One Pot Synthesis of Novel Dispiro[oxindole-thiazolidinedione/ thioxo-thiazolidinone /dihydro pyrazolone]-pyrrolidines via 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides†

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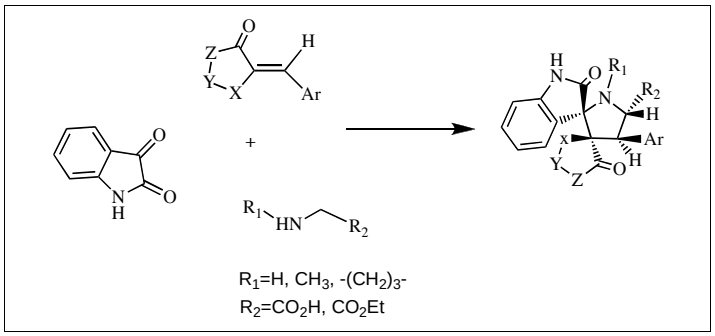

A series of novel dispiro[oxindole-thiazolidinedione]pyrrolidine, dispiro[oxindole-thioxothiazolidinone]-pyrrolidine, dispiro[oxindole-dihydro-pyrazolone]pyrrolidine were synthesized by both regio- and stereo-selective 1,3-dipolar cycloaddition reaction of azomethine ylide generated from amino acid and amino acid ester with π-deficient alkenes in a single pot protocol in good yield. X- ray crystallographic studies established orthogonal disposition between spiro-oxindole and spiro -thiazolidinedione rings in **4a** and **5a**.

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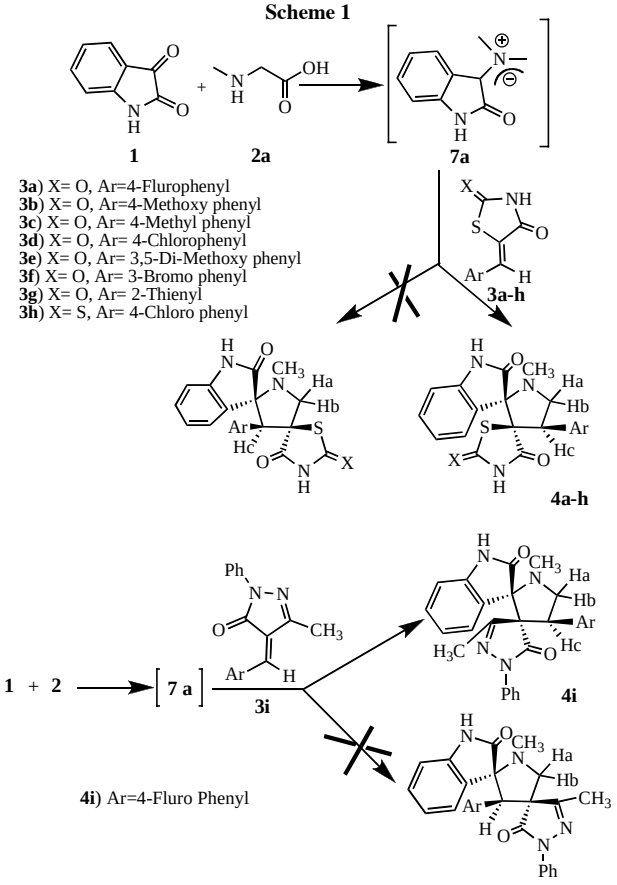
Introduction.

1, 3-Dipolar cycloaddition reactions are in general a powerful tool for constructing a variety of five member heterocyles in a convergent manner from relatively simple precursor [1-3]. Dipolar Cycloaddition of π-deficient alkenes with azomethine ylide allows a facile route for the synthesis of highly substituted and valuable pyrrolidine motif [4] with high regio- and stereo-chemical control of the peripheral substrates. This protocol has been widely exploited in the synthesis of natural products such as alkaloids and other pharmacologically important compounds.

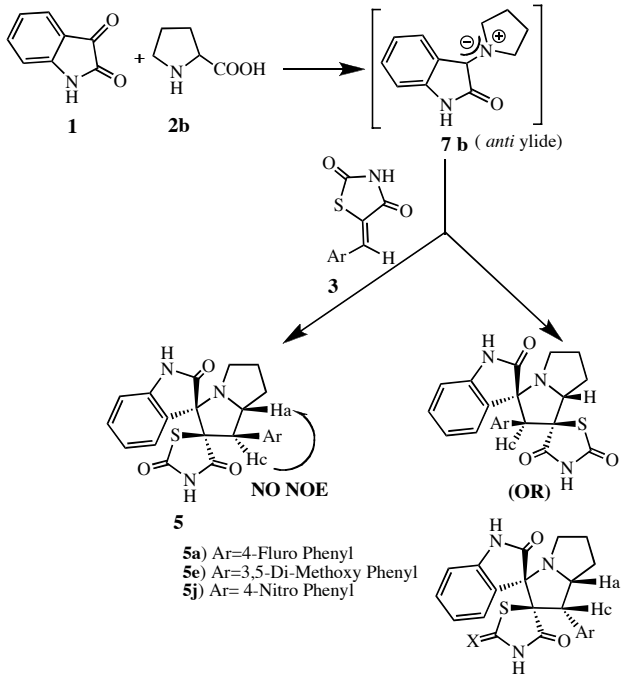
Oxindole and pyrrolidine alkaloids are an important class of heterocyclic compounds due to their wide application in medicinal and agro chemistry as well as scaffolds for generation of pharmacologically active agents [5] and these moieties also occur in natural products such as spiro Tryprostatine A and B, Lacomine [6], Rhyncophyline Corynoxeine, Nitraphylline, Vincatine, Horsifiline [7,8]. Thiazolidino-2,4-dione, 2-thioxo-thiazolidin-4-one motifs have drawn much attention as they are important pharmacophores present in anti-diabetic [9] and α-aldose reductase inhibitors [10]. The derivatives of spiro oxindole ring system have very broad spectrum of biological properties such as antimicrobial, antitumor antibiotic activities and inhibitors of human NK-1 receptor [11]. Synthesis of dispiro pyrrolidine scaffold containing pharmacophores such as oxindole and thiazolidinedione is

Scheme 1



of paramount importance due to their structural uniqueness and for probable affinity towards various pharmacological targets. Herein we report a facile synthesis of novel dispiro-heterocyclic scaffold containing oxindole, pyrrolidine and thiazolidinedione/ thioxo-thiazolidinone/ pyrazolone through highly regio- and stereo-selective cycloaddition reaction of ylide [12,13] derived from isatine and sarcosine / proline with various dipolarophiles such as 5-arylidene-thiazolidine-2,4-dione (**3a-3i**), 5-arylidene-2-thioxo-thiazolidin-4-one (**3h**), 4-benzylidene--2,4-dihydro-pyrazol-3-one (**3i**) derivatives (Scheme-1,2 & 3).

Scheme 2



Result and Discussion.

The required (*Z*)-5-arylidene-thiazolidine-2,4-dione (**3a-3g**), (*Z*)-5-arylidene-2-thioxo-thiazolidin-4-one (**3h**), (Z)- 4-benzylidene-2,4-dihydro-pyrazol-3-one (**3i**) were prepared by the Knoevenagel condensation of an aldehyde with thiazolidine-2,4-dione, 2-thioxo-thiazolidine-4-one and 5-methyl-2-phenyl-2,4-dihydro-pyrazol-3-one [9,10,14] respectively. The stereo-chemical configurations of all dipolarophiles were assigned *Z*-configuration on the basis of their NMR spectra [15].

On single pot annulations of sarcosine **2a**, isatine **1** and 4-fluorobenzylidene-2,4-thiazolidinedione **3a** in aqueous dioxane afforded a single product **4a** in high yield. The NMR spectra of **4a**, H_a appeared at 3.39 δ (dd, J_1, J_2 = 8 Hz), H_b at 3.83 δ (dd, J_1, J_2 = 8 Hz) and H_c at 4.96 δ (dd, J_1, J_2 = 8). The formation of a single diastereomeric product showed that the cycloaddition proceeded in a regio- and stereo- controlled fashion [16]. The stereochemical outcome was further confirmed from X-ray crystallographic data of **4a** (Figure 1). Presumably sterically favored *anti* ylide **7a** is involved in the transition state, which adds to the dipolarophile to afford observed product. The X-ray crystallographic data showed orthogonal disposition between spiro-thiazolidinedione ring at C_{13} and the oxindole ring at C_3. The high yield of the cyclo-adduct prompted to investigate the synthesis of a spiro-pyrrolidine library by employing dipolarophiles (**3a-3i**) to obtain structurally diverse and diastereomerically pure di-spiropyrrolidines of similar configuration from isatine and sarcosine. (Scheme-1).

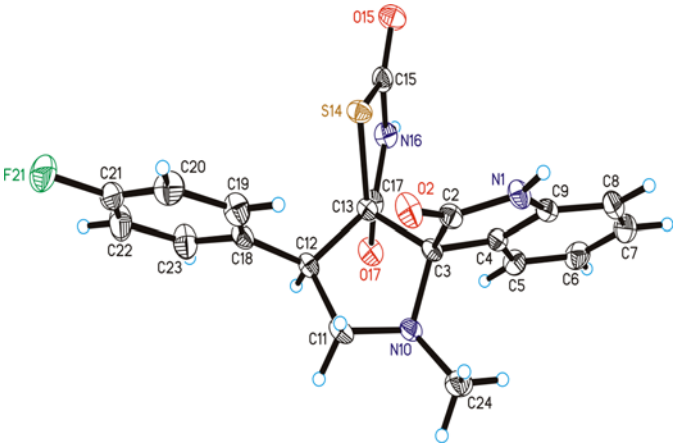


Figure 1. ORTEP diagram showing the molecular structure of **4a**.

The cycloaddition reaction of azomethine ylide **7b** generated from proline **2b** and isatine **1** with **3a** was carried out in a single pot, which furnished a single diastereomerically pure product **5a**. The ^{1}H NMR spectra of compound **5a** showed a doublet at 5.21δ (*J=10* Hz) for H_c proton and a multiplet at 4.06δ for H_a proton respectively (Scheme-2).

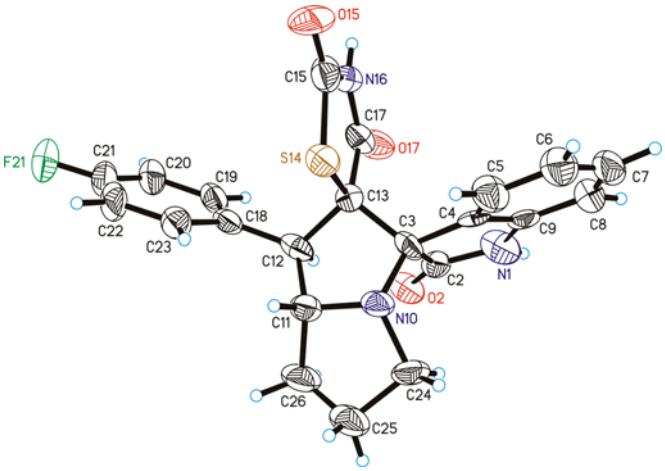


Figure 2. ORTEP view (at 50% probability) of compound 5a showing molecular conformation.

The cycloaddition reaction proceeded through *endo* transition state. The formation of *exo* transition state was ruled out by NOE experiments of (**5a**). Irradiation of C_{12} benzylic proton at 5.21 δ did not cause any enhancement of the signal for proton at C_{11}, which confirmed the *trans* alignment between H_a and H_c protons. The structure, stereo- and regio-selectivity of this reaction were further unambiguously assigned on the basis of X-ray crystallographic analysis of **5a**, which gave a conclusive support for the cycloaddition reaction being navigated *via* the *endo* transition state. The structures of the all products were also confirmed by the spectroscopic data. The X-ray crystallographic structure of **5a** showed the spiro thiazolidinone ring at C_{13} and the oxindole ring at C_3 being orthogonally disposed.

The molecular packing study of **4a** revealed the presence of intermolecular N-H…O and N-H…N hydrogen bonding. A strong N-H…O intermolecular H-bond occurs between N16-H16 of one molecule to O15 of other molecule (D…A =2.950 (2) A°; <dHA=175.5°; H…A= 2.10 A°; symm code: -X, Y+1/2, -Z+1/2) while a weak intermolecular H bond occur between N1-H1 of one molecule with N10 of other (D…A =3.028(2)A°; <dHA=158.5 °; H…A= 2.21 A°; symm code: -X, Y-1, Z)

The molecular packing study of **5a** revealed the absence of any weak or strong intermolecular interactions. This may be due to replacement of N-CH_3 in **4a** with pyrrolidine ring in **5a**.

Table 1

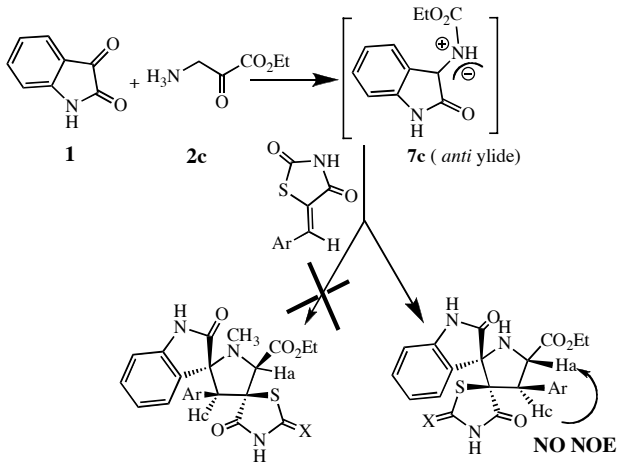
1,3-Dipolar cycloaddition reaction of azomethine ylide generated from sarcosine **2a** , proline **2b** and glycine ethyl ester **2c** with dipolarphile **3.**

Entry	Amino Acid/ester	Dipolarophile	Product	Yield %
1	**2a**	**3a**	**4a**	**83**
2	**2a**	**3b**	**4b**	**72**
3	**2a**	**3c**	**4c**	**69**
4	**2a**	**3d**	**4d**	**79**
5	**2a**	**3e**	**4e**	**82**
6	**2a**	**3f**	**4f**	**76**
7	**2a**	**3g**	**4g**	**70**
8	**2a**	**3i**	**4i**	**71**
9	**2a**	**3h**	**4h**	**58**
10	**2b**	**3a**	**5a**	**53**
11	**2b**	**3e**	**5e**	**42**
12	**2b**	**3j**	**5j**	**49**
13	**2c**	**3c**	**6c**	**60**
14	**2c**	**3d**	**6d**	**64**

To extend the scope of the cycloaddition reaction, we then investigated the synthesis of dispiro pyrrolidines from azomethine ylide generated from glycine ethyl ester (Scheme-3). The single pot muticomponent reaction of isatine **1**, glycine ethyl ester **2c** with dipolarpliles **3c** and **3d**, furnished **6c** and **6d** respectively. In the ^{1}H NMR spectrum of **6c**, two doublets at 4.37 δ (*J*=8 Hz) and 4.90 δ (*J*=10 Hz) assigned for H_a and H_c protons showed *trans* relationship between them. This cycloaddition reaction like earlier presumably proceeds through *endo* transition state. This is evidenced by NOE experimental studies of compound (**6c**). Irradiation of C_{12} benzylic proton at 4.37 δ did not cause any enhancement of the signal for the proton at C_{11} which confirmed *trans* alignment between H_a and H_c protons, moreover the stereo chemistry of spiro center was assigned on the basis of stereo chemical assignment of **5a**.

Incipient azomethine ylide **7c** thus formed undergo 1,3-dipolar cycloaddition with olefins both regio- and stereo selectively to furnish novel dispiro-pyrrolidine scaffold.

Scheme 3



6c) Ar= 4-Methyl Phenyl
6d) Ar= 4-Chloro Phenyl

The yields of the cycloaddition reactions conducted with different dipolarophiles containing *exo* cyclic double bond such as (*Z*)-5-arylidene-2-thioxo-thiazolidin-4-one (**3h**), (*Z*)- 4-benzylidene-2,4-dihydro-pyrazol-3-on (**3i**) are shown in Table 1.

Conculusion.

In summary a series of novel dispiropyrrolidines have been synthesized in good yield in a single-pot 3-component condensation of a reactive ketone (isatine) **1**, an amino acid or amino acid ester **2a-c** and olefin **3a-3i**. Incipient azomethine ylide **7** thus formed undergo 1,3-dipolar cycloaddition with olefins both regio- and stereo selectively to furnish novel dispiro-pyrrolidines scaffold. X-ray crystallographic analysis of **4a** and **5a** established orthogonal disposition between spiro-oxindole and thiazolidinedione rings.

EXPERIMENTAL

All melting points were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in the indicated solvent on Bruker WM 200 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in potassium bromide on Perkin–Elmer AC-1 spectrometer. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer. Microanalyses were performed on Carlo Erba EA-1108 element analyzer. High-resolution electron impact mass spectra (HR-EIMS) were obtained on a JEOL MS route 600H instrument.

General Procedure for the Cycloaddition Reaction of Azomethine Ylide Generated from Sarcosine (**2a**)/Proline (**2b**) and Isatine (**1**) with Various Dipolarophiles (**3a- 3j**).

A mixture of isatine (1 mmol), amino acid (1.1 mmol) and a dipolarophile (1.1 mmol) in 9:1 dioxane-water mixture was refluxed for 10-12 h. The solvent was then evaporated to dryness *in vacuo* and crude product was chromatographed on silica gel (90-120 mesh) using hexane-ethyl acetate (4:1) as eluent to give the cycloadducts.

General Procedure for the Cyloaddition Reaction of Azomethine Ylide **7c** Generated from Glycine ethyl ester hydrochloride (**2c**) *and* Isatine (**1**) with Various Dipolarophiles.

A mixture of isatine **1** (1 mmol), glycine ethyl ester hydrochloride **2c** (1.1 mmol), triethylamine (2 mmol) and dipolarophile 3 (1.1 mmol) in dioxane (10 mL) was refluxed for 8 h. The solvent was then evaporated to dryness *in vacuo* and crude product was chromatographed on silica gel (90-120) using hexane-ethyl acetate (4:1) as eluent to give the cycloadducts.

Crystal Data of **4a**.

Molecular formula: $C_{20}H_{16}FN_3O_3S$. Molecular weight 397.42, monoclinic, $P2_1/c$, a=18.2490(1) Å, b=6.257Å, c=17.0930(1) Å, β=112.780°(1), V=1799.5(1) Å^3, Z=4, D_c=1.467 g/cm^3, μ =0.218mm^{-1}, *F (000)*=824, A rectangular colorless crystal with dimensions of 0.275 X 0.15 X 0.125 mm was used on a Bruker P4 diffractometer at 293(k) using Mo-Kα radiation (λ=0.71073 Å) and a graphite monochromator for unit cell determination and intensity data collection (2θ =50°). A total of 4562 reflections were measured (3177 unique). R indices for all the data wR= 0.057 and conventional R= 0.0383 on F values of 3177 reflections with I>2 (I), S= 1.026 for all data. Structure solution was done by direct methods and refinements by full-matrix least squares methods on F^2. Programs used were XSCANS [17] (for data collection and processing), SHELX-97 [18] (for structure solution), and SHELXTL-N[19] (for refinements and graphics).

Crystal Data for **5a**.

Molecular formula: $C_{22}H_{18}FN_3O_3S$, Molecular weight 423.45, orthorhombic, space group Pna2$_1$, a = 9.109(2), b = 11.102(3), c = 19.018 (4) Å, α = 90.01(1)°, β = 90.03(3)°, γ = 90.01(2)°, V = 1923.22(76) Å^3, Z = 4, D_c= 1.464 gcm^{-3}, $F(000)$ = 880, μ = 0.209mm^{-1}. A colorless block crystal of size 0.250 x 0.300 x 0.075 mm was used on a Bruker P4 diffractometer at 293(2)K using Mo- K_α radiation (λ = 0.71073 Å) and a graphite monochromator for unit cell determination and intensity data collection . A total of 2597 reflections were measured (R_{int} = 0.0813) of which 2040 were unique. For all data wR2 = 0.3364 and conventional R = 0.1022 on F-values of 1414 reflections with $I > 2\sigma(I)$ and 0.1377 for all 2040 data. Goodness of fit S = 1.328 for all data, 271 parameters and 1 restrains. Unit cell determination and intensity data collection was performed on a Bruker P4 Diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix-least-squares methods on F^2. Programs used: XSCANS [17] for data collection and processing, SHELX-86 [18] for structure solutions and SHELXTL-NT [19] for structure refinements.

1-*N*-Methyl-spiro[2.3^1]oxindole-4^1-(4-florophenyl)-spiro[3.5^1]-2^{11},4^{11}-thiazolidin-one-3,3^1-pyrrolidine (**4a**).

This compound was obtained as white solid, mp: 205-207°C; ir (potassium bromide): 1511, 1617, 3167, cm^{-1}; ^{1}H nmr (Acetone d_6) δ 2.04 (s, 3H, CH_3), 3.39-3.43 (dd, J_1, J_2 = 8 Hz, 1Ha), 3.83-3.87 (dd, J_1 , J_2 = 8 Hz, 1Hb), 4.49-4.53 (dd, J_1 , J_2 = 8 Hz, 1Hc), 6.80-7.47 (m, 8H, Ar-H), 9.76(bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ 35.32, 53.13, 55.01, 68.28, 75.16, 80.60, 98.68, 111.10, 123.52, 127.63, 129.54, 131.55, 133.02, 134.05, 138.54, 144.79, 169.53, 177.08, 201.52; MS-FAB m/z: 398 $(M+H)^+$; HR-EIMS calcd for $C_{20}H_{16}FN_3O_3S$: 397.0896 found 397.0908.

1-*N*-Methyl-spiro[2.31]oxindole-41-(4-methoxyphenyl)-spiro-[3.5^1]-2^{11},4^{11}-thiazolidin-one-3,3^1-pyrrolidine (**4b**).

This compound was obtained as white solid, mp: 205-207°C; ir (potassium bromide) 1680, 1757, 3159, cm^{-1}; ^{1}H nmr (Acetone d_6) δ 2.80 (s, 3H, CH_3), 3.30-3.38 (dd, J_1, J_2 = 8 Hz, 1Ha), 3.65 (s, 3H, OMe) 3.80-3.89 (dd, J_1 =8, J_2 = 10 Hz, 1Hb), 4.37-4.46 (dd, J_1 =10, J_2 = 8 Hz, 1Hc), 6.76-7.32 (m, 8H, Ar-H), 9.62 (bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ 35.69, 52.62, 55.35, 55.92, 59.63, 71.70, 72.97, 76.26, 80.91, 111.33, 115.17, 123.77, 125.40, 128.16, 131.77, 132.60, 145.11, 160.63, 170.30, 177.76; MS-FAB m/z: 410 $(M+H)^+$.

Anal. Calcd for $C_{21}H_{19}N_3O_4S$: C, 61.60; H, 4.68; N, 10.26. Found: C, 60.48; H, 4.56; N, 10.03.

1-*N*-Methyl-spiro[2.3^1]oxindole-4^1-(4-methylphenyl)-spiro[3.5^1]-2^{11},4^{11}-thiazolidin-one-3,3^1-pyrrolidine (**4c**).

This compound was obtained as brown solid, mp: 205-207°C; ir (potassium bromide): 1595, 1695, 3233, cm^{-1}; ^{1}H nmr (Acetone d_6) δ 1.95 (s, 3H, CH_3) 2.09 (s, 3H, N-CH_3), 3.21-3.29 (dd, J_1, J_2 = 8 Hz, 1Ha), 3.74-3.83 (dd, J_1 =10, J_2 = 8Hz, 1Hb), 4.30-4.38 (dd, J_1= 6, J_2 = 8 Hz, 1Hc), 6.71-7.18 (m, 8H, Ar-H), 9.55 (bs, 1H, NH); ^{13}C nmr: δ 21.51, 35.67, 52.94, 59.48, 72.98, 76.00, 80.92, 111.30, 123.74, 125.41, 128.16, 130.47, 131.38, 131.74, 136.80, 138.47, 145.14, m170.29, 177.72; MS-FAB m/z: 394 $(M+H)^+$.

Anal. Calcd for $C_{21}H_{19}N_3O_3S$: C, 64.10; H, 4.87; N, 10.68; Found: C, 64.32; H, 4.62; N, 10.56.

1-*N*-Methyl-spiro[2.3^1]oxindole-4^1-(4-chlorophenyl)-spiro[3.5^1]-2^{11},4^{11}thiazolidin-one-3,3^1-pyrrolidine (**4d**).

This compound was obtained as light brown solid, mp: 220-222°C; ir (potassium bromide): 1593, 1705, 3195, cm^{-1}; ^{1}H nmr (Acetone d_6) δ 2.14 (s, 3H, CH_3), 3.45-3.54 (dd, J_1=8, J_2 = 6 Hz, 1Ha), 3.89-3.96 (dd, J_1,=8, J_2 = 4 Hz, 1Hb),4.52-4.60 (dd, J_1 , J_2 = 8 Hz, 1Hc), 6.90-7.54 (m, 8H, Ar-H), 9.76(bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ 35.32, 53.13, 55.01, 68.28, 75.16, 80.60, 98.68, 111.10, 123.52, 127.63, 129.54, 131.55, 133.02, 134.05, 138.54, 144.79, 169.53, 177.08, 201.52; MS-FAB m/z: 414 $(M+H)^+$.

Anal. Calcd for $C_{20}H_{16}ClN_3O_3S$: C, 58.08; H, 3.90; N, 10.15; Found: C, 58.31; H, 4.09; N, 9.87.

N-Methyl-spiro[2.3^1]oxindole-4^1-(3,5-dimethoxyphenyl)-spiro-[3.5^1]-2^{11},4^{11}-thiazolidin-one-3,3^1-pyrrolidine (**4e**).

This compound was obtained as white solid, mp: 205-207°C; ir ((potassium bromide): 1597, 1705, 3199, cm^{-1}; ^{1}H nmr (Acetone d_6) δ 2.35 (s, 3H, CH_3), 3.67-3.71 (dd, J_1, J_2 = 8 Hz, 1Ha), 3.94 (s, 6H, $(OMe)_2$) 3.96-4.37 (dd, J_1 =8, J_2 = 10 Hz, 1Hb), 4.47-4.66 (dd, J_1 , J_2 = 8 Hz, 1Hc), 6.60-7.50 (m, 8H, Ar-H), 9.96(bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ 35.67, 53,21, 56.01, 59.51, 73.20, 73.40, 73.78, 75.72, 80.92, 100.69, 109.46, 111.32, 123.74, 125.36, 128.04, 131.76, 142.17, 145.12, 162.50, 170.41, 177.56; MS-FAB m/z: 440 $(M+H)^+$.

Anal. Calcd for $C_{22}H_{21}N_3O_5S$: C, 60.12; H, 4.82; N, 9.56; Found: C, 59.68; H, 4.74; N, 9.36.

1-*N*-Methyl-spiro[2.3^1]oxindole-4^1-(3-bromophenyl)-spiro[3.5^1]-2^{11},4^{11}-thiazolidin-one-3,3^1-pyrrolidine (**4f**).

This compound was obtained as light brown solid, mp: 205-207°C; ir (potassium bromide): 1620, 1707, 3248, cm^{-1}; ^{1}H nmr (Acetone d_6) δ 2.24 (s, 3H, CH_3), 3.54-3.62 (dd, J_1, J_2 = 8 Hz, 1Ha), 3.95-4.04 (dd, J_1 =10, J_2 = 8 Hz, 1Hb), 4.57-4.66 (dd, J_1 , J_2 = 8 Hz, 1Hc), 6.97-7.82 (m, 8H, Ar-H), 9.86(bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ 35.64, 52.65, 59.53, 75.29, 80.91, 111.45, 123.47, 123.86, 125.10, 128.06, 130.73, 131.73, 131.89, 132.01, 134.40, 142.67, 145.14, 169.84, 117.34, 117.74. MS-FAB m/z: 458 $(M+H)^+$.

Anal. Calcd for $C_{20}H_{16}N_3O_3S$: C, 52.41; H, 3.52; N, 9.17; Found: C, 52.26; H, 3.76; N, 9.07

1-*N*-Methyl-spiro[2.31]oxindole-41-(thiophene-2-yl)-spiro[3.5^1]-2^{11},4^{11}-thiazolidin-one-3,3^1-pyrrolidine (**4g**).

This compound was obtained as light brown solid, mp: 220-222°C; ir (potassium bromide): 1593, 1705, 3195 cm^{-1}; ^{1}H nmr (Acetone d_6) δ 2.19 (s, 3H, CH_3), 3.57-3.66 (dd, J_1=10, J_2 = 8 Hz, 1Ha), 4.01-4.10 (dd, J_1,=8, J_2 = 10 Hz, 1Hb),4.79-4.88 (dd, J_1 , J_2 = 8 Hz, 1Hc), 6.94-7.43 (m, 8H, Ar-H), 9.72(bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ 35.85, 47.74, 60.15, 75.93, 79.49, 80.15, 111.49, 123.8, 125.00, 126.93, 128.08, 128.55, 129.21, 131.95, 142.69, 145.22, 177.54; MS-FAB m/z: 386 $(M+H)^+$.

Anal. Calcd for $C_{18}H_{15}N_3O_3S_2$: C, 56.09; H, 3.92; N, 10.90; Found: C, 55.96; H, 4.19; N, 10.74.

1-*N*-Methyl-spiro[2.3^1]oxindole-4^1-(4-chlorophenyl)-spiro[3.5^1]-2^{11}-thioxo-thiazolidin-4^{11}-one-3,3^1-pyrrolidine(**4h**).

This compound was obtained as white solid, mp: 198-200 °C; ir (potassium bromide): 3197, 2993, 1706, 1616, cm^{-1}; ^{1}H NMR (Acetone d_6) δ 2.03 (s, 3H, CH_3), 3.40 (dd, J_1, J_2 = 8 Hz, 1H), 3.53 (dd, J_1 =4, J2 = 8 Hz, 1H,), 4.44 (dd, J_1, J_2 = 8 Hz, 1H), 6.87-7.40 (m, 8H, Ar-H), 9.7 (bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ35.48, 53.33, 59.54, 68.28, 75.16, 77.83, 80.61, 111.49, 123.93, 125.04, 128.17, 129.96, 131.96, 133.19, 134.50, 138.44, 145.64, 177.71, 179.32, 200.83. MS-FAB m/z: 430 $(M+H)^+$.

Anal. Calcd for $C_{20}H_{16}ClN_3O_2S_2$: C, 55.87; H, 3.75; N, 9.77; Found: C, 55.69; H, 3.80; N, 9.57.

1-*N*-Methyl-spiro[2.3^1]oxindole-4^1-(4-fluorophenyl)-spiro[3.5^1]-3^{11}-phenyl-5^{11}-methyl-4^{11}, 5^{11}-dihydro-pyrazol-2^{11}-one (**4i**).

This compound was obtained as white solid, mp: 231-232°C; ir (potassium bromide): 1599, 1703, 3483, cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.25 (s, 3H) 2.32 (s, 3H), 3.68-3.73 (dd, J_1, J_2 = 10 Hz, 1H), 3.89-3.94 (dd, J_1, J_2 = 10 Hz, 1H),4.13-4.17 (dd, J_1, J_2 = 10 Hz, 1H), 6.77-7.57 (m, 13H, Ar-H), 8.75 (bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ 30.10, 44.08, 45.45, 55.00, 56.43, 76.82, 110.58, 115.96, 116.26, 119.69, 122.79, 123.36, 125.88, 127.17, 128.50, 129.16, 130.73, 142.35, 155.85, 160.17, 170.69, 176.01, 177.75; MS-FAB m/z: 455 $(M+H)^+$; HR-EIMS. calcd for $C_{27}H_{23}FN_4O_2$: 454.1805 found 454.1820.

Spiro[2.3^1]-(2^{1}oxindole)-spiro[3.5^1]-2^{11},4^{11}-thiazolidin-one-4^1-(4-fluorophenyl)-1-azabicyclo [3.3.0]octane (**5a**).

This compound was obtained as white solid, mp: 195-197°C; ir (potassium bromide): 1511, 1710, 3551 cm^{-1}; ^{1}H nmr (Acetone d_6) δ 1.90 (m, 2H) 1.93 (m, 2H), 2.48 (t, 2H), 4.06 (m, 1H), 5.21-5.16 (d, J=10 Hz, 1H), 6.71-7.54 (m, 8H, Ar-H), 9.45 (bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ47.98, 53.29, 55.93, 68.19, 72.60, 79.43, 83.36, 99.52, 108.47, 110.79, 116.08, 116.50, 122.35, 129.66, 131.38, 132.46, 162.20, 170.12, 173.09, 177.91; MS-FAB m/z: 451 $(M+H)^+$; HR-EIMS calcd for $C_{22}H_{18}FN_3O_3S$: 423.1053 found 423.1061.

Spiro[2.3^1]-(2^{1}oxindole)-spiro[3.5^1]-2^{11},4^{11}-thiazolidin-one-4^1-(3,5-dimethoxyphenyl)-1-azabicyclo [3.3.0]octane (**5e**).

This compound was obtained as brown solid, mp: 231-232°C; ir (potassium bromide): 1599, 1703, 3483, cm^{-1}; ^{1}H NMR (Acetone d_6) δ 1.11 (m, 2H) 2.25 (m, 2H), 2.90 (t, 2H), 3.97 (s, 6H, $(-OCH_3)_2$), 4.07 (m, 1H), 5.55-5.51 (d, J=9.3 Hz, 1H) 6.65-7.93 (m, 7H, Ar-H), 9.80 (bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ 47.99, 53.79, 55.97, 67.79, 72.58, 79.57, 83.40, 100.52, 108.43, 110.78, 122.33, 127.32, 129.68, 131.36, 139.19, 143.97, 162.18, 169.96, 174.08, 177.94; MS-FAB m/z: 466 $(M+H)^+$.

Anal. Calcd for $C_{22}H_{21}N_3O_5S$: C, 60.12; H, 4.82; N, 9.56; Found: C, 60.27; H, 4.66; N, 9.70.

Spiro[2.3^1]-(2^{1}oxindole)-spiro[3.5^1]-2^{11},4^{11}-thiazolidin-one-4^1-(4-nitrophenyl)-1-azabicyclo [3.3.0]octane (**5j**).

This compound was obtained as yellow solid, mp: 152°C (Decomp); ir (potassium bromide): 1595, 1675, 1708, 3452, cm^{-1}; ^{1}H nmr (DMSO d_6): δ 1.03 (m, 2H) 1.18 (m, 2H), 2.39 (t, 2H), 4.11(m, 1H), 5.10 (d, J=10 Hz, H), 6.70-8.13 (m, 8H, Ar-H), 10.54 (bs, 1H, NH);^{13}C nmr (Acetone d_6): δ 29.99, 30.43, 46.92, 51.90, 66.58, 78.27, 81.74, 110.00, 121.38, 123.82, 125.53, 128.30, 130.59, 142.89, 143.33, 147.46, 169.33, 172.20, 176.74; MS-FAB m/z: 451 $(M+H)^+$.

Anal. Calcd for $C_{22}H_{21}N_3O_5S$: C, 60.12; H, 4.82; N, 9.56; Found: C, 60.34; H, 4.76; N, 9.48.

Spiro(4-methylphenyl)-5-spiro[2.3^1]oxindole-2-carboethoxy pyrrolidine-4-2^{11},4^{11}-thiazolidinone (**6c**).

This compound was obtained as white solid, mp: 181-183°C; ir (potassium bromide): 1566, 1700, 3125 cm^{-1}. ^{1}H nrm ($CDCl_3$) δ 1.03 (t, 3H), 2.08 (s, 3H), 2.55 (bs, 1H), 4.10 (m, 2H), 4.25-4.30 (d, J=10 Hz, 1H), 4.96-5.01 (d, J=10 Hz, 1H), 6.77-7.26 (m, 8H), 8.93 (bs, 1H, NH); ^{13}C nmr (Acetone d_6): δ 19.26 26.33, 34.69, 65.46, 66.32, 70.18, 79.37, 115.75, 137.60, 115.75, 127.57, 129.23, 130.66, 137.60, 139.51, 142.52, 148.80, 175.49, 176.38, 182.74, 183.52; MS-FAB m/z: 452 $(M+H)^+$.

Anal. Calcd for $C_{23}H_{21}N_3O_5S$: C, 61.18; H, 4.69; N, 9.31; Found: C, 61.25; H, 4.57; N, 9.29.

Spiro(4-chlorophenyl)-5-spiro[2.3^1]oxindole-2-carboethoxy pyrrolidine-4-2^{11},4^{11}-thiazolidinone (**6d**).

This compound was obtained as white solid, mp: 199-201°C; ir (potassium bromide): 1566, 1700, 3125 cm^{-1}; ^{1}H nmr ($CDCl_3$)

δ 1.084 (t, 3H), 2.25 (bs, 1H), 4.13 (m, 2H), 4.37-4.41(d, J=8 Hz,1H), 4.90-4.95 (d, J=10 Hz, 1H), 6.90-7.63 (m, 7H), 10.89 (bs, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 14.27, 57.64, 61.21, 64.46, 73.56, 76.41, 110.58, 112.65, 124.41, 126.09, 128.94, 131.12, 132.30, 137.06, 143.67, 169.91, 170.74, 177.76, 178.19; MS-FAB m/z: 472 $(M+H)^+$.

Anal. Calcd for $C_{22}H_{18}ClN_3O_5S$: C, 55.99; H, 3.84; N, 8.90; Found: C, 56.16; H, 3.64; N, 9.06.

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Supplementary Material.

CCDC Nos. 610556 and 610557 contain the supplementary crystallographic data for compound **4a** and **5a** respectively. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223-336033.

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