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A New Class of Antiarrhythmic-Defibrillatory Agents

Ofra Levy,[a] Mordechai Erez,[a,*] Dalia Varon[b] and Ehud Keinan[a,c,†,*]

[a]*Department of Chemistry and Institute of Catalysis Science and Technology, Technion-Israel Institute of Technology, Technion City, Haifa 32000, Israel*

[b]*Departments of Physiology and Pharmacology, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

[c]*The Scripps Research Institute, Department of Molecular Biology and The Skaggs Institute of Chemical Biology, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*

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Abstract—Novel dibenzoazepine and 11-oxo-dibenzodiazepine derivatives are shown to be effective ventricular defibrillating drug candidates. They exhibit significant in vivo defibrillatory activity with no observed changes in ECG either before or after the VF event. These compounds also exhibit antifibrillatory activity by elevating the fibrillation threshold potential, all suggesting that such drugs could be used to treat VF either by themselves or together with electrical defibrillators.

Sudden cardiac death (SCD)[1] is a leading cause of human mortality among adults, mainly among patients suffering from either coronary heart disease[2,3] or congested heart failure.[4] It is commonly accepted that ventricular arrhythmia, such as ventricular tachycardia and ventricular fibrillation (VF), plays the major role in SCD. VF is fatal, unless either an external or implanted electrical defibrillator is applied within a few minutes from initiation. Considering the fact that 75% of VF incidents occur while the patient is far from any professional medical aid (CPR),[5] the implanted electrical defibrillator represents the preferred treatment. However, this invasive approach deals only with the symptoms and does not prevent reoccurrence of VF. Furthermore, since the number of patients having implanted devices is quite small, only a tiny proportion of cardiac arrest victims are saved every year worldwide by the use of electrical defibrillators.[5] Certainly, a safe pharmaceutical agent for treatment of high-risk patients is highly desirable.[4]

In principle, two chemical therapeutic strategies for the treatment of VF could be envisioned. One approach aims at prevention of VF and the other targets its termination. While drug development efforts have been focusing on the first strategy, no drug development effort has been dedicated to the chemical termination of VF. Consequently, all relevant drugs and drug candidates developed so far reflect efforts to decrease the incidence of ventricular arrhythmia that might end in VF.[6] Unfortunately, since VF may be initiated via several different mechanisms, the design of a universal prophylactic drug is difficult and all attempts in this direction have gained only partial success.[7] For example, the Cardiac Arrhythmia Suppression Trial, CAST I and II,[8,9] have clearly demonstrated the limitations of this therapeutic approach.

It has been commonly accepted that the ability of the mammalian heart to defibrillate spontaneously is related to its ventricular muscle mass.[10] Accordingly, small hearts defibrillate spontaneously because they do not contain the minimal number of cells required to maintain fibrillation.[10c] Consequently, it has been assumed that relatively large heart mass, such as the human heart ventricles, cannot defibrillate spontaneously. Following this conjecture no serious efforts have been directed toward the development of VF-terminating drugs. Nevertheless, the growing evidence for a non-fatal VF in humans suggests that VF can convert spontaneously into sinus rhythm.[11] For example, a comparative study of the occurrence of sustained VF (SVF) and transient VF (TVF) in untreated mammals of various species and ages has led to the conclusion that the heart ability to self-defibrillate is also a function of age, with TVF

*Corresponding authors. Tel./fax: +972-4-829-3913; e-mail: tmerez@netvision.net.il; keinan@tx.technion.ac.il

†Incumbent of the Benno Gitter & Ilana Ben-Ami chair of Biotechnology, Technion.

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occurring more readily in young rather than old mammalian hearts.[12]

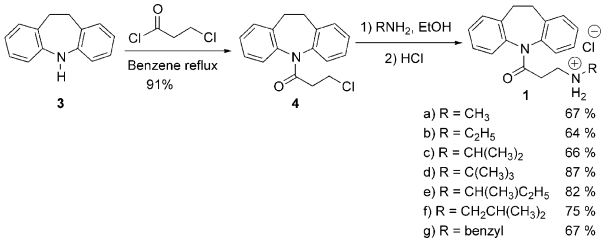
Assuming that spontaneous defibrillation requires a relatively high level of intercellular synchronization, [12a] and is enhanced by increased sympathetic activity,[10d] Manoach et al.[13] have been searching for chemical defibrillating agents that elevate extra-neuronal levels of catecholamines in the heart. They found that several psychotropic drugs (Scheme 1), such as dibenzoazepines (imipramine, desipramine, and bonnecore), maprotiline, dibenzepin and phenothiazines (chlorpromazine, moricizine, and trifluoperazine), can induce defibrillation and also increase the ventricular fibrillation threshold.[14] Tricyclic antidepressants (TCAD) also decreased the ischemic area in the heart following coronary occlusion.[15] Previous studies indicated that the TCAD derivatives are more effective as chemical defibrillators than the group of phenothiazines.[16] Nevertheless, all of these cardio-protective agents were effective only when high doses relative to their therapeutic index were employed.

Following the above described indications that chemical defibrillation could indeed be a feasible option for treatment of VF; we have initiated a drug discovery effort that focuses on the design and synthesis of new defibrillatory agents. In addition to high selectivity and an optimal therapeutic index in affecting defibrillation, we also aimed at antiarrhythmic and antiischemic activities. We have decided to initially focus on the two families of drug candidates that contain the nuclei of dibenzoazepine, **1**, and 11-oxo-dibenzodiazepine, **2**.

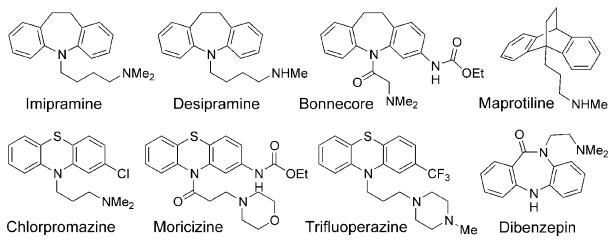
Here we report on the first compounds ever designed to serve as ventricular defibrillating agents. These drug candidates exhibit high defibrillatory activity with no observed changes in ECG either before or after the VF event. Preliminary SAR studies point at higher activity of derivatives of **1** in comparison with those related to **2**. These studies also highlight the superiority of the aminohydroxyalkyl side chain over the aminoacyl and the aminoalkyl groups. We also report on the VF initiation prevention activity of these compounds.

The seven dibenzoazepine derivatives, **1a**–**g**, were synthesized from the parent system, **3** (Scheme 2), which was prepared from 2-nitrotoluene using the Lapworth reaction.[17] Slow addition of a benzene solution of 3-chloropropanoyl chloride to **3**, followed by reflux for 3 h, produced amide **4**[18] in 91% yield after purification by column chromatography. A well-stirred suspension of **4** in ethanol was warmed to 65 °C, the appropriate alkylamine was slowly added and the mixture was stirred for 1 h at this temperature and than allowed to cool to room temperature. Work-up with 5% aq potassium bicarbonate, and CH_2Cl_2, followed by recrystallization from cold ethyl acetate, afforded the corresponding secondary amine. The latter was dissolved in dry toluene and treated with dry HCl gas to produce the hydrochloride **1a**–**g** in the form of a white powder.[19]

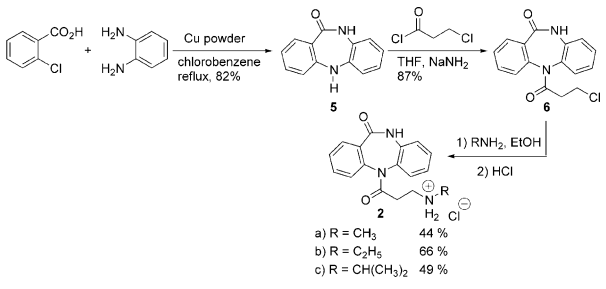
The parent system **2** was achieved in a one step reaction via the Ullmann–Golgber condensation (Scheme 3).[20] Thus, equimolar amounts of 2-chlorobenzoic acid, 1,2-diaminobenzene and copper powder (3 equiv) in chlorobenzene and molecular sieves (3) were stirred at 130 °C for 8 h. The hot mixture was filtered, the solvent was removed under reduced pressure, and the solid residue was recrystallized (ethanol) to give **2** in the form of bright yellow crystals. The latter was mixed in dry THF with $NaNH_2$ (2 equiv), cooled to 0 °C, 3-chloropropanoyl chloride (1.2 equiv) was added dropwise, the mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature, washed with 5% aq potassium bicarbonate, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was crystallized from ether to give **6** in the form of a yellow solid.[21] **A** suspension of **6** in ethanol (50 mL) was warmed to 65 °C, alkylamine (either methylamine, ethylamine, or isopropylamine) was added dropwise, and the mixture was stirred at this temperature for 1 h and then allowed to cool to room temperature. Work-up with aq potassium bicarbonate and CH_2Cl_2, followed by recrystallization from ethyl acetate, afforded the free amine in the form of a white powder. The latter was dissolved in toluene, dry HCl gas was bubbled through the solution, and the resultant powder, **2a**–**c**, was collected by filtration.[22]



Scheme 2.



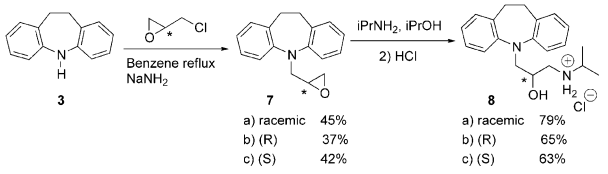
Scheme 1.



Scheme 3.

The amino alcohols **8** (Scheme 4) were obtained from **3** via epoxides **7**. Thus, a mixture of **3** and $NaNH_2$ in benzene was refluxed for 2 h, epichlorohydrin (either racemic or non-racemic, from Aldrich) was added dropwise, and the mixture was refluxed for 6 h. The solvent was removed under reduced pressure; the residue was washed with 5% aq HCl and extracted with CH_2Cl_2. The crude product was purified by flash chromatography to give **7** in the form of a white powder.[23] **A** suspension of **7** in isopropanol was warmed to 30 °C, and isopropyl amine (2 equiv) was added dropwise. The mixture was stirred overnight at this temperature and than allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was recrystallized (cold ethyl acetate) to give the amino alcohol in the form of a white powder. The latter was dissolved in toluene; dry HCl gas was bubbled through the solution, and the resultant powder, **8**, was collected by filtration.[24]

Pharmacological investigations were performed in an in vivo cat model. Each compound was tested in at least 3 male cats. The animals were anesthetized with sodium pentobarbital (15–25 mg/kg, intravenous). Hearts were exposed through midline thoracotomy, and a room air respirator was applied through a tracheal cannula. Lead II electrocardiogram and intra-arterial blood pressure were recorded on a Grass Polygraph recorder. Fibrillation stimuli (a train of rectangular pulses of 2–15 V, 100 pps and duration 0.1–1 ms, for a period of 0.5 s) were delivered through two silver needle electrodes attached to the pericardium on the left ventricle. Strength of the fibrillating stimuli was 1.5- to 2.0-fold the strength of the fibrillating threshold. Control experiments were carried out for each animal by induction of VF (followed by electrical defibrillation after 90 s) before drug administration. Thus, each animal served as its own control. The effect of the drugs was evaluated by injecting their saline solution intravenously at doses of 3, 2, 1 and 0.5 mg/kg 2-3 min before the first in a series of electrical inductions of VF was applied. A typical experiment is shown in Figure 1. It is important to note that no changes could be observed in the patterns of either the ECG or the blood pressure after the administration of any of the compounds used in this study either before or after the VF event.



Scheme 4.

In preliminary experiments with several compounds we found that their maximal defibrillating effect is achieved within 10–40 min after injection. Therefore, we consider the observation of the episode that was measured 10 min after drug administration as the representative value for each animal. Thus, the relative activity values presented in Table 1 refer to episodes carried out 10 min after injection. Animals that exhibited VF duration shorter than 90 s were designated as having TVF. Animals that failed to terminate their VF within 90 s, and therefore required electrical treatment for defibrillation, were defined as having SVF. The relative defibrillating activity (shown on a qualitative scale between + + + + and 0) of a given compound was defined as the ratio between the number of animals exhibiting TVF events out of the total VF events.

The results in Table 1 represent a qualitative structure activity relationship (SAR) study that points at several interesting trends. We selected the molecular nuclei of **1** and **2** because previous studies with similar nuclei, such as those of desipramine[16] and dibenzepine,[25] exhibited various levels of defibrillating activity (Table 1).[16] A common structural feature of all these and our compounds is a dihedral angle of approximately 60° between the two benzene rings.[26]

As may be concluded from Table 1, the dimethylene bridge of **1** renders this skeleton more active than the

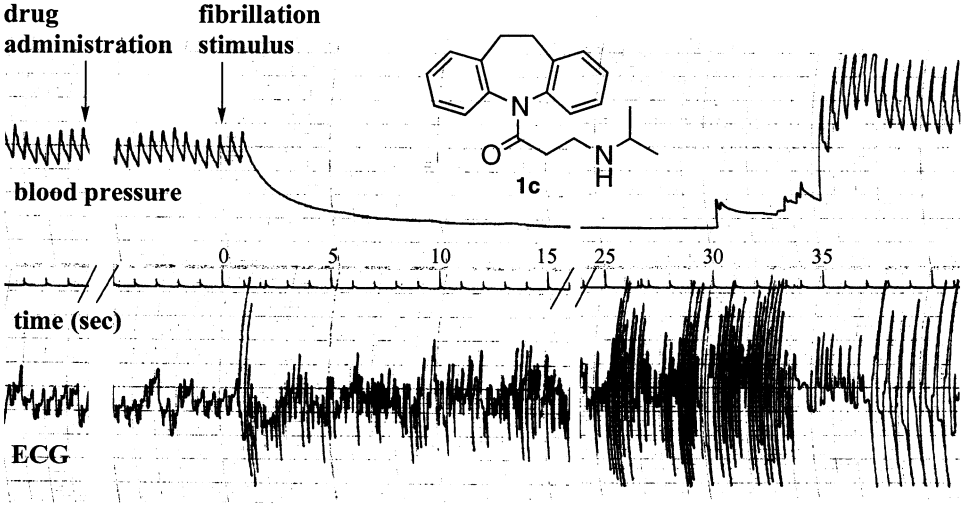


Figure 1. Electrocardiogram (ECG, LII) and blood pressure recorded during electrically induced ventricular fibrillation 10 min after administration of compound **1c** (3 mg/kg, cat).

Table 1. Relative defibrillating activity of compounds **1**, **2**, and **8**

Compd	3 mg/kg	2 mg/kg	1 mg/kg	0.5 mg/kg
1a	+ + + +	+ + + +	+	0
1b	+ + + +	+ + +	+ +	0
1c	+ + + +	+ + + +	+ + +	+
1d	+ + + +	+ + + +	+ +	
1e	0	0	0	
1f	0	0	0	
1g	0	0	0	
2a	0	0	0	
2b	0	0		
2c	0	0		
8a	+ + + +	+ + + +	+ +	+ +
8b		+ + + +	+ +	+ +
8c		+ + + +	+ + + +	+ + +
Dibenzepine[25]	+ + +	+ +	0	
Imipramine[16]	+ + +	+ +	0	
Desipramine[16]	+ + + +	+ + +	+	

All experiments where carried out 10 min after injection. Relative activity (+ + + + represents 100% and + represents 25%) is defined as the total TVF events out of total VF events.

amide bridge of **2**. Interestingly, attachment of the side chain onto the amide nitrogen of skeleton **2**, as in the case of dibenzepine,[25] leads to significantly higher activity than attachment to the amine nitrogen, as in the case of **2a**–**c**.

We focused on compounds containing side chains with secondary amines rather than primary or tertiary amines. Previous reports on SARs with similar defibrillation compounds, such as desipramine and imipramine, have indicated the superiority of secondary amines over the tertiary ones.[27] Similar trends were observed with other model systems, such as the reuptake of noradrenaline and antidepressant activity, where secondary amines were found to be more active than the primary and tertiary analogues.[27] Indeed, initial experiments with derivatives of **1** having tertiary amine side chains (data not shown) exhibited relatively low activity. Furthermore, the size of the alkylamino group is very important, with isopropylamino group (**1c**) showing the highest activity within the molecular skeleton of **1**. Small structural variations, such as switching from *tert*-butylamino group (**1d**) to either *iso*-butylamino (**1f**) or to *sec*-butylamino (**1e**) analogues resulted in remarkable decrease of activity.

Two side chains, β-aminoacyl and 3-amino-2-hydroxyalkyl, were used in this study. The choice of β-aminoacyl side chain was based on previous observations of the introduction of β-aminoacyl side chains in other systems (e.g., in bonnecore and moricizine), which resulted in increased antiarrhythmic activity and decreased psychotropic activity as compared with the β-aminoalkyl analogues.[28] The choice of 3-amino-2-hydroxyalkyl side chains was made on the basis of the analogy to epinephrine and norepinephrine. Comparison of **1c** and **8a**–**c** highlights the superiority of the 3-amino-2-hydroxyalkyl over the aminoacyl and the aminoalkyl (as is the case of imipramine) side chains in our screening model. The (*S*)-(−) enantiomer, **8c**, was found to be the most active defibrillating agent among the compounds studied here, exhibiting high activity at a dosage as low as 0.5 mg/kg. This value represents the highest chemical defibrillating activity ever reported. Interestingly, the absolute configuration of **8c** is identical to that of nor epinephrine and epinephrine.

In addition to the defibrillatory effect exhibited by most of the above-described compounds, several of them have also exhibited antifibrillatory effect, That is they caused elevation of the VF threshold potential. Thus, in preliminary experiments with compounds **1a**, **1c**, **8a**, and **8c** at 2 mg/kg an increase of the VF potential (by approximately 50%) was required in order to initiate a fibrillation event.

In conclusion, we have reported here on the first compounds ever designed to serve as ventricular defibrillating drugs. Several compounds, such as **1c** and **8c**, were found to exhibit potent defibrillatory activity while keeping the ECG unchanged after their administration. These drug candidates also exhibit antifibrillatory activity by elevating the fibrillation threshold potential. This activity as well as the antiischemic activity of the new compounds will be reported in due course. The SAR studies point at higher activity of derivatives of **1** in comparison with those related to **2**. These studies also highlight the superiority of the 3-amino-2-hydroxyalkyl side chain over the aminoacyl and the aminoalkyl chains. The (*S*)-(−) enantiomer, **8c**, was found to be the most active defibrillating agent discovered to date. These results suggest that defibrillatory drugs, such as those described here, could be used to treat VF either by themselves or together with electrical defibrillators.

Acknowledgements

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18. 3-Chloro-1-(10,11-dihydrodibenzo[*b,f*]azepine-5-yl)-propan-1-one (**4**): 3-chloropropanoyl chloride (0.5 mL, 5.2 mmol) was added dropwise to a solution of **3** (0.85 g, 4.4 mmol) in benzene (50 mL), the mixture was refluxed for 3 h, the solvent was removed under reduced pressure, the residue was washed with HCl (1 N, 30 mL), and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the crude product was purified by flash chromatography (silica gel, hexane–ethyl acetate 8:2) to give **4** (1.133 g, 91%) in the form of white crystals, mp 107.7 °C. ^{1}H NMR δ 7.16 (m, 8H), 3.82 (m, 2H), 3.46 (m, 1H), 2.85 (m, 2H), 2.51 (m, 1H). MS (CI) *m/z* 286 (M^+)
19. 1-(10,11-dihydrodibenzo[*b,f*]azepin-5-yl)-3-alkylamino-propan-1-one, HCl (**1a**–**g**): A well-stirred suspension of **4** (1.71 g, 6.0 mmol) in ethanol (50 mL) was warmed to 65 °C. Alkylamine (10 mmol) was added dropwise and the mixture was stirred for 1 h at this temperature, then allowed to cool to room temperature, washed with 5% aq potassium bicarbonate and extracted with dichloromethane. For the preparation of compounds **1d**–**g** isopropanol was used instead of ethanol and the mixture was refluxed for 16 h. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was recrystallized from ethyl acetate at −20 °C. The latter solid was dissolved in toluene, dry HCl was bubbled into the solution and the resultant precipitate was filtered and dried under reduced pressure. **1a**: Light-yellow solid (1.126 g, 67%), mp 158.5 °C, ^{1}H NMR (D_2O) δ 6.87 (b m, 8H), 3.15 (m, 1H), 2.82 (b m, 4H), 2.47 (s, 3H), 2.24 (b m, 3H); ^{13}C NMR (D_2O) δ 172.14, 130.69, 130.36, 129.23, 128.19, 127.85, 127.43, 46.22, 33.53, 30.87, 30.19. MS (FAB) *m/z* 281(MH^+), HRMS (MALDI-FTMS) expected for MH^+ 281.1654, found 281.1640, expected for MNa^+ 303.3541, found 303.1462. **1b**: Light-yellow solid (1.129 g, 64%), mp 165.6–166.8 °C, ^{1}H NMR (D_2O) δ 6.89 (b m, 8H), 3.12 (m, 1H), 2.84 (b m, 7H), 2.27 (b m, 2H), 1.02 (t, J = 7.4 Hz, 3H). MS (FAB) *m/z* 295 (MH^+), HRMS (MALDI-FTMS) expected for MH^+ 295.1810, found 295.1759, expected for MNa^+ 317.1630, found 317.1604. **1c**: Light-yellow solid (1.219 g, 66%), mp 198.4–199.1 °C, ^{1}H NMR (D_2O) δ 6.97 (b m, 8H), 3.14 (m, 1H), 2.97 (m, 4H), 2.67 (m, 1H), 2.42 (m, 1H), 2.38 (m, 2H), 1.08 (d, J = 6.6 Hz, 6H), ^{13}C NMR (D_2O) δ 172.12, 130.71, 130.02, 128.78, 128.42, 127.62, 127.46, 57.06, 32.89, 26.71, 20.16, 19.94. MS (FAB) *m/z* 309 (MH^+), HRMS (MALDI-FTMS) expected for MH^+ 309.1962, found 309.1955. **1d**: (280 mg, 87%), mp 224.5 °C, ^{1}H NMR (D_2O) δ 7.24 (m, 8H), 3.39 (m, 2H), 2.85 (m, 5H), 2.51 (m, 1H), 1.26 (s, 9H). MS (FAB) *m/z* 323 (MH^+), HRMS (MALDI-FTMS) expected for MH^+ 323.2118, found 323.2124. **1e**: (264 mg, 82%), mp 188.9–191 °C. ^{1}H NMR (D_2O) δ 7.23 (m, 8H), 3.35 (m, 2H), 2.82 (m, 4H), 2.74 (m, 2H), 1.84–1.42 (b m, 1H), 1.25 (d, J = 6.5 Hz, 3H), 1.19 (m, 2H), 0.89 (t, J = 6.6 Hz, 3H). MS (FAB) *m/z* 323 (MH^+), HRMS (MALDI-FTMS) expected for MH^+ 323.2118, found 323.2116. **1f**: (241 mg, 75%), mp 194.6–195.2 °C. ^{1}H NMR (D_2O) δ 7.25 (m, 8H), 3.37 (m, 2H), 2.82 (m, 4H), 2.65 (d, J = 6.7 Hz, 2H), 2.45 (m, 2H), 1.83 (m, 1H), 0.99 (q, J = 6.6, Hz, 6H); ^{13}C NMR (D_2O) δ 172.21, 130.72, 130.02, 128.91, 128.52, 127.65, 127.57, 58.06, 45.19, 32.91, 28.34, 20.42, 19.94. MS (FAB) *m/z* 323 (MH^+), HRMS (MALDI-FTMS) expected for MH^+ 323.2118, found 323.2127. **1g**: (367 mg, 67%). Mp 257.7–258.3 °C. ^{1}H NMR δ 7.31–7.15 (b m, 13H), 3.85 (m, 2H), 2.94 (m, 2H), 2.82 (m, 4H), 2.47 (m, 2H). MS (FAB) *m/z* 357 (MH^+), HRMS (MALDI-FTMS) expected for MH^+ 357.1962, found 357.1952.
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21. 5-(3-Chloro-propionyl)-5,10-dihydrodibenzo[*b,e*][1,4]-diazepine-11-one, **6**: white crystals (467 mg, 87%), mp 211.2 °C, ^{1}H NMR (DMSO-d_6) δ 8.78 (s, 1H), 7.98 (s, 1H), 7.59 (s, 1H), 7.4–7.26 (m, 6H), 3.77 (m, 4H). MS (CI) *m/z* 301(MH^+).
22. 5-(3-Alkylamino-propionyl)-5,10-dihydro-dibenzo[*b,e*] [1,4]-diazepin-11-one, hydrochloride, **2a**–**c**. A suspension of **6** (1.5 g, 5.0 mmol) in ethanol (50 mL) was warmed to 65 °C, the appropriate alkylamine (10 mmol) was added dropwise, the mixture was stirred for 1 h at this temperature and worked up as described above for the synthesis of **1**. **2a**: Light-pink solid (627 mg, 44%), mp 121 °C. ^{1}H NMR (D_2O) δ 7.33–7.06 (b m, 8H), 3.06 (t, J = 6 Hz, 2H), 2.9 (m, 1H), 2.48 (s, 3H), 2.39 (b m, 1H). HRMS (MALDI-FTMS) expected for MH^+ 296.1394, found 296.1392. **2b**: Light-yellow solid (1.023 g, 66%) mp 119.2 °C, ^{1}H NMR (D_2O) δ 7.62–7.09 (b m, 8H), 3.08 (t, J = 6.1 Hz, 2H), 2.86 (m, 3H), 2.38 (m, 1H), 1.06 (t, J = 7.3, 3H). HRMS (MALDI-FTMS) expected for MH^+ 310.1556, found 310.1542. **2c**: Light-orange solid (791 mg, 49%), mp 103–105 °C. ^{1}H NMR (D_2O) δ 7.45–7.10 (b m, 8H), 3.12 (m, 1H), 3.05 (t, J = 6.2 Hz, 2H), 2.85 (m, 1H), 2.33 (m, 1H), 1.08 (d, J = 6.6 Hz, 6H); ^{13}C NMR (D_2O) δ 172.65, 169.24, 142.21, 135.23, 134.12, 130.79, 130.09, 129.03, 128.41, 127.57, 126.96, 126.60, 122.29, 122.14, 50.86, 39.85, 29.91, 17.98. HRMS (MALDI-FTMS) expected for MH^+ 324.1707, found 324.1704.
23. Physical data of (*rac*) 5-oxiranylmethyl-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine, **7a**: white solid (0.75 g, 45%), mp 72.2 °C, ^{1}H NMR δ 7.07 (m, 6H), 6.92 (m, 2H), 3.90 (dd, J = 5.0, 3.0, Hz, 2H), 3.17 (s, 4H), 3.05 (m, 1H), 2.69 (m, 1H), 2.55 (m, 1H); ^{13}C NMR δ 147.37, 133.74, 129.97, 125.77, 122.25, 119.65, 53.33, 50.16, 46.01, 31.58. MS (FAB) *m/z* 251 (M^+). **(7b)**: white solid (0.95 g, 37%), mp 69–70 °C. **(7c)**: white solid (0. 82 g, 42%), mp 73–74 °C.
24. Physical data of **8**: (*rac*)-1-(10,11-dihydro-dibenzo[*b,f*]azepin-5-yl)-3-isopropylamino-propan-2-ol, HCl (**8a**): white solid (580 mg, 79%), mp 224.6 °C. ^{1}H NMR (D_2O) δ 7.09 (m, 6H), 6.91 (m, 2H), 4.00 (m, 1H), 3.81 (m, 2H), 3.15 (s, 4H), 2.80 (b m, 2H), 2.51 (m, 1H), 0.99 (d, J = 6.5 Hz, 6H). MS (CI) *m/z*

311 (MH^+), HRMS (MALDI-FTMS) expected for MH^+ 311.2118, found 311.2124. **8b**: white solid (350 mg, 65%), mp 225.9 °C. $[\alpha]_D^{20}$ + 7.05 (*c* 53%, H_2O), ee (by HPLC) = 96.7%. **8c**: white solid (608 mg, 63%). Mp 226.4 °C. $[\alpha]_D^{20}$ −7.43 (*c* 57%, H_2O), ee (by HPLC) > 99%.

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