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An atom economic synthesis and antitubercular evaluation of novel spiro-cyclohexanones

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ABSTRACT

The 1,3-dipolar cycloaddition of azomethine ylides derived from acenaphthenequinone and α-amino acids viz. sarcosine, phenylglycine, 1,3-thiazolane-4-carboxylic acid and proline to a series of 2,6-bis[(*E*)-arylmethylidene]cyclohexanones afforded novel spiro-heterocycles chemo-, regio- and stereoselectively in quantitative yields. These compounds were screened for their in vitro activity against *Mycobacterium tuberculosis* H37Rv (MTB) using agar dilution method. Two compounds, 4-(2,4-dichlorophenyl)-5-phenylpyrrolo(spiro[2.2″]acenaphthene-1″-one)spiro[3.2′]-6′-(2,4-dichlorophenylmethylidene)cyclohexanone (**4i**) and spiro[5.2″]acenaphthene-1″-onespiro[6.2′]-6′-(2,4-dichlorophenylmethylidene)cyclohexanone-7-(2,4-dichlorophenyl)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazole (**5i**) display maximum activity in vitro with a MIC value of 0.40 μg/mL against MTB and were 4 and 15.6 times more potent than ethambutol and pyrazinamide, respectively.

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* bacteria (MTB) is one of the most prevalent diseases, responsible for the death of about one billion people during the last two centuries.[1] TB remains a serious public health problem in India accounting for nearly one-third of the global burden, and it has been estimated that 3.5 million of the population are infected with TB.[1,2] In the last 50 years, only a few drugs have been approved by the Food and Drug Administration (FDA) to treat TB, which reflects the inherent difficulties in the discovery and clinical testing of new agents and the lack of pharmaceutical industry research in this area.[3] Hence, the discovery of fast-acting new drugs to effectively combat TB is imperative.

1,3-Dipolar cycloaddition of azomethine ylides to exocyclic olefins afford functionalized spiro-heterocycles such as pyrrolidines[4] and pyrrolizines.[5] In general, spiro compounds[6] and nitrogen heterocycles[7] display good antimycobacterial activities. Recently, we have reported an atom economic synthesis and evaluation of antimycobacterial activities of (i) spiro pyrido-pyrrolizines and pyrrolidines,[8] (ii) 4*H*-pyrano[3,2-*c*]pyridine derivatives[9a] and 2-aryl-3,4-dihydro-2*H*-thieno[3,2-*b*]indoles[9b] which inhibited in vitro MTB and multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB). In the course of screening to discover new compounds that could be useful for the chemotherapy of tuberculosis, we identified spiro-cyclohexanone derivatives **3–6**, which inhibited in vitro MTB. We present the preliminary results on the synthesis and the antimycobacterial activities of the first few representative series of this family.

In the present investigation, the 1,3-dipolar cycloaddition of azomethine ylides, generated in situ from acenaphthenequinone (**2**) and α-amino acids viz. (i) sarcosine, (ii) phenylglycine, (iii) 1,3-thiazolane-4-carboxylic acid and (iv) proline to **1a–j** afforded novel 1-methyl-4-arylpyrrolo(spiro[2.2″]acenaphthene-1″-one)spiro[3.2′]-6′-arylmethylidenecyclohexanones (**3a–j**), 4-aryl-5-phenylpyrrolo(spiro[2.2″]acenaphthene-1″-one)spiro[3.2′]-6′-arylmethylidenecyclohexanones (**4a–i**), spiro[5.2″]acenaphthene-1″-onespiro[6.2′]-6′-arylmethylidenecyclohexanone-7-aryltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazoles (**5a–i**) and spiro[2.2″]ace-naphthene-1″-one-spiro[3.2′]-6′-arylmethylidenecyclohexanone-4-arylhexahydro-1*H*-pyrrolizines (**6a–f**), respectively (Scheme 1).[10–13] All the reactions proceed chemo-, regio- and stereoselectively, as the cycloaddition (i) occurs on only one arylidene C=C bond of **1**, (ii) involves the addition of electron rich carbon of the dipole to the β carbon of **1** and (iii) results in the exclusive formation of one diastereomer in quantitative yields, although more than one stereocentres are present in these cycloadducts.

Twenty eight spiro-cyclohexanones have been synthesized in this investigation employing cycloadditions. These reactions were effected by refluxing an equimolar ratio of the reactants in methanol. After completion of the reactions (TLC), the reaction mixtures

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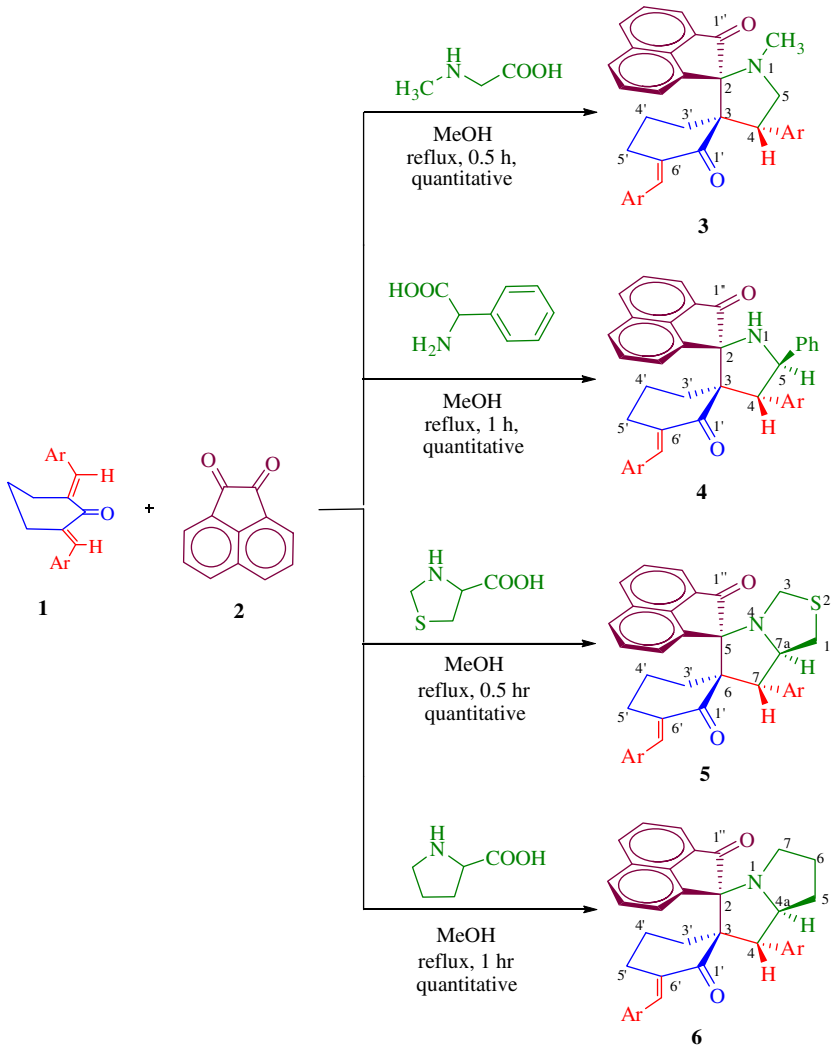

Scheme 1. Synthesis of spiro-cyclohexanones **3–6**.

were poured into water to get pure **3–6** as yellow solids. As quantitative yields of spiro-cycloadducts **3–6** were obtained, neither crystallization nor column chromatographic purification is necessary (Table 1). The only by-products of these cycloadditions are water and carbon dioxide and hence the atom economy is very high (~90%). The quantitative yield of the products in conjunction with high atom economy renders this protocol efficient and green. All the spiro compounds obtained in this work are in racemic form, although three of the amino acid precursors (phenylglycine, proline and 1,3-thiazolane-4-carboxylic acid) employed for the

Table 1
Yield and minimum inhibitory concentrations against mycobacterial species of spiro-cyclohexanones **3–6**

Compd **3–6**	Ar	Yield[a] (%)				MIC (μg/mL) against MTB[b,c]			
		3	**4**	**5**	**6**	**3**	**4**	**5**	**6**
a	C_6H_5	95	95	98	97	12.50	3.13	6.25	12.50
b	*p*-ClC_6H_4	97	97	97	96	12.50	6.25	6.25	1.78
c	*p*-$CH_3C_6H_4$	96	96	95	98	25.00	6.25	6.25	6.25
d	*p*-$CH_3OC_6H_4$	94	—[d]	—[d]	—[d]	25.00	—[e]	—[e]	—[e]
e	*p*-FC_6H_4	—[d]	98	98	97	—[e]	6.25	1.76	1.78
f	*o*-ClC_6H_4	96	96	95	96	6.25	0.78	0.78	3.13
g	*o*-$CH_3C_6H_4$	96	96	96	—[d]	12.50	1.78	0.78	—[e]
h	*m*-FC_6H_4	97	—[d]	—[d]	—[d]	12.50	—[e]	—[e]	—[e]
i	*o*,*p*-$Cl_2C_6H_3$	96	95	97	—[d]	3.13	0.40	0.40	—[e]
j	1-Naphthyl	95	—[d]	—[d]	—[d]	6.25	—[e]	—[e]	—[e]

[a] Yields were quantitative except the loss during workup.
[b] MTB: *Mycobacterium tuberculosis*.
[c] Standard drugs employed (MIC): Isoniazid (0.05 μg/mL), ethambutol (1.56 μg/mL), rifampicin (0.10 μg/mL) and pyrazinamide (6.25 μg/mL).
[d] These compounds could not be obtained as the reactions failed to occur.
[e] As these compounds were not obtained under the reaction conditions, they could not be screened.

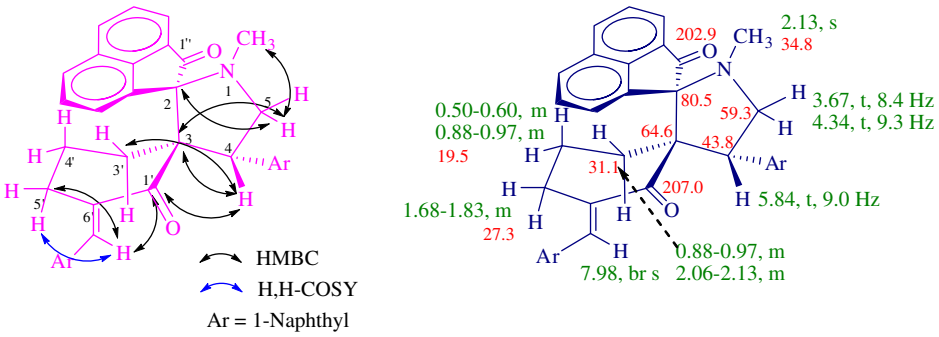

Figure 1. HMBC correlations and ^{1}H and ^{13}C NMR chemical shifts of **3j**.

generation of the azomethine ylides are chiral. This is ascribable to the fact that the intermediates involved in the cycloaddition, viz. the azomethine ylides generated from the amino acids are achiral.

The structure of the spiro-cycloadducts **3** was elucidated with the help of ^{1}H, ^{13}C and 2D NMR spectroscopic studies. The ^{1}H and ^{13}C NMR chemical shifts and selected HMBC correlations of a representative example, **3j** are shown in Figure 1. The complete stereochemical information of **3** was obtained from an X-ray crystallographic study of a single crystal of **3j** (Fig. 2).[14]

The structure of **4** was deduced from its NMR spectroscopic data as illustrated for **4f**. The ^{1}H NMR spectrum of **4f** has two doublets related by a H,H-COSY correlation at 5.24 and 5.71 ppm (J = 9.6 Hz), which can be assigned to H-4 and H-5, respectively. These signals were distinguished from the HMBC correlation (Fig. 3) of the signal at 5.24 ppm with the carbonyl carbon at 203.6 ppm. From the C,H-COSY spectrum, the carbon signals at 58.6 and 65.8 ppm can be readily assigned to C-4 and C-5, respectively. Further, from the HMBC correlations of H-4, C-2 and C-3 are assigned to signals at 64.4 and 78.4 ppm, respectively. The cyclohexanone ring hydrogens were assigned using H,H-COSY correlations. The benzylidene hydrogen appearing as a broad singlet at 7.95 ppm has an allylic coupling with 5′-CH_2 hydrogens affording multiplets at 2.23–2.35 and 2.03–2.09 ppm. The H,H-COSY correlations assign the multiplets at 0.04–0.57 and 1.05–1.17 ppm to 4′-CH_2 hydrogens and the multiplets at 1.25–1.33 and 1.84–1.88 ppm to 3′-CH_2 hydrogens. From the C,H-COSY spectrum, the signals at 19.3, 27.8, 30.3 and 135.8 ppm are assigned to C-4′, C-5′, C-3′ and the benzylidene carbon, respectively. The N–H of the pyrrolidine ring appears as a broad singlet at 3.32 ppm.

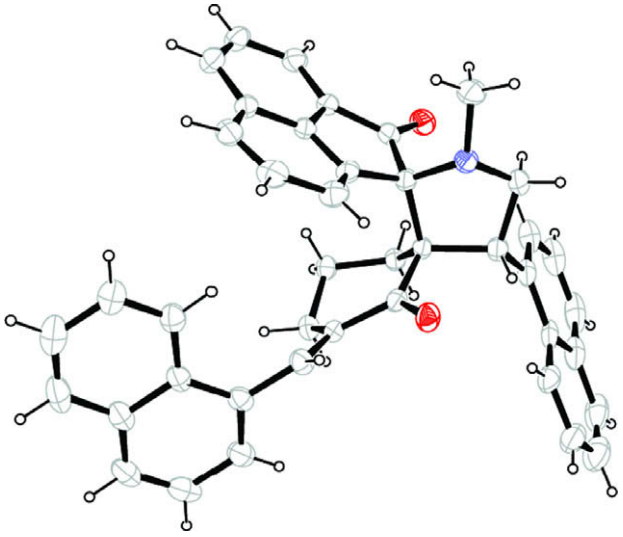

Figure 2. ORTEP diagram of **3j**.

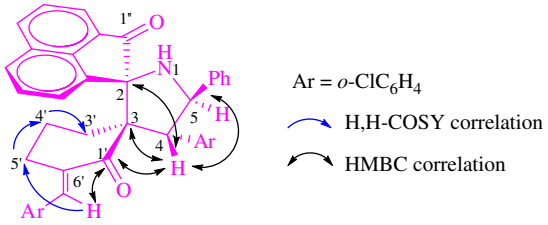

Figure 3. H,H-COSY and HMBC correlations of **4f**.

The structure of **5** has been elucidated using one and two dimensional NMR studies as described for **5c**. The H,H-COSY spectrum of **5c** assigns a doublet and multiplet at 4.59 ppm (J = 10.5 Hz) and 4.74–4.81 ppm to H-7 and H-7a. Further, H-7 shows HMBC correlations (Fig. 4) with C-1′, C-6, C-7a and C-1 at 201.9, 70.3, 69.4 and 34.8 ppm, respectively. The C,H-COSY spectrum assigns the 1-CH_2 hydrogens to the doublets of doublets at 2.91 and 3.11 ppm (J = 10.3 and 6.5 Hz). The doublets at 3.46 and 3.74 ppm (J = 9.5 Hz) of 3-CH_2 hydrogens show (i) a C,H-COSY correlation with C-3 at 50.5 ppm and (ii) HMBC correlations with C-1 at 34.8 ppm and C-5 at 78.9 ppm. Further, H-7 shows a HMBC correlation with C-3′ at 28.1 ppm. From the C,H-COSY spectrum, it is evident that the multiplets at 2.69–2.74 and 1.47–1.56 ppm are due to 3′-CH_2 hydrogens. From the H,H-COSY spectrum, the 2H multiplet at 1.12–1.34 ppm can be assigned to 4′-CH_2 hydrogens, while one of the 5′-CH_2 hydrogens appear as a multiplet at 1.86–2.01 ppm and the other overlaps with the methyl signal of the aryl rings at 2.24 ppm. The benzylidene hydrogen appears as a broad singlet at 6.00 ppm and the aromatic hydrogens give a multiplet in the range 6.58–8.04 ppm.

The ^{1}H and ^{13}C chemical shift assignments of **6** have also been done by straightforward considerations as done for **5**. As a representative example, the H,H-COSY correlations and the ^{1}H and ^{13}C chemical shifts of **6f** are shown in Figure 5. The relative stereochemistry of compounds **4–6** were assigned by comparing with the stereochemistry of similar structures reported by us earlier.[8]

The spiro-heterocycles **3–6** were screened for their in vitro antimycobacterial activity against log-phase cultures of MTB in Middlebrook 7H11agar medium supplemented with OADC by agar dilution method similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate. The MIC is defined as the minimum concentration of a compound required to completely inhibit the bacterial growth. The MIC's of the synthesized compounds along with the standard drugs for comparison are reported in Table 1. In the first

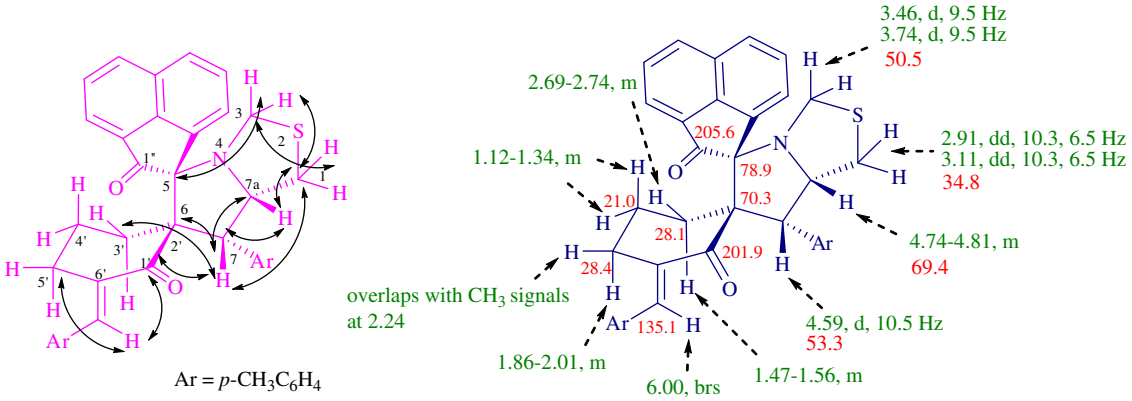

Figure 4. HMBC correlations and ^{1}H and ^{13}C NMR chemical shifts of **5c**.

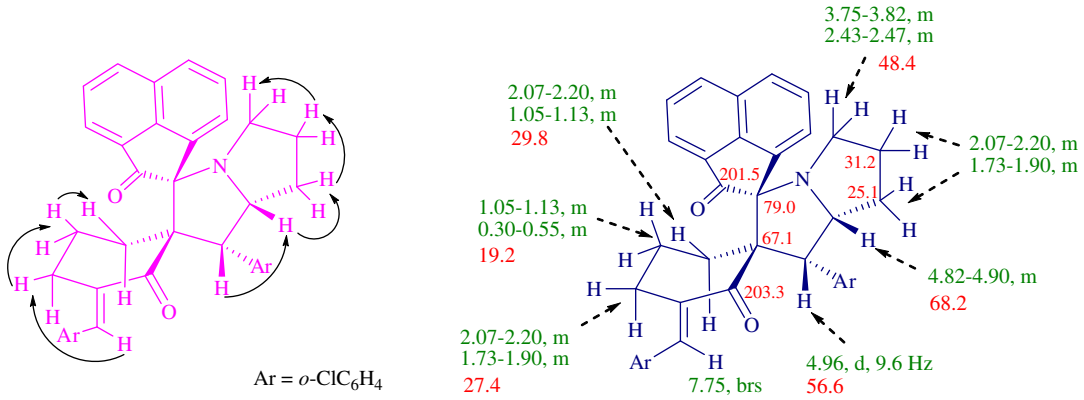

Figure 5. H,H-COSY correlations and ^{1}H and ^{13}C NMR chemical shifts of **6f**.

phase of screening, all the compounds showed in vitro activity against MTB with MIC's ranging from 0.40 to 25.00 μg/mL. Nine compounds (**4f**, **4g**, **4i**, **5e–g**, **5i**, **6b** and **6e**) inhibited MTB with less than 2 μg/mL. When compared to ethambutol (MIC of 1.56 μg/mL); five compounds (**4f**, **4i**, **5f**, **5g** and **5i**) were more potent with MIC less than 0.78 μg/mL and four compounds (**4g**, **5e**, **6b** and **6e**) were equally active. Twelve compounds were more potent than first-line anti-TB drug pyrazinamide (MIC of 6.25 μg/mL); and nine compounds were equipotent. All the compounds were less active than isoniazid and rifampicin. Two compounds, **4i** and **5i**, were found to be the most active in vitro with a MIC value of 0.40 μg/mL against MTB and were 4 and 15 times more potent than ethambutol and pyrazinamide, respectively. The influence of substituents at *N* as well as at carbon α to the *N* of the pyrrolidine ring and substituents at different positions of aryl rings was examined for structure–activity relationship (SAR). The results demonstrated that compounds from series **3** with MIC ranging from 3.13 to 25.00 μg/mL were less active against MTB than the series **4–6**. Further comparison of the activities of **3–6** reveals a general trend that either the structural differences such as the substitution of *N*–Me in **3** by *N*–H in series **4** and the presence of an aryl ring at carbon α-nitrogen in series **4** or bridging between *N* and the adjacent carbon in series **5** and **6** results in an enhancement of antimycobacterial activity. *ortho* Substitution in the aryl ring in series **4** and **5** and *para* substitution in the aryl ring of series **6** facilitates the activity.

The 1,3-dipolar cycloaddition of azomethine ylide generated in situ from acenaphthene-quinone and α-amino acids to 2,6-bis[(*E*)-arylmethylidene]cyclohexanones afforded novel spiro-heterocycles **3–6** in quantitative yields. These spiro-heterocycles displayed good in vitro antimycobacterial activity against MTB.

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10. Synthesis of 1-methyl-4-arylpyrrolo(spiro[2.2″]acenaphthene-1″-one)-spiro[3.2′]-6′-arylmethylidenecyclohexanones (**3a–j**): A mixture of 2,6-bis[(*E*)-arylmethylidene]cyclohexanone **1** (1 mmol), acenaphthenequinone (0.182 g, 1 mmol) and sarcosine (0.089 g, 1 mmol) was dissolved in methanol (10 mL) and refluxed for 30 min. After completion of the reaction as evident from TLC, the mixture was cooled to room temperature and poured into water (50 mL). The precipitated solid was filtered and washed with water to obtain pure **3** as yellow solid. *1-Methyl-4-phenylpyrrolo(spiro[2.2″]acenaphthene-1″-one)spiro[3.2′]-6′-phenylmethylidenecyclohexanone* (**3a**). Yield 95%, mp 197–198 °C. [$C_{34}H_{29}NO_2$ requires C, 84.44; H, 6.04; N, 2.90. Found: C, 84.40; H, 6.14; N, 2.83]; δ_H (300 MHz, $CDCl_3$) 6.96–8.07 (16H, m, Ar-H), 7.04 (1H, br s, C=CH), 4.99 (1H, dd, J = 9.3, 7.5 Hz, 4-CH), 4.04 (1H, t, J = 9.3 Hz, 5-CH_2), 3.52 (1H, t, J = 8.7 Hz, 5-CH_2), 2.07 (3H, s, N–CH_3), 2.05–2.14, 1.10–1.25, 0.69–0.76 (6H, m, 3′-, 4′- and 5′-CH_2); δ_C (75 MHz, $CDCl_3$) 206.8, 203.3, 142.1, 139.4, 137.8, 137.5, 136.8, 135.6, 132.4, 131.8, 130.3, 129.7, 128.7, 128.2, 128.1, 128.0, 127.9, 126.8, 125.2, 125.1, 120.2, 80.0, 65.4, 58.3, 49.6, 34.8, 30.9, 28.0, 20.2.
11. Synthesis of 4-aryl-5-phenylpyrrolo-(spiro[2.2″]acenaphthene-1″-one)-spiro[3.2′]-6′-arylmethylidenecyclohexanones (**4a–i**): A mixture of **1** (1 mmol), acenaphthenequinone (0.182 g, mmol) and phenylglycine (0.151 g, 1 mmol) was dissolved in methanol (10 mL) and refluxed for 1 h. After completion of the reaction as evident from TLC, the mixture was poured into water (50 mL), the precipitated solid was filtered and washed with water (100 mL) to obtain pure **4** as pale yellow solid. *4-Phenyl-5-phenylpyrrolo-(spiro[2.2″]acenaphthene-1″-one)spiro[3.2′]-6′-phenylmethylidenecyclohexan-one* (**4a**). Yield 95%, mp 156–157 °C. [$C_{39}H_{31}NO_2$ requires C, 85.84; H, 5.73; N, 2.57. Found: C, 85.90; H, 5.78; N, 2.52]; δ_H (300 MHz, $CDCl_3$) 7.06–8.07 (22H, m, Ar), 5.54 (1H, d, J = 10.0 Hz, 5-CH), 4.87 (1H, d, J = 10.0 Hz, 4-CH), 2.65–3.05 (1H, m, 5′-CH_2), 2.03–2.17 (1H, m, 5′-CH_2), 1.68–1.80 (1H, m, 3′-CH_2), 1.37–1.46 (1H, m, 3′-CH_2), 1.11–1.23 (1H, m, 4′-CH_2), 0.73–0.86 (1H, m, 4′-CH_2); δ_C (75 MHz, $CDCl_3$) 205.0, 204.4, 141.5, 141.3, 138.4, 137.8, 137.7, 137.1, 135.5, 131.8, 131.7, 130.6, 130.4, 129.8, 128.6, 128.3, 128.2, 128.1, 127.6, 127.4, 126.8, 125.1, 124.3, 121.6, 77.1, 66.1, 65.9, 61.6, 30.4, 28.1, 20.2.
12. Synthesis of spiro[5.2″]acenaphthene-1″-onespiro[6.2′]-6′-arylmethylidenecyclohexanone-7-arylterahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazoles (**5a–i**): A mixture of **1** (1 mmol), acenaphthenequinone (0.182 g, 1 mmol) and 1,3-thiazolane-4-carboxylic acid (0.133 g, 1 mmol) was dissolved in methanol (10 mL) and refluxed for 30 min. After completion of the reaction as evident from TLC, the mixture was poured into water (50 mL), the precipitated solid was filtered and washed with water (100 mL) to obtain pure **5** as pale yellow solid. *Spiro[5.2″]acenaphthene-1″-onespiro[6.2′]-6′-(2,4-dichlorophenylmethylidene) cyclohexanone-7-(2,4-dichlorophenyl)tetrahydro-1H-pyrrolo[1,2-c][1,3]thiazole* (**5i**). Yield 97%, mp 174–176 °C; [$C_{35}H_{25}Cl_4NO_2S$ requires C, 63.17; H, 3.79; N, 2.10. Found: C, 63.26; H, 3.72; N, 2.17]; δ_H (300 MHz, $CDCl_3$) 6.83–8.10 (13H, m, Ar), 4.91 (1H, d, J = 7.5 Hz, 7-CH), 4.70–4.80 (1H, m, 7a-CH), 3.31 (2H, s, 3-CH_2), 2.87–2.99 (2H, m, 1-CH_2), 1.87–2.27 (3H, m, 5′-CH_2 and 3′-CH_2), 0.98–1.20 (2H, m, 3′-CH_2 and 4′-CH_2), 0.50–0.60 (1H, m, 4′-CH_2); δ_C (75 MHz, $CDCl_3$) 205.2, 199.5, 137.7, 136.6, 135.5, 134.5, 134.4, 134.2, 133.3, 132.4, 132.3, 131.7, 131.4, 130.8, 130.5, 129.4, 129.2, 129.1, 127.9, 127.3, 126.4, 125.8, 125.6, 121.0, 77.4, 70.5, 68.7, 48.6, 45.2, 32.7, 31.2, 27.8, 19.3.
13. Synthesis of spiro[2.2″]acenaphthene-1″-onespiro[3.2′]-6′-arylmethylidenecyclohexanone-4-arylhexahydro-1*H*-pyrrolizines (**6a–i**): A mixture of **1** (1 mmol), acenaphthenequinone (0.182 g, 1 mmol) and proline (0.115 g, 1 mmol) was dissolved in methanol (10 mL) and refluxed for 1 h. After completion of the reaction as evident from TLC, the mixture was poured into water (50 mL), the precipitated solid was filtered and washed with water (100 mL) to obtain pure **6** as pale yellow solid. *Spiro[2.2″]acenaphthene-1″-onespiro[3.2′]-6′-phenylmethylidenecyclohexanone-4-phenylhexahydro-1H-pyrrolizine* (**6a**). Yield 97%, mp 137–139 °C; [$C_{36}H_{31}NO_2$ requires C, 84.84; H, 6.13; N, 2.75. Found: C, 84.77; H, 6.19; N, 2.84]; δ_H (300 MHz, $CDCl_3$) 6.78–8.00 (16H, m, Ar), 6.49 (1H, br s, C=CH), 4.85 (1H, d, J = 9.9 Hz, 4-CH), 4.38–4.45 (1H, m, 4a-CH), 1.77–3.16 (10H, m, 5-CH_2, 6-CH_2, 7-CH_2, 3′-CH_2 and 5′-CH_2), 1.04–1.18 (1H, m, 4′-CH_2), 0.40–0.90 (1H, m, 4′-CH_2); δ_C (75 MHz, $CDCl_3$) 207.2, 202.6, 141.0, 138.2, 138.0, 137.4, 135.2, 134.8, 133.4, 130.5, 130.3, 129.7, 129.3, 128.2, 128.1, 128.0, 127.9, 126.8, 124.9, 122.2, 119.8, 83.2, 70.8, 65.9, 58.2, 48.4, 33.6, 30.0, 27.3, 25.5, 21.3.
14. Athimoolam, S.; Radha, V. A.; Bahadur, S. A.; Ranjith Kumar, R.; Perumal, S. *Acta Crystallogr., Sect. E.* **2008**, *64*, 95.