Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 64 (2008) 2962–2971
www.elsevier.com/locate/tet

A highly atom economic, chemo-, regio- and stereoselective synthesis, and discovery of spiro-pyrido-pyrrolizines and pyrrolidines as antimycobacterial agents

Raju Ranjith Kumar [a], Subbu Perumal [a,*], Palaniappan Senthilkumar [b], Perumal Yogeeswari [b], Dharmarajan Sriram [b]

[a] *Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625021, India*
[b] *Medicinal Chemistry Research Laboratory, Pharmacy Group, Birla Institute of Technology and Science, Pilani 333031, India*

Received 19 October 2007; received in revised form 3 January 2008; accepted 17 January 2008
Available online 25 January 2008

Abstract

The 1,3-dipolar cycloaddition of azomethine ylides derived from acenaphthenequinone and α-amino acids viz. proline, phenylglycine and sarcosine to a series of 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones afforded novel spiro-pyrido-pyrrolizines and pyrrolidines chemo-, regio- and stereoselectively in quantitative yields. These compounds were screened for their in vitro activity against *Mycobacterium tuberculosis* H37Rv (MTB), multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB) and *Mycobacterium smegmatis* using agar dilution method. Among the synthesized compounds, spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-(2-chlorophenylmethylidene)-1′-methyltetrahydro-4′(1*H*)-pyridinone-4-(2-chlorophenyl)hexahydro-1*H*-pyrrolizine (**3e**) was found to be the most active with a minimum inhibitory concentration (MIC) of 0.4 μg/mL against MTB and MDR-TB.

Keywords: 1,3-Dipolar cycloaddition; Atom economic; Azomethine ylide; Pyrrolidine; Pyrrolizines; Tetrahydropyridinone; Antimycobacterial activity

1. Introduction

1,3-Dipolar cycloadditions form a subject of intensive research in organic synthesis in view of their great synthetic potential.[1] In particular, the cycloaddition of nonstabilized azomethine ylides with olefins represents one of the most convergent approaches for the construction of pyrrolidines,[2] which are prevalent in a variety of biologically active compounds[3] and find utility in the treatment of diseases such as diabetes,[4] cancer[5] and viral infections.[6] The pyrrolizine substructure occurs in many natural products of potential use in medicine and agriculture.[7] Acenaphthenequinone is a versatile precursor for azomethine ylide cycloaddition as it reacts with various α-amino acids generating reactive 1,3-dipoles.[8]

The synthesis of spiro compounds has drawn considerable attention of chemists, in view of their very good antimycobacterial activity.[9,10] Nitrogen heterocycles such as pyridines,[11] pyrroles[12] and pyrazolines[13] were also reported to display antimycobacterial activities. Recently, we have reported an atom economic green synthesis and antimycobacterial activities of tetrahydro-4*H*-pyrano[3,2-*c*]pyridine derivatives, which inhibited in vitro *Mycobacterium tuberculosis* H37Rv (MTB) and multidrug resistant *M. tuberculosis* (MDR-TB).[14] The biological importance of spiro compounds and nitrogen heterocycles and our continued interest in the synthesis of novel heterocycles[15] led us to synthesize novel spiro heterocycles via 1,3-dipoar cycloaddition of azomethine ylides to a series of 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**1**),

* Corresponding author. Tel./fax: +91 452 2459845.
E-mail address: subbu.perum@gmail.com (S. Perumal).

0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.01.072

screen them for antimycobacterial activities, and report the results in this paper.

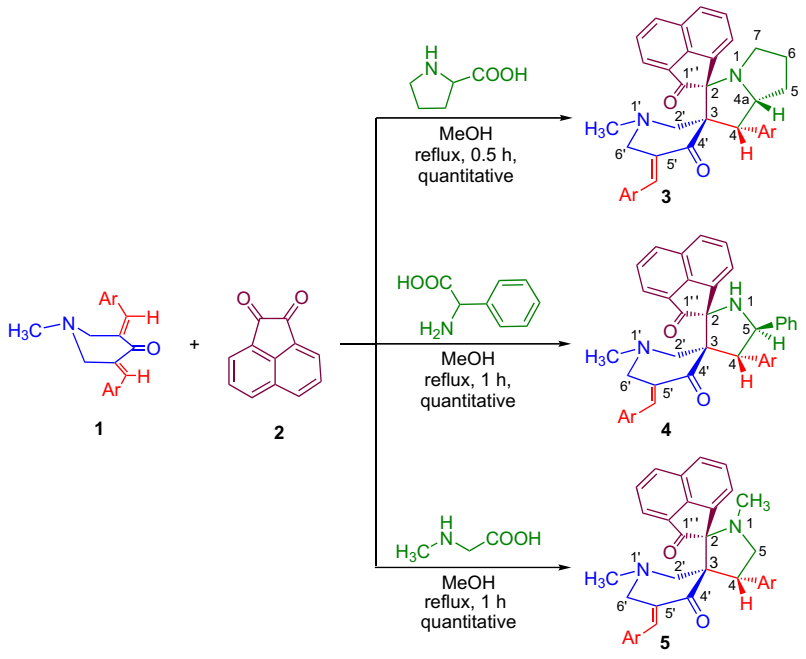
2. Results and discussion

2.1. Chemistry

In the present investigation, the 1,3-dipolar cycloaddition of an azomethine ylide generated in situ from acenaphthenequinone (**2**) and α-amino acids [(i) proline, (ii) phenylglycine and (iii) sarcosine] to **1a–i** afforded novel spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-arylmethylidene-1′-methyltetrahydro-4′(1*H*)-pyridinone-4-arylhexahydro-1*H*-pyrrolizines (**3a–i**), 4-aryl-5-phenylpyrrolo-(spiro[2.2″]acenaphthene-1″-one)-spiro[3.3′]-5′-arylmethylidene-1′-methyltetrahydro-4′(1*H*)-pyridinones (**4a–i**) and 1-methyl-4-arylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-arylmethylidene-1′-methyl tetrahydro-4′(1*H*)-pyridinones (**5a–i**), respectively (Scheme 1). All these reactions were effected by heating an equimolar mixture of the reactants to reflux in methanol on a water-bath. As these reactions afforded quantitative yield of product, no further purification was required. As the only by-products are water and carbon dioxide, the atom economy of these cycloadditions is very high. The quantitative yield in conjunction with high atom economy renders this protocol efficient and green.

All these cycloadditions proceed (i) regioselectively, as the electron rich carbon of the dipole adds to the β-carbon of the α,β-unsaturated moiety of **1**, (ii) chemoselectively, as the cycloaddition occurs on only one C=C of **1** ascribable to the steric hindrance exerted by **3–5** for the second cycloaddition and (iii) stereoselectively, as only one diastereomer is obtained exclusively in quantitative yields, although multiple stereocentres are present in each product **3–5**.

The structure of **3** was elucidated using ^{1}H, ^{13}C and 2D NMR spectroscopic data as discussed for **3a**. The ^{1}H NMR spectrum of **3a** has a doublet at 4.37 ppm (J=11.1 Hz) readily assignable to H-4 on the basis of multiplicity. From the H,H-COSY correlation with H-4, H-4a is assigned to the doublet of doublets of doublets at 4.75 ppm (J=11.1, 6.9 and 4.5 Hz).



Entry	Comp **1–5**	Ar	Yield (%)[a]		
			3	**4**	**5**
1	**a**	*p*-ClC_6H_4	97	98	97
2	**b**	*p*-$CH_3C_6H_4$	96	97	96
3	**c**	*p*-$CH_3OC_6H_4$	97	95	98
4	**d**	*p*-FC_6H_4	97	98	97
5	**e**	*o*-ClC_6H_4	96	96	98
6	**f**	*o*-$CH_3C_6H_4$	95	95	96
7	**g**	*o*-$CH_3OC_6H_4$	97	97	95
8	**h**	*m*-FC_6H_4	–	–	96
9	**i**	*o,p*-$Cl_2C_6H_3$	96	96	97

Scheme 1. Synthesis of spiro heterocycles **3–5**. [a]Yields were quantitative except the loss during workup.

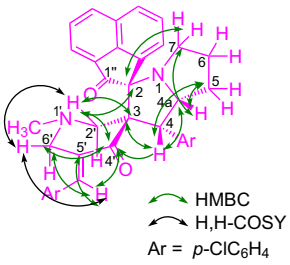
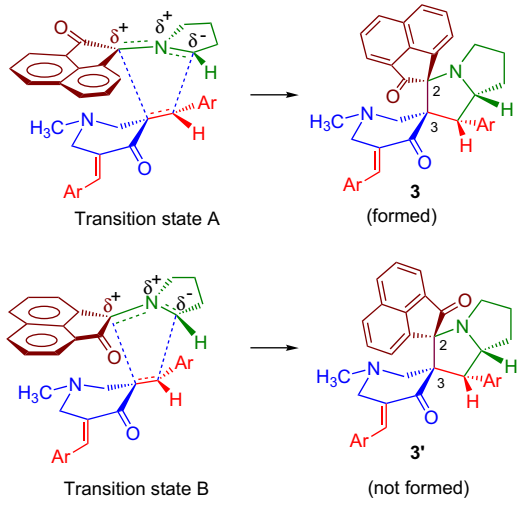


Figure 1. Selected HMBC correlations of **3a**.

The H-4 and H-4a are found in cis-relationship from the *J* value of 11.1 Hz. The C,H-COSY correlations assign the signals at 51.2 and 66.2 ppm to C-4 and C-4a, respectively. The 5- and 6-CH_2 hydrogens appear as multiplets in the range 1.60–2.15 ppm and the 7-CH_2 hydrogens afford multiplets at 2.55–2.64 and 3.14–3.22 ppm. Further, 7-CH_2 hydrogens show a HMBC correlation (Fig. 1) with a carbon signal at 77.4 ppm assigned to C-2 spiro carbon and hence the signal at 73.4 ppm is due to the other spiro carbon. The H-2′eq appears as a doublet of doublets at 3.38 ppm (*J*=12.3 and 1.8 Hz), the latter *J* value arising from the long range coupling (inferred from H,H-COSY spectrum) with H-6′eq, which appears as a multiplet at 2.55–2.64 ppm. The doublet at 1.78 ppm (*J*=12.3 Hz) is due to the H-2′ax. The H-6′ax appears as a doublet of doublets at 2.78 ppm (*J*=15.0 and 2.7 Hz), which has a H,H-COSY correlation with the broad singlet at 6.66 ppm (benzylidene proton) due to allylic coupling (*J*=2.7 Hz). From the C,H-COSY spectrum, the signals at 55.2 and 55.3 ppm are assigned to C-2′ and C-6′, respectively. The N–CH_3 protons appear as a singlet at 1.89 ppm.

It is pertinent to note that the chemical shifts of H-2′eq (3.38 ppm) and H-2′ax (1.78 ppm) of **3a** differ significantly (1.60 ppm). This suggests that presumably, H-2′eq is proximate to the carbonyl of spiroacenaphthylen-1(2*H*)-one ring shifting it downfield, while H-2′ax lies in the shielding zone of the spiroacenaphthylen-1(2*H*)-one ring shifting it upfield. This suggests that the two carbonyls linked to C-2 and C-3 of **3** are in *trans* relationship (Scheme 2). This stereoselectivity can be understood by the fact that the corresponding transition state (A) would require less free energy of activation than the transition state (B) leading to **3′** as the latter would result in electrostatic repulsion between the *cis* carbonyls increasing the free energy of activation (Scheme 2).

The assignment of proton and carbon signals of **4** and **5** has also been done by straightforward considerations as done for **3**. The ^{1}H, ^{13}C NMR chemical shifts and the HMBC correlations of **4a** and **5b**, helpful in the assignment of the chemical shifts of **4** and **5**, are shown in Figures 2 and 4, respectively. The structures of **4a** and **5a** deduced from NMR spectroscopic study have been further confirmed by the X-ray crystallographic study of their single crystals (Figs. 3 and 5). The structures of **4a**[16] and **5a**[17] in Figures 3 and 5 disclose that their stereochemistry is similar to that found for **3**.



Scheme 2. Stereochemistry of cycloadducts differing in their relative configurations at C-2 and C-3.

2.2. Pharmacology

The compounds were screened for their in vitro antimycobacterial activity against MTB and MDR-TB by agar dilution method for the determination of MIC in duplicates. The MDR-TB clinical isolate was resistant to isoniazid (INH), rifampicin, ethambutol and ciprofloxacin. The minimum inhibitory concentrations (MIC) of **3**–**5** along with that of the standard drugs for comparison are reported in Table 1.

In the first phase of screening, all the compounds showed excellent in vitro activity against MTB with a MIC of ≤12.5 μg/mL. Six compounds (**3e**, **3i**, **4e**, **5e**, **5h** and **5i**) inhibited MTB with a MIC of less than 1 μM and were more potent than standard fluoroquinolone ciprofloxacin (MIC: 1.56 μg/mL). The spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-(2-chlorophenylmethylidene)-1′-methyltetrahydro-4′(1*H*)-pyridinone-4-(2-chlorophenyl)hexahydro-1*H*-pyrrolizine (**3e**) was

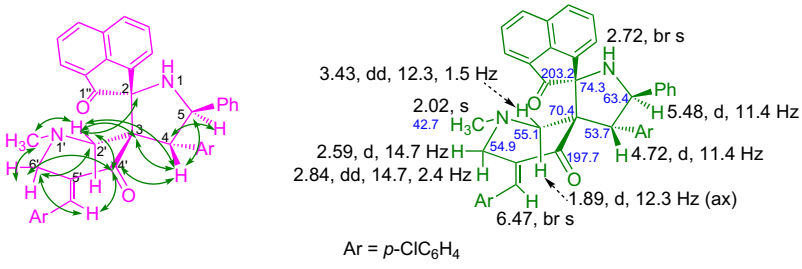


Figure 2. Selected HMBC correlations, ^{1}H and ^{13}C NMR chemical shifts of **4a**.

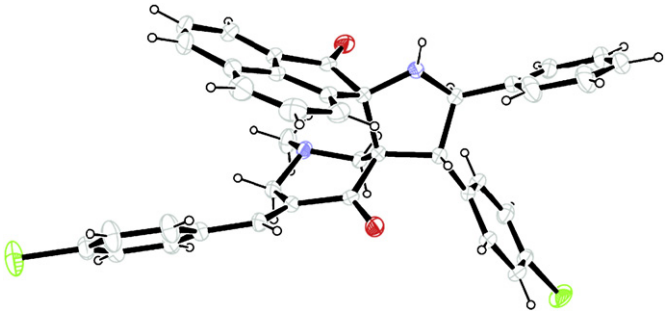


Figure 3. ORTEP diagram of **4a**.

found to be the most active compound in vitro with a MIC of 0.4 μg/mL against MTB and was four times more potent than ciprofloxacin.

Subsequently, some of the compounds were evaluated against MDR-TB, and all the eight compounds screened inhibited MDR-TB with MIC ranging from 0.4 to 3.13 μg/mL and were found to be more active than isoniazid (MIC: 1.56 μg/mL) and ciprofloxacin (MIC: 12.5 μg/mL). Five compounds (**3e**, **3i**, **4e**, **4i** and **5i**) inhibited MDR-TB with a MIC less than 1 μg/mL. Compounds **3e**, **3i**, **4e** and **4i** were found to be the most active ones in vitro with a MIC of 0.4 μg/mL against MDR-TB and were 4 and 31 times more potent than isoniazid and ciprofloxacin, respectively.

All the compounds were found to inhibit MC[2] with MIC ranging from 3.13 to 100 μg/mL and two of them, **3f** and **4f**, were found to be more active than isoniazid (MIC: 6.25 μg/mL). With respect to structure–MTB activity relationship, the results demonstrate that the antimycobacterial activity is enhanced by the presence of weakly electron-withdrawing halogens in the aryl rings, whilst introduction of electron-donating groups like methyl and methoxy diminished the activity.

3. Conclusions

In conclusion, a facile highly atom economic synthesis of novel spiro compounds has been achieved via 1,3-dipolar cycloaddition of azomethine ylides to 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones. These compounds display significant antimycobacterial activities. Further research on the synthesis and evaluation of antimycobacterial and other activities of structurally similar series of compounds is in progress in our research group. This will enable identification of new

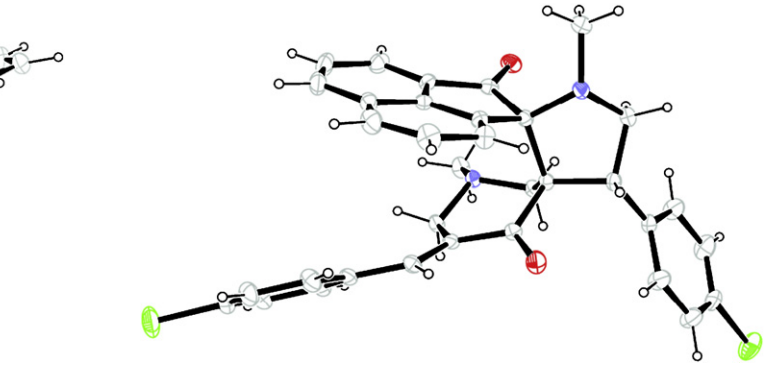


Figure 5. ORTEP diagram of **5a**.

potential leads and a broader application of the structure–activity relationships.

4. Experimental

4.1. Chemistry

The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H, ^{13}C and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. IR spectra were recorded on a JASCO FTIR instrument (KBr). Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHNS analyser.

4.2. General procedure for the synthesis of spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-arylmethylidene-1′-methyltetrahydro-4′(1H)-pyridinone-4-arylhexahydro-1H-pyrrolizines (3a–i)

A mixture of **1** (1 mmol), acenaphthenequinone **2** (1 mmol) and proline (1 mmol) was dissolved in methanol (15 mL) and heated to reflux 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 **3** as pale yellow solid.

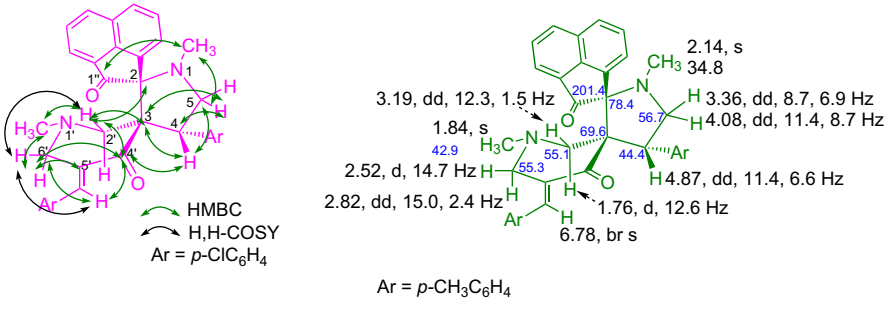


Figure 4. Selected HMBC correlations, ^{1}H and ^{13}C NMR chemical shifts of **5b**.

Table 1
Minimum inhibitory concentrations of **3**–**5** (μg/mL) against mycobacterial species

Comp.	MTB	MDR-TB	MC^2
3a	NT	NT	NT
3b	6.25	NT	25.0
3c	6.25	NT	100.0
3d	1.56	NT	50.0
3e	0.4	0.4	25.0
3f	1.56	NT	3.13
3g	3.13	NT	50.0
3i	0.78	0.4	25.0
4a	NT	NT	NT
4b	6.25	NT	12.5
4c	6.25	NT	25.0
4d	1.56	NT	6.25
4e	0.78	0.4	25.0
4f	3.13	NT	3.13
4g	12.5	NT	25.0
4i	0.78	0.4	25.0
5a	NT	NT	NT
5b	12.5	NT	50.0
5c	12.5	NT	12.5
5d	1.56	NT	25.0
5e	0.78	3.13	50.0
5f	12.5	NT	50.0
5g	12.5	NT	50.0
5h	0.78	1.56	25.0
5i	0.78	0.78	12.5
Isoniazid	0.05	1.56	6.25
Ciprofloxacin	1.56	12.5	0.78

MTB: *M. tuberculosis*; MDR-TB: multi-drug resistant *M. tuberculosis*; MC^2: *M. smegmatis*; NT: not tested.

*4.2.1. Spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-(4-chlorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone-4-(4-chlorophenyl)hexahydro-1H-pyrrolizine (**3a**)*

Obtained as yellow solid (0.32 g, 97%), mp 210–212 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 72.95; H, 5.01; N, 4.79. $C_{36}H_{30}Cl_2N_2O_2$ requires C, 72.85; H, 5.09; N, 4.72.] ν_{max} (KBr) 1675, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.66–7.86 (15H, m, Ar–H), 4.75 (1H, ddd, *J* 11.1, 6.9, 4.5 Hz, 4a-CH), 4.37 (1H, d, *J* 11.1 Hz, 4-CH), 3.34 (1H, dd, *J* 12.3, 1.8 Hz, 2′-CH_2), 3.14–3.22 (1H, m, 7-CH_2), 2.78 (1H, dd, *J* 15.0, 2.7 Hz, 6′-CH_2), 2.55–2.64 (2H, m, 6′-CH_2 and 7-CH_2), 1.93–2.15 (3H, m, 5-CH_2 and 6-CH_2), 1.89 (3H, s, N–CH_3), 1.78 (1H, d, *J* 12.3 Hz, 2′-CH_2), 1.60–1.71 (1H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 200.8, 198.4, 139.4, 136.5, 136.2, 135.4, 135.2, 134.6, 134.3, 133.1, 132.8, 132.6, 131.6, 130.9, 130.4, 129.5, 128.9, 128.4, 127.7, 127.5, 125.2, 119.1, 77.4, 73.4, 66.2, 55.3, 55.2, 51.2, 47.9, 43.1, 28.3, 25.8.

*4.2.2. Spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-(4-methylphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone-4-(4-methylphenyl)hexahydro-1H-pyrrolizine (**3b**)*

Obtained as yellow solid (0.33 g, 96%), mp 198–200 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 82.50; H, 6.77; N, 5.19. $C_{38}H_{36}N_2O_2$ requires C, 82.58; H, 6.65; N, 5.07.] ν_{max} (KBr) 1670, 1714 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.68–7.84 (14H, m, Ar–H), 6.78 (1H, s, C=CH), 4.80 (1H, ddd, *J* 11.1, 6.9, 4.5 Hz, 4a-CH), 4.40 (1H, d, *J* 11.1 Hz, 4-CH), 3.41 (1H, d, *J* 12.3 Hz, 2′-CH_2), 3.20–3.26 (1H, m, 7-CH_2), 2.83 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.61–2.65 (2H, m, 6′-CH_2 and 7-CH_2), 2.33 (3H, s, Ar–CH_3), 2.26 (3H, s, Ar–CH_3), 1.95–2.14 (3H, m, 5-CH_2 and 6-CH_2), 1.89 (3H, s, N–CH_3), 1.84 (1H, d, *J* 12.3 Hz, 2′-CH_2), 1.69–1.75 (1H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 200.9, 198.7, 139.5, 138.9, 136.9, 136.7, 136.3, 134.6, 134.4, 131.9, 131.8, 130.5, 130.2, 129.9, 129.4, 129.0, 128.8, 127.5, 127.4, 125.4, 124.9, 118.9, 77.9, 73.2, 66.3, 55.4, 55.3, 51.5, 48.2, 43.1, 28.4, 25.7, 21.3, 21.1.

*4.2.3. Spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-(4-methoxyphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone-4-(4-methoxyphenyl)hexahydro-1H-pyrrolizine (**3c**)*

Obtained as yellow solid (0.32 g, 97%), mp 192–195 °C. R_f (petroleum ether/EtOAc, 4:1) 0.35. [Found: C, 78.17; H, 6.32; N, 4.69. $C_{38}H_{36}N_2O_4$ requires C, 78.06; H, 6.21; N, 4.79.] ν_{max} (KBr) 1670, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.70–7.84 (15H, m, Ar–H), 4.76 (1H, ddd, *J* 11.1, 6.9, 4.5 Hz, 4a-CH), 4.39 (1H, d, *J* 11.1 Hz, 4-CH), 3.79 (3H, s, Ar–OCH_3), 3.75 (3H, s, Ar–OCH_3), 3.38 (1H, d, *J* 12.0 Hz, 2′-CH_2), 3.20–3.28 (1H, m, 7-CH_2), 2.83 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.58–2.63 (2H, m, 6′-CH_2 and 7-CH_2), 1.95–2.13 (3H, m, 5-CH_2 and 6-CH_2), 1.90 (3H, s, N–CH_3), 1.83 (1H, d, *J* 12.3 Hz, 2′-CH_2), 1.68–1.75 (1H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 200.9, 198.6, 159.8, 158.3, 139.4, 136.7, 136.6, 134.4, 132.3, 131.8, 130.6, 130.2, 130.1, 129.7, 129.4, 127.5, 127.3, 125.3, 124.8, 118.9, 113.6, 113.6, 77.9, 73.1, 66.4, 55.5, 55.2, 51.2, 48.2, 43.1, 28.4, 25.6.

*4.2.4. Spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-(4-fluorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone-4-(4-fluorophenyl)hexahydro-1H-pyrrolizine (**3d**)*

Obtained as yellow solid (0.33 g, 97%), mp 180–182 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 77.17; H, 5.30; N, 5.10. $C_{36}H_{30}F_2N_2O_2$ requires C, 77.12; H, 5.39; N, 5.00.] ν_{max} (KBr) 1670, 1710 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.75–7.88 (14H, m, Ar–H), 6.73 (1H, s, C=CH), 4.79 (1H, ddd, *J* 11.1, 6.9, 4.5 Hz, 4a-CH), 4.42 (1H, d, *J* 11.1 Hz, 4-CH), 3.42 (1H, d, *J* 12.3 Hz, 2′-CH_2), 3.18–3.27 (1H, m, 7-CH_2), 2.83 (1H, dd, *J* 14.7, 2.1 Hz, 6′-CH_2), 2.60–2.67 (2H, m, 6′-CH_2 and 7-CH_2), 1.99–2.19 (3H, m, 5-CH_2 and 6-CH_2), 1.93 (3H, s, N–CH_3), 1.82 (1H, d, *J* 12.3 Hz, 2′-CH_2), 1.68–1.76 (1H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 200.8, 198.5, 139.4, 136.6, 135.6, 134.4, 133.3, 132.4, 131.7, 131.6 (d, $^3J_{CF}$ 8.3 Hz), 130.5 (d, $^3J_{CF}$ 7.8 Hz), 130.2, 129.4, 127.7, 127.5, 125.2, 125.0, 119.0, 115.2 (d, $^2J_{CF}$ 21.5 Hz), 115.1 (d, $^2J_{CF}$ 20.9 Hz), 77.6, 73.3, 66.4, 55.2, 51.1, 47.9, 43.1, 28.3, 25.7.

*4.2.5. Spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-(2-chlorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone-4-(2-chlorophenyl)hexahydro-1H-pyrrolizine (**3e**)*

Obtained as yellow solid (0.31 g, 96%), mp 207–210 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 72.97; H, 5.17; N, 4.63. $C_{36}H_{30}Cl_2N_2O_2$ requires C, 72.85; H, 5.09; N, 4.72.] ν_{max} (KBr) 1675, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.76–8.04 (15H, m, Ar–H), 4.88–5.00 (2H, m, 4a-CH and 4-CH),

3.56–3.67 (1H, m, 7-CH_2), 3.27 (1H, dd, *J* 12.3, 1.8 Hz, 2′-CH_2), 2.82 (1H, dd, *J* 15.3, 2.7 Hz, 6′-CH_2), 2.58–2.66 (2H, m, 6′-CH_2 and 7-CH_2), 2.04–2.17 (2H, m, 5-CH_2), 1.76–1.86 (3H, m, 2′-CH_2 and 6-CH_2), 1.70 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 201.8, 198.3, 141.0, 136.2, 136.1, 134.8, 134.5, 134.2, 134.0, 133.8, 133.6, 133.3, 133.2, 130.6, 130.4, 130.3, 130.0, 129.9, 129.7, 129.6, 128.1, 127.9, 127.3, 126.6, 126.4, 126.3, 126.1, 124.8, 120.1, 78.7, 69.6, 68.6, 57.2, 55.6, 51.0, 48.9, 44.1, 28.8, 24.9.

*4.2.6. Spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-(2-methylphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone-4-(2-methylphenyl)hexahydro-1H-pyrrolizine (**3f**)*

Obtained as yellow solid (0.32 g, 95%), mp 198–200 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 82.66; H, 6.60; N, 5.01. $C_{38}H_{36}N_2O_2$ requires C, 82.58; H, 6.65; N, 5.07.] ν_{max} (KBr) 1670, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.73–8.08 (15H, m, Ar–H), 5.03 (1H, ddd, *J* 11.1, 6.9, 4.5 Hz, 4a-CH), 4.50 (1H, d, *J* 11.1 Hz, 4-CH), 3.40–3.47 (1H, m, 7-CH_2), 3.06 (1H, d, *J* 12.3 Hz, 2′-CH_2), 2.84 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.61–2.66 (1H, 7-CH_2), 2.53 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.31 (3H, s, Ar–CH_3), 2.20 (3H, s, Ar–CH_3), 1.85–2.30 (5H, m, 5-CH_2, 6-CH_2 and 2′-CH_2), 1.66 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 138.4, 137.6, 136.7, 136.6, 125.3, 133.4, 132.7, 130.5, 130.3, 130.0, 129.1, 128.9, 128.5, 128.1, 127.7, 127.5, 127.4, 126.5, 125.9, 125.6, 125.2, 124.8, 119.8, 78.4, 71.0, 69.1, 56.9, 49.5, 48.7, 43.8, 28.5, 25.1, 20.0, 19.9.

*4.2.7. Spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-(2-methoxyphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone-4-(2-methoxyphenyl)hexahydro-1H-pyrrolizine (**3g**)*

Obtained as yellow solid (0.32 g, 97%), mp 185–187 °C. R_f (petroleum ether/EtOAc, 4:1) 0.35. [Found: C, 78.10; H, 6.27; N, 4.85. $C_{38}H_{36}N_2O_4$ requires C, 78.06; H, 6.21; N, 4.79.] ν_{max} (KBr) 1675, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.66–8.10 (15H, m, Ar–H), 5.11 (1H, ddd, *J* 10.5, 6.9, 4.5 Hz, 4a-CH), 4.54 (1H, d, *J* 10.5 Hz, 4-CH), 3.84 (3H, s, Ar–OCH_3), 3.70–3.76 (4H, m, 7-CH_2 and Ar–OCH_3), 3.07 (1H, d, *J* 12.0 Hz, 2′-CH_2), 2.80 (1H, dd, *J* 15.0, 2.1 Hz, 6′-CH_2), 2.64–2.68 (1H, m, 7-CH_2), 2.54 (1H, d, *J* 15.0 Hz, 6′-CH_2), 1.94–2.34 (5H, m, 5-CH_2, 6-CH_2 and 2′-CH_2), 1.66 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 201.9, 198.7, 158.4, 141.5, 136.8, 132.7, 132.3, 130.2, 130.1, 129.8, 129.6, 127.7, 127.5, 127.2, 126.9, 124.5, 124.2, 120.4, 119.9, 119.7, 119.5, 110.7, 110.4, 109.8, 78.0, 69.8, 65.8, 55.4, 55.3, 54.6, 48.9, 48.5, 28.3, 24.6.

*4.2.8. Spiro-[2.2″]acenaphthene-1″-one-spiro[3.3′]-5′-(2,4-dichlorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone-4-(2,4-dichlorophenyl)hexahydro-1H-pyrrolizine (**3i**)*

Obtained as yellow solid (0.30 g, 96%), mp 215–218 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 65.39; H, 4.17; N, 4.29. $C_{36}H_{28}Cl_4N_2O_2$ requires C, 65.27; H, 4.26; N, 4.23.] ν_{max} (KBr) 1674, 1715 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.68–8.01 (13H, m, Ar–H), 4.86–4.93 (2H, m, 4a-CH and 4-CH), 3.53–3.60 (1H, m, 7-CH_2), 3.21 (1H, d, *J* 12.6 Hz, 2′-CH_2), 2.79 (1H, dd, *J* 15.6, 2.1 Hz, 6′-CH_2), 2.53–2.65 (2H, m, 7-CH_2 and 6′-CH_2), 1.79–2.25 (5H, m, 5-CH_2, 6-CH_2 and 2′-CH_2), 1.70 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 202.7, 197.9, 140.6, 136.8, 136.3, 134.9, 134.6, 134.1, 134.0, 133.8, 133.5, 133.1, 133.0, 130.9, 130.4, 130.1, 130.0, 129.8, 129.7, 129.6, 128.1, 127.7, 127.3, 126.9, 126.3, 126.2, 126.1, 124.1, 119.6, 77.9, 68.6, 67.1, 57.9, 55.1, 51.7, 48.1, 44.2, 28.7, 24.1.

*4.3. General procedure for the synthesis of 4-aryl-5-phenylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-arylmethylidene-1′-methyltetrahydro-4′(1H)-pyridinones (**4a–i**)*

A mixture of **1** (1 mmol), acenaphthenequinone **2** (1 mmol) and phenylglycine was dissolved in methanol (10 mL) and heated to reflux 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.

*4.3.1. 4-(4-Chlorophenyl)-5-phenylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(4-chlorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**4a**)*

Obtained as yellow solid (0.34 g, 98%), mp 190–191 °C. R_f (petroleum ether/EtOAc, 4:1) 0.45. [Found: C, 74.30; H, 4.87; N, 4.40. $C_{39}H_{30}Cl_2N_2O_2$ requires C, 74.40; H, 4.80; N, 4.45.] ν_{max} (KBr) 3310, 1677, 1724 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.59–7.82 (19H, m, Ar–H), 6.47 (1H, s, C=CH), 5.48 (1H, d, *J* 11.4 Hz, 5-CH), 4.72 (1H, d, *J* 11.4 Hz, 4-CH), 3.43 (1H, dd, *J* 12.3, 1.5 Hz, 2′-CH_2), 2.84 (1H, dd, *J* 14.7, 2.4 Hz, 6′-CH_2), 2.72 (1H, br s, 1-NH), 2.59 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.02 (3H, s, N–CH_3), 1.89 (1H, d, *J* 12.3 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 203.2, 197.7, 140.6, 140.2, 138.3, 135.2, 135.1, 134.6, 134.5, 132.8, 132.7, 132.6, 130.8, 129.8, 129.2, 128.4, 128.3, 127.9, 127.7, 127.6, 124.8, 123.1, 118.1, 74.3, 70.4, 63.4, 55.1, 54.9, 53.7, 42.7.

*4.3.2. 4-(4-Methylphenyl)-5-phenylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(4-methylphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**4b**)*

Obtained as yellow solid (0.36 g, 97%), mp 182–184 °C. R_f (petroleum ether/EtOAc, 4:1) 0.45. [Found: C, 83.71; H, 6.07; N, 4.71. $C_{41}H_{36}N_2O_2$ requires C, 83.64; H, 6.16; N, 4.76.] ν_{max} (KBr) 3312, 1670, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.57–7.77 (19H, m, Ar–H), 6.56 (1H, s, C=CH), 5.48 (1H, d, *J* 11.4 Hz, 5-CH), 4.73 (1H, d, *J* 11.4 Hz, 4-CH), 3.43 (1H, d, *J* 12.3 Hz, 2′-CH_2), 2.85 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.62 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.24 (6H, s, Ar–CH_3), 1.99 (3H, s, N–CH_3), 1.91 (1H, d, *J* 12.3 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 203.1, 197.8, 141.2, 140.4, 138.8, 138.3, 136.7, 136.2, 134.6, 133.7, 131.6, 131.5, 129.8, 129.7, 129.3, 129.1, 128.8, 128.7, 128.4, 128.2, 127.8, 127.7, 127.4, 124.6, 123.1, 117.8, 74.6, 70.6, 63.5, 55.1, 55.0, 53.9, 42.7, 21.3, 21.0.

*4.3.3. 4-(4-Methoxyphenyl)-5-phenylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(4-methoxyphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**4c**)*

Obtained as yellow solid (0.33 g, 95%), mp 175–177 °C. R_f (petroleum ether/EtOAc, 4:1) 0.30. [Found: C, 79.40; H, 5.78; N, 4.59. $C_{41}H_{36}N_2O_4$ requires C, 79.33; H, 5.85; N, 4.51.] ν_{max} (KBr) 3310, 1677, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.68–7.75 (19H, m, Ar–H), 6.54 (1H, s, C=CH), 5.45 (1H, d, *J* 11.4 Hz, 5-CH), 4.70 (1H, d, *J* 11.4 Hz, 4-CH), 3.73 (3H, s, Ar–OCH_3), 3.72 (3H, s, Ar–OCH_3), 3.40 (1H, d, *J* 12.0 Hz, 2′-CH_2), 2.86 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.59 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.00 (3H, s, N–CH_3), 1.91 (1H, d, *J* 12.0 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 203.0, 197.7, 159.8, 158.2, 141.2, 140.5, 138.3, 136.4, 134.6, 131.7, 130.4, 130.3, 129.8, 129.1, 128.8, 128.3, 128.2, 127.8, 127.6, 127.4, 127.1, 124.6, 123.1, 117.8, 113.4, 74.6, 70.5, 63.6, 55.2, 55.0, 54.9, 53.6, 42.7.

*4.3.4. 4-(4-Fluorophenyl)-5-phenylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(4-fluorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**4d**)*

Obtained as yellow solid (0.36 g, 98%), mp 170–171 °C. R_f (petroleum ether/EtOAc, 4:1) 0.45. [Found: C, 78.57; H, 5.00; N, 4.63. $C_{39}H_{30}F_2N_2O_2$ requires C, 78.51; H, 5.07; N, 4.70.] ν_{max} (KBr) 3315, 1670, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.62–7.78 (19H, m, Ar–H), 6.47 (1H, s, C=CH), 5.44 (1H, d, *J* 11.4 Hz, 5-CH), 4.70 (1H, d, *J* 11.4 Hz, 4-CH), 3.41 (1H, dd, *J* 12.3, 1.5 Hz, 2′-CH_2), 2.82 (1H, dd, *J* 14.7, 2.4 Hz, 6′-CH_2), 2.69 (1H, br s, 1-NH), 2.57 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.00 (3H, s, N–CH_3), 1.86 (1H, d, *J* 12.3 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 203.1, 197.7, 163.3, 140.8, 140.3, 138.3, 135.4, 134.5, 132.4, 132.1, 131.6 (d, $^3J_{CF}$ 8.3 Hz), 130.9 (d, $^3J_{CF}$ 7.8 Hz), 130.4, 129.8, 129.1, 128.4, 128.3, 127.8, 127.7, 124.7, 123.1, 118.0, 115.2 (d, $^2J_{CF}$ 21.5 Hz), 115.0 (d, $^2J_{CF}$ 20.8 Hz), 74.4, 70.3, 63.6, 55.1, 54.9, 53.6, 42.7.

*4.3.5. 4-(2-Chlorophenyl)-5-phenylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(2-chlorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**4e**)*

Obtained as yellow solid (0.33 g, 96%), mp 199–200 °C. R_f (petroleum ether/EtOAc, 4:1) 0.45. [Found: C, 74.47; H, 4.86; N, 4.51. $C_{39}H_{30}Cl_2N_2O_2$ requires C, 74.40; H, 4.80; N, 4.45.] ν_{max} (KBr) 3310, 1677, 1724 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.79–8.31 (20H, m, Ar–H), 5.64 (1H, d, *J* 9.6 Hz, 5-CH), 5.31 (1H, d, *J* 9.9 Hz, 4-CH), 3.05 (1H, d, *J* 12.3 Hz, 2′-CH_2), 2.86 (1H, d, *J* 15.3 Hz, 6′-CH_2), 2.68 (1H, d, *J* 15.3 Hz, 6′-CH_2), 1.93 (1H, d, *J* 12.3 Hz, 2′-CH_2), 1.67 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 204.7, 198.0, 141.1, 140.8, 138.0, 136.0, 134.9, 134.5, 134.2, 134.1, 133.5, 133.3, 132.9, 132.7, 130.8, 130.4, 130.3, 130.0, 129.9, 129.7, 128.5, 127.7, 126.7, 126.4, 126.1, 124.8, 123.9, 122.1, 119.9, 66.5, 65.9, 57.2, 56.6, 55.9, 53.0, 44.5.

*4.3.6. 4-(2-Methylphenyl)-5-phenylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(2-methylphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**4f**)*

Obtained as yellow solid (0.35 g, 95%), mp 176–178 °C. R_f (petroleum ether/EtOAc, 4:1) 0.45. [Found: C, 83.70; H, 6.09; N, 4.70. $C_{41}H_{36}N_2O_2$ requires C, 83.64; H, 6.16; N, 4.76.] ν_{max} (KBr) 3311, 1671, 1727 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.52–7.95 (20H, m, Ar–H), 5.52 (1H, d, *J* 10.8 Hz, 5-CH), 5.03 (1H, d, *J* 10.8 Hz, 4-CH), 3.54 (1H, d, *J* 12.0 Hz, 2′-CH_2), 2.84 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.65 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.26 (3H, s, Ar–CH_3), 1.95–2.00 (4H, m, Ar–CH_3 and 2′-CH_2), 1.88 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 203.9, 198.1, 141.4, 139.7, 138.3, 137.6, 136.5, 135.6, 133.9, 132.2, 130.5, 130.0, 129.2, 128.6, 128.5, 128.2, 128.1, 127.8, 127.4, 127.3, 126.5, 125.4, 125.2, 124.7, 123.8, 119.1, 75.8, 68.3, 66.5, 57.2, 55.5, 52.1, 43.8, 20.7, 19.9.

*4.3.7. 4-(2-Methoxyphenyl)-5-phenylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(2-methoxyphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**4g**)*

Obtained as yellow solid (0.34 g, 97%), mp 193–195 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 79.43; H, 5.77; N, 4.57. $C_{41}H_{36}N_2O_4$ requires C, 79.33; H, 5.85; N, 4.51.] ν_{max} (KBr) 3310, 1677, 1722 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.70–7.78 (19H, m, Ar–H), 6.57 (1H, s, C=CH), 5.48 (1H, d, *J* 11.4 Hz, 5-CH), 4.73 (1H, d, *J* 11.4 Hz, 4-CH), 3.75 (3H, s, Ar–OCH_3), 3.74 (3H, s, Ar–OCH_3), 3.42 (1H, d, *J* 12.3 Hz, 2′-CH_2), 2.89 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.62 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.03 (3H, s, N–CH_3), 1.94 (1H, d, *J* 12.3 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 203.0, 197.8, 159.8, 158.2, 141.2, 140.5, 138.3, 136.5, 134.6, 131.7, 130.4, 130.3, 129.8, 129.1, 128.8, 128.4, 128.2, 127.8, 127.7, 127.5, 127.1, 124.6, 123.1, 117.8, 113.5, 113.4, 74.6, 70.6, 63.6, 55.2, 55.1, 53.6, 42.7.

*4.3.8. 4-(2,4-Dichlorophenyl)-5-phenylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(2,4-dichlorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**4i**)*

Obtained as yellow solid (0.31 g, 96%), mp 210–211 °C. R_f (petroleum ether/EtOAc, 4:1) 0.45. [Found: C, 67.01; H, 4.00; N, 4.09. $C_{39}H_{28}Cl_4N_2O_2$ requires C, 67.06; H, 4.04; N, 4.01.] ν_{max} (KBr) 3311, 1677, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.74–8.12 (18H, m, Ar–H), 5.59 (1H, d, *J* 9.9 Hz, 5-CH), 5.27 (1H, d, *J* 9.9 Hz, 4-CH), 3.05 (1H, d, *J* 12.3 Hz, 2′-CH_2), 2.86 (1H, dd, *J* 15.3, 2.4 Hz, 6′-CH_2), 2.67 (1H, d, *J* 15.3 Hz, 6′-CH_2), 1.94 (1H, d, *J* 12.3 Hz, 2′-CH_2), 1.71 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 204.1, 197.6, 140.5, 137.8, 136.6, 135.6, 135.0, 134.6, 133.9, 133.3, 133.1, 132.7, 131.7, 131.3, 130.9, 130.4, 130.1, 129.6, 129.4, 128.6, 128.5, 127.9, 127.6, 127.0, 126.6, 124.9, 123.9, 120.0, 76.8, 66.2, 66.0, 57.2, 55.8, 52.5, 44.5.

*4.4. General procedure for the synthesis of 1-methyl-4-arylpyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-arylmethylidene-1′-methyltetrahydro-4′(1H)-pyridinones (**5a–i**)*

A mixture of **1** (1 mmol), acenaphthenequinone **2** (1 mmol) and sarcosine (1 mmol) was dissolved in methanol (10 mL) and heated to reflux for 1 h. After completion of the reaction as evident from TLC, the mixture was cooled to room temperature, poured into water (50 mL), the precipitated solid was

filtered and washed with water (100 mL) to obtain pure **5** as yellow solid.

*4.4.1. 1-Methyl-4-(4-chlorophenyl)pyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(4-chlorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**5a**)*

Obtained as yellow solid (0.30 g, 97%), mp 187–189 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 71.91; H, 4.90; N, 4.99. $C_{34}H_{28}Cl_2N_2O_2$ requires C, 71.96; H, 4.97; N, 4.94.] ν_{max} (KBr) 1672, 1724 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.64–7.83 (15H, m, Ar–H), 4.84 (1H, dd, *J* 11.1, 6.3 Hz, 4-CH), 4.04 (1H, dd, *J* 11.4, 8.7 Hz, 5-CH_2), 3.37 (1H, dd, *J* 8.7, 6.6 Hz, 5-CH_2), 3.15 (1H, dd, *J* 12.3, 2.1 Hz, 2′-CH_2), 2.78 (1H, dd, *J* 15.0, 2.7 Hz, 6′-CH_2), 2.48 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.16 (3H, s, 1-N–CH_3), 1.85 (3H, s, 1′-N–CH_3), 1.71 (1H, d, *J* 12.3 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 201.3, 197.9, 139.7, 138.4, 136.9, 135.6, 134.8, 134.5, 132.9, 132.8, 132.5, 130.9, 130.2, 129.8, 129.3, 128.4, 128.3, 128.2, 127.7, 124.8, 123.9, 117.5, 78.2, 69.6, 56.6, 55.4, 55.0, 44.1, 42.8, 34.8.

*4.4.2. 1-Methyl-4-(4-methylphenyl)pyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(4-methylphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**5b**)*

Obtained as yellow solid (0.32 g, 96%), mp 153–155 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 82.00; H, 6.60; N, 5.39. $C_{36}H_{34}N_2O_2$ requires C, 82.10; H, 6.51; N, 5.32.] ν_{max} (KBr) 1670, 1724 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.65–7.81 (14H, m, Ar–H), 6.78 (1H, br s, C=CH), 4.87 (1H, dd, *J* 11.4, 6.6 Hz, 4-CH), 4.08 (1H, dd, *J* 11.4, 8.7 Hz, 5-CH_2), 3.36 (1H, dd, *J* 8.7, 6.9 Hz, 5-CH_2), 3.19 (1H, dd, *J* 12.3, 1.5 Hz, 2′-CH_2), 2.82 (1H, dd, *J* 15.0, 2.4 Hz, 6′-CH_2), 2.52 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.33 (3H, s, Ar–CH_3), 2.26 (3H, s, Ar–CH_3), 2.14 (3H, s, 1-N–CH_3), 1.84 (3H, s, 1′-N–CH_3), 1.76 (1H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 201.4, 198.1, 139.7, 138.7, 138.6, 137.0, 136.2, 135.3, 134.9, 131.8, 131.6, 129.8, 129.7, 129.2, 128.9, 128.8, 128.7, 127.5, 124.7, 124.0, 117.2, 78.4, 69.6, 56.7, 55.3, 55.1, 44.4, 42.9, 34.8, 21.3, 21.1.

*4.4.3. 1-Methyl-4-(4-methoxyphenyl)pyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(4-methoxyphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**5c**)*

Obtained as yellow solid (0.31 g, 98%), mp 194–196 °C. R_f (petroleum ether/EtOAc, 4:1) 0.30. [Found: C, 77.50; H, 6.04; N, 4.95. $C_{36}H_{34}N_2O_4$ requires C, 77.40; H, 6.13; N, 5.01.] ν_{max} (KBr) 1672, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.68–7.80 (15H, m, Ar–H), 4.85 (1H, dd, *J* 11.4, 6.3 Hz, 4-CH), 4.05 (1H, t, *J* 10.8 Hz, 5-CH_2), 3.79 (3H, s, Ar–OCH_3), 3.74 (3H, s, Ar–OCH_3), 3.36 (1H, t, *J* 7.8 Hz, 5-CH_2), 3.15 (1H, d, *J* 12.3 Hz, 2′-CH_2), 2.83 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.50 (1H, d, *J* 14.7 Hz, 6′-CH_2), 2.16 (3H, s, 1-N–CH_3), 1.85 (3H, s, 1′-N–CH_3), 1.75 (1H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 201.4, 198.0, 159.8, 158.3, 139.7, 138.6, 136.8, 134.9, 131.8, 130.4, 130.3, 129.8, 129.7, 129.2, 128.2, 127.5, 127.3, 124.6, 123.9, 117.2, 113.6, 113.5, 78.4, 69.6, 56.9, 55.2, 44.0, 42.9, 34.8.

*4.4.4. 1-Methyl-4-(4-fluorophenyl)pyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(4-fluorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**5d**)*

Obtained as yellow solid (0.31 g, 97%), mp 184–186 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 76.33; H, 5.20; N, 5.29. $C_{34}H_{28}F_2N_2O_2$ requires C, 76.39; H, 5.28; N, 5.24.] ν_{max} (KBr) 1670, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.70–7.82 (15H, m, Ar–H), 4.85 (1H, dd, *J* 11.4, 6.6 Hz, 4-CH), 4.04 (1H, dd, *J* 11.1, 9.0 Hz, 5-CH_2), 3.38 (1H, dd, *J* 8.4, 6.9 Hz, 5-CH_2), 3.15 (1H, d, *J* 12.0 Hz, 2′-CH_2), 2.78 (1H, dd, *J* 15.0, 2.1 Hz, 6′-CH_2), 2.48 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.16 (3H, s, 1-N–CH_3), 1.85 (3H, s, 1′-N–CH_3), 1.70 (1H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 201.3, 198.0, 139.7, 138.5, 135.8, 134.8, 134.0, 132.1, 131.7 (d, $^3J_{CF}$ 8.2 Hz), 130.6, 130.3 (d, $^3J_{CF}$ 7.4 Hz), 129.8, 129.3, 128.2, 127.6, 124.8, 123.9, 117.4, 115.2 (d, $^2J_{CF}$ 21.5 Hz), 115.0 (d, $^2J_{CF}$ 20.8 Hz), 78.2, 69.6, 56.8, 55.4, 55.0, 44.0, 42.8, 34.8.

*4.4.5. 1-Methyl-4-(2-chlorophenyl)pyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(2-chlorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**5e**)*

Obtained as yellow solid (0.31 g, 98%), mp 175–176 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 72.03; H, 5.07; N, 5.01. $C_{34}H_{28}Cl_2N_2O_2$ requires C, 71.96; H, 4.97; N, 4.94.] ν_{max} (KBr) 1678, 1729 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.58–8.17 (15H, m, Ar–H), 5.17 (1H, t, *J* 7.5 Hz, 4-CH), 3.90 (1H, t, *J* 7.8 Hz, 5-CH_2), 3.64 (1H, t, *J* 7.8 Hz, 5-CH_2), 2.87 (1H, d, *J* 12.6 Hz, 2′-CH_2), 2.78 (1H, dd, *J* 15.0, 2.4 Hz, 6′-CH_2), 2.59 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.05 (3H, s, 1-N–CH_3), 1.79 (1H, d, *J* 12.6 Hz, 2′-CH_2), 1.65 (3H, s, 1′-N–CH_3); δ_C (75 MHz, $CDCl_3$) 204.0, 197.2, 140.9, 137.8, 136.6, 135.4, 134.6, 134.2, 134.0, 133.7, 133.4, 130.7, 130.4, 130.2, 129.7, 129.6, 129.5, 129.2, 128.6, 127.9, 127.3, 126.9, 126.0, 125.1, 124.6, 118.3, 79.6, 67.2, 59.8, 57.0, 55.4, 43.9, 41.9, 35.0.

*4.4.6. 1-Methyl-4-(2-methylphenyl)pyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(2-methylphenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**5f**)*

Obtained as yellow solid (0.32 g, 96%), mp 173–175 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 82.03; H, 6.57; N, 5.37. $C_{36}H_{34}N_2O_2$ requires C, 82.10; H, 6.51; N, 5.32.] ν_{max} (KBr) 1672, 1724 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.50–7.95 (15H, m, Ar–H), 5.06 (1H, dd, *J* 9.6, 7.5 Hz, 4-CH), 4.05 (1H, t, *J* 9.3 Hz, 5-CH_2), 3.48 (1H, t, *J* 7.5 Hz, 5-CH_2), 3.20 (1H, d, *J* 12.6 Hz, 2′-CH_2), 2.74 (1H, dd, *J* 15.0, 2.7 Hz, 6′-CH_2), 2.54 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.37 (3H, s, Ar–CH_3), 2.07 (3H, s, Ar–CH_3), 2.01 (3H, s, 1-N–CH_3), 1.71 (3H, s, 1′-N–CH_3), 1.65 (1H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 203.7, 198.1, 140.7, 137.8, 137.7, 137.5, 137.3, 136.6, 134.3, 134.0, 132.4, 130.3, 130.1, 130.0, 129.1, 128.5, 128.4, 128.1, 127.5, 126.5, 125.8, 125.2, 124.8, 124.6, 118.1, 79.4, 67.5, 59.7, 57.3, 55.4, 43.8, 41.3, 34.8, 21.0, 20.0.

*4.4.7. 1-Methyl-4-(2-methoxyphenyl)pyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(2-methoxyphenyl-methylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**5g**)*

Obtained as yellow solid (0.30 g, 95%), mp 180–181 °C. R_f (petroleum ether/EtOAc, 4:1) 0.30. [Found: C, 77.48; H, 6.21; N, 5.10. $C_{36}H_{34}N_2O_4$ requires C, 77.40; H, 6.13; N, 5.01.] ν_{max} (KBr) 1678, 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.55–7.91 (15H, m, Ar–H), 4.96 (1H, dd, *J* 9.9, 7.5 Hz, 4-CH), 4.18 (1H, t, *J* 9.9 Hz, 5-CH_2), 3.79 (3H, s, Ar–OCH_3), 3.72 (3H, s, Ar–OCH_3), 3.45 (1H, t, *J* 7.8 Hz, 5-CH_2), 2.89 (1H, d, *J* 12.3 Hz, 2′-CH_2), 2.76 (1H, d, *J* 15.3 Hz, 6′-CH_2), 2.49 (1H, d, *J* 15.3 Hz, 6′-CH_2), 2.10 (3H, s, 1-N–CH_3), 1.85 (1H, d, *J* 12.6 Hz, 2′-CH_2), 1.66 (3H, s, 1′-N–CH_3); δ_C (75 MHz, $CDCl_3$) 203.7, 197.0, 157.9, 140.7, 137.8, 134.4, 132.6, 132.0, 130.0, 129.8, 129.7, 129.6, 128.8, 128.4, 127.9, 127.5, 127.1, 125.4, 124.2, 120.4, 119.6, 117.5, 110.4, 109.9, 79.3, 67.2, 57.3, 55.4, 55.3, 55.2, 54.8, 43.6, 39.4, 35.0.

*4.4.8. 1-Methyl-4-(3-fluorophenyl)pyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(3-fluorophenylmethylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**5h**)*

Obtained as yellow solid (0.30 g, 96%), mp 162–163 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 76.48; H, 5.21; N, 5.31. $C_{34}H_{28}F_2N_2O_2$ requires C, 76.39; H, 5.28; N, 5.24.] ν_{max} (KBr) 1672, 1721 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.37–7.85 (14H, m, Ar–H), 6.67 (1H, s, C=CH), 4.86 (1H, dd, *J* 11.4, 6.3 Hz, 4-CH), 4.06 (1H, dd, *J* 11.1, 8.7 Hz, 5-CH_2), 3.39 (1H, dd, *J* 8.4, 6.9 Hz, 5-CH_2), 3.19 (1H, d, *J* 12.6 Hz, 2′-CH_2), 2.79 (1H, dd, *J* 15.0, 2.4 Hz, 6′-CH_2), 2.51 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.17 (3H, s, 1-N–CH_3), 1.86 (3H, s, 1′-N–CH_3), 1.73 (1H, d, *J* 12.3 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 201.1, 197.8, 160.5, 140.9 (d, $^3J_{CF}$ 7.1 Hz), 139.7, 138.3, 136.6 (d, $^3J_{CF}$ 8.2 Hz), 135.5, 134.8, 133.4, 129.8 (d, $^3J_{CF}$ 7.8 Hz), 129.6 (d, $^3J_{CF}$ 8.9 Hz), 129.3, 128.3, 127.7, 125.4, 124.9, 124.6, 123.9, 117.5, 115.9 (d, $^2J_{CF}$ 21.5 Hz), 115.6 (d, $^2J_{CF}$ 21.6 Hz), 115.3 (d, $^2J_{CF}$ 20.9 Hz), 113.7 (d, $^2J_{CF}$ 20.9 Hz), 78.1, 69.7, 56.4, 55.3, 54.8, 44.4, 42.8, 34.8.

*4.4.9. 1-Methyl-4-(2,4-dichlorophenyl)pyrrolo-(spiro[2.2″]-acenaphthene-1″-one)-spiro[3.3′]-5′-(2,4-dichlorophenyl-methylidene)-1′-methyltetrahydro-4′(1H)-pyridinone (**5i**)*

Obtained as yellow solid (0.29 g, 97%), mp 178–180 °C. R_f (petroleum ether/EtOAc, 4:1) 0.40. [Found: C, 64.10; H, 4.03; N, 4.47. $C_{34}H_{26}Cl_4N_2O_2$ requires C, 64.17; H, 4.12; N, 4.40.] ν_{max} (KBr) 1672, 1724 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.48–8.17 (12H, m, Ar–H), 7.15 (1H, s, C=CH), 5.07 (1H, t, *J* 6.9 Hz, 4-CH), 3.77 (1H, t, *J* 6.6 Hz, 5-CH_2), 3.65 (1H, t, *J* 7.5 Hz, 5-CH_2), 2.83 (1H, d, *J* 12.3 Hz, 2′-CH_2), 2.76 (1H, dd, *J* 15.0, 2.4 Hz, 6′-CH_2), 2.55 (1H, d, *J* 15.0 Hz, 6′-CH_2), 2.03 (3H, s, 1-N–CH_3), 1.77 (1H, d, *J* 12.3 Hz, 2′-CH_2), 1.69 (3H, s, 1′-N–CH_3); δ_C (75 MHz, $CDCl_3$) 203.6, 197.0, 140.7, 136.7, 136.3, 135.8, 135.3, 134.8, 134.1, 134.0, 132.9, 132.8, 131.7, 131.6, 130.5, 130.3, 130.2, 129.5, 128.9, 128.5, 127.5, 127.2, 126.5, 125.0, 124.8, 118.4, 79.3, 67.4, 60.3, 57.0, 55.4, 43.9, 41.4, 35.0.

4.5. Pharmacology

All compounds were screened for their in vitro antimycobacterial activity against MTB, MDR-TB and MC^2 in Middlebrook 7H11 agar 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 duplicate.[18] The MDR-TB clinical isolate was obtained from Tuberculosis Research Center, Chennai, India. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of a compound required to completely inhibit the bacterial growth.

Acknowledgements

S.P. thanks the Department of Science and Technology, New Delhi for funds under (i) major research project No. SR/S1/OC-70/2006 (ii) IRHPA programme for the purchase of a high resolution NMR spectrometer and (iii) FIST programme and the University Grants Commission, New Delhi for funds under the DRS and ASIST programmes.

References and notes

1. (a) Karthikeyan, K.; Perumal, P. T.; Etti, S.; Shanmugam, G. *Tetrahedron* **2007**, *63*, 10581; (b) Bortolini, O.; Nino, A. D.; Maiuolo, L.; Russo, B.; Sindona, G.; Tocci, A. *Tetrahedron Lett.* **2007**, *48*, 7125; (c) Hong, X.; France, S.; Padwa, A. *Tetrahedron* **2007**, *63*, 5962.
2. (a) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, NY, 1984; (b) Dondas, H. A.; Fishwick, C. W. G.; Grigg, R.; Kilner, C. *Tetrahedron* **2004**, *60*, 3473; (c) Boruah, M.; Konwar, D.; Sharma, S. D. *Tetrahedron Lett.* **2007**, *48*, 4535; (d) Kawashima, K.; Kakehi, A.; Noguchi, M. *Tetrahedron* **2007**, *63*, 1630.
3. (a) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265; (b) O'Hagan, D. *Nat. Prod. Rep.* **1997**, 637.
4. Horri, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038.
5. (a) Spearman, M. A.; Jamieson, J. C.; Wright, J. A. *Exp. Cell Res.* **1987**, *168*, 116; (b) Tsukamoto, K.; Uno, A.; Shimada, S.; Imokaw, G. *Clin. Res.* **1989**, *37A*, 722.
6. (a) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Mamgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229; (b) Fleet, G. W. J. *FEBS Lett.* **1988**, *237*, 128.
7. (a) Liddell, J. R. *Nat. Prod. Rep.* **1998**, *15*, 363; (b) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619; (c) Takahata, H.; Momose, T. *The Alkaloids*; Cordell, G. A., Ed.; Academic: New York, NY, 1993; Vol. 26, p 327.
8. (a) Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 305; (b) Ramesh, E.; Kathiresan, M.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 1835; (c) Aravindan, P. G.; Selvanayagam, S.; Velmurugan, D.; Ravikumar, K.; Sridhar, G.; Raghunathan, R. *Acta Crystallogr., Sect. E* **2004**, *60*, 2149.
9. Chande, M. S.; Verma, R. S.; Barve, P. A.; Khanwelkar, R. R. *Eur. J. Med. Chem.* **2005**, *40*, 1143.
10. Dandia, A.; Sati, M.; Arya, K.; Sharma, R.; Loupy, A. *Chem. Pharm. Bull.* **2003**, *51*, 1137.
11. Sriram, D.; Yogeeswari, P.; Madhu, K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 876.
12. Biava, M.; Porretta, G. C.; Poce, G.; Supino, S.; Deidda, D.; Pompei, R.; Molicotti, P.; Manetti, F.; Botta, M. *J. Med. Chem.* **2006**, *49*, 4946.
13. Shaharyar, M.; Siddiqui, A. A.; Ali, M. A.; Sriram, D.; Yogeeswari, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3947.
14. Ranjith Kumar, R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6459.

15. (a) Ranjith Kumar, R.; Perumal, S. *Tetrahedron* **2007**, *63*, 7850, 12220; (b) Suresh Kumar, R.; Perumal, S.; Kagan, H. B.; Guillot, R. *Tetrahedron: Asymmetry* **2007**, *18*, 170; (c) Ranjith Kumar, R.; Perumal, S.; Kagan, H. B.; Guillot, R. *Tetrahedron* **2006**, *62*, 12380.
16. Athimoolam, S.; Ranjith Kumar, R.; Vijaya, K.; Sayee Kannan, R.; Perumal, S. *Acta Crystallogr., Sect. E* **2007**, *63*, 4635.
17. Pandiarajan, S.; Saravanamoorthy, S. N.; Ravi Kumar, B.; Ranjith Kumar, R.; Athimoolam, S. *Acta Crystallogr., Sect. E* **2008**, *64*, 99.
18. National Committee for Clinical Laboratory Standards. *Antimycobacterial Susceptibility Testing for Mycobacterium tuberculosis. Proposed Standard M24-T*; National Committee for Clinical Laboratory Standards: Villanova, PA, 1995.