

RESEARCH ARTICLE

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Synthesis and crystal structures of 5'-phenylspiro[indoline-3, 2'-pyrrolidin]-2-one derivatives

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Abstract

Background: The spiro- indole-pyrrolidine ring system is a frequently encountered structural motif in many biologically important and pharmacologically relevant alkaloids. The derivatives of spirooxindole ring systems are used as antimicrobial, antitumour agents and as inhibitors of the human NK1 receptor besides being found in a number of alkaloids like horsifiline, spirotryprostatin and (+) elacomine. The recently discovered small-molecule MDM2 inhibitor MI-219 and its analogues are in advanced preclinical development as cancer therapeutics.

Results: In the crystal structures of the two organic compounds, 4'-Nitro-3',5'-diphenylspiro[indoline-3,2'-pyrrolidin]-2-one and 3'-(4-Methoxyphenyl)- 4'-nitro -5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one, N-H...O hydrogen bonds make the R²₂(8) ring motif. Further, the structures are stabilized by intermolecular hydrogen bonds.

Conclusion: The crystal structures of 4'-Nitro-3',5'-diphenylspiro[indoline-3,2'-pyrrolidin]-2-one and 3'-(4-Methoxyphenyl)- 4'-nitro -5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one have been investigated in detail. In both the compounds, the R²₂(8) motif is present. Due to the substitution of methoxyphenyl instead of phenyl ring, the entire configuration is inverted with respect to the 2-oxyindole ring.

Background

1,3-Dipolar cycloaddition of azomethineylides to exocyclic olefins constitutes a versatile protocol for the construction of poly functionalized spiro-heterocycles viz. pyrrolidines [1] and pyrrolizines [2], which widely occur in natural products and biologically active compounds. The spiro- indole-pyrrolidine ring system is a frequently encountered structural motif in many biologically important and pharmacologically relevant alkaloids. Compounds with an indole/oxindole framework are promising pharmacophore which exhibit interesting applications in the biological and pharmacological arena [3]. The derivatives of spirooxindole ring systems are used as antimicrobial, antitumour agents and as inhibitors of the human NK1 receptor besides being found in a number of alkaloids like horsifiline, spirotryprostatin and (+) elacomine [4]. The recently discovered small-molecule MDM2 inhibitor MI-219 and its analogues are in advanced preclinical development as cancer therapeutics [5]. Our interest in preparing pharmacologically active

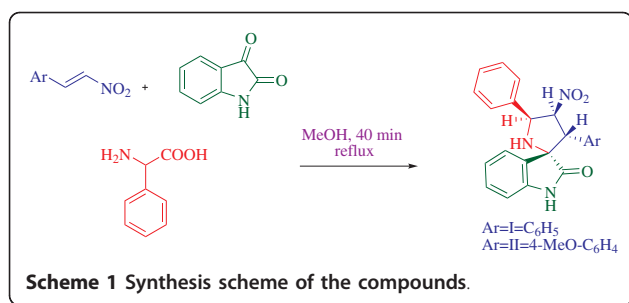
pyrrolidines led us to the compounds, 4'-Nitro-3',5'-diphenylspiro[indoline-3,2'-pyrrolidin]-2-one (**I**) and 3'-(4-Methoxyphenyl)- 4'-nitro -5'-phenylspiro[indoline-3, 2'-pyrrolidin]-2-one (**II**), and we have undertaken the X-ray crystal structure determination of these compounds in order to establish their conformations.

Experimental

The spiro compounds reported in the present work were prepared (Scheme 1) by following our earlier literatures method [6-8]. A mixture of (*E*)-(2-nitrovinyl) benzene or (*E*)-1-methoxy-4-(2-nitrovinyl) benzene (1 mmol), isatin (1 mmol) and phenylglycine (1 mmol) was heated to reflux in methanol on a water-bath for 40 min. The progress of the reaction was monitored by thin layer chromatography (TLC). The starting materials vanished in the TLC indicating the completion of the reaction i.e, the azomethineylide (dipole) reacts with the substituted vinyl benzene (dipolarophile). Then, the reaction mixture was poured into crushed ice, the resulting solid filtered and washed with water to afford pure regio and stereoselective 3'-Phenyl-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one or 3'-(4-Methoxyphenyl)-4'-nitro-5'-phenylspiro[indoline-3,2'-

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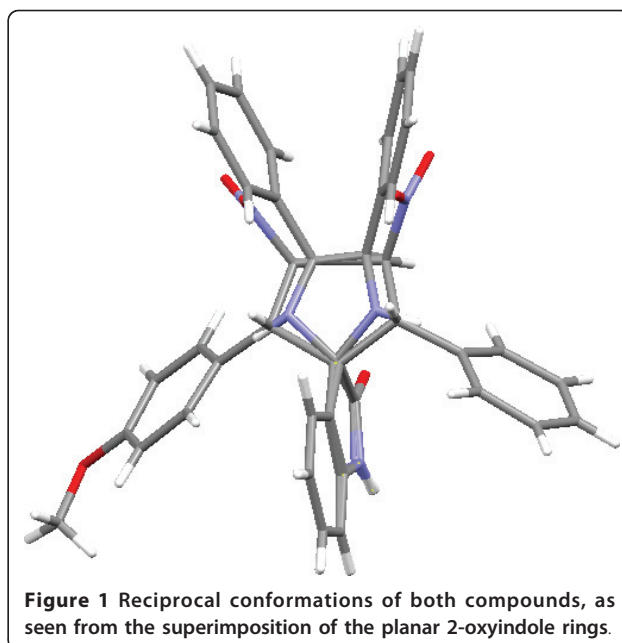
pyrrolidin]-2-one in good yields. The synthesis scheme of 3'-(aryl)-4'-nitro-5'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one is shown below. For compound (**I**): Yield 80%; M.p. 239°C. For compound (**II**): Yield 78%; M.p. 231°C.

Results and Discussion

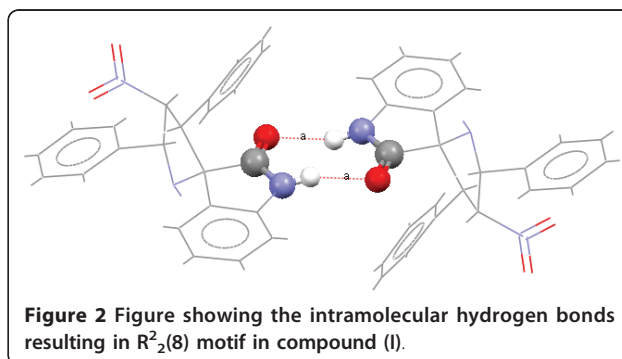
In both the molecules, the 2-oxyindole ring is planar (r. m.s deviation: 0.031 Å and 0.018 Å for **I** and **II**, respectively), which is common in spiro complexes [9,10]. The spiro rings of both molecules have the twisted envelope structure with the N atom at the flap position. The distance to the flap position from the mean plane of spiro carbon atoms, are 0.531(3) Å and 0.503(2) Å in compounds (**I**) and (**II**), respectively. The phenyl ring and methoxyphenyl rings are inclined by an angle of 31.45 (2)° in compound (**II**) which is similar to the inclination of the two phenyl rings in compound (**I**) (31.60(2)°). In compound (**II**), H9 and H8 have *trans* conformation with the torsion angle of 152.45(2)° (H9/C9/C8/H8) and H8 and H7 have *cis* conformation with the torsion angle of -5.43(2)° (H8/C8/C7/H7). In compound (**I**) also, similar conformation is found. The hydrogen conformation torsion angles in compound (**I**) are 152.81(3)° and 7.14(3)° for H9 & H8 and H8 & H7, respectively. Even though these conformations are similar, the directions in which the hydrogens are attached, are reciprocal in both the compounds. Figure 1, a superimposition of the planar 2-oxyindole rings, drawn using Mercury [11], clearly shows the reciprocal conformations of both the compounds. In both molecules, N-H...O hydrogen bonds make the R²₂(8) ring motifs (Figure 2 and Figure 3). Further, the structures are stabilized by intermolecular hydrogen bonds.

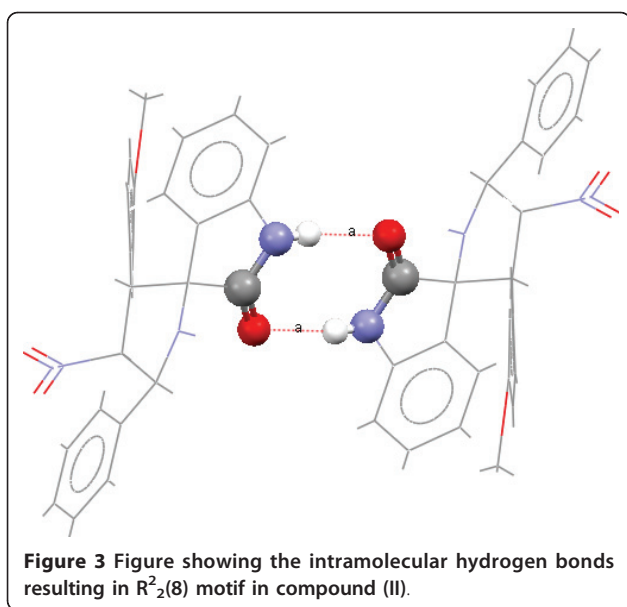
X-ray Crystallography

Single crystal X-ray intensity data for the compounds (Scheme 2) and (Scheme 3) were collected using a Nonius CAD-4 MACH 3 diffractometer with MoK_α (0.71073 Å) radiation at room temperature (293 K). The data reduction was carried out using XCAD4 [12]. The absorption corrections were applied using the ψ -scan method [13]. The structures of both the compounds were solved by direct methods using SHELXS97 [14] and all the non-hydrogen atoms were refined



anisotropically by full-matrix least-squares on F² taking all the unique reflections using SHELXL97 [14]. The hydrogen atoms attached with carbon atoms were placed in their calculated positions and included in the isotropic refinement using the riding model with C-H = 0.93Å (-CH) or 0.97Å (-CH₂) Å or 0.96Å (-CH₃) Å with Uiso(H) = 1.2 Ueq (parent C atom) and amino bound hydrogen atoms were located from the difference Fourier map and include in the refinement isotropically. The crystal data, experimental conditions and structure refinement parameters for the compounds (**I**) and (**II**) are presented in Table 1. The re-crystallization of the compound (**I**) and repeated data collection with different crystal samples did not improve the R value and other statistical parameters. Crystals of better quality could not be obtained for the compound (**I**). Table 2 gives the geometry of the hydrogen bonds present in **I** and **II**. The molecular structures of compounds (**I**) and





(II) showing the atom numbering scheme using ORTEP-3 [15] are given in Figures 4 and 5, respectively.

Conclusions

The title compounds were synthesized and the corresponding molecular crystal structures have been determined by single-crystal X-ray diffraction. In both the compounds, the $R^2_2(8)$ motif is present. Even though most of the conformational features are similar when seen separately, by super positioning the two structures it is found that the entire configuration is inverted with respect to the 2-oxyindole ring. This is due to the substitution of methoxyphenyl instead of phenyl ring in compound (I).

Additional material

Crystallographic data (excluding structure factors) for the structures of compounds (I) and (II) reported in this paper have been deposited with the Cambridge

Table 1 The crystal data, experimental conditions and structure refinement parameters for the compounds (I) and (II)

Parameters	Compound (I)	Compound (II)
Empirical formula	$C_{23}H_{19}N_3O_3$	$C_{24}H_{21}N_3O_4$
Formula weight	385.41	415.44
Wavelength	0.71073 Å	0.71073 Å
Crystal system, space group	Triclinic, P-1	Monoclinic, I 2/a
Unit cell dimensions	$a = 7.681(4)$ Å; $\alpha = 64.68(3)^\circ$ $b = 11.655(5)$ Å; $\beta = 76.11(4)^\circ$ $c = 12.824(3)$ Å; $\gamma = 71.43(3)^\circ$	$a = 17.888(4)$ Å $b = 11.260(3)$ Å; $\beta = 108.65(4)^\circ$ $c = 21.426(2)$ Å
Volume	$976.5(7)$ Å ³	$4089.0(18)$ Å ³
Z, Calculated density	2, 1.311 g/cm ³	8, 1.350 g/cm ³
Absorption coefficient	0.089 mm ⁻¹	0.094 mm ⁻¹
F(000)	404	1744
Crystal size	$0.27 \times 0.23 \times 0.21$ mm ³	$0.26 \times 0.23 \times 0.21$ mm ³
Theta range for data collection	2.10 to 19.98°	2.01 to 24.97°
Limiting indices	$-1 \leq h \leq 7$, $-11 \leq k \leq 11$, $-12 \leq l \leq 12$	$-21 \leq h \leq 21$, $-12 \leq k \leq 1$, $-25 \leq l \leq 25$
Reflections collected/unique	2367/1820 [R(int) = 0.0173]	9624/3499 [R(int) = 0.4799]
Completeness to theta	99.70%	97.50%
Absorption correction	Psi-scan	Psi-scan
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	1820/0/271	3499/0/290
Goodness-of-fit on F^2	1.265	1.157
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.1054$, $wR_2 = 0.4769$	$R_1 = 0.0768$, $wR_2 = 0.1874$
R indices (all data)	$R_1 = 0.1242$, $wR_2 = 0.4954$	$R_1 = 0.1941$, $wR_2 = 0.2171$
Extinction coefficient	0.004(8)	0.0011(6)
Largest diff. peak and hole	0.654 and -0.691 e.Å ⁻³	0.642 and -0.228 e.Å ⁻³

Table 2 The geometry of the hydrogen bonds (Å, °)

D-H...A	D(D-H)	D(H...A)	D(D...A)	<(DHA)
Compound (I)				
N(2)-H(6)...O(1)vi	0.87(3)	2.55	3.360(3)	153
N(3)-H(10)...O(3)v	0.83(3)	2.16	2.894(3)	148
C(2)-H(2)...O(1)iv	0.93	2.54	3.450(3)	165
C(5)-H(5)...N(2)	0.93	2.58	2.888(3)	100
C(7)-H(7)...O(3)	0.98	2.55	3.055(3)	112
C(9)-H(9)...O(2)	0.98	2.34	2.810(3)	108
Compound (II)				
N(3)-H(10)...O(3)iii	0.84(3)	2.06	2.892(3)	170
C(1)-H(1)...O(1)i	0.93	2.39	3.275(3)	160
C(5)-H(5)...N(2)	0.93	2.54	2.871(3)	101
C(9)-H(9)...O(2)	0.98	2.41	2.857(3)	107
C(23)-H(23)...O(2)ii	0.93	2.54	3.318(3)	142

Symmetry transformation used: (i) 1/2-x,y,-z; (ii) 1/2-x,1/2-y,1/2-z; (iii) -x,1-y,-z; (iv) -x,1-y,1-z; (v) 2-x,-y,1-z; (vi) 1+x,y,z

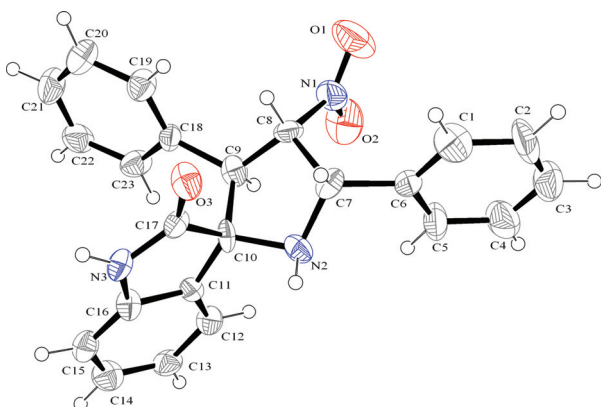


Figure 4 The molecular structure of compound (I) showing the atom numbering scheme. Displacement ellipsoids are drawn at the 40% probability level, using ORTEP-3. Hydrogen atoms are drawn as spheres of arbitrary size.

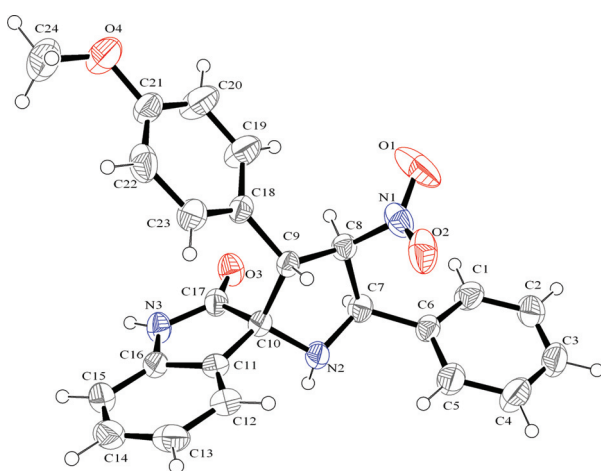
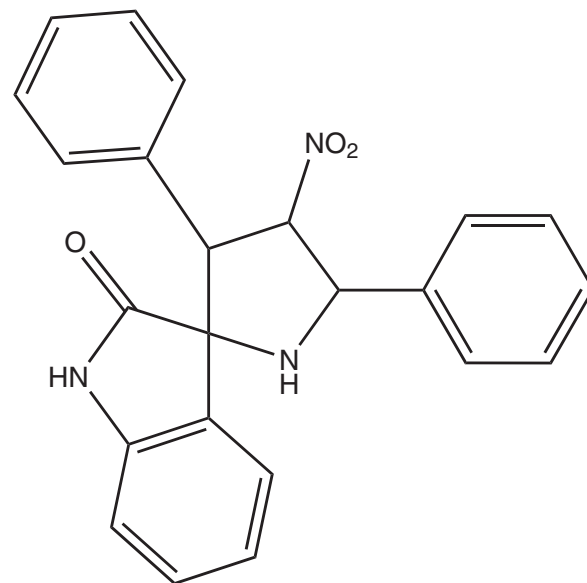
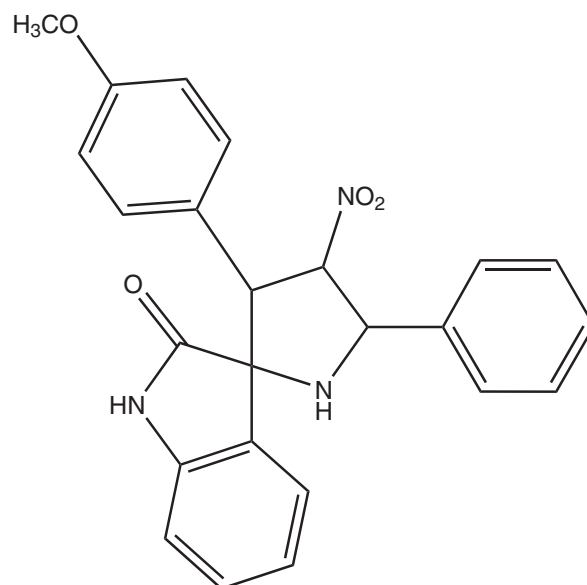


Figure 5 The molecular structure of compound (II) showing the atom numbering scheme. Displacement ellipsoids are drawn at the 40% probability level, using ORTEP-3. Hydrogen atoms are drawn as spheres of arbitrary size.



Scheme 2 Scheme showing the structural formula of compound (I).

Crystallographic Data Centre as supplementary publication numbers, CCDC 802309 and CCDC 802308, respectively. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK. (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).



Scheme 3 Scheme showing the structural formula of compound (II).

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Authors' contributions

JKS collected the X-ray data and solved the crystal structures under the guidance of SN. SMR and JS synthesized the title compounds under the guidance of SP. All the authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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