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A facile regio- and stereoselective synthesis of novel spiro [indolin-3,2′-pyrrolidin]-2-one's *via* 1,3-dipolar cycloaddition of azomethine ylides

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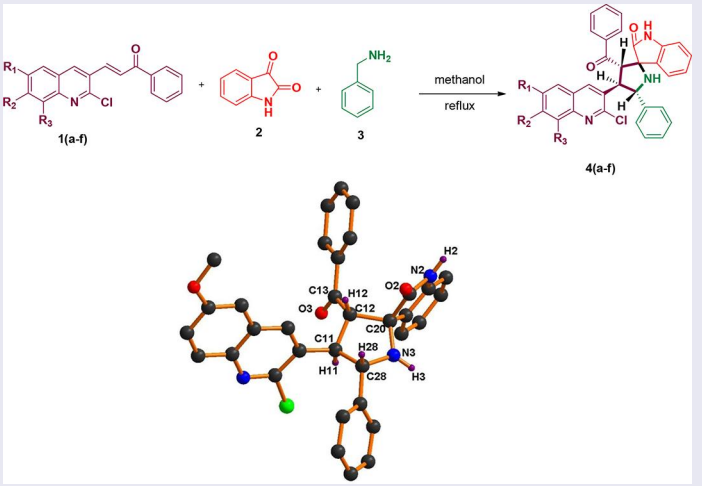
ABSTRACT

A facile regio and stereoselective synthesis of novel spiro[indolin-3,2′-pyrrolidin]-2-one's have been accomplished through 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the reaction of isatin and benzyl amine with quinoline bearing dipolarophiles in good yields. The synthesized compounds were well characterized through different spectroscopic techniques, such as single crystal XRD, FTIR, NMR, and mass spectral analysis.

GRAPHICAL ABSTRACT



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KEYWORDS
Benzyl amine methanol; isatin; quinoline dipolarophiles; spiro[indolin-3,2′-pyrrolidin]-2-one

Introduction

The spirocyclic oxindoles describe characteristic structural motifs of a variety of medicinal molecules and biologically dynamic natural products.[1,2] The spiro[pyrrolidin-3,2′-oxindoles] are exemplify by the fused five-membered N-heterocyclic frameworks and adjoining nitrogen atoms to the spirocenters found in many pharmaceutically relevant compounds and naturally occurring alkaloids. Natural products that contain

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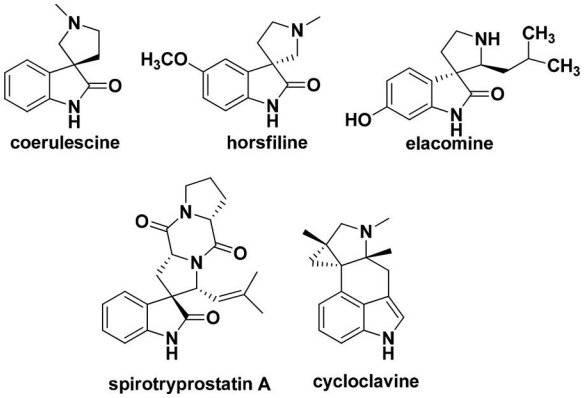


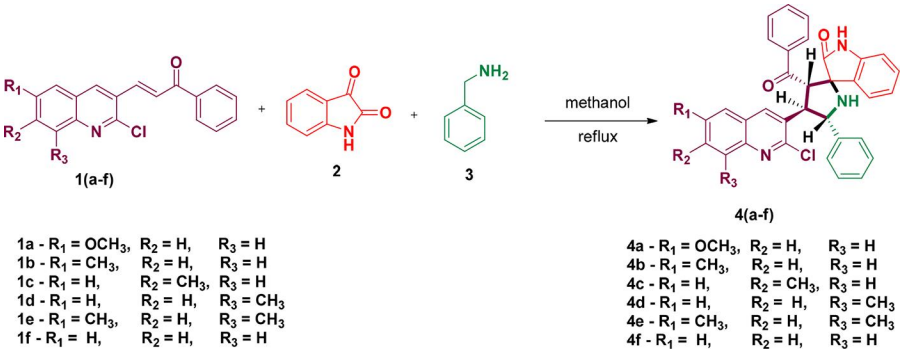
Figure 1. Naturally occurring bioactive spirocyclic oxindoles.

3-spiropyrrolidine oxindole framework (Fig. 1) exhibit significant pharmacological properties. For example, coerulescine, horsfiline, and elacomine are inhibitors of the mammalian cell cycle at the G2/M interphase,[3] spirotryprostatin A also showed anticancer activity.[4] Various biological activities have been found for synthetic spirooxindoles, such as antidiabetic,[5] acetylcholinesterase (AChE) inhibitory properties,[6] antiviral,[7] antitumoric,[8] antifungal,[9] antitubercular,[10] antimalarial,[11] and anti-inflammatory[12] activities.

Azomethine ylides are extremely versatile building blocks in organic synthesis, and are recognized to take part in 1,3-dipolar cycloaddition reactions with a wide array of dipolarophiles.[13] Cycloadditions of azomethine ylides to alkenes are well reputable reactions in which pyrrolidines and pyrrolizidines are formed, frequently with a high degree of stereo chemical control.[14] This mode of cycloaddition simultaneously constructs two carbon–carbon bonds and forms ring systems with regio- and stereocontrol.[15] From the abovementioned significances in the synthesis of spiro oxindoles, herein we report the synthesis of quinoline substituted spiro[indolin-3,2′-pyrrolidin]-2-one through [3 + 2] cycloaddition reaction of azomethine ylide generated *in situ* from isatin and benzyl amine to quinolinyl chalcones.

Results and discussion

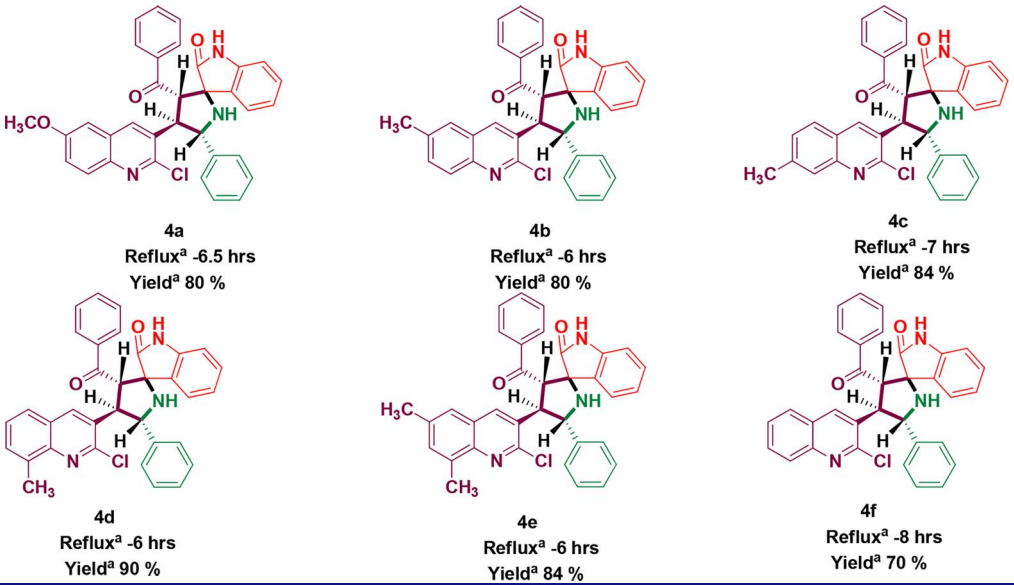
1,3-Dipolar cycloaddition of ylidic species, for example azomethine ylides with dipolarophiles, is a useful method for the construction of five-membered heterocycles, such as pyrrolidines and pyrrolizidines.[16] Recently our group reported the synthesis of bioactive spiro-indenoquinoxaline pyrrolizines through multicomponent reaction of quinoline derived dipolarophile, ninhydrin, *o*-phenylenediamine derivatives and l-proline in methanol.[17] Initially, quinoline based dipolarophile **1(a–f)** were synthesized by the Claizen Schmidt condensation reaction between 2-chloro-3-formyl quinoline derivatives and acetophenone under alcoholic KOH condition. An equimolar mixture of dipolarophile **1(a–f)**, isatin **2**, and benzyl amine **3** in methanol condition were allow to reflux for 6–8 h (Scheme 1). After completion of reaction monitored by TLC, which afforded a single product, was separated by evaporation of solvent in good yields were mentioned in Table 1.



Scheme 1. Synthetic pathway of spiro[indolin-3,2′-pyrrolidin]-2-one's.

All the compounds **4a–f** were characterised by FTIR, ^{1}H-NMR, ^{13}C-NMR, **4a** included single crystal XRD, COSY, NOSEY, HSQCE, mass spectral analysis, whereas spectrum (All characterisation data are presented in supporting information). As a typical analysis, **4a** showed FTIR stretching frequency at 3327, 3061 cm^{-1} for the N-H group, two C=O stretching at 1715 and 1617 cm^{-1} (acetophenone and isatin) whilst the C-H occurred at 2925 cm^{-1}. The ^{1}H NMR spectrum showed four singlets at δ 8.48, 7.80, 2.71, and 3.91 corresponding to the quinoline C4-H, C5-H isatin ring N–H, and quinoline OCH_3 group, respectively. The benzyl amine N-H speak at δ 6.49 ($J = 7.6$ Hz) and seventeen aromatic protons were found at the region of δ 6.98 to 7–84. The specific regioisomer were decided on the basis of triplet at δ 4.98 ($J = 6.8$ Hz) for the C2′-H proton and the C3′-H proton appeared as a doublet instead of a triplet at δ 5.03 ($J = 10$ Hz) and the C4′-H proton appeared as a

Table 1. Reaction conditions for the synthesis of spiro[indolin-3,2′-pyrrolidin]-2-one's **4(a–f)**.



[a]Isolated yield, Reaction condition: quinoline chalcones **1**(1 mmol), isatin **2** (1 mmol), benzyl amine **3** (1 mmol), and methanol (10 ml).

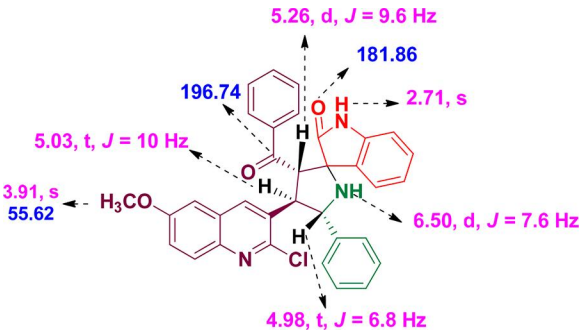


Figure 2. ^{1}H- and ^{13}C-NMR chemical shift values of compound **4a**.

doublet at δ 5.26 ($J = 9.6$ Hz). The ^{13}C-NMR spectrum showed the presence of four spiro carbon C2′, C3′, C4′, and C5′ peaks at δ 68.66, 62.45, 51.52, and 69.04, respectively (Fig. 2). The methoxy C9 –OCH_3 carbon peaks were at δ 55.62 and quinoline C5 carbon speak at δ 104.81 and isatin ring carbon C7″ at speak at δ 109.46 which were confirmed on the ^{13}C, ^{1}H-COSY correlation spectrum. The two carbonyl peaks were at δ 196.74 and 181.06, respectively.

The COSY spectrum of the compound revealed one doublet at δ 5.26 ($J = 9.6$ Hz), two singlet at δ 8.48 and 7.80. Two diastereotopic methane proton triplet at δ 5.03 ($J = 10$ Hz), δ 4.98 ($J = 6.8$ Hz). NOESY spectrum of the compound confirmed doublet at δ 6.49 ($J = 6$ Hz). In the ^{1}H–^{13}C, COSY spectrum, the signal at δ 51.52, 55.62, 62.45, 68.66, 123.33, 123.18, 126.23, 127.12, 127.64, 128.22, 128.46, 129.08, 129.42, 132.97, and 136.79 was assigned to C-4′, C-9, C-3′, C-5′, C-4″, C-6″, C-7, C-5‴, C-6‴, C-6′‴, C-5′‴, C-6‴, C-4‴, C-5″, and C-4 carbons. Selected ^{1}H-, ^{13}C-NMR chemical shifts of **4a** are given in based on the above spectral details and its single crystal analysis (Fig. 3), the structure

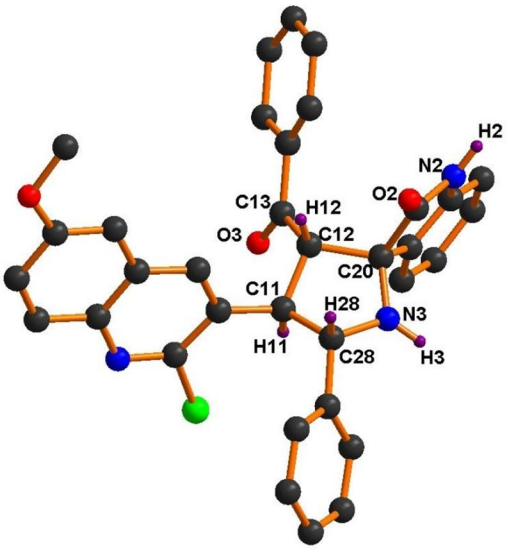
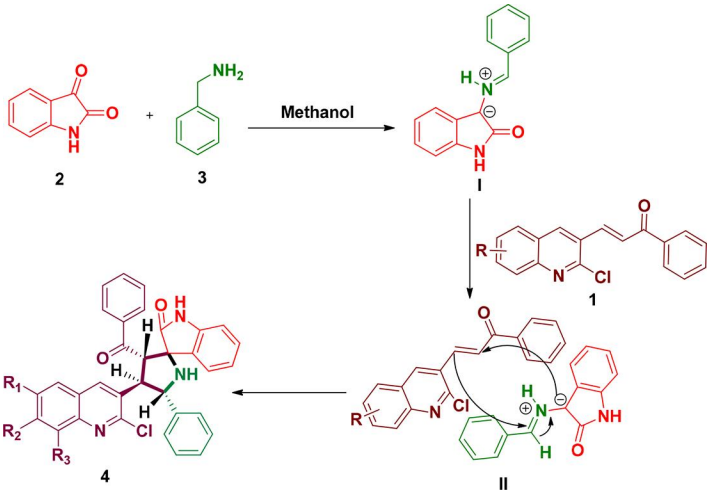


Figure 3. Molecular structure of **4a**; Hydrogen atoms are omitted for clarity (CCDC 1815649).



Scheme 2. Proposed mechanism for the formation of products **4(a–f)**.

was confirmed as of 3′-benzoyl-4′-(2-chloro-6-methoxyquinolin-3-yl)-5′-phenylspiro [indoline-3,2′-pyrrolidin]-2-one (**4a**).

A proposed mechanism for the formation of spiropyrrolidinyloxindole heterocycles is represented in Scheme 2. The azomethine ylide **I** generated *in situ* from the reaction of isatin **2** and benzyl amine **3**, has one potential nucleophilic carbon, which undergoes 1,3-dipolar cycloaddition with dipolarophile **1** to afford novel cycloadduct **4** as a single regioisomer. The proposed mechanism is confirmed in accordance with previous reported procedures.[18]

Conclusion

In conclusion, we have performed an efficient synthesis of novel spiro heterocycles using 1,3-dipolar cycloaddition methodology in which the 1,3-dipole generated by 1,5-prototropic shift is reacted with quinoline chalcones as dipolarophiles under refluxing in methanol. This method provides an easy access to the spiropyrrolidinyloxindole scaffold with high regio- and stereoselectivity. The synthesized compounds were well characterized through different spectroscopic techniques including single crystal XRD, FTIR, NMR, and mass spectral analysis.

Experimental

All chemicals and reagents were purchased from Sigma-Aldrich and were used as such. Commercial grade solvents were distilled according to literature procedure. IR Spectra were recorded on JASCO FT IR 4100 spectrometer using KBr disc and the absorption frequencies quoted in reciprocal centimeters. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker advance (400 MHz for ^{1}H and 100 MHz for ^{13}C) in $CDCl_3$ and DMSO-d_6 solvents. The reaction courses were monitored by TLC on silica gel precoated F254 Merck plates. Chemical shifts are reported in δ values (ppm) downfield from tetramethylsilane and coupling constants are reported in Hertz (Hz). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Elemental analyses were

performed on a Perkin Elmer 2400 series II Elemental CHNS analyzer. LC–MS analyses were performed on waters Q-TOF micro mass spectrometer. Melting point was recorded in a Guna melting point apparatus and was uncorrected.

Synthesis

An equimolar mixture of quinoline chalcones **1(a–f)** (1 mmol), isatin **2** (1 mmol), and benzyl amine **3** (1 mmol) were refluxed in methanol (10 ml). The progress of the reaction was monitored using TLC. After completion of the reaction, the solvent was evaporated to afford a single product **4(a–f)** in good yields. The pure product was obtained through recrystallization using acetonitrile as solvent.

3′-Benzoyl-4′-(2-chloro-6-methoxyquinolin-3-yl)-5′-phenylspiro[indoline-3,2′-pyrrolidin]-2-one (4a)

Brown solid; mp 128–131 °C; IR (KBr) υ (cm^{-1}): 3327, 2925, 1715, 1617; ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ: 8.48 (s, 1H), 7.84 (d, $J = 7.6$ Hz, 1H), 7.80 (s, 1H), 7.47–6.98 (m, 15H), 6.50 (d, $J = 7.6$ Hz, 1H), 5.27 (d, $J = 9.6$ Hz, 1H, Pyrrolidin-H), 5.03 (t, $J = 10$ Hz, 1H, Pyrrolidin-H), 4.98 (t, $J = 6.8$ Hz, 1H, Pyrrolidin-H), 3.91 (s, 3H), 2.71 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm) δ: 196.745, 181.868, 158.158, 149.019, 142.702, 139.873, 139.159, 136.899, 136.793, 132.975, 131.626, 129.537, 129.426, 129.084, 128.564, 128.463, 128.221, 128.180, 127.690, 127.123, 126.239, 123.334, 123.189, 109.462, 104.815, 69.045, 68.666, 62.456, 55.627, 51.524; Anal. Calcd. for $C_{34}H_{26}ClN_3O_3$: C, 72.92; H, 4.68; N, 7.50; Found: C, 72.94; H, 4.67; N, 7.53.

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