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PhD Thesis

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SYNTHESIS AND STRUCTURAL ANALYSIS OF SOME NEW SPIRANES AND RECEPTORS WITH HYDROGEN BONDING BASED RECOGNITION ABILITIES

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GENERAL INTRODUCTION

This thesis is structured into two major parts, both of them containing some literature data and original contributions.

In part A having the title " Synthesis and Structural Analysis of Some New Receptors with Hidrogen Bonding Based Recognition Abilities", at the beginning, I present my results regarding the synthesis and structural analysis of functionalized nucleobases (A, T, U) and of one podand with triphenyl amine core. These nucleobases were further subjected to "click reaction" with different podands. The obtained compounds are important candidates for further studies concerning the H-bonding associations.

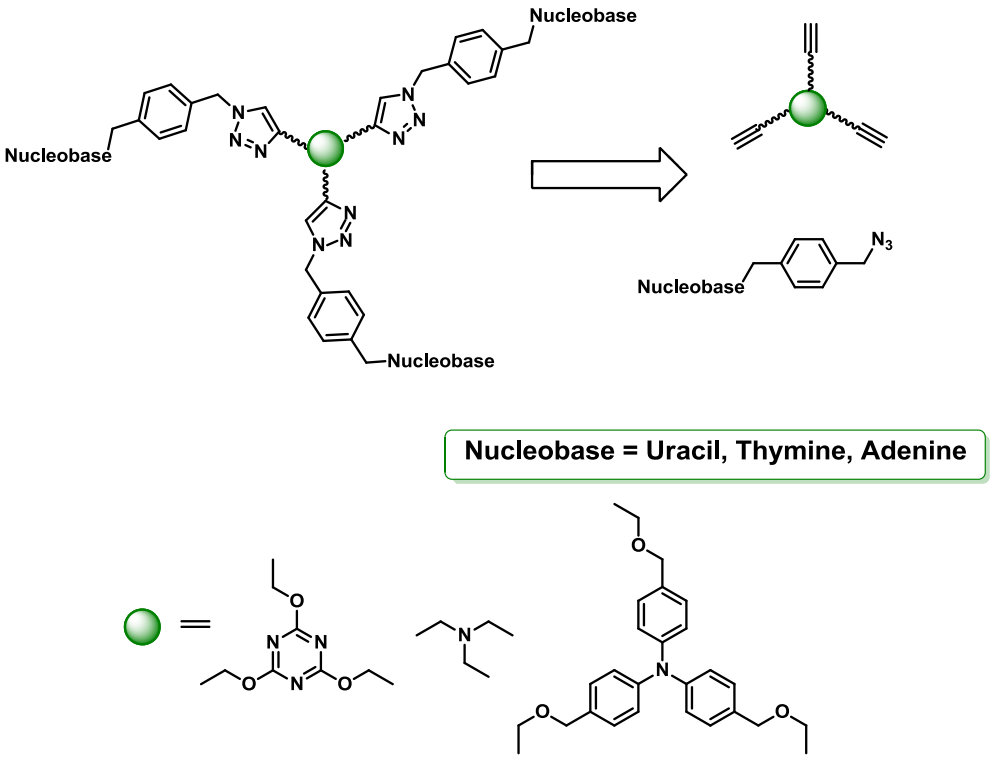
In part B "Some New Spiro [1.3]-Oxathianes", I present the synthesis and stucture of some new spiro compounds exhibiting two anancomeric 1,3-oxathiane rings. The structure of the compounds was investigated by NMR spectroscopy, mass spectrometry and molecular modelling. The calculations were performed using Gaussian03 series of programs.

PART A – SYNTHESIS AND STRUCTURAL ANALYSIS OF SOME NEW RECEPTORS WITH HIDROGEN BONDING BASED RECOGNITION ABILITIES

1. ORIGINAL CONTRIBUTIONS

1.1 OBJECTIVES

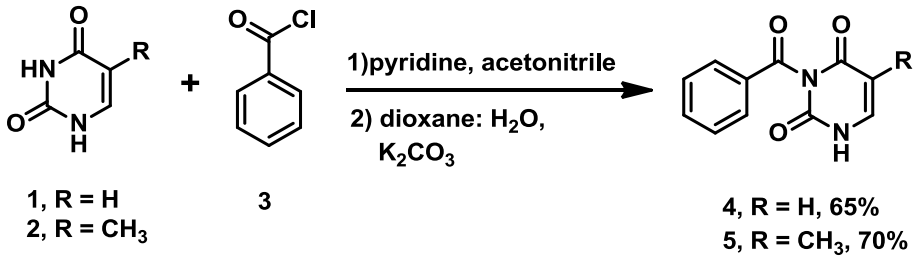
This work presents the synthesis of new tripodands with terminal nucleobases as intermediates for supramolecular architecturs by hydrogen bonding. These molecules are formed by the reaction of a central unit having pendant arms with triple terminal bonds and nucleobases bearing azide functions. The formation of 1,2,3-triazole ring by Cu-catalyzed [2+3] cycloaddition offers an elegant and high-yielding approach to our proposed building-blocks formation. The mild reaction conditions and the good yields provided by "click chemistry" justifies the use of this synthetic methodology[1]. The tripodands were fully characterized by NMR spectroscopy and MS spectrometry. Preliminary studies regarding the hydrogen bonding capacity are still under investigation.



[1]a) Gil, M. V.; Arevalo, M. J.; Lopez, O. *Synthesis***2007**, *11*, 1589-1620; b) Dichtel, W. R.; Milijanic, O. S.; Spruell, J. M.; Heath, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.***2006**, *128*, 10388-10390.

1.2 RESULTS AND DISCUSSIONS

The first step to obtain the target molecules was the protection of nucleobases (uracil and thymine, **Scheme 3**, and adenine **Scheme 4**).



Scheme 1

The protection of compounds **1** and **2** was made in two steps. The first step was a reaction of benzoylation using a mixture of pyridine and acetonitrile as solvents, in presence of K_2CO_3 and next step was a reaction of debenzoylation, according to the literature, in order to obtain compounds **4** and **5 (**65-70% yields, **Scheme 2).** The structure of these compounds was confirmed by NMR spectroscopy[2].

In the ^{1}H NMR spectrum (**Figure 1**) of compound **4**, the signals for the uracil protons appear at 5.74 ppm and 7.67 ppm, the aromatic protons 6-H as a doublet at 7.95 ppm, 7-H and 8-Has triplets at 7.62 and 7.78 ppm respectively and the specific proton for the NH group shows a singlet at 11.62 ppm.

[2]Zhou J.; Shevlin P. B. *Synthetic Comm.*, **1997**, *27*, 3591-3597.

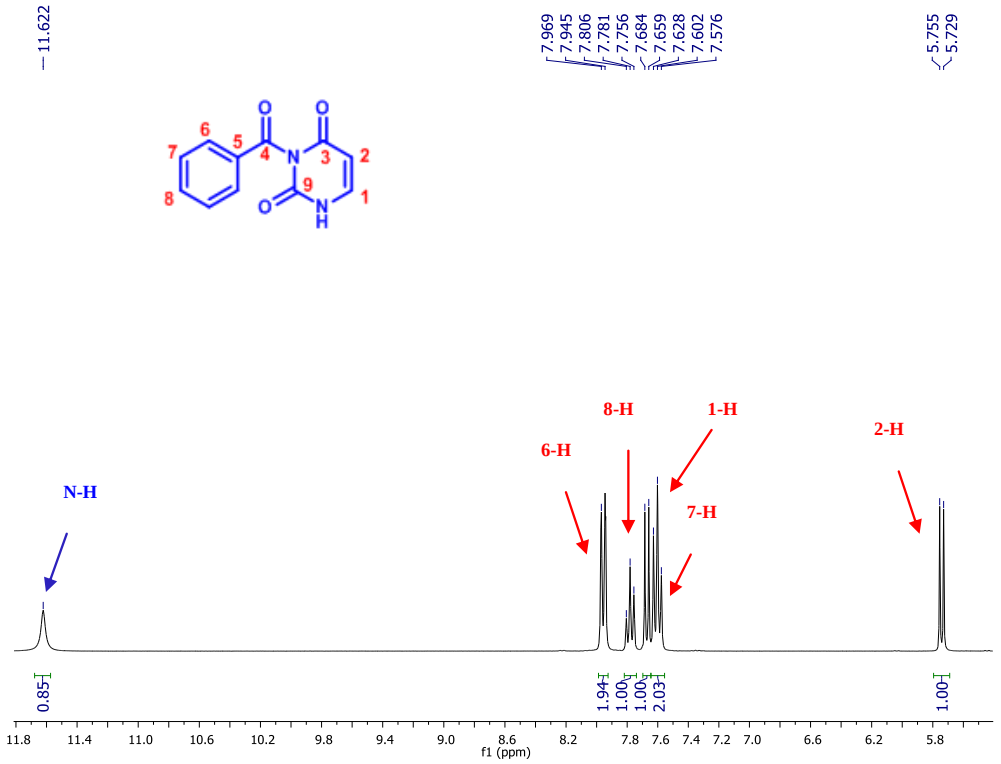
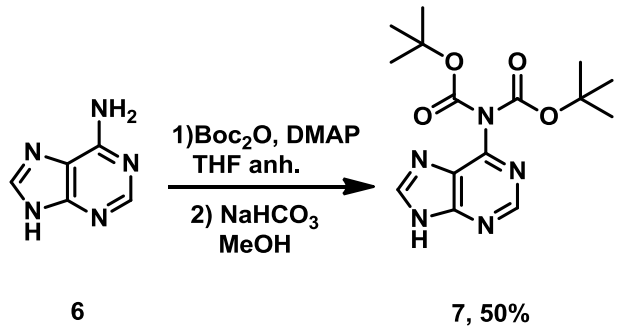


Figure 1. Fragment of ^{1}H NMR for the compound **4** (300 MHz, DMSO-d_6)

The protection of adenine **6** was also made in two steps. In the first step was carried out the protection of all the N atoms and in the next step was made the deprotection of N^9 atom (**Scheme 4**)[3].



6 **7, 50%**

Scheme 2

In the ^{1}H NMR spectrum of compound **7** (**Figure 2**) one can see two singlets corresponding to the protons 15-H and 2-H at 8.39 and 8.83 ppm respectively. The singlet for the CH_3 protons appears at 1.52 ppm.

[3] Michel, B. Y., Strazewski, P.*Tetrahedron*,**2007**, 63, 9836-9841.

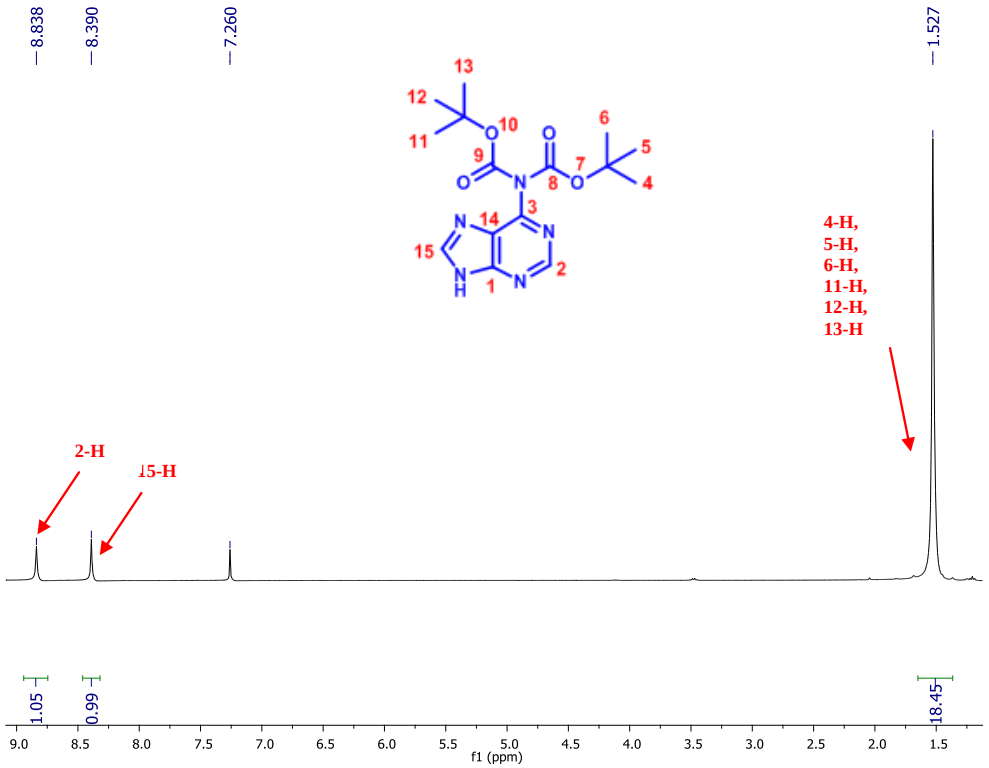
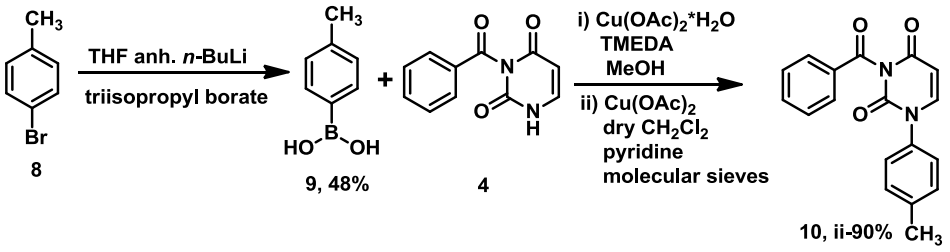


Figure 2. Fragment of ^{1}H NMR for the compound **7** (300 MHz, $CDCl_3$)

The next step to have access to the nucleobases decorated with azide groups the boronic acid **9** was obtainedstarting from commercially available *p*-bromo toluene **8**[4],followed by the coupling of compound **9** with the protected uracil in order to form compound **10**. This reaction was tried using two methods. The first method involve a reaction at room temperature in methanol by mixing and stiring overnight $Cu(OAc)_2*H_2O$, TMEDA, boronic acid and compound **4** (**Scheme 5-i**). Than at the end of this reaction we observed that we did not obtained the desired compound. The next method was basedon the stirred a mixture at room temperature boronic acid, $Cu(OAc)_2$ and compound **4**, pyridine in dry CH_2Cl_2. The solvent was dried using activated 3Å molecular sieves. The mixture was stirred for 5 days underAr. With this method (inspired from similar case found in literature[5]) compound **10** was obtained in good yields (90%) (**Scheme 5-ii**). The structure of this compound was confirmed by NMR spectroscopy and mass spectrometry.

[4] James, W. R.; Gareth, P. J.; Schiffers, S.; Raithby, P. R.; Frost, C. G.; Plucinski, P. K. *Tetrahedron Lett.***2010,** *51*, 3913 – 3917.
[5]Jacobsen, M. F.; Knudsen, M. M.; Gothelf, K. V. *J. Org. Chem.*, **2006**, *71*, 9183-9190.



Scheme 3

^{1}H NMR fragment of compound **10** is presented in **Figure 3.** The singlet for the CH_3 protons appears at 2.39 ppm. The most deshielded signals are those corresponding to the aromatic protons (δ = 5.90-7.99 ppm).

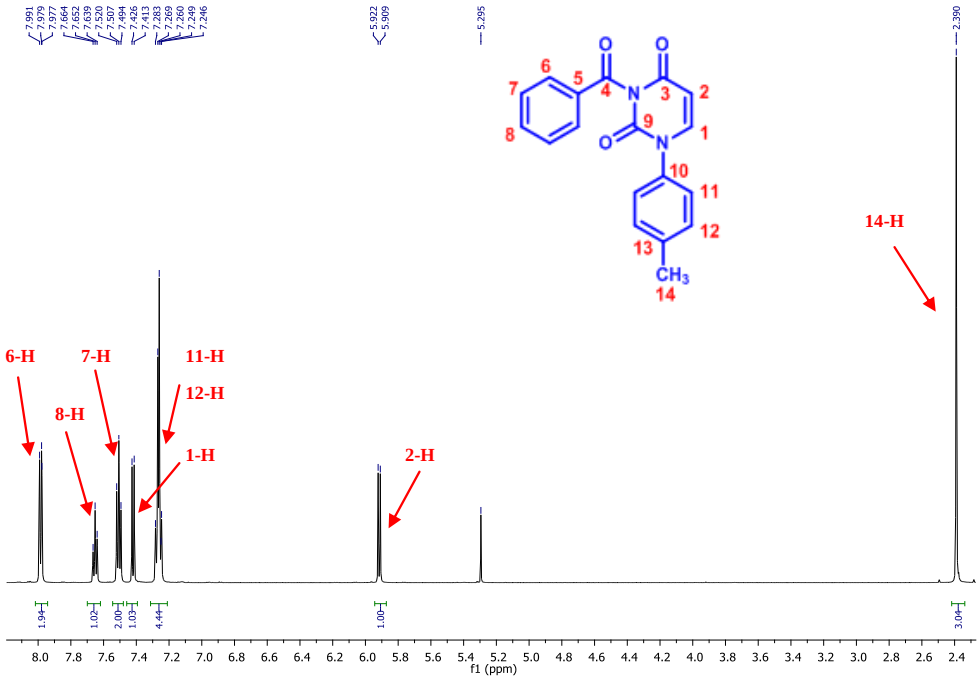
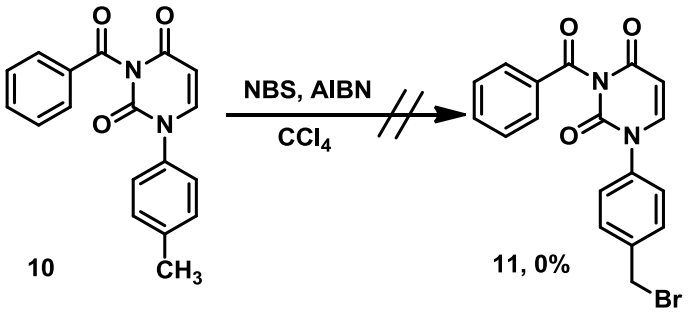


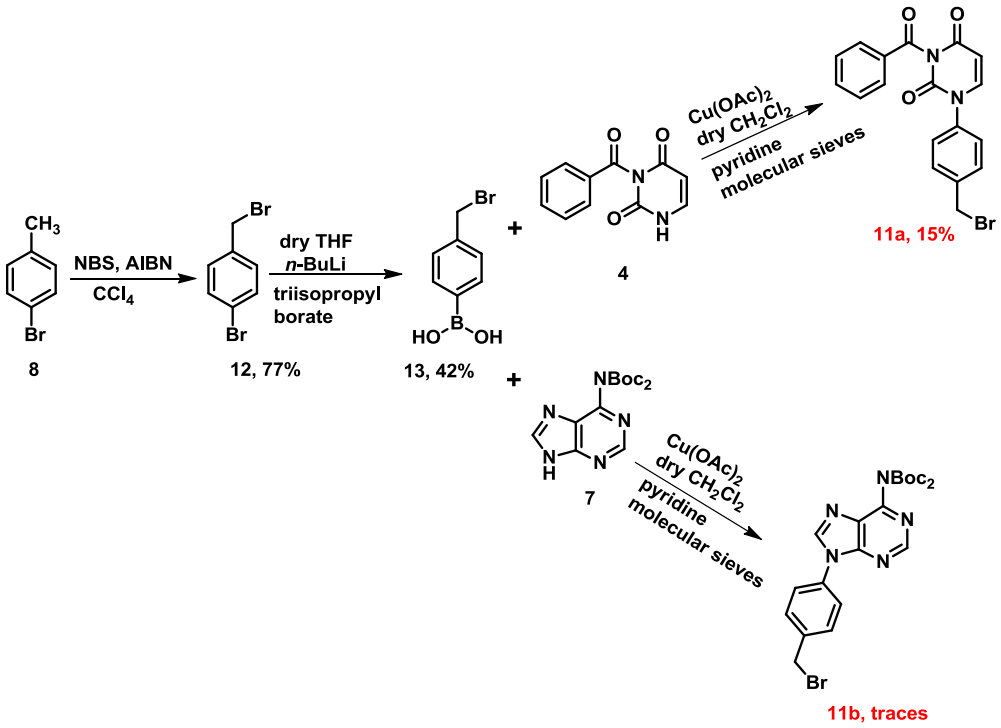
Figure 3. Fragment of ^{1}H NMR for the compound **10** (300 MHz, $CDCl_3$)

The next step in our strategy was the radicalic bromination of compound **10** (**Scheme 6**). At the beginning we dissolved the compound **10** in CCl_4 and then we added N-bromosuccinimide and AIBN. The mixture was heated under reflux for 2 days. After this reaction's work-up, was recovered only the starting materials.



Scheme 4

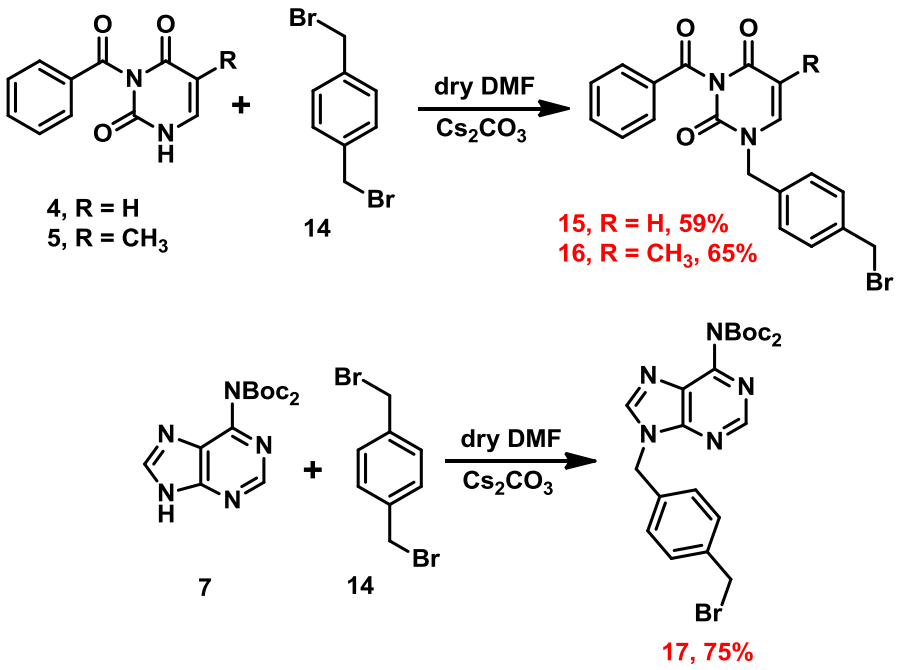
Because we failed to obtain the desired compound **11**, the strategy was changed (**Scheme 7**). The target of the first step was to obtain the boronic acid **13**[69] and then to make a coupling reaction of **13** with the protected uracil or protected adenine to obtain compounds **11a** or **11b**. The reaction was carried out in dry CH_2Cl_2 and pyridine using activated 3Å molecular sieves, boronic acid and compound **4** or **7**. The mixture was stirred for 6 days under Ar. Compound **11a** was obtain in low yield (15%)[6] and **11b** in traces and the structure of these compounds were confirmed by NMR spectroscopy.



Scheme 5

[6]Rawle, S. C.; Moore, P.; Alcock, N. W.*Chem. Commun.*, **1992**, *9*, 684.

Due to the low yields, we change again the strategy. The target of the new strategy was to obtain intermdiates **15**, **16** and **17**. This time we used as spacer another compound, *p*-xylene dibromide (**Scheme 8**). The reactions occurred in dry DMF as solvent, anhydrous Cs_2CO_3 as base, protected uracil, thymine or adenine and *p*-xylene dibromide (inspired from similar case found in literature[7]). These new brominated derivatives were obtained in good yields. The structures were analyzed using NMR spectroscopy and mass spectrometry.



Scheme 6

^{1}H NMR spectrum of compound **15,** recorded in $CDCl_3$ shows the expected signals (**Figure 5**) : two singlets for CH_2 group at 4.48 ppm and 4.92 ppm respectively and a doublet for the 2-H protons which appears at 5.81 ppm. In the aromatic region the specific signals for this region: four doublets at 7.25 ppm for 1-H, 7.30 ppm for 12-H, 7.42 ppm for 13-H respectively 7.93 ppm for 6-H and two triplets at 7.50 ppm for 7-H and 7.66 ppm for 8-Hare observed.

[7]Paryzek, Z.; Tabaczka, B. *Org. Prep. Proc. Int.* **2010,** *33*, 400-405.

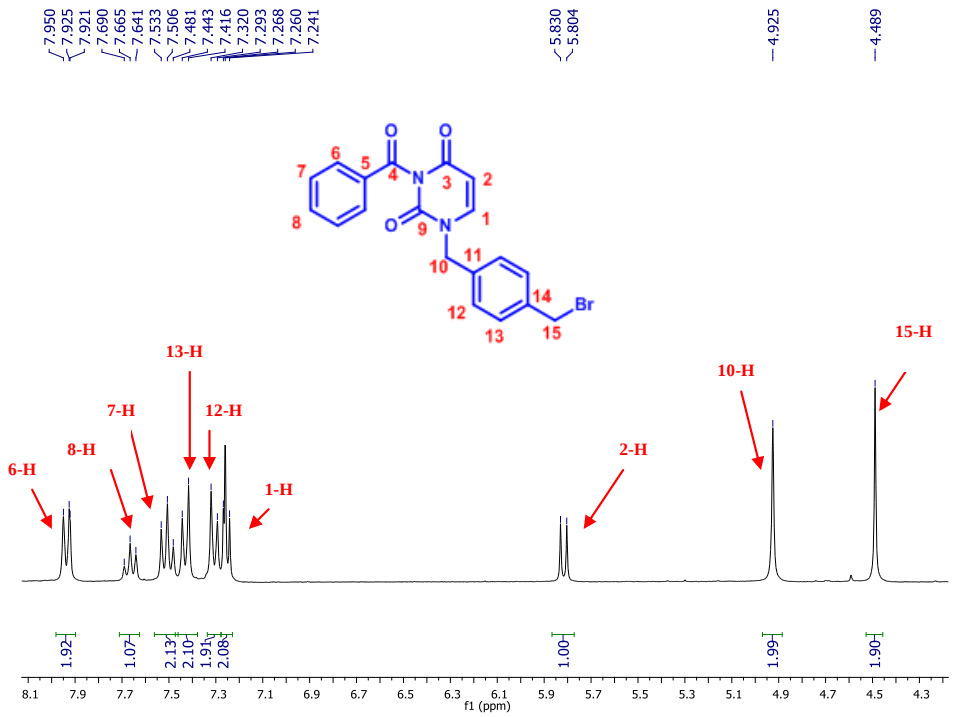


Figure 4. Fragment of ^{1}H NMR for the compound **15** (300 MHz, $CDCl_3$)

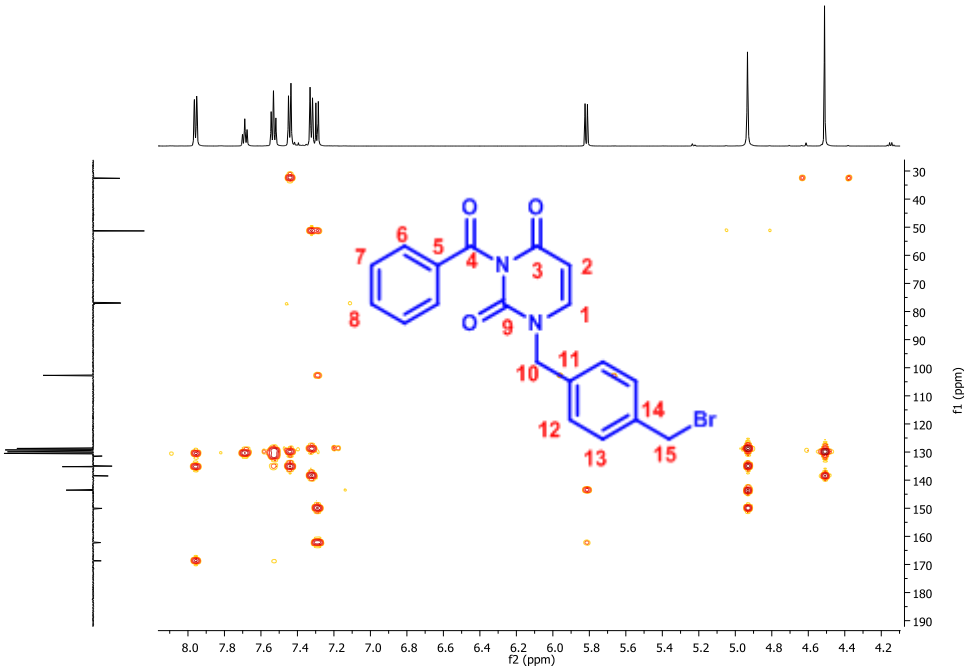


Figure 5. HMQC spectrum of compound **15**

In ^{13}C NMR of compound **16** (**Figure 7**) we can seethe signals corresponding for theprimarycarbon atoms (3-C) at 12.44 ppm. The signals at 32.65 ppm and 50.91 ppm are for the secondary carbonsatoms(16-C and 11-C). The signals which appear at 128,58 ppm, 129.12 ppm, 129.80 ppm, 130.39 ppm, 135.01 ppm and 139.34 ppm are corresponding to the tertiary carbons

atoms (13-C, 7-C, 14-C, 8-C, 9-Cand 1-C). Other signals, at 111.38 ppm, 131.49 ppm, 135.37 ppm, 138.25 ppm, 150.05 ppm, 162.91 ppm and 168.88 ppm are assigned to the quaternary carbon atomsatoms(2-C, 15-C, 6-C, 12-C, 10-C, 4-C and 5-C).

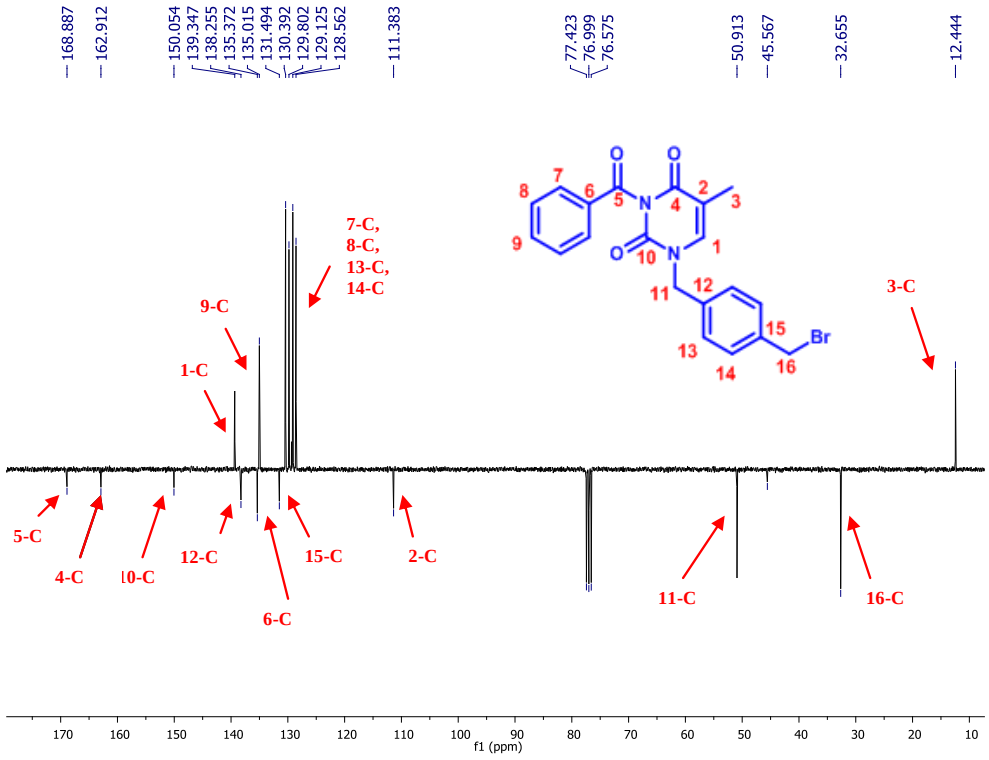


Figure 6. Fragment of ^{13}C NMR for the compound **16** (75 MHz, $CDCl_3$)

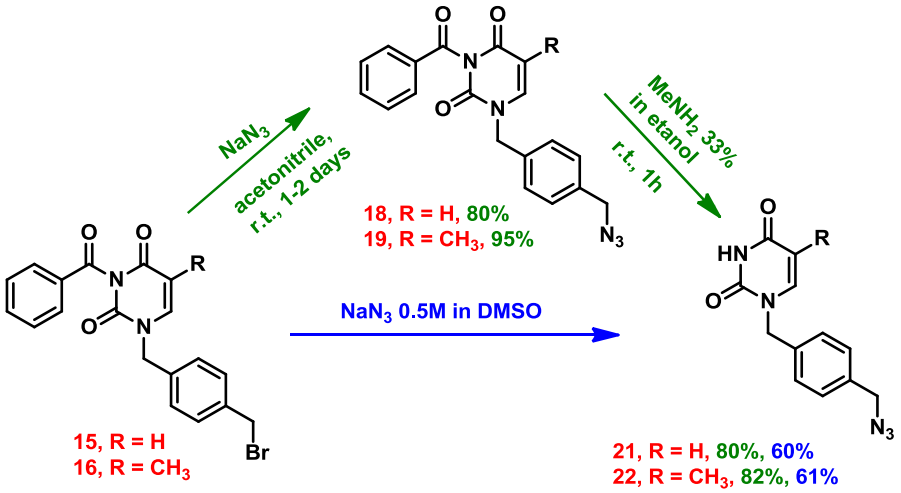
The new azido derivatives **18**, **19** and **20** were obtained in good yields using a typical procedure for the substitution of benzylic type bromine atoms with azido groups (NaN_3 in CH_3CN) (**Scheme 9**)[8]and they were characterized by NMR spectroscopy and mass spectrometry.

The deprotection of **18** and **19** was carried out using the CH_3NH_2 procedure for debenzoylation reactions[9] and the azides of the free nucleobases were obtained in good yields (80 and 95 %, respectively). The deprotection of **20**, in order to obtain the azide of the free nucleobase **23**, was done in good yields (90 %) by adapting the classic procedure for BOC removal (TFA in THF)[10] (**Scheme 9** and **10**).

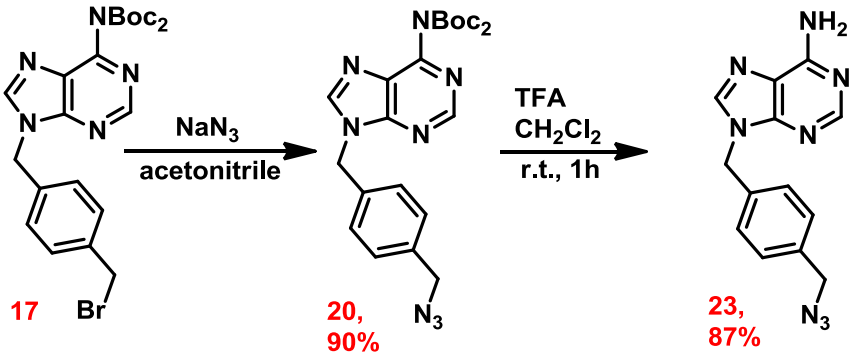
In order to increase the solubility of the reagents, the reactions of **15** and **16** with NaN_3 were carried out using DMSO as solvent[11]. Surprisingly at the end of the reaction instead of the protected azides **18** and **19**, the deprotected target compounds **21** and **22** were isolated in good yields (60 and

[8]Fedorov, A. Y.; Shchepalov, A. A.; Bolshakov, A. V.; Shavyrin, A. S.; Kurskii, Y. A.; Finet, J. P.; Zelentsov, S. V. *Russ. Chem. Bull. Int. Ed.***2004**, *53*, 370-375.
[9]Ferrer, E.; Alibés, R.; Busqué, F.; Figueredo, M.; Font, J.; March. P. *J. Org. Chem* **2009**, *74*, 2425–2432.
[10]Shendage, D. M.; Froehlich, R.; Haufe, G.; *Org. Lett.*,**2004**, *6*, 3675-3678.
[11]Alvarez, S. G.; Alvarez, M. T. *Synthesis*, **1997**,413–414.

61%, respectively) (**Scheme 9**). The excess of NaN_3 made the debenzoylation of the protected uracil and thymine units and this debenzoylation reaction is a new method for the deprotection of these two nucleobases.



Scheme 7



Scheme 8

In ^{13}C NMR spectrum of compound **18** (**Figure 8**) the 15-Cshows a signal at 54.18 ppm which is more deshielded as the signal of 15-C in the starting material. The other signals exhibit similar δ values to those of the starting material.

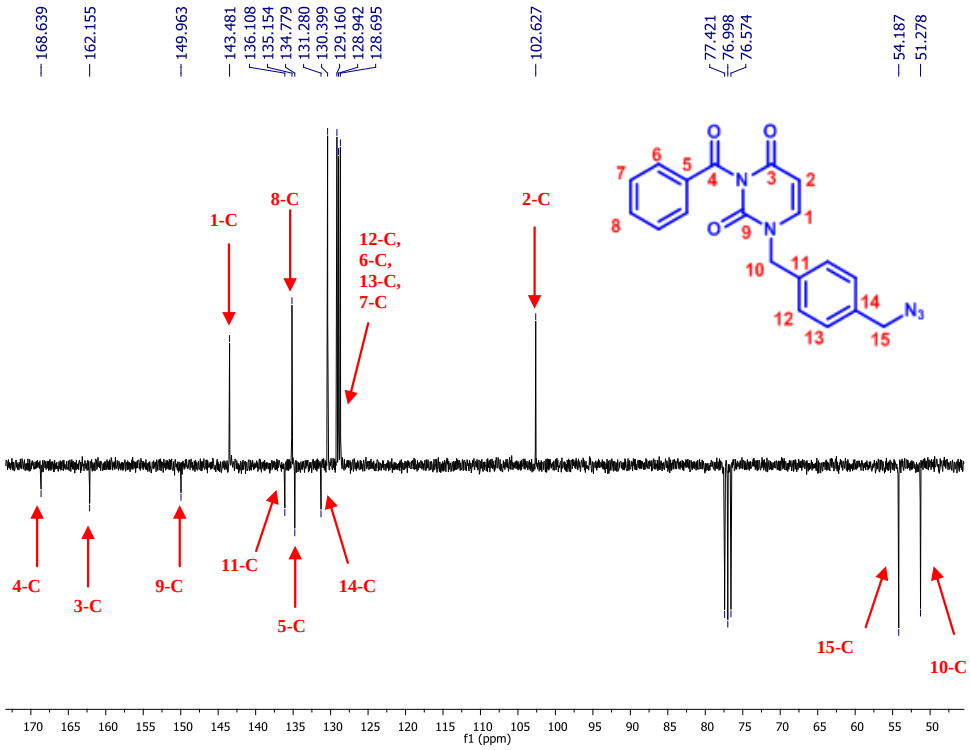


Figure 8. Fragment of ^{13}C NMR for the compound **18** (75 MHz, $CDCl_3$)

In ^{1}H NMR spectrum of compound **20** (**Figure 9**) the signal for protons 21-H is at 4.32 ppm and it is more deshielded than the signal of the similar proton of the starting material. The signals belonging to the protons 18-H and 19-H in the starting material are two doublets, but in compound **20** their signal is a singlet at 7.29 ppm. The other signals are similar to those of the starting material.

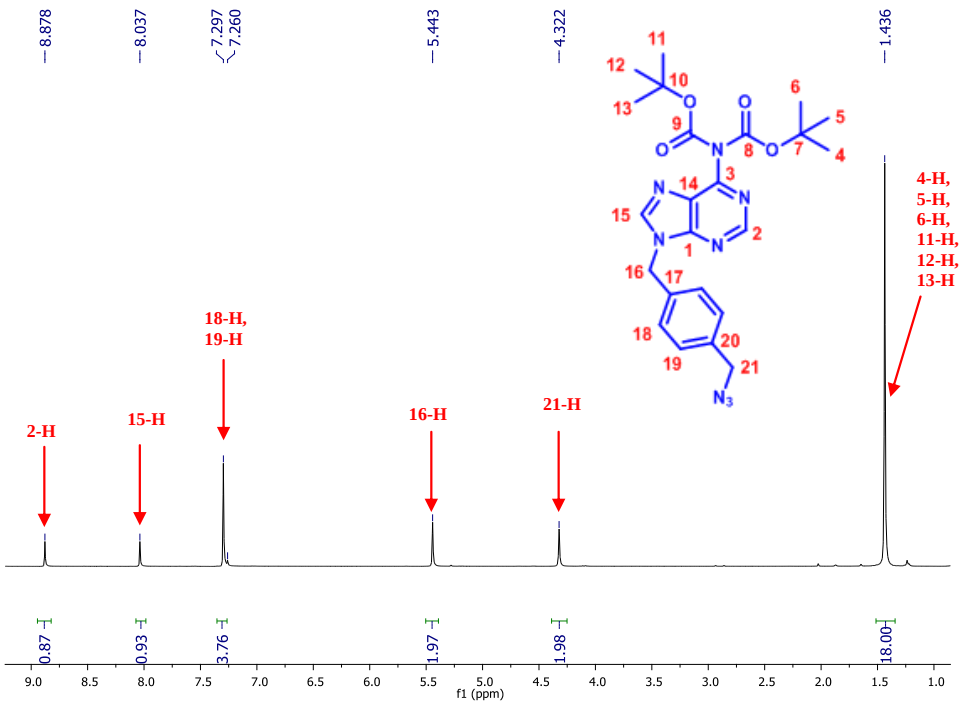


Figure 9. Fragment of ^{1}H NMR for the compound **20** (300 MHz, $CDCl_3$)

Crystals for X-Ray diffraction were obtained by slow evaporation from chloroform of **20**. DIAMOND diagram showing the molecular structure of compound **20** is presented in **Figure 10**.

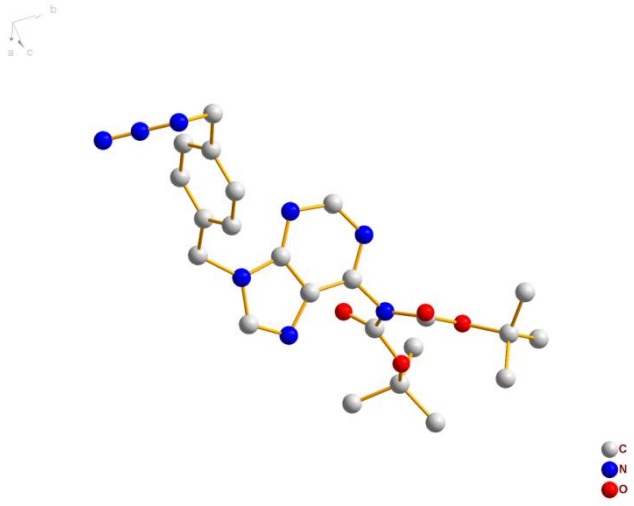


Figure 10. DIAMOND diagram of compound **20** (Hydrogen atoms are removed for clarity)

In **Figure 11** is shown the packing pathern of **20** which forms a network with a *zigzag* arrangement of the molecules.

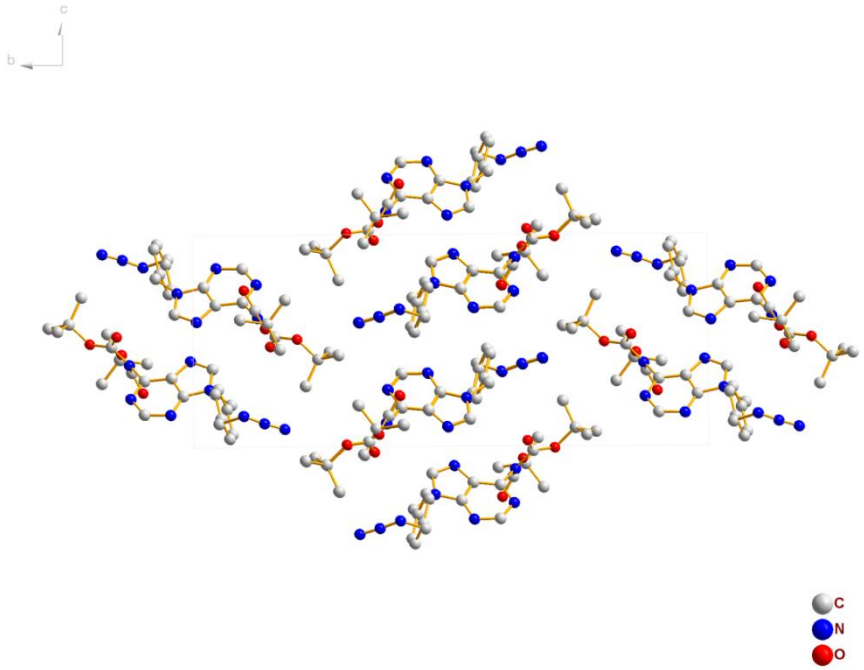


Figure 11. Molecular packing of compound **20** (Hydrogen atoms are removed for clarity)

In the proton spectrum of compound **22 (Figure 12)** appear all the expected signals; we noticed at 11.35 ppm the signal for the -NH group and for the 8-Hand 9-Hwe have found an AB system (δ= 7.30 and 7.35 ppm, respectively).

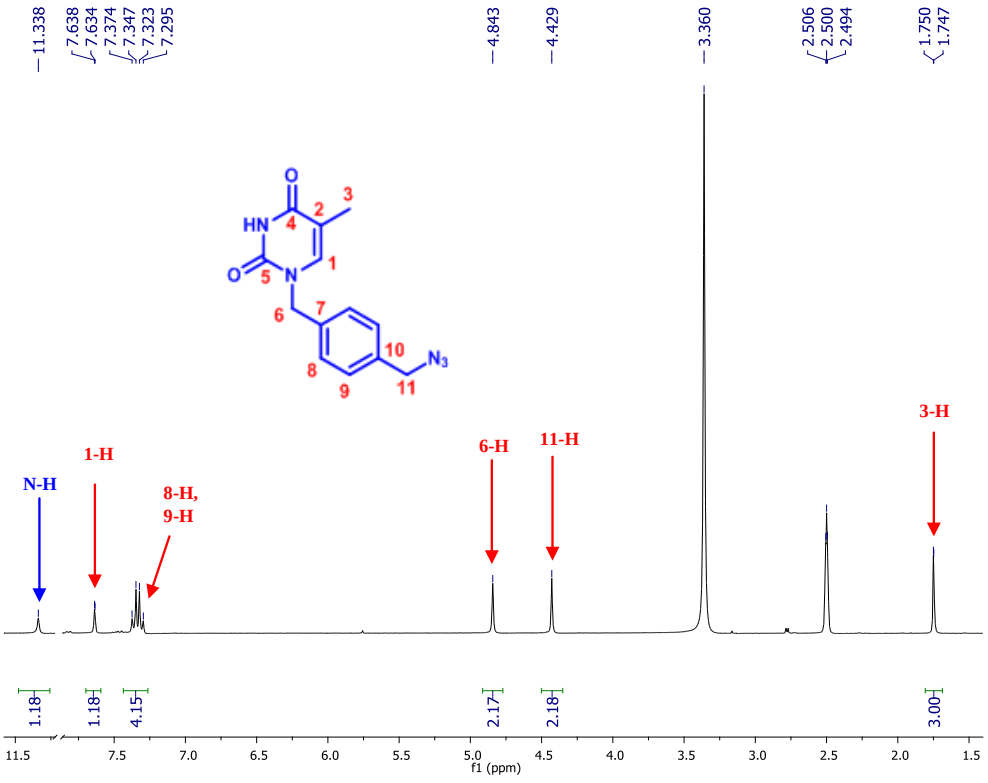


Figure 12. Fragment of ^{1}H NMR for the compound **22** (300 MHz, DMSO-d_6)

In the **Figure 13** is presented the ^{13}C NMR spectrum of compound **23.** In this spectrum we indentified all the signals for the proposed structure.

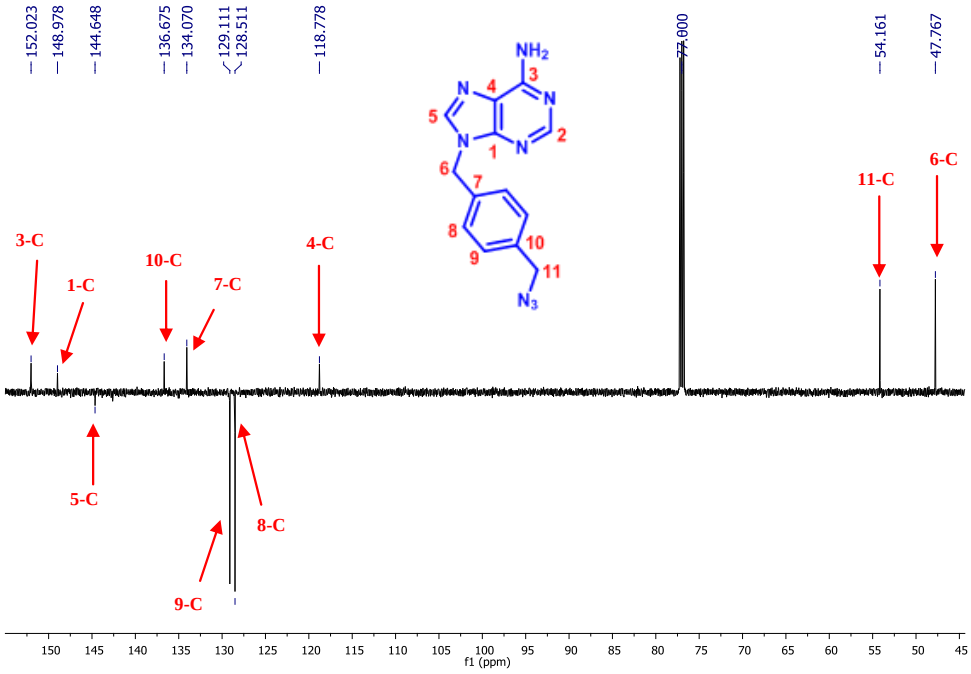
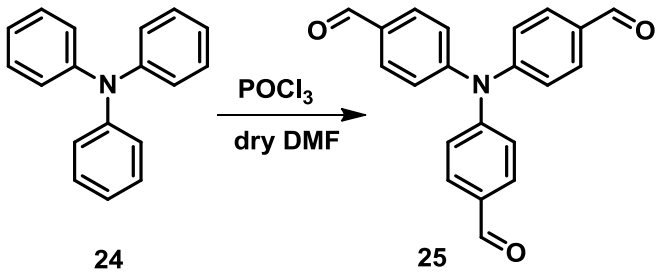


Figure 13. Fragment of ^{13}C NMR for the compound **23** (150 MHz, $CDCl_3$)

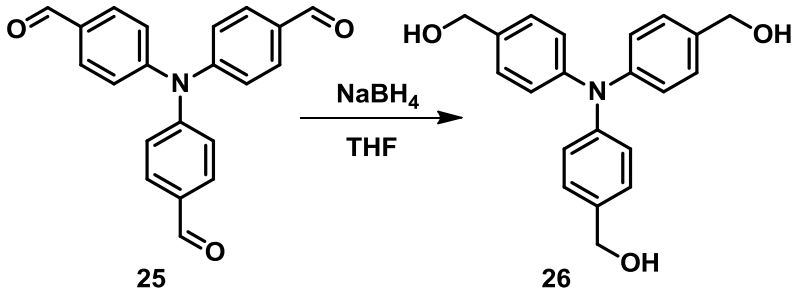
After we obtained the decorated nucleobases, the next step to achieve the target molecules was to synthesized the tripodands with triple terminals bonds. The first step was to obtained the compound **25** (**Scheme 11**) by a double Vilsmeier-Haak reaction formylation. Compound **25** was obtained according to literature data[12] and its structures was confirmed by NMR spectroscopy.

[12]Mallegol, T.; Mough, S.; Mezziane, M. A. A.; Blanchard, D. M.; Mongin, O.*Synthessis* 11, **2005**, 1771-1774.



Scheme 9

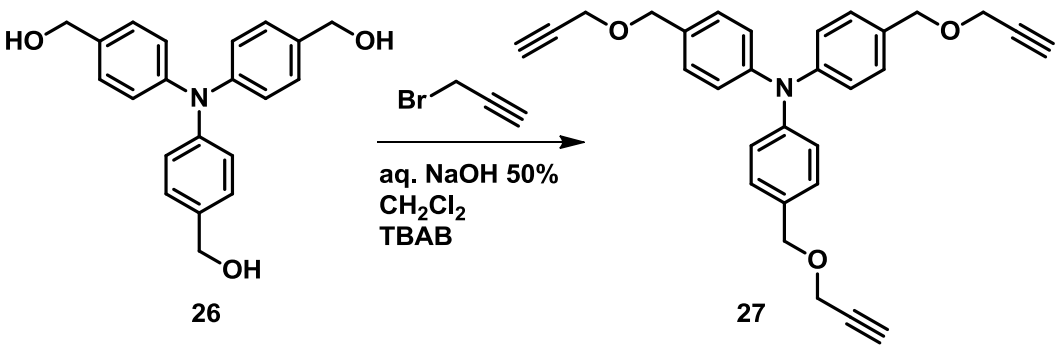
The next step was to obtain compound **26** by a reduction reaction of compound **25** with $NaBH_4$ in THF (**Scheme 12**). The structure of this compound was analyzed using NMR spectroscopy and it was in concordance with literature data[13].



Scheme 10

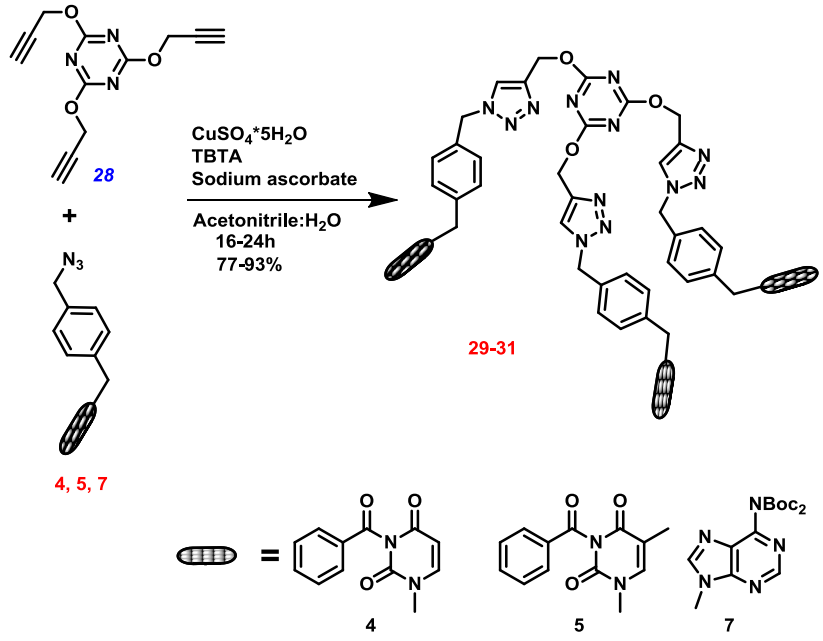
In order to obtain the tripodands with terminal triple bonds (**Scheme 13**) we disolved the compound **26** in CH_2Cl_2 and we add a solution ofpropargyl bromide 80% in toluene, TBAB and a solution of NaOH 50%.Compound **27** was obtained in good yield and the structure of it was confirmed by NMR spectroscopy[14].

[13]Borch, R.F.; Liu, J.; Schmidt, J.P.; Marakovitz, J.T.; Joswig, C.; Gipp, J.J.; Mulcahy, R.T.*J. Med Chem* 43,**2000**, 2258-2265.
[14]Bogdan, N. D.; Matache, M.; Meier, V. M.; Dobrota, C.; Dumitru, I.;. Roiban, G. D; Funeriu, D.P., *Chem. Eur. J*, **2010,** 2170-2180.



Scheme 11

The next step to obtain the desired compounds was the reaction between the protected nucleobases (**21-23)** and the terminal alkyne **28** (**Scheme 14**). These reactions were made with $CuSO_4*5H_2O$, TBTA and sodium ascorbate in CH_3CN and H_2O. The reaction mixtures were stirred at room temperature overnight. These compounds were obtained as white precipitates and were isolated in good yields (77-93%) by filtration.



Scheme 12

^{1}H NMR fragment of compound **29** is presented in **Figure 14**. The singlets for the CH_2 protons appear at 4.93 ppm, 5.46 and 5.60 ppm respectively. The signals for the protons of protected group appear as a doublet at 7.93 ppm and two triplets, at 7.57 ppm and 7.76 ppm, respectively. The other doublets corresponding to the protons of the uracil moiety were found at 5.88 and 8.00 ppm, respectively. The signal for 12-H and 13-H appears like a singlet at 7.33 ppm and the signal for 16-H

is observed as a singlet at 8.32 ppm. The spectrum confirms that we have obtained the desired compound.

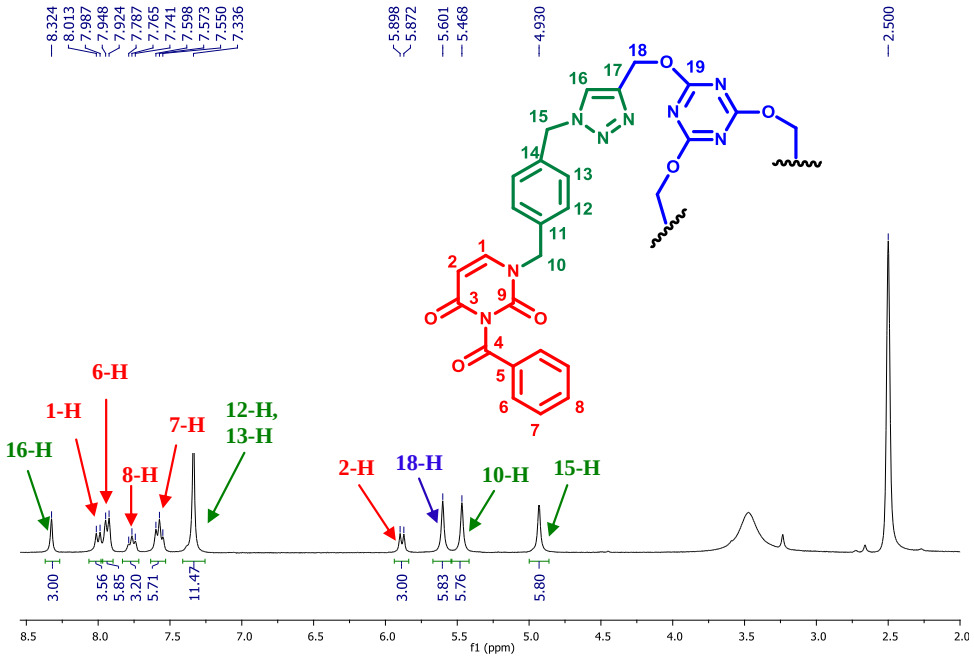


Figure 14. Fragment of ^{1}H NMR for the compound **29** (300 MHz, DMSO-d_6)

The ^{1}H NMR spectrum of compound **30** (**Figure 15**) shows in the aliphatic region the following signals: one singlet at 1.81 ppm for the CH_3 group, three signals for the CH_2 groups at 4.89 ppm, 5.60 ppm and 5.60 ppm, respectively. The signal for 13-H and 14-H appearsas a singlet at 7.33 ppm. In the aromatic region, at 7.57 ppm , 7.76 and 7.91 respectively there are three triplets for 8-H, 9-H, 1-H and 7-H. The most deshielded signal, at 8.32 ppm, is a singlet corresponding to 17-H.

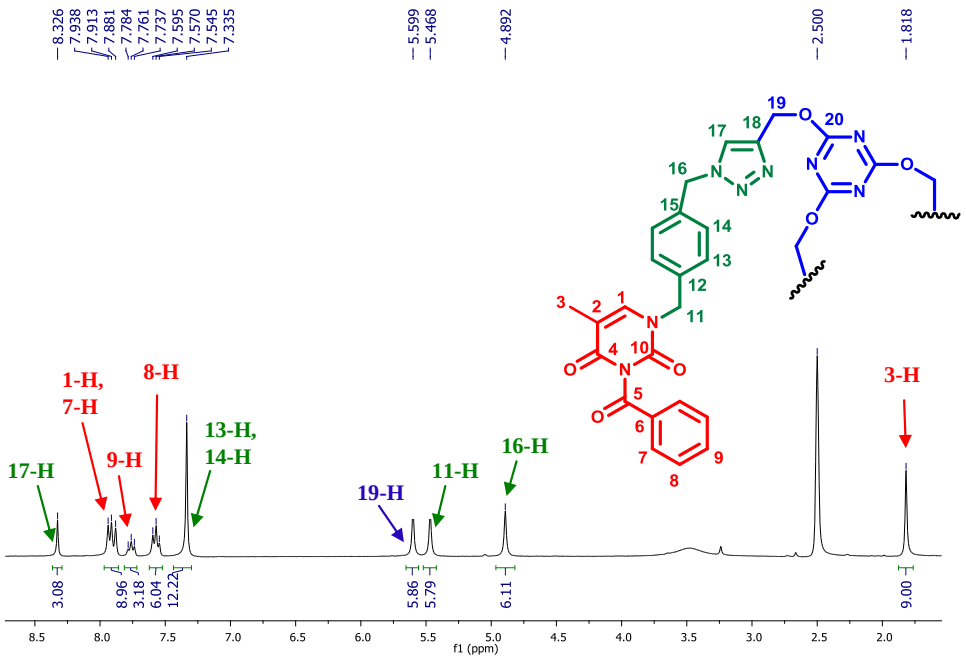


Figure 75. Fragment of ^{1}H NMR for the compound **30** (300 MHz, DMSO-d_6)

^{1}H NMR spectrum of compound **31**, recorded in DMSO-d_6, shows the expected signals (**Figure 16**): one singlet for CH_3 group at 1.44 ppm , two singlets for CH_2 groups at 5.45 and 5.50 ppm andin the aromatic region the spectrum exhibits in additionan AB system (7.27 and 7.29 ppm) for 18-H and 19-H and three singlets (7.65 ppm, 8.07 and 8.77 ppm) for 22-H, 15-H and 2-H.

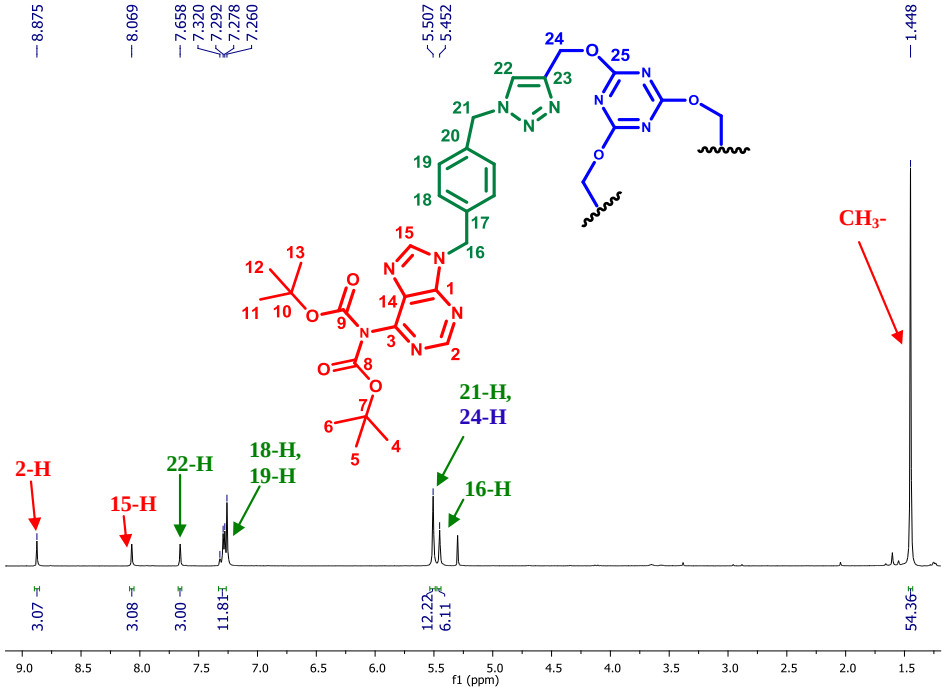
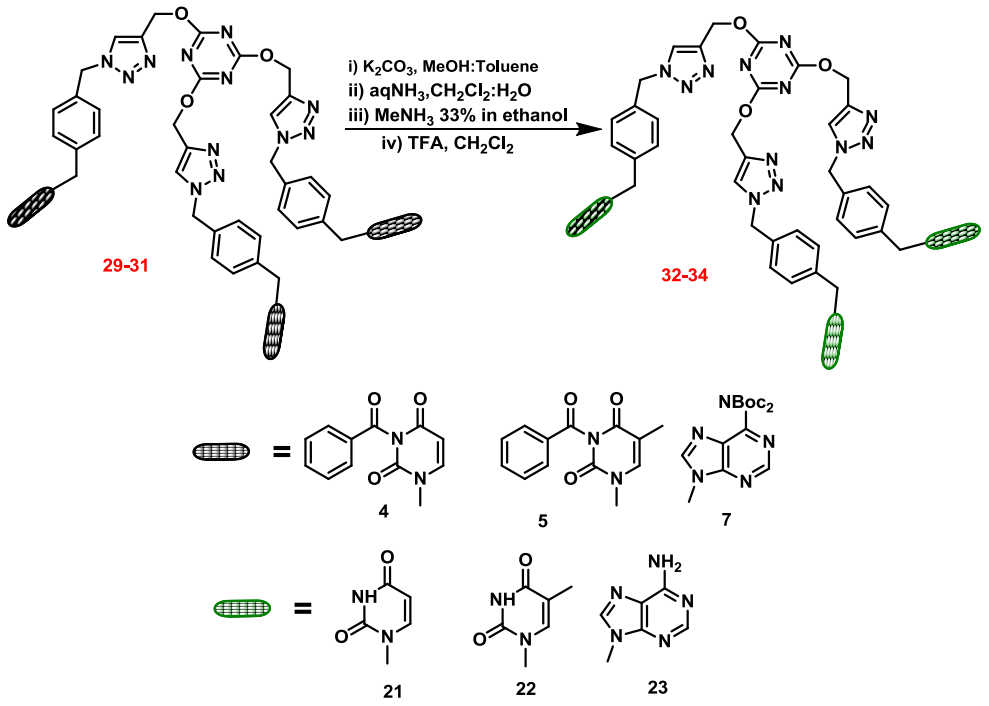


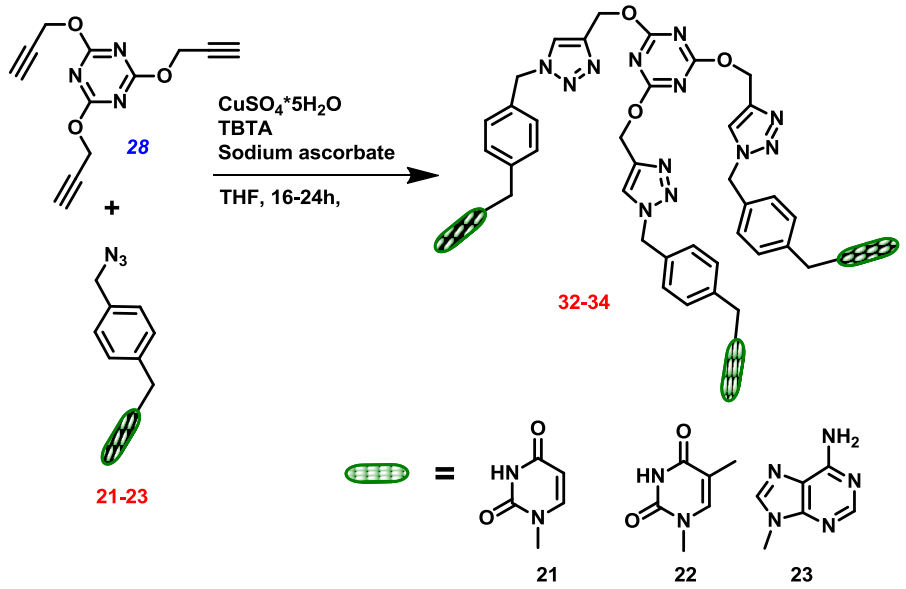
Figure 16. Fragment of ^{1}H NMR for the compound **31** (300 MHz, DMSO-d_6)

Another step to access the target compounds was the nucleobase units deprotection. In the cases of the compounds with uracil and thymine units we tried three methodes of deprotection. The first two methods used K_2CO_3 in MeOH and toluene (**Scheme 15-i**) and aqueous NH_3 in CH_2Cl_2 and H_2O, respectively (**Scheme 15-ii**). In these cases we didn't obtained the deprotected compounds and we recovered just the starting materials. We tried the deprotection with $MeNH_3$ 33% in ethanol but the deprotected compounds were obtained in low yields (**Scheme 15-iii**). The deprotection in the case of the compound with adenine units was made with TFA in CH_2Cl_2 and we obtained the deprotected compound in quantitative amount (**Scheme15-iv**).



Scheme 13

Because we obtained compounds **32-34** in low yields the strategy was changed. We tried to obtain compounds **32-34** starting from deprotected nucleobases (**21-23, Scheme 16**) and tripodand **28** using the reaction with $CuSO_4*5H_2O$, TBTA and sodium ascorbate in THF. Compounds **32-34** were obtained as precipitates, in good yields (70-75%).



Scheme 14

The relevent fragment of the ^{1}H NMR spectrum of compound **32** is presented in **Figure 17**. The singlets for the CH_2 protons appear at 4.84 ppm and 5.45 ppm. The more deshielded siglet is overlapped with the doublet belonging to 2-H of the uracil moiety at 5.57 ppm. The other doublet corresponding to the protons of uracil unit is observed at 7.72 ppm. The signals for 7-H and 8-H appear like an AB system (7.27 and 7.31 ppm) and the signal for 11-H is observed as a singlet at 8.32 ppm.

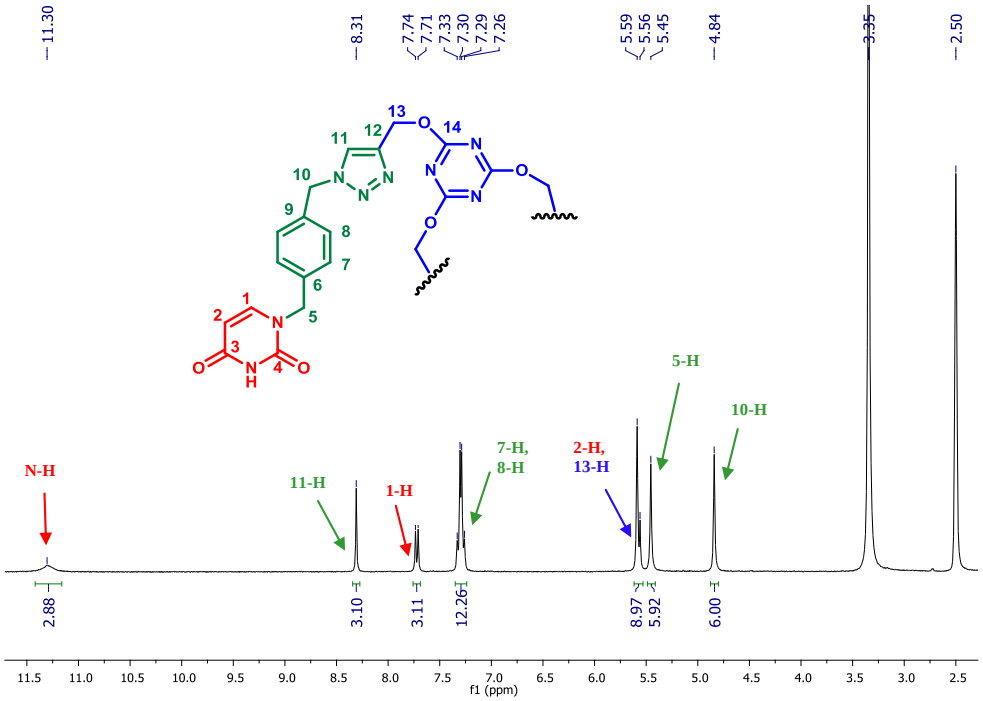


Figure 17. Fragment of ^{1}H NMR for the compound **32** (300 MHz, DMSO-d_6)

In the mass spectrum, HRMS, of compound **32** (**Figure 18**) the corresponding peaks for the protonated dimer and for it's complexes with Na^+ and K^+ are observed at *m/z* 2030.6885, at *m/z* 2051.6672 and *m/z* 2068.6436, respectively.

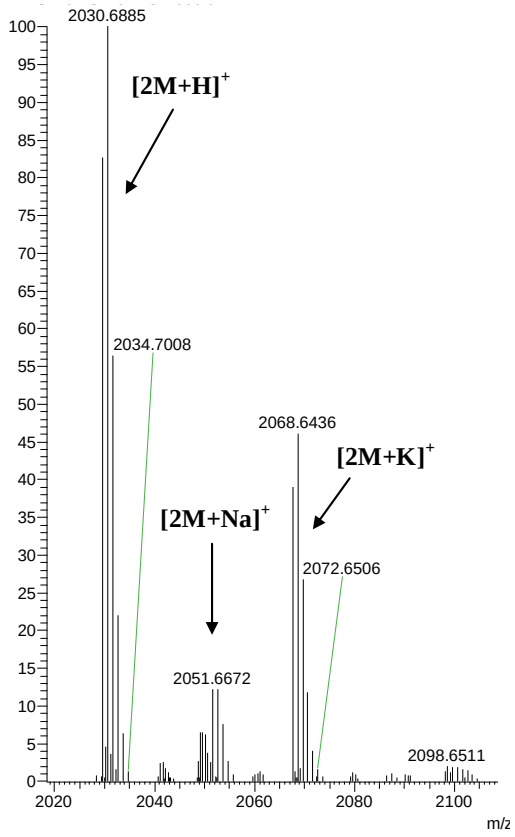


Figure 18. Fragment of ESI^+ of compound **32**

The ^1H NMR spectrum of compound **33** (**Figure 19**) shows the following signals: one singlet at 1.72 ppm for the CH_3 group and three singlets for the CH_2 groups at 4.80 ppm, 5.45 ppm and 5.58 ppm respectively. The signal for 8-H and 9-H appears like a singlet at 7.33 ppm. In the aromatic region, a singlet at 7.58 ppm for 1-H and 7-H is observed. The more deshielded signal, at 8.30 ppm, is a singlet corresponding to 12-H.

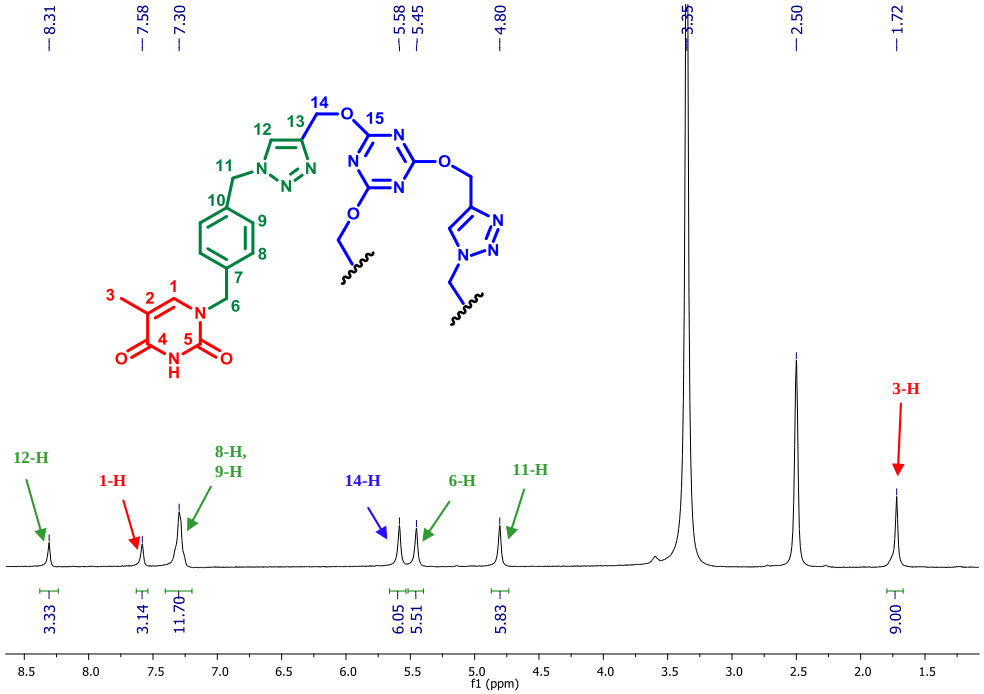


Figure 19. Fragment of ^{1}H NMR for the compound **33** (300 MHz, DMSO-d_6)

Mass spectrum, HRMS, of compound **33** (**Figure 20**) shows the corresponding signals for the protonated dimer and for the complex with K^+ at *m/z*:2114.7814 and *m/z*: 2152.7383, respectively.

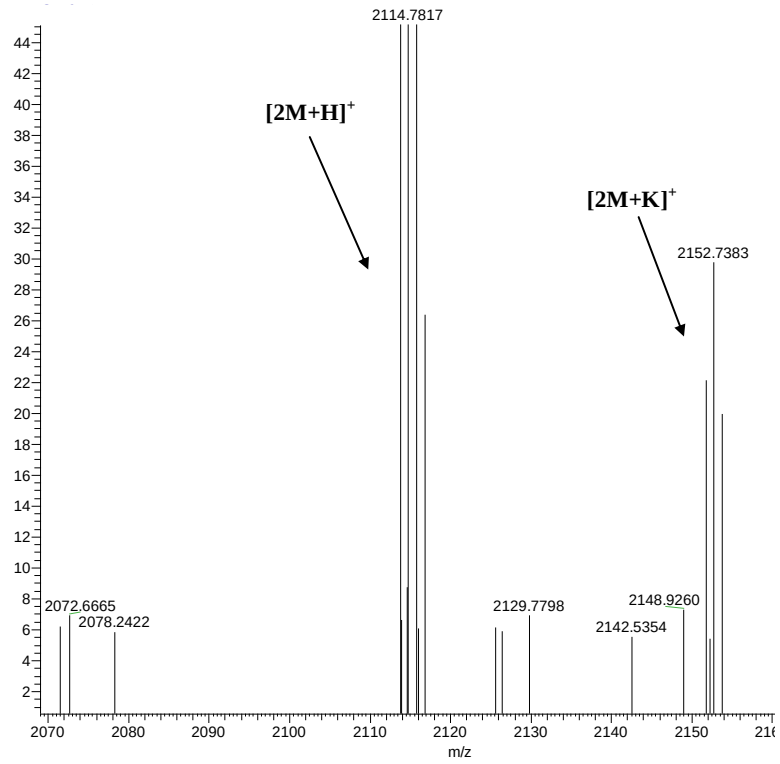


Figure 20. Fragment of ESI^+ of compound **33**

^1H NMR spectrum of compound **34**, recorded in DMSO-d_6 shows the expected signals (**Figure 21**): three singlets for the CH_2 groups at 5.38 ppm, 5.44 and 5.57 ppm, respectivelyand in the aromatic region one can see an AB system (7.29 and 7.31 ppm) for 8-H and 9-H and three singlets (8.22 ppm, 8.28 and 8.34 ppm) for 12-H, 5-H and 2-H.

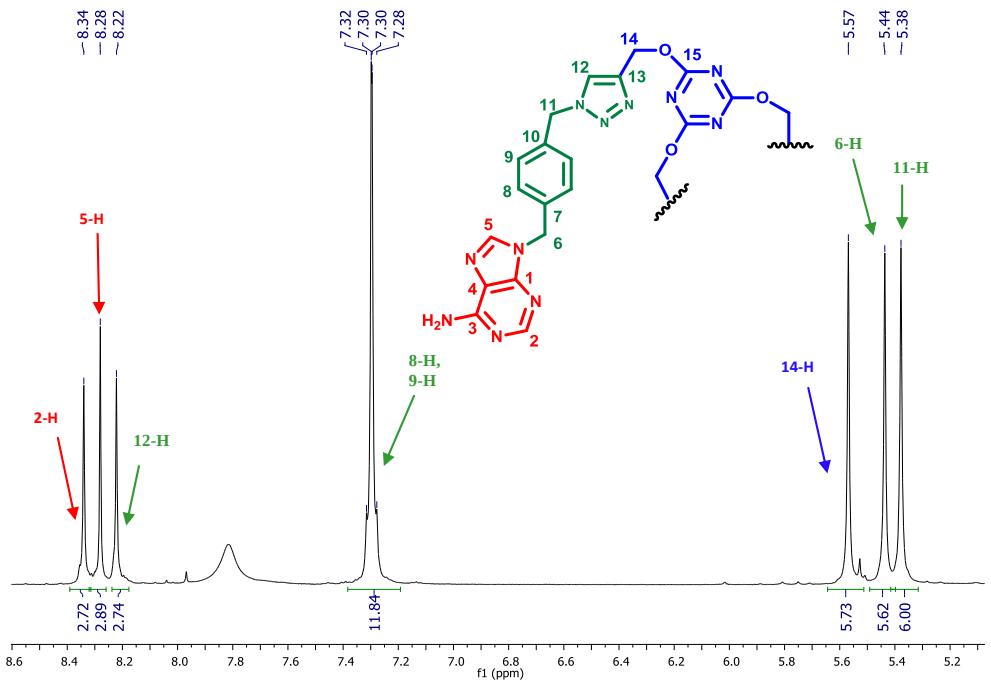


Figure 21. Fragment of ^{1}H NMR for the compound **34** (300 MHz, DMSO-d_6)

In the mass spectrum, HRMS, of compound **34** (**Figure 22**) the signal for protonated compound at *m/z*:1084.4324 is observed.

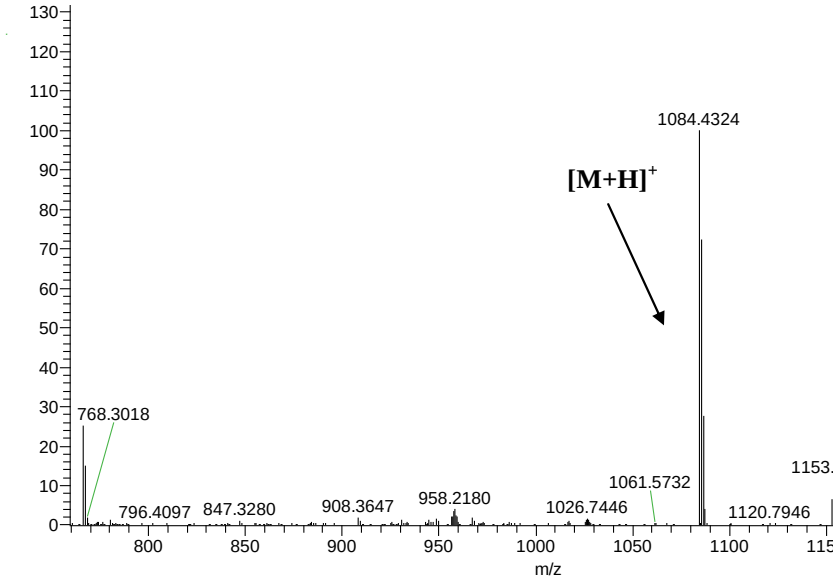
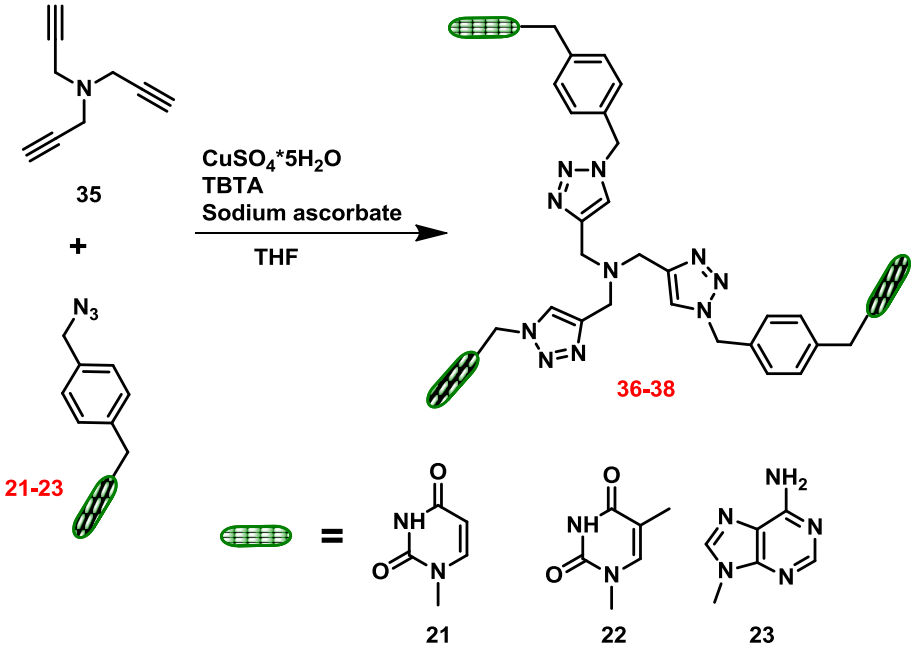


Figure 22. Fragment of ESI^{+} of compound **34**

Podand **35** and the same nucleobases were also used in "click reaction" **(Scheme 17**). Compounds **36-38** were obtained in good yields as precipitates and they were fully characterized by NMR spectroscopy and mass spectrometry.



Scheme 15

A fragment of the ^{1}H NMR spectrum of compound **36** is presented in **Figure 23**. Two of the singlets for the CH_2 protons appear at 3.34 ppm and 4.84 ppm. The third singlet for CH_2 group is overlapped with the doublet belonging to 2-H of the uracil unit at 5.57 ppm. The other doublet corresponding for the protons of uracil moiety exhibits a signal at 7.72 ppm. The signal for 8-H and 9-H appears like a singlet at 7.27 ppm and the signal for 11-H is observed as a singlet at 8.05 ppm. The ^{1}H NMR spectrum prouved that we obtained the desired compound. The singlet for the –NH group is found at 11.33 ppm.

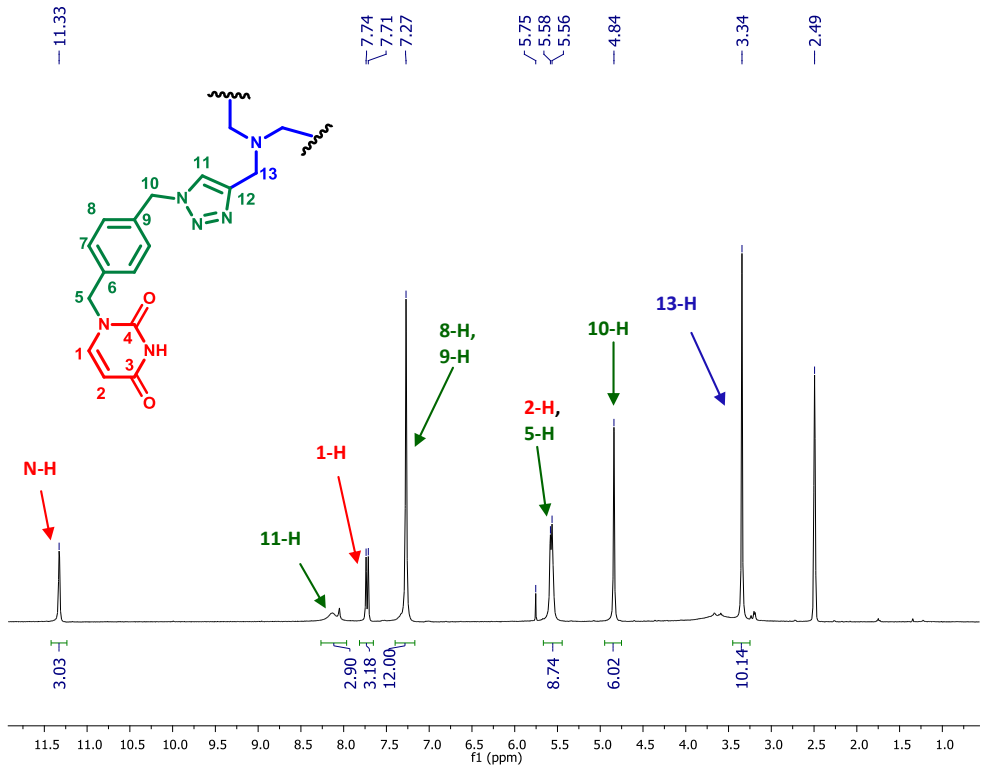


Figure 23. Fragment of ^{1}H NMR for the compound **36** (300 MHz, DMSO-d_6)

The mass spectrum of compound **36** is presented in **Figure 24**: in this spectrum we noticed the peak corresponding for the protonated dimer at *m/z*:1806.71.

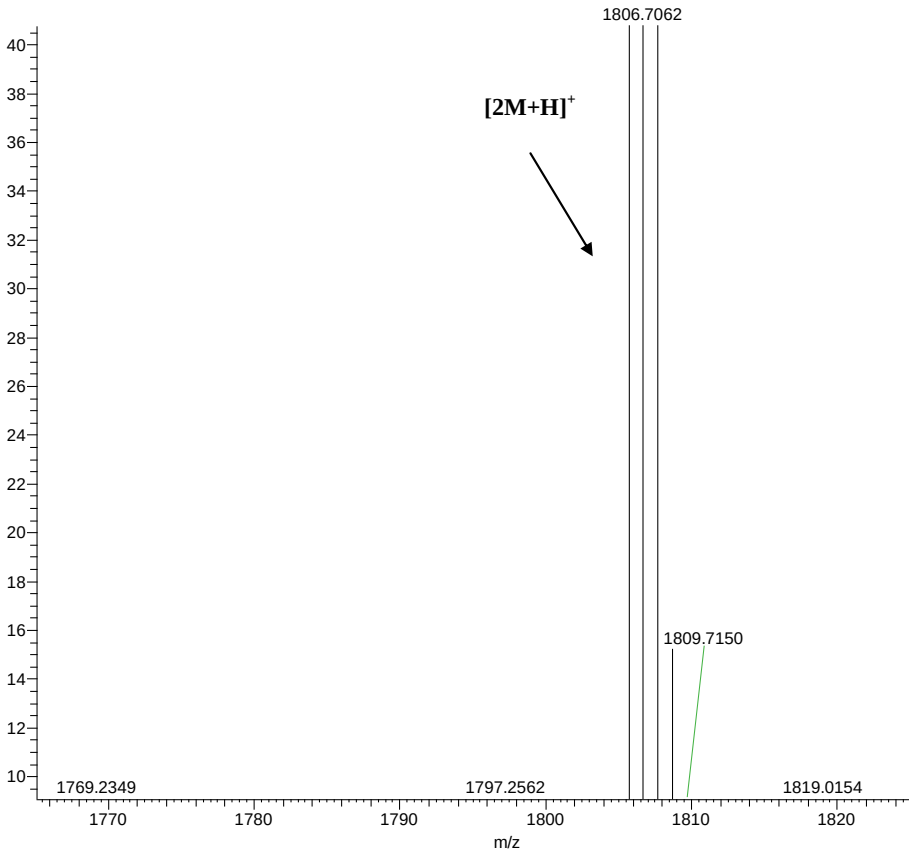


Figure 24. Fragment of ESI^+ of compound **36**

The ^1H NMR spectrum (**Figure 25**) of compound **37** shows the following signals in the aliphatic area: one singlet at 1.72 ppm for the CH_3 group and three signals for the CH_2 groups at 3.59 ppm, 4.80 ppm and 5.56 ppm respectively. The signal for 8-H and 9-H appears like a singlet at 7.27 ppm. In the aromatic region, at 7.59 and 8.08 ppm, respectively the spectrum exhibits two singlets for 1-H and 12-H. The more deshielded signal, at 11.32 ppm, is a singlet corresponding to NH proton.

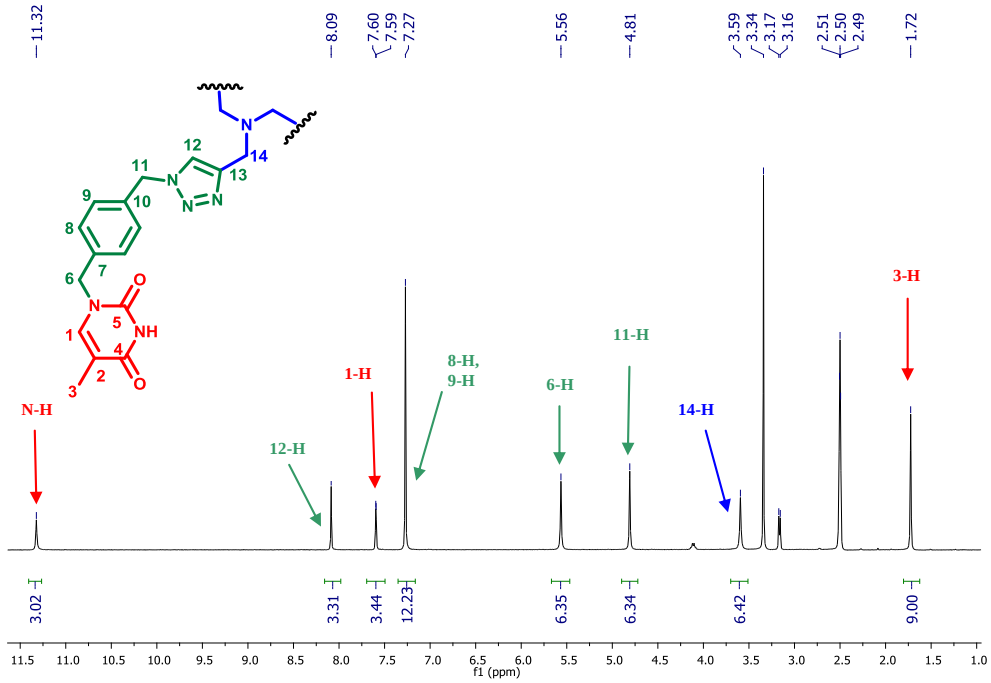


Figure 25. Fragment of ^{1}H NMR of compound **37** (300 MHz, DMSO-d_6)

The ^{1}H spectrum of compound **37**, recorded in DMSO-d_6, shows the expected signals (**Figure 26**): three singlets for protons of CH_2groups at 4.40 ppm, 5.37 ppm and 5.58 ppm and in the aromatic region the spectrum exhibits three singlets at 7.32 ppm, 8.13 ppm and 8.25 ppm.

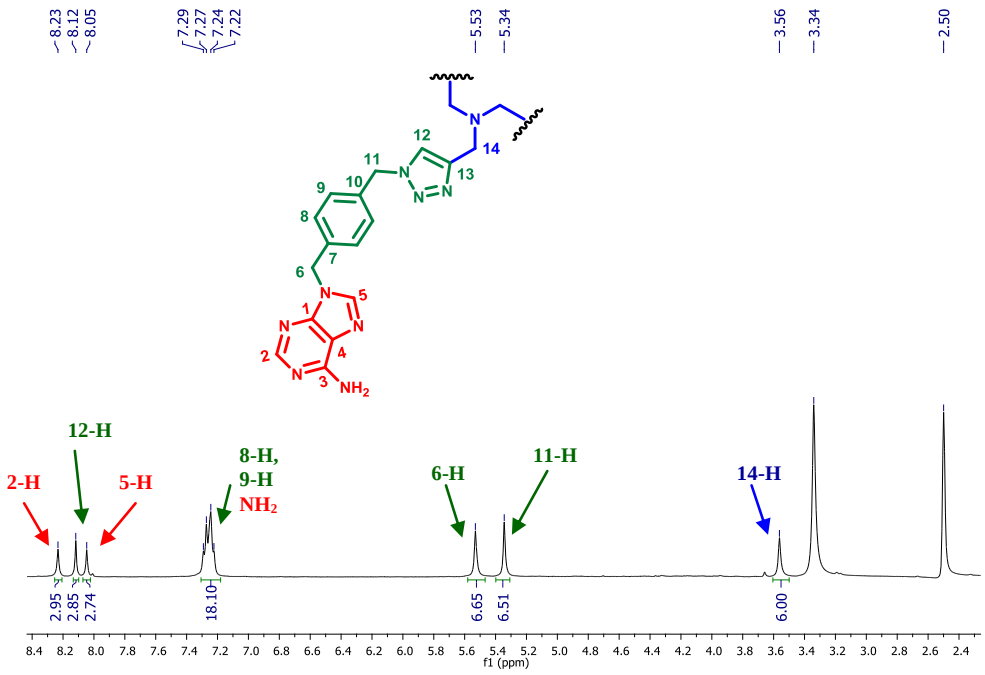
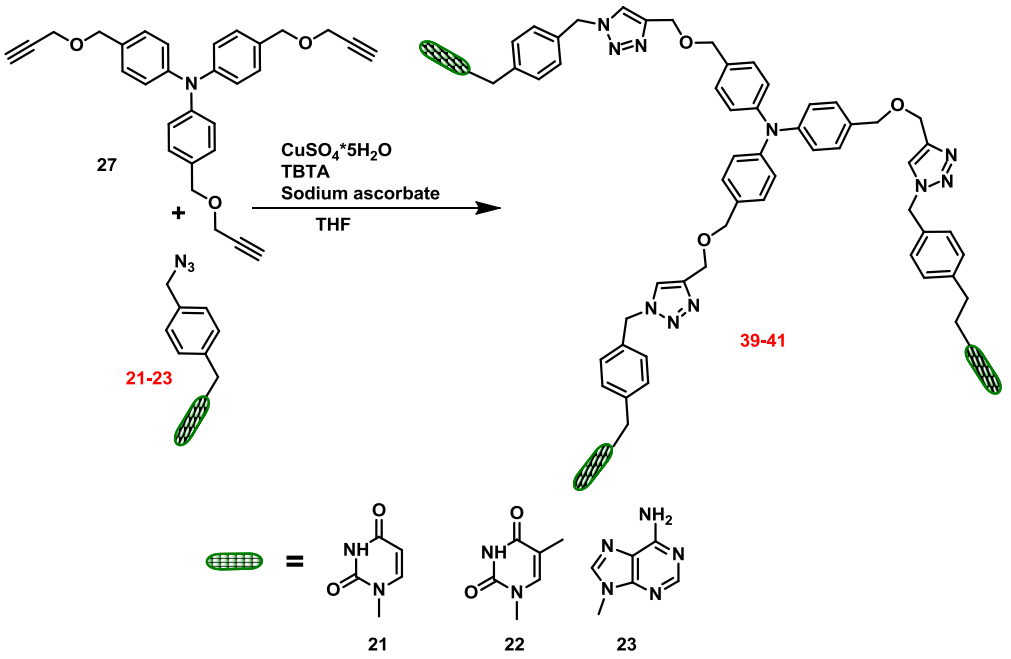


Figure 26. Fragment of ^{1}H NMR of compound **37** (300 MHz, DMSO-d_6)

The last podand used to obtained the target host molecules was compound **27** (**Scheme 18**). The nucleobases decorated compounds **39-41** were obtained in good yields as precipitates and were fully characterized by NMR spectroscopy and mass spectrometry.



Scheme 16

A fragment of ^{1}H NMR of compound **39** is presented in **Figure 27**. Three of the singlets belonging to the CH_2 protons appear at 4.44 ppm, 4.54 ppm, 4.83 while the fourth one is overlapped with the doublet of 2-H of the uracil unit at 5.56 ppm. The other doublet corresponding for the protons of uracil is observed at 7.71 ppm. The signal for 7-H, 8-H and 16-H is a multiplet at 7.28 ppm. For 17-H a doublet at 6.94 ppm and for 11-H a singlet at 8.18 ppm are observed. The singlet for the –NH group appears at 11.32 ppm.

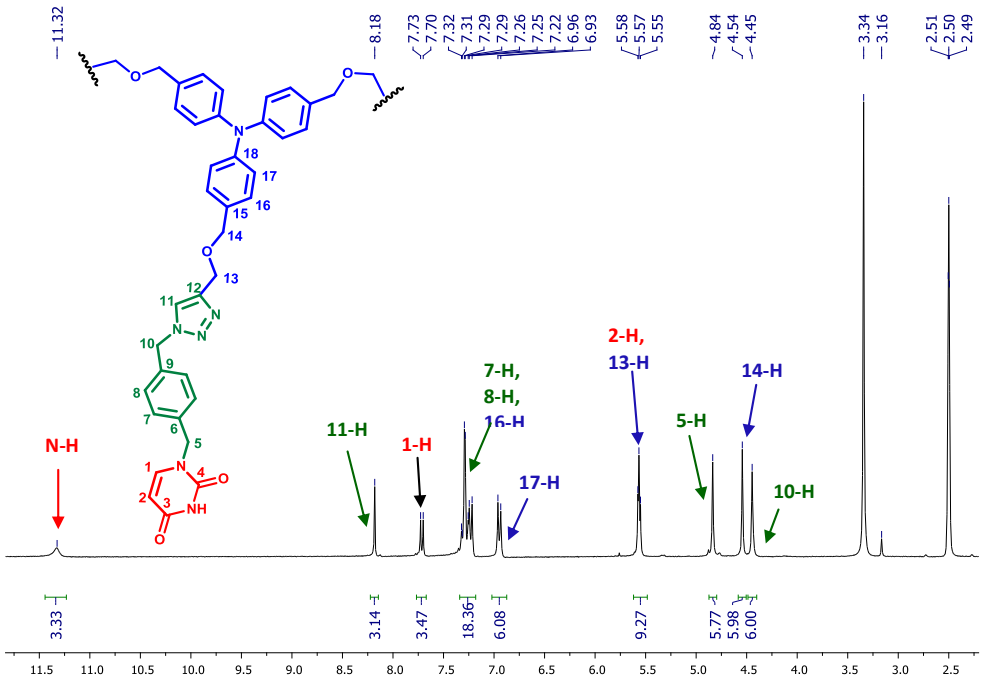


Figure 27. Fragment of ^{1}H NMR for the compound **39** (300 MHz, DMSO-d_6)

The mass spectrum, HRMS, of compound **39** (**Figure 28**) shows the corresponding peak for the protonated dimer at *m/z*:2442.9482.

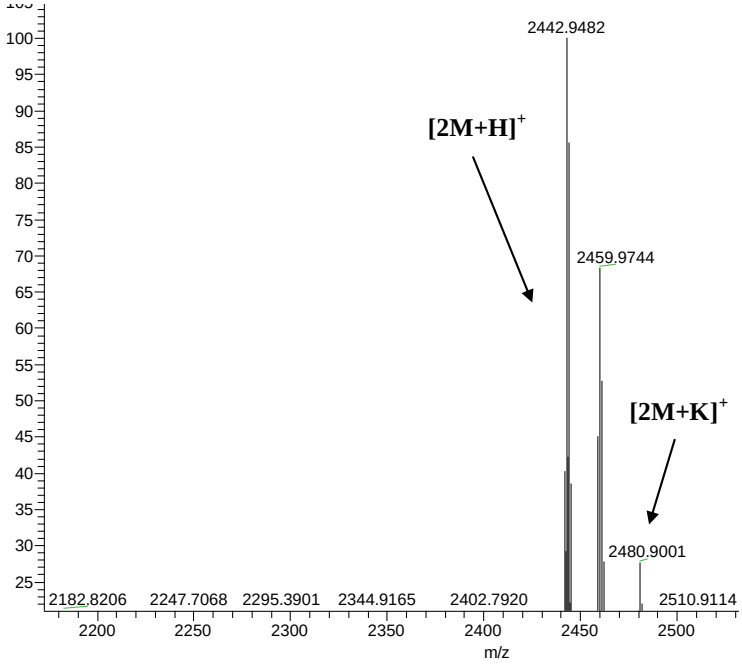


Figure 28. Fragment of ESI^{+} of compound **39**

The ^{1}H NMR spectrum of compound **40** shows the following signals (**Figure 29**): one singlet at 1.72 ppm for the CH_3 group, four signals for the CH_2 group at 4.45 ppm, 4.50 ppm, 4.80 ppm and

5.56 ppm respectively. The signals for 17-H and 18-H appear as two doublets at 6.95 and 7.23 ppm respectively. In the aromatic region, at 7.28 ppm and 7.30 ppm an AB system corresponding to protons 8-H and 9-H is observed. Two singlets , at 7.58 ppm and 8.18 ppm were recordedfor 1-H and 12-H. The most deshielded signal, at 11.31 ppm, is a singlet corresponding to the NH proton.

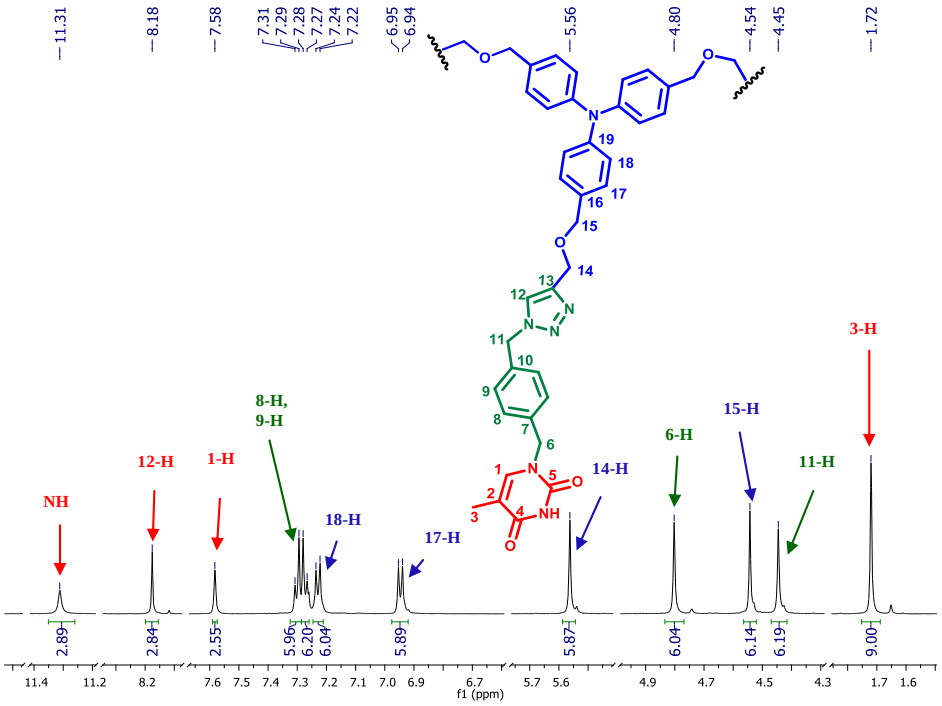


Figure 29. Fragment of ^{1}H NMR for the compound **40** (300 MHz, DMSO-d_6)

^{1}H NMR spectrum of compound **41**, recorded in DMSO-d_6 shows the expected signals (**Figure 30**): four singlets for the CH_2 groups at4.43 ppm, 4.53 ppm, 5.34 and 5.54 ppm respectively and in thearomatic region one can see an AB system (6.94 and 7.22 ppm) for 17-H and 18-H and two singlets (7.27 ppm and 8.15 ppm) 8-H, 9-H and 12-H.

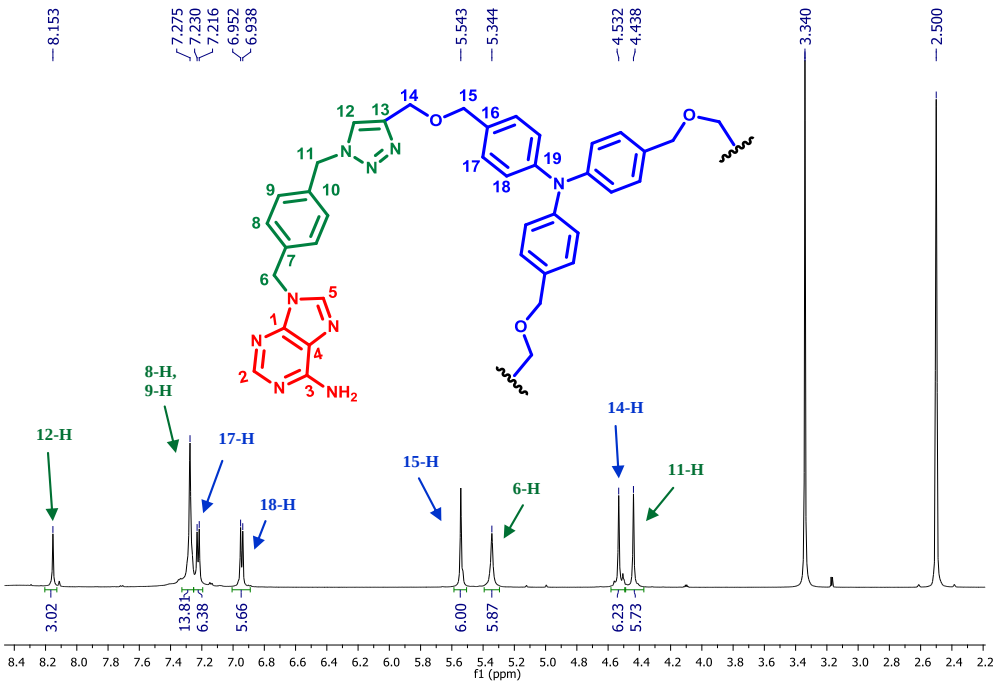


Figure 30. Fragment of ^{1}H NMR for the compound **41** (600 MHz, DMSO-d_6)

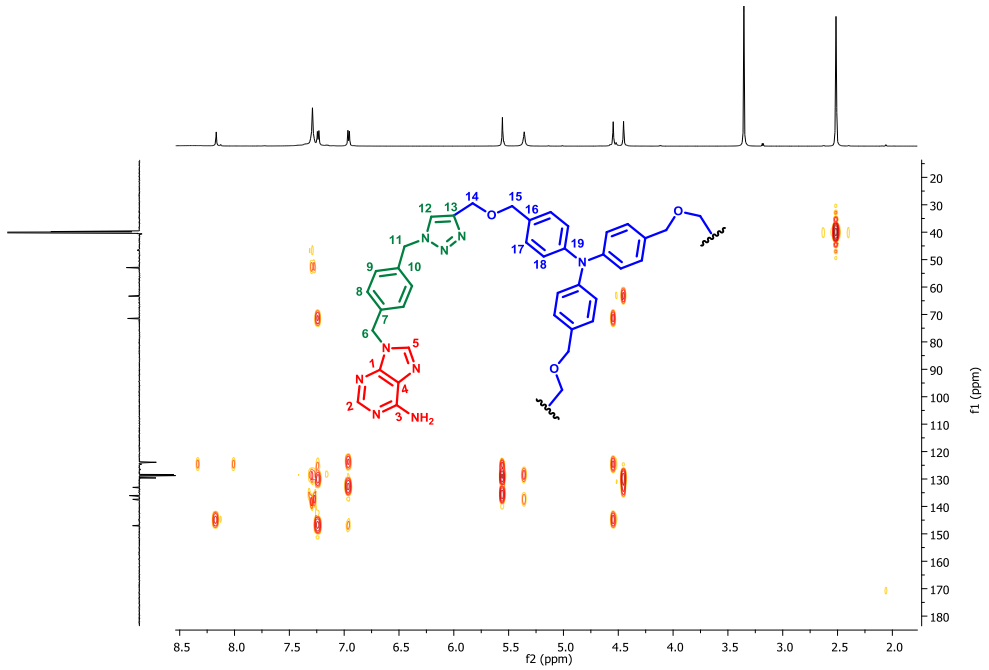


Figure 81. HMQC spectrum of compound **41**

3.3 CONCLUSIONS

Eleven new compounds decorated with nucleobases (compounds **10**, **11a**, **15**, **16**, **17**, **18**, **19**, **20**, **21**, **22** and **23**) were obtained. They were analyzed and fully characterized by NMR spectroscopy and Mass spectrometry.

An efficient method for the synthesis of new azido-functionalized nucleobases which contain a low flexible linker between the azido group and the nucleobase unit was developed. The method allows concomitant bromine-azide substitution and benzoyl deprotection. This is the first reported successful result of azide mediated deprotection of *N*-benzoyl protected nucleobases (i.e. uracil and thymine).

Twelve new compounds (**29**, **30**, **31**, **32**, **33**, **34**, **36**, **37**, **38**, **39**, **40** and **41**) we synthesized using "click reaction". They were fully characterized by NMR spectroscopy and Mass spectrometry. Further studies regarding H-bonding are running.

PART B – SOME NEW SPIRO [1,3]-OXATHIANES

2. ORIGINAL CONTRIBUTIONS

2.1 RESULTS AND DISCUSSIONS

We have investigated different heterocyclic compounds which can be obtained from reactions between $(HO\text{-}CH_2)_2C(CH_2\text{-}SH)_2$ with several aldehydes.

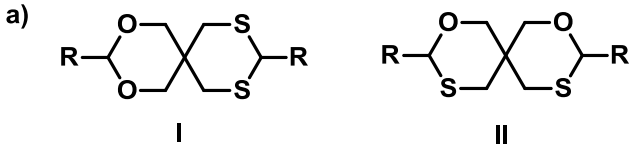
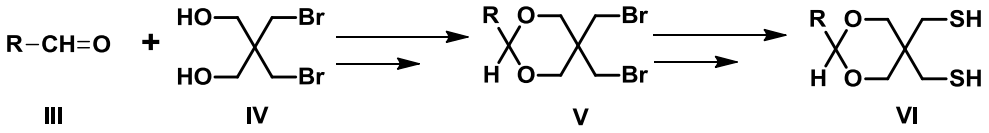


Figure 32. Target symmetrically substituted 1,3-dioxane-1,3-dithiane (I)and bis(1,3-oxathiane (**II**) compounds

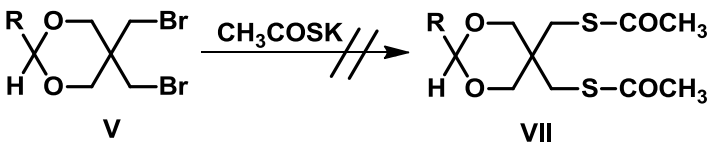
Our initial interest was the obtaining and isolation of symmetrically substituted derivatives of types II (**Figure 32**) and their structural analysis using NMR spectroscopy, mass spectrometry and molecular modeling[15].

In order to have a rapid access to compounds of type I in the absence of compounds II we have tried to obtain the intermediates **VI** starting from compounds of type **III** and **IV** (**Scheme 19**), but these attempts proved to be unsuccessful, so the synthetic strategy needed to be changed.



Scheme 19

The intermediates were obtained by acetalization reaction[16]. In the final step we could not change the bromine with sulphur atom (**Scheme 20**) and this synthetic strategy needed to be changed.



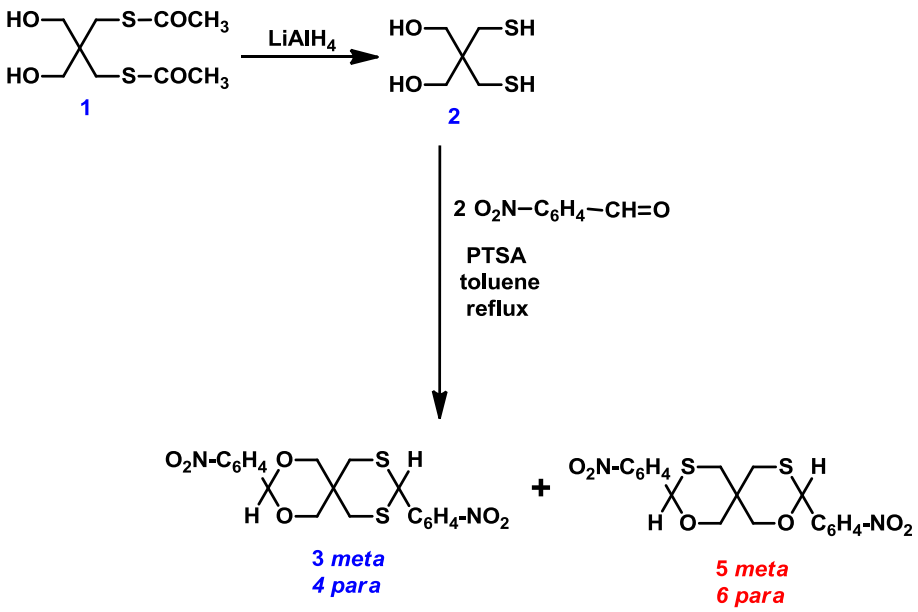
Scheme 20

[15]Mihis, A.; Golban, L. M.; Rat, C. I.; Bogdan, E.; Terec, A.; Grosu, I. *Struct. Chem.*, **2012**, *23*, 61-69.

[16]Mihis, A.; Golban, L. M.; Bogdan, E.; Terec, A.; Grosu, I. *Stud. Univ. Babes-Bolyai, Chemia*, **2010**, *55 (3)*, 157-163.

In order to achieve our goals, the proposed strategy was to carry out the (thio)acetalization reaction of 2,2-bis(mercaptomethyl)-1,3-propandiol with different aldehydes.

The (thio)acetalization (**Scheme 21**) of *m*- or *p*-nitrobenzaldehyde with compound **2** (obtained by the reduction of **1** with $LiAlH_4$), resulted into a mixture of 1,3-dioxane-1,3-dithiane spiranes (**3** or **4**) and the corresponding bis(1,3-oxathiane) derivatives (**5** or **6**).



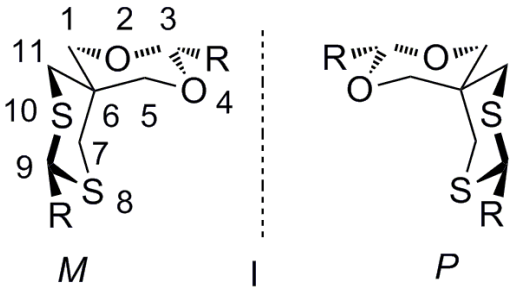
Scheme 21

The composition of the crude products in 1,3-dioxane-1,3-dithiane spiranes and bis(1,3-oxathiane) derivatives could be correlated with the reaction time (**Table 1**). The diminishing of the reaction time lead to smaller overall yields but increased the ratio in bis(1,3-oxathiane) spiranes (**Table 1**). Separation of the crude mixtures by column chromatography (pentane/ethylace-tate = 2/1) allowed the isolation of 1,3-dioxane-1,3-dithiane compounds (**3** and **4**) along with fractions containing mixtures of isomers of bis(1,3-oxathiane) derivatives (**5** and **6**).

Table 1. Results of the synthesis of compounds **3**, **4**, **5** and **6** using different reaction times

Nr. Crt.	Time reaction	Yields %			
		3	**5**	**4**	**6**
1	10h	45	<3	38	<3
2	2h	27	8	21	11

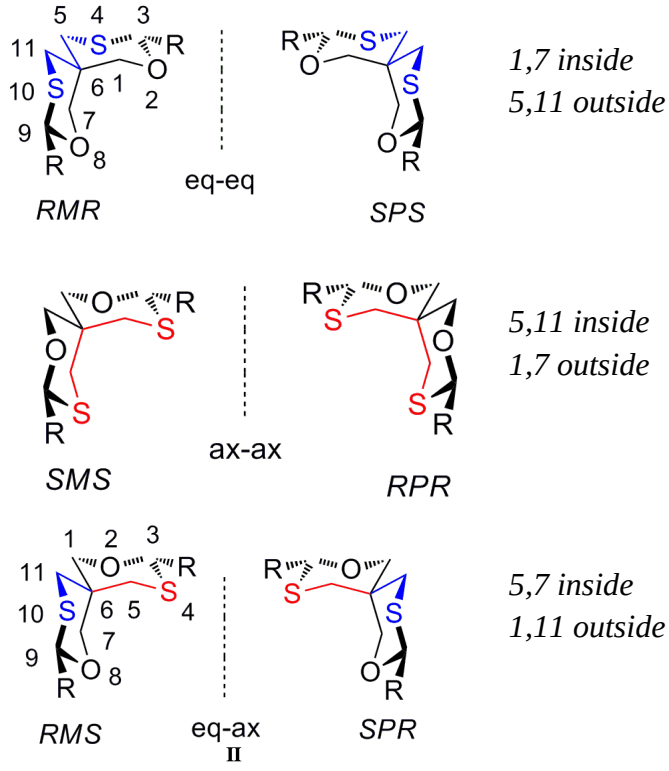
Compounds **3** and **4** (type I, **Figure 32**) are anancomeric and exhibit stable enantiomers (P or M configuration of the helix, theoretically separable) (**Scheme 22**).



5,7 methylene inside groups
1, 11 methylene outside groups

Scheme 22. Enantiomers of **3** and **4**

The bis(1,3-oxathiane) spiro compounds **5** and **6** (type II) are also anancomeric, but they have a more complex stereochemistry. In agreement with the fact that type III structures (**Figure 32**) exhibit three chiral elements (besides the helicity of the spirane unit, there are two tricoordinated virtual chiral centers belonging to the 1,3-oxathiane rings), the bis(1,3-oxathianes) II exhibit three diastereoisomers all with the substituents at positions 3 and 9 in equatorial orientations (**Scheme 23**). The $–CH_2S–$ unit (with highest precedence) incorporated in one cycle can be considered as a substituent of the other cycle and it can exhibit either axial or equatorial positions. The three diastereoisomers are denoted as equatorial–equatorial (eq–eq), axial–equatorial (ax–eq), or axial–axial (ax–ax) (**Scheme 23**).

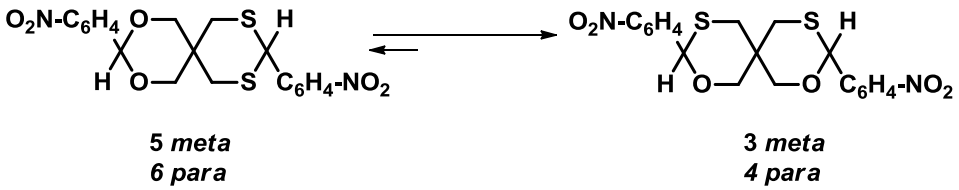


Scheme 23. Stereoisomers of **5** and **6**

Two of the three isomers of **6** could be isolated by a second column chromatography separation

(pentane/ dichloromethane = 1/2) of the isomeric mixture and they were identified by the NMR spectra as being the equatorial–equatorial (eq–eq) and equatorial–axial (eq–ax) isomers. All column chromatography attempts to separate the isomers of **5** were unsuccessful.

In order to determine the ratios at equilibrium between compounds with 1,3-dioxane-1,3-dithiane (**3** or **4**) and bis(1,3-oxathiane) (**5** or **6**) structures, compound **3** (or **4**) was refluxed for 2 days in toluene (PTSA was used as acidic catalyst). Investigation of the crude (TLC and NMR) showed the recovery of spirane **3** (**4**, respectively) and no formation of **5** (**6**) could be observed. However, when a mixture of isomers of **5** (or **6**) was submitted to the same equilibration procedure, the total transformation of **5** (**6**) into compound **3** (**4**, respectively) was noticed (**Scheme 24**). Transformation of **5** or **6** into the more stable **3** or **4** was observed even for samples stored in the refrigerator.



Scheme 24

It is to suppose that the two types of compounds [1,3-dioxane-1,3-dithiane and bis(1,3-oxathiane) spiranes] are both formed during the direct thioacetalization reaction. The fact that compounds **3** and **4** are obtained as major products by these method could be explained by considerably higher stability of these compounds. Meanwhile, the less stable bis(1,3-oxathiane) spiranes **5** and **6** are transformed (isomerized) into the more stable derivatives **3** and **4**.

When these methods were used, the reaction was stopped before the isomerisation of entire amount of **5** or **6** into **3** or **4**.

Structural investigation

The optimized geometries of the 1,3-dioxane-1,3-dithiane **4** and the isomers of the bis(1,3-oxathiane) **6** were obtained using DFT methods. The representations of the equilibrium structures obtained by calculations at the BP86/ TZ2P level of theory are shown in **Figure 33**.

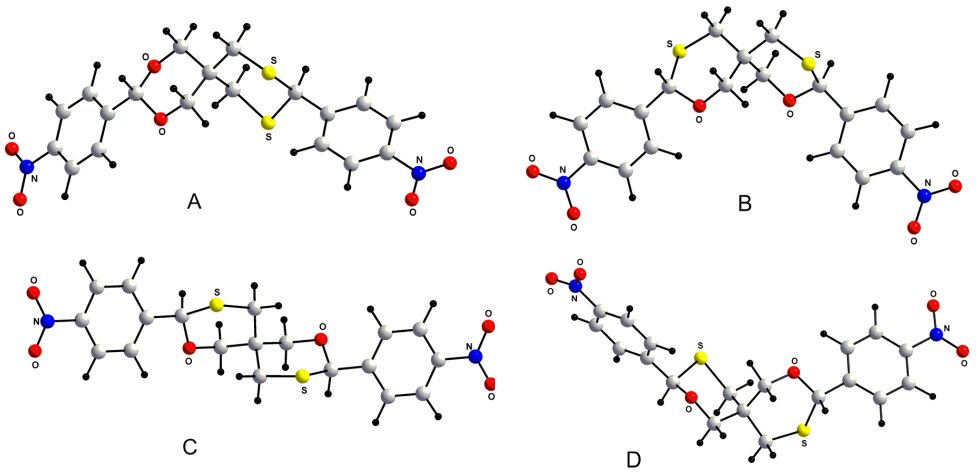


Figure 33. Equilibrium structures for **4** (**A**) and **6** (eq-eq) (**B**), **6** (ax-ax) (**C**) and **6** (eq-ax) (**D**)

The results of theoretical calculations on **4** and **6** are consistent with the experimental data. In the gas phase, **4** with ca. 3 kcal/mol is more stable than the isomers of **6** (**Table 2**). The values of the energy differences between the isomers of the bis(1,3-oxathiane) **6** are small and dependent on the chosen functional and basis sets, respectively. Still, a higher stability induced by the equatorial orientation of the CH_2S groups can be suggested. Considering the experimental data, the proposed order of stability for structures I and II is I>>II(eq–eq) > II(eq–ax) > II(ax–ax).

Table 2. Calculated relative energies between 6 and the isomers of 4 at different levels of theory

Compound	E_{rel}^{*} [kcal/mol]	$E_{rel}^{\dagger}$ [kcal/mol]	$E_{rel}^{\ddagger}$ [kcal/mol]
6 (ax-ax)	3.07	3.35	3.45
6 (ax-eq)	3.06	3.02	3.18
6 (eq-eq)	3.57	3.13	3.06
4	0	0	0

[a]ADF BP86/TZ2P; [b]GAMESS B3LYP/6-31G(d);[c]ORCA B3LYP/6-31G(d,p)

The structure of compounds **3** and **4** in solution was investigated by NMR spectroscopy. ^{1}H NMR spectra exhibit different signals for the protons at positions 3 and 9 and for the protons of the two aromatic units. The CH_2 groups of the 1,3-dioxane ring (positions 1 and 5) as well as those of the 1,3-dithiane ring (7 and 11) are diastereotopic (**Scheme 22**). Positions 5 and 7 represent methylene inside groups being oriented toward the other heterocycle of the spirane, while positions 1 and 11 are considered methylene outside groups (**Scheme 22**). The equatorial protons of the methylene inside positions are strongly deshielded by the influence (through space) of the two heteroatoms of the other heterocycle (**Table 3**). The relevant fragment of the ^{1}H NMR spectrum of **4** is presented in **Figure 34A**.

Table 3. ^{1}H-NMR data (selected, δ, ppm)* for compounds **3**, **4** and **6**

Compound	3-H	9-H	-O-CH_2- (inside)		-S-CH_2- (inside)		-O-CH_2- (outside)		-S-CH_2- (outside)	
			Heq	Hax	Heq	Hax	Heq	Hax	Heq	Hax
3	5.55	5.19	5.30 (5)	3.71 (5)	3.59 (7)	3.05 (7)	3.99 (1)	3.88 (1)	2.54 (11)	2.90 (11)
4	5.54	5.18	5.29 (5)	3.70 (5)	3.59 (7)	3.04 (7)	3.99 (1)	3.87 (1)	2.53 (11)	2.90 (11)
6(eq-eq)	5.86		5.19 (1,7)	3.53 (1,7)	-	-	-	-	2.56 (5, 11)	3.18 (5, 11)
6(eq-ax)	5.81; 5.85		5.28 (7)	3.03 (7)	3.58-3.61 (5)	3.91-3.93 (5)	3.91-3.93 (1)	3.58-3.61 (1)	2.41 (11)	3.16 (11)

*The numbering of the inside and outside positions in different structures is shown inside the brackets

As expected, the NMR spectra of isomeric **6** (eq–eq) and **6** (eq–ax) are quite different. In the spectrum of the eq–eq isomer, the two –CH_2O– groups (positions 1 and 7) and the two –CH_2S– groups (positions 5 and 7) have similar pattern in NMR. The methylene groups connected to the oxygen atoms (–CH_2O–) are both methylene inside, while those of the –CH_2S– moieties are both methylene outside groups. The equatorial protons of the methylene inside –CH_2O– groups are very deshielded (d_e = 5.19 ppm, **Figure 34B**) in agreement with the data obtained for the similar protons in **4** (d_e = 5.29 ppm, methylene inside –CH_2O– group). The protons of positions 3 and 9 in **6** (eq–eq) are equivalent and they give a unique signal (d = 5.86 ppm, **Figure 34B**). The assignment of this spectrum (**Figure 34B** to the eq–eq isomer and not to the ax–ax isomer (which should exhibit a similar ^{1}H NMR pattern) was based on the chemical shifts (desh-ielding) of the signals. In the ax–ax isomer of **6**, both –CH_2–O– groups are methylene outside, while the –CH_2S– groups are both methylene inside. The signals for the methylene outside –CH_2–O– group in **4** appear at de = 3.99 and da = 3.87 ppm), while the signals pertain-ing to the methylene inside –CH_2S– in **4** give the signals de = 3.59 and da = 3.04 ppm. The spectrum in **Figure 34B** was assigned to the eq–eq isomer on the basis of the very deshielded signal (de = 5.19 ppm) which belongs to equatorial protons of methylene inside –CH_2O– groups and such groups exist only in the eq–eq isomer.

The ^{1}H NMR spectrum of the eq–ax isomer of **6** is more complicated, for either –CH_2O– or –CH_2S– frag-ments there are methylene inside and methylene outside groups. The protons at positions 3 and 9 give different signals (d = 5.81 and 5.85 ppm, **Figure 34C**) as one of them is connected to the ring having methylene inside group of –CH_2O– moiety and the other one is attached to the ring in which the methylene inside group belongs to the –CH_2S– fragment. The protons at positions 1 and 7 as well as those at positions 5 and 11 give different signals. The more deshielded signal belongs to the

equatorial proton of the $–CH_2O–$ methylene inside fragment (d_e = 5.28 ppm), while the equatorial proton of the methylene outside $–CH_2S–$ moiety is the most shielded one (**Figure 34C**; **Table 3**).

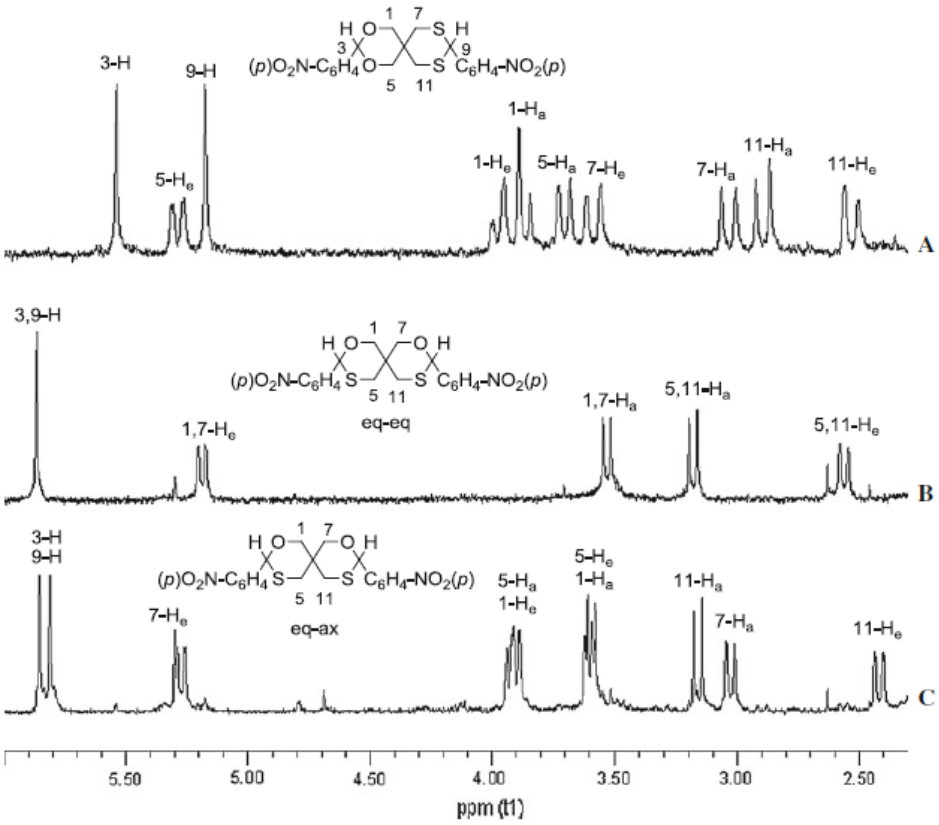


Figure 34. ^{1}H NMR spectra (fragments) of compounds **4** (**A**), **6** (eq-eq) (**B**) and **6** (eq-ax) (**C**)

2.2. CONCLUSIONS

Spiro[5.5]undecane derivatives with oxygen and sulphur atoms in the rings exhibit different stabilities in correlation with the nature of the constituent heterocycles (1,3-oxathiane, 1,3-dioxane and 1,3-dithiane).

The molecular modeling and the equilibrium experiments showed that bis(1,3-oxathiane) spiranes are less stable than the isomeric spiranes bearing 1,3-dioxane and 1,3-dithiane rings.

The structures ofcompounds (**5**, $\mathbf{6}_{\mathbf{eq\text{-}eq}}$, $\mathbf{6}_{\mathbf{eq\text{-}ax}}$) were deduced using NMR experiments.

GENERAL CONCLUSIONS

In PART A of this thesis were reported the synthesis of some new derivatives decorated with nucleobases which were used for "click chemistry" to obtained the target compounds. These compounds are subjected at the present moment to studies concerning the H-bonding associations.

We obtained new nucleobases decorated with azide functions which were fully characterized by NMR spectroscopy and mass spectrometry.

An efficient method for the synthesis of new azido-functionalized nucleobases which contain a low flexible linker between the azido group and the nucleobase unit was elaborated. This method allows concomitant bromine-azide substitution and benzoyl deprotection. This is the first reported successful result of azide mediated deprotection of *N*-benzoyl protected nucleobases (i.e. uracil and thymine).

One new tripodand with terminal triple bonds was obtained and it was characterized by NMR spectroscopy.

New tripodands exhibiting nucleobase units at the end of the pendant arms were obtained by "click reaction" between a compound having attached to the central units pendant arms with terminal triple bonds and nucleobases decorated with azide functions. The new compounds which were investigated and fully characterized by NMR spectroscopy and mass spectrometry. These compounds can be used as building blocks for supramolecular architecture by hydrogen bonding.

In the PART B some new spiro[5.5]undecane derivatives were synthesized and structurally investigated.

Spiro[5.5]undecane derivatives with oxygen and sulphur atoms in the rings exhibit different stabilities in correlation with the nature of the constituent heterocycles (1,3-oxathiane, 1,3-dioxane and 1,3-dithiane). The higher stability of the 1,3-dioxane-1,3-dithiane system versus the bis(1,3-oxathiane) structure was predicted by molecular modelling and experimentally demonstrated by equilibration reactions.

The structure of compounds (**5**, $\mathbf{6}_{\mathbf{eq\text{-}eq}}$, $\mathbf{6}_{\mathbf{eq\text{-}ax}}$) was deduced using NMR experiments.

The results regarding the structure and characterization of the compounds described in the two parts of the thesis were published in 3 articles (one of them under evaluation) and were presented in two communications at international conferences.