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***Dedicated to the memory of***
***Professor Ecaterina Ciorănescu-Nenitzescu (1909–2000)***

# SYNTHESIS OF NEW DIBENZO[*b*,*f*]AZEPINE DERIVATIVES

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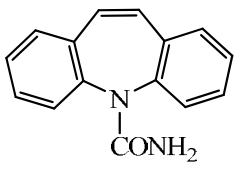
This work is focused on synthesis and chemical characterization of new polycyclic compounds having dibenzo[*b*,*f*] azepine and 10,11-dihydrodibenzo[*b*,*f*]azepine moieties. We report the synthesis of four new compounds, obtained by reacting 5*H*-dibenzo[*b*,*f*]azepine-5-carbonyl chloride and 10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-5-carbonyl chloride with 1-phenylpiperazine, and pyrrolidine, respectively. The newly synthesized compounds were characterized using chromatographic and spectroscopic methods (HPLC-UV-VIS $^{1}$H-NMR, $^{13}$C-NMR, mass spectrometry by ESI technique).

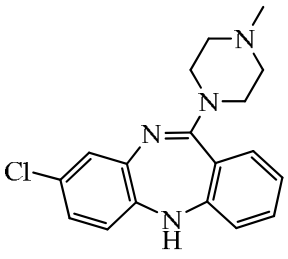
## INTRODUCTION

Dibenzoazepine and dibenzodiazepine derivatives are important and valuable compounds in medicinal chemistry. An effective anticonvulsant drug, 5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide (carbamazepine) (**3**) was first synthesized by Schindler[1] in 1960 and since then it has become the most frequently prescribed first-line drug for the treatment of epilepsy. A drug belonging to dibenzodiazepine class is clozapine[2] **4** which exhibits antidepressant activity and effectively reduces the schizophrenia symptoms. Several chemical modifications of compounds **3** and **4** have been reported in an attempt to improve their physiological properties and to diminish unwanted medication side-effects.

In 1990 a better tolerated antiepileptic drug, oxacarbazepine **5**, was introduced. Several esters of its corresponding alcohol **6a**, which is a metabolite of **5**, have been synthesized *e.g.* the enantiomeric acetates **6b**, as well as their racemate, conferring to the product a greater activity than that of the parent drug **5** itself.[3]




**3**
Carbamazepine - a dibenzoazepine derivative




**4**
Clozapine - a dibenzodiazepine derivative

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Regarding the modifications of clozapine **4** tricyclic structure, the side benzene rings were alternatively replaced by pyridine[4] giving rise to two series of derivatives, each one comprising four position isomers (*see* Figure 1). It has been proved that compounds such as **9b**, **9c**, **7a** have an antipsychotic profile similar to clozapine, while some side effects were either completely absent or strongly reduced for comparable doses.

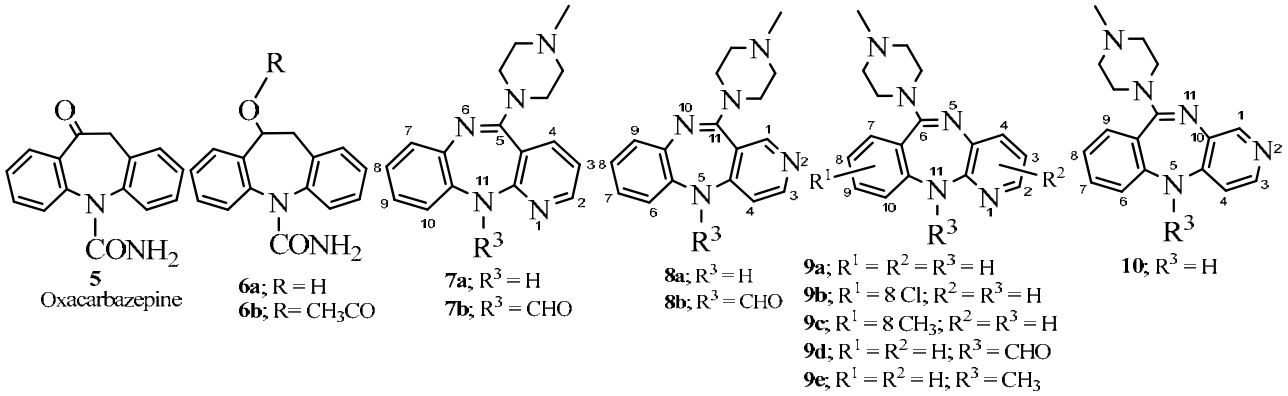



Fig. 1 – Chemical modifications of oxacarbazepine **5** and clozapine **4**.

The most recent concept developed in antipsychotic therapy is that of broad-spectrum psychotropic agents.[5] Drugs belonging to the second generation of antipsychotics have the ability to simultaneously interact with different monoaminergic systems, such as the dopaminergic-, serotonergic-, muscarinic-, α-adrenergic-, and histamine $H_1$-$H_4$-sites. For instance, clozapine and some analogues fit the histamine receptors binding site and can be used in the treatment of histamine-induced diseases[6] like asthma, inflammatory bowel disease, and several dermatologic disorders. Mirtazapine **11** and mianserin **12** both interact with several monoaminergic system receptors, broadening thus their potential application to different depressive conditions.[7]

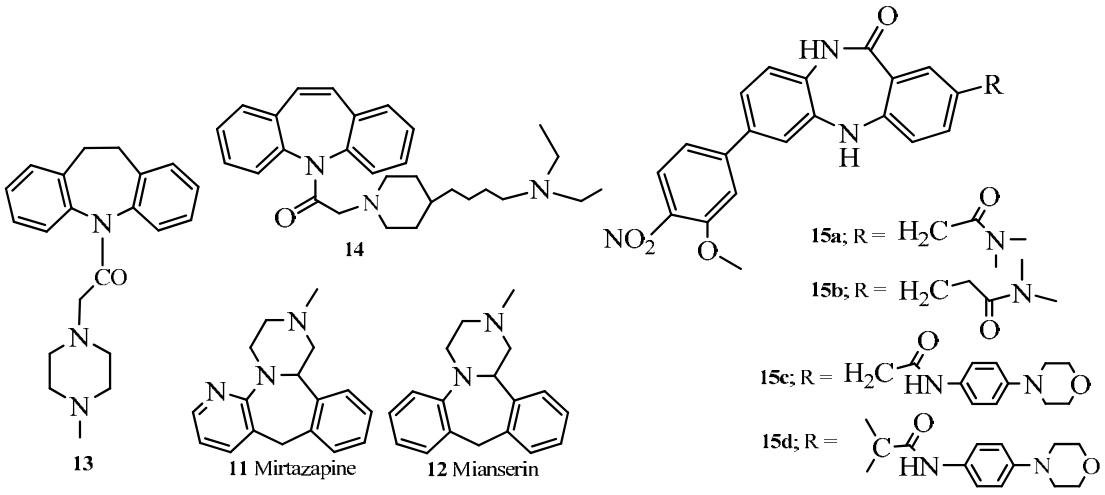
Although a broad-spectrum antipsychotic is desirable for treatment efficacy in some central nervous system disorders, selectivity is equally important in many other cases. A selective antimuscarinic compound with high affinity to the intestinal muscarinic receptors is the 10,11-dihydrodibenzoazepine derivative **13**.[8] This compound, unlike other prototype tricyclic psychotropics, does not exhibit an abundant variety of neurological and cardiotoxic effects, representing therefore an alternative for the safe and unproblematic treatment of gastritis and duodenal and peptic ulcer. By contrast, the dibenzoazepine derivative **14**[9] shows high affinity to the cardiac and low affinity to the intestinal muscarinic receptors and appears to be a promising cardioselective antimuscarinic agent for the treatment of dysfunctions of the cardiac conduction system, such as sinus or nodal bradycardia and atrioventricular block.

Furthermore, besides its anticonvulsant activity, carbamazepine **3** also exhibits effective properties as voltage-gated sodium channel blocker reducing the pain associated with nervous system injuries.[10, 11]

Finally, we have to mention the recent discovery of a series of 5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-ones acting as potent and selective checkpoint kinase 1 (Chk1) inhibitors[12]. Chk1 is a serine / threonine kinase that is closely involved in the regulation of the cell cycle. Thus, Chk1 inhibitors may be useful in cancer therapy as sensitizing agents, enhancing the citotoxicity of anti-cancer drugs.[13] Dibezodiazepine derivative **15d** was shown to have the best potentiating capability.[12]

Despite of this rich pharmacological profile, there are relatively few dibenzoazepine and dibenzodiazepine derivatives able to ensure an efficient and selective treatment of a certain condition. For instance, in the case of epilepsy that affects 1% of the world's population, current clinically available drugs produce satisfactory seizure control only in a 60-70% rate,[14] while the rest of patients are not well-controlled, largely unresponsive to treatment with carbamazepine[15] and suffering from unwanted medication side effects.[16] Therefore, the need for more effective and less toxic drugs for the treatment of central nervous system disorders still exists. Based on the rich and interesting pharmacological profile of dibenzoazepine derivatives and on the close chemical similitude to other structures

with known physiological activity, we decided to synthesize (5*H*-dibenzo[*b*,*f*]azepin-5-yl)(pyrrolidin-1-yl)methanone (**16a**), (5*H*-dibenzo[*b*,*f*]azepin-5-yl)(4-phenylpiperazin-1-yl)methanone (**16b**), (10,11-dihydro-5-*H*-dibenzo[*b*,*f*]azepin-5-yl)(pyrrolidin-1-yl)methanone (**17a**), and (10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)(4-phenylpiperazin-1-yl)methanone (**17b**), as potential neuropharamacological active compounds.




## RESULTS AND DISSCUSSION

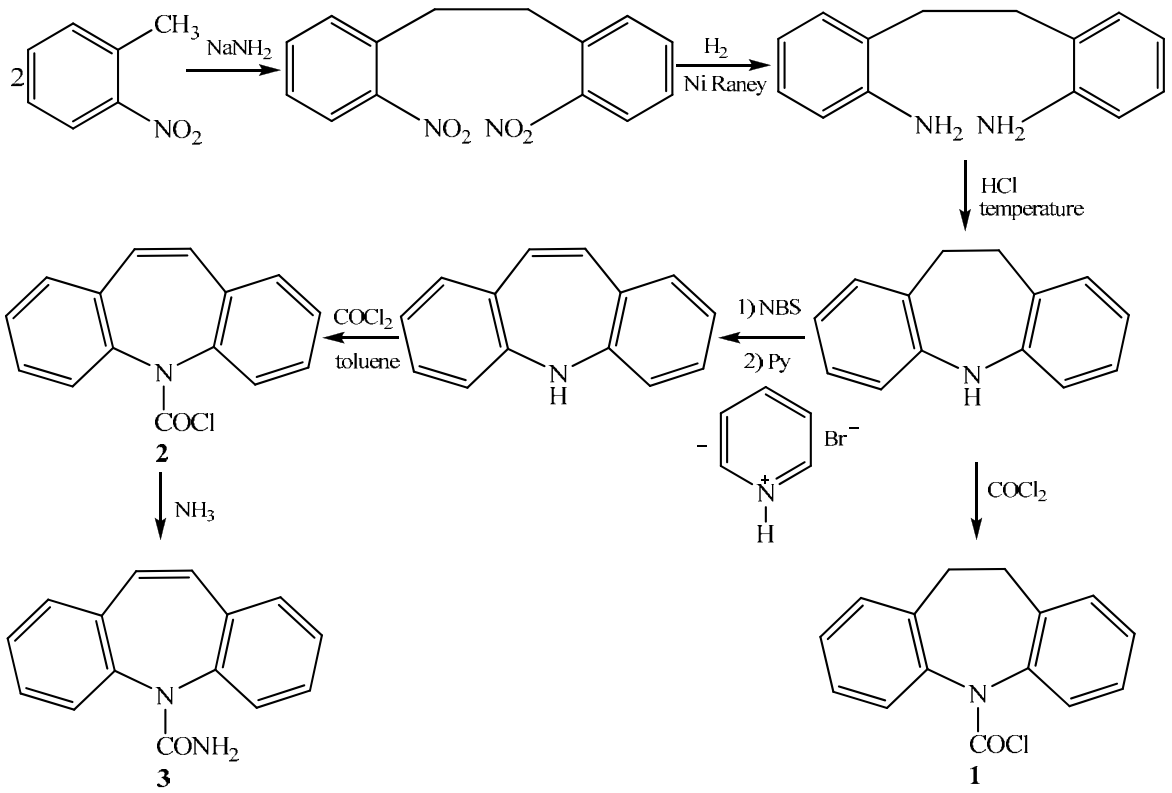
5*H*-Dibenzo[*b*,*f*]azepine-5-carbonyl chloride (**2**) and 10,11-dihydro-5-*H*-dibenzo[*b*,*f*]azepine-5-carbonylchloride (**1**) were obtained in a sequence of reactions starting with *o*-nitrotoleuene[17] as depicted in Scheme 1. We have prepared the compounds **16a,b** and **17a,b** by reacting pyrrolidine and 1-phenylpiperazine with the corresponding carbamoyl chlorides **2** and **1**, respectively, as shown in Scheme 2.

The purified compounds were analyzed by $^{1}$H- and $^{13}$C-NMR spectrometry, mass spectrometry using ESI technique, and UV spectroscopy. All the results of the used analytical methods are in very good agreement and confirm the structures of the newly synthesized compounds. In the following, we will exemplify discussing the NMR spectra of compound **16a**. The spectra of all newly synthesized compounds are given in the experimental part.

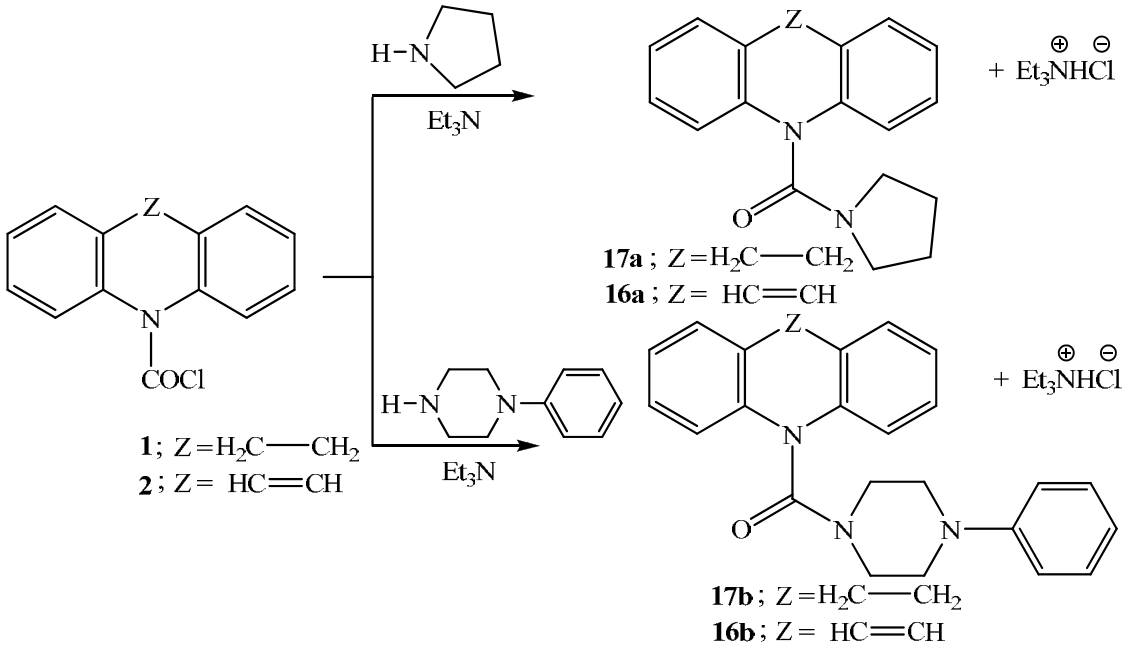
In the $^{1}$H-NMR spectrum of the compound **16a**, there are three groups of signals corresponding to aromatic protons in a relative intensity ratio of 1:1:2. The most deshielded signal is centered, in the case of compound **16a,** at the chemical shift $\delta$ = 7.594 ppm, but it is clearly visible throughout the series of the newly synthesized compounds. It has a relative intensity of two protons, a multiplicity that corresponds to a doublet of doublets (dd), and it is clearly assigned to the aromatic protons $H_1$, $H_{10}$, neighboring the nitrogen atom (*see* Figure 2). They are simultaneously coupled both to the protons $H_2$ and $H_9$ respectively ($J_{1,2}$ = 8.0 Hz; *see* Table 1), and to $H_3$ and $H_8$ respectively ($J_{13}$ = 1.0 Hz).

The next group of signals in the $^{1}$H-NMR spectrum of compound **16a** is a multiplet of eight lines, centered at $\delta$ = 7.400 ppm, and corresponding to the protons $H_2$, and $H_9$ respectively. These protons are simultaneously coupled to the protons $H_1$ and, $H_{10}$ respectively, $H_3$ and $H_8$ respectively, and $H_4$ and $H_7$ respectively, with the following coupling constants: $J_{2,1}$ = 8.0 Hz, $J_{2,3}$ = 7.0 Hz, and $J_{2,4}$ = 1.95 Hz.

The final group of aromatic protons in compound **16a** has a relative intensity of 2, as compared to previous groups (relative intensity 1), corresponding thus to four aromatic protons. These protons are $H_4$ and $H_7$ respectively, which appear as a doublet of doublets (dd) centered at $\delta$ = 7.292 ppm, and $H_3$ and $H_8$ respectively, which appear as a multiplet of six lines centered at the chemical shift $\delta$ = 7.235ppm. The protons $H_4$, respectively $H_7$, are simultaneously coupled to the protons $H_3$, respectively $H_8$, coupling constant $J_{4,3}$ = 7.0 Hz, and $H_2$, respectively $H_9$, coupling constant $J_{4,2}$ = 1.95 Hz. The protons $H_3$, respectively $H_8$, are coupled to the protons $H_2$ and $H_4$, respectively $H_7$ and $H_9$, with the same coupling constant $J_{3,4} = J_{3,2}$ = 7.0 Hz, and to the proton $H_1$, respectively $H_{10}$, with the coupling constant $J_{3,1}$ = 1.0 Hz. The two equivalent, both benzylic and vinylic, protons $H_5$ and $H_6$ appear highly deshielded at $\delta$ = 6.97 ppm.




Scheme 1 – Synthesis of carbamoyl chlorides **1** and **2**.




Scheme 2 – Synthesis of the new dibenzo[*b,f*]azepine derivatives **16a, b** and **17a, b**.

Finally, there are other two signals in the $^1$H-NMR spectrum of compound **16a**, corresponding to the protons of the pyrrolidine moiety. A slightly distorted triplet centered at $\delta$ = 2.965 ppm corresponds to the two equivalent protons $H_{16}$ and $H_{19}$, neighboring the nitrogen atom, which are coupled to the other two equivalent protons in the pyrrolidine moiety, $H_{17}$ and $H_{18}$ with the coupling constant $J_{16,\,17}$ = 6.8 Hz. Another slightly distorted triplet centered at $\delta$ = 1.668 ppm obviously corresponds to the protons $H_{17}$ and $H_{18}$ which are coupled to their neighboring protons $H_{16}$, respectively

$H_{19}$, with the above coupling constant, $J_{17,16}$ = 6.8 Hz. Thus, the chemical shifts, the splitting patterns, and the coupling constants in Table 1 undoubtedly confirm the chemical structure of the newly synthesized compound **16a**.

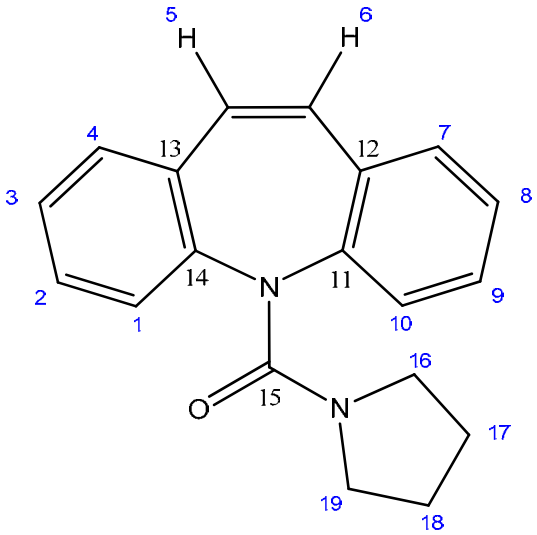



Fig. 2 – Chemical structure of the newly synthesized compound **16a**.

*Table 1*

The $^{1}$H-NMR spectrum of compound **16a**.

| **Chemical shift $\delta$ (ppm)** | **Intensity** | **Splitting pattern** | **Coupling constants (Hz)** | **Attribution** |
|---|---|---|---|---|
| **7.609-7.578** | 2H | Doublet of doublets (dd) | $J_{1,2}$ = 8.0<br>$J_{1,3}$ =1.0 | $H_1$, $H_{10}$ |
| **7.428-7,372** | 2H | Multiplet (m,eight lines) | $J_{2,1}$ = 8.0<br>$J_{2,3}$ = 7.0<br>$J_{2,4}$ = 1.95 | $H_2$, $H_9$ |
| **7.308-7.275** | 2H | Doublet of doubles (dd) | $J_{4,3}$ = 7.0<br>$J_{4,2}$ = 1.95 | $H_4$, $H_7$ |
| **7.260-7.207** | 2H | Multiplet (m,six lines) | $J_{3,4}$ = 7.0<br>$J_{3,2}$ = 7.0<br>$J_{3,1}$ = 1.0 | $H_3$, $H_8$ |
| **6.970** | 2H | Singlet (s) | - | $H_5$, $H_6$ |
| **2.988-2.944** | 4H | Triplet (t) | $J_{16,17}$ = 6.8 | $H_{16}$, $H_{19}$ |
| **1.692-1.646** | 4H | Triplet (t) | $J_{17,16}$ = 6.8 | $H_{17}$, $H_{18}$ |

As expected, the $^{13}$C-NMR spectrum of compound **16a** exhibits 10 lines, corresponding to the ten non-equivalent carbon atoms in the molecule. We remark the signals of the three types of quaternary carbon atoms, appearing at the following chemical shifts expressed in ppm: 159.173 (corresponding to the carbonyl carbon atom $C_{15}$), 142.850 (corresponding to the aromatic quaternary carbon atoms $C_{11}$ and $C_{14}$ next to the nitrogen atom), and 134.861(corresponding to aromatic carbon atoms $C_{12}$ and $C_{13}$). The secondary carbon atoms in the pyrrolidine ring correspond to other two signals in the $^{13}$C-NMR spectrum, one for the carbon atoms $C_{16}$ and $C_{19}$, neighboring the nitrogen atom, appearing at 48.175 ppm, while the other one appearing at 25.683 ppm corresponds to the carbon atoms $C_{17}$ and $C_{18}$. The four pairs of equivalent aromatic tertiary carbon atoms ($C_1$, $C_{10}$), ($C_2$, $C_9$), ($C_3$, $C_8$), ($C_4$, $C_7$), as well as the equivalent tertiary carbon atoms $C_5$, $C_6$ (both vinylic and benzylic), exhibit normal chemical shifts values between 131.500 and 126.452 ppm.

The mass spectrum of compound **16a**, recorded with a mass spectrometer using the electrospray ionization (ESI) technique, reveals the molecular mass of the compound as adduct with one pro-

ton[M+H] at m/z = 291, as well as other two peaks: one at m/z = 192 corresponding to the dibenzo[*b*,*f*]azepinyl fragment, and the other one at m/z = 98 corresponding to the pyrrolidine moiety, as indicated in Figure 3.

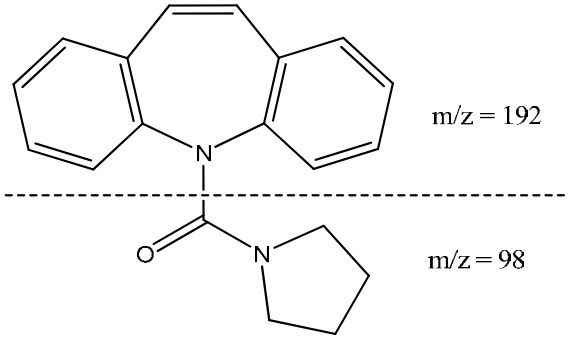



Fig. 3 – Fragmentation pattern for compound **16a**, as revealed by ESI mass spectrometry.

Thus, the mass spectrometry analysis also confirms the chemical structure of the new dibenzo[*b*,*f*]azepine derivative **16a**. Similar fragmentation patterns were observed for all the newly synthesized compounds, and the mass of the resulted fragments are in perfect agreement with the chemical structure of these compounds, proving the synthetic success. Two other possible fragmentations modes were observed in the case of the compound **17b**, as shown in Figure 4.

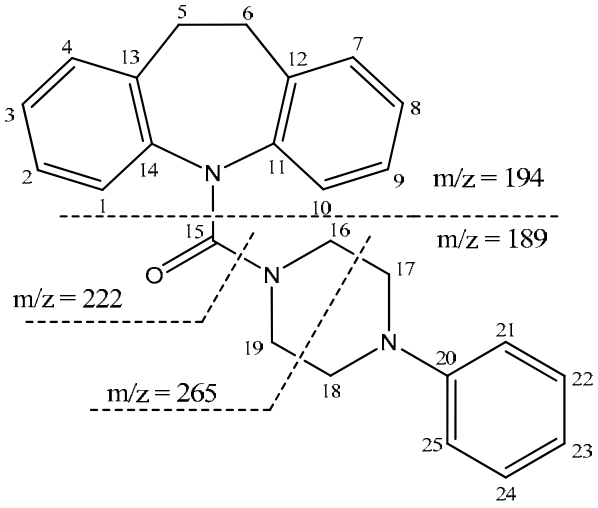



Fig. 4 – Fragmentation patterns for compound **17b**, as revealed by ESI mass spectrometry.

The compounds possessing the dibenzo[*b*,*f*] azepine moiety were compared to those with the 10,11-dihydrodibenzo[*b*,*f*]azepine moiety with respect to their UV spectra. The compounds were subjected to chromatographic analysis using a liquid-chromatograph with UV–VIS detection. Compounds **17a**,**b**, belonging to the 10,11-dihydrodibenzo[*b*,*f*]azepine class, exhibit two absorption maxima, corresponding to the two chromophores in their molecule, the aromatic rings and the carbonyl double bond. The dibenzo[*b*,*f*]azepine derivatives **16a**,**b** show an additional absorption, corresponding to the supplemental carbon-carbon double bond in the azepine ring. Numerical values of these absorption maxima are given in the experimental part.

## EXPERIMENTAL

The NMR spectra were recorded on a 300 MHz VARIAN spectrometer, using $CDCl_3$ as a solvent. The ESI mass spectra were recorded on a 1200 L/MS/MS VARIAN triple-quadrupol mass spectrometer, using methanol as a solvent, nitrogen as nebulizer gas, and air as drying gas.

The chromatographic analyses were performed using a HPLC-UV-DAD instrument equipped with a PROSTAR 240 SDM pump, a PROSTAR 410 auto-sampler, and a PROSTAR 330 PDA UV-VIS detector.

A column NOVAPAK C 18 with a length of 150 mm, an interior diameter of 4.6 mm, and a size of particles of 4 μm was used. A mixture water-methanol in a volumetric ratio of 1:4 was used as eluent at a flow rate of 1mL/min. The UV spectra were recorded running a POLYVIEW soft. The detector range is between 200 and 270 nm.

All melting points are uncorrected.

The chemical syntheses were performed according to a general procedure in which the carbamoyl chlorides **1** or **2** were stirred with the appropriate cyclic secondary amines for 24 hours at room temperature, in anhydrous media (benzene or dioxane), in the presence of triethylamine. An insoluble precipitate of triethylamine chlorohydrate was gradually formed during the reactions. The reaction mixtures were worked-up by a standard procedure by pouring into water, separation of the organic phase, extraction of the aqueous phase with methylene chloride, followed by drying the reunited organic phases and vacuum evaporation of the solvent. The residues were purified by recrystallization from isopropyl alcohol.

(5H-dibenzo[b,f]azepin-5-yl)(pyrrolidin-1-yl)methanone (**16a**). In an 100 mL two-necked round bottomed flask equipped with reflux condenser, dropping funnel, and magnetic stirrer, 0.28 g (0.35 mL, 0.004 mol) pyrrolidine are introduced together with 0.4 g (0.6 mL, 0.004 mol) triethylamine, and 15 mL of dry dioxane. A solution of 1g (0.004 mol) of 5*H*-dibenzo[*b,f*]azepine-5-carbonyl chloride (**2**) dissolved in 30 mL of dry dioxane is added dropwise under magnetic stirring. A precipitate of triethylamine hydrochloride gradually appears. The reaction mixture was stirred for 24 hours at room temperature and then was worked-up according to the aforesaid standard procedure yielding 0.93 g (80%) of the compound **16a**.

Melting point: 185˚C

UV-VIS spectrum (methanol-water, λ, nm): 206.09 (aromatic rings); 248.55 (C=O ); 288.09 (C=C).

(10,11-dihydro-5-H-dibenzo[b,f]azepin-5-yl)(pyrrolidin-1-yl)methanone (**17a**). The same quantities of each starting material as above were used, but the solvent was changed for dry benzene. Yield 0.97 g (85%) of the compound **17a**.

Melting point: 151˚C

UV-VIS spectrum (methanol-water, λ, nm): 210.16 (aromatic rings); 248.27 (C=O ).

$^1$H-NMR spectrum ($CDCl_3$, $\delta$, ppm, $J$, Hz): 7.719 (dd, $J_{1,2}$ = 7.7 Hz, $J_{1,3}$ = 1.5 Hz, 2H, $H_1$, $H_{10}$); 7.422-7.361 (m, 6H, $H_2$ – $H_4$, $H_7$ – $H_9$); 3.417 (m, 8H, $H_5$, $H_6$, $H_{16}$, $H_{19}$); 2.016-1.983 (t, $J_{17,16}$ = 6.8 Hz, 4H, $H_{17}$, $H_{18}$).

$^{13}$C-NMR spectrum ($CDCl_3$, $\delta$, ppm): 157.810 ($C_q$, $C_{15}$); 143.351 ($C_q$, $C_{11}$, $C_{14}$); 135.719 ($C_q$, $C_{12}$, $C_{13}$); 130.000 (CH); 128.040 (CH); 126.790 (CH); 126.560 (CH); 48.300 ($CH_2$, $C_{16}$, $C_{19}$); 31.240 ($CH_2$, $C_5$, $C_6$); 25.630 ($CH_2$, $C_{17}$, $C_{18}$).

ESI Mass spectrum ($CH_3OH$, m/z): 293 [M+H], 194, 98.

(5H-dibenzo[b,f]azepin-5-yl)(4-phenylpiperazin-1-yl)methanone (**16b**). Starting with 0.64 g (0.6 mL, 0.004 mol) 1-phenylpiperazine, 1 g (0.004 mol) 5*H*-dibenzo[*b,f*]azepine-5-carbonyl chloride, and 0.4 g (0.6 mL, 0.004 mol) triethylamine in 45 mL dry dioxane, we finally obtained 1.26 g (82%) of compound **16b**.

Melting point: 135˚C

UV-VIS spectrum (methanol-water, λ, nm): 204.26 (aromatic rings); 247.29 (C=O ); 287.59 (C=C).

$^1$H-NMR spectrum ($CDCl_3$, $\delta$, ppm, $J$, Hz): 7.499 (dd, $J_{1,2}$ = 8.0 Hz, $J_{1,3}$ = 1.0 Hz, 2H, $H_1$, $H_{10}$); 7.324-7.268 (m, eight lines, $J_{2,1}$ = 8.0 Hz, $J_{2,3}$ = 7.0 Hz, $J_{2,4}$ = 1.95 Hz, 2H, $H_2$, $H_9$); 7.203-7.110 (m, 6H, $H_3$, $H_4$, $H_7$, $H_8$, $H_{21}$, $H_{25}$); 6.873 (s, 2H, $H_5$, $H_6$); 6.752-6.702 (m, 3H, $H_{22}$, $H_{24}$, $H_{23}$); 3.206-3.172 (t, $J_{16,17}$ = 5.0 Hz, 4H, $H_{16}$, $H_{19}$); 2.825-2.791 (t, $J_{17,16}$ = 5.0 Hz, 4H, $H_{17}$, $H_{18}$).

$^{13}$C-NMR spectrum ($CDCl_3$, $\delta$, ppm): 159.427 ($C_q$, $C_{15}$); 151.308 ($C_q$, $C_{20}$); 142.896 ($C_q$, $C_{11}$, $C_{14}$); 134.362 ($C_q$, $C_{12}$, $C_{13}$); 131.578 (CH); 129.361 (CH); 129.172 (CH); 127.926 (CH); 126.712 (CH); 120.221 (CH); 116.390 (CH); 48.894 ($CH_2$, $C_{16}$, $C_{19}$); 46.189 ($CH_2$, $C_{17}$, $C_{18}$).

ESI Mass spectrum ($CH_3OH$, m/z): 382 [M+H], 192, 189.

(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)(4-phenylpiperazin-1-yl)methanone (**17b**). We used the same quantities of each starting material as for the synthesis of compound **16b**. Yield 1.25 g (83%) compound **17b**.

Melting point: 154˚C

UV-VIS spectrum (methanol-water, λ, nm): 206.98 (aromatic rings); 248.27 (C=O ).

$^1$H-NMR spectrum ($CDCl_3$, $\delta$, ppm, $J$, Hz): 7.526-7.498 (m, 2H, $H_1$, $H_{10}$); 7.283-7.169 (m, 8H, $H_2$ – $H_4$, $H_7$ – $H_9$, $H_{21}$, $H_{25}$); 6.909-6.876 (m, 3H, $H_{22}$, $H_{24}$, $H_{23}$); 3.540-3.506 (t, $J_{16,17}$ = 5.0 Hz, 4H, $H_{16}$, $H_{19}$); 3.217 (s, 4H, $H_5$, $H_6$); 3.070-3.036 (t, $J_{17,16}$ = 5.0 Hz, 4H, $H_{17}$, $H_{18}$).

$^{13}$C-NMR spectrum ($CDCl_3$, $\delta$, ppm): 158.991 ($C_q$, $C_{15}$); 151.345 ($C_q$, $C_{20}$); 143.223 ($C_q$, $C_{11}$, $C_{14}$); 135.286 ($C_q$, $C_{12}$, $C_{13}$); 130.187 (CH); 129.408 (CH); 127.880 (CH); 127.764 (CH); 126.995 (CH); 116.559 (CH); 49.126 ($CH_2$, $C_{16}$, $C_{19}$); 46.263 ($CH_2$, $C_{17}$, $C_{18}$); 31.283 ($CH_2$, $C_5$, $C_6$).

ESI Mass spectrum ($CH_3OH$, m/z): 385 [M+2H], 265, 222, 194, 189.

## CONCLUSIONS

Four new polycyclic compounds, two bearing a dibenzo[*b,f*]azepine moiety, and the other two a 10,11-dihydrodibenzo[*b,f*]azepine moiety, were synthesized by reacting carbamoyl chlorides **1** or **2** with pyrrolidine and 1-phenylpiperazine, respectively. After purification by recrystallization from isopropanol, the compounds were characterized using various physical methods (NMR, HPLC with UV-VIS detection, mass spectrometry using ESI technique). All analytical data undoubtedly confirm the chemical structures of the newly synthesized compounds **16a,b** and **17a,b**, proving that we succeeded in our goals. We envisage to test the compounds **16a,b** and **17a,b** for their physiological activity.

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