(a.c., 4H); 2.63(t, J=5.5Hz, 2H); 3.09(m, 2H); 4.21(t, J=7.1Hz, 2H); 5.97(m, 1H); 6.98(t, J=8.1Hz, 2H); 7.20-7.35(a.c., 4H); 7.40(m, 1H); 7.80(m, 1H); 7.89(s, 1H) (CDCl ₃)
31a	H	H	F	H	H	CH	N	CH=CH-CH=CH-C	CH=CH-CH=CH-C	HCl	2930, 1600, 1510, 1275 KBr	1.70-2.00(a.c., 4H); 2.78(m, 2H); 3.20(m, 2H); 3.20-3.60(b.a., 2H); 3.81(m, 2H); 4.38(t, J=6.6Hz, 2H); 6.13(s, 1H); 7.19(t, J=8.7Hz, 2H); 7.33(m, 2H); 7.49(m,

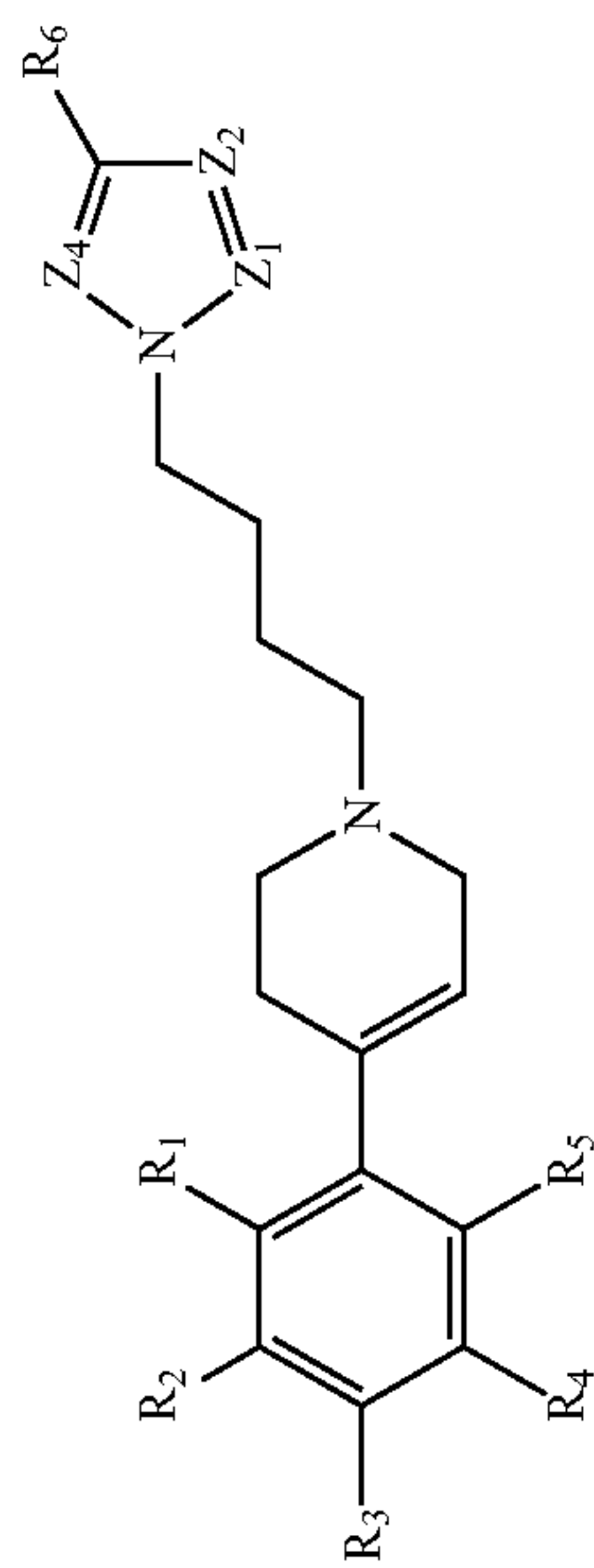


TABLE 2-continued

Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	Z ₁	Z ₂	R ₆	Z ₄	Salt/m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
40a	H	H	F	H	H	CCH ₃	N	CH=CH-CH=CH-C	C	oil	1227, 1161, 1140, 846, 824, 681 film	1.63(m, 2H); 1.88(m, 2H); 2.42-2.55(a.c., 4H); 2.61(s, 3H); 2.65(t, J=5.5Hz, 2H); 3.09(m, 2H); 4.14(t, J=7.3Hz, 2H); 5.97(m, 1H); 6.99(m, 2H); 7.19-7.35(a.c., 5H); 7.68(m, 1H); (CDCl ₃)
41a	H	H	F	H	H	N	CH	CH=CH-CH=CH-C	C	oil	1404, 1231, 744 film	1.57(m, 2H); 1.99(m, 2H); 2.42-2.50(a.c., 4H); 2.62(t, J=5.6Hz, 2H); 3.06(m, 2H); 4.42(t, J=6.9Hz, 2H); 5.95(m, 1H); 6.97(t, J=8.8Hz, 2H); 7.12(m, 1H); 7.25-7.41(a.c., 4H); 7.71(d, J=8Hz, 1H); 7.99(s, 1H) (CDCl ₃)
42a	H	H	F	H	H	N	C-CH=CH-CH=CH	CH	CH	102-103° C.	2941, 1510, 1374, 1226, 1162, 806, 759, 741 KBr	1.59(quin, J=7.0Hz, 2H); 2.09(quin, J=7.5Hz, 2H); 2.40-2.50(a.c., 4H); 2.64(t, J=6.2Hz, 2H); 3.10(m, 2H); 4.45(t, J=7.1Hz, 2H); 5.96(m, 1H); 6.98(t, J=8.8Hz, 2H); 7.07(t, J=7.6Hz, 1H); 7.20-7.35(a.c., 3H); 7.63(d, J=8.5Hz, 1H); 7.71(d, J=8.6Hz, 1H); 7.90(s, 1H) (CDCl ₃)
43a	H	H	F	H	H	N	C-CH=CH-CH=CH	N	N	HCl 208-209° C.	2574, 2482, 1510, 1231, 745 KBr	1.80(m, 2H); 2.11(quin, J=7.2Hz, 2H); 2.69(m, 1H); 2.83(m, 1H); 3.10-3.20(a.c., 3H); 3.52(m, 1H); 3.71(m, 1H); 3.88(m, 1H); 4.80(t, J=6.3Hz, 2H); 6.11(s, 1H); 7.19(m, 2H); 7.41(m, 2H); 7.50(m, 2H); 7.91(m, 2H); 11.07(b.a., 1H) (DMSO-d ₆)
44a	H	H	F	H	H	N	C-CH=CH-CH=CH	N	N	76-77° C.	2931, 1511, 1470, 1380, 1327, 1224, 1172, 1132, 851, 826, 757 KBr	1.60(quin, J=7.5Hz, 2H); 2.19(quin, J=8.2Hz, 2H); 2.41-2.59(q, c., 4H); 2.64(t, J=5.7Hz, 2H); 3.08(m, 2H); 4.77(t, 7.0Hz, 2H); 5.95(m, 1H); 6.97(t, J=8.8Hz, 2H); 7.25-7.40(a.c., 4H); 7.85(m, 2H) (CDCl ₃)
45a	H	H	F	H	H	N	CH=CH-CH=CH-C	C	C	HCl 204-205° C.	2928, 2680, 2573, 2559, 1515, 1454, 1272, 1242, 1224, 1166, 819, 745 KBr	1.81(m, 2H); 1.99(m, 2H); 2.67(m, 1H); 2.48(m, 1H); 3.10-3.20(a.c., 3H); 3.53(m, 1H); 3.72(m, 1H); 3.90(m, 1H); 4.76(t, J=6.9Hz, 2H); 6.12(s, 1H); 7.19(t, J=8.8Hz, 2H); 7.39(t, J=7.6Hz, 1H); 7.45-7.60(a.c., 3H); 7.94(d, J=8.3Hz, 2H); 8.03(d, J=8.3Hz, 2H); 11.04(b.a., 1H) (CDCl ₃)
46a	H	H	F	H	H	N	CH=CH-CH=CH-C	C	C	88-90° C.	2939, 1510, KBr	1.58(quin, J=7.5Hz, 2H); 2.07(quin, J=7.5Hz, 2H);

TABLE 2-continued

Ex.											IR cm ⁻¹	Salt/m.p.	Z ₄	R ₆	Z ₂	Z ₁	R ₅	R ₄	R ₃	R ₂	R ₁	¹ H-RMN (300 MHz), δ (solvent)	
	Z ₃																						
54a	H	H	H	H	H	N	CCl	CH=CH-CH=CH-C	Cl	CCl	CCl	N	H	H	H	H	H	H	H	H	H	4.36(t, J=7.1Hz, 2H); 6.04(m, 1H); 7.18-7.42(a.c., 8H); 7.67(d, J=7.6Hz, 1H) (CDCl ₃) 1.80(m, 2H); 1.90(m, 2H); 2.70(m, 1H); 2.87(m, 1H); 3.07-3.22(a.c., 3H); 3.52(m, 1H); 3.72(m, 1H); 3.87(m, 1H); 4.43(t, J=6.6Hz, 2H); 6.14(s, 1H); 7.20-7.52(a.c., 7H); 7.65(m, 1H); 7.7(m, 1H); 11.16(b.a., 1H) (DMSO-d ₆)	
55a	H	H	H	H	H	CCH ₃	N	Cl	Cl	CCl	CCl	N	OH	H	H	H	H	H	H	H	H	1.69(m, 2H); 1.75(m, 2H); 2.33(s, 3H); 2.68(m, 1H); 2.79(m, 1H); 3.14(a.c., 3H); 3.55(m, 1H); 3.68(m, 1H); 3.87-4.00(a.c., 3H); 5.97(s, 1H); 6.77(Syst. ab, J=8.8Hz, 2H); 7.28(Syst. ab, J=8.8Hz, 2H); 9.62(s, 1H); 10.82(b.a., 1H) (DMSO-d ₆) 1.75(a.c., 4H); 2.70(m, 1H); 2.87(m, 1H); 3.17(a.c., 3H); 3.56(m, 1H); 3.74(m, 1H); 3.87-4.15(a.c., 3H); 6.17(s, 1H); 7.27-7.40(a.c., 3H); 7.47(m, 2H); 7.91(s, 1H); 11.02(b.a., 1H) (DMSO-d ₆)	
56a	H	H	H	H	H	CH	N	Cl	Cl	CCl	CCl	N	H	H	H	H	H	H	H	H	H	1.90(m, 2H); 2.08(quint., J=7.5Hz, 2H); 2.86(AB, J=15.5Hz, 4H); 2.93(b.a., 2H); 3.29(m, 2H); 3.54(t, J=5.9Hz, 2H); 3.93(b.a., 2H); 4.43(t, J=6.6Hz, 2H); 6.17(b.a., 1H); 7.19(m, 2H); 7.59(m, 2H); 8.10(s, 1H); 8.60(s, 1H) (MeOH-d ₄) 1.55(m, 2H); 1.95(m, 2H); 2.40-2.55(a.c., 4H); 2.64(m, 2H); 3.08(m, 2H); 4.20(t, J=7.1Hz, 2H); 6.03(m, 1H); 7.22(AB, J=8.5Hz, 2H); 7.40(AB, J=7.93(s, 1H); 8.05(s, 1H) (CDCl ₃)	
57a	H	H	H	H	H	CH	N	H	H	N	N	N	F	H	H	H	H	H	H	H	H	1720, 1709, 1513, 1225, 1193, 1166, 1133 KBr Citrate 132-133° C.	7.93(s, 1H); 7.27-7.40(a.c., 3H); 7.47(m, 2H); 7.91(s, 1H); 11.02(b.a., 1H) (DMSO-d ₆) 1.90(m, 2H); 2.08(quint., J=7.5Hz, 2H); 2.86(AB, J=15.5Hz, 4H); 2.93(b.a., 2H); 3.29(m, 2H); 3.54(t, J=5.9Hz, 2H); 3.93(b.a., 2H); 4.43(t, J=6.6Hz, 2H); 6.17(b.a., 1H); 7.19(m, 2H); 7.59(m, 2H); 8.10(s, 1H); 8.60(s, 1H) (MeOH-d ₄) 1.55(m, 2H); 1.95(m, 2H); 2.40-2.55(a.c., 4H); 2.64(m, 2H); 3.08(m, 2H); 4.20(t, J=7.1Hz, 2H); 6.03(m, 1H); 7.22(AB, J=8.5Hz, 2H); 7.40(AB, J=7.93(s, 1H); 8.05(s, 1H) (CDCl ₃)
58a	H	H	H	H	H	CH	N	H	H	N	N	N	Br	H	H	H	H	H	H	H	H	2939, 2773, 2736, 1509, 1490, 1380, 1271, 1140, 1071, 1006, 961, 844, 827, 800, 680 KBr 113-115° C.	1.76(m, 2H); 1.84(m, 2H); 2.71(m, 1H); 2.85(m, 1H); 3.17(a.c., 3H); 3.55(m, 1H); 3.74(m, 1H); 3.80(m, 1H); 4.23(t, J=6.6Hz, 2H); 6.22(s, 1H); 7.42(Syst. AB, J=8.1Hz, 2H); 7.56(Syst. AB, J=8.1Hz, 2H); 7.98(s, 1H); 8.60(s, 1H) (DMSO-d ₆) 1.56(quint, J=7.5Hz, 2H); 1.97(quint, J=7.5Hz, 2H); 2.40-2.70(a.c., 4H); 2.66(t, J=5.7Hz, 2H); 3.10(d, J=3 Hz, 2H); 4.21(t, J=7.0Hz, 2H); 6.04(s, 1H); 7.20-7.35(m, 4H); 7.94(s, 1H); 8.06(s, 1H) (CDCl ₃)
59a	H	H	H	H	H	CH	N	H	H	N	N	N	Br	H	H	H	H	H	H	H	H	3066, 2937, 2479 (b.a.) 1514, 1146, 1012, 802 KBr 162-164° C.	1.76(m, 2H); 1.84(m, 2H); 2.71(m, 1H); 2.85(m, 1H); 3.17(a.c., 3H); 3.55(m, 1H); 3.74(m, 1H); 3.80(m, 1H); 4.23(t, J=6.6Hz, 2H); 6.22(s, 1H); 7.42(Syst. AB, J=8.1Hz, 2H); 7.56(Syst. AB, J=8.1Hz, 2H); 7.98(s, 1H); 8.60(s, 1H) (DMSO-d ₆) 1.56(quint, J=7.5Hz, 2H); 1.97(quint, J=7.5Hz, 2H); 2.40-2.70(a.c., 4H); 2.66(t, J=5.7Hz, 2H); 3.10(d, J=3 Hz, 2H); 4.21(t, J=7.0Hz, 2H); 6.04(s, 1H); 7.20-7.35(m, 4H); 7.94(s, 1H); 8.06(s, 1H) (CDCl ₃)
60a	H	H	H	H	H	CH	N	H	H	N	N	N	Cl	H	H	H	H	H	H	H	H	2930, 2775, 2737, 1509, 1493, 1381, 1271, 1141, 1091, 1010, 961, 847, KBr 101-103° C.	1.76(m, 2H); 1.84(m, 2H); 2.71(m, 1H); 2.85(m, 1H); 3.17(a.c., 3H); 3.55(m, 1H); 3.74(m, 1H); 3.80(m, 1H); 4.23(t, J=6.6Hz, 2H); 6.22(s, 1H); 7.42(Syst. AB, J=8.1Hz, 2H); 7.56(Syst. AB, J=8.1Hz, 2H); 7.98(s, 1H); 8.60(s, 1H) (DMSO-d ₆) 1.56(quint, J=7.5Hz, 2H); 1.97(quint, J=7.5Hz, 2H); 2.40-2.70(a.c., 4H); 2.66(t, J=5.7Hz, 2H); 3.10(d, J=3 Hz, 2H); 4.21(t, J=7.0Hz, 2H); 6.04(s, 1H); 7.20-7.35(m, 4H); 7.94(s, 1H); 8.06(s, 1H) (CDCl ₃)

TABLE 2-continued

Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	Z ₁	Z ₂	R ₆	Z ₄	Salt/m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
61a	H	H	Cl	H	H	H	CH	N	H	N	HCl 165–166° C.	2951, 2505 (b.a.) 1502, 1494, 1275, 1136, 1098, 1013, 810, 686 KBr	1.73(m, 2H); 1.83(m, 2H); 2.70(m, 1H); 2.85(m, 1H); 3.10–3.20(a.c., 3H); 3.54(m, 1H); 3.73(m, 1H); 3.88 (m, 1H); 4.22(t, J=6.6Hz, 2H); 6.20(s, 1H); 7.42(Syst. AB, J=8.6Hz, 2H); 7.49(Syst. AB, J=8.6Hz, 2H); 7.97 (s, 1H); 8.59(s, 1H); 11.17(b.a., 1H) (DMSO-d ₆)
62a	H	H	Cl	H	H	H	CPh	N	H	CH	oil	1445, 1379, 1271, 774, 681 film	1.48(m, 2H); 1.80(m, 2H); 2.36(t, J=7.4Hz, 2H); 2.47 (m, 2H); 2.59(m, 2H); 3.04(d, J=3Hz, 2H); 4.03(t, J=7.4Hz, 2H); 6.01(s, 1H); 7.01(d, J=1.2Hz, 1H); 7.11(d, J=1.2Hz, 1H); 7.27(m, 4H); 7.35–7.60(a.c., 5H) (CDCl ₃)
63a	H	H	Cl	H	H	H	CPh	N	H	CH	HCl 70° C. (hygrosc.)	2935, 2695, 2591, 1493, 1094, 777, 702 KBr	1.65(m, 2H); 1.80(m, 2H); 2.67(m, 1H); 2.82(m, 1H); 3.05–3.21(a.c., 3H); 3.55(m, 1H); 3.69(m, 1H); 3.88 (m, 1H); 4.20(t, 6.6Hz, 2H); 6.18(s, 1H); 7.40(Syst. AB, J=8.7Hz, 2H); 7.47(Syst. AB, J=8.7Hz, 2H); 7.60– 7.88(a.c., 5H); 7.86(s, 1H); 7.96(s, 1H) (DMSO-d ₆ + TEA)
64a	H	H	H	H	H	H	CCH ₃	CH	H	CCH ₃	oil	2929, 1408, 1299, 746, 693 film	1.65(a.c., 4H); 2.23(s, 6H); 2.48(m, 2H); 2.58(m, 2H); 2.69(m, 2H); 3.15(m, 2H); 3.76(t, J=7.2Hz, 2H); 5.76 (s, 2H); 6.06(s, 1H); 7.20–7.40(a.c., 5H) (CDCl ₃)
65a	H	H	H	H	H	H	CCH ₃	CH	H	CCH ₃	HCl 178–180° C.	3434, (b.a.), 2935, 2560, 1443, 1405, 1298, 748, 692	1.56(m, 2H); 1.77(m, 2H); 2.15(s, 6H); 2.70(m, 1H); 2.84(m, 1H); 3.08–3.22(a.c., 3H); 3.59(m, 1H); 3.70– 3.80(a.c., 3H); 3.93(m, 1H); 5.59(s, 2H); 6.17(s, 1H); 7.25–7.50(a.c., 5H); 10.72(b.a., 1H) (DMSO-d ₆)
66a	H	H	Cl	H	H	H	CCH ₃	CH	H	CCH ₃	86–88° C.	2933, 1493, 1412, 1376, 1300, 750 film	1.65(a.c., 4H); 2.24(s, 6H); 2.48(m, 2H); 2.54(m, 2H); 2.69(m, 2H); 3.15(m, 2H); 3.77(t, J=7.1Hz, 2H); 5.77 (s, 3H); 6.06(s, 1H); 7.30(m, 4H) (CDCl ₃)
67a	H	H	Cl	H	H	H	CCH ₃	CH	H	CCH ₃	HCl 182–184° C.	3432 (b.a.), 2936, 258-, 1495, 1410, 1298, 1097, 804, 752 KBr	1.56(m, 2H); 1.76(m, 2H); 2.14(s, 6H); 2.70(m, 1H); 2.84(m, 1H); 3.00–3.28(a.c., 3H); 3.58(m, 1H); 3.69– 3.77(a.c., 3H); 3.92(m, 1H); 5.58(s, 2H); 6.22(s, 1H); 7.42(AB, J=8.6, 2H); 7.50(AB, J=8.6, 2H); 10.65 (b.a., 1H) (DMSO-d ₆)
68a	H	H	Cl	H	H	H	CH	CH	H	CH	102–104° C.	2931, 1492, 1280, 1090, 967, 828, 727 KBr	1.59(t, J=7.5Hz, 2H); 1.84(t, J=7.4Hz, 2H); 2.46 (t, J=7.5Hz, 2H); 2.53(m, 2H); 2.66(t, J=5.6Hz, 2H); 3.12(m, 2H); 3.92(t, J=7.1Hz, 2H); 6.05(m, 1H); 6.15 (d, J=1.8Hz, 2H); 6.66(d, J=1.8Hz, 2H); 7.26ab, J=8.4, 2H); 7.30(AB, J=8.4, 2H) (CDCl ₃)
69a	H	H	Cl	H	H	H	CH	CH	H	CH	HCl	2937, 2479,	1.72(m, 4H); 2.65(m, 1H); 2.87(m, 1H); 3.08–3.22

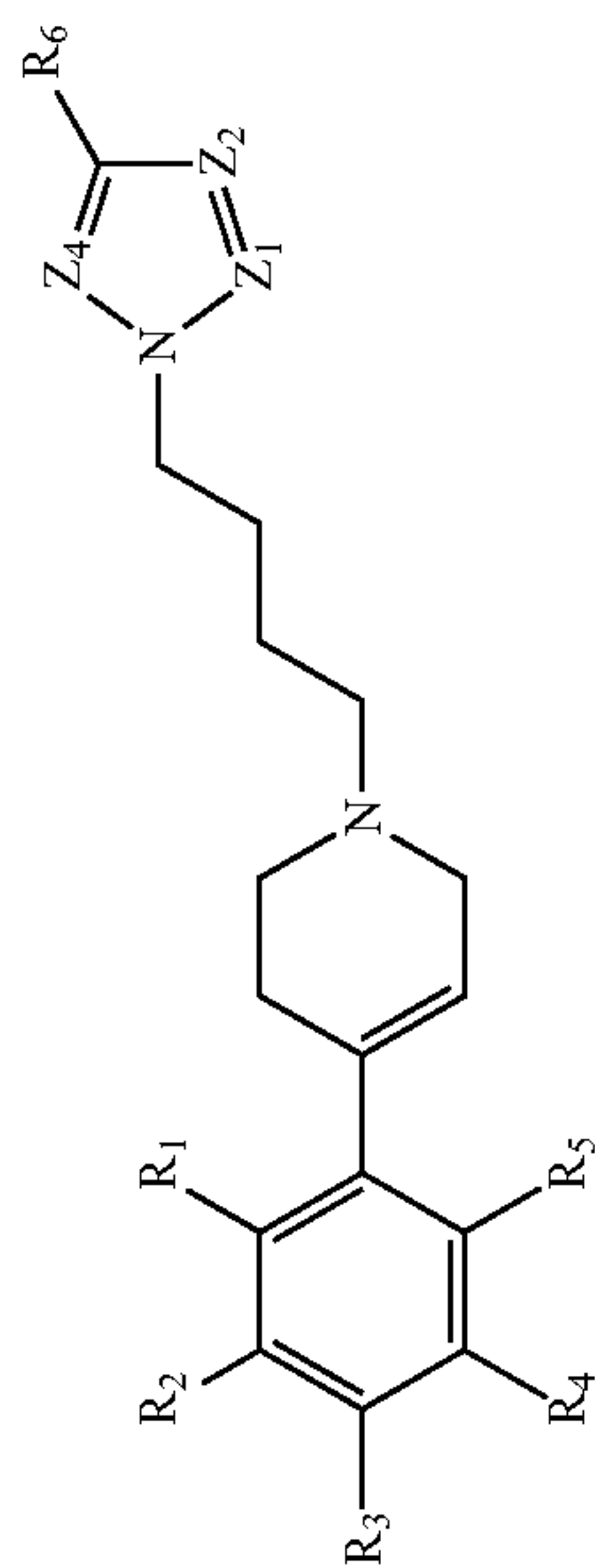
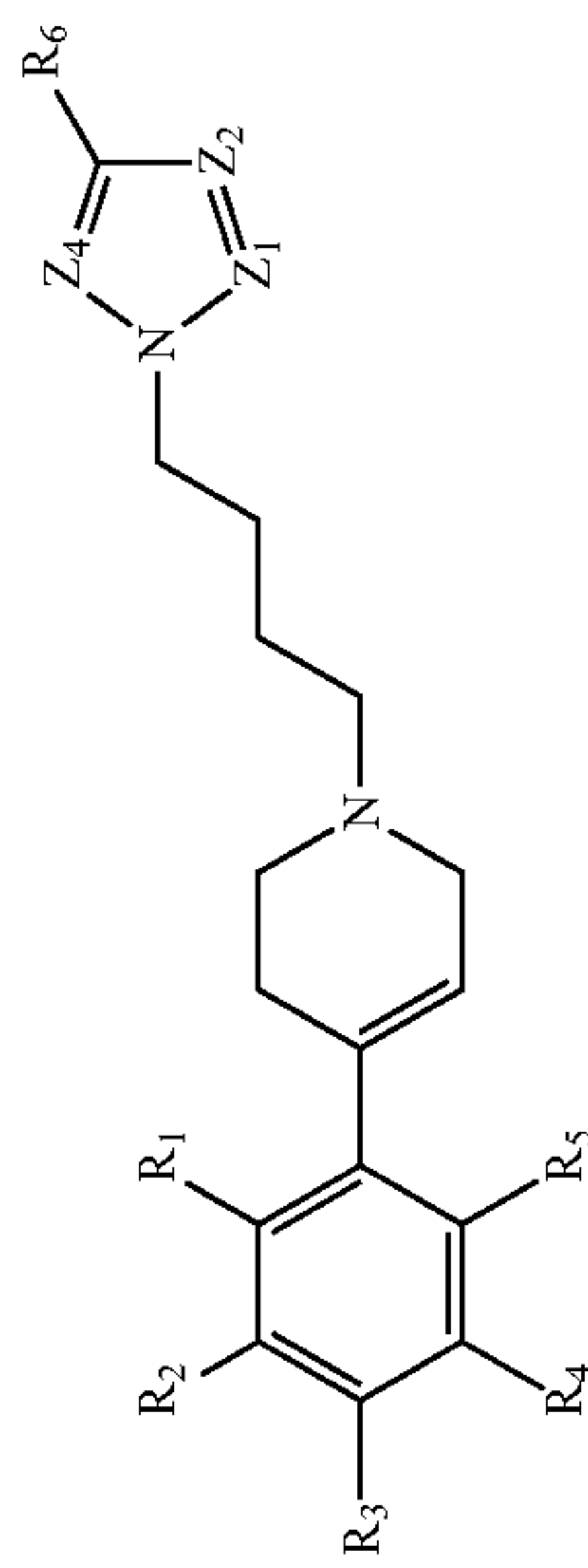


TABLE 2-continued

Ex.	R ₁	R ₂	R ₃	R ₄	R ₅	Z ₁	Z ₂	R ₆	Z ₄	Salt/m.p.	IR cm ⁻¹	¹ H-RMN (300 MHz), δ (solvent)
70a	H	H	Cl	H	H	CH	N	H	N	194–195° C.	1492, 1282, 1096, 810, 737 KBr	(a.c., 3H); 3.52(m, 1H); 3.70(m, 1H); 3.80–4.00(a.c., 3H); 5.96(t, J=2.1Hz, 2H); 6.19(s, 1H); 6.76(t, J=2.1Hz, 2H); 7.42(AB, J=8.6Hz, 2H); 7.48(AB, J=8.6Hz, 2H); 11.12(b.a., 1H) (DMSO-d ₆)
										Citrate	3384 (b.a.), 3200– 2200 (b.a.) 1726, 1702, 1594, 1432, 1221, 1131, 802 KBr	1.54(m, 2H); 1.83(m, 2H); 2.54(Syst. AB, J=15Hz, 2H); 2.63(Syst. AB, J=15Hz, 2H); 2.82(m, 2H); 3.03(m, 2H); 3.20–3.50(a.c., 4H); 4.21(t, J=6.8Hz, 2H); 6.20(s, 1H); 7.40(Syst. AB, J=8.8Hz, 2H); 7.48(Syst. AB, J=8.8Hz, 2H); 7.97(s, 1H) (DMSO-d ₆)



E BIOLOGICAL ASSAYS

The analgesic activity of the products object of the invention have been studied in several assays using the Swiss albino mice as the experimental animal. The assay of contortions induced by phenylbenzoquinone, the hot-plate assay and the hot-point assay are now described. The examples that are presented by way of illustration describe some of the pharmacological assays and should not limit the scope of the invention in any way.

The assay of contortions induced by phenylbenzoquinone was carried out following the method described by E. Siegmund et al. (Proc. Soc. Exp. Biol. Med. 95: 729-731, 1957). In this assay the mice received [th]e product orally or sub-cutaneously (s.c.) and after 60 minutes (after oral administration) or after 30 minutes (after s.c. administration) they received an intraperitoneal (i.p.) injection of an 0.02% aqueous solution of phenylbenzoquinone, at a dosage of 10 ml/kg. The degree of analgesic was expressed as a percentage of the contortions with respect to the control group at each one of the dosages assayed. Using the results tained the effective dose-50 (ED-50) was calculated, that is to say the dose able to inhibit by 50% the contortions induced by phenylbenzoquinone.

The hot-plate assay was carried out following the method described by M. Ocana et al. (Europ J. Pharmacol. 186: 377-378, 1990). The product under study was administered s.c. or i.p. and 30 minutes later the analgesic effect was registered. For this the animals were placed on a metallic surface kept at 50° C. or 55° C. and the time registered (latency) until the licked their hind legs and a jump. The analgesic activity was calculated at each dose, comparing the potency of the treated group with the control group. Using the results obtained the ED-50 was calculated.

The assay of withdrawal of the tail from a hot spot (tail flick) was carried out following the method described by M. Ocana et al. (Br. J. Pharmacol. 110: 1049-1054, 1993). The mice were introduced into an immobiliser and placed on the tail-flick apparatus (LI7100, Letica, S.A). A beam of light was focussed on the tail, at 4 cm from the tip, and the latency for withdrawal of the tail automatically registered. Ten minutes before administering the product of the study the basal latency was registered.

After the product had been administered s.c. the tail withdrawal latencies at 10, 20, 30, 40, 45, 60, 90 and 120 minutes were registered. For each animal the area below curve of the latency was calculated during the time period following the method described by R. J. Tallarida and R. B. Murray (Manual of pharmacologic calculations with computer programs, Springer-Verlag, Berlin, p. 297, 1987). The degree of analgesic of each dosage was calculated comparing the area under curve of latency of the group treated with the medicament with the control group. Using these data the ED-50 was calculated.

The products object of the invention have a notable analgesic activity in the assay of contortions induced by phenylbenzoquinone. Several products have activity of the same order as morphine and clearly better that the products that inhibit biosynthesis of prostaglandins, such as aspirin and dipirone (see table 3).

The analgesic activity has also been demonstrated in the hot-plate assay, considered as a demonstration of analgesic action at the central nervous system level (see table 4).

The analgesic activity has also been demonstrated in the hot-beam assay applied to the mouse's tail, finding a good correspondence between the results obtained in the assay of the hot-plate and the assay of the calorific beam (see table 5).

Furthermore, the capacity of the products object of the invention for exhibiting synergistic analgesic activity with other analgesics, for example, pentazocine, has also been demonstrated. This has been shown for the compound of example 47a (see table 6). Effectively, the latency time in responding licking of the paws when the mice were placed on the hot-plate at 55° C., is much greater after the combined treatment with the compound of example 47a and pentazocine than the sum of the latencies of each one of the treatments carried out separately.

In summary, the products object of the invention have shown a clear analgesic activity in different assays, such as phenylbenzoquinone, hot-plate and calorific beam applied to the tail of the mouse. The activity of these products has been clearly superior to that of the inhibitors of the biosynthesis of prostaglandins such as aspirin and dipirone, and the activity has been shown to of the order of that of morphine. Furthermore, the capacity for forming synergistic combinations with other analgesics has been demonstrated, as can be seen for the case of the compound of example 47a administered along with pentazocine in the hot-plate assay for mice.

TABLE 3

Analgesic activity in the assay of contortions induced by phenylbenzoquinone in mouses

PRODUCT	ED-50 (mg/kg)	
	Oral route	S.C. route
Example 5	20	28
Example 6	80	34
Example 33a	30	2
Example 35a	37	1
Example 38a	5	1
Example 41a	58	6
Example 47a	19	26
Example 48a	38	1
Example 49a	2	1
Example 50a	10	2
Example 51a	9	3
Example 59a	13	2
Example 61a	22	2
Example 63a	44	33
Morfine	4	1
Dipirone	223	24
Aspirin	100	80

TABLE 4

Analgesic activity in the hot-plate assay (55° C.) in mouses

PRODUCT	ED-50 (mg/kg, sc)
Example 38a	7
Example 47a	89
Example 48a	5
Example 49a	4
Example 50a	58
Example 51a	2
Example 59a	43
Example 61a	48
Morfine	2

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TABLE 5

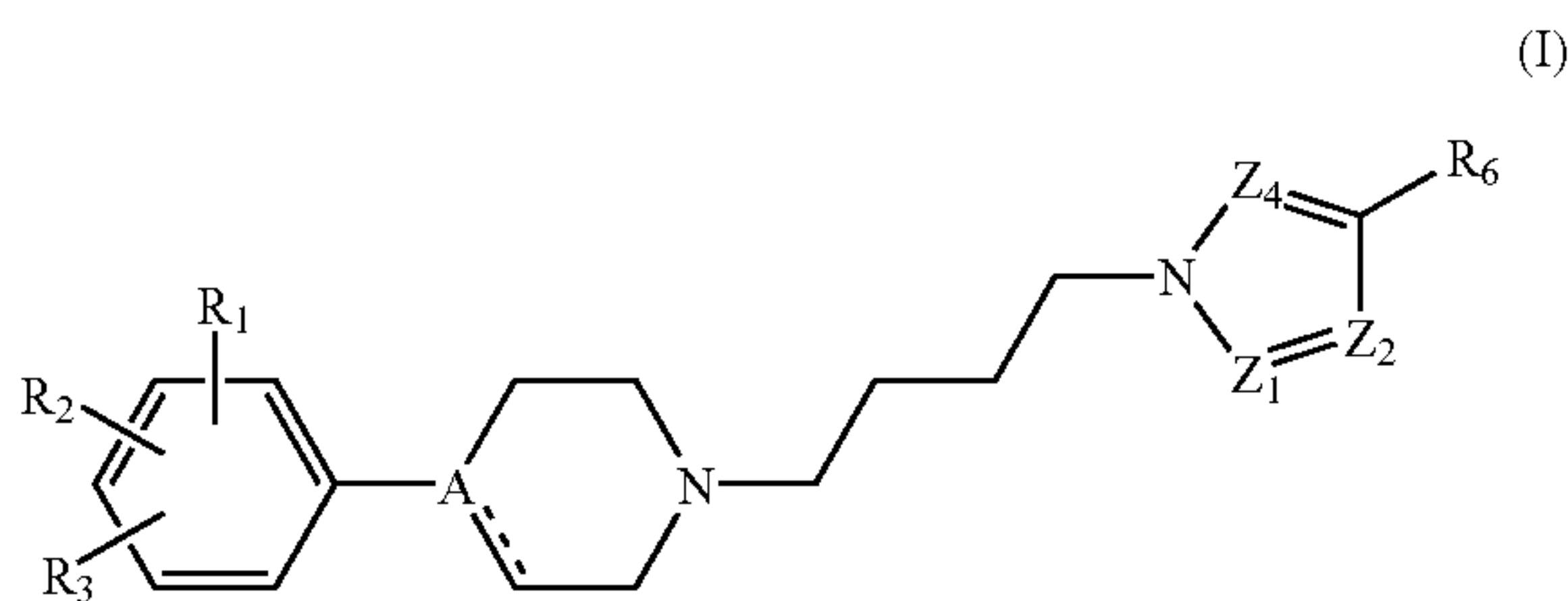
Analgesic activity in the calorific beam assay in mouse's tail.	
PRODUCT	ED-50 (mg/kg, sc)
Example 51a	5
Example 59a	60
Example 63a	70
Morfine	4

TABLE 6

Analgesic activity in the hot plate assay in mouse.		
PRODUCT	DOSE (mg/kg, ip)	Δ Latency (Seconds)
Example 47a	40	5
Pentazocine	10	6
Example 47a	40	
+	+	20
Pentazocine	10	

What is claimed is:

1. A method of treating acute pain, neuropathic pain or nociceptive pain in a mammal which comprises administering to a patient in need thereof an effective amount of a derivative of tetrahydropyridines of formula (II)



wherein

R₁, R₂ and R₃ are identical or different and are selected from hydrogen, halogen, C₁-C₄ alkyl group, trifluoroethyl radical, hydroxyl or alkoxy radical; and two adjacent radicals can form part of a six-member aromatic ring;

A is selected from a carbon atom or a carbon atom bound to a hydroxyl group (C—OH); wherein when A is a carbon atom the dotted line (---) represents a bond, and when A is a carbon atom bound to a hydroxyl group (C—OH) the dotted line (- - -) represents no bond;

Z₁, is a nitrogen atom or a substituted carbon atom represented by the formula C—R₄;

Z₂ is a nitrogen atom or a substituted carbon atom represented by the formula C—R₅;

Z₄ is a nitrogen atom or a substituted carbon atom represented by the formula C—R₇;

with the condition that Z₁; Z₂ and Z₄ taken together can represent, at most, two nitrogen atoms; and

R₄, R₅, R₆ and R₇, are identical or different and are selected from hydrogen, halogen, C₁-C₄ alkyl group, aryl or substituted aryl group, and two adjacent radicals can form part of a six-member aromatic ring;

or physiologically acceptable salts thereof.

2. The method as claimed in claim 1, wherein R₁, R₂ and R₃ are selected from hydrogen, fluorine, chlorine, bromine, trifluoromethyl, hydroxyl, methoxyl, methyl, ethyl, propyl, isopropyl, sec-butyl and a tert-butyl radical.

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3. The method as claimed in claim 1, wherein R₁, R₂ and R₃ are selected so that two adjacent radicals can form part of a six-membered aromatic ring.

4. The method as claimed in claim 1, wherein R₄, R₅, R₆ and R₇ are selected from hydrogen, fluorine, chlorine, bromine, [trifluoromethyl, hydroxyl, methoxyl,] methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, unsubstituted phenyl, or a substituted phenyl wherein the substituent is selected [front halogen atoms] from fluorine, chlorine and bromine.

5. The method as claimed in claim 1, wherein R₄, R₅, R₆ and R₇ are selected so wt two adjacent radicals form part of a six-membered aromatic ring.

6. The method as claimed in claim 1, further comprising an analgesic used for the treatment of pain.

[7. The method as claimed in claim 1, wherein the compound of formula (I) is selected from the group consisting of:

4-chloro-1-[4-(4hydroxy-4-phenyl-1-piperidiny)butyl]-1H-pyrazole;

4,5chloro-1-[4-(4-hydroxy-phenyl-1-piperidiny)butyl]-2-ethyl-1H-imidazole;

1-[4-(4hydroxy[]phenyl-1-piperdiny)butyl]-1H-benzimidazole;

1-[(4hydroxy-phenyl-1-piperdiny)butyl]-1H-1,2,4-triazole;

4-chloro-1-{4-[4chlorophenyl)-4-hydroxy-1-piperidiny]butyl}-1H-pyrazole;

4,5-dichloro-1-{4-[4-hydroxy-4-(chlorophenyl)-1-piperidiny]butyl}-2-methyl-1H-imidazole;

4-chloro-1-{4-[4-hydroxy-4-(3-trifluoromethylphenyl)-1-piperidiny]-butyl}-1H-pyrazole;

4,5-dichloro-1-{4-[4-hydroxy-4-(3-trifluoromethylphenyl)-1-piperidiny]-butyl}-2H-imidazole;

4,5-dichloro-1-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidiny]butyl}-2H-methyl-1H-imidazole;

1-[4-(4-hydroxy-4-phenyl-1-piperidiny)-butyl]-1H-indole 4,5-dichloro-1-{[4-hydroxy-(fluorophenyl)-4-hydroxy-1-piperidiny]butyl}-2-methyl-1H-imidazole;

1-[4(4-hydroxy-4-phenyl-1-piperidiny)butyl]-1H-indole 4,5-dichloro-1-{4-[4hydroxy 4-(4-methylphenyl)1-piperyl]-butyl}-2-methyl-1H-imidazole;

1-[4-(4-hydroxy-4-phenyl-1-piperidiny)butyl]-1H-pyrazole;

1-[4-(4-hydroxy-4-phenyl-1-piperidiny)butyl]-1H-imidazole;

2-[4-(4-hydroxy-4-phenyl-1-piperidiny)butyl]-2H-imidazole;

4-chloro-1-{4-[4-hydroxy-4-(4-methylphenyl)-1-piperidiny]-butyl}-1H-pyrazole;

4-chloro-1-{4-[4-hydroxy-4-(4-methoxyphenyl)-1-piperidiny]-butyl}-1H-pyrazole;

1-[4(4hydroxy-4-phenyl-1-piperidiny)butyl]-2-phenyl-1H-imidazole 1-{4-[4-hydroxy-4-(4-methylphenyl)-1-piperidiny]butyl}-1H-benzimidazole;

4,5-diphenyl-1-[4-(4-hydroxy-4-phenyl-1-piperidiny)butyl]-1H-imidazole

4-chloro-1-{4-[4-hydroxy-4-(1-naphthyl)-1-piperidiny]butyl}-1H-pyrazole;

4-chloro-1-{4-[4-hydroxy4-(2-naphthyl-1-piperidiny)butyl]-1H-pyrazole;

4-chloro-1-{4-[4-phenyl-1-(1,2,3,6-tetrahydropyridiny)]-butyl}-1H-pyrazole;

4-chloro-1-{4-[4-phenyl-1-(1,2,3,6-tetrahydropyridiny)]-butyl}-1H-pyrazole;

1-{4-[4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-benzimidazole;

1-{4-[4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-1,2,4-triazole;

4chloro-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole;

4,5-dichloro-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2-methyl-1H-imidazole;

4chloro-1-{4-[4-(3-trifluoromethylphenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole;

4,5-dichloro-2-methyl-1-{4-[4-(3-trifluoromethylphenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole;

4-chloro-1-{4-[4-(1-naphthyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole;

4chloro-1-{4-[4-(2-naphthyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole;

1-{2-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]ethyl}-1H-benzimidazole;

1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-benzimidazole hydrochloride;

1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-benzimidazole;

1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-benzimidazole hydrochloride;

4,5-dichloro-2-methyl-1-{4-[4-(3-trifluoromethylphenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole hydrochloride;

4-chloro-1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole hydrochloride;

1-{4-[1-phenyl-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole hydrochloride;

4,5-dichloro-1-{4-[4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2-methyl-1H-imidazole hydrochloride;

4-(chlorophenyl)-1-{4-[4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole hydrochloride;

4-(4-chlorophenyl)-1-{4-[4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole;

1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole hydrochloride;

1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole;

1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2-methyl-1H-benzimidazole;

1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole;

2-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2H-imidazole;

2-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2H-benzotriazole hydrochloride;

2-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2H-benzotriazole;

1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-benzotriazole hydrochloride;

1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-benzotriazole;

4chloro-1-{4-[4(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole hydrochloride;

1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole hydrochloride;

1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole hydrochloride;

2-phenyl-1-{4-[4-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole hydrochloride;

1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole;

4-(4-chlorophenyl)-1-[4-(4-hydroxy-4-phenyl-1-piperidinyl)]butyl]-1H-pyrazole;

1-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]butyl}-1H-benzimidazole;

4-chloro-1-{4-[4-hydroxy-4-(3-trifluoromethylphenyl)-1-piperidinyl]butyl}-1H-pyrazole;

1-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]butyl}-1H-imidazole;

2-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]butyl}-2H-imidazole;

2-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]butyl}-2H-benzotriazole;

1-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]butyl}-1H-benzotriazole;

3-chloro-1-{4-[4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole;

3-chloro-1-{4-[4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole hydrochloride;

1-{4-[4-hydroxy-4-(4-fluorophenyl)-1-piperidinyl]butyl}-1H-triazole;

1-{4-[4-hydroxy-4-(4-chlorophenyl)-1-piperidinyl]butyl}-1H-triazole;

4,5-dichloro-1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole hydrochloride;

1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole citrate;

1-{4-[4-(4-bromophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole;

1-{4-[4-(4-bromophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole hydrochloride;

1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole;

1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole hydrochloride;

2-phenyl-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole;

2-phenyl-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole hydrochloride;

2,5-dimethyl-1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole;

2,5-dimethyl-1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole hydrochloride;

2,5-dimethyl-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole;

2,5-dimethyl-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole hydrochloride;

1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole;

1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole hydrochloride;

1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole hydrochloride.]

8. The method as claimed in claim 1, wherein the compound of formula 1 is selected from the group consisting of:

4-chloro-1-[4-(4-hydroxy-4-phenyl-1-piperidinyl)butyl]-1H-pyrazole;

4,5-dichloro-1-[4-(4-hydroxy-4-phenyl-1-piperidinyl)butyl]-2-methyl-1H-imidazole;

1-[4-(4-hydroxy-4-phenyl-1-piperidinyl)butyl]-1H-benzimidazole;

1-[4-(4-hydroxy-4-phenyl-1-piperidinyl)butyl]-1H-1,2,4-triazole;

4-chloro-1-[4-(4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl)butyl]-1H-pyrazole;

4,5-dichloro-1-[4-(4-hydroxy-4-(4-chlorophenyl)-1-piperidinyl)butyl]-2-methyl-1H-imidazole;

4-chloro-1-[4-(4-hydroxy-4-(3-trifluoromethylphenyl)-1-piperidinyl)butyl]-1H-pyrazole;

4,5-dichloro-1-[4-(4-hydroxy-4-(3-trifluoromethylphenyl)-1-piperidinyl)butyl]-2-methyl-1H-imidazole;

4,5-dichloro-1-[4-(4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl)butyl]-2-methyl-1H-imidazole;

1-[4-(4-hydroxy-4-phenyl-1-piperidinyl)butyl]-1H-indole;

4,5-dichloro-1-[4-(4-hydroxy-4-(4-methylphenyl)-1-piperidinyl)butyl]-2-methyl-1H-imidazole;

1-[4-(4-hydroxy-4-phenyl-1-piperidinyl)butyl]-1H-pyrazole;

1-[4-(4-hydroxy-4-phenyl-1-piperidinyl)butyl]-1H-indazole;

2-[4-(4-hydroxy-4-phenyl-1-piperidinyl)butyl]-2H-indazole;

4-chloro-1-[4-(4-hydroxy-4-(4-methylphenyl)-1-piperidinyl)butyl]-1H-pyrazole;

4-chloro-1-[4-(4-hydroxy-4-(4-methoxyphenyl)-1-piperidinyl)butyl]-1H-pyrazole;

1-[4-(4-hydroxy-4-phenyl-1-piperidinyl)butyl]-2-phenyl-1H-imidazole;

1-[4-(4-hydroxy-4-(4-methylphenyl)-1-piperidinyl)butyl]-1H-benzimidazole;

4,5-diphenyl-1-[4-(4-hydroxy-4-phenyl-1-piperidinyl)butyl]-1H-imidazole;

4-chloro-1-[4-(4-hydroxy-4-(1-naphthyl)-1-piperidinyl)butyl]-1H-pyrazole;

4-chloro-1-[4-(4-hydroxy-4-(2-naphthyl)-1-piperidinyl)butyl]-1H-pyrazole;

4-chloro-1-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole];

1-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-benzimidazole];

1-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-1,2,4-triazole];

4-chloro-1-[4-(4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole];

4,5-dichloro-1-[4-(4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-2-methyl-1H-imidazole];

4-chloro-1-[4-(4-(3-trifluoromethylphenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole];

4,5-dichloro-2-methyl-1-[4-(4-(3-trifluoromethylphenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-imidazole];

4-chloro-1-[4-(4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole];

4,5-dichloro-1-[4-(4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-2-methyl-1H-imidazole];

4,5-dichloro-1-[4-(4-[4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl]-2-methyl-1H-imidazole];

4,5-dichloro-1-[4-(4-[4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl]-2-methyl-1H-imidazole hydrochloride];

4,5-dichloro-1-[4-(4-[4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl]-2-methyl-1H-imidazole dihydrochloride];

1-[4-(4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-indole];

1-[4-(4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-indole];

4,5-dichloro-2-methyl-1-[4-(4-(4-methylphenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-imidazole];

1-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole];

1-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-indazole];

2-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-indazole];

4-chloro-1-[4-(4-(4-methylphenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole];

4-chloro-1-[4-(4-(4-methoxyphenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole];

4-chloro-1-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)propyl)-1H-pyrazole];

4,5-dichloro-1-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)propyl)-2-methyl-1H-imidazole];

2-phenyl-1-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-imidazole];

1-[4-(4-(4-methylphenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-benzimidazole];

4,5-diphenyl-1-[4-(4-[4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl]-1H-imidazole];

4-chloro-1-[4-(4-(1-naphthyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole];

4-chloro-1-[4-(4-(2-naphthyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole];

1-[2-(4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)ethyl)-1H-benzimidazole];

1-[4-(4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-benzimidazole hydrochloride];

1-[4-(4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-benzimidazole];

1-[4-(4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-benzimidazole hydrochloride];

4,5-dichloro-2-methyl-1-[4-(4-(3-trifluoromethylphenyl)-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-imidazole hydrochloride];

4-(4-chlorophenyl)-1-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole hydrochloride];

4-(4-chlorophenyl)-1-[4-(4-phenyl-1-(1,2,3,6-tetrahydropyridinyl)butyl)-1H-pyrazole];

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1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole hydrochloride;
 1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole;
 1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2-methyl-1H-benzimidazole;
 1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-indazole;
 2-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2H-indazole;
 2-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2H-benzotriazole hydrochloride;
 2-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2H-benzotriazole;
 1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-benzotriazole hydrochloride;
 1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-benzotriazole;
 4-chloro-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole hydrochloride;
 1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrazole hydrochloride;
 1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole hydrochloride;
 2-phenyl-1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole hydrochloride;
 1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole hydrochloride;
 1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole;
 4-(4-chlorophenyl)-1-[4-(4-hydroxy-4-phenyl)-1-piperidinyl]butyl-1H-pyrazole;
 1-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]butyl}-1H-benzimidazole;
 4-chloro-1-{4-[4-hydroxy-4-(3-trifluoromethylphenyl)-1-piperidinyl]butyl}-1H-pyrazole;
 1-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]butyl}-1H-indazole;
 2-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]butyl}-2H-indazole;
 2-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]butyl}-2H-benzotriazole;
 1-{4-[4-(4-fluorophenyl)-4-hydroxy-1-piperidinyl]butyl}-1H-benzotriazole;
 3-chloro-1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-indazole;

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3-chloro-1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-indazole hydrochloride;
 1-{4-[4-(4-hydroxy-4-(4-fluorophenyl)-1-piperidinyl)]butyl}-1H-triazole;
 1-{4-[4-(4-hydroxy-4-(4-chlorophenyl)-1-piperidinyl)]butyl}-1H-triazole;
 4,5-dichloro-1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-2-methyl-1H-imidazole hydrochloride;
 4,5-dichloro-1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole hydrochloride;
 1-{4-[4-(4-fluorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole citrate;
 1-{4-[4-(4-bromophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole;
 1-{4-[4-(4-bromophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole hydrochloride;
 1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole;
 1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole hydrochloride;
 2-phenyl-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole; 2-phenyl-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-imidazole hydrochloride;
 2,5-dimethyl-1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole;
 2,5-dimethyl-1-{4-[4-(4-phenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole hydrochloride;
 2,5-dimethyl-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole;
 2,5-dimethyl-1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole hydrochloride;
 1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole;
 1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-pyrrole hydrochloride;
 and
 1-{4-[4-(4-chlorophenyl)-1-(1,2,3,6-tetrahydropyridinyl)]butyl}-1H-triazole citrate,
 in the preparation of a medicament for the treatment of acute pain, neuropathic pain or nociceptive pain in mammals, including man.

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