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Synthesis, characterisation and biological activity of novel spiroheterocycles from semicarbazones

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ABSTRACT

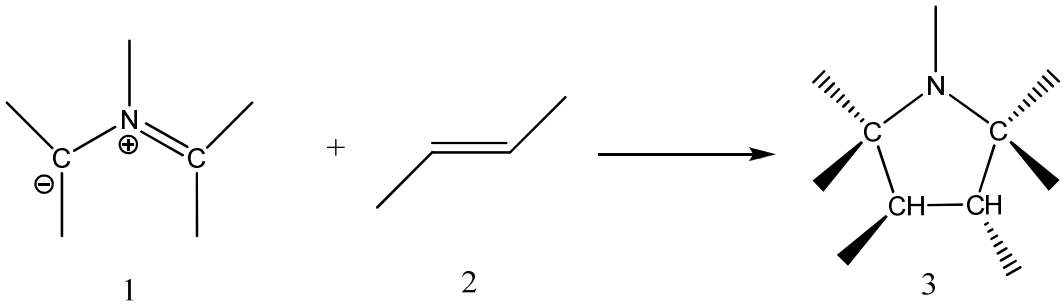
A facile synthesis and characterization of novel spiropyrrolidines is reported. Reaction of isatin and L-proline with semicarbazone gave the corresponding spiropyrrolidines. Intermolecular 1, 3-dipolarcycloaddition reaction of azomethine ylides, generated through decarboxylation route, with various semicarbazone as dipolarphiles has been investigated. A new class of functionalized spiroheterocycles with pyrrolidine moiety has been synthesized. The formation of spiro heterocycles was confirmed from the UV-VIS, FT-IR, ^{1}H-NMR and ^{13}C-NMR studies. Antimicrobial studies were carried out for synthesized compounds. Among the three spiroheterocycles, compound 18 showed maximum zone inhibition against Shigella flexneri and Staphylococcus epidermis, whereas compound 13 showed moderate activity,

Keywords: 1,3 – Dipolar cycloaddition, Azomethine ylides, Semicarbazone, Spiropyrrolidines, Antimicrobial activity.

INTRODUCTION

The 1,3-dipolar cycloaddition, also known as the Huisgen cycloaddition or Huisgen reaction, is an organic chemical reaction belonging to the larger class of concerted, pericyclic cycloadditions. It is the reaction between a 1, 3-dipole and a dipolarophile, most of which are substituted alkenes, to form a five-membered ring. Rolf Huisgen first saw the prospects of varying the 1, 3-dipole and its high value for synthesis of 5-membered heterocycles [1]. The addition of a 1, 3-dipole to an alkene for the synthesis of five-membered rings is a classic reaction in organic chemistry. The 1, 3-dipolar cycloaddition reactions are used for the preparation of molecules of fundamental importance for both academia and industry. The history of 1, 3-dipoles goes back to Curtius, who in 1883 discovered diazoacetic ester [2].

The 1,3-dipolar cycloaddition reaction of azomethine ylides**(1)** with alkenes**(2)** leads to the formation of the pyrrolidines**(3)**. 1, 3-Dipolar cycloaddition reaction of azomethine ylides forms highly substituted heterocyclic compounds.



SCHEME 1

Azomethine ylides are unstable species which have to be prepared in situ. A number of methods have been developed for the generation of azomethine ylides, such as proton abstraction from imine derivatives of R-amino acids, thermolysis or photolysis of aziridines, and dehydrohalogenation of imonium salts. The reaction of azomethine ylides with alkenes has been investigated from a theoretical point of view inorder to understand the reaction course, selectivity, and influence of Lewis acids on the reaction. The product can be used as new catalyst or serve as important biologically active molecules [3].

Spiro-cyclic compounds have attracted the attention of organic chemists due to their unique structural and reactivity pattern [4]. 1, 3-dipolar cycloaddtion offers a convenient route for the construction of five membered heterocyclic compounds. The 1, 3-dipolar cycloaddition reaction has been applied to the synthesis of natural products such as sugar derivatives, β-lactams, aminoacids and alkaloids. Isooxazoline derivatives have been extended to many natural product synthesis and also proved to be an efficient precursor for many synthetic intermediates including γ-amino alcohols, β-hydroxy ketones etc. The high synthetic versatility and the pharmacological importance have prompted to synthesize some biologically interesting spiroisocazoline derivatives. Manikandan and his coworkers done their work in the construction of novel spiroheterocyclic derivatives, and also to study their biological applications, the reactions of the versatile 1, 3-dipole nitrile oxide with 9-arylidene anthrone have been studied [5].

S.Kathiravan and his coworkers reported (E)5H-2-(arylidine)-5-phenyl-6,7-di-hydrothiazolo[2,3-b]benzo[h]quinazolines through a regioselective 1,3-dipolar cycloaddition reaction with azomethine ylide derived from ninhydrin and sarcosine to give a new class of complex dispiropyrrolidines in good yield. The structures of the synthesized cycloadducts have been elucidated by spectral methods [6].

T. Augustine and his coworkers reported the cycloaddition reaction of azomethine ylides, generated through decarboxylation, with (E)-3-arylidene-4-chromanones and Chalcones as dipolarophiles. A high degree of regioselectivity has been observed in the synthesis of a new class of functionalized dispiroheterocyclic compounds bearing chromanone, chalcones and acenaphthenequinone framework [7][8]. Spiro-oxindole ring system represents an important class of naturally occurring substances characterised by highly pronounced biological properties[9-11].Oxindole derivatives are found to be potent aldose reductase inhibitors(ARI) , which help to treat and prevent diabetic complications arising from elevated levels of sorbitol[12].

The literature survey shows that some work has been carried out in spiropyrrolidines and their application in different field. As a part of our ongoing research program in the area of cycloaddition reaction of azomethine ylides with semicarbazones, we herein report the highly regioselective synthesis of spiro pyrrolidines through 1,3–dipolar cycloaddition methodology. The prepared compounds were characterized by spectroscopic techniques and its biological applications like antibacterial studies were carried out.

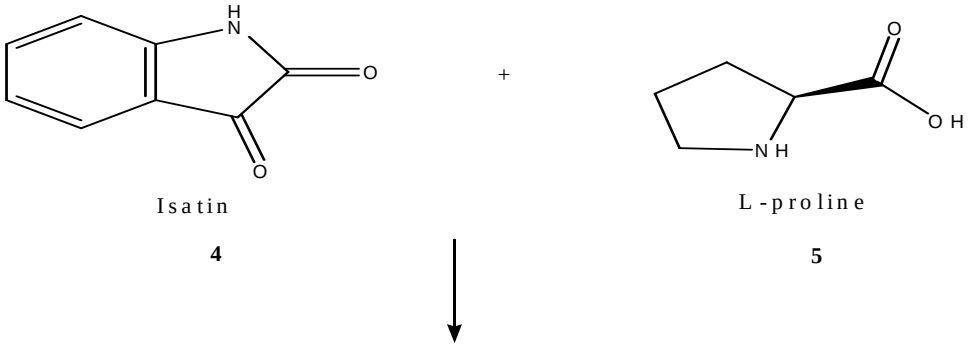
MATERIALS AND METHODS

All chemicals used were of analytical grade, supplied from Sigma-Aldrich and used as received.The first step in this synthesis involves nucleophilic addition reaction between acetophenone and semicarbazide hydrochloride using the literature procedure. The second step involves 1,3-Dipolar cycloaddition reaction between formed semicarbazone

and dipolarphiles. The structures of these products were established by physical and spectral methods. Melting points were measured on Gallen-Kamp apparatus**.**

Synthesis of Spiro[5.3']oxidolino(4-methyl-(2,4-dihydroxyphenyl)hexahydro[pyrrolo[2,3]imidazole]-2-yl]diamide

A mixture of isatin(0.147g, 1 mmole), L-proline(0.115g. 1 mmole) and 2-(1-(2,4-dihydroxyphenyl)ethylidene)hydrazinecarboxamide(0.209g, 1 mmole) in methanol(40 ml) was refluxed for 5 hours at a temperature of 60˚C. After the reaction was over, the reaction mixture was extracted with methanol and dried; then it was recrystallised using acetone. The melting point and chemical yield are 179˚C -183˚C and 87.7% **(8)**.



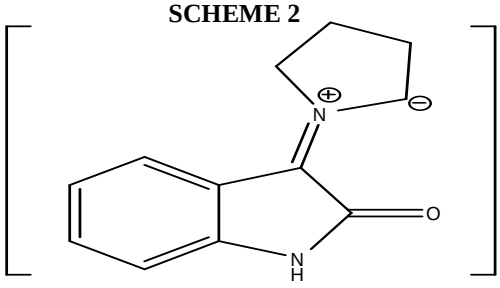
Isatin

4

L-proline

5

SCHEME 2



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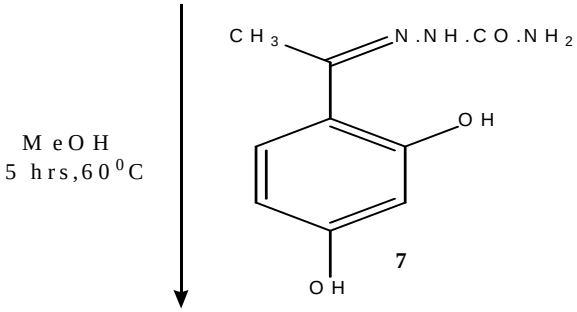

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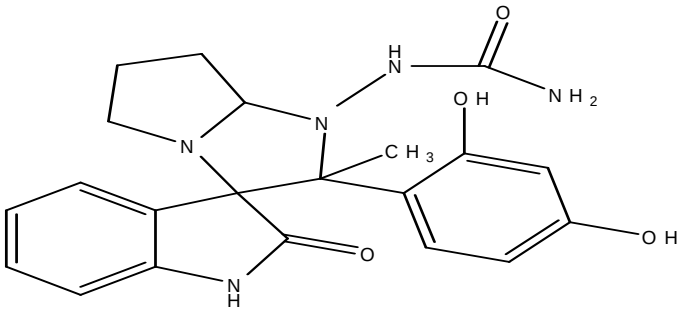
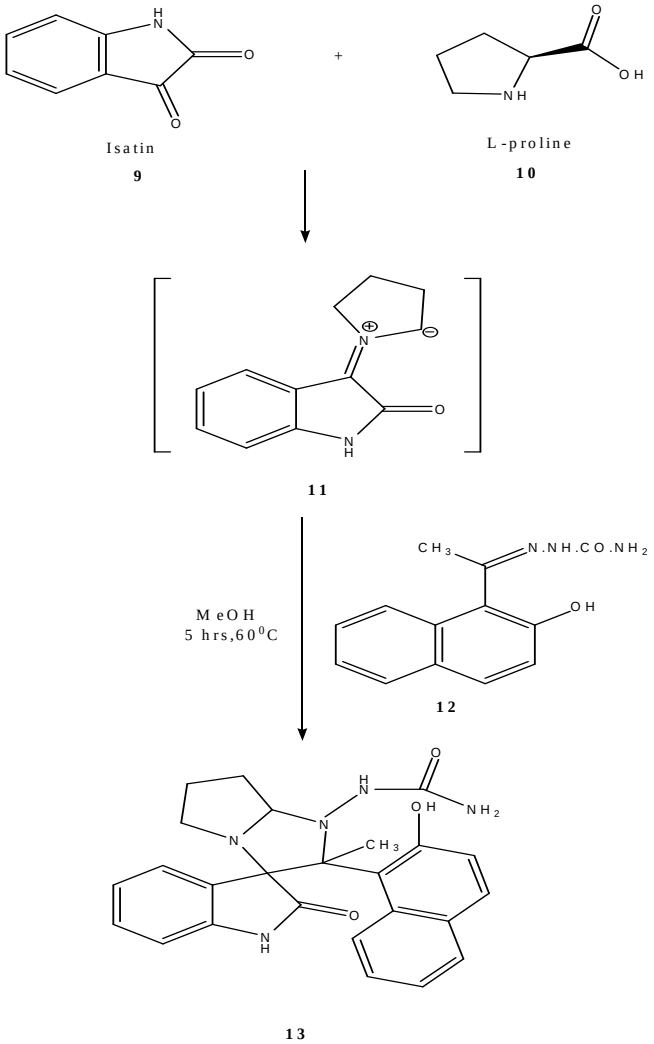


8

Synthesis of spiro[5.3']oxidolino(4-methyl-(2-hydroxynaphthalen-1-yl)hexahydro[pyrrolo[2,3]imidazole]-2-yl]diamide

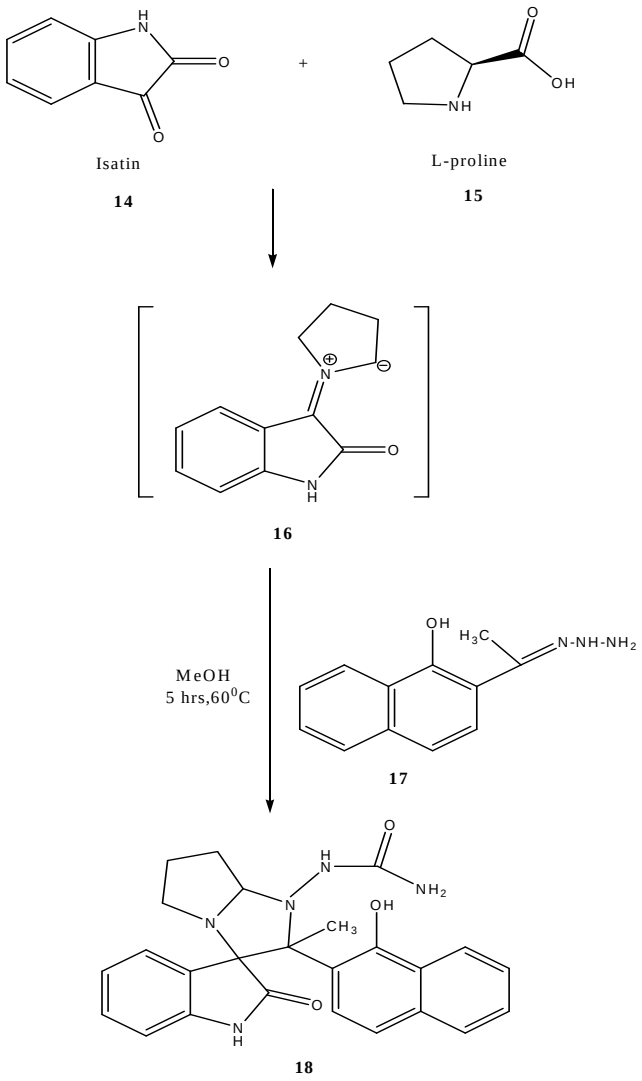
A mixture of isatin (0.147 g, 1 mmole), L-proline (0.115 g. 1 mmole) and 2-(1-(2-hydroxynapthalen-1-yl)ethylidene)hydrazinecarboxamide (0.243g, 1 mmole) in methanol (40 ml) was refluxed for 5 hours at a temperature of 60˚C. After the reaction was over, the reaction mixture was extracted with methanol and dried; then it was recrystallised using acetone. The melting point and chemical yield are 140˚C -145˚C and 79.6% **(13)**.



SCHEME 3

Synthesis of spiro[5.3']oxidolino(4-methyl-(1-hydroxynaphthalen-2-yl)hexahydro[pyrrolo[2,3]imidazole]-2-yl]diamide

A mixture of isatin (0.147 g, 1 mmole), L-proline (0.115 g. 1 mmole) and 2-(1-(1-hydroxynapthalen-2-yl)ethylidene)hydrazinecarboxamide (0.243 g, 1 mmole) in methanol(40 ml) was refluxed for 5 hours at a temperature of 60˚C. After the reaction was over, the reaction mixture was extracted with methanol and dried; then it was recrystallised with acetone. The melting point and chemical yield are 115˚C -117˚C and 45.1% **(18)**.



SCHEME 4

RESULTS AND DISCUSSION

Spiro compound 7**:** IR (KBr): 1609, 1711 cm^{-1}; ^{1}H NMR (DMSO/400 MHz): δ 2.16(s,3H), 1.25-1.59 (m, 2H), 2.59 (t, -NCH), 6.3-7.5 (m,aromatic), 6.3-9.5 (-NH,-NH_2 protons); ^{13}C-NMR (DMSO/400 MHz): δ 77.81,151,191,162,14.4.

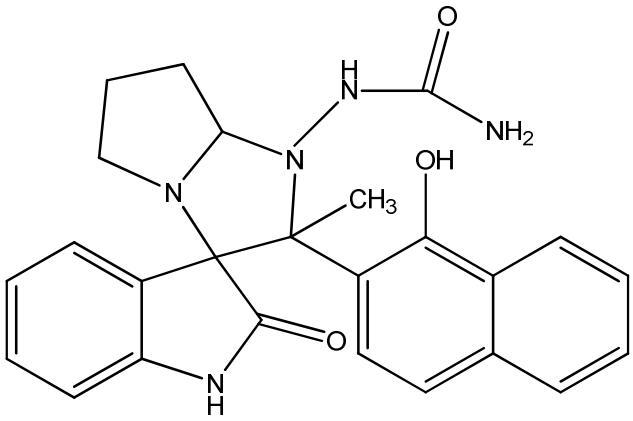
Spiro compound 11: IR (KBr): 1605, 1721 cm^{-1}; ^{1}H NMR (DMSO/400 MHz): δ 2.36 (s,3H), 7.63 (S, -CONH), 3.1 (t, -NCH), 6.9-7.58 (m,aromatic), 6.3-9.5 (-NH,-NH_2 protons); ^{13}C-NMR (DMSO/400 MHz): δ 77.81, 155, 195, 165, 13.14.

Spiro compound 15: IR (KBr): 1620, 1718 cm^{-1}, ^{1}H- NMR (DMSO/400 MHz): δ 2.56 (s,3H), 7.41 (S, -CONH), 2.56 (t, -NCH), 6.74-7.63 (m,aromatic), 6.9-9.08 (-NH,-NH_2 protons); ^{13}C-NMR (DMSO/400 MHz): δ 77.95, 152.46, 186, 186, 161, 18.25.

Antibacterial Activity

The synthesized compounds were tested for antibacterial activity against *Salmonella typhimurium*, MRSA-Methicillin resistance *Staphylococcus aureus, Proteus vulgaris, Staphylococcus epidermis; Klebsiella pneumonia*, SPB-*Salmonella typhi*-B, MIC- *Micrococcus luteus, Shigella flexneri and* their zone inhibition(in cm) as shown in the table. Among the six compounds screened for biological activity, Compound **(18)** showed maximum zone inhibition against *Shigella flexneri* and *Staphylococcus epidermis.* Compound **(7)** , compound**(12)**, and compound **(8)** showed no activity against the test organisms, whereas compound **(17)** and compound **(13)** showed moderate activity . The significant activity of compound **(18)** may be attributed to the presence of aromatic rings and pyrrolidine moiety.

Structure of compound 18



Compounds / Microbes	7	12	17	8	13	18
1251	-	-	-	-	-	10
MRSA	-	-	10	-	10	11
1771	-	-	-	-	-	-
3615	-	-	15	-	-	18
109	-	-	-	-	11	12
SPB	-	-	-	-	-	-
MIC	-	-	10	-	-	11
1457	-	-	12	-	14	21

1251-*Salmonella typhimurium;* MRSA- Methicillin resistance *Staphylococcus aureus;*1771- *Proteus vulgaris;*3615- *Staphylococcus epidermis;* 109- *Klebsiella pneumonia;* SPB-*Salmonella typhi*-B; MIC- *Micrococcus luteus*; 1457- *Shigella flexneri*;

CONCLUSION

We had synthesized six compounds out of which three are novel spiroheterocycles. The synthesized compounds were characterized using UV, IR, ^{1}H-NMR and ^{13}C-NMR and their structures were determined. The six compounds were subjected for testing their biological activity out of which compounds 7,12 and 8 showed no activity against the test organisms, whereas compounds 17 and 13 showed moderate activity .The significant activity of compound 18 may be attributed to the presence of aromatic rings and pyrrolidine moiety.

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