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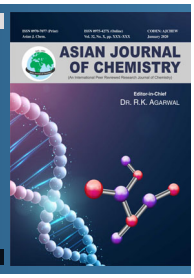

Synthesis and Biological Activities of Some Novel Spiro Heterocyclic Pyrrolizidine Derivatives of 11*H*-indeno[1,2-*b*]quinoxaline through 1,3-Dipolar Cycloaddition

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The synthesis of spiropyrrolidines by the Knoevenagel condensation has been reported as highly bioactive natural and synthetic organic products. The synthesis was initiated by Knoevenagel condensation of indole-2-one with an appropriate benzaldehyde in presence of L-proline to afford spiropyrrolidines. Herein, a design and pathway of syntheses of a library of spiropyrrolidines bearing spiro heterocyclic indeno[1,2-*b*]quinoxaline-11-one motifs were reported, which also demonstrated an exceptional inhibitory activity against the anticancer cells. A novel series of dispiroindenoquinoxaline pyrrolizidines were synthesized by the condensation of indeno[1,2-*b*]quinoxalin-11-one and starting material (a product of ninhydrin and aldehyde derivatives). The structure of the synthesized compounds was established by spectral data.

Keywords: Spiropyrrolidines, Knoevenagel condensation, L-proline, Ninhydrin, Benzaldehyde, 1,3-Dipolar cycloaddition.

INTRODUCTION

In recent years, interest has been increased to the study of the indeno[1,2-*b*] quinoxalin-11-one derivatives. In the present work, we have reported a multicomponent reaction for the synthesis of spiro 1,3-indenoquinoxaline by the condensation of ninhydrin, phenylenediamine, l-proline and substituted aldehydes under reflux conditions. A 1,3-dipolar cycloaddition reaction was found in the one-pot cascade process [1]. Ionova *et al*. [2] reported the synthesis of spiropyrrolidines using 11H-indeno[1,2-*b*]quinoxalin-2-one by aldolcrotonic condensation. In recent time, Sosnovskikh *et al*. [3] reported the regio- and stereoselective 1,3-dipolar cycloaddition of indenoquinoxalinoneazomethineylides to β-nitrostyrenes, which involves multicomponent reactions. Simiarly, Shi *et al*. [4] reported an efficient regioselective synthesis of novel functionalized dispiropyrrolidines *via* a three-component [3+2] cycloaddition reaction. This molecule dispiroindenoquinoxaline pyrrolizines get attention of the researchers because of their multicomponent intermolecular 1,3-dipolar cycloaddition reactions [5]. Some new dispiroindenoquinoxaline pyrrolizines has also showed the AChE inhibitory activity [6]. A serious consideration has been concerned in recent years to the study of 1,3-dipolar cycloaddition reactions involving stabilized azomethineylides, which can be easily obtained from β-amino acids and some carbonyl compounds such as isatin, ninhydrin and indeno[1,2-*b*]quinoxalin-11-one [7] (a product of reaction between ninhydrin and *o*-phenylenediamine). This is associated to the fact that 1,3-dipolar cycloaddition reactions provide the simplest route to the synthesis of complex alkaloid-like compounds with spiro-fused pyrrolidine or pyrrolizidine moiety, which have been shown to exhibit a broad spectrum of biological activities [8-10].

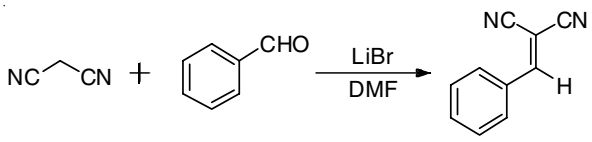
Spiro-pyrrolidines and spiro pyrrolizidines derivatives are subjected to highly bioactive characteristics due to their spiro structures. Several works have described that spiropyrrolidines compounds are highly potent receptors and exhibited interesting fluorescent characteristics [11]. A substantial amount of literature is available about the 1,3-dipolar cycloaddition reactions involving azomethineylides obtained from isatin, ninhydrin and indeno[1,2-*b*] quinoxalin-11-one, but the results of every new reaction and product are not obvious as it depends on several many factors. Nitrogen containing spiro-heterocyclic

compounds [12] have been recognized as an important class of potentially bioactive compounds often constructed and produced *via* 1,3-dipolar cycloaddition of azomethineylides. In the present work, an insistence was given on developing a constructive approach for assembling different moieties on a multicomponent reaction platform for the synthesis of spiroquinoxaline pyrrolizine derivatives. Multi-component reactions (MCRs) are regarded as the tool box for the formation and breakage of several carbon-carbon and carbon-heteroatom bonds in one pot [13]. Assisted by the choice of readily available starting materials, ease of one-pot procedure and associated atom economy, MCRs have been broadly employed in the synthesis of a diversified array of valuable heterocyclic ensembles [14]. It was expected that introduced indenoquinoxaline to a chiral pyrrolidine or pyrrolizidine ring in the molecule, through a spiro-atom at the C-3 position could lead to the formation of chiral spiro-indenoquinoxalinepyrrolidine or spiro-indenoquinoxaline pyrrolizidine systems, thus availing more opportunities to the formation of a wide range of biologically active compounds [15]. Hence, because of the predetermined reasons and in continuous monitoring towards the synthesis of various spiro heterocyclic compounds, herein reported, a mild, early, and facile multi-component, one-pot synthesis of novel heterocyclic chiral spiro-indenoquinoxaline pyrrolidine and spiro-indenoquinoxaline pyrrolizidine systems through a catalyst free, one-pot, four-components 1,3-dipolar cycloaddition reaction of L-proline with ninhydrin, phenylenediamines and starting materials synthesized by malononitrile and substituted aldehyde [16].

EXPERIMENTAL

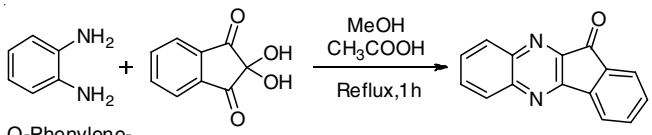
NMR spectra were recorded on a Bruker AVANCE III HD 500 MHz spectrometer using TMS as an internal standard. $CDCl_3$ was used as the solvent for dissolving the samples for NMR. Chemical shifts are given in ppm. The chemicals were obtained from Sigma-Aldrich and Spectrochem Pvt. Ltd. India and used without further purification. Commercial grade solvents were used through the experimental work. Analytical thin layer chromatography was performed on silica gel coated on aluminum sheets and monitored using UV light of wavelength 254 nm. Column chromatography was performed on 60-120 mesh silica gel. Compounds were eluted by a mixture of hexane and ethyl acetate as required.

Starting material was synthesized by the simple reaction of malononitrile and substituted aldehyde with lithium bromide (catalytic amount) and DMF as a solvent. Reaction was stirred for 1 h at room temperature for 10 min. After the completion of reaction, a mixture filtered by Whatman filter paper and dried under vacuum (**Scheme-I**).



Scheme-I

Synthesis of indeno[1,2-*b*]quinoxalin-11-one: A mixture of *o*-phenylenediamine (1.782 g, 15 mmol), ninhydrin (2.672 g, 15 mmol) in 10 mL of acetic acid and 30 mL of methanol as solvent stirred and refluxed for 1 h. The reaction was monitored by TLC. The precipitate formed was filtered and washed by methanol (three times) and dried under vacuum to yield the pure compound as solid yellow coloured (**Scheme-II**).



O-Phenylene-1,2-diamine — Ninhydrin — 11*H*-Indeno[1,2-*b*]-quinoxalin-11-one

Scheme-II

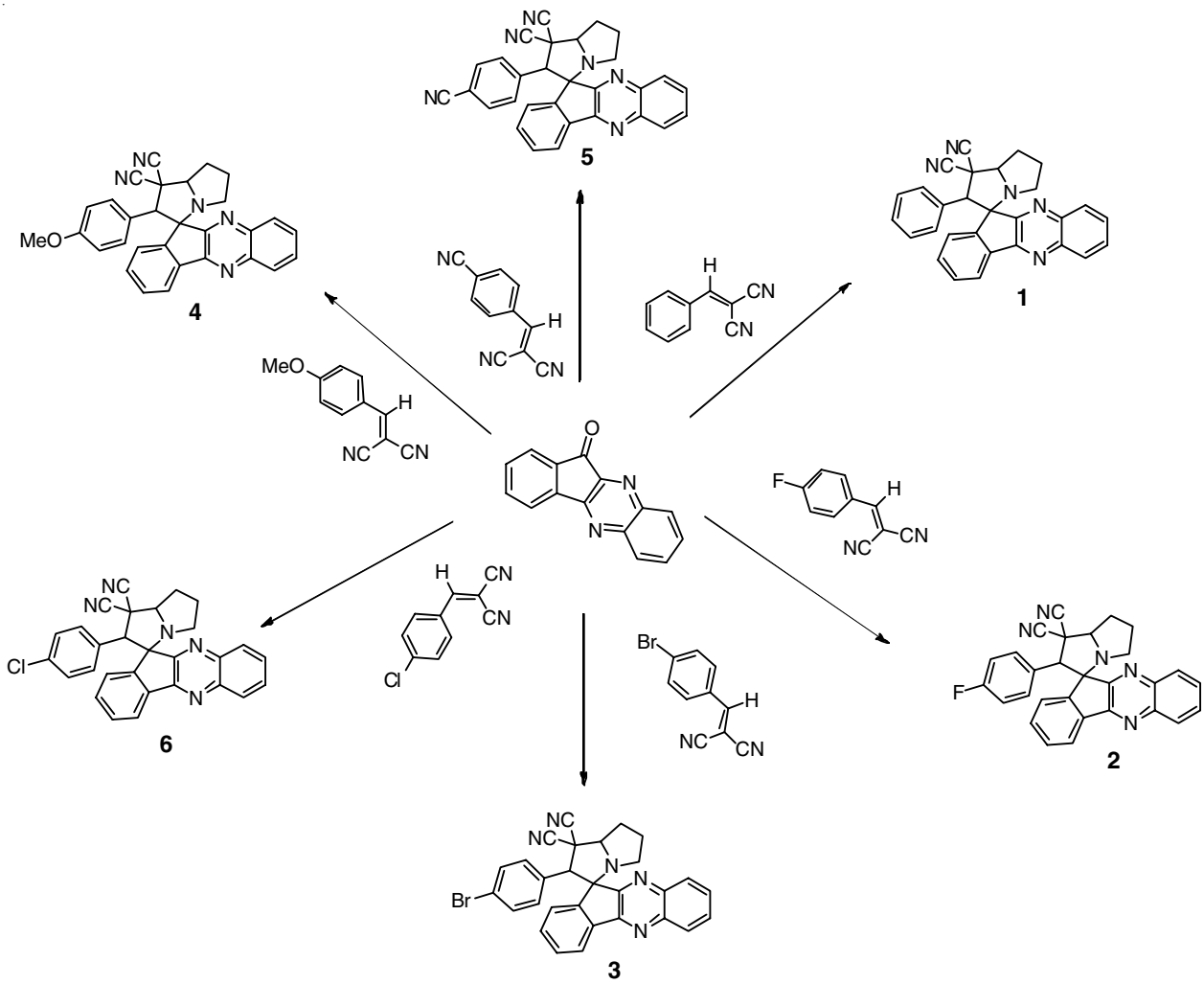
Synthesis of spiro pyrrolizidines: A series of spiro pyrrolizidines were synthesized by condensation of indenoquinoxaline and synthesized starting material (a product of ninhydrin and aldehyde derivatives) with L-proline and acetonitrile used as a solvent. A 10 mL of acetonitrile (as a solvent), indeno[1,2-*b*]quinoxalin-11-one (232 mg), 2-benzylidenemalononitrile (154 mg) and L-proline (127 mg) were added in a round bottom flask. Reaction was refluxed for 3-4 h until the reaction mixture becomes homogeneous. Reaction was optimized by TLC after 0.5, 1 and 2 h continuously. After completion the reaction, the reaction mixture was washed with dichloromethane three times. The compound was purified by column chromatography by frictional collection and solvent evaporated by rota evaporator in order to remove the by products if formed (**Scheme-III**).

2'-Phenyl-7',7a'-dihydrospiro[indeno[1,2-*b*]quinozaline-11,3'-pyrrolizine]-1',1'(2'H)-dicarbonitrile (spiro indenoquinoxaline) (1) synthesized by following method (Scheme-III): Colour: Light yellow solid, yield: 86%, ^{1}H NMR 500 MHz ($CDCl_3$) δ_H ppm: 8.22 (d, 1H), 7.84 (d, 1H), 7.66 (s, 1H), 7.44 (t, 1H), 7.24 (m, 1H), 5.45 (d, 1H), 5.29 (s, 1H), 4.65 (d, 1H), 2.68 (m, 1H), 2.30-1.96 (m, 2H), 1.68 (s, 1H), 1.26 (m, 1H), 0.87 (d, 1H). MS. *m/z* 438 (m+1).

2'-(4-Fluorophenyl)-7',7a'-dihydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1',1'(2'H)-dicarbonitrile (2): Colour: Dark yellow solid, yield: 84%, ^{1}H NMR, 500 MHz, ($CDCl_3$) δ_H ppm: 8.22-8.19 (m, 1H), 7.85 (t, 1H), 7.80 (t, 1H), 7.71-7.67 (m, 1H), 7.45-7.41 (m, 1H), 7.36 (d, 1H), 7.26 (s, 1H), 7.14 (t, 1H), 5.45 (d, 1H), 5.30 (s, 1H), 4.60 (d, 1H), 2.70-2.67 (m, 1H), 2.31-2.28 (m, 1H), 2.16 (m, 1H), 2.05 (s, 1H), 2.00 (d, 1H), 1.58 (s, 1H), 1.26 (s, 1H). MS. *m/z* 457.

2'-(4-Bromophenyl)-7',7a'-dihydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1',1'(2'H)-dicarbonitrile (3): Light yellow solid, yield: 83%, ^{1}H NMR, 500 MHz, ($CDCl_3$) δ_H ppm: 8.20 (d, 1H), 7.95 (t, 1H), 7.85 (t, 1H), 7.80 (d, 1H), 7.71-7.67 (m, 1H), 7.6 (d, 1H), 7.52 (d, 1H), 7.26 (s, 1H), 5.41 (s, 1H), 4.59 (dd, 1H), 2.69-2.66 (m, 1H), 2.29 (d, 1H), 2.21-2.0 (m, 3H), 1.63-0.88 (m, 3H). MS. *m/z* 518.

2'-(4-Methoxyphenyl)-7',7a'-dihydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1',1'(2'H)-dicarbonitrile (4): ^{1}H NMR 500 MHz ($CDCl_3$), δ_H ppm: 8.21 (s, 1H), 7.92 (d, 2H), 7.84-7.78 (m, 1H), 7.70-7.66 (m, 2H), 7.57 (d, 1H), 7.26 (s, 1H), 7.02-6.99 (m, 3H), 5.39 (d, 1H), 4.60 (dd, 1H), 3.91 (d, 1H), 3.84 (s, 1H), 2.69-2.65 (m, 1H), 2.29 (dd, 1H), 2.20-2.10 (m, 1H), 2.02-1.94 (m, 1H), 1.58 (d, 1H), 1.25 (s, 1H). MS. *m/z* 470 (m+1).



Scheme-III: Synthetic route of novel spiro heterocyclic pyrrolizidine derivatives of 11*H*-indeno[1,2-*b*]quinoxaline

2'-(4-Cyanophenyl)-7',7a'-dihydrospiro[indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizine]-1',1'(2'H)-dicarbonitrile (5): ^{1}H NMR 500 MHz ($CDCl_3$), δ_H ppm: 8.25-8.21 (M, 1H), 7.95 (d, 1H), 7.86-7.76 (m, 2H), 7.72-7.68 (m, 1H), 7.26 (t, 1H), 7.15 (s, 1H), 5.52 (d, 1H), 5.30 (s, 1H), 4.62 (d, 1H), 4.12 (d, 1H), 3.49 (s, 1H), 2.71-2.68 (m, 1H), 2.30 (d, 1H), 2.23-2.15 (m, 1H), 2.02 (s, 1H), 1.61 (d, 1H), 1.40 (s, 1H), 1.27-1.23 (m, 1H). MS. *m/z* 464.

2'-(4-Chlorophenyl)-3a',4'-dihydro-2'H-spiro[indeno-[1,2-*b*]quinoxaline-11,1'-pentalene]-3',3'(6a'H)-dicarbonitrile (6): Colour: yellow, ^{1}H NMR 500 MHz ($CDCl_3$), δ_H ppm: 8.20 (s, 1H), 7.85 (t, 1H), 7.80-7.77 (m, 1H), 7.72-7.67 (m, 1H), 7.58 (d, 1H), 7.52 (d, 1H), 7.39 (s, 1H), 7.26 (s, 1H), 7.21-7.16 (m, 1H), 5.42 (d, 1H), 5.30 (s, 1H), 5.29 (d, 1H), 2.70-2.66 (m, 1H), 2.30 (d, 1H), 2.20-2.18 (m, 1H) 2.14-2.10 (m, 1H), 2.04-1.95 (m, 1H), 1.58 (s, 1H), 1.25 (s, 1H). MS. *m/z* 473.

RESULTS AND DISCUSSION

Inspite of the enormous importance of heterocyclic indenoquinoxaline derivatives due to their biological activities, only a few reports are available on the assembly of spiropyrrolidines derivatives that incorporate both bioactive moieties in a single structural framework. Consequently, the synthesis of structurally complex and diverse analogous the aldehyde derivatives and indenoquinoxalines structure both are challenging and interesting. Considering the potential biological activities of spiropyrrolidines derivatives and stimulating by the growing interest in multicomponent reactions, we have synthesized the spiropyrrolidines compounds with the reaction of indenoquinoxalines and aldehyde derivatives of malononitrile and L-proline. When they were reacted acetonitrile and indenoquinoxaline resulted in the 1,3-dipolar cycloaddition reaction to afford spiro pyrrolizidines.

A series of spiroindenoxalinepyrrolidines derivatives were synthesized through 1,3-dipolar cycloaddition reaction. In this work, spiropyrrolidines were synthesized using Knoevenagel condensation reaction [17]. Starting material was synthesized by malononitrile and substituted aldehyde in acetic acid and dimethyl formamide (DMF) as a solvent. It was challenging to synthesize starting material with excellent yield and purity.

Biological activities: Moreover, spiro-pyrrolidines and spiro-pyrrolizidines showed a partial resistance to chemotherapeutic agents with respect to the breast cancer cells MCF-7 and lung cancer cell A-549 [18,19]. In this work, a series of spiro-pyrrolizidines had been tested for cytotoxicity in the two human cancer cell lines MCF-7 and non-small cell lung A-549.

Anti-proliferative activity of the synthesized compound was evaluated in two different human cancer cells, breast cancer (MCF-7) and lung cancer (A-549) using MTT assay. Percentage cell viability was determined using the relationship between percentage cell viability and drug concentration plot of survival curve of the tested cell line. Amongst all the tested compounds **IV** and **VI** showed a very high activity against breast cancer MCF-7 and A-549 lung cancer cell line (Table-1). These spiro-pyrrolidine compounds can be promising therapeutic agents for A-549 lung adenocarcinoma cancer cell line.

TABLE-1
ANTICANCER ACTIVITY OF NOVEL SPIRO HETEROCYCLIC PYRROLIZIDINE DERIVATIVES (**1-6**)

Compound	Tested cell line (mm)	
	Breast cancer (MCF-7)	Lung cancer (A-549)
1	13 ± 1.6	16 ± 1.2
2	13 ± 1.8	15 ± 1.7
3	14 ± 1.2	15 ± 1.5
4	14 ± 1.7	15 ± 1.8
5	14 ± 1.8	15 ± 1.2
6	13 ± 1.2	16 ± 1.3

Conclusion

In conclusion, a highly stereoselective and regioselective synthesis and characterization of novel spiroindinoquinoxaline pyrrolidines and spiroindenoquinoxaline pyrrolizidines derivatives containing indenoquinoxaline moiety is reported. The simplification of this method is established by the regio-selective synthesis of 11*H*-indeno[1,2-*b*]quinoxalin-11-one, and substituted aldehydes. Indeno[1,2-*b*]quinoxalin-11-one have been employed as dipolarophiles for the first time in azo-methineylide in 1,3-dipolar cycloaddition reactions. Thus, the present methodoloy paves the way for the synthesis of a variety of spiroheterocycles in high yields using easily available starting materials.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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