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Graphical Abstract

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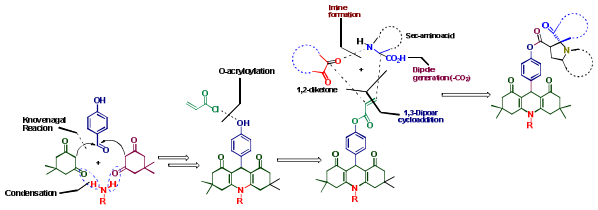
R. Rajesh, M. Suresh, R. Selvam , R. Raghunathan*



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Synthesis of acridinedione derived mono spiro-pyrrolidine/pyrrolizidine derivatives-A facile approach *via* intermolecular [3+2] cycloaddition reaction

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ABSTRACT

A facile synthesis of acridinedione derived mono spiro-pyrrolidine and pyrrolizidine derivatives has been accomplished by 1,3–dipolar cycloaddition reaction. The O- acryloylacridinediones, as dipolarophiles reacted with azomethine ylide derived from di-/tri-ketones and sec-amino acids to give acridinedione derived mono spiropyrrolidine/pyrrolizidine derivatives in good yield.

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Acridine and its derivatives are class of compounds, which were first used as pigments and dyes[1] and as probes for nucleic acid structure and conformation determination. Their importance is due to their chemotherapeutics and foot-printing applications and gene manipulation in biotechnology and medicines.[2-4] These scaffolds possess a broad range of biological activities such as antibacterial, antimalarial, anticancer, antimicrobial activity, DNA-binding and DNA photo-damaging ability.[5-7] Moreover, there are a number of fused ring alkaloids having acridine skeleton with good biological activity.[8]

Substituted acridinedione is known to exhibit wide spectrum of biological activities such as antimalarial,[9] antitumor, and cytotoxic activity.[10] Moreover, they structurally resemble to 1,4-dihydropyridines which are analogs of the biologically important coenzymes, β-dihydronicotinamide adenine dinucleotide (NADH).[11] Apart from this, acridinedione possess valuable physical properties, such as fluorescence quenching by forming complex with α, β and γ-cyclodextrins in ground and excited state and acid-base properties,.[12-14]

Highly functionalized pyrrolidines and pyrrolizidines, a core structural unit found in many alkaloids such as (–)-codonopsinine[15] and broussonetines[16] are used as intermediates in the synthesis of natural products with remarkable medicinal activities.[17] Substituted pyrrolidines and its derivatives are endowed with significant biological activities18-22 Furthermore, optically pure pyrrolidines has also been used as a chiral auxiliary and organocatalyst in asymmetric synthesis.[23]

We were interested in synthesizing acridinedione substituted pyrrolidine and pyrrolizidine derivatives which are expected to have better bioactivity than the individual molecules. Literature survey showed that there is only one report on the synthesis of pyrrolidine-acridine heterocyclic hybrids[24] and no report was available on the synthesis of acridinedione substituted pyrrolidine and pyrrolizidine derivatives.

Among the various synthetic strategies, 1,3-dipolar azomethine ylide cycloaddition is an expedient route for the synthesis of pyrrolidine derivatives and spiro heterocycles in a highly regio- and stereoselective manner.[25] In continuation of our work in the area of 1,3-dipolar cycloaddition,[26] herein we report the synthesis of acridinedione substituted mono spiro-pyrrolidine/pyrrolizidine derivatives *via* 1,3- dipolar cycloaddition reaction.

The synthetic strategy for the construction of acridinedione derived monospiro heterocycles is shown in Figure 1.

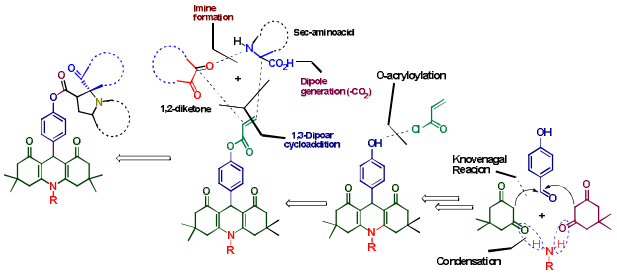

Figure 1. Synthetic approaches to acridinedione derived monospiro heterocycles.

Accordingly, the monospiro cycloadducts were synthesized by 1,3-dipolar cycloaddition of azomethine ylide generated from 1,2-diketone and secondary amino acids with *p*-*O*-acryloylphenyl acridinedione as dipolarophile. (Figure 1)

Our studies commenced with the synthesis of acridinediones **4a-b** which were synthesized by the reaction of dimedone **1** (5,5-dimethyl cyclohexane-1,3-dione) with 4-hydroxy benzaldehyde

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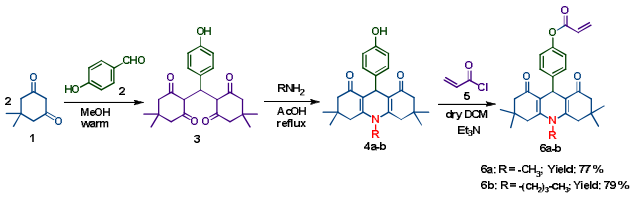
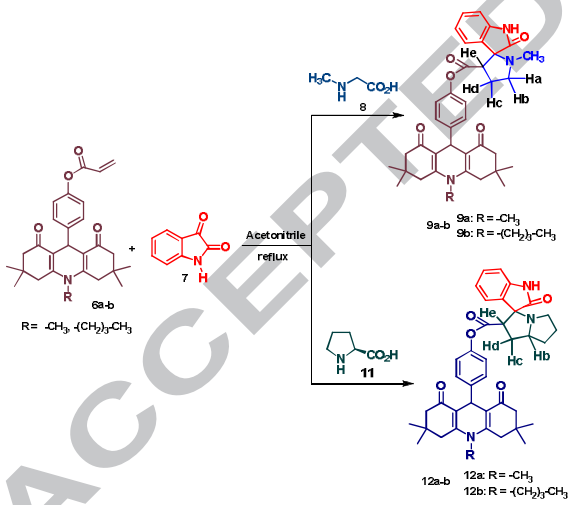
2 in methanol to give 4-hydroxyphenyltetraketone **3**. It was refluxed with methyl amine/n-propyl amine in acetic acid to yield acridinedione **4a/4b**. The acridinediones **4a-b** were treated with freshly distilled acryloyl chloride **5** in DCM in the presence triethylamine, at 0 °C to afford *O*-acryloylacridinediones **6a** and **6b** in 77 % and 79 % yield respectively (Scheme 1).



Scheme 1. Synthesis of *O*-acryloyl acridinedione derivatives.

In a one-pot three component reaction, *O*-acryloylacridinedione **6a/6b** was reacted with non-stabilized azomethine ylide generated by the decarboxylative condensation of isatin and sarcosine in refluxing acetonitrile, to give mono spiro-oxindolopyrrolidines **9a/9b** in good yield (Scheme 2).[27] The reaction occurred with good regioselectivity and no trace of the other regioisomer was isolated even after prolonged reaction time. The reaction was initially carried out in different solvents such as methanol, toluene, tetrahydrofuran and 1,4-dioxane. It was observed that the reaction in methanol failed to give the expected product, and other solvents gave only poor yield. Best results were obtained with acetonitrile as efficient solvent, giving high yield of the product.

Under similar reaction conditions the azomethine ylide generated *in situ* from isatin and proline reacted with dipolarophile **6a/6b** to yield spiro-oxindolopyrrolizidine **12a/12b** in good yield (Scheme 3).



Scheme 2. Synthesis of monospirooxindolopyrrolidine/pyrrolizidine derivatives.

. The ^{1}H NMR spectrum of compound **9a** showed a sharp singlet at δ 2.09 due to *N*-methyl proton of pyrrolidine ring. The H_e proton in pyrrolidine ring showed a triplet at δ 3.81. If other regioisomer **10a** was formed, one would expect a multiplet instead of a triplet.: Similarly, the azomethine ylide generated *in situ* by decarboxylative condensation of isatin and sarcosine underwent 1,3-dipolar cycloaddition reaction with *O*-acryloylacridinediones regioselectively as shown in figure 2.

The regioselectivity of cycloadducts can be explained by secondary orbital interaction (**SOI**)[28] of the carbonyl group of dipolarophile **6a/6b** and the ylide **7a** as shown in Figure 2.

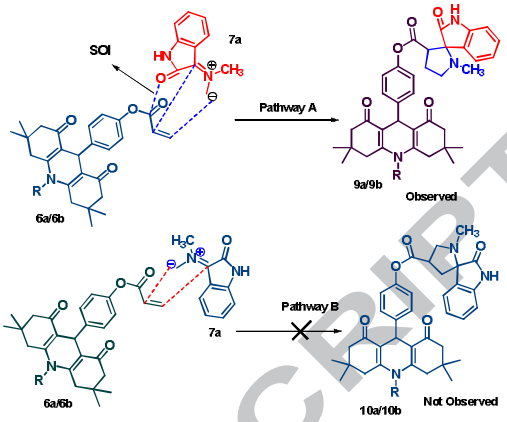


Figure 2. Mode of approach of azomethine ylide

Accordingly, the regioisomer **9a** *via* path **A** is more favorable because of the secondary orbital interaction which is not possible in path **B** (carbonyl group of dipole is far away from the dipolarophile carbonyl group).Hence, the cycloadduct corresponding to path **B** was not observed.

The product **9a** showed a multiplet in the range δ 3.35-3.43 and 3.03-3.10. for the protons of methylene group of pyrrolidine ring (-*N*CH_2). H_c proton showed a multiplet in the range δ 2.37-2.46 and H_d proton showed a multiplet in the range δ 2.61-2.70. The broad peak appeared at δ 8.81 is due to the –NH proton. The *gem*-dimethyl protons showed two singlets at δ 1.00 and 1.03, and a sharp singlet appeared at δ 3.23 due to N-CH_3protons of acridinedione. The ^{13}C NMR spectrum of cycloadduct **9a** showed two peaks at δ 168.85 and 177.58 for oxindole and ester carbonyl carbons. The spiro carbon showed a peak at 72.28 ppm. The DEPT 135 spectrum showed four peaks in negative region at 24.01, 39.42, 48.84, and 52.33 ppm for four methylene carbons of cycloadduct (Figure 3).[29]

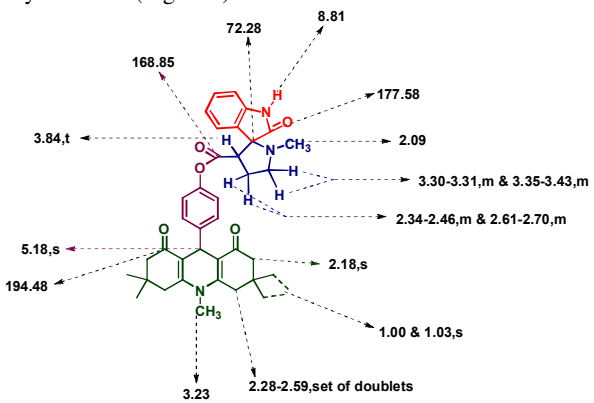


Figure 3. Selected ^{1}H and ^{13}C NMR chemical shifts of **9a**.

The same reaction was extended to other di- and triketones acenaphthequinone and ninhydrin and the cycloaddition of *O*-acryloylacridinedione **6a/6b** with the azomethine ylide generated from acenapthequinone **13** and sarcosine **8**/proline **11** under the same reaction conditions resulted in the formation of monospiroacenapthenopyrrolidines **14a/14b** and

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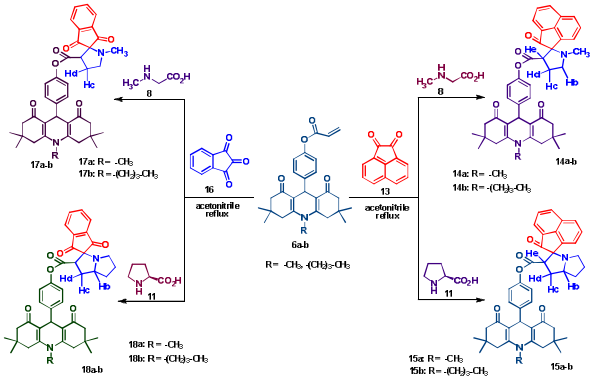
monospiroacenapthenopyrrolizidine **15a/15b** in good yield. In a similar way, the reaction of ninhydrin **16** and sarcosine **8**/proline **11** with *O*-acryloylacridinedione **6a/6b** afforded mono-spiro-1,3–indanedionopyrrolidine **17a/17b** and mono-spiro-1,3–indanedionopyrrolizidine **18a/18b** in good yield (Scheme 4).



Scheme 3. Synthesis of mono spiroacenaphtheno/indano-pyrrolidine/pyrrolizidine derivatives.

The structure and regiochemistry of all cycloadducts were unambiguously established by their spectroscopic analysis. The ^{1}H NMR spectrum of the cycloadduct **15b** exhibited a multiplet in the range δ 1.84-2.61 for the pyrrolizidine ring methylene protons. The *gem*-dimethyl protons showed two singlets at δ 0.91 and 1.10 and a triplet appeared at δ 0.90-0.95 for *N*-butyl methyl protons (–CH_2-CH_2-CH_2-$\underline{CH_3}$); two multiplets appeared at δ 1.30 and 1.42 for two methylene protons in *N*-butyl group (–CH_2-$\underline{CH_2}$-$\underline{CH_2}$-CH_3). The ^{13}C NMR spectrum of the cycloadduct **15b,** showed two peaks at 169.24 and 206.27 ppm for ester and acenapthenenone carbonyl carbons. The spiro carbon showed peak at 76.42 ppm. In addition, the DEPT 135 spectrum showed nine peaks in negative region at 19.81, 28.64, 32.77, 33.42, 34.11, 40.34, 44.57, 47.45 and 49.84 ppm confirmed the presence of nine methylene carbons present in cycloadduct **15b**.[29]

The formations of all cycloadducts are summarized in Table **1.**

In conclusion, we have accomplishedthe synthesis of novel acridinedione derived mono spiropyrrolidineandmonospiropyrrolizidine derivatives from simple precursors in a one-pot reaction. The azomethine ylide generated by decarboxylation condensation of di-/triketones yield. All cycloadducts are obtained in highly stereo- and regioselective manner and confirmed by spectral analysisTable 1. Synthesis of acridinedione substituted mono spiropyrrolidine/pyrrolizidine derivatives from di/tri ketones isatin/acenaphthenequinone/ninhydrin and secondary amino acids sarcosine/proline underwent [3+2]-cycloaddition with *O*-acryloylacridinediones afforded monospiro heterocycles in good yield. All cycloadducts are obtained in highly stereo- and regioselective manner and confirmed by spectral analysis

Table 1. Synthesis of acridinedione substituted mono spiropyrrolidine/pyrrolizidine derivatives from di/tri ketones

Entry	Dipolorophile	Di/tri-ketone	*Sec*-amino acid	Time (h)[a]	Yield (%)[b]	Products
1	**6a**	7	8	5.5	84	**9a**
2	**6b**	7	8	6.0	82	**9b**
3	**6a**	7	11	6.0	84	**12a**
4	**6b**	7	11	6.5	85	**12b**
5	**6a**	13	8	4.5	83	**14a**
6	**6b**	13	8	4.5	79	**14b**
7	**6a**	13	11	5.5	81	**15a**
8	**6b**	13	11	5.0	79	**15b**
9	**6a**	16	8	4.0	80	**17a**
10	**6b**	16	8	4.5	81	**17b**
11	**6a**	16	11	5.0	83	**18a**
12	**6b**	16	11	5.5	84	**18b**

a.Completion of the reaction based on TLC analysis
[b] Yield of isolated product after column chromatography

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Acknowledgments

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27. *General procedure for the synthesis of acridinedione derived mono spiropyrrolidine/pyrrolizidine derivatives.*
To a solution of *O*-acryloylacridinedione dipolarophile **6a** (1.0 mmol) in acetonitrile (20 ml), was added sarcosine **8** (1.1 mmol) and isatin **7** (1.0 mmol). The resulting solution was refluxed for 8 h. After the completion of reaction as indicated by TLC, acetonitrile was evaporated under reduced pressure and extracted with dichloromethane (50 ml). The organic layer was washed with water and brine solution, dried with anhydrous sodium sulfate and concentrated in *vacuo*. The residue was purified by column chromatography using silica gel column with chloroform-methanol (8:2) as an eluent.
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29. *Representative spectral data of the products.*
Compound **9a**: Brown solid, (84 %), Mp: 210-212 °C; IR (KBr): 3141, 1744, 1712, 1686 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 6H), 1.03 (s, 6H), 2.09 (s, 3H), 2.18 (s, 4H), 2.28-2.34 (d, 2H, *J* = 16.8 Hz), 2.52-2.59 (d, 2H, *J* = 16.8 Hz), 2.37-2.46 (m, 1H), 2.61-2.70 (m, 1H), 3.03-3.10 (m,1H), 3.23(s, 3H), 3.35-3.43 (m,1H), 3.81-3.88 (t, 1H, *J* = 9.3, 9.6 Hz), 5.186 (s, 1H), 5.987-6.01 (d, 2H, *J*=8.4 Hz), 6.84-6.87 (d, 1H, *J* = 7.8 Hz), 6.95-6.98 (d, 2H, *J* = 8.4 Hz), 7.02-7.04 (d, 1H, *J* = 7.2 Hz), 7.14-7.16 (d, 1H, *J* = 7.5Hz), 7.22 -7.24 (d, 1H, *J* = 7.5 Hz), 8.81 (s, 1H)**.** ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.0, 27.3, 27.9, 29.8, 31.7, 32.4, 34.3, 39.4, 48.8, 51.2, 52.3, 72.2, 109.4, 113.5, 113.6, 119.5, 121.6, 124.6, 125.5, 127.1, 128.5, 140.5, 141.9, 147.1, 150.5, 168.8, 177.5, 194.4 ppm. Mass: *m/z* 607.78 (M^+). Anal. Calcd. For $C_{37}H_{41}N_3O_5$: C, 73.12; H, 6.80; N, 6.91 %; Found: C, 73.19; H, 6.84; N, 6.88 %.
Compound **15b**: Pale yellow solid, (79 %), Mp: 198-200 °C; IR (KBr): 1756, 1743, 1675 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 0.90-0.95 (t, 3H), 0.92 (s, 6H), 0.96(s, 6H), 1.25-1.33 (m, 2H),

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1.42-1.52 (m, 2H), 1.84-1.93 (m, 2H), 2.06-2.10 (m, 1H), 2.14 (s, 4H), 2.23-2.29 (m, 1H), 2.32 (d, 2H, *J* = 16.8 Hz), 2.40-2.41 (d, 2H, *J* = 17.1 Hz), 2.35-2.38 (m, 1H), 2.46-2.61 (m, 3H), 3.53-3.57 (t, 2H, *J*=7.5 Hz, 7.2 Hz), 4.17-4.19 (m, 1H), 4.13-4.17 (m, 1H), 5.04 (s, 1H), 5.47-5.50 (d, 2H, *J* = 8.4 Hz), 6.78-6.81 (d, 2H, *J* = 8.4 Hz), 7.46-7.49 (d, 1H, *J* = 6.9 Hz), 7.62-7.67 (t, 1H, *J*=6.9, 8.4 Hz), 7.69-7.74 (t, 1H, *J* = 7.5 Hz, 7.8 Hz), 7.90-7.93 (d, 1H, *J* = 8.1 Hz), 7.96-7.99 (d, 1H, *J* = 6.9 Hz), 8.11-8.14 (d, 1H, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 19.8, 28.0, 28.6, 29.0, 30.9, 32.5, 32.7, 33.4, 34.1, 40.3, 44.5, 47.4, 49.8, 55.7, 65.2, 76.4, 115.1, 119.8, 121.9, 122.5, 125.5, 127.9, 128.1, 128.4, 130.7, 131.7, 132.1, 136.0, 142.2, 142.7, 147.6, 150.2, 169.2, 195.4, 206.2 ppm. Mass: *m/z* 710.95 (M^+). Anal. Calcd. For $C_{46}H_{50}N_2O_5$: C, 77.72; H, 7.09; N, 3.94 %; Found: C, 77.79; H, 7.05; N, 3.98 %.

Compound **17a**: Pale yellow solid, (80 %), Mp: 194-196 °C; IR (KBr): 1765, 1762, 1733, 1689 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 6H), 1.05 (s, 6H), 2.18 (s, 3H), 2.22 (s, 4H), 2.28-2.34 (d, 2H, *J* = 16.8 Hz), 2.52-2.57 (d, 2H, *J* = 16.5 Hz), 2.42-2.50 (m, 1H), 2.64-2.74 (m, 1H), 3.21(s, 3H), 3.25-3.28 (m, 1H), 3.30-3.38 (m, 1H), 3.78-3.84 (t, 1H, *J* = 9.6 Hz), 5.19 (s, 1H), 6.45-6.48 (d, 2H, *J* = 8.1 Hz), 7.02-7.05 (d, 2H, *J* = 8.4 Hz), 7.83-7.88 (m, 2H), 7.92-7.94 (m, 1H), 7.98-8.00 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6, 28.1, 28.5, 28.4, 30.6, 32.4, 32.4, 33.1, 35.9, 40.2, 49.5, 51.1, 53.9, 73.1, 114.3, 119.9, 122.3, 128.0, 135.8, 136.2, 141.3, 142.8, 147.7, 151.0, 169.1, 195.0, 201.3, 202.4 ppm. Mass: *m/z* 620.81 (M^+). Anal. Calcd. For $C_{38}H_{40}N_2O_6$: C, 73.53; H, 6.50; N, 4.51 %; Found: C, 73.59; H, 6.53; N, 4.55 %

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