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Hybrid Pyridine *Bis*-Anthracene-Imidazolium Salt: NMR Studies on Zn-Acetate Complexation

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Abstract: We report here the design and synthesis of a new hybrid *bis*-anthracene-imidazolium salt, having a pyridine scaffold. NMR studies of dimer generation, as well as complexation with zinc acetate were performed.

Keywords: hybrid salt; dimer generation; Zn complexation; NMR studies

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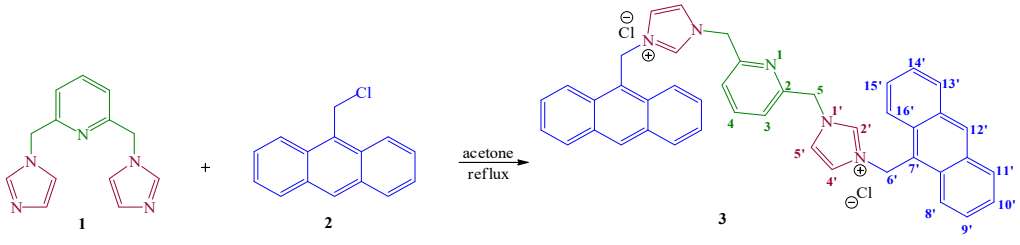
1. Introduction

In the field of supramolecular chemistry, the design and synthesis of chemosensors for the detection of metal ions have been widely exploited, due to their biological and environmental significance [1–3]. Most of these receptors can be considered hybrid compounds based on a moiety of imidazole, benzimidazole and pyridine, attached to the fluorophore, which is the anthracene unit [1–5].

Considering our experience in the field of the synthesis of hybrid compounds with imidazole/benzimidazole, pyridine and anthracene units [2,6–11], and our previous experience in the area of cycloimonium ylides [12–22], we decided to synthesize a novel hybrid pyridine *bis*-anthracene-imidazolium salt, and also to study its complexation to Zn acetate by NMR.

2. Results and Discussion

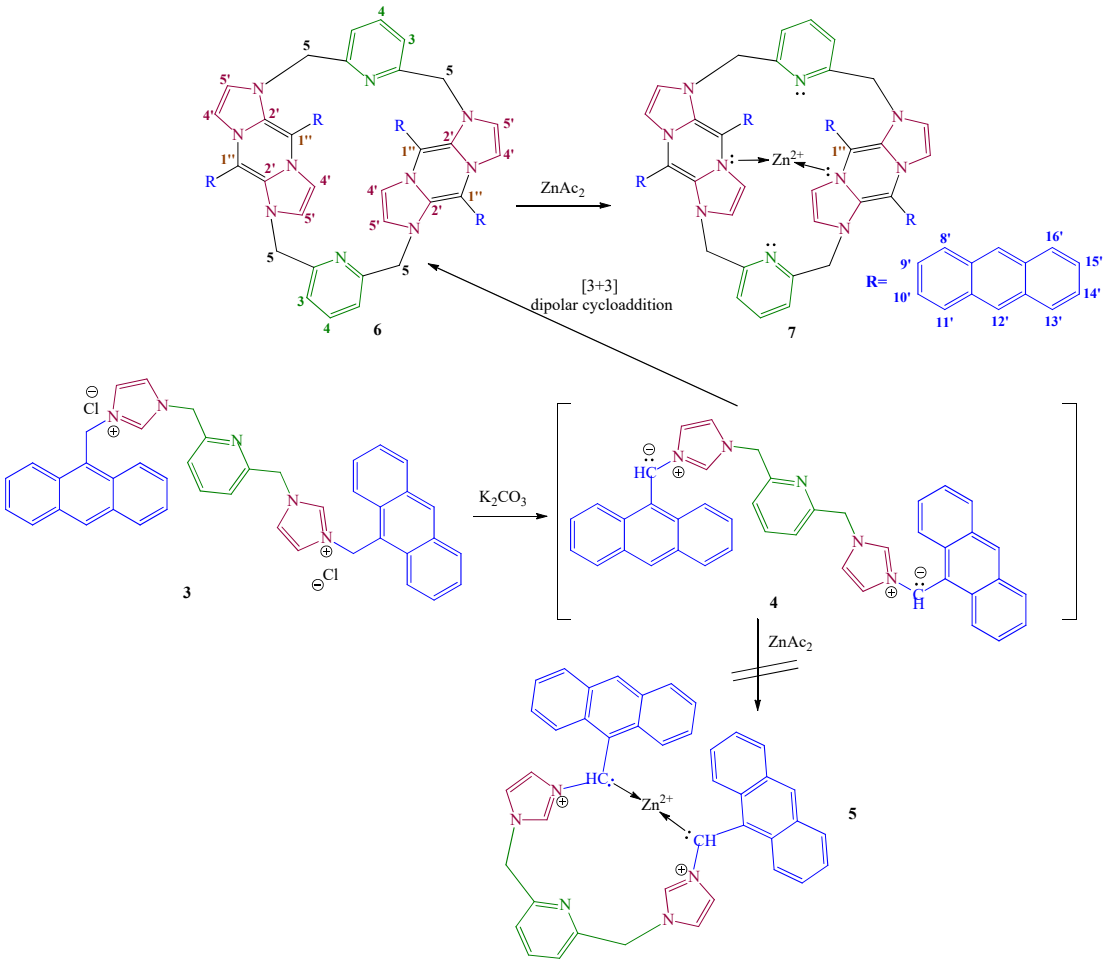
The reaction pathway to obtain the new hybrid pyridine *bis*-anthracene-imidazolium salt **3** involve a quaternization reaction of 2,6-*bis*((1*H*-imidazol-1-yl)methyl)pyridine **1**, previous reported [7], with and 9-(chloromethyl)anthracene **2**, Scheme 1. The structure of new hybrid salt **3** was proved by NMR experiments (^{1}H-, ^{13}C-NMR, 2D: COSY, HMQC, HMBC).



Scheme 1. The route of synthesis of hybrid pyridine *bis*-anthracene-imidazolium salt **3**.

In the next stage, we studied the complexation process of ylide **4** with Zn^{2+} cation [Zn^{2+} cation was generated from aqueous deuterated solution of zinc acetate (1.25×10^{-2} M)]. The ylide **4**, was generated in situ from the corresponding *bis*-anthracene-imidazolium salt **3** [previous dissolved in deuterated DMSO (2.5×10^{-3} M)] using aqueous deuterated solutions of potassium carbonate (2×10^{-3} M and 2.5×10^{-1} M).

Our expectation was to obtain a complex of ylide **4** with Zn^{2+} of type **5**, Scheme 2 as in related cases [5]. Instead, because of high reactivity of ylide **4**, a dimerisation process took place (*via* a 3 + 3 dipolar cycloaddition of an ylide molecule to another) when the dimeric structure type **6** was obtained. In the next step, the dimer **6** complexes with Zn^{2+}, leading to the final product, the dimer complex with Zn^{2+}, type **7**. The structure of Zn complex, type **7**, is a proposed structure but different coordination of Zn^{2+} ion cannot be excluded.



Scheme 2. The complexation process with Zn^{2+} of ylide **4**.

In Figure 1 are presented the overlapped ^{1}H-NMR spectra of salt **3**, dimeric structure **6** and dimeric complex with Zn^{2+} type **7**. Here are described the quantities of reactants used in the experiments and the exchange of the color of solutions.

In the ^{1}H-NMR spectrum of dimeric structure type **6** it can be observed the disappearance of protons $(–CH_2–)_{6'}$, which in salt **3** appears as a singlet at 6.48 ppm. Also, the signal around 9.06 ppm of $H_{2'}$ from imidazole nucleus of salt **3** does not appear in the NMR spectrum of dimer **6**.

The dimer complexation with Zn^{2+} induces a visible shielding effect on the chemical shifts of the protons from aliphatic and aromatic zone.

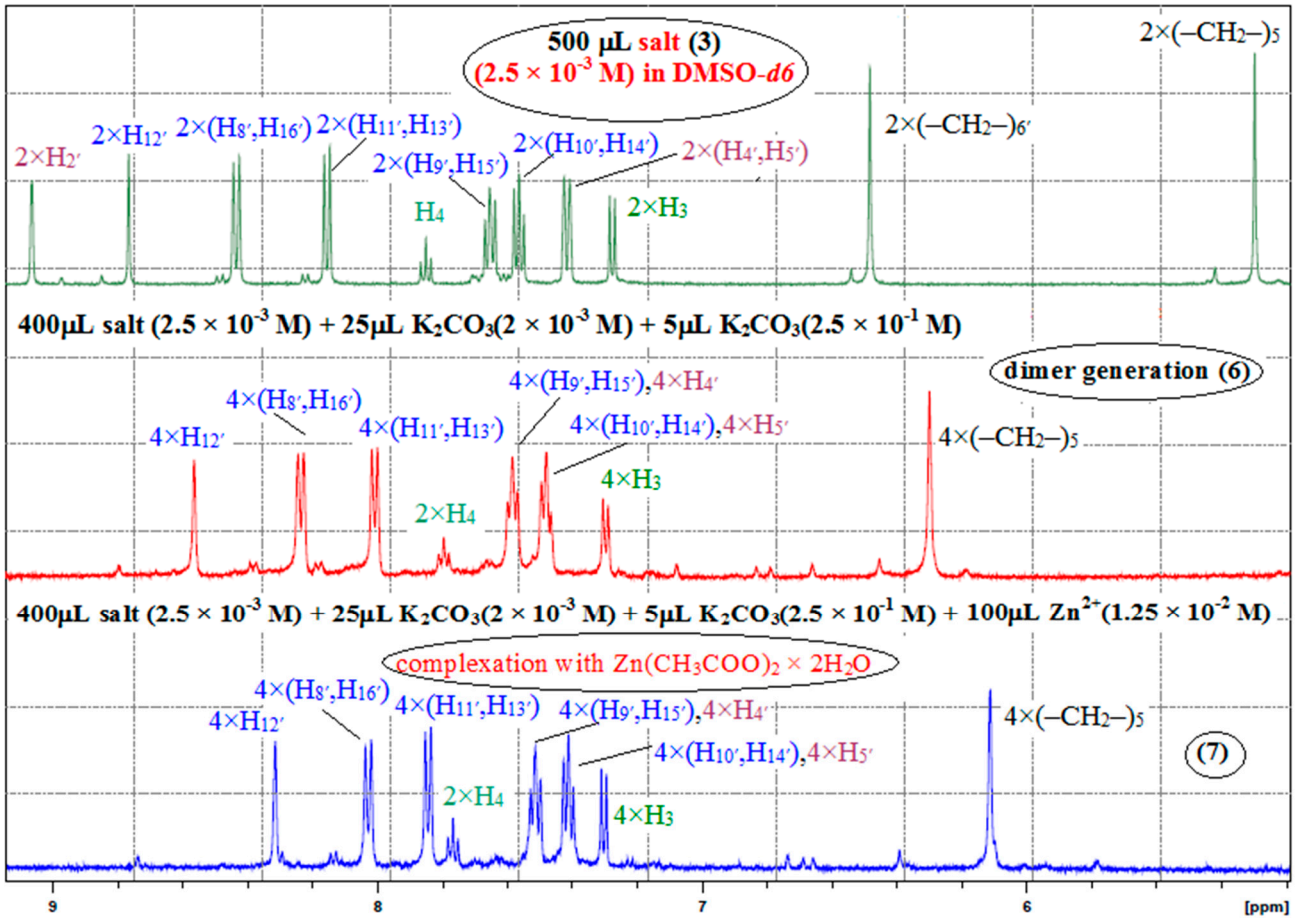


Figure 1. The ^{1}H-NMR spectra of salt **3**, dimeric structure **6** and dimeric complex **7**.

3. Materials and Methods

3.1. Instrumentation

The solvents and reagents were purchased from commercial sources, being used without further purification. The melting point (uncorrected) of compound **3** was determined using an open capillary tubes introduced in a MEL-TEMP Electrothermal apparatus. The nuclear magnetic resonance experiments have been recorded on a Bruker AVANCE III 500 MHz spectrometer (Iasi, Romania), equipped with a 5 mm PABBO detection probe, operating at 500.19 and 125.7 MHz for ^{1}H and respectively ^{13}C nuclei. In ^{1}H and ^{13}C spectra, chemical shifts are reported in δ units (ppm) relative to the residual peak of solvent (ref: DMSO-d_6, ^{1}H: 2.50 ppm; ^{13}C: 39.52 ppm). The coupling constants (*J*) are given in Hz. In the NMR spectra to appointed the multiplicity of signals, were used the abbreviations: s = singlet, d = doublet, t = triplet. The microanalyses were in satisfactory agreement with the calculated values: C, ±0.15; H, ±0.10; N, ±0.30.

3.2. General Procedure for Synthesis of Hybrid Quaternary Salt **3**

To a solution of 2,6-*bis*((1*H*-imidazol-1-*yl*)methyl)pyridine **1** (1 mmol, 1 equiv., 0.24 g, dissolved in 40 mL acetone using the ultrasound bath) was added dropwise a solution of 9-(chloromethyl)anthracene **2** (2.8 mmol, 2.8 equiv., 0.63 g, dissolved in 15 mL acetone using the ultrasound bath). The reaction mixture was refluxed for 12 h, and stirred at room temperature for another 24 h to give the corresponding hybrid quaternary salt **3**. The completion of the reaction was carried out using TLC. The obtained salt was filtered off, washed two times with the same solvent (10 mL) and dried *in vacuum*. No other purification required.

1,1′-(pyridine-2,6-diylbis(methylene))bis(3-(anthracen-9-ylmethyl)-1H-imidazol-3-ium) chloride (**3**): Light brown powder. mp 223–224 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) (ppm): 9.06 (s, 2H, 2×$H_{2'}$), 8.76 (s, 2H, 2×$H_{12'}$), 8.43 (d, 4H, J = 9.0 Hz, 2×($H_{8'}$,$H_{16'}$)), 8.15 (d, 4H, J = 8.5 Hz, 2×($H_{11'}$,$H_{13'}$)), 8.85 (t, 1H, J = 8.0 Hz, H_4), 7.75 (t, 4H, J = 8.5 Hz, J = 7.0 Hz, 2×($H_{9'}$,$H_{15'}$)), 7.56 (t, 4H, J = 8.0 Hz, J = 7.0 Hz, 2×($H_{10'}$,$H_{14'}$)), 7.41 (d, 4H, J = 9.0 Hz, 2×($H_{4'}$,$H_{5'}$)), 7.27 (d, 2H, J = 8.0 Hz, 2×H_3), 6.48 (s, 4H, 2×(–CH_2–)$_{6'}$), 5.29 (s, 4H, 2×(–CH_2–)$_5$). ^{13}C-NMR (125 MHz, DMSO-d_6) (ppm): 153.5 (2×C_2), 138.8 (C_4), 136.5 (2×$C_{2'}$), 131.0 (2×($C_{11'a}$,$C_{12'a}$)), 130.6 (2×($C_{7'a}$,$C_{16'a}$)), 130.1 (2×$C_{12'}$), 129.3 (2×($C_{11'}$,$C_{13'}$)), 127.7 (2×($C_{9'}$,$C_{15'}$)), 125.5 (2×($C_{10'}$,$C_{14'}$)), 123.6 (2×$C_{7'}$), 123.5 (2×($C_{8'}$,$C_{16'}$)), 123.1 (2×$C_{4'}$), 122.1 (2×$C_{5'}$), 122.0 (2×C_3), 52.5 (2×(–CH_2–)$_5$), 44.9 (2×(–CH_2–)$_{6'}$). Anal. Calcd. for $C_{43}H_{35}Cl_2N_5$ C, 74.56; H, 5.09; N, 10.11. Found C, 74.66; H, 5.19; N, 10.01.

3.3. General Procedure for NMR Studies

3.3.1. Dimer Generation **6**

To 400 µL (2.5 × 10^{-3} M) solution in DMSO-d_6 of hybrid quaternary salt **3** was added 25 µL (2 × 10^{-3} M) solution in D_2O of K_2CO_3 and also 5 µL (2.5 × 10^{-1} M) solution of K_2CO_3. It was observed that the solution become pale pink when adding the base (K_2CO_3). After the preparation of the solution, the NMR spectra were registered and the existence of the dimer **6** was highlighted.

Weak pink solution. ^{1}H-NMR (500 MHz, DMSO-d_6) (ppm): 8.56 (s, 4H, 4×$H_{12'}$), 8.23 (d, 8H, J = 8.5 Hz, 4×($H_{8'}$,$H_{16'}$)), 8.00 (d, 8H, J = 8.0 Hz, 4×($H_{11'}$,$H_{13'}$)), 7.79 (t, 2H, J = 8.0 Hz, 2×H_4), 7.58 (t, 12H, J = 7.0 Hz, J = 7.5 Hz, 4×($H_{9'}$,$H_{15'}$,$H_{4'}$)), 7.48 (t, 12H, J = 7.0 Hz, J = 8.0 Hz, 4×($H_{10'}$,$H_{14'}$,$H_{5'}$)), 7.29 (d, 4H, J = 7.5 Hz, 4×H_3), 6.30 (s, 8H, 4×(–CH_2–)$_5$). ^{13}C-NMR (125 MHz, DMSO-d_6) (ppm): 157.7 (4×$C_{2'}$), 153.5 (4×C_2), 139.2 (2×C_4), 131.2 (4×($C_{11'a}$,$C_{12'a}$)), 130.8 (4×($C_{7'a}$,$C_{16'a}$)), 130.5 (4×$C_{12'}$), 129.7 (4×($C_{11'}$,$C_{13'}$)), 128.2 (4×($C_{4'}$,$C_{9'}$,$C_{15'}$)), 127.5 (4×$C_{1''}$), 125.9 (4×($C_{5'}$,$C_{10'}$,$C_{14'}$)), 123.4 (4×($C_{7'}$,$C_{8'}$,$C_{16'}$)), 122.3 (4×C_3), 45.9 (4×(–CH_2–)$_5$).

3.3.2. Dimer Complex with Zn^{2+} **7**

To the solution of generated dimer 6 (400 µL (2.5 × 10^{-3}M) salt 3, 25 µL (2 × 10^{-3}M) K_2CO_3, 5 µL (2.5 × 10^{-1} M) K_2CO_3) was added 100 µL (1.25 × 10^{-2} M) solution in D_2O of $Zn(CH_3COO)_2$ × $2H_2O$, when the solution becomes poorly colored. After the preparation of the solution, the NMR spectra were recorded and the complex formation with zinc ions was evidenced.

Poorly colored solution. ^{1}H-NMR (500 MHz, DMSO-d_6) (ppm): 8.31 (s, 4H, 4×$H_{12'}$), 8.02 (d, 8H, J = 8.5 Hz, 4×($H_{8'}$,$H_{16'}$)), 7.84 (d, 8H, J = 8.5 Hz, 4×($H_{11'}$,$H_{13'}$)), 7.76 (t, 2H, J = 8.0 Hz, 2×H_4), 7.51 (t, 12H, J = 7.0 Hz, J = 8.5 Hz, 4×($H_{9'}$,$H_{15'}$,$H_{4'}$)), 7.41 (t, 12H, J = 7.5 Hz, 4×($H_{10'}$,$H_{14'}$,$H_{5'}$)), 7.30 (d, 4H, J = 8.0 Hz, 4×H_3), 6.11 (s, 8H, 4×(–CH_2–)$_5$). ^{13}C-NMR (125 MHz, DMSO-d_6) (ppm): 177.5 (4×$C_{2'}$), 153.6 (4×C_2), 139.9 (2×C_4), 131.6 (4×($C_{11'a}$,$C_{12'a}$)), 131.3 (4×$C_{1''}$), 131.2 (4×$C_{12'}$), 130.3 (4×($C_{11'}$,$C_{13'}$)), 129.0 (4×($C_{4'}$,$C_{9'}$,$C_{15'}$)), 126.5 (4×($C_{5'}$,$C_{10'}$,$C_{14'}$)), 123.6 (4×($C_{8'}$,$C_{16'}$)), 123.3 (4×$C_{7'}$), 123.1 (4×C_3), 45.6 (4×(–CH_2–)$_5$).

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References

1. Tolpygin, I.E.; Revinskii, Y.V.; Starikov, A.G.; Dubonosov, A.D.; Bren, V.A.; Minkin, V.I. Effective pH sensors based on 1-(anthracen-9-ylmethyl)-1*H*-benzimidazol-2-amine. *Chem. Heterocycl. Compd.* **2012**, *47*, 1230–1236. [CrossRef]
2. Ciobanu, C.I.; Antoci, V.; Mantu, D.; Mangalagiu, I.I. One Pot Synthesis of Cyclophane with Imidazolium Skeleton. An Improved Method. *Rev. Chim.* **2015**, *66*, 497–498.
3. Quang, D.T.; Kim, J.S. Calixarene-Derived Fluorescent Probes. *Chem. Rev.* **2007**, *107*, 3780–3799.
4. Ghosh, K.; Sen, T. Anthracene coupled adenine for the selective sensing of copper ions. *Beilstein J. Org. Chem.* **2010**, *6*, 1–8. [CrossRef] [PubMed]
5. Sabater, P.; Zapata, F.; Caballero, A.; Fernández, I.; Ramirez de Arellano, C.; Molina, P. 2,4,5-Trimethylimidazolium Scaffold for Anion Recognition Receptors Acting Through Charge-Assisted Aliphatic and Aromatic C–H Interactions. *J. Org. Chem.* **2016**, *81*, 3790–3798. [CrossRef]
6. Lungu, C.N.; Bratanovici, B.I.; Grigore, M.M.; Antoci, V.; Mangalagiu, I.I. Hybrid imidazole-pyridine derivatives: An approach to novel anticancer DNA intercalators. *Curr. Med. Chem.* **2020**, *27*, 154–169. [CrossRef]
7. Antoci, V.; Cucu, D.; Zbancioc, G.; Moldoveanu, C.; Mangalagiu, V.; Amăriucăi-Mantu, D.; Aricu, A.; Mangalagiu, I.I. Bis-(imidazole/benzimidazole)-pyridine derivatives: Synthesis, structure and antimycobacterial activity. *Future Med. Chem.* **2020**, *12*, 207–222. [CrossRef]
8. Mangalagiu, I.I.; Amăriucăi-Mantu, D.; Antoci, V.; Zbancioc, G.; Moldoveanu, C.; Cucu, D.; Dănac, R.; Mangalagiu, V. Obtaining class of anthracene-imidazole compounds with anti-tuberculosis effect by performing N-alkylation imidazole and benzimidazole with 9-chloromethyl-anthracene, and subjecting intermediates to quaternization/Procedeu pentru obţinerea unei noi clase de compuşi antracen-imidazolici cu activitate antituberculoasă. Patent RO (State Office for Inventions and Trademarks-OSIM) no. RO134192-A0/2020; Derwent Primary Accession Number: 2020-605892, 30 June 2020.
9. Cucu, D.; Mangalagiu, V. Pyridine-Imidazolium Salts: Oxidatively Cleavage of N-C Bond via Nitration. *Molbank* **2019**, *2019*, M1095. [CrossRef]
10. Antoci, V.; Humelnicu, I.; Vasilache, V.; Mantu, D. Synthesis, Structure and Biological Activity of Some Hybrid Benzimidazole/Quinoline Derivatives. *Rev. Chim.* **2016**, *67*, 1713–1716.
11. Mantu, D.; Antoci, V.; Moldoveanu, C.; Zbancioc, G.; Mangalagiu, I.I. Hybrid imidazole (benzimidazole)/pyridine(quinoline) derivatives and evaluation of their anticancer and antimycobacterial activity. *J. Enz. Inhib. Med. Chem.* **2016**, *31* (Suppl. S2), 96–103. [CrossRef]
12. Antoci, V.; Moldoveanu, C.; Danac, R.; Mangalagiu, V.; Zbancioc, G. Huisgen [3+2] Dipolar Cycloadditions of Phthalazinium Ylides to Activated Symmetric and Non-Symmetric Alkynes. *Molecules* **2020**, *25*, 4416. [CrossRef] [PubMed]
13. Cucu, D.; Mangalagiu, V.; Amăriucăi-Mantu, D.; Antoci, V.; Mangalagiu, I.I. Imidazolium ylides: Cycloaddition *versus* hydrolysis. *Studia UBB Chem.* **2019**, *64*, 59–66. [CrossRef]
14. Moldoveanu, C.; Amăriucăi-Mantu, D.; Mangalagiu, V.; Antoci, V.; Maftei, D.; Mangalagiu, I.I.; Zbancioc, G. Microwave Assisted Reactions of Fluorescent Pyrrolodiazine Building Blocks. *Molecules* **2019**, *24*, 3760. [CrossRef] [PubMed]
15. Popovici, L.; Amarandi, R.M.; Mangalagiu, I.I.; Mangalagiu, V.; Danac, R. Synthesis, molecular modelling and anticancer evaluation of new pyrrolo[1,2-b]pyridazine and pyrrolo[2,1-a]phthalazine derivatives. *J. Enz. Inhib. Med. Chem.* **2019**, *34*, 230–243. [CrossRef] [PubMed]
16. Moldoveanu, C.; Zbancioc, G.; Mantu, D.; Maftei, D.; Mangalagiu, I.I. The Cycloaddition of the Benzimidazolium Ylides with Alkynes: New Mechanistic Insights. *PLoS ONE* **2016**, *11*, e0156129. [CrossRef]
17. Al Matarneh, C.M.; Mangalagiu, I.I.; Shova, S.; Danac, R. Synthesis, structure, antimycobacterial and anticancer evaluation of new pyrrolo-phenanthroline derivatives. *J. Enz. Inhib. Med. Chem.* **2016**, *31*, 470–480. [CrossRef]
18. Al Matarneh, C.M.; Apostu, M.O.; Mangalagiu, I.I.; Danac, R. Reactions of ethyl cyanoformate with cycloimmonium salts: A direct pathway to fused or substituted azaheterocycles. *Tetrahedron* **2016**, *72*, 4230–4238. [CrossRef]
19. Antoci, V.; Mantu, D.; Cozma, D.G.; Usru, C.; Mangalagiu, I.I. Hybrid anticancer 1,2-diazine derivatives with multiple mechanism of action. Part 3 [4,5]. *Med. Hypotheses* **2014**, *82*, 11–15. [CrossRef]
20. Mantu, D.; Maftei, D.; Iurea, D.; Ursu, C.; Bejan, V. Synthesis, structure, and in vitro anticancer activity of new polycyclic 1,2-diazines. *Med. Chem. Res.* **2014**, *23*, 2909–2915. [CrossRef]

21. Tucaliuc, R.; Cotea, V.; Niculaua, M.; Tuchilus, C.; Mantu, D.; Mangalagiu, I.I. New pyridazine–fluorine derivatives: Synthesis, chemistry and biological activity. Part II. *Eur. J. Med. Chem.* **2013**, *67*, 367–372. [CrossRef]
22. Mantu, D.; Maftei, D.; Iurea, D.; Bejan, V. Crystal Structure of Ethyl 5,10-dioxo-5,10-dihydrobenzo[f]pyridazino[6,1-a]isoindole-11-carboxylate. *Rev. Chim.* **2012**, *63*, 1239–1242.