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Highly regio- and stereoselective 1,3-dipolar cycloaddition of stabilised azomethine ylides to 3,3,3-trihalogeno-1-nitropropenes: synthesis of trihalomethylated spiro[indoline-3,2′-pyrrolidin]-2-ones and spiro[indoline-3,3′-pyrrolizin]-2-ones

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PII: S0040-4020(16)30924-3

DOI: 10.1016/j.tet.2016.09.017

Reference: TET 28088

To appear in: *Tetrahedron*

Received Date: 23 June 2016

Revised Date: 28 August 2016

Accepted Date: 9 September 2016

Please cite this article as: Barkov AY, Zimnitskiy NS, Korotaev VY, Kutyashev IB, Moshkin VS, Sosnovskikh VY, Highly regio- and stereoselective 1,3-dipolar cycloaddition of stabilised azomethine ylides to 3,3,3-trihalogeno-1-nitropropenes: synthesis of trihalomethylated spiro[indoline-3,2′-pyrrolidin]-2-ones and spiro[indoline-3,3′-pyrrolizin]-2-ones, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.09.017.

Graphical Abstract

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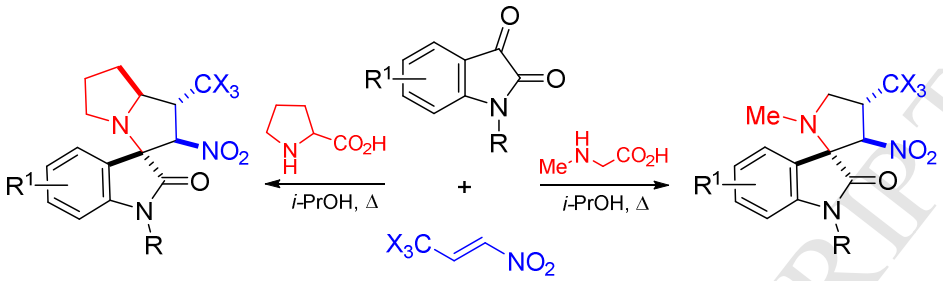

X = F, Cl, Br; R = H, Me, Am, Bn; R^1 = H, 5-NO_2, 5,7-di-Br

Highly regio- and stereoselective 1,3-dipolar cycloaddition of stabilised azomethine ylides to 3,3,3-trihalogeno-1-nitropropenes: synthesis of trihalomethylated spiro[indoline-3,2'-pyrrolidin]-2-ones and spiro[indoline-3,3'-pyrrolizin]-2-ones

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Keywords: 3,3,3-Trihalogeno-1-nitropropenes; Stabilised azomethine ylides; 1,3-Dipolar cycloaddition; Spirooxindoles

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Reactions of 3,3,3-trihalogen-1-nitropropenes with *N*-alkyl-α-amino acids (sarcosine, proline) and isatins proceed regio- and diastereoselectively to give a wide range of trihalomethylated spiro[indoline-3,2'-pyrrolidin]-2-ones and spiro[indoline-3,3'-pyrrolizin]-2-ones in good yields as a result of a 1,3-dipolar cycloaddition of the intermediate stabilised azomethine ylide at the double bond of the nitroalkenes.

Introduction

The 1,3-dipolar cycloaddition reaction of azomethine ylides with olefins is an efficient methodology for regio- and stereoselective synthesis of structurally complex pyrrolidines with a few chiral centres from relatively simple precursors.[1] Synthesis of oxindoles derivatives, in particular pyrrolidinyl 3-spirooxindoles, has attracted considerable attention due to their highly pronounced biological activities. The presence of the chiral spiro carbon leads to the sterically constrained spiro structure and is one of the important factors of the biological activities. It is not surprising, therefore, that the heterocyclic spirooxindole system containing one carbon atom common to two rings is a widely distributed structural framework present in a number of pharmaceuticals and natural products.[2]

Compounds of this class represent a wide range of structural complexity, from the simpler members such as horsfiline (**1**)[3] and elacomine (**2**)[4] to the more complex members such as spirotryprostatin A (**3**), in which the pyrrolidine portion is part of a tricyclic system. The latter was isolated from the fermentation broth of *Aspergillus fumigatus* and has been shown to completely inhibit the G2/M progression of mammalian tsFT210 cells.[2a] Moreover, the spirooxindole ring system is present in pharmacologically important compounds. For instance, non-natural 3,3′-pyrrolidinyl spirooxindoles, such as compound **4**, exhibit micromolar activities against bacterial cell division;[5] the synthetic derivatives **5** and **6** are representatives of a novel type of potent non-peptidic inhibitor of the p53-MDM2 interaction that is crucial for the regulation of the tumour-suppressing activity of the p53 protein (Fig. 1).[6]

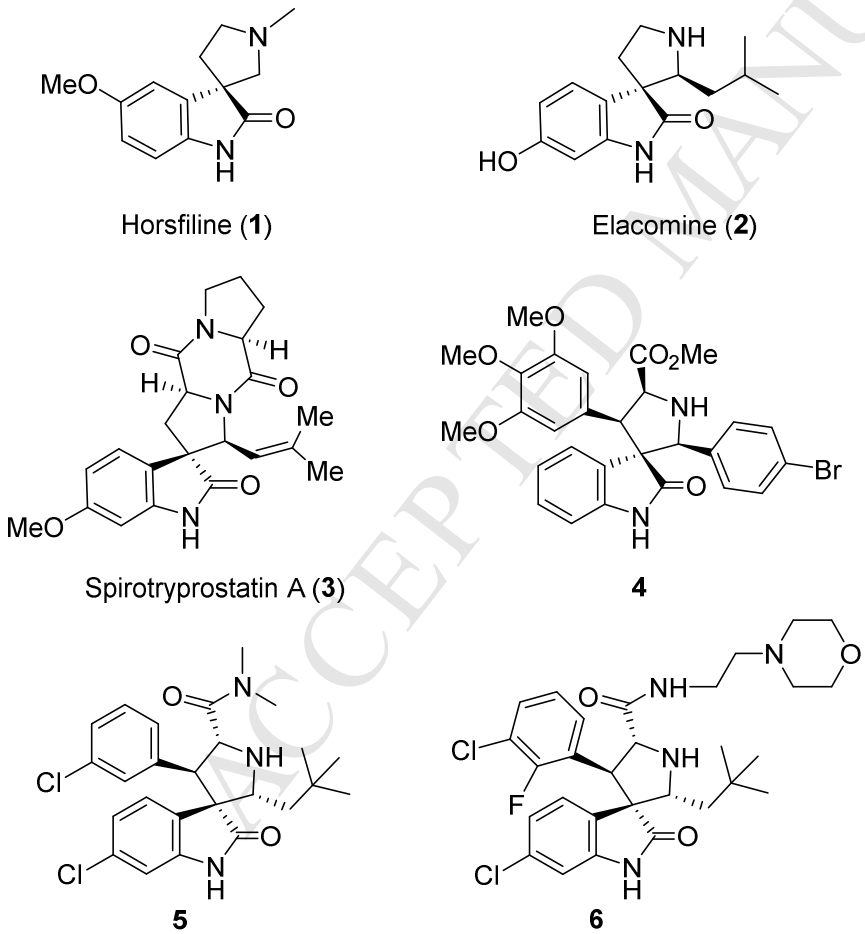


Fig. 1. Natural (**1–3**) and synthetic (**4–6**) spirocyclic oxindoles.

Undoubtedly, the abandance of natural and unnatural bioactive oxindoles have encouraged the design and synthesis of novel spirocyclic oxindoles with relevant and notable medicinal properties. In this regard, many useful methods have been established for the construction of this valuable heterocyclic system.[7] Thus, the 1,3-dipolar cycloadditions of azomethine ylides and 3-methylene-2-oxindoles provided an efficient approach to highly functionalized 3,3′-pyrrolidinyl spirooxindoles with excellent regio- and stereoselectivities.[5,8] Alternatively, the 1,3-dipolar cycloadditions of azomethine ylides generated from decarboxylative condensation of isatins and *N*-alkyl-α-amino acids with electron-poor alkenes serve as an expedient route for the construction of 3,2′-pyrrolidinyl spirooxindoles. Olefins, such as chalcone,[9] β-nitrostyrenes,[10] 3-nitro-2*H*-chromenes,[11] acrylates,[12] maleimides,[13] and various arylidene derivatives,[14] have been used efficiently as trapping dipolarophiles in good yield and high selectivity. Despite these recent advances, to the best of our knowledge a stereoselective [3+2] cycloaddition reaction of azomethine ylides with trihalomethylated nitroalkenes has never been reported, while new advances in this area could afford a convenient approach to CX_3-containing spirooxindoles derivatives.

Partially fluorinated heterocycles represent important molecules in organic and medicinal chemistry (undesirable metabolic transformations are often avoidable because the C−F bond is hard for enzymes to cleave) and their one-pot preparation is one of the challenging problems in organic synthesis.[15] We envisaged that introduction of such powerful electron-withdrawing substituents like CF_3, CCl_3 and CBr_3 groups into the conjugated nitroalkene moiety would increase their reactivity toward 1,3-dipolar cycloaddition with azomethine ylides and open up a new synthetic usefulness of these molecules. Of particular interest is the fact that introduction of a trihalomethyl group, especially a trifluoromethyl group, into bioactive spirooxindoles can have profound and unexpected results on biological activity of the derived halogenated compounds.[15a]

Trihalomethylated nitroolefins possess unique chemical reactivity toward both nucleophilic and cycloaddition reactions because of their reactive double bond. Owing to this, *trans*-3,3,3-trifluoro(trichloro)-1-nitropropenes have attracted attention as excellent building blocks for the

preparation of CX_3-containing compounds.[16] Most pertinent to the present research is the 1,3-dipolar cycloaddition of benzonitrile oxide and nitrones to CX_3-nitroalkenes (X = F, Cl) providing a straightforward route to isoxazolines[17] and isoxazolidines.[18] These compounds were also used as dienophiles in Diels–Alder reaction[19] and as heterodienes in an inverse electron-demand Diels–Alder reaction.[20] However, published data on their participation in 1,3-dipolar cycloaddition reactions with azomethine ylides is lacking. Moreover, there are no literature data for the participation of *trans*-3,3,3-tribromo-1-nitropropene in any cycloaddition reactions.

In the present paper we wish to report that the cycloaddition of isatin azomethine ylides with conjugated nitroolefins additionally activated by the trihalomethyl group provides a simple and convenient synthesis of CX_3-containing 3,2′-pyrrolidinyl spirooxindoles (X = F, Cl, Br), which are of interest from the view point of pharmacological activity because of their spiro skeleton and CX_3 functionality. The major products of the reaction with isatin–proline ylide showed different regioselectivity from the reported spirooxindole derivatives, prepared from β-nitrostyrenes. The regio- and stereochemistry of the cycloadducts has been established by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy and X-ray diffraction analysis.

2. Results and discussion

The CF_3-containing 3-spirooxindole derivatives have emerged as attractive synthetic targets due to their applications in such fields as pharmacy and medicine.[21] In continuation of our research program dedicated to the chemistry of trihalomethylated nitroolefins[20,22] we decided to study the reactions of nitroolefins **1a–c** with a set of stabilised azomethine ylides generated from decarboxylative condensation of readily available isatins **2a–f** and *N*-alkyl-α-amino acids such as sarcosine and proline (Fig. 2). Nitroolefins **1a–c** were synthesized by one of the known methods starting from nitro alcohols, prepared by condensation of equimolecular amounts of nitromethane with the corresponding trihaloacetaldehyde in the presence of K_2CO_3.[23]

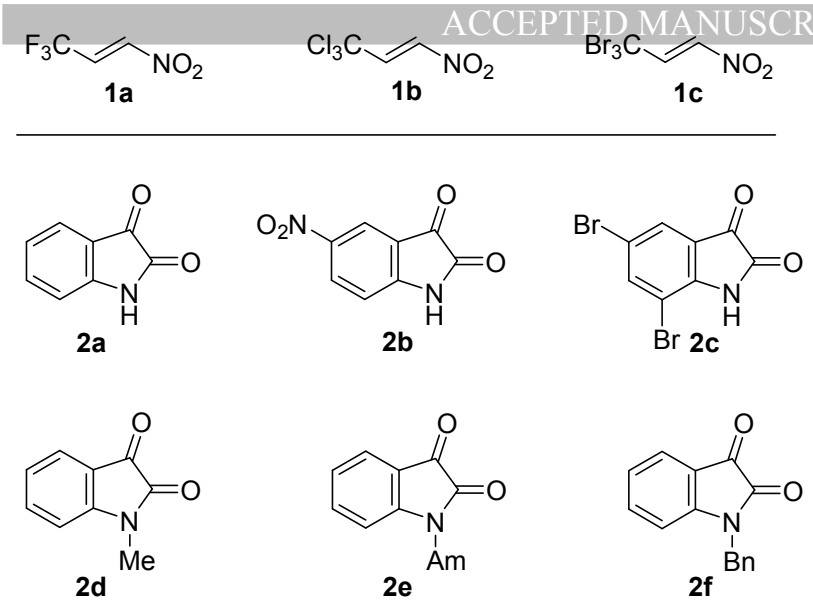
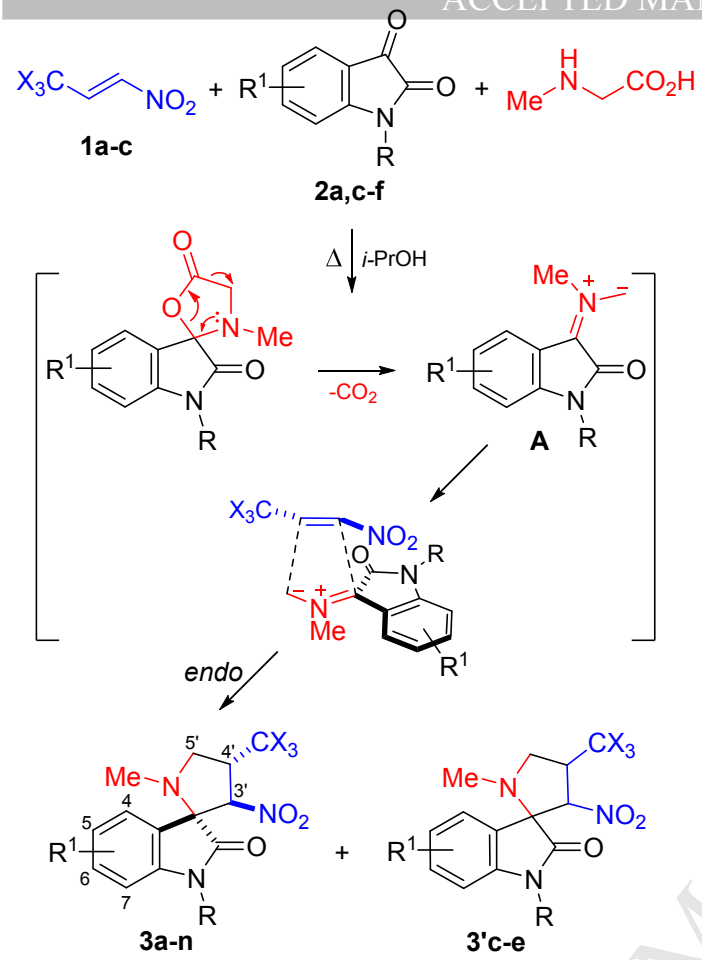


Fig. 2. Nitroalkenes **1** and isatins **2** used in this study.

In the initial study we have developed the synthesis of the hitherto unknown spiro[indoline-3,2'-pyrrolidin]-2-ones **3a–n** starting from CX_3-nitroalkenes **1**, isatins **2a,c–f** and sarcosine by a one-pot, three-component procedure depicted in Scheme 1. To our delight, the cycloaddition proceeds in a high regio- and stereocontrolled fashion. We have found that refluxing of these reactants in isopropanol for 48 h resulted in the formation of cycloadducts **3a–n** in 55–98% yields as single regioisomeric products, the structures of which were fully characterized by spectroscopic methods and X-ray diffraction analysis (see below). The progress of the reaction was monitored by TLC, and the results are summarized in Table 1. The desired 3-spirooxindoles precipitate upon dilution of the reaction mixtures with brine and a simple filtration provides analytically pure material. Among different solvents (benzene, ethanol, acetonitrile and isopropanol), which have been tested to perform the reaction, isopropanol was identified as the best solvent in terms of yield and selectivity. It is necessary to be mentioned that in the case of *N*-allylisatin the reaction led to a mixture of starting materials and unidentified products. Isatin **2a** and *N*-methylisatin **2d** reacted especially smoothly with **1a–c** to give the desired products in 65–98% yields, while azomethine ylide from 5-nitroisatin **2b** and sarcosine did not work under our reaction conditions.



Scheme 1. Synthesis of compounds **3a–n** by the reaction of nitroalkenes **1a–c** with isatin–sarcosine ylides.

Table 1
Isolated yields of compounds **3a–n** (all structures are racemic)

Nitroalkene **1**	Isatin **2**	Adduct **3**	Yield (%)
1a	**2a**	**3a**	89
1a	**2c**	**3b**	66
1a	**2d**	**3c**	90[a]
1a	**2e**	**3d**	68[b]
1a	**2f**	**3e**	55[c]
1b	**2a**	**3f**	70
1b	**2c**	**3g**	67
1b	**2d**	**3h**	98
1b	**2e**	**3i**	79
1b	**2f**	**3j**	71
1c	**2a**	**3k**	69
1c	**2d**	**3l**	65
1c	**2e**	**3m**	66
1c	**2f**	**3n**	59

[a] Ratio of **3c** : **3'c** = 93 : 7.
[b] Ratio of **3d** : **3'd** = 86 : 14.
[c] Ratio of **3e** : **3'e** = 95 : 5.

Herein, some common comments are desired. It is well-known[24] that a prediction of the regioselectivity in the cycloaddition reaction of an unsymmetrical dipole and dipolarophile is based on the preferred transition state, which involves interaction of the larger terminal coefficients. Steric effects also play an important part in these reactions and may influence the regioselectivity. In addition to regioselectivity issues, up to four new chiral centers are generated in such reactions, however, high levels of stereoselectivity are typically obtained. The chiral centers at C-2 and C-5 atoms of the newly forming pyrrolidine ring derive from the azomethine ylide geometry (the W- and S-shaped ylides), while the orientation of substituents at C-3 and C-4 derive from the alkene geometry. This result is expected on the basis of a concerted cycloaddition reaction, however, concerted process may not always be operative and a stepwise pathway, involving zwitterionic intermediates, cannot be ruled out. The relative configurations at C-2/C-3 and C-4/C-5 are determined by an *endo*/*exo* approach. The general preference is for the formation of the *endo* isomer, as found for the isoelectronic Diels-Alder reaction. Stabilised azomethine ylides are not exclusion from this rule and usually show high *endo* selectivity to the electron-poor olefins.[9,10]

As expected, azomethine ylides **A** derived from isatins and sarcosine are involved in the transition state where *endo* addition (with respect to the NO_2 group) of nitroalkenes **1a–c** to the triangle of the ylide prevails and results in the formation of *endo*-adducts **3a–n** with *trans*-arrangement of the CX_3 and NO_2 groups due to the synchronism of the reaction (Scheme 1). Note that chalcone[9c] and β-nitrostyrene[10f] react with isatin–sarcosine ylides in a similar manner. Compounds **3** were formed exclusively as the regioisomers with the NO_2 group at C-3' and the CX_3 group at C-4'. The alternative regiochemistry does not look very favorable in terms of the steric repulsion of the bulky CX_3 group from the electron density of the amide moiety or a π-system of the benzene ring. In general, in the case of ylides **A** and electron-poor alkenes (nitrostyrenes, chalcones, acrylates, cinnamates), the more electrophilic alkene atom reacts with the more nucleophilic and accessible terminal ylide atom. The indicated regio- and stereochemistry of spirooxindoles **3** was unambiguously confirmed by X-ray single crystal analysis of **3k** as a representative example (Fig. 3).

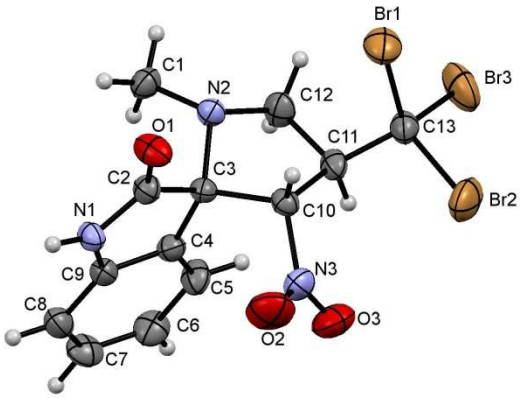


Fig. 3. X-ray crystal structure of **3k** (ORTEP drawing, 50% probability level).

Moreover, the assignment of structure **3** to the *endo*-adduct and 3'-NO_2-regioisomer is based on the ^{1}H NMR chemical shifts for the H-3' and H-4' protons. A comparison of these chemical shifts with the data reported for the parent compound, prepared from isatin–sarcosine ylide **A** and β-nitrostyrene,[10f] supports the validity of the structures (Fig. 4).

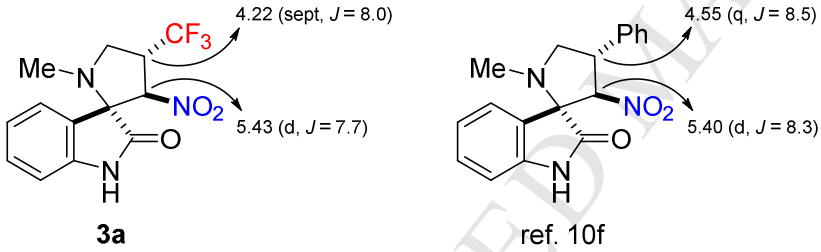
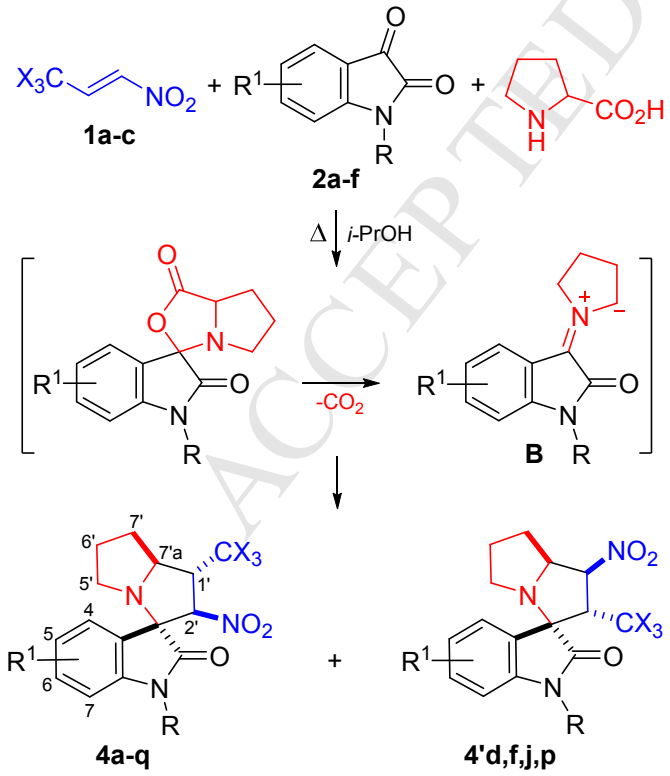


Fig. 4. Diagnostic ^{1}H NMR signals (δ, ppm, J/Hz, $CDCl_3$) of spirooxindole **3a** and its literature analog.

The nature of the CX_3 group and the substitution pattern of the azomethine ylides used are not very important for this transformation, however, replacement of the CCl_3 and CBr_3 groups with a more electron-withdrawing CF_3 group had some effect on the diastereoselectivity. Thus, the appearance of the stereoisomers **3'c–e** (5–14% according to the ^{1}H NMR spectroscopic data, the downfield doublet of H-3' at δ = 5.17–5.23 ppm) was observed in the crude products (Scheme 1). Noteworthy is the fact that minor adducts **3'** are formed only with the acceptor CF_3-containing alkene **1a**, and we assume that it can react nonselectively and asynchronously, stabilizing the initial Michael intermediate by retention of the negative charge up to the final stage of the second C–C bond formation.

The stereochemistry of these by-products was not determined, however, coupling constants J = 6.8–7.0 Hz between H-3' and H-4' in the structures **3'c–e** make their *trans*-arrangement more preferable.

For further demonstrating the synthetic values of CX_3-nitroalkenes **1**, the similar [3+2] cycloaddition reaction of stabilised azomethine ylides derived from isatins **2a–f** and proline was also investigated. This reaction under the conditions described above afforded hexahydrospiro[indoline-3,3'-pyrrolizin]-2-ones **4a–q** in 51–85% yields (Scheme 2, Table 2). In contrast to the results found in the sarcosine series, when 5-nitroisatin **2b** was employed, the corresponding nitropyrrolizines with spirooxindole moieties **4b,h,n** were obtained in good yields (59–63%). As in the cycloaddition reactions involving sarcosine, compounds **4a–q** were formed mainly as the same regioisomer in relation to the position of the trihalomethyl and nitro groups. However, in the case of isatin–proline ylides, the appearance of regioisomers **4'd,f,j,p** was observed in the crude products (7–11% according to the ^{1}H NMR data). The pure cycloadducts **4d,f,j,p** were obtained by recrystallizing the crude reaction mixture from the mixture hexane/CH_2Cl_2 (2:1). Thus, this three-component reaction has a wide variety of substrates and proceeds with high efficiency and selectivity.



Scheme 2. Synthesis of compounds **4a–q** by the reaction of nitroalkenes **1a–c** with isatin–proline ylides.

Table 2
Isolated yields of compounds **4a–q** (all structures are racemic)

Nitroalkene **1**	Isatin **2**	Adduct **4**	Yield (%)
1a	**2a**	**4a**	85
1a	**2b**	**4b**	60
1a	**2c**	**4c**	62
1a	**2d**	**4d**	62[a,b]
1a	**2e**	**4e**	59
1a	**2f**	**4f**	81[c]
1b	**2a**	**4g**	71
1b	**2b**	**4h**	63
1b	**2c**	**4i**	81
1b	**2d**	**4j**	56[d]
1b	**2e**	**4k**	57
1b	**2f**	**4l**	70
1c	**2a**	**4m**	74
1c	**2b**	**4n**	59
1c	**2c**	**4o**	55
1c	**2d**	**4p**	72[e]
1c	**2f**	**4q**	51

[a] Ratio of **4d** : **4'd** = 89 : 11.
[b] Ratio of **4d** : **4'd** = 95 : 5 in hexafluoroisopropanol (yield 69%).
[c] Ratio of **4f** : **4'f** = 91 : 9.
[d] Ratio of **4j** : **4'j** = 93 : 7.
[e] Ratio of **4p** : **4'p** = 91 : 9.

The structure of the spirooxindoles **4** was established by the usual spectroscopic analyses, and the indicated regio- and stereochemistry was further unambiguously confirmed by X-ray single crystal analysis performed for compound **4a** (Fig. 5). The ORTEP diagram of **4a** represents that the *trans*-geometry of CX_3-nitroalkenes is preserved in the product and also shows the relative configurations at all four chiral centers. The stereochemistry of cycloadducts is consistent with an ylide **B** and subsequent cycloaddition by an *endo* transition state (*endo*-TS 1); the cycloadduct corresponding to *exo*-TS 2 was not observed at all (Fig. 6). Possible structures for the minor regioisomers **4'd,f,j,p** are also presented in Fig. 6 (*endo*-TS 3). Although these by-products were not isolated in a pure state, their stereochemistry was established by 2D ^{1}H–^{1}H NOESY experiment of a 89 : 11 mixture of compounds **4d** and **4'd**. The most important proof of their stereochemistry was the NOE connectivities indicated with pink and blue arrows in Fig. 7. The 2D NOESY experiment on **4d** and **4'd** demonstrates the spatial contiguity of H-1' to H-4 and H-2' to H-4 (pink arrows), respectively; cross-peaks for H-1' with H-4 and H-2' with H-4 show that these protons are sited close to each other, thus establishing the indicated stereochemistry in Fig. 8 (about regiochemistry see below).

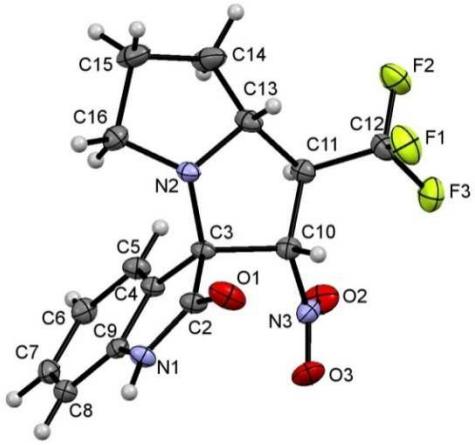


Fig. 5. X-ray crystal structure of **4a** (ORTEP drawing, 50% probability level).

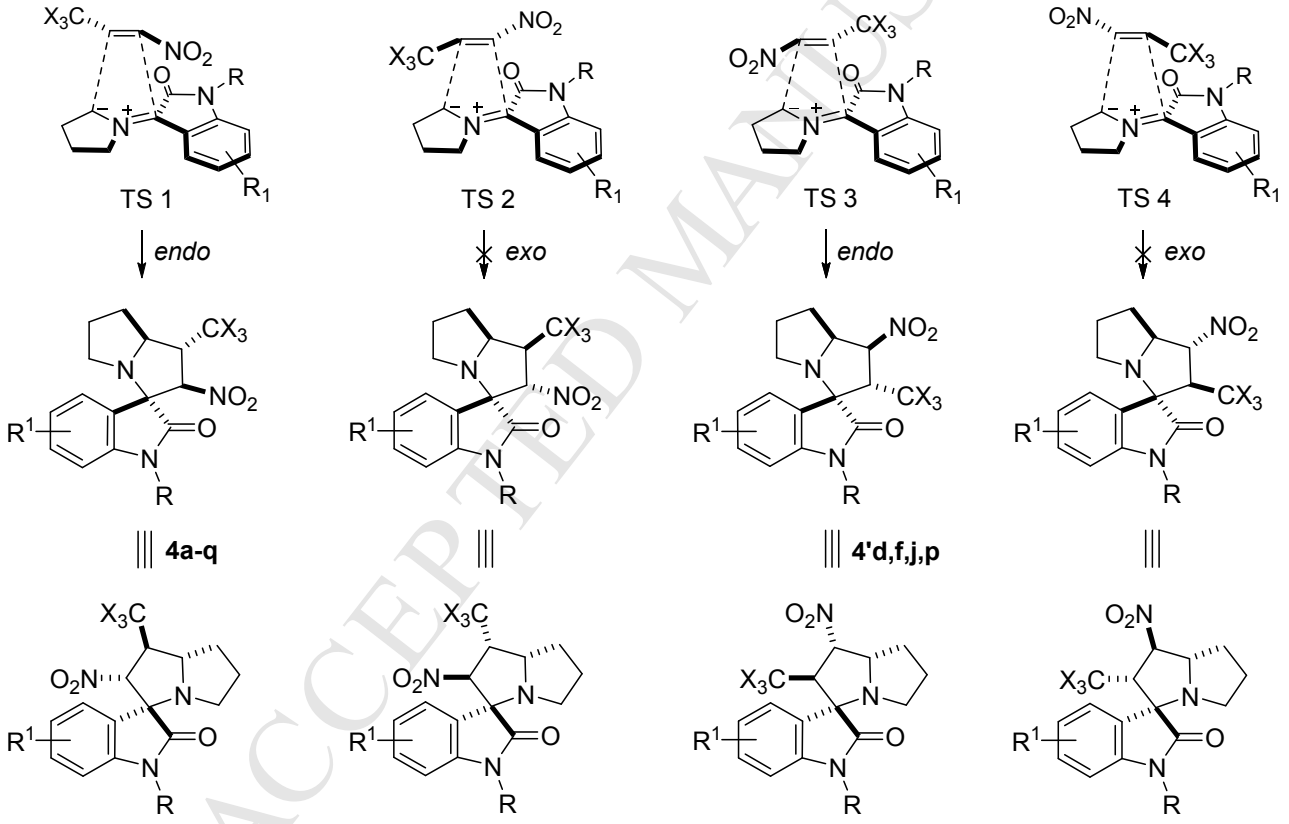


Fig. 6. Possible transition states for the formation of spirooxindoles **4a–q** and **4'd,f,j,p**.

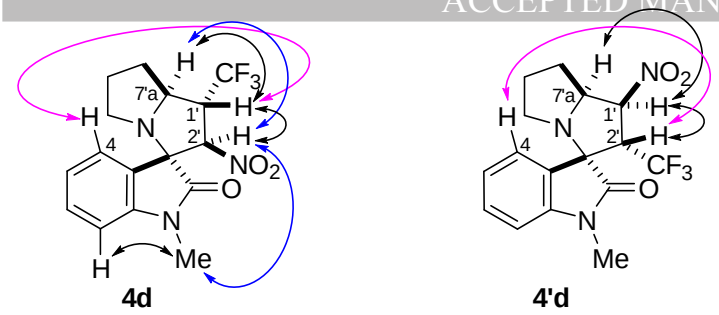


Fig. 7. Diagnostic 2D ^{1}H–^{1}H NOESY correlations of compounds **4d** and **4'd**.

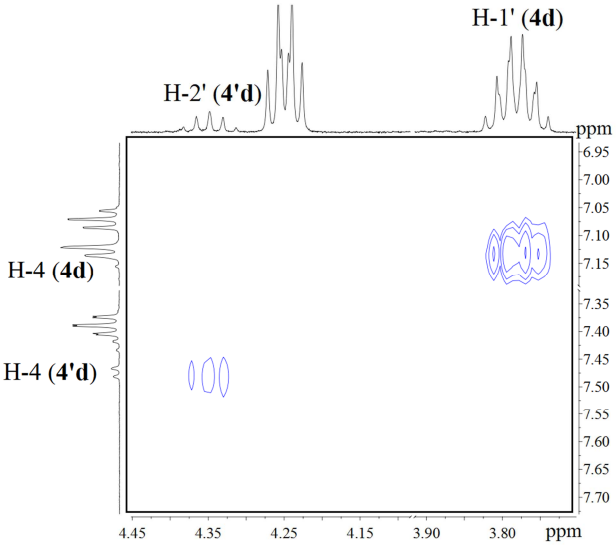


Fig. 8. A fragment of the 2D ^{1}H–^{1}H NOESY spectrum of compounds **4d** and **4'd**.

A characteristic feature of the ^{1}H NMR spectra of compounds **4** and **4'** in a $CDCl_3$ solution is the chemical shifts and multiplicity of the pyrrolizine methine protons. The assignment of structures **4'** to the 2'-CX_3-regioisomer is based on the ^{1}H NMR chemical shifts of the protons H-1' and H-2'. A comparison of these chemical shifts in by-products **4'** with the values disclosed for 1'-CX_3-regioisomers **4** supports the validity of their regiochemistry (Fig. 9). For example, for the minor isomer **4'd**, the pyrrolizine H-1' proton is shifted downfield to 2.18 ppm due to the NO_2 group, while the H-2' proton is shifted upfield to 1.28 ppm. The significant ^{1}H NMR chemical shifts of the pyrrolizine methine protons H-1', H-2' and H-7'a for regioisomeric pairs **4d,j,p** and **4'd,j,p** are presented in Fig. 9. The ^{13}C NMR spectra of all synthesized spirooxindoles showed two peaks at δ 72.0–75.9 and 173.6–177.2 ppm for the spiro carbon and the oxindole carbonyl group, respectively.

The CF_3 group in their ^{19}F NMR spectra ($CDCl_3$) manifests itself as a doublet at δ 91.9–93.4 ppm due to coupling with the CH proton ($^3J_{F,H}$ = 7.3–8.4 Hz), all in good accordance with the given structures.

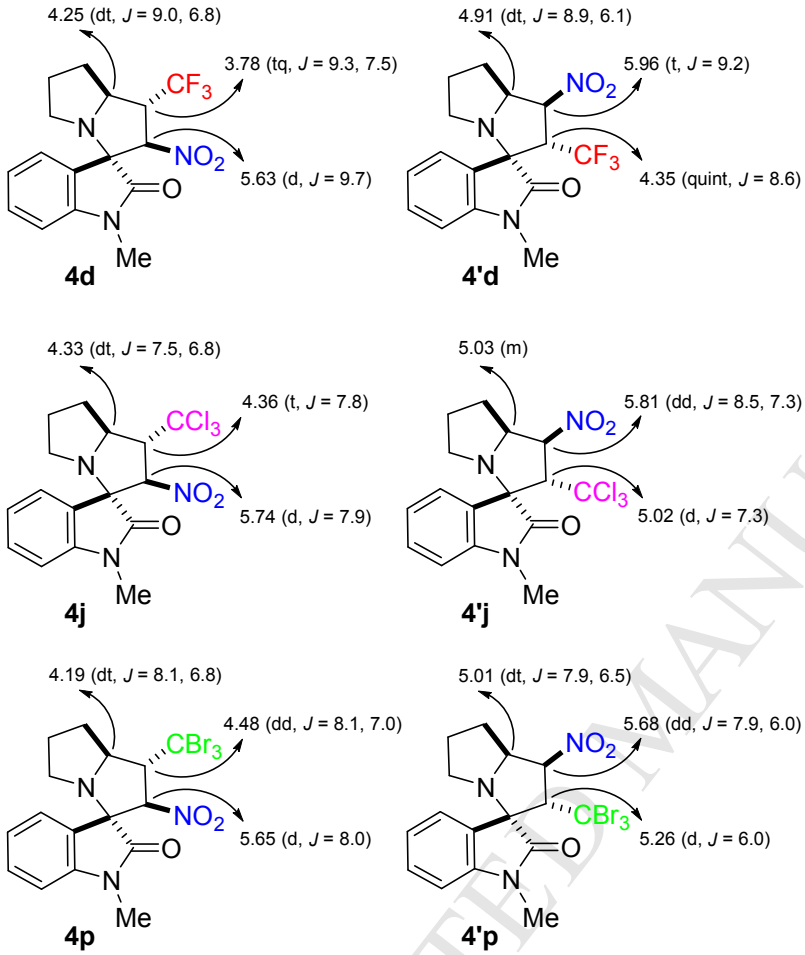


Fig. 9. Diagnostic ^1H NMR signals (δ, ppm, *J*/Hz, $CDCl_3$) of regioisomeric pairs **4d,j,p** and **4'd,j,p**.

It should be noted that our result is in contrast to the commonly observed regioselectivity outcome in this type of 1,3-dipolar cycloaddition reactions with β-nitrostyrenes. All previously published studies concerning β-nitrostyrenes showed that the products were formed selectively through an *endo* approach between the dipolarophile and S-shaped ylide **B** and almost exclusively as the regioisomers with the NO_2 group at C-1' (Fig. 6, TS 3). In fact, spirooxindoles **5** and **6** were previously obtained from β-nitrostyrene[10c] and 3,4-dimethoxy-β-nitrostyrene[10a] (Fig. 10). Since the stereochemistry of compound **6** has been indicated incorrectly,[10a] we repeated its synthesis and proved the structure **6** using X-ray diffraction analysis (Fig. 11).

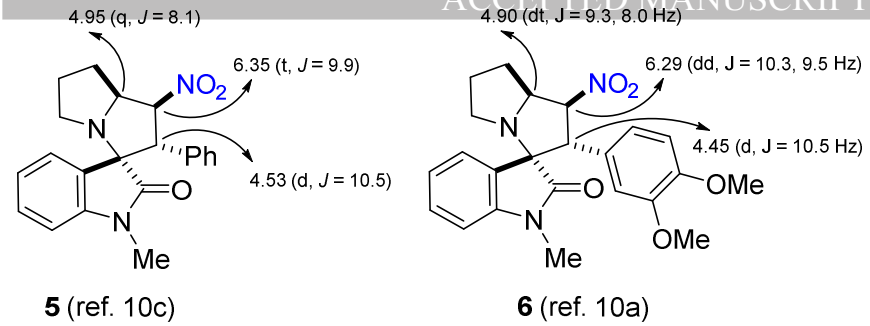


Fig. 10. Diagnostic ^{1}H NMR signals (δ, ppm, *J*/Hz, $CDCl_3$) of known spirooxindoles **5** and **6**.

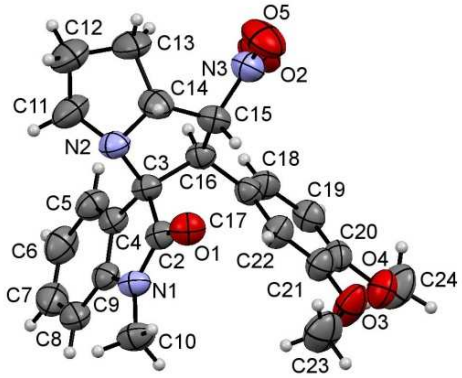


Fig. 11. X-ray crystal structure of compound **6** (ORTEP drawing, 50% probability level).

Nitroalkenes **1** differ significantly from β-nitrostyrenes by the presence of a bulky CX_3 group instead of the planar benzene ring. Probably, in our case, 1'-NO_2-regioisomers **4'** were formed in a small amount due to the unfavorable steric interactions between a large CX_3 group and an amide fragment, which are absent in the nitrostyrene molecule. In accordance with this, from the literature it is known[10c] that the introduction of the bulky methyl group into β-nitrostyrene also changes the regioselectivity and gives adducts of type **4**.

3. Conclusion

In conclusion, we have successfully developed a highly selective, one-pot and three-component method for the synthesis of a wide range of CX_3-containing 3-spirooxindoles by a [3+2] cycloaddition of 3,3,3-trihalogen-1-nitropropenes with isatins and *N*-alkyl-α-amino acids (sarcosine, proline).

The products constitute an important structural subunit of a variety of biologically active compounds, which may be of interest for medicinal chemistry. The advantages of this reaction included usage of readily available starting compounds, milder reaction conditions, simple separation process and good yields.

4. Experimental

4.1. General

NMR spectra were recorded on Bruker DRX-400 (^{1}H – 400 MHz, ^{19}F – 376 MHz) and AVANCE-500 (^{1}H – 500 MHz, ^{19}F – 471 MHz, ^{13}C – 126 MHz) spectrometers in DMSO-d_6 and $CDCl_3$ with TMS and C_6F_6 as internal standards, respectively. IR spectra were recorded on a Nicolet 6700 instruments (FTIR mode, ZnSe crystal). Mass spectra were recorded on a Waters Xevo Q-ToF mass spectrometer (ESI) with Acquity UPLC system and maxis mass spectrometer Impact HD Bruker Daltonik GmbH. Melting points were determined on a Stuart SMP40 apparatus. The starting 3,3,3-trihalogen-1-nitroprop-1-enes **1a–c** were prepared according to described procedures.[23]

4.2. General procedure for the preparation of spiro[indoline-3,2'-pyrrolidin]-2-ones 3 and spiro[indoline-3,3'-pyrrolizin]-2-ones 4 and 6

A mixture of corresponding isatin **2** (1.0 mmol) and sarcosine (0.13 g, 1.5 mmol) or prolyne (0.17 g, 1.5 mmol) was stirred in isopropanol (4 mL), and corresponding nitroalkene **1** (1.0 mmol) was added in one portion. The resulting mixture was stirred at reflux for 48 h and the reaction progress was monitored by TLC. Upon completion, the mixture was diluted with brine (10 mL), resulting precipitate was filtered off and washed with water and hexane and vacuum dried. In some cases, additional recrystallisation from the mixture hexane/CH_2Cl_2 (2 : 1) was necessary.

4.2.1. (3R,3'R*,4'S*)-1'-Methyl-3'-nitro-4'-(trifluoromethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3a**)*. Yield 0.28 g (89%), mp 135–136 ºC, colorless prisms. IR (ATP): 3215, 1716, 1561,1375 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (s, 3H, Me), 3.44 (t, J = 9.1 Hz, 1H, H-5′a), 3.59 (dd, J = 9.5, 7.7 Hz, 1H, H-5′b), 4.22 (sept, J = 8.0 Hz, 1H, H-4′), 5.43 (d, J = 7.7 Hz, 1H, H-3′), 6.90 (d, J = 7.8 Hz, 1H, H-7), 7.06 (td, J = 7.6, 0.8 Hz, 1H, H-5), 7.10 (dd, J = 7.6, 1.5 Hz, 1H, H-4), 7.33 (td, J = 7.7, 1.5 Hz, 1H, H-6), 8.05 (br s, 1H, NH); ^{19}F NMR (471 MHz, $CDCl_3$) δ 91.9 (d, CF_3, J = 8.4 Hz,

CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 34.9, 44.7 (q, ^2J = 29.9 Hz, C-4′), 51.4 (br s), 73.7, 89.0, 110.8, 122.7, 123.6, 125.0, 125.4 (q, ^1J = 277.9 Hz, CF_3), 131.1, 141.4, 176.2. HRMS (ESI): calcd for $C_{13}H_{12}F_3N_3NaO_3$ $[M+Na]^+$ 338.0723, found 338.0720.

4.2.2. (3R,3'R*,4'S*)-5,7-Dibromo-1'-methyl-3'-nitro-4'-(trifluoromethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3b**)*. Yield 0.31 g (66%), mp 171–172 ºC, yellowish powder. IR (ATP): 3177, 1722, 1562, 1361 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, Me), 3.44 (t, J = 8.9 Hz, 1H, H-5′a), 3.56 (t, J = 8.9 Hz, 1H, H-5′b), 4.18 (sept, J = 8.0 Hz, 1H, H-4′), 5.40 (d, J = 7.8 Hz, 1H, H-3′), 7.15 (d, J = 1.5 Hz, 1H, H-4/6), 7.63 (d, J = 1.5 Hz, 1H, H-6/4), 7.75 (s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ 92.1 (d, J = 8.2 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.0 (s), 44.9 (q, ^2J = 30.3 Hz, C-4′), 51.4 (q, J = 2.5 Hz), 74.6, 89.4, 104.3, 116.5, 125.0 (q, ^1J = 278.1 Hz, CF_3), 126.1, 127.0, 136.2, 140.0, 174.7. HRMS (ESI): calcd for $C_{13}H_{10}Br_2F_3N_3NaO_3$ $[M+Na]^+$ 493.8933, found 493.8930.

4.2.3. (3R,3'R*,4'S*)-1,1'-Dimethyl-3'-nitro-4'-(trifluoromethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3c**)*. Yield 0.30 g (90%), (**3c:3'c** = 93:7), mp 133–134 ºC, colorless prisms. IR (ATP): 1716, 1561, 1375 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer **3c** (93%): δ 2.09 (s, 3H, Me-1′), 3.25 (s, 3H, Me-1), 3.43 (t, J = 8.8 Hz, 1H, H-5′a), 3.61 (dd, J = 9.4, 8.1 Hz, 1H, H-5′b), 4.22 (sept, J = 8.1 Hz, 1H, H-4′), 5.39 (d, J = 7.6 Hz, 1H, H-3′), 6.86 (d, J = 7.9 Hz, 1H, H-7), 7.04–7.12 (m, 2H, H-4, H-5), 7.38 (ddd, J = 7.8, 7.1, 1.9 Hz, 1H, H-6), minor isomer **3'c** (7%): δ 2.05 (s, 3H, Me), 3.15 (s, 3H, Me), 3.31 (dd, J = 9.9, 2.9 Hz, 1H, H-5′a), 3.80 (t, J = 9.8 Hz, 1H, H-5′b), 5.19 (d, J = 6.8 Hz 1H, H-3′) (other signals are masked by the major isomer); ^{19}F NMR (376 MHz, $CDCl_3$) major isomer **3c** (93%): δ 92.1 (d, CF_3, J = 8.4 Hz), minor isomer **3'c** (7%): δ 90.3 (d, J = 9.1 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.4, 34.8, 44.9 (q, ^2J = 30.0 Hz, C-4′), 51.3 (q, J = 2.5 Hz), 73.2, 89.4, 108.7, 122.5, 123.6, 124.6, 125.3 (q, ^1J = 277.8 Hz, CF_3), 131.1, 144.4, 174.3. HRMS (ESI): calcd for $C_{14}H_{14}F_3N_3NaO_3$ $[M+Na]^+$ 352.0879, found 352.0879.

4.2.4. (3R,3'R*,4'S*)-1'-Methyl-3'-nitro-1-pentyl-4'-(trifluoromethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3d**)*. Yield 0.26 g (68%), (**3d:3'd** = 86:14), mp 64–65 ºC, beige powder. IR (ATP): 1716, 1559, 1371 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) major isomer **3d** (86%): δ 0.90 (t, J = 6.9 Hz, 3H, CH_2*Me*), 1.31–1.41 (m, 4H, $(CH_2)_2$), 1.75–1.59 (m, 2H, CH_2), 2.09 (s, 3H, Me-1′), 3.43 (t, J = 9.0 Hz, 1H, H-5′a), 3.60 (dd, J = 9.2, 8.0 Hz, 1H, H-5′b), 3.72 (t, J = 7.3 Hz, 2H, NCH_2), 4.21 (sept, J = 8.2 Hz, 1H, H-4′), 5.39 (d, J = 7.7 Hz, 1H, H-3′), 6.86 (d, J = 7.9 Hz, 1H, H-7), 7.05 (td, J = 7.5, 0.6 Hz, 1H, H-5), 7.10 (dd, J = 7.5, 1.3 Hz, 1H, H-4), 7.36 (td, J = 7.7, 1.3 Hz, 1H, H-6), minor isomer **3'd** (14%): δ 0.89 (t, J = 6.9 Hz, 3H, CH_2*Me*), 2.05 (s, 3H, Me-1′), 3.31 (dd, J = 9.8, 2.9 Hz, 1H, H-5′a), 3.66 (dt, J = 14.0, 7.4 Hz, 1H, NCH*H*), 3.80 (t, J = 10.0 Hz, 1H, H-5′b),

5.17 (d, 1H, *J* = 7.0 Hz, H-3′), 6.87 (d, *J* = 7.6 Hz, 1H, H-7), 7.17 (td, *J* = 7.6, 0.7 Hz, 1H, H-5), 7.39 (td, *J* = 7.8, 1.1 Hz, 1H, H-6) (other signals are masked by the major isomer); ^{19}F NMR (471 MHz, $CDCl_3$) major isomer **3d** (86%): δ 92.0 (d, *J* = 8.4 Hz, CF_3), minor isomer **3'd** (14%): δ 90.4 (d, *J* = 9.1 Hz, CF_3). HRMS (ESI): calcd for $C_{18}H_{22}F_3N_3O_3$ $[M+Na]^+$ 408.1505, found 408.1505.

4.2.5. (3R,3'R*,4'S*)-1-Benzyl-1'-methyl-3'-nitro-4'-(trifluoromethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3e**).* Yield 0.22 g (55%), (**3e:3'e** = 95:5), mp 115–116 ºC, beige powder. IR (ATP): 1715, 1565, 1367 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer **3e** (95%): δ 2.12 (s, 3H, Me), 3.46 (t, *J* = 9.0 Hz, 1H, H-5′a), 3.63 (dd, *J* = 9.3, 8.0 Hz, 1H, H-5′b), 4.24 (sept, *J* = 8.2 Hz, 1H, H-4′), 4.92 (d, *J* = 15.6 Hz, 1H, C*H*H), 4.98 (d, *J* = 15.6 Hz, 1H, CH*H*), 5.48 (d, *J* = 7.8 Hz, 1H, H-3′), 6.73 (d, *J* = 7.8 Hz, 1H, H-7), 7.03 (td, *J* = 7.5, 0.7 Hz, 1H, H-5), 7.11 (dd, *J* = 7.6, 1.1 Hz, 1H, H-4), 7.23–7.37 (m, 6H, H-6, Ph), minor isomer **3'e** (5%): δ 2.09 (s, 3H, Me), 3.34 (dd, *J* = 9.9, 3.2 Hz, 1H, H-5′a), 3.84 (t, 1H, *J* = 9.9 Hz, H-5′b), 5.23 (d, 1H, *J* = 6.9 Hz, H-3′) (other signals are masked by the major isomer); ^{19}F NMR (376 MHz, $CDCl_3$) major isomer **3e** (95%): δ 92.0 (d, *J* = 8.3 Hz, CF_3), minor isomer **3'e** (5%): δ 90.4 (d, *J* = 9.2 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 34.9, 44.1, 44.8 (q, ^2J = 30.0 Hz, C-4′), 51.5 (q, *J* = 2.2 Hz), 73.2, 89.3, 109.9, 122.5, 123.5, 124.7, 125.4 (q, ^1J = 277.7 Hz, CF_3), 127.1, 127.9, 128.9, 131.0, 135.0, 143.5, 174.5. HRMS (ESI): calcd for $C_{20}H_{18}F_3N_3NaO_3$ $[M+Na]^+$ 428.1192, found 428.1197.

4.2.6. (3R,3'R*,4'S*)-1'-Methyl-3'-nitro-4'-(trichloromethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3f**).* Yield 0.25 g (70%), mp 263–264 ºC, beige powder. IR (ATP): 3243, 1749, 1558, 1366 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 (s, 3H, Me), 3.41 (dd, *J* = 10.3, 4.6 Hz, 1H, H-5′a), 3.59 (t, *J* = 9.7 Hz, 1H, H-5′b), 4.87–4.95 (ddd, *J* = 8.8, 7.4, 4.8 Hz, 1H, H-4′), 5.35 (d, *J* = 7.4 Hz, 1H, H-3′), 6.89 (d, *J* = 7.8 Hz, 1H, H-7), 7.01 (t, *J* = 7.5 Hz, 1H, H-5), 7.32 (t, *J* = 7.6 Hz, 1H, H-6), 7.41 (d, *J* = 7.5 Hz 1H, H-4), 10.88 (s, 1H, NH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.0, 55.4, 60.9, 74.6, 91.9, 98.1, 110.4, 122.9, 123.5, 125.4, 131.1, 141.2, 175.8. HRMS (ESI): calcd for $C_{13}H_{12}Cl_3N_3O_3$ $[M+Na]^+$ 385.9836, found 385.9836.

4.2.7. (3R,3'R*,4'S*)-5,7-Dibromo-1'-methyl-3'-nitro-4'-(trichloromethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3g**).* Yield 0.34 g (67%), mp 235–238 ºC, beige powder. IR (ATP): 3172, 1719, 1559, 1363 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H, Me), 3.59 (dd, *J* = 9.5, 8.4 Hz, 1H, H-5′a), 3.70 (dd, *J* = 9.6, 7.7 Hz, 1H, H-5′b), 4.71 (q, *J* = 7.8 Hz, 1H, H-4′), 5.50 (d, *J* = 7.3 Hz, 1H, H-3′), 7.21 (d, *J* = 1.6 Hz, 1H, H-4/6), 7.63 (d, *J* = 1.6 Hz, 1H, H-6/4), 7.69 (s, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 34.5, 55.3, 58.0, 75.9, 91.0, 99.5, 104.0, 114.6, 124.9, 127.4, 135.7, 141.5, 173.6. HRMS (ESI): calcd for $C_{13}H_{10}Br_2Cl_3N_3O_3$ $[M+Na]^+$ 541.8047, found 541.8048.

4.2.8. (3R,3'R*,4'S*)-1,1'-Dimethyl-3'-nitro-4'-(trichloromethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3h**).* Yield 0.37 g (98%), mp 131–132 ºC, colorless prisms. IR (ATP): 1709, 1561, 1366 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09 (s, 3H, Me-1′), 3.24 (s, 3H, Me-1), 3.59 (dd, *J* = 9.4, 8.2 Hz, 1H, H-5′a), 3.75 (dd, *J* = 9.4, 7.8 Hz, 1H, H-5′b), 4.75 (q, *J* = 7.8 Hz, 1H, H-4′), 5.48 (d, *J* = 7.3 Hz, 1H, H-3′), 6.85 (d, *J* = 7.7 Hz, 1H, H-7), 7.08 (td, *J* = 7.6, 0.7 Hz, 1H, H-5), 7.16 (dd, *J* = 7.5, 1.2 Hz, 1H, H-4), 7.38 (td, *J* = 7.7, 1.2 Hz, 1H, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.3, 34.8, 55.2, 61.1, 74.2, 92.2, 98.0, 108.6, 122.7, 123.5, 124.9, 131.1, 144.3, 174.5. HRMS (ESI): calcd for $C_{14}H_{14}Cl_3N_3O_3$ $[M+Na]^+$ 399.9993, found 399.9991.

4.2.9. (3R,3'R*,4'S*)-1'-Methyl-3'-nitro-1-pentyl-4'-(trichloromethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3i**).* Yield 0.34 g (79%), mp 104–105 ºC, beige powder. IR (ATP): 1706, 1561, 1359 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.7 Hz, 3H, CH_2*Me*), 1.29–1.42 (m, 4H, $(CH_2)_2$), 1.63–1.74 (m, 2H, CH_2), 2.10 (s, 3H, Me-1′), 3.60 (t, *J* = 8.9 Hz, 1H, H-5′a), 3.69–3.77 (m, 3H, H-5′b, NCH_2), 4.76 (q, *J* = 7.6 Hz, 1H, H-4′), 5.48 (d, *J* = 7.3 Hz, 1H, H-3′), 6.86 (d, *J* = 7.8 Hz, 1H, H-7), 7.07 (t, *J* = 7.6 Hz, 1H, H-5), 7.18 (d, *J* = 7.5 Hz, 1H, H-4), 7.36 (t, *J* = 7.6 Hz, 1H, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.3, 26.9, 28.9, 34.9, 40.3, 55.3, 60.9, 74.2, 92.1, 98.1, 108.9, 122.7, 123.2, 125.1, 131.0, 143.7, 174.2. HRMS (ESI): calcd for $C_{18}H_{23}Cl_3N_3O_3$ $[M+H]^+$ 434.0800, found 434.0807.

4.2.10. (3R,3'R*,4'S*)-1-Benzyl-1'-methyl-3'-nitro-4'-(trichloromethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3j**).* Yield 0.32 g (71%), mp 182–184 ºC, beige powder. IR (ATP): 1705, 1563, 1366 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (s, 3H, Me), 3.61 (dd, *J* = 9.6, 8.2 Hz, 1H, H-5′a), 3.76 (dd, *J* = 9.6, 7.4 Hz, 1H, H-5′b), 4.77 (q, *J* = 7.6 Hz, 1H, H-4′), 4.91 (d, *J* = 15.7 Hz, 1H, C*H*H), 4.97 (d, *J* = 15.7 Hz, 1H, CH*H*), 5.57 (d, *J* = 7.3 Hz, 1H, H-3′), 6.73 (d, *J* = 7.9 Hz, 1H, H-7), 7.04 (t, *J* = 7.6 Hz, 1H, H-5), 7.17 (d, *J* = 7.2 Hz, 1H, H-4), 7.23–7.35 (m, 6H, H-6, Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.0, 44.1, 55.4, 60.9, 74.3, 92.1, 98.1, 109.8, 122.6, 123.5, 125.0, 127.1, 127.9, 128.9, 131.0, 135.0, 143.4, 174.6. HRMS (ESI): calcd. for $C_{20}H_{18}Cl_3N_3O_3$ $[M+Na]^+$ 476.0306, found 476.0307.

4.2.11. (3R,3'R*,4'S*)-1'-Methyl-3'-nitro-4'-(tribromomethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3k**).* Yield 0.34 g (69%), mp 244–245 ºC, white powder. IR (ATP): 3249, 1748, 1554, 1363 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.92 (s, 3H, Me), 3.30 (dd, *J* = 10.4, 4.6 Hz, 1H, H-5′a), 3.59 (t, *J* = 9.6 Hz, 1H, H-5′b), 4.90 (ddd, *J* = 8.8, 7.3, 4.6 Hz, 1H, H-4′), 5.20 (d, *J* = 7.3 Hz, 1H, H-3′), 6.88 (d, *J* = 7.8 Hz, 1H, H-7), 7.01 (t, *J* = 7.5 Hz, 1H, H-5), 7.31 (t, *J* = 7.6 Hz, 1H, H-6), 7.43 (d, *J* = 7.5 Hz, 1H, H-4), 10.86 (s, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 34.5, 42.0, 57.2, 60.6, 75.2,

92.5, 110.4, 121.7, 122.0, 125.9, 130.8, 142.5, 174.2. HRMS (ESI): calcd for $C_{13}H_{12}Br_3N_3O_3$ $[M+H]^+$ 499.8466, found 499.8472.

4.2.12. (3R,3'R*,4'S*)-1,1'-Dimethyl-3'-nitro-4'-(tribromomethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3l**).* Yield 0.33 g (65%), mp 193–194 ºC, beige powder. IR (ATP): 1721, 1552, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H, Me-1′), 3.24 (s, 3H, Me-1), 3.63–3.73 (m, 2H, CH_2), 4.89 (q, *J* = 7.5 Hz, 1H, H-4′), 5.37 (d, *J* = 7.2 Hz, 1H, H-3′), 6.85 (d, *J* = 7.9 Hz, 1H, H-7), 7.09 (td, *J* = 7.5, 0.9 Hz, 1H, H-5), 7.18 (d, *J* = 7.5 Hz, 1H, H-4), 7.39 (td, *J* = 7.7, 1.0 Hz, 1H, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.3, 34.9, 38.6, 57.4, 63.3, 74.6, 93.4, 108.6, 122.8, 123.5, 125.0, 131.1, 144.2, 174.4. HRMS (ESI): calcd for $C_{14}H_{15}Br_3N_3O_3$ $[M+H]^+$ 509.8663, found 509.8648.

4.2.13. (3R,3'R*,4'S*)-1'-Methyl-3'-nitro-1-pentyl-4'-(tribromomethyl)spiro[indoline-3,2'-pyrrolidin]-2-one (**3m**).* Yield 0.38 g (66%), mp 176–177 ºC, beige powder. IR (ATP): 1698, 1560, 1357 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.41–1.32 (m, 4H, $(CH_2)_2$), 1.74–1.64 (m, 2H, CH_2), 2.09 (s, 3H, Me), 3.66 (d, *J* = 7.2 Hz, 2H, CH_2), 3.68–3.77 (m, 2H, NCH_2), 4.89 (q, *J* = 7.5 Hz, 1H, H-4′), 5.37 (d, *J* = 7.2 Hz, 1H, H-3′), 6.85 (d, *J* = 7.9 Hz, 1H, H-7), 7.07 (td, *J* = 7.5, 0.5 Hz, 1H, H-5), 7.18 (dd, *J* = 7.5, 1.2 Hz, 1H, H-4), 7.37 (td, *J* = 7.7, 1.2 Hz, 1H, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.3, 26.9, 28.9, 34.9, 39.0, 40.3, 57.6, 63.1, 74.6, 93.3, 108.9, 122.8, 123.2, 125.1, 131.0, 143.7, 174.2. HRMS (ESI): calcd for $C_{18}H_{22}Br_3N_3O_3$ $[M+H]^+$ 567.9290, found 567.9227.

4.2.14. (3R,3'R*,4'S*)-1-Benzyl-1'-methyl-3'-nitro-4'-(tribromomethyl)spiro[indoline-3,2'-pyrrolidin]-2-one* (***3n***). Yield 0.35 g (59%), mp 196–197 ºC, beige powder. IR (ATP): 1699, 1559, 1345 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.12 (s, 3H, Me), 3.65–3.72 (m, 2H, CH_2), 4.91 (q, *J* = 7.6 Hz, 1H, H-4′), 4.91 (d, *J* = 15.7 Hz, 1H, C*H*H), 4.98 (d, *J* = 15.7 Hz, 1H, CH*H*), 5.45 (d, *J* = 7.2 Hz, 1H, H-3′), 6.73 (d, *J* = 7.8 Hz, 1H, H-7), 7.05 (td, *J* = 7.7, 0.6 Hz, 1H, H-5), 7.19 (d, *J* = 7.5 Hz, 1H, H-4), 7.23–7.36 (m, 6H, H-6, Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.0, 44.1, 57.6, 63.0, 74.8, 77.2, 93.3, 109.8, 122.6, 123.4, 125.1, 127.2, 127.9, 128.9, 131.0, 135.0, 143.3, 174.5. HRMS (ESI): calcd for $C_{20}H_{18}Br_3N_3O_3$ $[M+H]^+$ 585.8977, found 585.9008.

4.2.15. (1'R,2'S*,3S*,7a'R*)-2'-Nitro-1'-(trifluoromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one* (***4a***). Yield 0.29 g (85%), mp 179–180 ºC, colorless prisms. IR (ATP): 3299 1747, 1559, 1361 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.75–2.34 (m, 4H, $2CH_2$), 2.61–2.75 (m, 2H, NCH_2), 3.74–3.84 (m, 1H, H-1′), 4.19 (q, *J* = 7.6 Hz, 1H, H-7′a), 5.68 (d, *J* = 10.1 Hz, 1H, H-2′), 6.92 (d, *J* = 7.8 Hz, 1H, H-7), 7.06 (t, *J* = 7.5 Hz, 1H, H-5), 7.11 (d, *J* = 7.5 Hz, 1H, H-4), 7.33 (t, *J* = 7.7 Hz, 1H, H-6), 8.28 (s, 1H, NH); ^{19}F NMR (471 MHz, $CDCl_3$) δ 93.2 (d, *J* = 7.3 Hz,

CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.2, 31.8, 47.4, 50.6 (q, ^2J = 28.3 Hz, C-1′), 63.4 (q, J = 2.7 Hz), 73.2, 91.0, 111.1, 122.1, 123.0, 125.2 (q, ^1J = 278.7 Hz, CF_3), 125.9, 131.3, 141.6, 177.2. HRMS (ESI): calcd for $C_{15}H_{15}F_3N_3O_3$ $[M+H]^+$ 342.1060, found 342.1058.

4.2.16. (1'S,2'R*,3R*,7a'S*)-2',5-Dinitro-1'-(trifluoromethyl)-1',2',5',6',7',7a'-hexahydrospiro-[indoline-3,3'-pyrrolizin]-2-one (**4b**).* Yield 0.25 g (60%), mp 233–234 ºC, orange powder. IR (ATP): 3156, 1747, 1563, 1341 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.67–2.09 (m, 4H, $2CH_2$), 2.43–2.52 (m, 2H, NCH_2), 3.93 (dt, J = 8.7, 7.1 Hz, 1H, H-7′a), 4.68–4.78 (m, 1H, H-1′), 5.79 (d, J = 10.7 Hz, 1H, H-2′), 7.11 (d, J = 9.3 Hz, 1H, H-7), 8.26–8.31 (m, 2H, H-4, H-6), 11.54 (s, 1H, NH); ^{19}F NMR (471 MHz, DMSO-d_6) δ 95.2 (d, J = 7.6 Hz, CF_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 26.9, 30.1, 47.1, 47.6 (q, ^2J = 27.3 Hz, C-1′), 63.3 (br s), 72.3, 90.2, 110.9, 121.8, 123.0, 125.5 (q, ^1J = 278.6 Hz, CF_3), 128.2, 142.4, 149.2, 176.8. HRMS (ESI): calcd for $C_{15}H_{13}F_3N_4NaO_5$ $[M+Na]^+$ 409.0730, found 409.0729.

4.2.17. (1'S,2'R*,3R*,7a'S*)-5,7-Dibromo-2'-nitro-1'-(trifluoromethyl)-1',2',5',6',7',7a'-hexa-hydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4c**).* Yield 0.31 g (62%), mp 204–205 ºC, beige powder. IR (ATP): 3159, 1719, 1563, 1364 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.69–2.07 (m, 4H, $2CH_2$), 2.28–2.53 (m, 2H, NCH_2), 3.87 (q, J = 7.7 Hz, 1H, H-7′a), 4.54–4.68 (m, 1H, H-1′), 5.75 (d, J = 10.9 Hz, 1H, H-2′), 7.76 (d, J = 1.4 Hz, 1H, H-4/6), 7.82 (d, J = 1.4 Hz, 1H, H-6/4), 11.26 (s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ 95.1 (d, J = 7.4 Hz, CF_3). HRMS (ESI): calcd for $C_{15}H_{13}Br_2F_3N_3O_3$ $[M+H]^+$ 499.9255, found 499.9255.

4.2.18. (1'S,2'R*,3R*,7a'S*)-1-Methyl-2'-nitro-1'-(trifluoromethyl)-1',2',5',6',7',7a'-hexahydro-spiro[indoline-3,3'-pyrrolizin]-2-one (**4d**) and 1-methyl-1'-nitro-2'-(trifluoromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4'd**).* Yield 0.22 g (62%), (**4d:4'd** = 89:11), mp 173–174 ºC, beige powder. IR (ATP): 1724, 1559, 1375 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) major isomer **4d** (89%): δ 1.78–2.32 (m, 4H, $2CH_2$), 2.63–2.73 (m, 2H, NCH_2), 3.24 (s, 3H, Me), 3.78 (tq, J = 9.3, 7.5 Hz, 1H, H-1′), 4.25 (dt, J = 9.0, 6.8 Hz, 1H, H-7′a), 5.63 (d, J = 9.7 Hz, 1H, H-2′), 6.86 (d, J = 7.8 Hz, 1H, H-7), 7.07 (t, J = 7.2 Hz, 1H, H-5), 7.13 (d, J = 6.9 Hz, 1H, H-4), 7.39 (td, J = 7.6, 1.2 Hz, 1H, H-6), minor isomer **4'd** (11%): δ 1.37–2.20 (m, 4H, $2CH_2$), 2.75–3.06 (m, 2H, NCH_2), 3.19 (s, 3H, Me), 4.35 (quint, J = 8.6 Hz, 1H, H-2′), 4.91 (td, J = 8.9, 6.1 Hz, 1H, H-7′a), 5.96 (t, J = 9.2 Hz, 1H, H-1′), 6.87 (d, J = 7.8 Hz, 1H, H-7), 7.14 (t, J = 7.2 Hz, 1H, H-5) 7.42 (td, J = 7.6, 1.0 Hz, 1H, H-6), 7.47 (d, J = 6.9 Hz, 1H, H-4); ^{19}F NMR (471 MHz, $CDCl_3$) major isomer **4d** (89%): δ 93.4 (d, J = 7.5 Hz, CF_3), minor isomer **4'd** (11%): δ 97.4 (d, J = 8.5 Hz, CF_3). HRMS (ESI): calcd for $C_{16}H_{16}F_3N_3NaO_3$ $[M+Na]^+$ 378.1036, found 378.1039.

4.2.19. (1'S,2'R*,3R*,7a'S*)-2'-Nitro-1-pentyl-1'-(trifluoromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4e**).* Yield 0.24 mg (59%), mp 73–74 ºC, beige powder. IR (ATP): 1731, 1556, 1364 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3H, CH_2*Me*), 1.28–1.43 (m, 4H, $2CH_2$), 1.62–1.73 (m, 2H, NCH_2), 1.74–2.31 (m, 4H, $2CH_2$), 2.57–2.67 (m, 2H, NCH_2), 3.63–3.82 (m, 3H, NCH_2, H-1′), 4.20 (td, J = 8.5, 7.2 Hz, 1H, H-7′a), 5.65 (d, J = 10.1 Hz, 1H, H-2′), 6.87 (d, J = 7.9 Hz, 1H, H-7), 7.05 (t, J = 7.5 Hz, 1H, H-5), 7.11 (d, J = 7.5 Hz, 1H, H-4), 7.36 (td, J = 7.7, 1.1 Hz, 1H, H-6); ^{19}F NMR (471 MHz, $CDCl_3$) δ 93.2 (d, J = 7.3 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.3, 26.8, 27.2, 28.9, 31.7, 40.5, 47.2, 50.6 (q, ^2J = 28.2 Hz, C-1′), 63,3 (q, J = 2.3 Hz), 72.6, 91.1, 109.4, 121.9, 122.6, 125.4 (q, ^1J = 278.3 Hz, CF_3), 125.7, 131.1, 144.1, 175.2. HRMS (ESI): calcd for $C_{20}H_{24}F_3N_3NaO_3$ $[M+Na]^+$ 434.1662, found 434.1660.

4.2.20. (1'S,2'R*,3R*,7a'S*)-1-Benzyl-2'-nitro-1'-(trifluoromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4f**) and 1-benzyl-1'-nitro-2'-(trifluoromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4'f**).* Yield 0.35 g (81%), (**4f:4'f** = 91:9), mp 149–150 ºC, beige powder. IR (ATP): 1720, 1563, 1366 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) major isomer **4f** (91%): δ 1.67–2.12 (m, 4H, $2CH_2$), 2.30–2.53 (m, 2H, NCH_2), 3.95 (q, J = 7.8 Hz, 1H, H-7′a), 4.42–4.54 (m, 1H, H-1′), 4.92 (d, J = 15.9 Hz, 1H, C*H*H), 4.98 (d, J = 15.9 Hz, 1H, CH*H*), 5.81 (d, J = 10.7 Hz, 1H, H-2′), 6.94 (d, J = 7.9 Hz, 1H, H-7), 7.06 (t, J = 7.6 Hz, 1H, H-5), 7.23–7.36 (m, 6H, H-6, Ph), 7.52 (d, J = 7.4 Hz, 1H, H-4), minor isomer **4'f** (9%): δ 6.12 (t, J = 9.9 Hz, 1H, H-1′), 6.96 (d, J = 7.9 Hz, 1H, H-7), 7.11 (td, J = 7.7, 1.0 Hz, 1H, H-5), 7.96 (d, J = 7.4 Hz, 1H, H-4) (other signals are masked by the major isomer); ^{19}F NMR (471 MHz, $CDCl_3$) major isomer **4f** (91%): δ 93.2 (d, J = 7.3 Hz, CF_3), minor isomer **4'f** (9%): δ 97.7 (d, J = 8.4 Hz, CF_3). HRMS (ESI): calcd for $C_{22}H_{20}F_3N_3NaO_3$ $[M+Na]^+$ 454.1349, found 454.1346.

4.2.21. (1'S,2'R*,3R*,7a'S*)-2'-Nitro-1'-(trichloromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4g**).* Yield 0.27 g (71%), mp 263–264 ºC, white powder. IR (ATP): 1742, 1563, 1366, 3162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.85–2.43 (m, 4H, $2CH_2$), 2.61–2.73 (m, 2H, NCH_2), 4.26 (q, J = 7.2 Hz, 1H, H-7′a), 4.38 (t, J = 7.9 Hz, 1H, H-1′), 5.80 (d, J = 8.5 Hz, 1H, H-2′), 6.89 (d, J = 7.8 Hz, 1H, H-7), 7.07 (t, J = 7.6 Hz, 1H, H-5), 7.18 (d, J = 7.6 Hz, 1H, H-4), 7.32 (t, J = 7.7 Hz, 1H, H-6), 8.04 (s, 1H, NH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.1, 32.7, 46.6, 65.7, 67.6, 73.1, 95.1, 98.2, 110.8, 122.7, 123.1, 126.2, 131.2, 141.5, 177.0. HRMS (ESI): calcd for $C_{15}H_{14}Cl_3N_3NaO_3$ $[M+Na]^+$ 411.9993, found 411.9990.

4.2.22. (1'S,2'R*,3R*,7a'S*)-2',5-Dinitro-1'-(trichloromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4h**).* Yield 0.26 mg (63%), mp 250 ºC (dec.), beige powder. IR (ATP): 1340, 1558, 1723, 3140 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.71–2.24 (m, 4H,

2CH_2), 2.42–2.54 (m, 2H, NCH_2), 4.00 (q, *J* = 7.3 Hz, 1H, H-7′a), 5.02 (dd, *J* = 9.3, 7.3 Hz, 1H, H-1′), 5.70 (d, *J* = 9.3 Hz, 1H, H-2′), 7.10 (d, *J* = 8.6 Hz, 1H, H-7), 8.27 (d, *J* = 2.3 Hz, 1H, H-4), 8.30 (dd, *J* = 8.6, 2.3 Hz, 1H, H-6), 11.54 (s, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6) *δ* 26.8, 31.3, 46.3, 62.8, 67.5, 72.4, 94.4, 98.5, 110.9, 122.3, 123.1, 128.2, 142.5, 149.1, 176.5. HRMS (ESI): calcd for $C_{15}H_{13}Cl_3N_4O_5$ $[M+Na]^+$ 456.9844, found 456.9844.

4.2.23. (1'S,2'R*,3R*,7a'S*)-5,7-Dibromo-2'-nitro-1'-(trichloromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4i**).* Yield 0.44 g (81%), mp 244–245 ºC, yellow powder. IR (ATP): 1361, 1553, 1725, 3153 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) *δ* 1.71–2.22 (m, 4H, 2CH_2), 2.32–2.54 (m, 2H, NCH_2), 3.92 (dt, *J* = 8.7, 6.9 Hz, 1H, H-7′a), 4.99 (dd, *J* = 9.7, 6.9 Hz, 1H, H-1′), 5.64 (d, *J* = 9.7 Hz, 1H, H-2′), 7.78 (d, *J* = 1.7 Hz, 1H, H-4/6), 7.82 (d, *J* = 1.7 Hz, 1H, H-6/4), 11.30 (s, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6) *δ* 27.0, 31.5, 46.3, 61.8, 68.0, 74.2, 93.8, 98.7, 103.9, 114.4, 125.8, 128.7, 135.9, 141.7, 175.6. HRMS (ESI): calcd for $C_{15}H_{13}Br_2Cl_3N_3O_3$ $[M+H]^+$ 549.8339, found 549.8345.

4.2.24. (1'S,2'R*,3R*,7a'S*)-1-Methyl-2'-nitro-1'-(trichloromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4j**) and 1-methyl-1'-nitro-2'-(trichloromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4'j**).* Yield 0.23 g (56%), (**4j:4'j** = 93:7), mp 157–158 ºC, beige powder. IR (ATP): 1373, 1559, 1724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) major isomer **4j** (93%): *δ* 1.84–2.42 (m, 4H, 2CH_2), 2.58–2.74 (m, 2H, NCH_2), 3.23 (s, 3H, Me), 4.33 (dt, *J* = 7.5, 6.8 Hz, 1H, H-7′a), 4.36 (t, *J* = 7.8 Hz, 1H, H-1′), 5.74 (d, *J* = 7.9 Hz, 1H, H-2′), 6.85 (d, *J* = 7.9 Hz, 1H, H-7), 7.08 (td, *J* = 7.6, 0.8 Hz, 1H, H-5), 7.19 (d, *J* = 6.9 Hz, 1H, H-4), 7.38 (td, *J* = 7.8, 1.1 Hz, 1H, H-6), minor isomer **4'j** (7%): *δ* 3.20 (s, 3H, Me), 5.00–5.06 (m, 2H, H-7′a), 5.02 (d, *J* = 7.3 Hz, 1H, H-2′), 5.81 (dd, *J* = 8.5, 7.3 Hz, 1H, H-1′), 6.83 (d, *J* = 7.9 Hz, 1H, Ar), 7.13 (td, Ar, *J* = 7.6, 0.9 Hz, 1H, H-5), 7.57 (d, *J* = 7.7 Hz, 1H, H-4) (other signals are masked by the major isomer); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 26.5, 26.9, 32.1, 46.7, 66.4, 67.0, 72.0, 95.8, 98.0, 108.8, 122.4, 123.1, 125.7, 131.1, 144.5, 175.3. HRMS (ESI): calcd for $C_{16}H_{16}Cl_3N_3O_3$ $[M+Na]^+$ 426.0149, found 426.0147.

4.2.25. (1'S,2'R*,3R*,7a'S*)-2'-Nitro-1-pentyl-1'-(trichloromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4k**).* Yield 0.25 g (57%), mp 99–100 ºC, beige powder. IR (ATP): 1361, 1555, 1732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 0.89 (t, *J* = 7.0 Hz, 3H, Me), 1.27–2.65 (m, 12H, 6CH_2), 3.65–3.76 (m, 2H, NCH_2), 4.27 (dt, *J* = 7.5, 6.5 Hz, 1H, H-7′a), 4.36 (dd, *J* = 8.5, 7.5 Hz, 1H, H-1′), 5.76 (d, *J* = 8.5 Hz, 1H, H-2′), 6.85 (d, *J* = 7.9 Hz, 1H, H-7), 7.06 (td, *J* = 7.5, 0.8 Hz, 1H, H-5), 7.18 (dd, *J* = 7.5, 1.2 Hz, 1H, H-4), 7.36 (td, *J* = 7.7, 1.2 Hz, 1H, H-6); ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.9, 22.3, 26.8, 27.1, 28.9, 32.4, 40.4, 46.3, 65.8, 67.4, 72.4, 95.4,

98.2, 109.1, 122.6, 122.7, 125.9, 131.0, 144.0, 175.2. HRMS (ESI): calcd for $C_{20}H_{24}Cl_3N_3O_3$ $[M+Na]^+$ 482.0775, found 482.0775.

4.2.26. (1'S,2'R*,3R*,7a'S*)-1-Benzyl-2'-nitro-1'-(trichloromethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4l**).* Yield 0.33 g (70%), mp 217–218 ºC, beige powder. IR (ATP): 1364, 1556, 1730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.86–2.42 (m, 4H, $2CH_2$), 2.56–2.70 (m, 2H, NCH_2), 4.29 (dt, J = 7.5, 7.0 Hz, 1H, H-7′a), 4.40 (dd, J = 8.5, 7.5 Hz, 1H, H-1′), 4.94 (s, 2H, CH_2-1), 5.86 (d, J = 8.5 Hz, 1H, H-2′), 6.70 (d, J = 7.9 Hz, 1H, H-7), 7.04 (t, J = 7.5 Hz, 1H, H-5), 7.19 (d, J = 7.4 Hz, 1H, Ar), 7.36–7.22 (m, 6H, H-6, Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.1, 32.5, 44.1, 46.4, 65.7, 67.6, 72.6, 95.3, 98.2, 110.0, 122.4, 123.0, 125.8, 127.0, 127.8, 128.9, 131.0, 135.0, 143.6, 175.6. HRMS (ESI): calcd for $C_{22}H_{20}Cl_3N_3O_3$ $[M+Na]^+$ 502.0462, found 502.0457.

4.2.27. (1'S,2'R*,3R*,7a'S*)-2'-nitro-1'-(tribromomethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4m**).* Yield 0.39 g (74%), mp 235 ºC (dec.), white powder. IR (ATP): 1361, 1554, 1742, 3180 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.65–2.56 (m, 6H, $3CH_2$), 3.80 (dt, J = 9.0, 6.2 Hz, 1H, H-7′a), 4.59 (dd, J = 9.0, 6.2 Hz, 1H, H-1′), 5.50 (d, J = 9.0 Hz, 1H, H-2′), 6.85 (d, J = 7.7 Hz, 1H, H-7), 7.02 (td, J = 7.6, 0.8 Hz, 1H, H-5), 7.31 (td, J = 7.7, 1.0 Hz, 1H, H-6), 7.42 (d, J = 7.5 Hz, 1H, H-4), 10.75 (s, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 26.6, 32.5, 41.1, 46.4, 64.9, 70.0, 73.9, 95.4, 110.3, 121.9, 122.4, 126.9, 130.9, 142.8, 175.8. HRMS (ESI): calcd for $C_{15}H_{14}Br_3N_3O_3$ $[M+H]^+$ 521.8663, found 521.8645.

4.2.28. (1'S,2'R*,3R*,7a'S*)-2',5-Dinitro-1'-(tribromomethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4n**).* Yield 0.34 g (59%), mp 250 ºC (dec), beige powder. IR (ATP): 1340, 1560, 1757, 3150 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.69–2.35 (m, 4H, $2CH_2$), 2.36–2.56 (m, 2H, NCH_2), 3.85 (dt, J = 8.4, 6.6 Hz, 1H, H-7′a), 4.88 (dd, J = 8.9, 6.6 Hz, 1H, H-1′), 5.57 (d, J = 9.0 Hz, 1H, H-2′), 7.09 (d, J = 8.7 Hz, 1H, H-7), 8.24 (d, J = 2.2 Hz, 1H, H-4), 8.29 (dd, J = 8.7, 2.2 Hz, 1H, H-6), 11.52 (s, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 26.7, 32.0, 40.5, 46.2, 64.2, 69.9, 72.9, 96.0, 110.9, 122.3, 123.4, 128.2, 142.5, 149.1, 176.4. HRMS (ESI): calcd for $C_{15}H_{13}Br_3N_4O_5$ $[M+H]^+$ 566.8514, found 566.8521.

4.2.29. (1'S,2'R*,3R*,7a'S*)-5,7-Dibromo-2'-nitro-1'-(tribromomethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4o**).* Yield 0.37 g (55%), mp 239–240 ºC, yellow powder. IR (ATP): 1361, 1552, 1723, 3157 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 1.70–2.26 (m, 4H, $2CH_2$), 2.28–2.55 (m, 2H, NCH_2), 3.76 (dt, J = 8.0, 6.3 Hz, 1H, H-7′a), 4.88 (dd, J = 9.3, 6.3 Hz, 1H, H-1′), 5.53 (d, J = 9.3 Hz, 1H, H-2′), 7.77 (d, J = 1.7 Hz, 1H, H-4/6), 7.82 (d, J = 1.7 Hz, 1H, H-6/4), 11.28 (s, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 26.9, 32.0, 41.0, 46.3, 63.3, 70.4,

74.7, 95.5, 103.8, 114.4, 126.1, 128.8, 135.8, 141.7, 175.6. HRMS (ESI): calcd for $C_{15}H_{13}Br_5N_3O_3$ $[M+H]^+$ 683.6812, found 683.6834.

4.2.30. (1'S,2'R*,3R*,7a'S*)-1-Methyl-2'-nitro-1'-(tribromomethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4p**) and 1-methyl-1'-nitro-2'-(tribromomethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4'p**).* Yield 0.39 g (72%), (**4p:4'p** = 91:9), mp 160–161 ºC, beige powder. IR (ATP): 1374, 1558, 1729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) major isomer **4p** (91%): δ 1.82–2.09 (m, 4H, $2CH_2$), 2.57–2.69 (m, 2H, NCH_2), 3.23 (s, 3H, Me), 4.19 (dt, *J* = 8.1, 6.8 Hz, 1H, H-7′a), 4.48 (dd, *J* = 8.1, 7.0 Hz, 1H, H-1′), 5.65 (d, *J* = 8.0 Hz, 1H, H-2′), 6.85 (d, *J* = 7.8 Hz, 1H, H-7), 7.08 (td, *J* = 7.6, 0.8 Hz 1H, H-5), 7.20 (d, *J* = 7.7 Hz, 1H, H-4), 7.38 (td, *J* = 7.8, 1.0, Hz 1H, H-6), minor isomer **4'p** (9%): δ 3.21 (s, 3H, Me), 5.01 (dt, *J* = 7.9, 6.5 Hz, 1H, H-7′a), 5.26 (d, *J* = 6.0 Hz, 1H, H-2′), 5.68 (dd, *J* = 7.9, 6.0 Hz, 1H, H-1′), 6.81 (d, *J* = 8.0 Hz, 1H, Ar), 7.15 (t, *J* = 7.3 Hz, 1H, Ar), 7.62 (d, *J* = 7.5 Hz, 1H, Ar) (other signals are masked by the major isomer). HRMS (ESI): calcd for $C_{16}H_{16}Br_3N_3O_3$ $[M+H]^+$ 535.8820, found 353.8838.

4.2.31. (1'S,2'R*,3R*,7a'S*)-1-Benzyl-2'-nitro-1'-(tribromomethyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**4q**).* Yield 0.31 g (51%), mp 185–187 ºC, beige powder. IR (ATP): 1365, 1553, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.85–2.73 (m, 6H, $3CH_2$), 4.16 (dt, *J* = 8.1, 6.5 Hz, 1H, H-7′a), 4.52 (dd, *J* = 8.1, 6.6 Hz, 1H, H-1′), 4.93 (d, *J* = 16.0 Hz, 1H, C*H*H), 4.97 (d, *J* = 16.0 Hz, 1H, CH*H*), 5.77 (d, *J* = 8.2 Hz, 1H, H-2′), 6.70 (d, *J* = 7.8 Hz, 1H, H-7), 7.04 (td, *J* = 7.4, 0.5 Hz 1H, H-5), 7.18–7.36 (m, 7H, H-4, H-6, Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.0, 33.0, 39.5, 44.2, 46.3, 67.3, 70.1, 73.1, 96.7, 109.9, 122.6, 123.0, 125.8, 127.0, 127.8, 128.9, 131.0, 135.0, 143.6, 175.6. HRMS (ESI): calcd for $C_{22}H_{20}Br_3N_3O_3$ $[M+H]^+$ 613.9113, found 613.9117.

4.2.32. *(1'S*,2'S*,3S*,7a'S*)-2'-(3,4-Dimethoxyphenyl)-1-methyl-1'-nitro-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**6**).* Yield 0.31 g (84%, 90% in EtOH), mp 146–147 ºC (lit.[9a] mp 103–105 ºC), white powder. ^1H NMR (400 MHz, $CDCl_3$) δ 1.45−2.23 (m, 4H, $2CH_2$), 2.89 (t, *J* = 7.2 Hz, 1H, CH), 2.94 (s, 3H, NMe), 3.25−3.33 (m, 1H, CH), 3.60 (s, 3H, MeO), 3.76 (s, 3H, MeO), 4.45 (d, *J* = 10.5 Hz, 1H, H-2'), 4.89 (dt, *J* = 9.0, 7.9 Hz, 1H, H-7'a), 6.29 (dd, *J* = 10.5, 9.6 Hz, 1H, H-1'), 6.47 (d, *J* = 1.9 Hz, 1H, H-2''), 6.61 (d, *J* = 8.4 Hz, 1H, H-6''), 6.64 (d, *J* = 7.9 Hz, 1H, H-7), 6.68 (dd, *J* = 8.4, 1.9 Hz, 1H, H-5''), 7.12 (td, *J* = 7.6, 0.8 Hz, 1H, H-5), 7.30 (td, *J* = 7.8, 1.0 Hz, 1H, H-6), 7.59 (d, *J* = 7.5 Hz, 1H, H-4).

4.3. X-ray diffraction study of compounds 3k, 4a and 6

Intensity data for the compounds **3k**, **4a** and **6** were collected on a "Xcalibur E" diffractometer at 295(2) and 120(10) K, corresponding (Mo-Kα radiation, graphite monochromator, ω-scan, radiation wavelength = 0.7107). The structures were solved by direct methods and refined by full-matrix least-squares method using the SHELX-97 program package.[25] All non-hydrogen atoms were refined with anisotropic atomic displacement and hydrogen atoms were included at calculated position using a riding model.

4.3.1. Crystal data for ***3k***. $C_{13}H_{12}Br_3N_3O_3$, M = 497.97. Ortorombic crystals space group $P2_12_12_1$, a = 8.6851(3), b = 10.9040(6), c = 16.7223(7) Å, $\alpha = \beta = \gamma = 90.00°$, V = 1583.64(12) Å^3, D_c = 2.089g/cm^3, absorption coefficient μ = 7.657 mm^{-1}, Z = 4. The intensities of 3790 independent reflections (R_{int} = 0.0295) were measured. The final discrepancy factors R_1 = 0.0427, wR_2 = 0.1032, GooF = 1.002 for 2734 reflections with $I > 2\sigma(I)$; R_1 = 0.0768, wR_2 = 0.1404 (all data). Largest different peak and hole: 0.813 and –1.076 eÅ^{-3}. Completeness to θ = 28.22° (99.96%). Deposition number CCDC 1477914.

4.3.2. Crystal data for ***4a***. $C_{15}H_{14}F_3N_3O_5$, M = 341.29. Monoclinic crystals space group $P2_1/c$, a = 12.6467(7), b = 8.3854(4), c = 14.6826(7) Å, $\alpha = \gamma = 90.00$, β = 110.114(6)°, V = 1462.09(13) Å^3, D_c = 1.550 g/cm^3, absorption coefficient μ = 0.135 mm^{-1}, Z = 4. The intensities of 3939 independent reflections (R_{int} = 0.0236) were measured. The final discrepancy factors R_1 = 0.0508, wR_2 = 0.1629, GooF = 1.032 for 3187 reflections with $I > 2\sigma(I)$; R_1 = 0.0640, wR_2 = 0.1794 (all data). Largest different peak and hole: 0.556 and –0.296 eÅ^{-3}. Completeness to θ = 28.22° (99.95%). Deposition number CCDC 1477917.

4.3.3. Crystal data for ***6***. $C_{23}H_{25}N_3O_5$, M = 341.29. Monoclinic crystals space group $P2_1/c$, a = 10.7513(8), b = 26.4813(15), c = 8.8733(7) Å, $\alpha = \gamma = 90.00$, β = 108.766(8)°, V = 2392.01 Å^3, D_c = 1.176 g/cm^3, absorption coefficient μ = 0.084 mm^{-1}, Z = 4. The intensities of 5683 independent reflections (R_{int} = 0.0283) were measured. The final discrepancy factors R_1 = 0.0575, wR_2 = 0.1446, GooF = 1.000 for 3079 reflections with $I > 2\sigma(I)$; R_1 = 0.1081, wR_2 = 0.1663 (all data). Largest different peak and hole: 0.227 and –0.177 eÅ^{-3}. Completeness to θ = 28.22° (95.67%). Deposition number CCDC 1477919.

Acknowledgments

This work was financially supported by the Russian Science Foundation (Grant 14-13-00388).

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