Accepted Manuscript

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PII: S0040-4020(16)30570-1

DOI: 10.1016/j.tet.2016.06.048

Reference: TET 27862

To appear in: *Tetrahedron*

Received Date: 17 April 2016

Revised Date: 10 June 2016

Accepted Date: 20 June 2016

Please cite this article as: Ledovskaya MS, Molchanov AP, Kostikov RR, Panikorovsky TL, Gurzhiy VV, Ryazantsev MN, Boitsov VM, Stepakov AV, Anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines via an endocyclic *N*-acyliminium ion cyclization: a joint experimental and theoretical study, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.06.048.

Graphical Abstract

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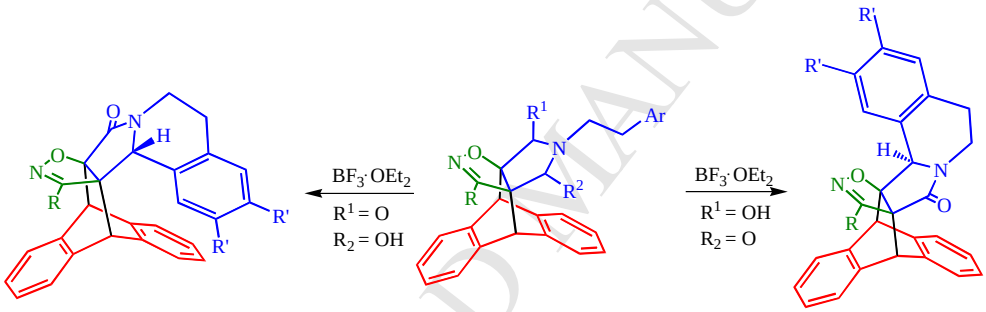

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Anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines *via* an endocyclic *N*-acyliminium ion cyclization: a joint experimental and theoretical study

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
dihydroisoxazoles
hydroxylactams
N-acyliminium ion
intramolecular cyclization
quantum chemical investigation

ABSTRACT

A simple and efficient strategy is reported for the synthesis of anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines *via* an endocyclic *N*-acyliminium ion cyclization. The cyclization of 18-aryl-21-(2-arylethyl)-22-hydroxy-16-oxa-17,21-diazahexacyclo[6.6.5.3^{15,19}.0^{2,7}.0^{9,14}.0^{15,19}]docosa-2,4,6,9,11,13,17-heptaen-20-ones proceeds with high stereoselectivity, leading to 28-aryl-30-oxa-12,29-diazaoctacyclo[13.6.6.3^{2,14}.0^{2,14}.0^{3,12}.0^{4,9}.0^{16,21}.0^{22,27}]triaconta-4,6,8,16,18,20,22,24,26,28-decaen-13-ones. The *N*-acyliminium cyclization of 18-aryl-21-(2-arylethyl)-20-hydroxy-16-oxa-17,21-diazahexacyclo[6.6.5.3^{15,19}.0^{2,7}.0^{9,14}.0^{15,19}]docosa-2,4,6,9,11,13,17-heptaen-22-ones occurs only for substrates with electron-rich aromatic groups in the arylalkyl fragment. In these cases, cyclization also proceeds with a high stereoselectivity with the formation of anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines as single diastereomers. To understand the mechanisms that allow for cyclization of *N*-acyliminium ion a quantum chemical investigation was performed.

1. Introduction

Efficient creation of structural, functional and stereochemical complexity from simple precursors is one of the most desired aspects of new synthetic methodology development. Despite the fact that some of natural and artificial biologically active compounds have fairly simple structures, a variety of them consist of several subunits. That dramatically complicates their synthesis and requires the development of new efficient and effective synthetic strategies. Present research focused at the compounds bearing pyrrolo[2,1-*a*]isoquinoline, isoxazoline and anthracene subunits.

Natural products containing a pyrrolo[2,1-*a*]isoquinoline framework display a variety of pharmacological effects including cytotoxic [crispine B (**1**)],[1] antitumor [crispine B (**1**) and crispine A (**2b**)],[1,2] antibacterial and antiviral activites [trolline (salsoline A) (**2a**)],[3] DPPH free radical scavenging activity and inhibitory activity [oleracein E (**2c**)][4] (Fig. 1). Synthetic pyrroloisoquinolines are reported to exhibit wide variety of biological activities such as antineoplastic,[5] antitumor,[6] antidepressant,[7] antileukemic,[5a] antiviral[8] and activity as α2-adrenoreceptor antagonists.[9] It is well documented that compounds containing isoxazoline units are known for their various bioactive properties such as antibacterial (**3**),[10] antituberculosis (**4**),[11] antiplatelet,[12] antiviral,[13] anticonvulsant,[14] immunostimulatory[15] and antihypertensive.[16]

Various biological activities have been found for anthracene based compounds, e.g., antioxidant,[17] analgesic,[18] anti-inflammatory,[18] antibacterial[19] and activity as calcium channel blockers **5a**[20] and P-glycoprotein inhibitors **5b**[21] (Fig. 1).

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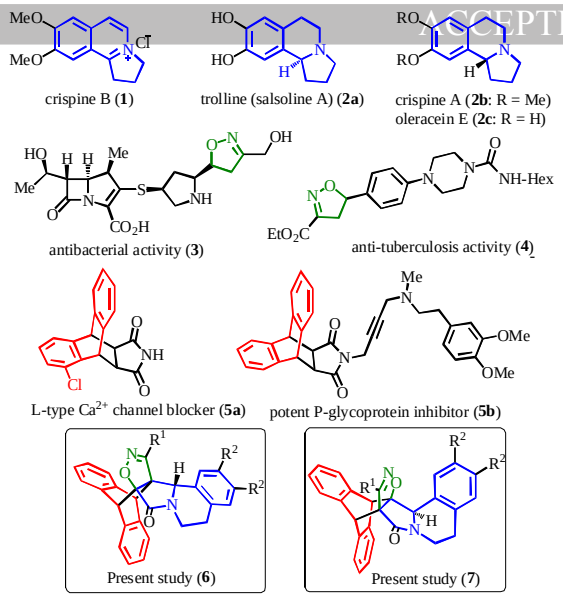
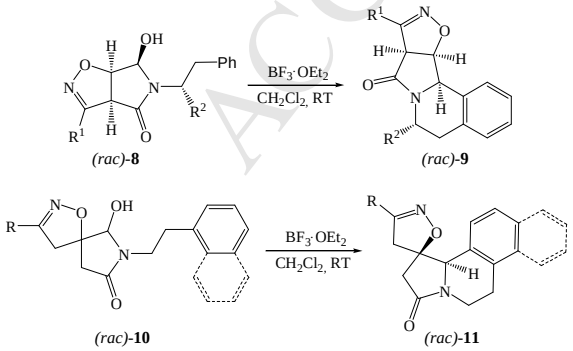


Fig. 1 Natural active pyrrolo[2,1-*a*]isoquinolines **1** and **2a-c**, dihydroisoxazole-containing bioactive compounds **3** and **4**, anthracene based bioactive compounds **5a**,**b** and the anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines **6** and **7** from this work.

The interest in the compounds of these classes is not limited only by their pharmacological action. They have found a wide range of implementation and at the other fields. *N*-Substituted 3,4-(9',10'-dihydroanthracene-9',10'-diyl)succinimides have been used as model compounds to study the interaction of an aromatic π system with aliphatic H atoms and heteroatoms such as oxygen, sulfur, and fluorine.[22] Maleimide cycloadducts of anthracene derivatives can evolve into the realization of valuable molecular probes for imaging applications based on fluorescence photoactivation.[23]

Thereby the development of simple, efficient and effective synthetic methods for compounds containing pyrrolo[2,1-*a*]isoquinoline, isoxazole and anthracene structural fragments is still an important and actual challenge of organic chemistry. In the present work we report a simple and efficient approach to synthesise anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines *via* an endocyclic *N*-acyliminium ion cyclization as the key synthetic step.[24]

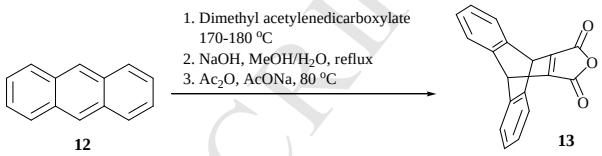
Previously, we described the first synthesis of isoxazolopyrroloisoquinolines **9** and spiro[isoxazolopyrroloisoquinolines] **11** *via* the diastereoselective intramolecular trapping of an *N*-acyliminium ion (Scheme 1).[25]



Scheme 1 Previous works: synthesis of isoxazolopyrroloisoquinolines **9** and spiro[isoxazolopyrroloisoquinolines] **11** *via* diastereoselective intramolecular trapping of an *N*-acyliminium ion.

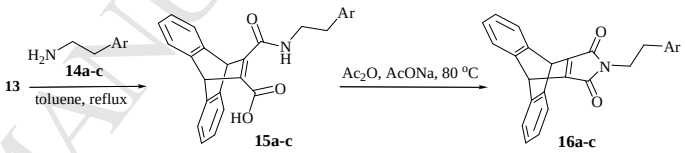
2. Results and discussion

Synthesis: We have chosen an anthracene as the first subunit to be involved in the target compound and substituted maleimides – as the simple basis for further construction of isoxazolopyrroloisoquinoline ring system (according to our previous study,[25] Scheme 1). So the first key intermediates have to be prepared are imides **16**. They were easily prepared from anhydride **13**. The latter in turn was synthesized in good overall yield starting from anthracene and dimethyl acetylenedicarboxylate by a slight modification of the original procedure of Diels and Alder (Scheme 2).[26] Treating **13** with amines **14a–c** in toluene at 110 °C gave the ring opened amides **15a–c** which could be isolated, but more conveniently were cyclized immediately with acetic anhydride and AcONa to yield the maleimides **16a–c** (Table 1).[26b]



Scheme 2 Synthesis of anhydride **13**.

Table 1 Synthesis of maleimide derivatives **16a–c**.

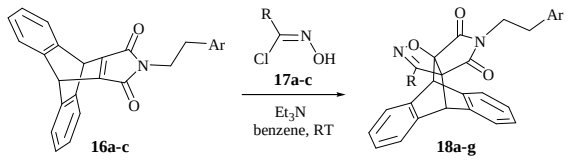


Entry	Ar	Product	Yield (%)[a]
1	Ph (**14a**)	**16a**	72
2	3,4-$(MeO)_2C_6H_3$ (**14b**)	**16b**	75
3	1-naphthyl (**14c**)	**16c**	53

[a] Isolated yield over two steps.

In the second part of this work we examined 1,3-dipolar cycloaddition of maleimides **16a–c** to nitrile oxides, generated from the corresponding hydroximoyl chlorides **17a–c** in the presence of triethylamine (Table 2). Benzonitrile oxide (generated *in situ* from the hydroximoyl chloride **17a** in the presence of Et_3N) was treated with **16a** in benzene at 20 °C to give isoxazole **18a** in 67% yield (Table 2, entry 1). A similar reaction occurred between imide **16a** and nitrile oxide generated from **17b**, giving isoxazole **18b** in 93% yield (Table 2, entry 2). The reactions of maleimides **16b,c** with nitrile oxides generated from hydroximoyl chlorides **17a–c** led to isoxazoles **18c–g** in yields ranging from 47% up to 98% (Table 2, entries 3-7). The structural assignment of the isolated isoxazoles **18a–g** was made on the basis of their spectroscopic data. The ^1H NMR spectrum of **18a** exhibited two singlets at δ = 5.10 and 5.15 ppm which can be assigned to the methine protons. The ^{13}C NMR spectrum of **18a** have signals at δ = 47.7 and 48.2 ppm belonging to the carbons of methine groups. The quaternary carbon atoms of the isoxazole **18a** is observed at δ = 74.9 and 96.7 ppm.

Table 2 1,3-Dipolar cycloaddition of nitrile oxides to maleimides **16a–c**[a]

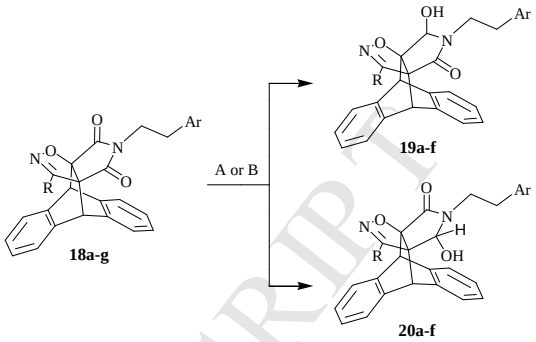


Entry	Ar	R	Product	Yield (%)[b]
1	Ph (**16a**)	4-MeC_6H_4 (**17a**)	**18a**	67
2	Ph (**16a**)	4-ClC_6H_4 (**17b**)	**18b**	93
3	3,4-$(MeO)_2C_6H_3$ (**16b**)	CO_2Et (**17c**)	**18c**	47
4	3,4-$(MeO)_2C_6H_3$ (**16b**)	4-MeC_6H_4 (**17a**)	**18d**	63
5	3,4-$(MeO)_2C_6H_3$ (**16b**)	4-ClC_6H_4 (**17b**)	**18e**	70
6	1-naphthyl (**16c**)	4-MeC_6H_4 (**17a**)	**18f**	98
7	1-naphthyl (**16c**)	4-ClC_6H_4 (**17b**)	**18g**	72

[a] Reaction conditions: **16** (1 equiv), **17** (1.5 equiv), Et_3N (1.5 equiv), benzene, RT. [b] Isolated yield.

For the next step in our study, the reduction of the imide function of substrates **18a–g** were investigated. Recently we have shown, that the reduction of some substituted pyrrolo[3,4-d]isoxazol-4,6-diones and 1-oxa-2,7-diazaspiro[4.4]non-2-ene-6,8-diones with sodium borohydride in methylene chloride–ethanol at –80 to –20 °C proceeds regioselectively to yield corresponding hydroxylactams. In all cases, only the carbonyl group at the *β*-position with respect to the oxygen atom of the dihydroisoxazole ring was reduced. Presumably, this is related to the inductive effect of the oxygen atom of the isoxazole ring.[27] The reduction of imide **18a** with $NaBH_4$ was carried out in methylene chloride–ethanol at room temperature for 30 d, to provide the regioisomeric hydroxylactams **19a** and **20a** in yields of 29% and 42% respectively (Table 3, entry 1). A ^{1}H NMR analysis of the crude reaction mixtures showed that the hydroxylactams **19a** and **20a** formed as single diastereomers. The stereochemistry of **19a** was not determined. The hydroxylactam **20a** is an epimer of **23a**. The compound **23a** was prepared from **20a** by treatment with $BF_3{\cdot}OEt_2$ (see scheme 3 and fig. 3). The reaction **18a** with $NaEt_3BH$ in tetrahydrofuran at –80 to –20 °C for 3 d gave **19a** in 36% yield along with regioisomeric adduct **20a** in 31% yield (Table 3, entry 2). The desired hydroxylactam **19b** was obtained in 41% yield along with product **20b** in 30% yield, when the reaction of **18b** was carried out with two molar equivalents of $NaBH_4$ in methylene chloride–ethanol at room temperature for 36 d (Table 3, entry 3). The reaction **18b** with $NaEt_3BH$ in tetrahydrofuran at –80 to –20 °C for 4 d gave **19b** in 51% yield along with regioisomeric adduct **20b** in 35% yield (Table 3, entry 4). Unfortunately, reaction of imide **18c** with $NaEt_3BH$ or $NaBH_4$ as hydride sources led to the formation of complex mixture (products of ester groups hydrolysis and opening of the imide ring) that was difficult to separate (Table 3, entry 5). Sodium triethylborohydride reduction of the imides **18d** and **18e** in tetrahydrofuran gave mixture of hydroxylactams **19c**, **20c** and **19d**, **20d** respectively, which were separated chromatographically (Table 3, entries 6 and 7). Addition of a tetrahydrofuran solution of $NaEt_3BH$ (3 equiv.) to a pre-cooled (–78 °C) tetrahydrofuran solution of **18e** resulted (after warming to –20 °C for 3 d) in the formation of regioisomeric hydroxylactams **19d** and **20d** in yields of 30 and 63% respectively. The hydroxylactams derivatives **19e** and **20e** with (naphthalen-1-yl)ethyl substituent at the pyrrolidine ring were obtained in 45 and 31% yields respectively by the reaction of **18f** with the $NaBH_4$ for 45 d (Table 3, entry 8). The reduction of imide **18g** with $NaEt_3BH$ was then attempted (THF, –78 to –20 °C, 3 d). Separation of the crude mixture on silica gel gave pure sample of lactam **20f** as a single diastereomer in 20 % yield (Table 3, entry 9). The other regioisomeric product **19f** was not isolated in pure form. The use of $NaBH_4$ led to similar results. Thus, reduction of the amide **18a–g** by $NaBH_4$ or $NaEt_3BH$ occurred non-selectively to give regioisomeric hydroxylactams **19** and **20**.

Table 3 Reduction of compounds **18a–g** with $NaBH_4$ and $NaEt_3BH$

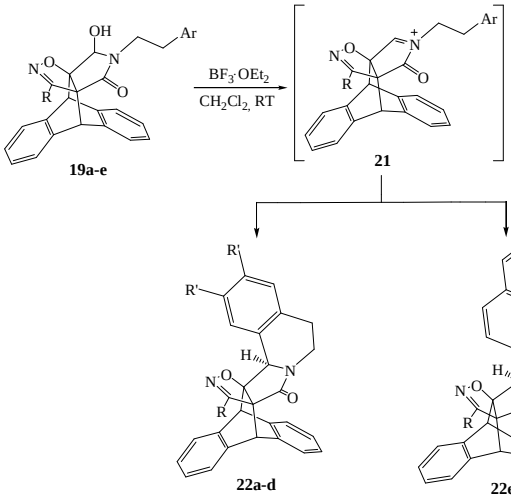


Entry	Ar	R	Yield of **19** (%)[c]	Yield of **20** (%)[c]
1[a]	Ph	4-MeC_6H_4 (**18a**)	**19a** (29)	**20a** (42)
2[b]	Ph	4-MeC_6H_4 (**18a**)	**19a** (36)	**20a** (31)
3[a]	Ph	4-ClC_6H_4 (**18b**)	**19b** (41)	**20b** (30)
4[b]	Ph	4-ClC_6H_4 (**18b**)	**19b** (51)	**20b** (35)
5[a,b]	3,4-$(MeO)_2C_6H_3$	CO_2Et (**18c**)	complex mixture	
6[b]	3,4-$(MeO)_2C_6H_3$	4-MeC_6H_4 (**18d**)	**19c** (43)	**20c** (24)
7[b]	3,4-$(MeO)_2C_6H_3$	4-ClC_6H_4 (**18e**)	**19d** (30)	**20d** (63)
8[a]	1-naphthyl	4-MeC_6H_4 (**18f**)	**19e** (45)	**20e** (31)
9[b]	1-naphthyl	4-ClC_6H_4 (**18g**)	**19f** (–) [d]	**20f** (20)

[a] Reaction conditions: **18**, $NaBH_4$ (2 equiv), CH_2Cl_2/EtOH, 5 to 20 °C.
[b] Reaction conditions: **18**, $NaEt_3BH$ (3 equiv), THF, -78 to -20 °C.
[c] Isolated yield. [d] Was not isolated from the reaction mixture.

Next, the intramolecular Friedel-Crafts–type reactions of hydroxylactams **19a–e** were investigated (Table 4). Treatment of *N*-acyliminium precursors **19a** and **19b** with an excess of $BF_3{\cdot}OEt_2$ (6 equiv.) in CH_2Cl_2 at room temperature gave the anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines **22a** and **22b** as single diastereomers in 93 and 82% yield respectively (Table 4, entries 1 and 2). The signals of the other possible diastereomers were not found in ^{1}H NMR spectra of crude reaction mixtures. The *N*-acyliminium ion cyclization of hydroxylactams with methoxy-substituted aromatic ring **19c,d** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature proceeded cleanly to provide isoxazolopyrroloisoquinolines **22c,d** in 92 and 91 % yields respectively (Table 4, entries 3 and 4). Furthermore, the polycyclic compound **22e** was formed in 99% yield in the case of the 1-naphthyl substituted *N*-acyliminium ion precursor **19e** (Table 4, entry 5). From the analysis of ^{1}H NMR spectrum of the crude reaction mixtures it was concluded that the cyclization of hydroxylactams **19a–e** produced only single diastereomers. The relative stereochemistry of anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines **22** was determined by single-crystal X-ray diffraction (for compound **22a**) (Fig. **2**).

Table 4 $BF_3{\cdot}OEt_2$-catalyzed intramolecular diastereoselective Friedel-Crafts–type cyclization of hydroxylactams **19a–e**[a]



Entry	Ar	R	R′	Time, d	Yield of **22** (%)[b]
1	Ph	4-MeC_6H_4 (**19a**)	H	1	**22a** (93)
2	Ph	4-ClC_6H_4 (**19b**)	H	5	**22b** (82)
3	3,4-$(MeO)_2C_6H_3$	4-MeC_6H_4 (**19c**)	MeO	1	**22c** (92)
4	3,4-$(MeO)_2C_6H_3$	4-ClC_6H_4 (**19d**)	MeO	7	**22d** (91)
5	1-naphthyl	4-MeC_6H_4 (**19e**)	–	1	**22e** (99)

[a] Reaction conditions: **19** (1 equiv.), $BF_3{\cdot}OEt_2$ (5 equiv.), CH_2Cl_2, RT.
[b] Isolated yield.

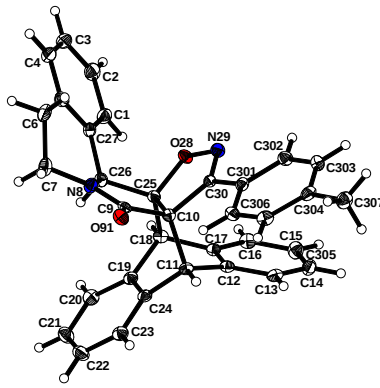
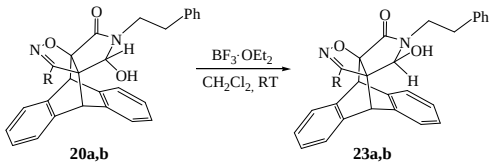


Fig. 2. ORTEP representation of compound **22a**

Interestingly, that *N*-acyliminium cyclization does not occur for phenethyl-substituted *N*-acyliminium precursors **20a**,**b**. For example, the treatment of hydroxylactams **20a**,**b** with an excess of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature led to the formation of the corresponding epimers **23a**,**b** in good yields (**23a**: 91%, **23b**: 83%) (Scheme 3). We were able to obtain sufficiently good crystals of **23a** for an X-ray crystallographic study that confirmed its structure (Fig. 3). At the same time, the *N*-acyliminium cyclization of hydroxylactams **20c** and **20d** with electron-rich dimethoxy-functionalised aromatic group led to the polycyclic compounds **25a** and **25b** as single diastereomers in 99 and 82% yield respectively (Table 5, entries 1 and 2). Analogous cyclizations were also achievable for the 1-naphthyl substituted hydroxylactams **20e**,**f**. The single diastereomers **25c**,**d** were obtained by the treatment of *N*-acyliminium ion precursors **20e**,**f** with an excess of $BF_3{\cdot}OEt_2$ (5 equiv.) in CH_2Cl_2 at room temperature (Table 5, entries 3 and 4). The structural elucidation and the attribution of the relative stereochemistry of the products **25a**–**d** were based upon NMR analysis and were unequivocally confirmed by X-ray diffraction of single crystals of **25c** (Fig. 4).



Scheme 3 Reaction of compounds **20a**,**b** with $BF_3{\cdot}OEt_2$.

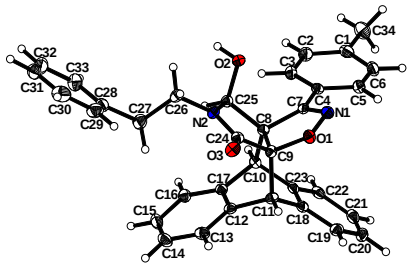
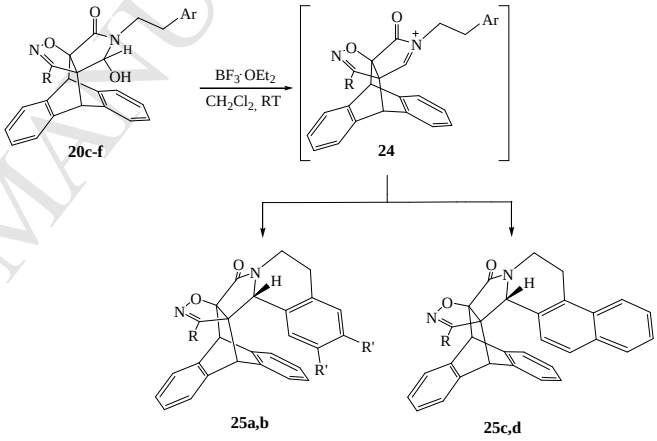


Fig. 3 ORTEP representation of compound **23a**.

Table 5 $BF_3{\cdot}OEt_2$-catalyzed intramolecular diastereoselective Friedel-Crafts–type cyclization of hydroxylactams **20c–f**[a]



Entry	Ar	R	R′	Time, d	Yield of **25** (%)[b]
1	3,4-$(MeO)_2C_6H_3$	4-MeC_6H_4 (**20c**)	MeO	1	**25a** (99)
2	3,4-$(MeO)_2C_6H_3$	4-ClC_6H_4 (**20d**)	MeO	7	**25b** (82)
3	1-naphthyl	4-MeC_6H_4 (**20e**)	–	7	**25c**(85)
4	1-naphthyl	4-ClC_6H_4 (**20f**)	–	2	**25d** (52)

[a] Reaction conditions: **20** (1 equiv.), $BF_3{\cdot}OEt_2$ (5 equiv.), CH_2Cl_2, RT.
[b] Isolated yield.

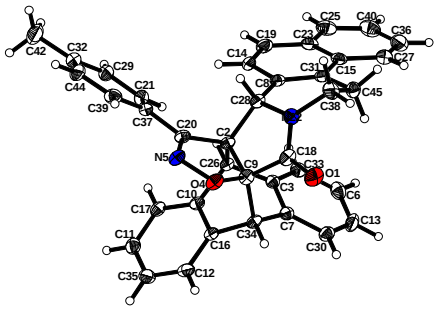


Fig. 4 ORTEP representation of compound **25c**.

Computational investigation of the reaction mechanisms: Since for all of the studied reactions *N*-acyliminium cyclization products were observed (except hydroxylactames **20a,b**), we limited our investigation by dimethoxy-substituted hydroxylactames **19c**, **20c** and **20a**. We assumed that the key stage of the process is the unimolecular π-nucleophile attack of an *N*-acyliminium ion with the formation of corresponding σ-complex. Indeed, for all investigated compounds the reaction with $BF_3 \cdot OEt_2$ should result in formation of an *N*-acyliminium ion (**21** and **24**). On other side, the release of the hydrogen atom in the sigma-complex formed after the π-nucleophile attack should be energetically favorable due to an aromatic ring formation. Therefore, we focus on a search of the transition states that describe the cyclization process with a subsequent calculations of the reaction path starting from each found transition state and moving in both possible directions: to the product and to the reactant. Results of these calculations are summarized in the schemes 4-6. For all reactions, we found two types of transition states that differ in relative arrangement of hydrogens on the reactive carbon atoms: *cis*- and *trans-ts* (Fig. 5 and 6). For all investigated compounds *trans*-σ-complexes (Fig. 5b and 6b) are substantially lower in energy than *cis*-σ-complex (Fig. 5a and 6a) and reactions proceed *via* transition states of this kind. According to the calculations, the barriers for the cyclization of *N*-acyliminium cations **21** and **24** (Schemes 4-6) that leads to *cis*-σ-complexes are higher by 6.7-19.1 kcal/mol then the barriers for the reactions to form *trans*-σ-complexes (Table S1).

Possible pathways for cyclization of generated from **19c** *N*-acyliminium cation **21** are shown in the scheme 4. The formation of the sigma-complex *A trans* that leads to experimentally observed compound is favorable both kinetically (the barrier is only 4.0 kcal/mol) and thermodynamically (the energy difference is 1.7 kcal/mol).

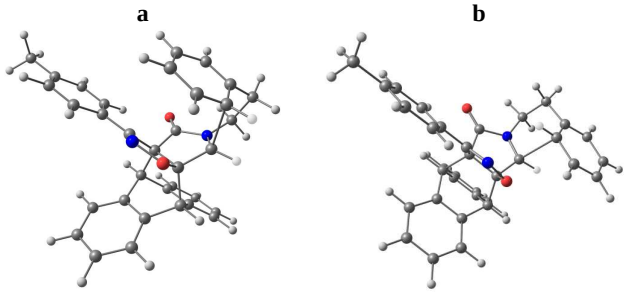


Fig. 5 *Cis*- (a) and *trans*- (b) σ-complex after π-nucleophile attack on the *N*-acyliminium ion **21** from isoxazoline moiety.

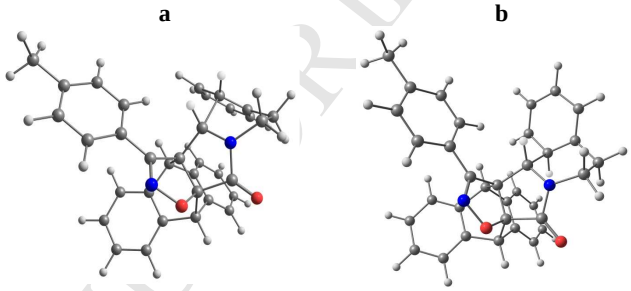
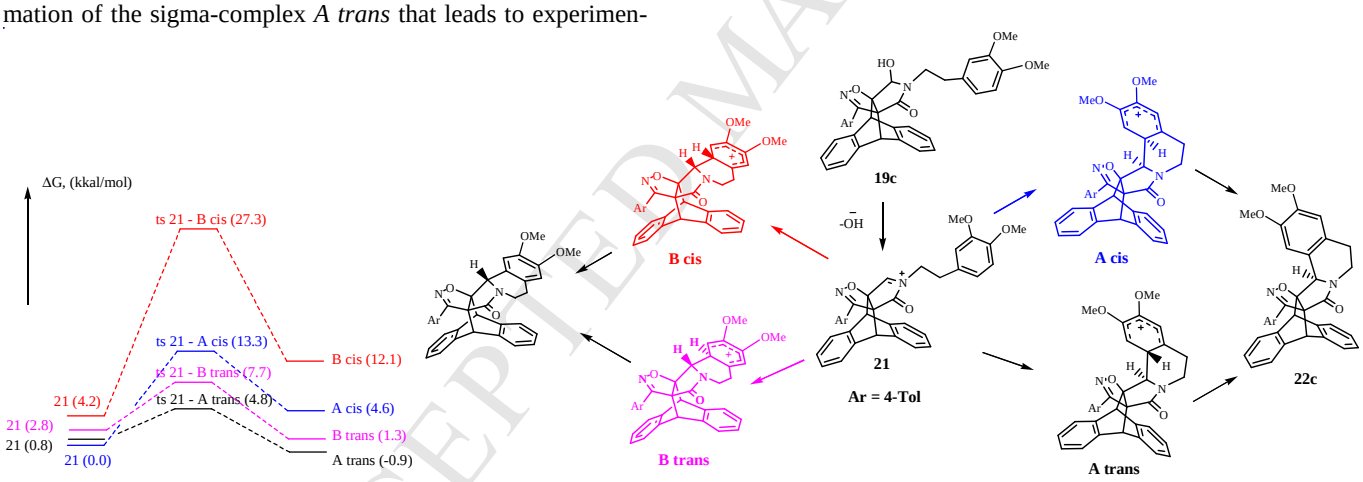


Fig. 5 *Cis*- (a) and *trans*- (b) σ-complex after π-nucleophile attack on the *N*-acyliminium ion **24** from isoxazoline moiety.

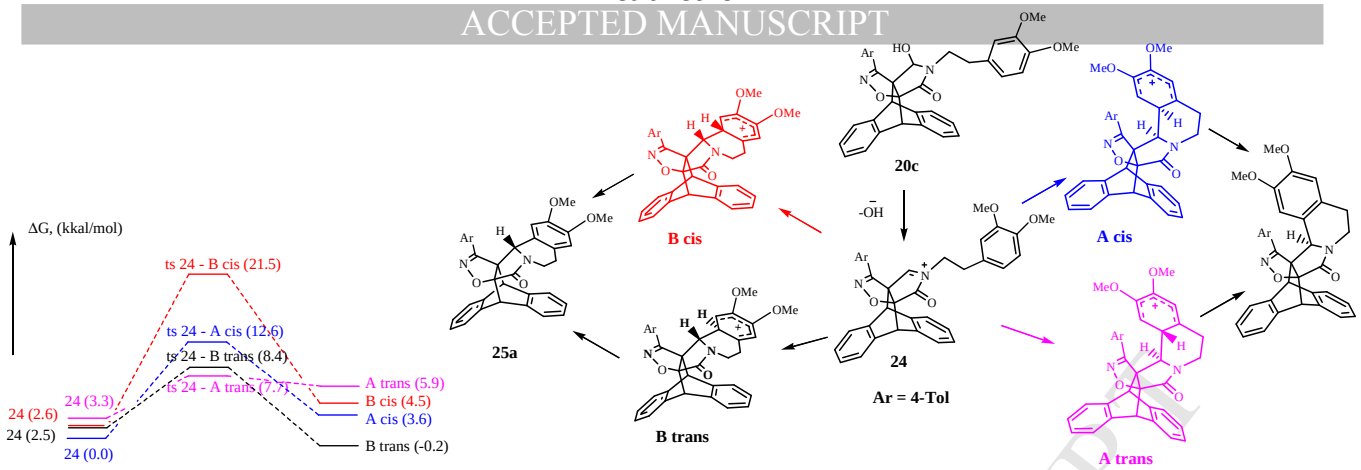


Scheme 4 Calculated reaction mechanism for the formation of **22c**.

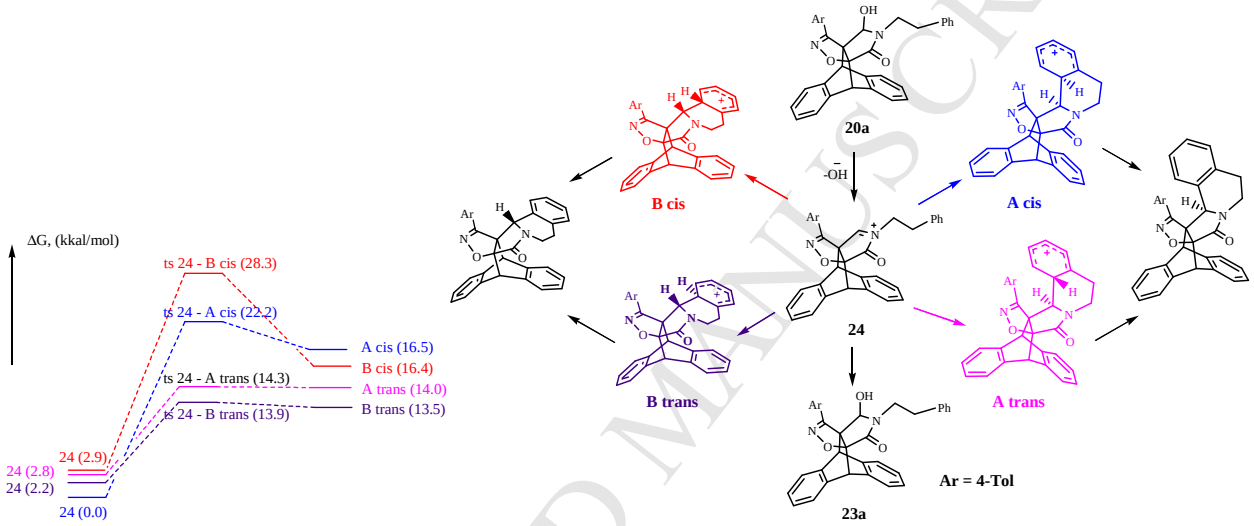
The free energy barrier for the cyclization of *N*-acyliminium cation **21** into sigma-complex *B trans* are higher by 1.0 kcal/mol than those for cyclization into *A trans*. The routes that lead to other products are forbidden thermodynamically or both thermodynamically and kinetically.

For the investigated reaction routes shown in scheme 5 for *N*-acyliminium cation **24**, the only favorable path is the path that proceeds through the sigma-complex *B trans* to **25a** in full agreement with experiment. This product is formed via a transition state with the 5.9 kcal/mol barrier and the stabilization energy is 2.7 kcal/mol.

No cyclization products were observed at the same condition for **20a** (Scheme 6). Our calculations are in full agreement with this finding. All cyclization reactions are forbidden thermodynamically or both thermodynamically and kinetically.



Scheme 5 Calculated reaction mechanism for the formation of **25a**.



Scheme 6 Calculated reaction mechanism for the compound **20a**.

From the obtained results it is evident that the *N*-acyliminium cyclization for substrates **19a–e** (**20c**–**f**) occurs by direct attack the *N*-acyliminium ion intermediate **21**(**24**) by the π-aromatic system linked to the nitrogen atom of the pyrrolidinone ring producing the anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines **22** (**25**).

3. Conclusion

In conclusion, we have shown simple and efficient approach to the synthesis of anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines in good yield by $BF_3{\cdot}OEt_2$-mediated *N*-acyliminium ion cyclisation. The cyclization of 18-aryl-21-(2-arylethyl)-22-hydroxy-16-oxa-17,21-diazahexacyclo-[6.6.5.3^{15,19}.0^{2,7}.0^{9,14}.0^{15,19}]docosa-2,4,6,9,11,13,17-heptaen-20-ones proceeds with high stereoselectivity, leading to 28-aryl-30-oxa-12,29-diazaoctacyclo[13.6.6.3^{2,14}.0^{2,14}.0^{3,12}.0^{4,9}.0^{16,21}.0^{22,27}]-triaconta-4,6,8,16,18,20,22,24,26,28-decaen-13-ones. The *N*-acyliminium cyclization of 18-aryl-21-(2-arylethyl)-20-hydroxy-16-oxa-17,21-diazahexacyclo[6.6.5.3^{15,19}.0^{2,7}.0^{9,14}.0^{15,19}]docosa-2,4,6,9,11,13,17-heptaen-22-ones occurs only for substrates with electron-rich aromatic groups in arylalkyl fragment. In these cases, cyclization also proceeds with a high stereoselectivity with the formation of anthracene-fused isoxazolopyrrolo[2,1-*a*]isoquinolines as single diastereomers. A quantum chemical investigation was performed to understand the mechanisms that allow for cyclization of the *N*-acyliminium ion.

4. Experimental section

4.1. General remarks

IR spectra were obtained on a Bruker Tensor 27 spectrometer. Melting points were determined on a Boetius instrument and are uncorrected. NMR spectra were recorded on a Bruker Avance III spectrometer (^{1}H, 400 MHz; ^{13}C, 100 MHz). Chemical shifts δ are reported in ppm relative to residual $CHCl_3$ (^{1}H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.16) as internal standard. High-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF 10223 spectrometer using electrospray ionization (ESI). The X-ray diffraction data were performed by means of a Bruker APEX-II CCD diffractometer with Mo-K X-ray radiation. Reactions were monitored by TLC analysis using Silufol UV-254 plates. Thin layer chromatography was performed on silica gel 5–40 mesh eluted with dichloromethane/methanol. Crystallographic data for compounds **22a**, **23a**, and **25c** have been deposited at the Cambridge Crystallographic Data Centre (Deposition No. CCDC-1403120, CCDC-1402997, and CCDC-1403317, respectively) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. Preparation and characterization of compounds **22a–e and 25a–d** are disclosed below, while compounds **13**, **16a–c**, **18a–g**, **19a–e**, **20a–f** and **23a,b** described in the Supplementary data.

Computational methodology: A number of minima and saddle points were located on the potential energy surface to obtain equilibrium structures and transition states. The type of all sta-

tionary points found was confirmed by harmonic frequencies calculations. The accessibility of products and reactants from a given transition state were confirmed by IRC calculations. Gibbs free energies were calculated at 273 K using energies and harmonic frequencies calculated at the previous step. Calculations were done at the M06-2X/6-31g* level of theory. Gaussian 09 quantum chemistry software package was used for all calculations.[28]

4.2. General procedure for the preparation of substituted isoxazolopyrroloisoquinolines (22a–e and 25a–d).

To vigorously stirred solution of corresponding hydroxylactam (**19** or **20**) in anhyd. dichloromethane under argon atmosphere was added 5 equiv. of boron trifluoride diethyl etherate. The reaction mixture was stirred in a capped vial for 1–7 d at room temperature (see tables 4 and 5). After completion of the reaction, water was added carefully to the reaction mixture (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated to dryness. The residue was then purified by preparative thin-layer chromatography (using a mixture of CH_2Cl_2/MeOH as eluent), or crystallized from methanol (or ethanol).

*4.2.1. 28-(p-Tolyl)-30-oxa-12,29-diazaoctacyclo-[13.6.6.3^{2,14}.0^{2,14}.0^{3,12}.0^{4,9}.0^{16,21}.0^{22,27}]triaconta-4,6,8,16,18,20,22,24,26,28-decaen-13-one (**22a**).* 13 mg (93 %) yield (m. p. 235–238 ºC, methanol) as a colorless solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.39 (s, 3H, Me), 2.59 (dd, 1H, CH_2, J = 15.7, 3.2 Hz), 2.67–2.74 (m, 1H, CH_2), 2.79–2.87 (m, 1H, CH_2), 4.15 (dd, 1H, CH_2, J = 12.6, 5.3 Hz), 4.66 (s, 1H, CH), 4.95 (s, 1H, CH), 5.16 (s, 1H, CH), 6.76 (d, 1H, J = 7.3 Hz), 6.96–7.00 (m, 1H), 7.06 (d, 1H, J = 7.6 Hz), 7.18–7.25 (m, 6H), 7.33–7.37 (m, 1H), 7.44–7.57 (m, 4H), 7.96 (d, 2H, J = 8.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.5 (Me), 28.4 (CH_2), 38.2 (CH_2), 47.5 (CH), 54.2 (CH), 63.7 (CH), 78.3 (C), 96.9 (C), 124.7 (CH_{Ar}), 125.2 (C_{Ar}), 125.7 (CH_{Ar}), 125.8 (CH_{Ar}), 126.3 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 127.0 (CH_{Ar}), 127.17 (CH_{Ar}), 127.23 (CH_{Ar}), 127.3 (CH_{Ar}), 127.7 (CH_{Ar}), 128.3 ($2CH_{Ar}$), 129.1 ($2CH_{Ar}$), 129.5 (CH_{Ar}), 131.0 (C_{Ar}), 133.7 (C_{Ar}), 138.3 (C_{Ar}), 138.6 (C_{Ar}), 138.8 (C_{Ar}), 139.3 (C_{Ar}), 140.1 (C_{Ar}), 154.5 (C=N), 166.5 (CO); IR (KBr, cm^{-1}): 3031, 2918, 2859, 2129, 1688, 1458, 1434, 1334, 1294, 920; HRMS (ESI): calcd for $C_{34}H_{27}N_2O_2$ $[M+H]^+$ 495.2067, found 495.2071.

*4.2.2. 28-(4-Chlorophenyl)-30-oxa-12,29-diazaoctacyclo-[13.6.6.3^{2,14}.0^{2,14}.0^{3,12}.0^{4,9}.0^{16,21}.0^{22,27}]triaconta-4,6,8,16,18,20,22,24,26,28-decaen-13-one (**22b**).* 28 mg (82 %) yield [m. p. 177 ºC (dec.), methanol] as light yellow solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.60 (dd, 1H, CH_2, J = 15.7, 3.2 Hz), 2.71–2.75 (m, 1H, CH_2), 2.80–2.88 (m, 1H, CH_2), 4.15 (dd, 1H, CH_2, J = 12.5, 5.0 Hz), 4.67 (s, 1H, CH), 4.96 (s, 1H, CH), 5.09 (s, 1H, CH), 6.74 (d, 1H, J = 7.3 Hz), 6.97–7.01 (m, 1H), 7.07 (d, 1H, J = 7.6 Hz), 7.17–7.26 (m, 4H), 7.34–7.35 (m, 3H), 7.37–7.56 (m, 4H), 8.03 (d, 2H, J = 8.9 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): 28.3 (CH_2), 38.2 (CH_2), 47.3 (CH), 54.1 (CH), 63.7 (CH), 78.0 (C), 97.4 (C), 124.6 (CH_{Ar}), 125.7 (CH_{Ar}), 125.8 (CH_{Ar}), 126.3 (CH_{Ar}), 126.6 (CH_{Ar}), 126.7 (CH_{Ar} + C_{Ar}), 127.1 (CH_{Ar}), 127.3 ($2CH_{Ar}$), 127.4 (CH_{Ar}), 127.8 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 129.6 (CH_{Ar}), 129.7 ($2CH_{Ar}$), 130.8 (C_{Ar}), 133.6 (C_{Ar}), 136.1 (C_{Ar}), 138.2 (C_{Ar}), 138.4 (C_{Ar}), 138.6 (C_{Ar}), 139.0 (C_{Ar}), 153.9 (C=N), 166.3 (CO); HRMS (ESI): calcd for $C_{33}H_{24}{}^{35}ClN_2O_2$ $[M+H]^+$ 515.1521, found 515.1550.

*4.2.3. 6,7-Dimethoxy-28-(p-tolyl)-30-oxa-12,29-diazaoctacyclo-[13.6.6.3^{2,14}.0^{2,14}.0^{3,12}.0^{4,9}.0^{16,21}.0^{22,27}]triaconta-4,6,8,16,18,20,22,24,26,28-decaen-13-one (**22c**).* 40 mg (92%) yield [m. p. 240 ºC (dec.), methanol] as colorless solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.39 (s, 3H, Me), 2.47 (dd, 1H, CH_2, J = 15.9, 2.4 Hz), 2.65–2.69 (m, 1H, CH_2), 2.73–2.82 (m, 1H, CH_2), 3.83 (s, 3H, OMe), 4.06 (s, 3H, OMe), 4.12 (dd, 1H, CH_2, J = 12.3, 4.1 Hz), 4.60 (s, 1H, CH), 4.89 (s, 1H, CH), 5.16 (s, 1H, CH), 6.52 (s, 1H), 6.78 (d, 1H, J = 7.3 Hz), 6.97–7.01 (m, 2H), 7.17–7.23 (m, 5H), 7.47–7.54 (m, 3H), 7.98 (d, 2H, J = 8.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.5 (Me), 28.0 (CH_2), 38.3 (CH_2), 47.6 (CH), 54.4 (CH), 55.9 (OMe), 56.5 (OMe), 63.6 (CH), 78.4 (C), 96.9 (C), 110.6 (CH_{Ar}), 111.9 (CH_{Ar}), 123.1 (C_{Ar}), 124.7 (CH_{Ar}), 125.2 (C_{Ar}), 125.7 (CH_{Ar}), 125.8 (CH_{Ar}), 126.3 (C_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 127.0 (CH_{Ar}), 127.2 (CH_{Ar}), 127.7 (CH_{Ar}), 128.3 ($2CH_{Ar}$), 129.1 ($2CH_{Ar}$), 138.3 (C_{Ar}), 138.5 (C_{Ar}), 138.8 (C_{Ar}), 139.4 (C_{Ar}), 140.1 (C_{Ar}), 147.6 (C_{Ar}), 148.4 (C_{Ar}), 154.5 (C=N), 166.5 (CO). IR (KBr, cm^{-1}): 2923, 1685, 1520, 1466, 1436, 1359, 1332, 1291, 1259, 1230, 1148, 1113, 1010, 938, 908; HRMS (ESI): calcd for $C_{36}H_{31}N_2O_4$ $[M+H]^+$ 555.2278, found 555.2273.

*4.2.4. 6,7-Dimethoxy-28-(4-chlorophenyl)-30-oxa-12,29-diazaoctacyclo[13.6.6.3^{2,14}.0^{2,14}.0^{3,12}.0^{4,9}.0^{16,21}.0^{22,27}]triaconta-4,6,8,16,18,20,22,24,26,28-decaen-13-one (**22d**).* 16 mg (91 %) yield (m. p. 117–120 ºC, methanol) as yellow solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.49 (dd, 1H, CH_2, J = 15.5, 3.0 Hz), 2.66–2.70 (m, 1H, CH_2), 2.74–2.82 (m, 1H, CH_2), 3.84 (s, 3H, OMe), 4.06 (s, 3H, OMe), 4.12 (dd, 1H, CH_2, J = 12.4, 5.0 Hz), 4.61 (s, 1H, CH), 4.89 (s, 1H, CH), 5.09 (s, 1H, CH), 6.53 (s, 1H), 6.75 (d, 1H, J = 7.3 Hz), 6.95 (s, 1H), 6.98–7.02 (m, 1H), 7.18–7.26 (m, 3H), 7.36 (d, 2H, J = 8.7 Hz), 7.47–7.54 (m, 3H), 8.05 (d, 2H, J = 8.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 27.9 (CH_2), 38.3 (CH_2), 47.4 (CH), 54.3 (CH), 55.9 (OMe), 56.5 (OMe), 63.6 (CH), 78.0 (C), 97.3 (C), 110.6 (CH_{Ar}), 111.9 (CH_{Ar}), 122.9 (C_{Ar}), 124.6 (CH_{Ar}), 125.7 (CH_{Ar}), 125.9 (CH_{Ar}), 126.2 (C_{Ar}), 126.59 (CH_{Ar}), 126.64 (CH_{Ar}), 126.7 (C_{Ar}), 127.1 (CH_{Ar}), 127.3 (CH_{Ar}), 127.8 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 129.7 ($2CH_{Ar}$), 136.1 (C_{Ar}), 138.2 (C_{Ar}), 138.3 (C_{Ar}), 138.6 (C_{Ar}), 139.1 (C_{Ar}), 147.7 (C_{Ar}), 148.5 (C_{Ar}), 153.9 (C=N), 166.3 (CO); IR (KBr, cm^{-1}): 2934, 2853, 2249, 1694, 1615, 1518, 1459, 1358, 1330, 1289, 1258, 1228, 1147, 1112, 1014, 908; HRMS (ESI): calcd for $C_{35}H_{28}{}^{35}ClN_2O_4$ $[M+H]^+$ 575.1732, found 575.1739.

*4.2.5. 32-(p-Tolyl)-34-oxa-16,33-diazanonacyclo-[17.6.6.3^{2,18}.0^{2,18}.0^{3,16}.0^{4,13}.0^{7,12}.0^{20,25}.0^{26,31}]tetratriaconta-4,6,7,9,11,12,20,22,24,26,28,30,32-tridecaen-17-one (**22e**).* 28 mg (99 %) yield (m. p. > 260 ºC, methanol) as colorless solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.39 (s, 3H, Me), 2.77–2.84 (m, 1H, CH_2), 2.97–3.06 (m, 1H, CH_2), 3.14 (dd, 1H, CH_2, J = 16.3, 4.5 Hz), 4.36 (dd, 1H, CH_2, J = 13.1, 5.9 Hz), 4.84 (s, 1H, CH), 5.05 (s, 1H, CH), 5.21 (s, 1H, CH), 6.79 (d, 1H, J = 7.2 Hz), 6.97-7.01 (m, 1H), 7.18–7.28 (m, 5H), 7.49–7.58 (m, 5H), 7.68 (d, 1H, J = 8.5 Hz), 7.82–7.88 (m, 3H), 7.97 (d, 2H, J = 8.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.5 (Me), 24.7 (CH_2), 37.8 (CH_2), 47.5 (CH), 54.4 (CH), 64.0 (CH), 78.5 (C), 97.3 (C), 122.9 (CH_{Ar}), 124.7 (CH_{Ar}), 124.9 (CH_{Ar}), 125.2 (C_{Ar}), 125.7 (CH_{Ar}), 125.9 ($2CH_{Ar}$), 126.4 (CH_{Ar}), 126.5 (CH_{Ar}), 126.56 (CH_{Ar}), 126.60 (CH_{Ar}), 127.0 (CH_{Ar}), 127.3 (CH_{Ar}), 127.8 (CH_{Ar}), 128.3 ($2CH_{Ar}$), 128.6 (CH_{Ar}), 128.8 (C_{Ar}), 129.1 ($2CH_{Ar}$), 129.2 (C_{Ar}), 132.1 (C_{Ar}), 132.6 (C_{Ar}), 138.3 (C_{Ar}), 138.6 (C_{Ar}), 138.8 (C_{Ar}), 139.4 (C_{Ar}), 140.1 (C_{Ar}), 154.5 (C=N), 166.5 (CO). IR (KBr, cm^{-1}): 2920, 1698, 1514, 1444, 1367, 1292, 1189, 1118, 929; HRMS (ESI): calcd for $C_{38}H_{29}N_2O_2$ $[M+H]^+$ 545.2224, found 545.2252.

*4.2.6. 6,7-Dimethoxy-30-(p-tolyl)-28-oxa-12,29-diazaoctacyclo-[13.6.6.3^{2,14}.0^{2,14}.0^{3,12}.0^{4,9}.0^{16,21}.0^{22,27}]triaconta-4,6,8,16,18,20,22,24,26,29-decaen-13-one (**25a**).* 9 mg (99 %) yield (m. p. > 265 ºC, ethanol) as colorless solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 2.30 (s, 3H, Me), 2.40–2.44 (m, 1H, CH_2), 2.51–2.55 (m, 1H, CH_2), 2.75–2.79 (m, 1H, CH_2), 3.63 (s, 3H, OMe), 3.79 (s, 3H, OMe), 4.23 (dd, 1H, CH_2, J = 12.6, 4.3 Hz), 4.48 (s, 1H, CH), 5.13 (s, 1H, CH), 5.14 (s, 1H, CH), 6.17 (s, 1H), 6.40 (s, 1H), 6.93 (br.s, 4H), 7.18–7.25 (m, 4H), 7.49–7.52 (m, 3H), 7.57–7.59 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.2 (Me), 29.7 (CH_2), 38.5 (CH_2), 47.5 (CH), 50.8 (CH), 55.2 (OMe), 56.0 (OMe), 63.8 (CH), 74.1 (C), 99.2 (C), 110.5 (CH_{Ar}), 111.8 (CH_{Ar}), 122.2 (C_{Ar}), 124.8 (CH_{Ar}), 125.9 (CH_{Ar}), 126.4 (CH_{Ar}), 126.8 (CH_{Ar}), 127.19 (CH_{Ar} + C_{Ar}), 127.22 (2CH_{Ar}), 127.27 (CH_{Ar}), 127.30 (CH_{Ar}), 127.8 (CH_{Ar}), 127.9 (C_{Ar}), 128.6 (2CH_{Ar}), 138.0 (C_{Ar}), 138.7 (C_{Ar}), 138.9 (C_{Ar}), 139.6 (C_{Ar}), 140.1 (C_{Ar}), 146.8 (C_{Ar}), 148.4 (C_{Ar}), 156.3 (C=N), 167.3 (CO). IR (KBr, cm^{-1}): 2921, 2851, 1706, 1615, 1520, 1459, 1292, 1258, 1229, 1144, 1110, 1016, 902; HRMS (ESI): calcd for $C_{36}H_{30}N_2O_4Na$ [M+Na]$^+$ 577.2098, found 577.2109.

*4.2.7. 30-(4-Chlorophenyl)-6,7-dimethoxy-28-oxa-12,29-diazaoctacyclo[13.6.6.3^{2,14}.0^{2,14}.0^{3,12}.0^{4,9}.0^{16,21}.0^{22,27}]triaconta-4,6,8,16,18,20,22,24,26,29-decaen-13-one (**25b**).* 32 mg (82 %) yield [m. p. 240 ºC (dec.), methanol] as beige solid. ^{1}H (400.1 MHz, $CDCl_3$): 2.40–2.44 (m, 1H, CH_2), 2.51–2.55 (m, 1H, CH_2), 2.70– 2.78 (m, 1H, CH_2), 3.67 (s, 3H, OMe), 3.79 (s, 3H, OMe), 4.22 (dd, 1H, CH_2, J = 12.4, 4.2 Hz), 4.49 (s, 1H, CH), 5.13 (s, 1H, CH), 5.14 (s, 1H, CH), 6.42 (s, 1H), 6.22 (s, 1H), 6.99 (d, 2H, CH, J = 8.2 Hz), 7.13 (d, 2H, CH, J = 8.2 Hz), 7.18– 7.25 (m, 4H), 7.49– 7.57 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.2 (CH_2), 38.5 (CH_2), 47.4 (CH), 50.7 (CH), 55.7 (OMe), 56.2 (OMe), 63.7 (CH), 74.2 (C), 99.7 (C), 111.1 (CH_{Ar}), 112.4 (CH_{Ar}), 122.2 (C_{Ar}), 124.6 (CH_{Ar}), 125.9 (CH_{Ar}), 126.4 (CH_{Ar}), 126.9 (CH_{Ar}), 127.3 (CH_{Ar}), 127.41 (CH_{Ar}), 127.43 (CH_{Ar}), 127.5 (C_{Ar}), 128.0 (CH_{Ar}), 128.2 (2CH_{Ar}), 128.7 (2CH_{Ar}), 129.4 (C_{Ar}), 135.1 (C_{Ar}), 137.8 (C_{Ar}), 138.5 (C_{Ar}), 139.5 (C_{Ar}), 139.9 (C_{Ar}), 147.1 (C_{Ar}), 148.8 (C_{Ar}), 155.5 (C=N), 167.1 (CO). IR (KBr, cm^{-1}): 2941, 2851, 2252, 1708, 1612, 1518, 1466, 1435, 1355, 1291, 1257, 1228, 1144, 1110, 1012, 905; HRMS (ESI): calcd for $C_{35}H_{28}{}^{35}ClN_2O_4$ [M+H]$^+$ 575.1732, found 575.1732.

*4.2.8. 34-(p-Tolyl)-32-oxa-16,33-diazanonacyclo-[17.6.6.3^{2,18}.0^{2,18}.0^{3,16}.0^{4,13}.0^{7,12}.0^{20,25}.0^{26,31}]tetratriaconta-4,6,7,9,11,12,20,22,24,26,28,30,33-tridecaen-17-one (**25c**).* 19 mg (85 %) yield [m. p. 258 ºC (dec.), methanol] as colorless solid. ^{1}H (400.1 MHz, $CDCl_3$): δ 1.52–1.59 (m, 1H, CH_2), 2.51 (s, 3H, Me), 2.75–2.83 (m, 2H, CH_2), 4.23–4.28 (m, 1H, CH_2), 4.98 (s, 1H, CH), 5.09 (s, 1H, CH), 5.19 (d, 1H, CH_{Ar}, J = 7.3 Hz), 5.30 (s, 1H, CH), 6.16–6.20 (m, 1H), 6.89–6.93 (m, 1H), 7.12–7.19 (m, 2H), 7.27–7.36 (m, 2H), 7.41 (d, 2H, J = 7.9 Hz), 7.49–7.62 (m, 4H), 7.68–7.71 (m, 3H), 7.88–7.97 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.5 (Me), 24.9 (CH_2), 37.6 (CH_2), 47.3 (CH), 49.0 (CH), 63.2 (CH), 71.8 (C), 100.2 (C), 123.1 (CH_{Ar}), 124.26 (CH_{Ar}), 124.30 (CH_{Ar}), 125.3 (CH_{Ar}), 125.4 (CH_{Ar}), 125.5 (CH_{Ar}), 125.9 (C_{Ar}), 126.3 (CH_{Ar}), 126.6 (2CH_{Ar}), 126.7 (CH_{Ar}), 126.9 (CH_{Ar}), 127.1 (CH_{Ar}), 127.2 (CH_{Ar}), 127.4 (C_{Ar}), 128.4 (CH_{Ar}), 128.8 (2CH_{Ar}), 129.7 (2CH_{Ar}), 131.9 (C_{Ar}), 132.2 (C_{Ar}), 133.7 (C_{Ar}), 137.9 (C_{Ar}), 139.2 (C_{Ar}), 139.49 (C_{Ar}), 139.52 (C_{Ar}), 140.8 (C_{Ar}), 158.6 (C=N), 167.6 (CO). IR (KBr, cm^{-1}): 2923, 2853, 1705, 1512, 1458, 1293, 1118, 902; HRMS (ESI): calcd for $C_{38}H_{29}N_2O_2$ [M+H]$^+$ 545.2224, found 545.2239.

*4.2.9. 34-(4-Chlorophenyl)-32-oxa-16,33-diazanonacyclo[17.6.6.3^{2,18}.0^{2,18}.0^{3,16}.0^{4,13}.0^{7,12}.0^{20,25}.0^{26,31}]tetratriaconta-4,6,7,9,11,12,20,22,24,26,28,30,33-tridecaen-17-one (**25d**).* 8 mg (52 %) yield (m. p. 115–116 ºC, isolated by PTLC) as colorless solid. ^{1}H (400.1 MHz, $CDCl_3$): δ 1.60 (1H, CH_2, overlapped with H_2O), 2.77–2.85 (m, 2H, CH_2), 4.27 (dd, 1H, CH_2, J = 12.1, 5.4 Hz), 4.93 (s, 1H, CH), 5.09 (s, 1H, CH), 5.19 (d, 1H, CH_{Ar}, J = 7.3 Hz), 5.28 (s, 1H, CH), 6.17–6.21 (m, 1H), 6.90-6.94 (m, 1H), 7.11–7.23 (m, 6H), 7.51–7.75 (m, 7H), 7.90–7.95 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.9 (CH_2), 37.7 (CH_2), 47.3 (CH), 48.9 (CH), 63.2 (CH), 71.5 (C), 100.6 (C), 123.1 (CH_{Ar}), 124.0 (CH_{Ar}), 124.1 (CH_{Ar}), 125.3 (CH_{Ar}), 125.52 (CH_{Ar}), 125.54 (CH_{Ar}), 126.4 (CH_{Ar}), 126.67 (CH_{Ar}), 126.70 (CH_{Ar}), 126.9 (CH_{Ar}), 126.99 (CH_{Ar}), 127.04 (C_{Ar}), 127.3 (CH_{Ar}), 127.35 (CH_{Ar}), 127.43 (C_{Ar}), 128.5 (CH_{Ar}), 129.4 (2CH_{Ar}), 130.1 (2CH_{Ar}), 131.9 (C_{Ar}), 132.3 (C_{Ar}), 133.9 (C_{Ar}), 136.8 (C_{Ar}), 137.6 (C_{Ar}), 138.9 (C_{Ar}), 139.3 (C_{Ar}), 139.4 (C_{Ar}), 157.8 (C=N), 167.4 (CO). IR (KBr, cm^{-1}): 2922, 1771, 1703, 1607, 1514, 1467, 1427, 1395, 1326, 1227, 1092, 1015, 954, 933, 900; HRMS (ESI): calcd for $C_{37}H_{26}{}^{35}ClN_2O_2$ [M+H]$^+$ 565.1677, found 565.1689.

Acknowledgements

We gratefully acknowledge the financial support from the Russian Science Foundation (Project No 14-13-00126). This research made use of resources from the X-ray Diffraction Centre, Centre for Magnetic Resonance, Educational Resourse Center of Chemistry and the Centre for Chemical Analysis and Materials of Saint-Petersburg State University.

Supplementary Material

Supplementary data (experimental procedures, characterization data, and copies of NMR spectra) associated with this article can be found in the online version, at doi:

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