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Regioselective & diastereoselective Synthesis and antibacterial studies of (1'R,2'S)-7''-chloro-6''-(2-chloroethyl)-2'-aryl-5',6',7',7a'-tetrahydro-2'H-dispiro[indene-2,3'-pyrrolizine-1',3''-indoline]-1,2'',3-trione through 1,3-dipolar cycloaddition

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KEYWORDS
(3-Z)-6-chloro-3-(benzylidene-5-(2-chloroethyl-1,3-dihydro-2H-indol-2-one, azomethine ylide, 1,3-dipolar cycloaddition

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ABSTRACT

Regioselective & diastereoselective Synthesis and antibacterial studies of (1'R,2'S)-7''-chloro-6''-(2-chloroethyl)-2'-aryl-5',6',7',7a'-tetrahydro-2'H-dispiro[indene-2,3'-pyrrolizine-1',3''-indoline]-1,2'',3-trione was successfully performed through the 1,3-dipolar cycloaddition of azomethine ylide generated *insitu* by the reaction between L-proline and ninhydrin with the (3-Z)-6-chloro-3-(benzylidene-5-(2-chloroethyl-1,3-dihydro-2H-indol-2-one. These dispiro compounds were prepared in high yield in shorter reaction time. Since there was no waste produced in the reaction, one can consider this as a green method of synthesis. The synthesised compounds were subjected to the anti-bacterial studies.

INTRODUCTION

An efficient and most powerful method for designing and developing an effective new route towards novel and complex structured molecules is the Multi Component Reaction [1-3]. In MCRs, in a single step three or more starting materials react to form a product that has substantial portions of all reactants without any waste production. This is one of the conditions of the green synthesis. This strategy provides a high-throughput generation of combinatorial compound libraries in drug discovery research [4-6] Importantly, MCRs comply with the principles of green chemistry by saving reagents, solvents and time, while including the high atom-economy and selectivity of a reaction. In recent years, ninhydrin has become an unparalleled tricarbonyl compound participating in many MCRs to afford diverse structural scaffolds. It is worth mentioning that vicinal tricarbonyl compounds are rich sources of heterocyclic scaffolds [7-10]

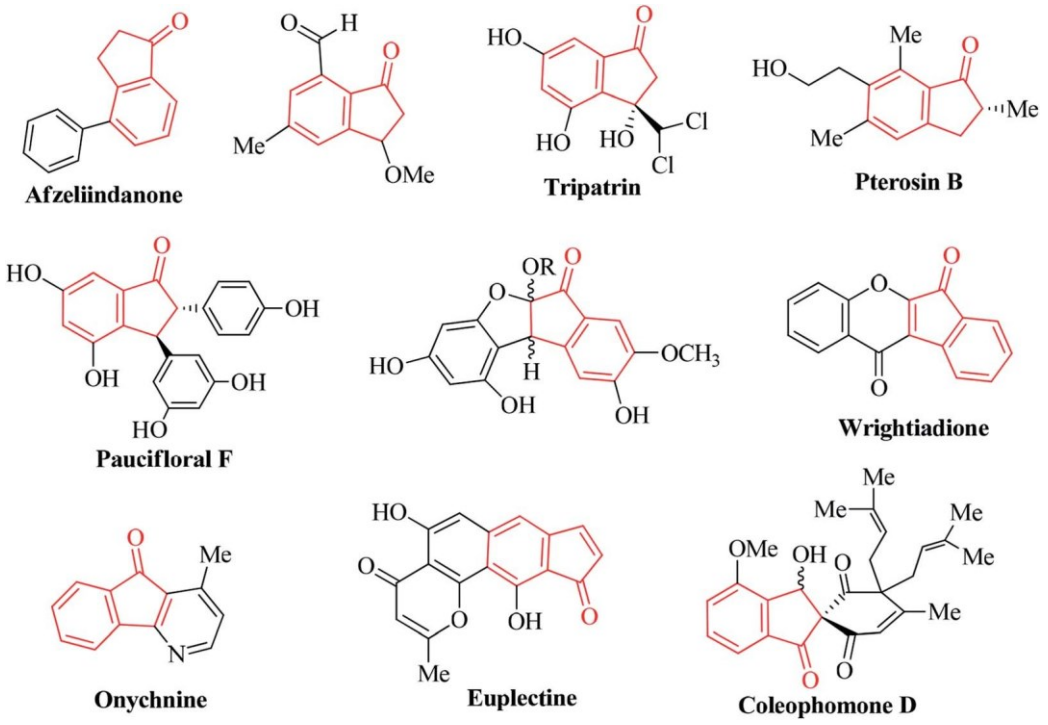


Figure 1: Some examples of natural products containing the indanone motif

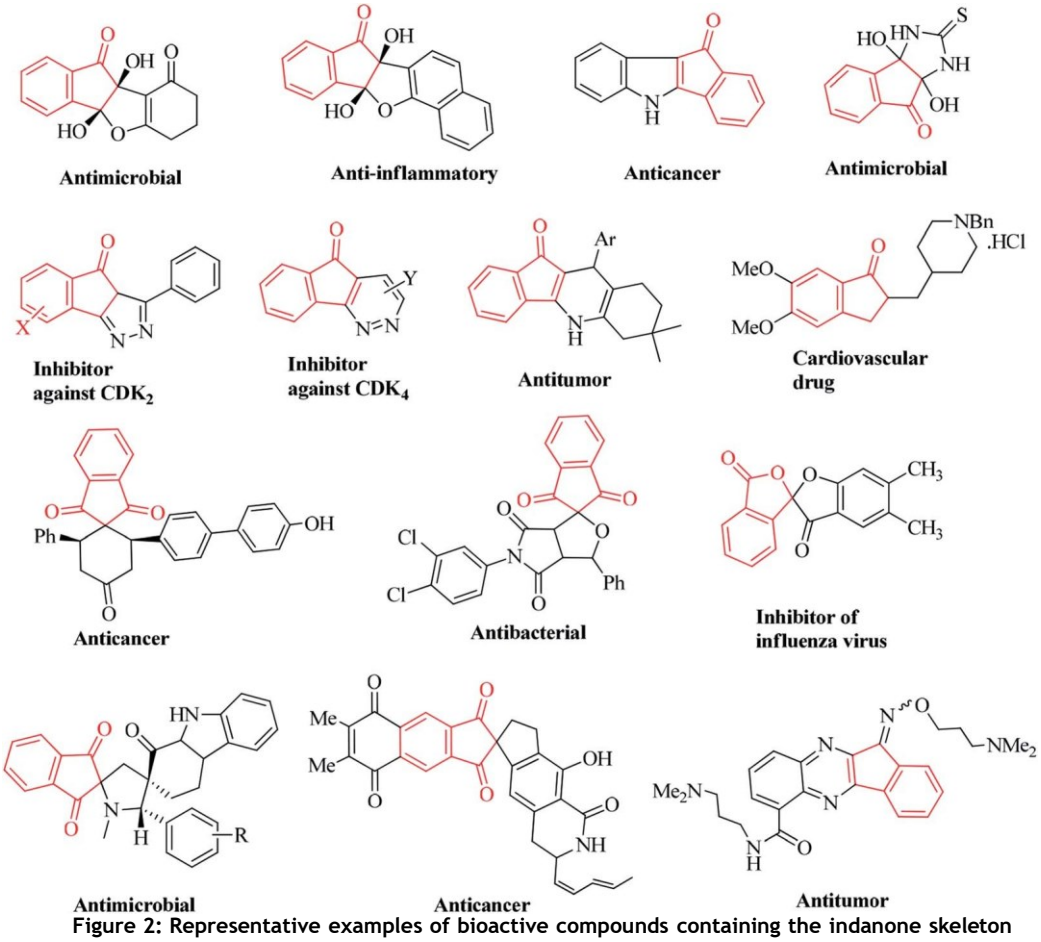
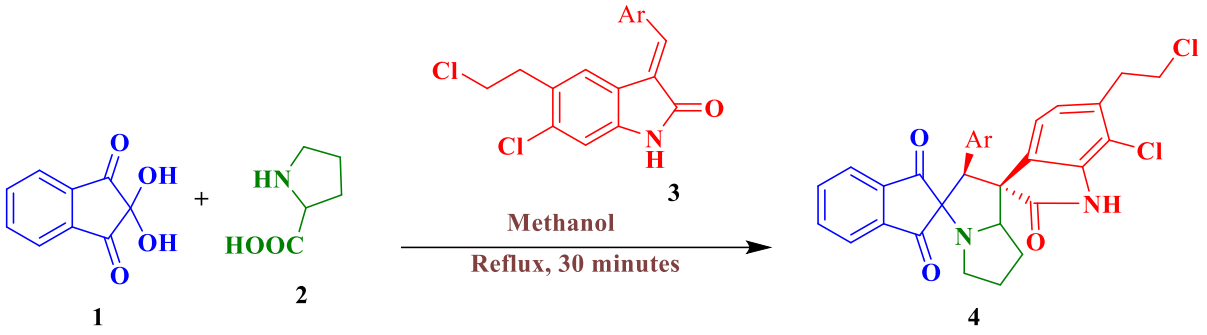


Figure 2: Representative examples of bioactive compounds containing the indanone skeleton

RESULTS & DISCUSSSION:

In the Present work a regioselective & diastereoselective Synthesis and antibacterial studies of (1'R,2'S)-7''-chloro-6''-(2-chloroethyl)-2'-aryl-5',6',7',7a'-tetrahydro-2'H-dispiro[indene-2,3'-pyrrolizine-1',3''-indoline]-1,2'',3-trione was successfully performed through the 1,3-dipolar cycloaddition of azomethine ylide generated *insitu* by the reaction between L-proline and ninhydrin with the (3-Z)-6-chloro-3-(benzylidene-5-(2-chloroethyl-1,3-dihydro-2H-indol-2-one. **(Sheme 1)** These dispiro compounds were prepared in high yield in shorter reaction time. Since there was no waste produced in the reaction, one can consider this as a green method of synthesis. The synthesised compounds were subjected to the anti-bacterial studies.



Scheme 1: Synthesis of (1'R,2'S)-7''-chloro-6''-(2-chloroethyl)-2'-aryl-5',6',7',7a'-tetrahydro-2'H-dispiro[indene-2,3'-pyrrolizine-1',3''-indoline]-1,2'',3-trione

A mixture ninhydrin **1** (1 mmol), L-proline **2** (1.2 mmol) and (3-Z)-6-chloro-3-(benzylidene-5-(2-chloroethyl-1,3-dihydro-2H-indol-2-one **3** (1 mmol) was taken in 100ml Round bottomed flask. To this 20 ml of methanol is added and refluxed in a water bath for 30 minutes. After the completion of the reaction, as monitored using TLC, the reaction mixture was poured into the water taken in a beaker. The solid obtained was filtered and recrystallised from ethanol to obtain the compound **4** . Further purification was not needed.

The yield and reaction time was given in the **Table 1**.

Table 1 Synthesis of compound **4**

Code	Ar	Reaction Time (min)	Yield (%)	m.p (°C)
4a	*p*-MeOC$_6$H$_4$	30	98	210-211
4b	*p*-MeC$_6$H$_4$	30	96	223-234
4c	*p*-ClC$_6$H$_4$	30	96	209-210
4d	*p*-FC$_6$H$_4$	30	95	222-223
4e	*p*-MeOC$_6$H$_4$	30	95	195-196
4f	*p*-MeC$_6$H$_4$	30	98	201-202
4g	*p*-Cl-C$_6$H$_4$	30	97	206-207
4h	*p*-MeOC$_6$H$_4$	30	98	189-190
4i	*p*-MeC$_6$H$_4$	30	94	217-218
4j	*p*-ClC$_6$H$_4$	30	96	184-185
4k	*p*-FC$_6$H$_4$	30	98	225-226

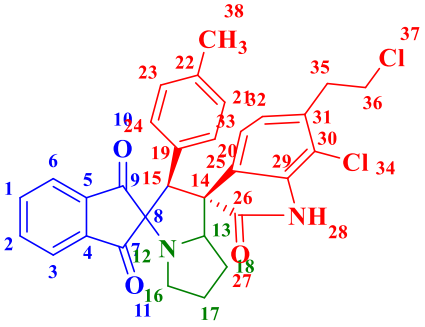


Figure 2. Atomic Labelling of compound 12b

The structure of these (1'R,2'S)-7''-chloro-6''-(2-chloroethyl)-2'-aryl-5',6',7',7a'-tetrahydro-2'H-dispiro[indene-2,3'-pyrrolizine-1',3''-indoline]-1,2'',3-trione is in accord with elemental analyses and ^{1}H, ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example **4b**. In the ^{1}H NMR spectrum of **4b**, The -CH$_2$ hydrogens (methylene hydrogens) appeared as at C-16 as triplet at 2.83 ppm (*J* = 8 *Hz*), which showed HMBCs with C-7 at 197.6 and C-8 at 101.4 ppm. The two methylene hydrogens attached to the benzene ring with chlorine (C-35 & C-36) appears appeared as a triplet at 3.19 and 3.91 respectively.The carbonyl carbon C-26 that appears at 180.7 ppm showed HMBC correlation with C-17 at 1.74 ppm. (**Figures 2 & 3**). After the addition of the D$_2$O, the peak at 8.21 disappears, which shows the presence of -NH group.

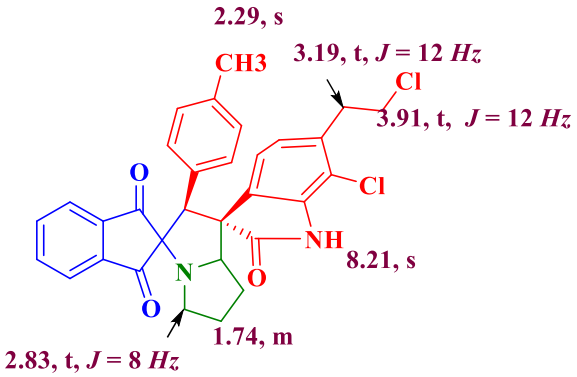


Figure 3. Selected ^{1}H NMR values for compound 4

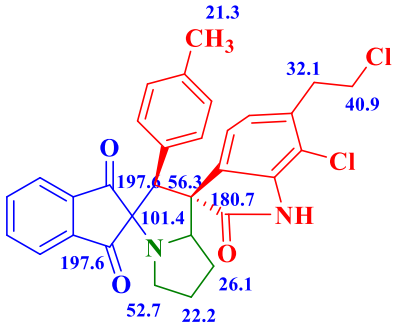


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Figure 4. Selected ^{13}C NMR values for compound 4

ANTIBACTERIAL STUDIES:

The antibacterial activity of the compounds (**4a-4k**) were measured *in vitro* against bacteria such as *Streptococcus*, *Staphylococcus*, *pseudomonas aeruginosa* and *salmonella typhi* by paper disc plate method[25] with Nutrient Agar media. The compounds were tested using 25, 50, 75 and 100 mmol solutions in DMSO and compared with that of known antibiotics *viz tetracyclin* (**Table 2**). For fungicidal activity, compounds were screened *in vitro* against *Aspergillus Niger, Trichoderma* and *Candida albicans* by mycelia dry weight method[26] with glucose nitrate media. The activity of the compounds measured at 25, 50, 75 and 100 mmol concentrations in DMSO were compared with that of kanamycin.

Table 2. Antibacterial activity (1'R,2'S)-7''-chloro-6''-(2-chloroethyl)-2'-aryl-5',6',7',7a'-tetrahydro-2'H-dispiro[indene-2,3'-pyrrolizine-1',3''-indoline]-1,2'',3-trione

S.No	Code	*Strepto coccus*				*Stephylo coccus*				*Pseudomanas aeruginosa*				*Salmonella typhi*			
		25mM	50mM	75mM	100mM	25 mM	50mM	75mM	100mM	25mM	50mM	75mM	100mM	25mM	50mM	75mM	100mM
1	4a	+	++	+++	++++	+	++	++	+++	_	++	++	+++	++	+++	+++	+++
2	4b	++	++++	+++++	++++	_	++	++	++++	+	++	++	++++	+	++	+++	+++
3	4c	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_
4	4d	_	_	_	_	_	_	_	_	+	+	+	+	_	_	_	_
5	4e	+	++	+++	+++	_	_	_	_	+	++	++	++	+	++	++	++
6	4f	+	+++	+	+	+	++	+	+	_	_	_	_	++	++	+++	++++
7	4g	_	_	_	_	_	_	_	_	+	+	+	+	+	+	++	+++

8	4h	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
9	4i	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
10	4j	–	–	–	–	+	+	++	++	–	–	–	–	–	–	–	–
11	4k	–	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–
28	*Tetracy Cline*	+	++	+++	++++	++	++	+++	++++	+	+	++	++++	++	++	+++	++++

+ mild activity ++ moderate activity +++ high activity ++++ very high activity - No activity

CONCLUSION

In this article we described a regioselective & diastereoselective Synthesis and antibacterial studies of (1'R,2'S)-7"-chloro-6"-(2-chloroethyl)-2'-aryl-5',6',7',7a'-tetrahydro-2'H-dispiro[indene-2,3'-pyrrolizine-1',3"-indoline]-1,2",3-trione was successfully performed through the 1,3-dipolar cycloaddition of azomethine ylide generated *insitu* by the reaction between L-proline and ninhydrin with the (3-Z)-6-chloro-3-(benzylidene-5-(2-chloroethyl-1,3-dihydro-2H-indol-2-one. These dispiro compounds were prepared in high yield in shorter reaction time. Since there was no waste produced in the reaction, one can consider this as a green method of synthesis. The synthesised compounds were subjected to the anti-bacterial studies.

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