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## **Synthesis and crystallographic analysis of short pyridine based oligoamides as DNA targeting supramolecular binders**

Thorfinnur Gunnlaugsson, Daniel Omar Frimannsson, Thomas McCabe, Mark Lawler

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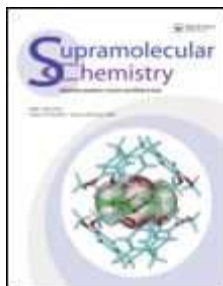
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## Synthesis and crystallographic analysis of short pyridine based oligoamides as DNA targeting supramolecular binders

Journal:	<i>Supramolecular Chemistry</i>
Manuscript ID:	GSCH-2009-0134.R2
Manuscript Type:	Communications
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Keywords:	Oligoamides, polyamides, pyridine, DNA binders, X-ray crystallography
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
compound2.cif compound 5.cif	



## checkCIF/PLATON report

No syntax errors found. CIF dictionary Interpreting this report

## Datablock: shelxl

Bond precision: C-C = 0.0023 A Wavelength=0.71070

Cell: a=7.2480(16) b=7.7467(19) c=16.949(4)  
 alpha=82.609(6) beta=80.612(8) gamma=81.488(8)

Temperature: 121 K

	Calculated	Reported
Volume	923.2(4)	923.2(4)
Space group	P -1	P-1
Hall group	-P 1	?
Moiety formula	C18 H20 N4 O5	?
Sum formula	C18 H20 N4 O5	C18 H20 N4 O5
Mr	372.38	372.38
Dx,g cm-3	1.340	1.340
Z	2	2
Mu (mm-1)	0.100	0.100
F000	392.0	392.0
F000'	392.19	
h,k,lmax	8,9,20	8,9,20
Nref	3261	3247
Tmin,Tmax	0.980,0.980	0.980,0.980
Tmin'	0.980	


Correction method= MULTI-SCAN

Data completeness= 0.996 Theta(max)= 25.000

R(reflections)= 0.0408( 2927) wR2(reflections)= 0.1426( 3247)

S = 1.120 Npar= 245

The following ALERTS were generated. Each ALERT has the format  
 test-name\_ALERT\_alert-type\_alert-level.  
 Click on the hyperlinks for more details of the test.

 Alert level B

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 PLAT391\_ALERT\_3\_B Deviating Methyl C14 H-C-H Bond Angle ..... 124.00 Deg.  
 PLAT391\_ALERT\_3\_B Deviating Methyl C17 H-C-H Bond Angle ..... 96.00 Deg.

 Alert level C

1 ABSTY02\_ALERT\_1\_C An \_exptl\_absorpt\_correction\_type has been given without  
2 a literature citation. This should be contained in the  
3 \_exptl\_absorpt\_process\_details field.  
4 Absorption correction given as multi-scan  
5 PLAT220\_ALERT\_2\_C Large Non-Solvent C Ueq(max)/Ueq(min) ... 3.03 Ratio  
6 PLAT351\_ALERT\_3\_C Long C-H Bond (0.96A) C18 - H20 ... 1.14 Ang.  
7 PLAT390\_ALERT\_3\_C Deviating Methyl C14 X-C-H Bond Angle ..... 102.00 Deg.  
8 PLAT390\_ALERT\_3\_C Deviating Methyl C17 X-C-H Bond Angle ..... 118.00 Deg.  
9 PLAT194\_ALERT\_1\_C Missing \_cell\_measurement\_reflms\_used datum .... ?  
10 PLAT195\_ALERT\_1\_C Missing \_cell\_measurement\_theta\_max datum .... ?  
11 PLAT196\_ALERT\_1\_C Missing \_cell\_measurement\_theta\_min datum .... ?

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12  
13 0 **ALERT level A** = In general: serious problem

14 3 **ALERT level B** = Potentially serious problem

15 9 **ALERT level C** = Check and explain

16 0 **ALERT level G** = General alerts; check

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18 4 **ALERT type 1** CIF construction/syntax error, inconsistent or missing data

19 1 **ALERT type 2** Indicator that the structure model may be wrong or deficient

20 7 **ALERT type 3** Indicator that the structure quality may be low

21 0 **ALERT type 4** Improvement, methodology, query or suggestion

22 0 **ALERT type 5** Informative message, check

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### 23 24 25 26 **Publication of your CIF in IUCr journals**

27  
28 **A basic structural check has been run on your CIF. These basic checks will be run on all**  
29 **CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied***  
30 ***Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta***  
31 ***Crystallographica Section C* or *E*, you should make sure that full publication checks are run**  
32 **on the final version of your CIF prior to submission.**

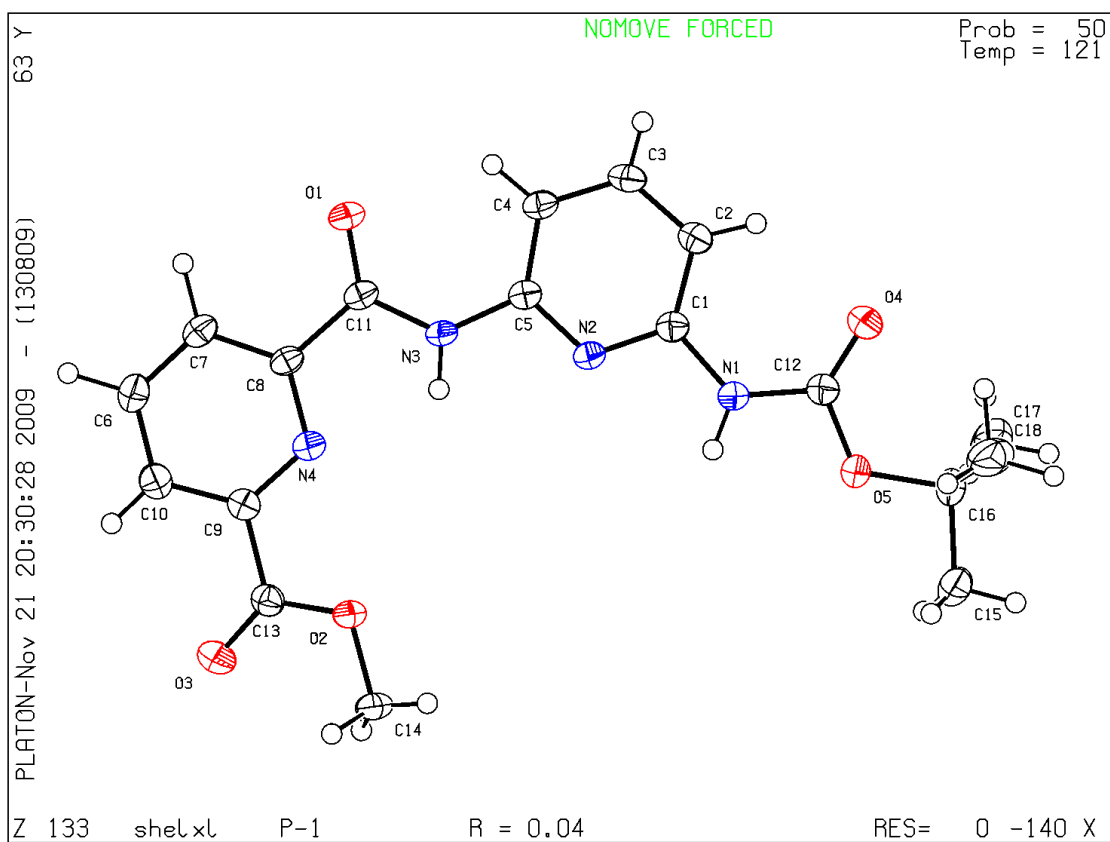
### 33 34 **Publication of your CIF in other journals**

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36 **Please refer to the *Notes for Authors* of the relevant journal for any special instructions**  
37 **relating to CIF submission.**

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40 **PLATON version of 13/08/2009; check.def file version of 12/08/2009**

Datablock shelxl - ellipsoid plot



## checkCIF/PLATON report

No syntax errors found. CIF dictionary Interpreting this report

## Datablock: df1m

Bond precision: C-C = 0.0069 Å Wavelength=0.71073

Cell: a=11.771(3) b=11.903(3) c=9.525(2)  
 alpha=90 beta=92.399(5) gamma=90

Temperature: 121 K

	Calculated	Reported
Volume	1333.4(6)	1333.4(6)
Space group	P 21/c	P21/c
Hall group	-P 2ybc	?
Moiety formula	C14 H14 N4 O2	?
Sum formula	C14 H14 N4 O2	C14 H14 N4 O2
Mr	270.29	270.29
Dx, g cm <sup>-3</sup>	1.346	1.346
Z	4	4
Mu (mm <sup>-1</sup> )	0.094	0.094
F000	568.0	568.0
F000'	568.23	
h,k,lmax	13,14,11	13,14,11
Nref	2347	2346
Tmin,Tmax	0.978,0.981	
Tmin'	0.968	


Correction method= Not given

Data completeness= 1.000 Theta(max)= 25.000


R(reflections)= 0.0736( 1194) wR2(reflections)= 0.2164( 2346)

S = 1.018 Npar= 183

The following ALERTS were generated. Each ALERT has the format  
 test-name\_ALERT\_alert-type\_alert-level.  
 Click on the hyperlinks for more details of the test.

 Alert level B

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PLAT230_ALERT_2_B	Hirshfeld Test Diff for	C8	--	C9	..	11.36	su
PLAT230_ALERT_2_B	Hirshfeld Test Diff for	C9	--	C10	..	9.49	su

 Alert level C

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1 PLAT230_ALERT_2_C Hirshfeld Test Diff for N3 -- C8 .. 6.66 su
2 PLAT241_ALERT_2_C Check High Ueq as Compared to Neighbors for N3
3 PLAT241_ALERT_2_C Check High Ueq as Compared to Neighbors for C10
4 PLAT242_ALERT_2_C Check Low Ueq as Compared to Neighbors for C9
5 PLAT340_ALERT_3_C Low Bond Precision on C-C Bonds (x 1000) Ang .. 7
6 PLAT194_ALERT_1_C Missing _cell_measurement_reflms_used datum .... ?
7 PLAT195_ALERT_1_C Missing _cell_measurement_theta_max datum .... ?
8 PLAT196_ALERT_1_C Missing _cell_measurement_theta_min datum .... ?
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9 0 ALERT level A = In general: serious problem
10 3 ALERT level B = Potentially serious problem
11 8 ALERT level C = Check and explain
12 0 ALERT level G = General alerts; check
13
14 3 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
15 7 ALERT type 2 Indicator that the structure model may be wrong or deficient
16 1 ALERT type 3 Indicator that the structure quality may be low
17 0 ALERT type 4 Improvement, methodology, query or suggestion
18 0 ALERT type 5 Informative message, check
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A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

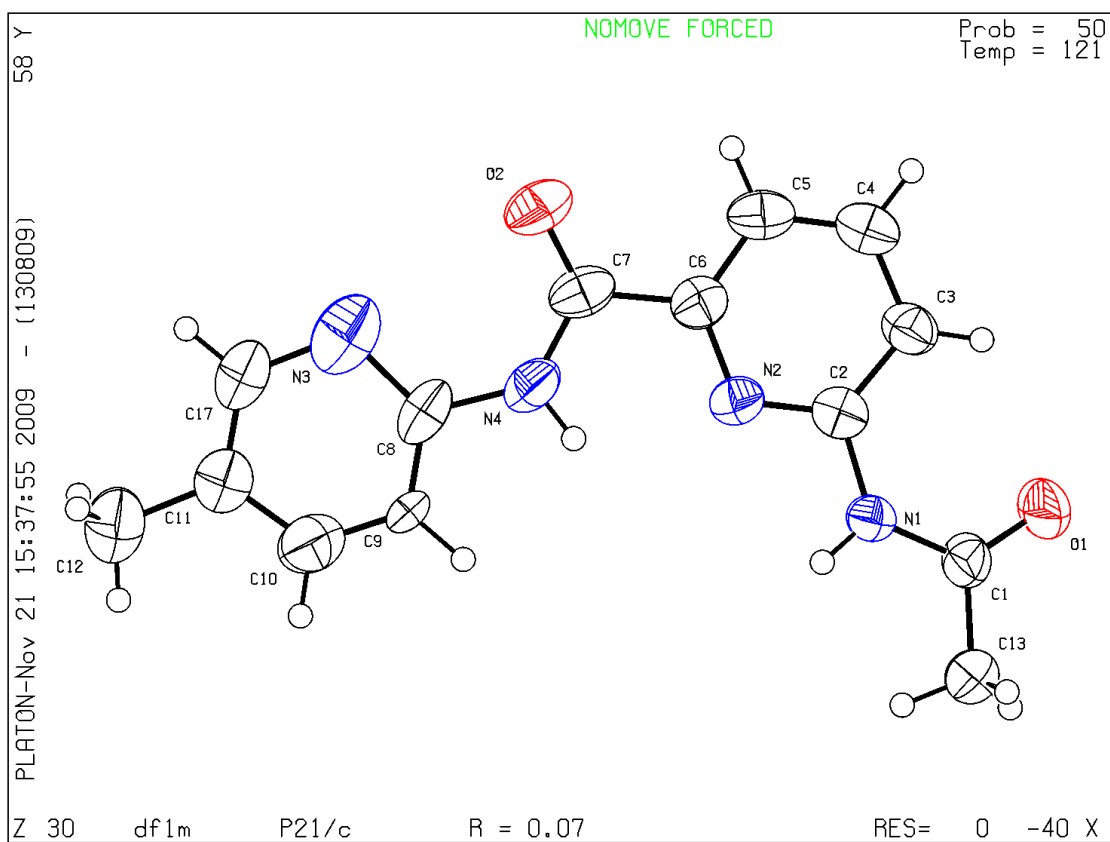
### Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

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PLATON version of 13/08/2009; check.def file version of 12/08/2009

Datablock df1m - ellipsoid plot



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# Synthesis and crystallographic analysis of short pyridine based oligoamides as DNA targeting supramolecular binders

Daniel O. Frimannsson,<sup>a,b</sup> Thomas McCabe,<sup>a</sup> Wolfgang Schmitt,<sup>a</sup> Mark Lawler<sup>b</sup> and Thorfinnur Gunnlaugsson<sup>a\*</sup>

*a) School of Chemistry, Centre for Synthesis and Chemical Biology, Trinity College Dublin, Dublin 2, Ireland and b) School of Medicine, Institute of Molecular Medicine, St. James's Hospital, Trinity College Dublin, Dublin 8, Ireland*

*E-mail: gunnlaut@tcd.ie*

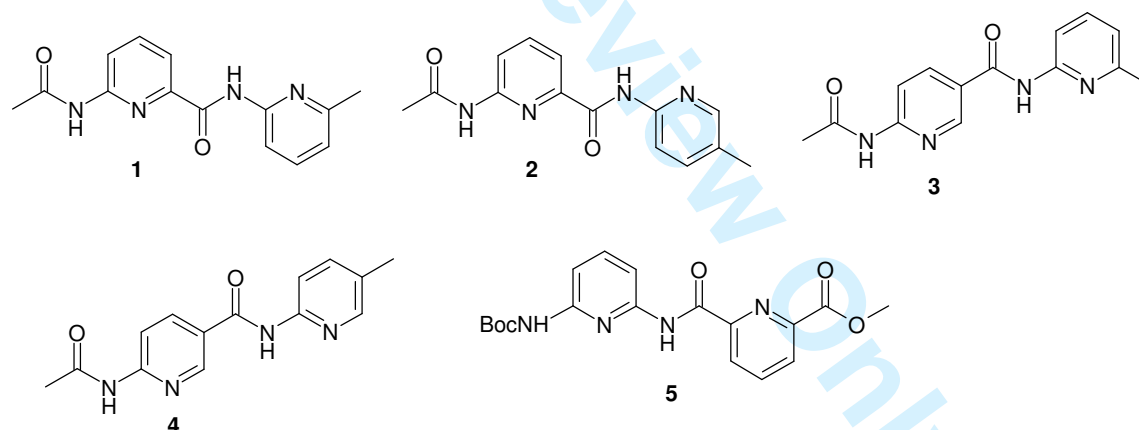
**Abstract:** The synthesis of the pyridine peptides **1-4**, formed from amino picolinic acid, and **5**, made from coupling of a mono-protected pyridine diamine to a mono protected pyridine dicarboxylic acid and the X-ray crystallographic structures of **1** and **5** is discussed, as well as their supramolecular interactions in the solid state. The structure of these showed that they possess concave appearance that can be employed to bind to nucleic acids through multiple hydrogen-bonding, which would facilitate the formation of helical based pyridine oligoamides as novel DNA binding molecules. This was proven by carrying out DNA denaturation studies and ethidium displacement assay on **5**, but **5** was also shown using MTT assays to be cytotoxic against drug resistant chronic myeloid leukemia K562 cell-line.

**Keywords:** Oligoamides, pyridine, DNA binders, X-ray crystallography

## INTRODUCTION

The development of novel polyamide ligands, such as aromatic oligoamides,<sup>1,2</sup> for investigating folding conformations in solution and/or self-assembly formation, is of great current interest within the field of supramolecular chemistry.<sup>3</sup> Such 'non-natural' polyamide

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3 based structures, based on the use of pyrrole-imidazole polyamides and bicyclic ring  
4 structures, have also been synthesized with the view of mimicking hydrogen bonding driven  
5 protein-DNA interactions and for studying the binding and cellular uptake of such  
6 polyamides.<sup>4,5,6</sup> We have developed several examples of luminescent imaging and potential  
7 therapeutic agents as DNA targeting molecules. These have been based on the use of simple  
8 heterocyclic structures,<sup>7</sup> naphthalimide derived Ru(II) complexes<sup>8</sup> and Tröger's bases,<sup>9</sup> or by  
9 using mixed lanthanide (Yb(III) and Nd(III)) transition-metal (Ru(II)) complexes,<sup>10</sup> In this  
10 communication, we present the synthesis of five bis-pyridines di-peptides **1-5**, based on the  
11 use of acetyl-protected amino-picolinic acid, and the coupling of Boc-protected pyridine  
12 diamine to pyridine di-carboxylic acid. The solid state structure of both **1** and **5** is also  
13 presented, which display **complex** crystallographic packing consisting of both intra- and  
14 intermolecular hydrogen bonding networks. These building blocks were synthesized with the  
15 aim of investigating their ability to form a helical construct, a structural feature important for  
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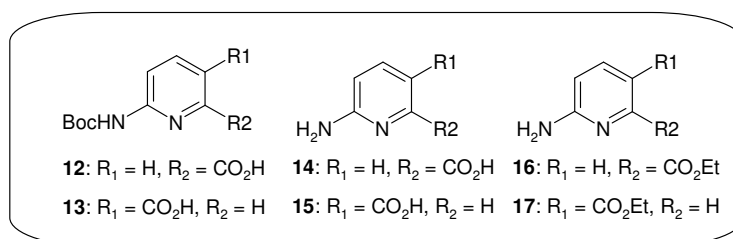
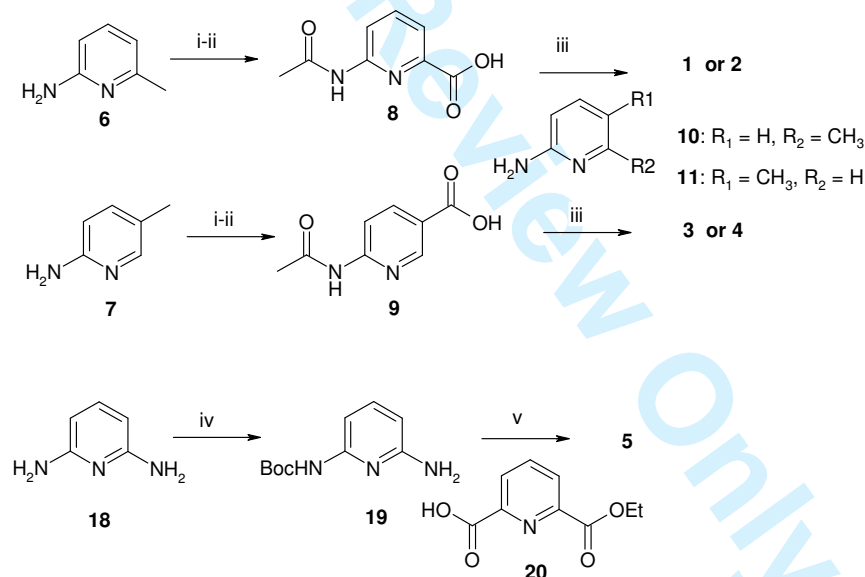
**Figure 1.** Structure of di-pyridine peptides **1-5**

DNA interactions (See Graphical Abstract), by incorporating them into pyridine based  
oligoamides.<sup>11</sup> To the best of our knowledge, only a few such pyridine di-amines have been  
developed to date.<sup>12-19</sup> Examples include those of Rozanski *et. al.*,<sup>18</sup> who made several  
pyridine oligo amides from symmetrical 2,6-diamino pyridine or 2,6-pyridine di-carboxylic

acid. However, structures **1-5** have not been previously formed as building blocks for the incorporation into such pyridine based oligoamides.

## RESULTS AND DISCUSSION

**Synthesis:** The synthesis of **1-4** required the initial preparation of the acetal protected pyridine amino acid units, possessing the carboxylic acid functionality in either the fifth or the sixth positions of the pyridine ring. For the synthesis of **1** and **2**, a two-step synthesis for the *N*-acetyl-2-amino-6-picolinic acid **8** and **9** was undertaken,<sup>17b</sup> Scheme 1, which initially involved the protection of 2-amino-6-picoline (**6**) and 2-amino-5-picoline (**7**) with acetic anhydride in toluene overnight at 95 °C, which yielded the two structural isomers in 87 and 90% yield, respectively.<sup>18</sup> The protection of the amine was employed to prevent oxidation of this moiety and increase the stability of the resulting pyridine amino acid. Oxidation of the



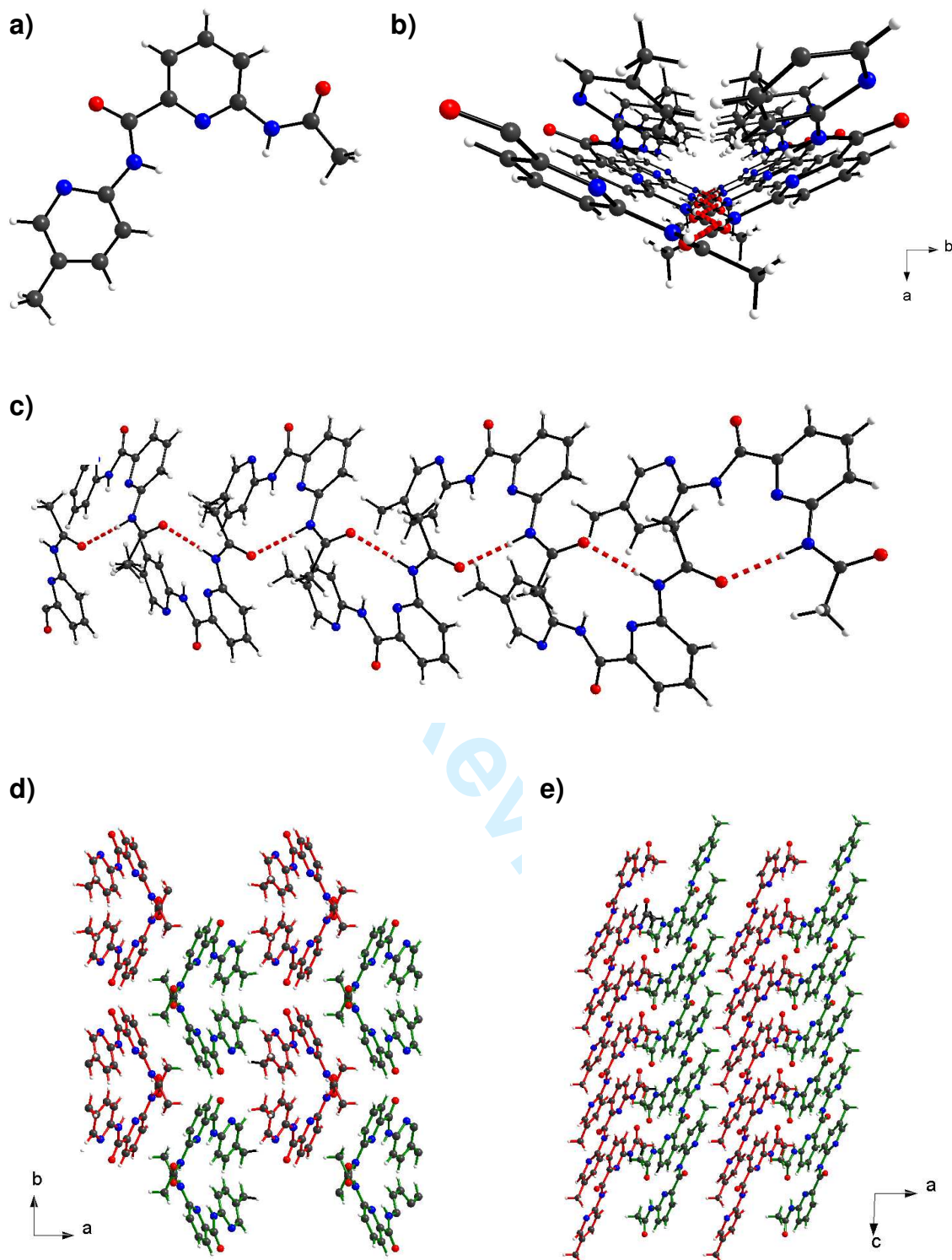
**Scheme 1.** (i) Acetic anhydride, toluene, 95 °C. (ii) KMnO<sub>4</sub>, NaOH, H<sub>2</sub>O, reflux. (iii) DCC (or EDCI) HOBt, DMF, RT. (iv) Boc anhydride, THF, room temperature, (v) DCC, HOBt, Et<sub>3</sub>N, THF, RT.

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3 methyl groups gave the corresponding carboxylic acids **8** and **9** as white precipitates, in 62%  
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5 and 45% yields, respectively, after reflux in water in the presence of two equivalents  $\text{KMnO}_4$   
6  
7 and NaOH overnight, followed by acidification to pH 4 using **conc.** HCl. These syntheses  
8  
9 were also repeated using Boc anhydride, as the amino protecting group, with the aim of  
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11 facilitating their incorporation into oligoamides using peptide coupling protocols. While the  
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13 two Boc-protected picolines were obtained in good yield, the oxidation of these structures to  
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15 their corresponding acids **12** and **13** was unsuccessful using either  $\text{KMnO}_4$ , or  $\text{K}_2\text{CrO}_7$ , only  
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17 resulting in the recovery of the two starting materials. With the aim of forming the free amine,  
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19 which could then be coupled to **10** or **11**, the hydrolysis of **8** and **9** was also undertaken by  
20  
21 refluxing these derivatives in 10% aqueous NaOH solution for 6 hours, followed by acidic  
22  
23 workup. This gave the corresponding pyridine amino acids **14** and **15** in 58% and 46% yields,  
24  
25 respectively. **By reacting either **11** or **12** in a 3:20 mixture of  $\text{H}_2\text{SO}_4$  and ethanol under reflux**  
26  
27 **for five hours under argon,<sup>19</sup> followed by aqueous  $\text{NH}_4^+$  workup, resulted in deprotection of**  
28  
29 **the *N*-acetyl group and in the esterification of the carboxylic acids, giving **16** and **17** in ca.**  
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31 **50% yields.**

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39 The two amino acids **14** and **15** were also reacted in an excess of oxalyl chloride in  
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41  $\text{CHCl}_3$  for four days at 45 °C under anhydrous conditions, this gave their corresponding acid  
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43 chlorides. Further treatment of this solution with methanol, gave the corresponding methyl  
44  
45 esters protected pyridine amino acids analogues of **16** and **17**, and in ca. 50% overall yield.  
46  
47 Having obtained several pyridine amino acid building blocks, we next formed the bis-pyridine  
48  
49 di-peptides **1-4**. Initially, the acid derivatives **8** and **9** were treated with  $\text{SOCl}_2$ , resulting only  
50  
51 in the recovery of the starting materials. Consequently, the peptide coupling reagents  
52  
53 dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide  
54  
55 hydrochloride (EDCI) were employed. Here, **10** and **11** were coupled to **8** or **9** in DMF at  
56  
57 room temperature using these reagents, which after aqueous base workup and crystallization  
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3 from EtOAc, gave the desired di-peptides **1-4** in moderate yields. These were all characterised  
4 using conventional methods. With the view of coupling **1-4** to another di-peptide possessing  
5 an alternative hydrogen donating pattern, the synthesis of the orthogonal protected **5** was also  
6 undertaken, commencing with the mono-protection of **18**, to give **19**.<sup>25</sup> As for the synthesis of  
7 bis-pyridine di-peptides **1-4**, the **19** and the mono protected di-acid **20**<sup>26</sup> were coupled  
8 together using HOBt, DCC and triethylamine in dry THF at 0 °C overnight at room  
9 temperature. The resulting residues were purified by column chromatography on flash silica  
10 (using 40/60 EtOAc/CH<sub>2</sub>Cl<sub>2</sub>), giving the protected di-peptide **5** as a white solid in 27% yield.  
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**X-Ray Crystallographic Analysis:** Crystals suitable for X-ray crystallographic analysis of **2**  
24 were grown from DMSO solution,<sup>23</sup> and crystallises in the monoclinic crystal system in the  
25 space group P2<sub>1</sub>/c. Crystallographic data and details of the structure refinement for **2** are  
26 provided in Table 1. The structure shows that the pyridine units are *anti* to each other in the  
27 solid state, and that the angle between the amide hydrogen atoms is 105°. Viewing the crystal  
28 structure through the 2,6-substituted pyridine plane, the second pyridine unit appears slightly  
29 twisted out of plane. The angle between the planar pyridine units is equal to the sum of three  
30 torsion angle deviations in the bonds that connect the pyridine units (-7.3° + 4.7° + 0.2°) and  
31 was calculated as -2.4°. In a similar manner, the pyrrole ring planes in the well known DNA  
32 groove binding drug netropsin have been reported to have a twisted angle to one another. This  
33 angle is slightly larger than that seen herein.<sup>25</sup> The difference between the pyrrole and the  
34 pyridine units in Figure 2, we believe, arises from the non-planarity of the pyrrole units,  
35 which is ascribed to the steric clash between the pyrrole CH and the adjacent amide group.<sup>24</sup>  
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In addition, the angle formed between the amide hydrogens was measured as 105°, suggesting  
that repeated units of the 2,6-substituted pyridines would span 360° after nearly 5 repeating  
units (360°/75° = 4.8), while DNA has about 10 base pairs per turn. The results for **2**, suggest



**Figure 2.** *a)* Structure of **2**. *b)* and *c)* H-bonded 1D chain structure of **2**. *d)* and *e)* Packing diagrams with view in the direction of the crystallographic *c*- and *b*-axis

that the pyridine oligoamides based on **2** could be over-curved in relation to DNA (See Graphical Abstract). However, as mentioned earlier, both these angles and the distortion

**Table 1.** Summary of crystal data, data collection and structure refinement for X-ray diffraction study of **2** and **5**.

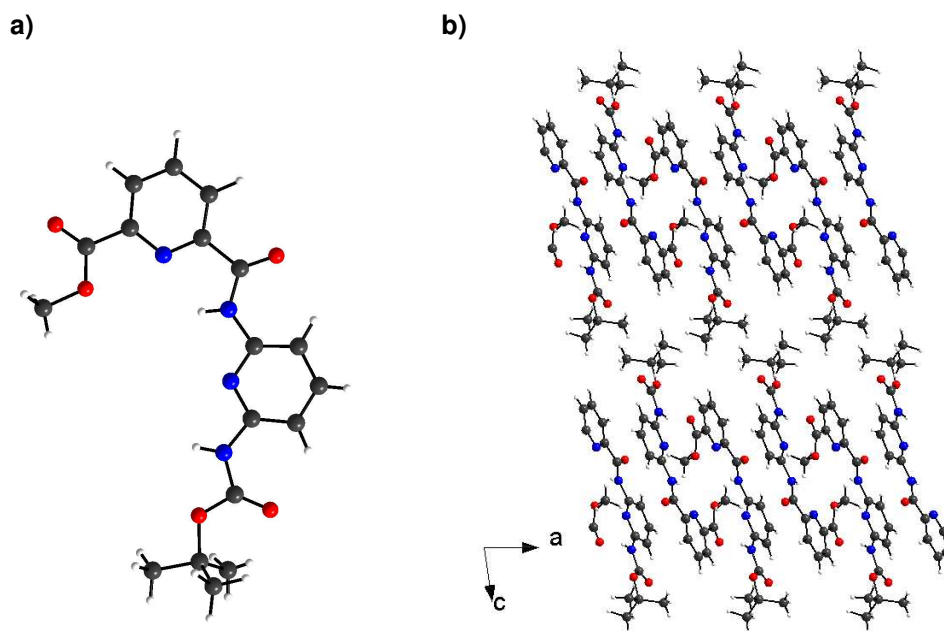
	Compound <b>2</b>	Compound <b>5</b>
Chemical formula	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	C <sub>18</sub> H <sub>20</sub> N <sub>4</sub> O <sub>5</sub>
Formula weight (g mol <sup>-1</sup> )	270.29	372.38
Crystal system	monoclinic	triclinic
Space group	<i>P</i> 21/ <i>c</i> (no. 14)	<i>P</i> -1 (no. 2)
<i>a</i> (Å)	11.771 (3)	7.2480 (16)
<i>b</i> (Å)	11.903 (3)	7.7467 (19)
<i>c</i> (Å)	9.525 (2)	16.949 (4)
$\alpha$ (°)	90	82.609 (6)
$\beta$ (°)	92.399 (5)	80.612 (8)
$\gamma$ (°)	90	81.488 (8)
<i>V</i> (Å <sup>3</sup> )	1333.4 (6)	923.2 (4)
<i>Z</i>	4	2
<i>D</i> <sub>calc</sub> (g cm <sup>-3</sup> )	1.346	1.340
$\mu$ (mm <sup>-1</sup> )	0.094	0.100
<i>F</i> (000)	568.0	392.0
Radiation (Å)	0.71073	0.71073
Temperature (K)	121(2)	121(2)
$2\theta$ Range (°)	50	50
<i>h, k, l</i> Ranges	-13→13, -13→14, -11→11	-8→8, -9→9, -20→20
Measured reflections	10397	14143
Unique reflections	2346 ( <i>R</i> <sub>int</sub> = 0.0910)	3247 ( <i>R</i> <sub>int</sub> = 0.0257)
Reflections used [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	1194	2927
Parameters refined	183	245
GoF (on <i>F</i> <sup>2</sup> )	1.018	1.120
<i>R</i> 1 [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	0.0736	0.0408
<i>wR</i> 2 [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	0.1727	0.1201
( $\Delta\rho$ ) <sub>max</sub> / ( $\Delta\rho$ ) <sub>min</sub> (e Å <sup>-3</sup> )	0.315/-0.480	0.062/-0.357

angles could change upon binding in the minor groove as has been shown to be the case for netropsin.<sup>25</sup>

The supramolecular arrangement of **2** and the involved intermolecular forces might give further indications of how this compound could interact with DNA, and these were

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3 investigated by looking at the packing arrangement of the molecule. The supramolecular  
4 structure of **2** is characterised by intermolecular H bonds involving the N and O atoms of the  
5 amide functionality that bridges the aromatic moieties. This hydrogen bond results in a 1D  
6 chain structure that runs in the direction of the crystallographic *c*-axis. The distance between  
7 the hydrogen donor N atom and the O acceptor atom is 2.935(5) Å. The alkyl moiety of the  
8 terminating ester functionality and the methyl substituent of the aromatic ring prohibit strong  
9  $\pi$ - $\pi$  interactions in the crystal structure. The Figures 2b and 2c show the 1D H-bonded chain  
10 structure; Figure 2d and Figure 2e highlight the arrangement of the chain within the crystal  
11 structure.  
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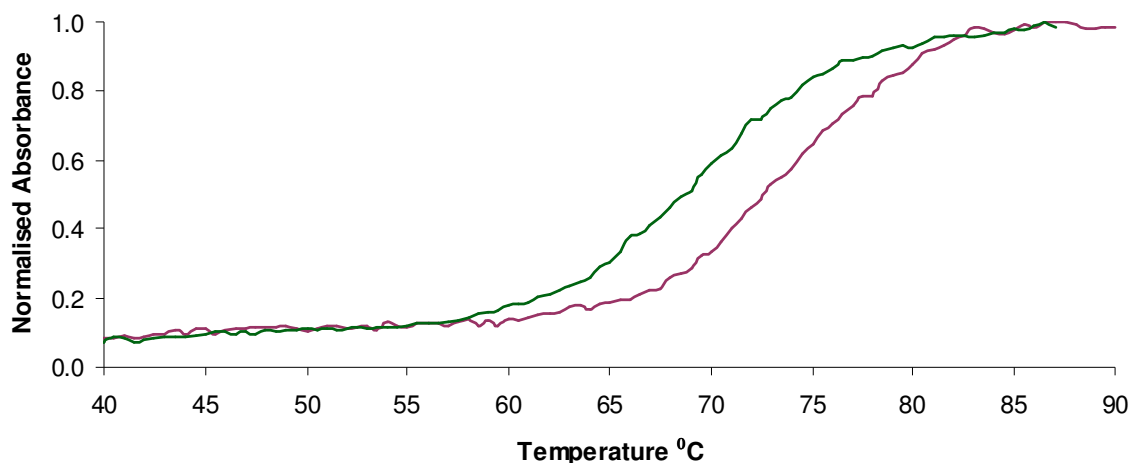
25 Crystals suitable for X-ray crystal structure analysis of **5** were obtained by slow  
26 evaporation from a methanol solution. Compound **5** crystallises in the triclinic crystal system  
27 in the space group P-1. The resulting structure is shown in Figure 3a. Crystallographic data  
28 for **2** are provided in Table 1. The crystal structure consists of isolated molecules, held  
29 together through weak dispersion forces. In contrast to the crystal structure of **2**, shown in  
30 Figure 2a, the crystal structure of **5** shows the pyridine rings *syn* to each other. This  
31 orientation and binding pattern (H-donor/H-acceptor) could preferentially target i) **G**  
32 sequences, by hydrogen bonds between the pyridine nitrogen and the NH<sub>2</sub> of **G** and by ii) the  
33 amide hydrogen and the lone pair of the **G** base (See Graphical Abstract). As for the crystal  
34 structure of **2**, the angle between the relatively planar pyridine aromatic rings was calculated  
35 from the three torsion angles that connect the pyridine units (-1.28° -0.56° + 1.48°) as -0.36°,  
36 which is of similar magnitude to that seen for **2**, demonstrating a small rise between the two  
37 pyridine units. Furthermore, the angle formed between the two 'amide' protons was  
38 determined as 130°, which is somewhat larger than seen for **2**. These results indicate that the  
39 configuration of the 2,6-diaminopyridine units would span 360° after 7 units (360° / 50° =  
40 7.2), an improvement on that seen for **2**. The supramolecular arrangement of **5** was also  
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**Figure 3.** a) Structure of **5**. b) Packing of **5** in the crystal structure with view in the direction of the crystallographic *b*-axis (C grey, O red, N blue, H white).

analysed. Figure 3b shows the packing of **5** with view in the direction of the crystallographic *b*-axis. Unlike that seen for **2** above, the intramolecular arrangement of H-donor and acceptor atoms within **5** does not allow the molecule to be involved in extended H-bonded networks. Furthermore, the alkyls substituents of the ester functionalities hamper efficient  $\pi$ - $\pi$  stacking in the crystal structure.

**Biological Studies:** With the aim of evaluating the potential binding of **2** to DNA, we carried out thermal denaturation experiments. A typical melting curve for *ct*-DNA in aqueous buffered solvent at physiological pH 7.4, is shown in Figure 4, from which the melting temperature  $T_m$  for calf thymus *ct*-DNA was determined as 69 °C. When a small molecule binds to DNA, they either stabilise, or destabilise, the double helix and hence modulates the  $T_m$  number. The denaturation studies were conducted in 10 mM phosphate buffer (pH 7.4) with a P/D ratio of 10. As shown in Figure 4, it is clear that the binding of **2** stabilises the DNA structure, with a  $T_m$  value of 75 °C, being determined (from first derivatives plots of



**Figure 4.** Thermal denaturation curves of ct-DNA (150  $\mu$ M) in 10 mM phosphate buffer, pH 7.4, in the absence (green) and in the presence of **2** (purple) at a P/D of 10.

the melting curve) for the binding of **2**, which is of similar magnitude seen for the binding of many positively charged organic molecules or transition metal complexes to ct-DNA.<sup>7</sup>

To evaluate if these structures could bind to DNA *in situ* or/and induce apoptosis in cancer cell-lines, the cytotoxicity of the di-peptides **1-4** were investigated against drug resistant chronic myeloid leukemia K562 cell-line. These acetate protected di-peptides were only found to be moderately soluble in water. However, the incubation of **2** with K562 for 48 hours and subsequent assessment of efficacy by the MTT assay, demonstrated that **2** was indeed cytotoxic. Here, compound **2** was shown to reduce cell numbers at relatively high doses, with an  $EC_{50}$  value of 82  $\mu$ M, and cell morphology indicated that cells had undergone apoptosis. Hence, this result indicated that these structures are able to cross the cell membrane and induce cellular death at high concentrations. This makes them excellent candidates for incorporation into oligoamides with the view of achieving site selective targeting of DNA *in situ*

## CONCLUSION

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3 In summary, we have undertaken the synthesis of several pyridine amino acid derivatives and  
4 bis-pyridine di-peptides for the formation or the incorporation into pyridine based  
5 oligoamides. We have shown, using X-ray crystal structure analysis, that the bis-pyridines di-  
6 peptides **2** and **5** have curved molecular structures, which could facilitate the formation of  
7 helically shaped pyridyl oligoamides. The supramolecular structure of **2** is characterised by  
8 1D chains which run parallel to the crystallographic *c*-axis and in which single molecules are  
9 connected through H-bonds. In contrast to **2**, the arrangement of N-atoms in **5**, does not allow  
10 the molecule to be engaged in strong intermolecular H-bonds. The packing of **5** in the crystal  
11 structure is characterised by isolated molecules held together through weak dispersion forces.  
12 We have further shown that in the case of **2**, the binding of the oligopyridine units stabilizes  
13 the DNA structure at the same time as we demonstrated that **2** entered cells and gave rise to  
14 apoptosis with an EC<sub>50</sub> value of 82 μM in a drug resistant chronic myeloid leukemia K562  
15 cell-line. We are currently undertaking the synthesis of other oligoamid derivatives based on  
16 these building blocks presented herein and investigating their binding to DNA as well as their  
17 cytotoxicity in cancer cell lines.  
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42 We thank Trinity College Dublin, CSCB, SFI and IRCSET for financial support. We also like  
43 to thank Dr. John E. O'Brien for his help and Dr. Tony McElligot for his initial help and  
44 support, and Dr. Emma B. Veale for helping out with analysis of DNA denaturation studies.  
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## 51 EXPERIMENTAL

52 **General:** Reagents (obtained from Aldrich) and solvents were purified using standard  
53 techniques. Melting points were determined using a Gallenkamp melting point apparatus.  
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55 Infrared spectra were recorded on a Mattson Genesis II FTIR spectrophotometer equipped  
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3 with a Gateway 2000 4DX2-66 workstation.  $^1\text{H}$  NMR spectra were recorded at 400 MHz  
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5 using a Bruker Spectrospin DPX-400 instrument.  $^{13}\text{C}$  NMR spectra were recorded at 100  
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7 MHz using a Bruker Spectrospin DPX-400 instrument.  
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### 10 11 12 13 **Synthesis:**

#### 14 15 **6-Acetylamino-pyridine-2-carboxylic acid (6-methyl-pyridin-2-yl)-amide (1) Compound 8**

16 (0.28 g, 1.57 mmol) along with 2-amino-6-picoline (0.21 g, 1.88 mmol) and HOBt (0.25 g,  
17  
18 1.84 mmol) were dissolved in DMF. To this solution DCC (0.35 g, 1.67 mmol) was added at  
19  
20 0 °C. The reaction was stirred overnight under argon at room temperature. The reaction  
21  
22 mixture was then kept at 4 °C for 3 hours before filtering it through celite. The solvent was  
23  
24 evaporated under reduced pressure and the product was obtained as a white solid dried (0.06  
25  
26 g, 0.22 mmol, 14%) that was dried under high vacuum. m.p. 205-207 °C;  $^1\text{H}$  NMR  $\delta_{\text{H}}$  (400  
27  
28 MHz, DMSO- $d_6$ ): 10.9 (1H, s, Ar-NH-CO-Ar), 10.2 (1H, s, Ar-NH-CO-CH $_3$ ), 8.34 (1H, d,  $J$   
29  
30 = 8.4 Hz, Ar-H), 8.11 (1H, d,  $J$  = 8.0 Hz, Ar-H), 8.03 (1H, t,  $J$  = 8.0 Hz, Ar-H), 7.86 (1H, d,  $J$   
31  
32 = 7.6 Hz, Ar-H), 7.77 (1H, t,  $J$  = 7.8 Hz, Ar-H), 7.05 (1H, d,  $J$  = 7.2 Hz; Ar-H), 2.43 (3H, s,  
33  
34 CO-CH $_3$ ), 2.16 (3H, s, Ar-CH $_3$ );  $^{13}\text{C}$  NMR  $\delta_{\text{C}}$  (100 MHz, DMSO- $d_6$ ), 169.6, 161.6, 157.0,  
35  
36 151.0, 150, 146.8, 140.4, 139.0, 119.5, 117.0, 116.9, 110.0, 24.0, 23.6; Accurate MS (m/z)  
37  
38 Calculated: 271.1190 (M+H) $^+$ , Found: 271.1195; IR  $\nu_{\text{max}}$  (cm $^{-1}$ ): 3354 (NH), 3251 (NH),  
39  
40 1689 (C=O), 1668 (C=O), 1449 (Pyridine).  
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#### 50 51 **6-Acetamido-N-(5-methylpyridin-2-yl)picolinamide (2):** Compound 8 (0.61 g, 3.4 mmol),

52  
53 2-amino-5-picoline (0.44 g, 4.1 mmol) and HOBt (0.15 g, 4.0 mmol) were dissolved in DMF.  
54  
55 DCC (0.76 g, 3.7 mmol) was dissolved in CH $_2$ Cl $_2$  and added at 0 °C under argon. The reaction  
56  
57 mixture was stirred for 2 hours and then additional DCC (0.38 g, 1.8 mmol) was added and  
58  
59 the reaction allowed to stir overnight at room temperature. The reaction mixture was then  
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3 filtered through celite and the filtrate was evaporated under reduced pressure. After  
4  
5 purification by silica flash column chromatography eluting with 20% EtOAc/ CH<sub>2</sub>Cl<sub>2</sub>, the  
6  
7 product was obtained as a white solid (0.15 g, 0.56 mmol, 16%). m.p. 204-206 °C; <sup>1</sup>H NMR  
8  
9 δ<sub>H</sub> (400 MHz, DMSO-d<sub>6</sub>): 10.9 (1H, s, NH-CO-Pyr), 10.4 (1H, s, CO-NH-Me), 8.34 (1H, d, *J*  
10  
11 = 8.0 Hz, Ar-H), 8.24 (1H, s, Ar-H), 8.20 (1H, d, *J* = 8.4 Hz, Ar-H), 8.06 (1H, t, *J* = 8.0 Hz,  
12  
13 Ar-H), 7.87 (1H, d, *J* = 7.6 Hz, Ar-H), 7.73 (1H, dd, *J* = 8.4; 2.0 Hz, Ar-H), 2.30 (3H, s, Ar-  
14  
15 CH<sub>3</sub>), 2.16 (3H, s, CH<sub>3</sub>-CO); <sup>13</sup>C NMR δ<sub>C</sub> (100 MHz, DMSO-d<sub>6</sub>): 169.6, 161.4, 156.6, 151.0,  
16  
17 148.2, 146.8, 140.5, 139.0, 119.5, 117.0, 116.9, 110.0, 24.0, 23.6; IR ν<sub>max</sub> (cm<sup>-1</sup>): 3354 (NH),  
18  
19 3252 (NH), 1689 (C=O), 1668 (C=O).  
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27 **6-Acetamido-*N*-(5-methylpyridin-2-yl)nicotinamide (3):** To a stirred solution of **9** (0.18 g,  
28  
29 1.0 mmol), 2-amino nicoline (0.12 g, 1.1 mmol) and HOBt (0.17 g, 1.3 mmol) was suspended  
30  
31 in DMF and, DCC (0.26 g, 1.3 mmol) and triethylamine were added and stirred for 30  
32  
33 minutes at 0–4 °C under argon and then at room temperature overnight. The reaction was  
34  
35 filtered through celite and the solvent was evaporated under reduced pressure. After  
36  
37 purification by silica flash column chromatography eluting with 20% EtOAc/CH<sub>2</sub>Cl<sub>2</sub> → 50%  
38  
39 EtOAc/CH<sub>2</sub>Cl<sub>2</sub> the product was obtained as a white solid. (0.06 g, 0.24 mmol, 24% yield).  
40  
41 m.p 217-218 °C; <sup>1</sup>H NMR δ<sub>H</sub> (400 MHz, DMSO-d<sub>6</sub>): 10.9 (1 H, s, Ar-NH-CO-Pyr), 10.2 (1  
42  
43 H, s, Ar-NH-CO-Me), 8.34 (1 H, d, *J* = 8.4 Hz, Ar-H), 8.11 (1 H, d, *J* = 8.0 Hz, Ar-H), 8.0.3  
44  
45 (1 H, t, *J* = 8.0 Ar-H), 7.86 (1 H, d, *J* = 7.6 Hz, Ar-H), 7.77 (1 H, t, *J* = 8.0 Hz, Ar-H), 7.05 (1  
46  
47 H, d, *J* = 7.2 Hz, Ar-H), 2.43 (3 H, s, Ar-CH<sub>3</sub>), 2.16 (3 H, s, CH<sub>3</sub>-CO); <sup>13</sup>C NMR δ<sub>C</sub> (100  
48  
49 MHz, DMSO-d<sub>6</sub>): 170.0, 161.6, 157.0, 151.0, 150.0, 146.8, 140.3, 139.0, 119.5, 117.2, 116.9,  
50  
51 110.0, 24.0, 23.6; Accurate MS (m/z) Calculated: 293.1008 (M+Na)<sup>+</sup>, Found: 293.1014; IR  
52  
53 ν<sub>max</sub> (cm<sup>-1</sup>): 3355 (NH), 3251 (NH), 1689 (C=O), 1668 (C=O), 1447 (pyridine).  
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3 **6-Acetamido-N-(6-methylpyridin-2-yl)nicotinamide (4):** Compound **9** (0.18 g, 1.0 mmol),  
4  
5 2-amino-5-picoline (0.15 g, 1.0 mmol) and HOBt (0.15 g, 1.1 mmol) was weighed out and  
6  
7 dried under reduced pressure before dissolved in dry THF (10 mL) and cooled in an ice bath  
8  
9 for 30 minutes. EDCI. HCl (0.21 g, 1.1 mmol) was added and stirred for further 30 minutes at  
10  
11 0 °C and then stirred overnight at R.T. The solvent was removed and the solid dried under  
12  
13 reduce pressure before CH<sub>2</sub>Cl<sub>2</sub> was added. The mixture was washed three times with saturated  
14  
15 NaHCO<sub>3</sub> and the organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to give white  
16  
17 crystals (0.04 g, 0.16 mmol, 16% yield); m.p 216-217 °C; <sup>1</sup>H NMR δ<sub>H</sub> (400 MHz, DMSO-d<sub>6</sub>):  
18  
19 10.84 (1H, s, CO-NH-Pyr), 10.83 (1H, s, CO-NH-Me), 8.93 (1H, d, *J* = 2.4 Hz, Ar-H), 8.37  
20  
21 (1H, dd, *J* = 8.8; 2.8 Hz, Ar-H), 8.22 (1H, s, Ar-H), 8.16 (1H, d, *J* = 8.8 Hz, Ar-H), 8.08 (1H,  
22  
23 d, *J* = 8.4 Hz, Ar-H), 7.67 (1H, dd, *J* = 8.4; 2.0 Hz, Ar-H), 2.29 (3H, s, Ar-CH<sub>3</sub>), 2.14 (3H, s,  
24  
25 CH<sub>3</sub>-CO); <sup>13</sup>C NMR δ<sub>C</sub> (100 MHz, DMSO-d<sub>6</sub>): δ 169.8, 163.9, 154.2, 149.9, 148.3, 147.7,  
26  
27 138.5, 138.1, 128.9, 125.0, 114.3, 112.0, 24.1, 17.4; Accurate MS (m/z) Calculated: 293.1008  
28  
29 (M+Na)<sup>+</sup>, Found: 293.1014; IR ν<sub>max</sub> (cm<sup>-1</sup>): 3355 (NH), 3251 (NH), 1689 (C=O), 1668  
30  
31 (C=O), 1449 (Pyridine).

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41 **Methyl 6-(6-(tert-butoxycarbonylamino)pyridin-2-ylcarbamoyl)-picolinate (5):** To a  
42  
43 stirred solution of **19** (0.50 g, 2.4 mmol) and **20** (0.50 g, 2.8 mmol) and HOBt (0.38 g, 2.8  
44  
45 mmol) were suspended in THF. Triethylamine (0.5 mL, 2.6 mmol) and DCC (0.55 g, 2.4  
46  
47 mmol) were added to this solution at 4 °C and under argon. This reaction was stirred at 4 °C  
48  
49 for 15 minutes and then overnight at room temperature. The reaction was filtered and the  
50  
51 solvent was removed under reduced pressure. The reaction mixture was dried and then  
52  
53 suspended in CH<sub>2</sub>Cl<sub>2</sub>. The residue was separated by silica flash column chromatography (4%  
54  
55 EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) resulting in the product as a white solid (0.24 g, 0.64 mmol, 27%). m.p.  
56  
57 153.2-154.0 °C; <sup>1</sup>H NMR δ<sub>H</sub> (400 MHz, DMSO-d<sub>6</sub>): 10.1 (1H, s, NH), 9.98 (1H, s, NH), 8.42  
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59  
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2  
3 (1H, dd,  $J = 6.8; 2.4$  Hz, Ar-H), 8.33-8.30 (2H, m, 2 x Ar-H), 7.92 (1H, dd,  $J = 8.0; 2.0$  Hz,  
4  
5 Ar-H), 7.83 (1H, t,  $J = 7.8$  Hz, Ar-H), 7.63 (1H, dd,  $J = 8.0; 0.8$  Hz, Ar-H), 3.37 (3H, s, CH<sub>3</sub>),  
6  
7 1.48 (9H, s, (CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR δ<sub>C</sub> (100 MHz, DMSO-d<sub>6</sub>): 178.3, 164.6, 153.1, 152.0, 149.2,  
8  
9 141.1, 128.7, 126.0, 109.0, 107.4, 80.1, 68.8, 53.4, 28.5, 27.9, 22.2; IR ν<sub>max</sub> (cm<sup>-1</sup>): 3344  
10  
11 (NH<sub>2</sub>), 1693 (C=O).  
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8 23. The data for crystal **2** (CCDC 743207) was collected on a Rigaku Saturn 724 CCD  
9  
10 Diffractometer. A suitable crystal was mounted using inert oil on a 0.30mm quartz fibre tip  
11  
12 and immediately placed on the goniometer head in a 121K N<sub>2</sub> gas stream. The data set was  
13  
14 collected using Crystalclear-SM 1.4.0 software and 1926 diffraction images, of 0.5° per  
15  
16 image, were recorded. Data integration and reduction were performed using Crystalclear-  
17  
18 SM 1.4.0 software.  
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22 The data for crystal **5** (CCDC 743208) was collected on a Bruker Smart Apex  
23  
24 Diffractometer. A suitable crystal was mounted using inert oil on a glass fibre tip and  
25  
26 immediately placed on the goniometer head in a 121K N<sub>2</sub> gas stream. The data was  
27  
28 collected using Bruker Smart Version 5.625 software run in multirun mode and 2400  
29  
30 image frames, of 0.3° per frame, were recorded. Data integration and reduction were  
31  
32 carried out using Bruker Saint+ Version 6.45 software and corrected for absorption and  
33  
34 polarization effects using Sadabs Version 2.10 software.  
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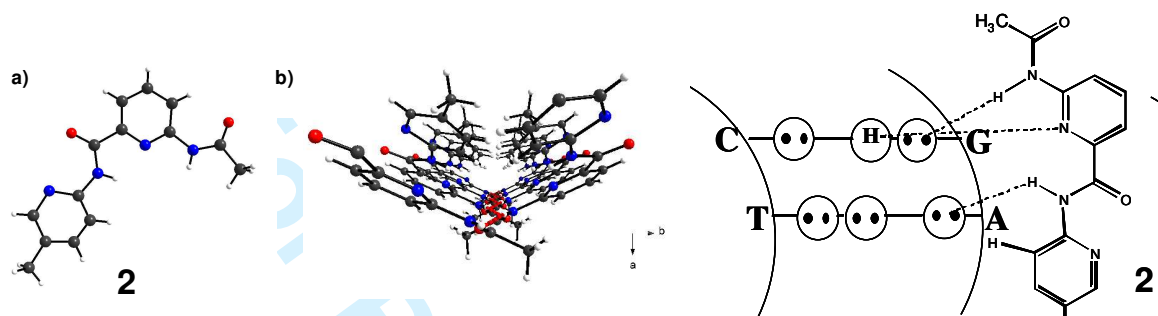
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## Graphical abstract

## Synthesis and crystallographic analysis of short pyridine based oligoamides as DNA targeting supramolecular binders

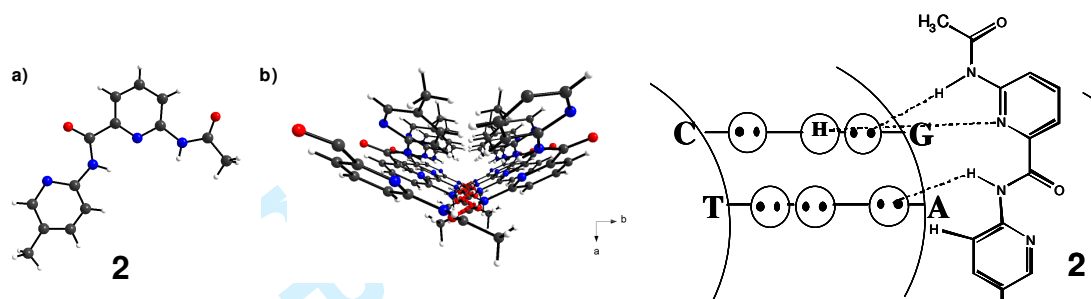
Daniel O. Frimannsson, Thomas McCabe, Wolfgang Schmitt, Mark Lawler and Thorfinnur Gunnlaugsson



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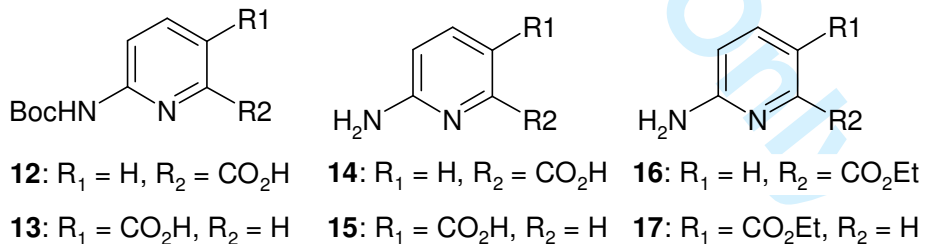
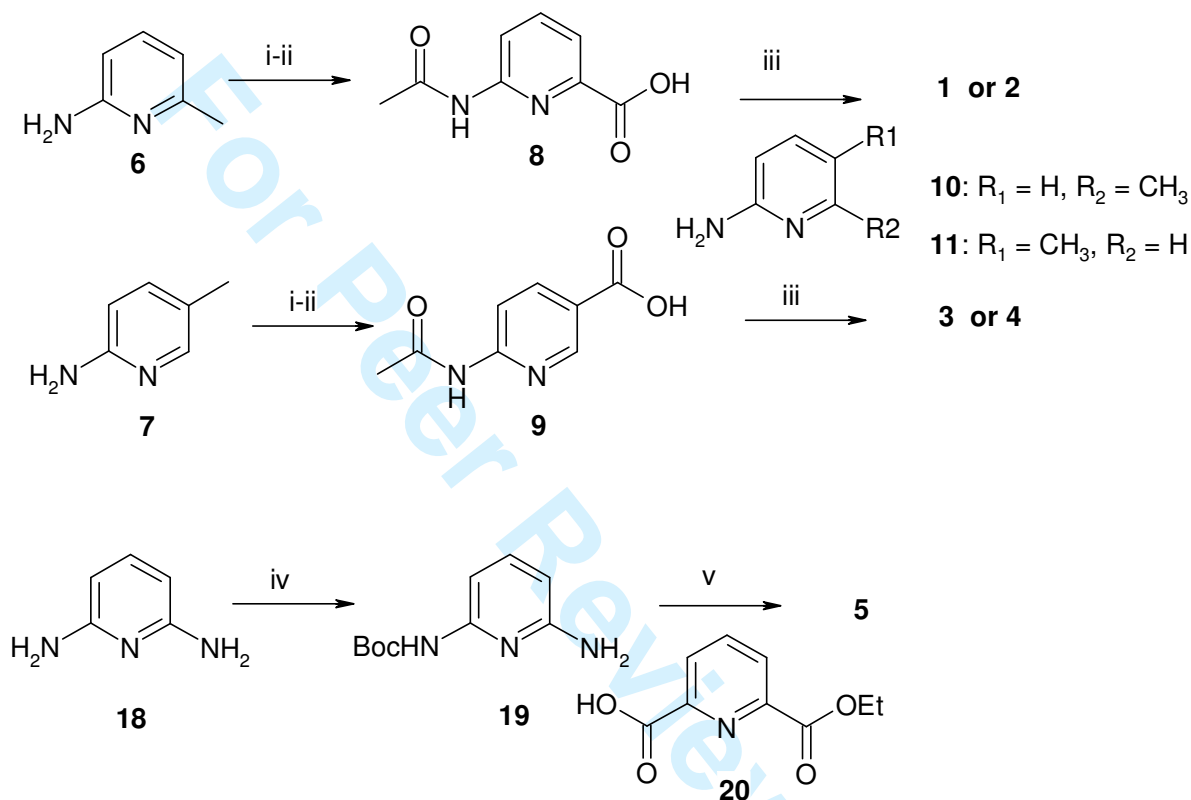
## Synthesis and crystallographic analysis of short pyridine based oligoamides as DNA targeting supramolecular binders

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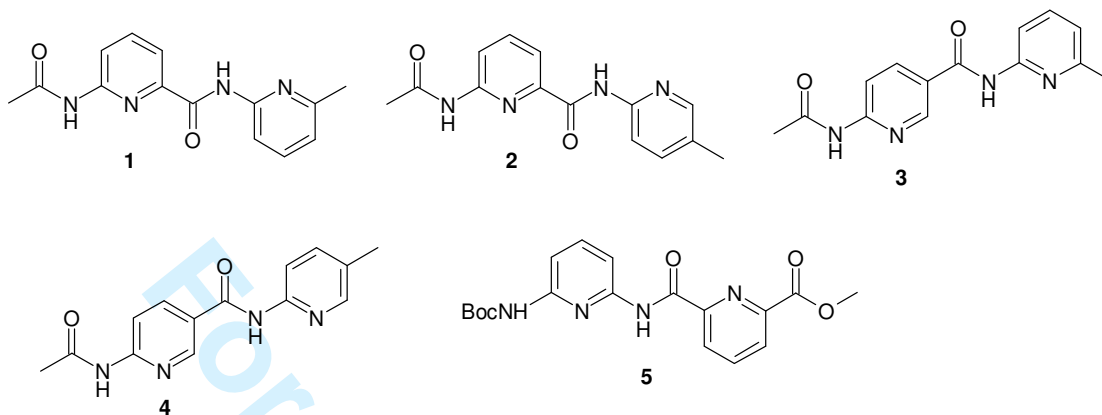


## Schemes and Figures

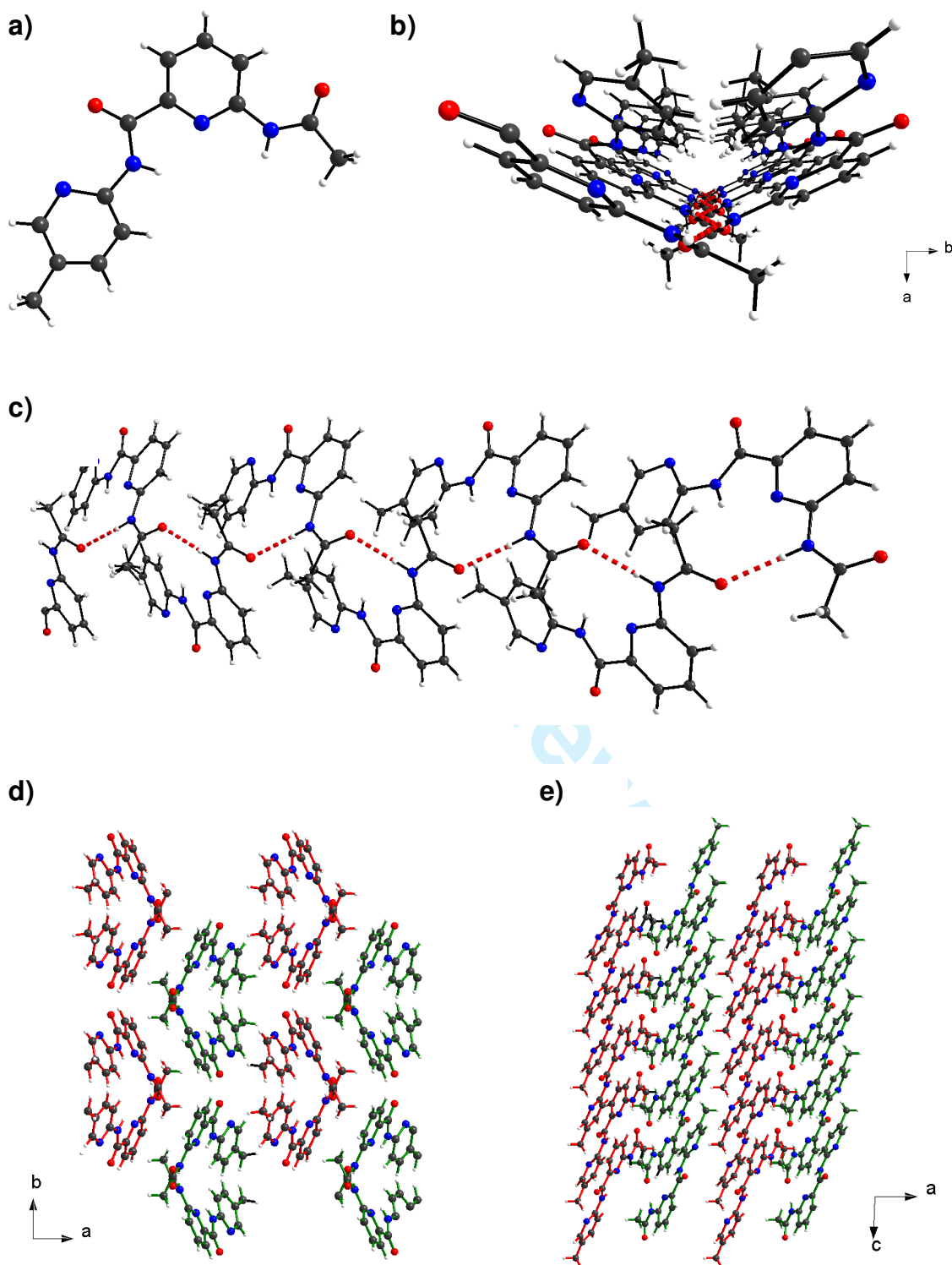
**Scheme 1.** (i) Acetic anhydride, toluene, 95 °C. (ii) KMnO<sub>4</sub>, NaOH, H<sub>2</sub>O, reflux. (iii) DCC (or EDCI) HOBt, DMF, RT. (iv) Boc anhydride, THF, room temperature, (v) DCC, HOBt, Et<sub>3</sub>N, THF, RT.



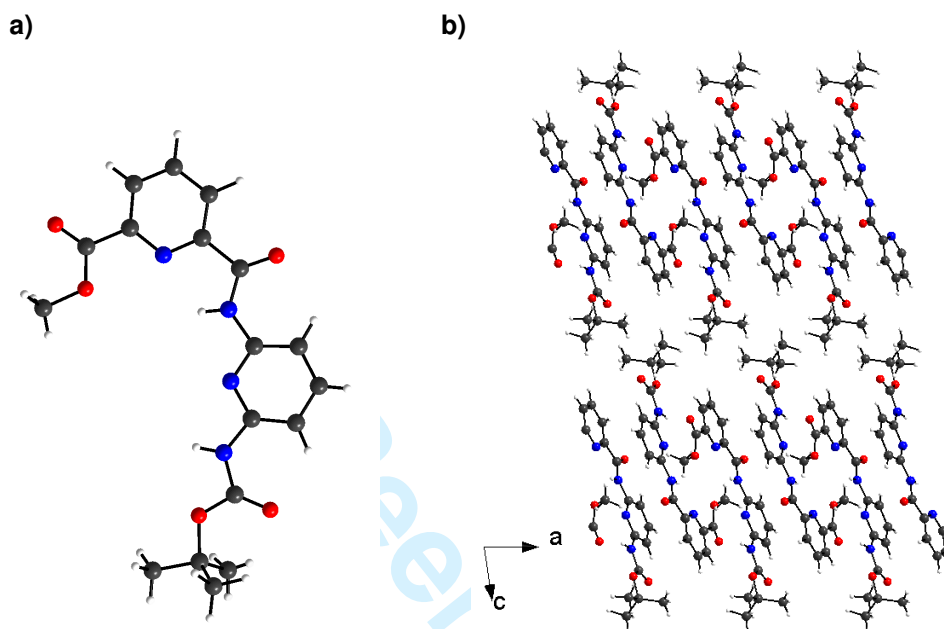
**Figure 1.** Structure of di-pyridine peptides **1-5**



**Figure 2.** *a)* Structure of **2**. *b)* and *c)* H-bonded 1D chain structure of **2**. *d)* and *e)* Packing diagrams with view in the direction of the crystallographic *c*- and *b*-axis



**Figure 3.** a) Structure of **5**. b) Packing of **5** in the crystal structure with view in the direction of the crystallographic *b*-axis (C grey, O red, N blue, H white).



**Figure 4.** Thermal denaturation curves of ct-DNA (150  $\mu$ M) in 10 mM phosphate buffer, pH 7.4, in the absence (green) and in the presence of **2** (purple) at a P/D of 10.

