Discovery of Antimycobacterial Spiro-piperidin-4-ones: An Atom Economic, Stereoselective Synthesis and Biological Intervention

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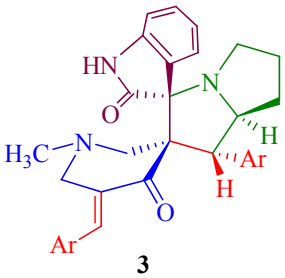
Supplementary Data



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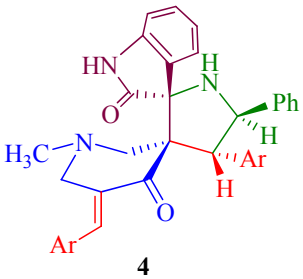

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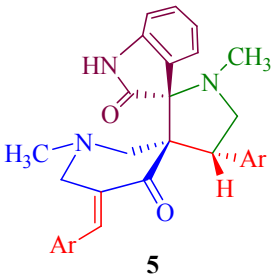

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Experimental

General

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 ^{o}C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

Synthesis of spiro-[2.3″]-oxindole-spiro[3.3′]-1′-methyl-5′-(arylidene)tetrahydro-4′-(1*H*)-pyridinone-4-arylhexahydro-1*H*-pyrrolizine (3).

General procedure. A mixture of **1** (1 mmol), isatin **2** (0.147 g, 1 mmol) and proline (0.115 g, 1 mmol) was dissolved in methanol (10 mL) and warmed on a water bath for 1–2 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 to obtain pure **3**.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(phenylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-phenylhexahydro-1*H*-pyrrolizine (3a). Obtained as white solid (0.46 g, 95%), m.p. 116–117 ^{o}C; [Found: C, 78.57; H, 6.46; N, 8.50. $C_{32}H_{31}N_3O_2$ requires C, 78.50; H, 6.38; N, 8.58%]; δ_H (300 MHz, $CDCl_3$) 8.51 (1 H, s, NH), 6.92 (1 H, s, C═CH-Ar), 6.71–7.44 (13 H, m Ar), 4.72 (1 H, ddd, *J* 11.2, 7.2, 4.2 Hz, 4a-CH), 4.38 (1 H, d, *J* 11.2 Hz, 4-CH), 3.60 (1 H, dd, *J* 12.3, 2.1 Hz, 2′-CH_2), 3.41 (1 H, d, *J* 14.4 Hz, 6′-CH_2), 3.13–3.21 (1 H, m, 7-CH_2), 2.88 (1 H, dd, *J* 14.4, 2.7 Hz, 6′-CH_2), 2.58–2.65 (1 H, m, 7-CH_2), 2.05 (3 H, s, N-CH_3), 1.89–2.17 (3 H, m, 5-CH_2 and 6-CH_2), 1.78 (1 H, d, *J* 12.3 Hz, 2′-CH_2), 1.65–1.73 (1 H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 198.2, 179.0, 140.9, 136.6, 135.9, 134.1, 132.9, 128.9, 128.4, 128.0, 127.8, 127.6, 127.3, 127.2, 125.8, 125.3, 120.0, 108.3, 73.3, 70.0, 64.7, 55.7, 55.4, 51.3, 46.9, 43.5, 27.2, 24.5.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(4-chlorophenylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(4-chlorophenyl)hexahydro-1*H*-pyrrolizine (3b). Obtained as white solid (0.52 g, 93%), m.p. 115–117 ^{o}C; [Found: C, 68.89; H, 5.31; N, 7.60. $C_{32}H_{29}Cl_2N_3O_2$ requires C, 68.82; H, 5.23; N, 7.52%]; δ_H (300 MHz, $CDCl_3$) 7.90 (1 H, s, NH), 6.65–7.28 (13 H, m Ar), 4.63 (1 H, ddd, *J* 4.2, 7.2, 11.2 Hz, 4a-CH), 4.32 (1 H, d, *J* 11.2 Hz, 4-CH), 3.51 (1 H, dd, *J* 12.3, 2.1 Hz, 2′-CH_2), 3.33 (1 H, d, *J* 14.4 Hz, 6′-CH_2), 3.14 (1 H, q, *J* 8.6 Hz, 7-CH_2), 2.87 (1 H, dd, *J* 14.4, 2.4 Hz, 6′-CH_2), 2.58 (1 H, td, *J* 8.6, 3.0 Hz, 7-CH_2), 2.09 (3 H, s, N-CH_3), 1.84–2.06 (3 H, m, 5-CH_2 and 6-CH_2), 1.75 (1 H, d, *J* 12.3 Hz, 2′-CH_2),

1.56–1.64 (1 H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 198.9, 179.1, 141.7, 136.0, 134.7, 134.1, 133.3, 132.6, 131.0, 130.6, 128.9, 128.5, 128.4, 126.1, 121.0, 109.2, 73.9, 70.6, 65.6, 56.7, 56.4, 51.5, 47.8, 44.6, 27.8, 25.2.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(4-methylphenylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(4-methylphenyl)hexahydro-1*H*-pyrrolizine (3c). Obtained as white solid (0.49 g, 95%), m.p. 114–115 ^oC; [Found: C, 78.77; H, 6.71; N, 8.19. $C_{34}H_{35}N_3O_2$ requires C, 78.89; H, 6.81; N, 8.12%]; δ_H (300 MHz, $CDCl_3$) 8.75 (1 H, s, NH), 6.67–7.27 (13 H, m Ar), 4.68 (1 H, ddd, *J* 3.9, 6.9, 11.1 Hz, 4a-CH), 4.33 (1 H, d, *J* 11.4 Hz, 4-CH), 3.55 (1 H, d, *J* 12.0 Hz, 2′-CH_2), 3.39 (1 H, d, *J* 14.1 Hz, 6′-CH_2), 3.17 (1 H, q, *J* 8.7 Hz, 7-CH_2), 2.88 (1 H, dd, *J* 14.4, 2.4 Hz, 6′-CH_2), 2.57 (1 H, td, *J* 8.7, 2.7 Hz,7-CH_2), 2.34 (3 H, s, Ar-CH_3), 2.32 (3 H, s, Ar-CH_3), 2.05 (3 H, s, N-CH_3), 1.80–2.11 (3 H, m, 5-CH_2 and 6-CH_2), 1.78 (1 H, d, *J* 12.3 Hz, 2′-CH_2), 1.63–1.70 (1 H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 199.2, 180.1, 142.0, 138.9, 137.1, 136.3, 134.4, 133.1, 132.3, 130.5, 130.0, 129.2, 128.9, 128.7, 126.3, 120.9, 109.3, 74.4, 70.7, 65.7, 56.8, 56.3, 52.0, 48.0, 44.5, 28.2, 25.3, 21.3, 21.1.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(4-methoxyphenylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(4-chlorophenyl)hexahydro-1*H*-pyrrolizine (3d). Obtained as white solid (0.50 g, 92%), m.p.105–106 ^oC; [Found: C, 74.23; H, 6.45; N, 7.68. $C_{34}H_{35}N_3O_4$ requires C, 74.29; H, 6.42; N, 7.64%]; δ_H (300 MHz, $CDCl_3$) 9.06 (1 H, s, NH), 6.67–7.29 (13 H, m Ar), 4.63–4.70 (1 H, m, 4a-CH), 4.30 (1 H, d, *J* 11.1 Hz, 4-CH), 3.78 (3 H, s, Ar-OCH_3), 3.77 (3 H, s, Ar-OCH_3), 3.53 (1 H, d, *J* 12.0 Hz, 2′-CH_2), 3.38 (1 H, d, *J* 14.1 Hz, 6′-CH_2), 3.13–3.21 (1 H, m, 7-CH_2), 2.87 (1 H, d, *J* 14.4 Hz, 6′-CH_2), 2.55–2.60 (1 H, m, 7-CH_2), 2.04 (3 H, s, N-CH_3), 1.85–1.97 (3 H, m, 5-CH_2 and 6-CH_2), 1.77 (1 H, d, *J* 12.0 Hz, 2′-CH_2), 1.63–1.69 (1 H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 199.1, 180.3, 159.9, 158.3, 142.1, 136.9, 131.9, 130.3, 129.5, 128.9, 128.7, 127.7, 126.3, 120.8, 113.7, 113.6, 109.3, 74.5, 70.4, 65.8, 56.9, 56.3, 55.2, 55.1, 51.7, 48.1, 44.6, 28.2, 25.8.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(4-fluorophenylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(4-fluorophenyl)hexahydro-1*H*-pyrrolizine (3e). Obtained as white solid (0.50 g, 96%), m.p. 110–111 ^{o}C; [Found: C, 73.25; H, 5.67; N, 8.07. $C_{32}H_{29}F_2N_3O_2$ requires C, 73.13; H, 5.56; N, 7.99%]; δ_H (300 MHz, $CDCl_3$) 8.81 (1 H, s, NH), 6.69–7.33 (13 H, m Ar), 4.59–4.66 (1 H, m, 4a-CH), 4.32 (1 H, d, *J* 11.4 Hz, 4-CH), 3.52 (1 H, d, *J* 12.3 Hz, 2′-CH_2), 3.34 (1 H, d, *J* 14.4 Hz, 6′-CH_2), 3.09–3.17 (1 H, m, 7-CH_2), 2.85 (1 H, dd, *J* 14.4, 2.4 Hz, 6′-CH_2), 2.54–2.60 (1 H, m, 7-CH_2), 2.05 (3 H, s, N-CH_3), 1.83–1.99 (3 H, m, 5-CH_2 and 6-CH_2), 1.72 (1 H, d, *J* 12.3 Hz, 2′-CH_2), 1.59–1.70 (1 H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 199.0, 180.0, 142.0, 135.9, 133.5, 133.1, 132.3, 131.7, 131.1, 130.7, 128.9, 126.2, 120.9, 115.7, 115.1, 109.4, 74.2, 70.6, 65.8, 56.6, 56.3, 51.5, 47.9, 44.5, 28.1, 25.3.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(2-chlorophenylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(2-chlorophenyl)hexahydro-1*H*-pyrrolizine (3f). Obtained as white solid (0.53 g, 96%), m.p. 112–114 ^{o}C; [Found: C, 68.87; H, 5.10; N, 7.44. $C_{32}H_{29}Cl_2N_3O_2$ requires C, 68.82; H, 5.23; N, 7.52%]; δ_H (300 MHz, $CDCl_3$) 8.66 (1 H, s, NH), 6.70–7.87 (13 H, m Ar), 4.80–4.89 (2 H, m, 4a-CH and 4-CH), 3.50–3.58 (1 H, m, 7-CH_2), 3.29 (1 H, d, *J* 12.3 Hz, 2′-CH_2), 3.14 (1 H, d, *J* 14.7 Hz, 6′-CH_2), 2.92 (1 H, dd, *J* 14.7, 2.4 Hz, 6′-CH_2), 2.56–2.62 (1 H, m, 7-CH_2), 2.04–2.10 (2 H, m, 5-CH_2), 1.94 (3 H, s, N-CH_3), 1.73–1.86 (3 H, m, 2′-CH_2 and 6-CH_2); δ_C (75 MHz, $CDCl_3$) 198.5, 178.5, 142.0, 136.2, 136.1, 135.0, 134.7, 134.2, 134.0, 133.5, 130.7, 129.8, 129.7, 129.5, 129.2, 128.6, 127.8, 126.6, 126.4, 126.2, 121.9, 109.2, 75.6, 67.7, 67.5, 58.0, 57.0, 51.1, 47.9, 45.2, 28.7, 24.9.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(2-methylphenylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(2-methylphenyl)hexahydro-1*H*-pyrrolizine (3g). Obtained as white solid (0.47 g, 92%), m.p.98–99 ^{o}C; [Found: C, 79.02; H, 6.94; N, 8.17. $C_{34}H_{35}N_3O_2$ requires C, 78.89; H, 6.81; N, 8.12%]; δ_H (300 MHz, $CDCl_3$) 8.88 (1 H, s, NH), 6.74–7.71 (13 H, m Ar), 4.77–4.83 (1 H, m, 4a-CH), 4.62 (1 H, d, *J* 10.5 Hz, 4-CH), 3.62 (1 H, d, *J* 12.6 Hz, 2′-

CH_2), 3.37–3.45 (1 H, m, 7-CH_2), 3.18 (1 H, d, *J* 14.7 Hz, 6′-CH_2), 2.87 (1 H, dd, *J* 14.7, 2.4 Hz, 6′-CH_2), 2.56–2.63 (1 H, m, 7-CH_2), 2.38 (3 H, s, Ar-CH_3), 2.16 (3 H, s, Ar-CH_3), 2.00–2.09 (5 H, s, N-CH_3, 5-CH_2 and 6-CH_2), 1.80–1.90 (1 H, m, 5-CH_2), 1.74 (1 H, d, *J* 12.6 Hz, 2′-CH_2), 1.63–1.72 (1 H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 199.4, 179.1, 142.3, 138.3, 137.9, 136.9, 136.8, 134.2, 133.2, 130.4, 130.1, 129.3, 129.0, 128.7, 128.3, 126.6, 125.6, 125.3, 121.3, 109.4, 75.1, 68.6, 68.2, 58.3, 57.1, 49.7, 47.9, 45.0, 28.3, 24.9, 21.1, 20.1.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(2-methoxyphenylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(2-methoxyphenyl)hexahydro-1*H*-pyrrolizine (3h). Obtained as white solid (0.52 g, 95%), m.p. 105–107 ^oC; [Found: C, 74.43; H, 6.56; N, 7.70. $C_{34}H_{35}N_3O_4$ requires C, 74.29; H, 6.42; N, 7.64%]; δ_H (300 MHz, $CDCl_3$) 8.66 (1 H, s, NH), 7.76 (1 H, s, C═CH), 6.67–7.53 (12 H, m Ar), 4.95–5.02 (1 H, m, 4a-CH), 4.41 (1 H, d, *J* 11.1 Hz, 4-CH), 3.83 (3 H, s, Ar-OCH_3), 3.71 (3 H, s, Ar-OCH_3), 3.56–3.64 (1 H, m, 7-CH_2), 3.18–3.25 (2 H, m, 2′-CH_2 and 6′-CH_2), 2.91 (1 H, dd, *J* 15.0, 2.1 Hz, 6′-CH_2), 2.59–2.64 (1 H, m, 7-CH_2), 2.16–2.25 (1 H, m, 5-CH_2), 1.94 (3 H, s, N-CH_3), 1.70–1.88 (4 H, m, 2′-CH_2, 5-CH_2 and 6-CH_2); δ_C (75 MHz, $CDCl_3$) 198.6, 178.8, 158.4, 158.2, 142.2, 133.0, 132.6, 130.2, 129.8, 129.6, 128.5, 128.2, 127.4, 127.1, 126.7, 124.5, 121.2, 120.4, 119.8, 110.5, 109.7, 109.0, 75.0, 67.5, 64.6, 57.3, 56.6, 55.3, 54.3, 48.4, 47.9, 45.0, 28.2, 24.5.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(3-fluorophenylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(3-fluorophenyl)hexahydro-1*H*-pyrrolizine (3i). Obtained as white solid (0.50 g, 96%), m.p. 123–124 ^oC; [Found: C, 73.06; H, 5.50; N, 8.05. $C_{32}H_{29}F_2N_3O_2$ requires C, 73.13; H, 5.56; N, 7.99%]; δ_H (300 MHz, $CDCl_3$) 8.43 (1 H, s, NH), 6.62–7.29 (13 H, m Ar), 4.58–4.66 (1 H, m, 4a-CH), 4.32 (1 H, d, *J* 11.4 Hz, 4-CH), 3.53 (1 H, dd, *J* 12.3, 1.8 Hz, 2′-CH_2), 3.35 (1 H, d, *J* 14.4 Hz, 6′-CH_2), 3.07–3.17 (1 H, m, 7-CH_2), 2.85 (1 H, dd, *J* 14.4, 2.7 Hz, 6′-CH_2), 2.53–2.60 (1 H, m, 7-CH_2), 2.05 (3 H, s, N-CH_3), 1.83–2.99 (3 H, m, 5-CH_2 and 6-CH_2), 1.72 (1 H, d, *J* 12.3 Hz, 2′-CH_2), 1.59–1.68 (1 H, m, 5-CH_2); δ_C (75

MHz, $CDCl_3$) 198.8, 179.6, 164.0, 161.1, 141.9, 140.1, 137.0, 135.8, 134.7, 129.8, 129.7, 128.9, 126.1, 125.5, 125.0, 121.1, 116.3, 116.1, 115.6, 113.8, 109.4, 74.0, 70.9, 65.6, 56.5, 56.2, 51.8, 47.8, 44.5, 28.0, 25.3.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(2,4-dichlorophenylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(2,4-dichlorophenyl)hexahydro-1*H*-pyrrolizine (3j). Obtained as white solid (0.58 g, 92%), m.p. 112–114 ^{o}C; [Found: C, 61.20; H, 4.22; N, 6.77. $C_{32}H_{27}Cl_4N_3O_2$ requires C, 61.26; H, 4.34; N, 6.70%]; δ_H (300 MHz, $CDCl_3$) 8.77 (1 H, s, NH), 6.69–7.82 (11 H, m Ar), 4.76 (2 H, s, 4a-CH and 4-CH), 3.46–3.51 (1 H, m, 7-CH_2), 3.23 (1 H, d, *J* 12.3 Hz, 2′-CH_2), 3.09 (1 H, d, *J* 15.0 Hz, 6′-CH_2), 2.91 (1 H, d, *J* 15.0 Hz, 6′-CH_2), 2.56–2.62 (1 H, m, 7-CH_2), 2.07 (2 H, br s, 5-CH_2), 1.96 (3 H, s, N-CH_3), 1.67–1.86 (3 H, m, 2′-CH_2 and 6-CH_2).

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(2-thienylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(2-thienyl)hexahydro-1*H*-pyrrolizine (3k). Obtained as white solid (0.45 g, 90%), m.p.106–107 ^{o}C; [Found: C, 66.95; H, 5.50; N, 8.32. $C_{28}H_{27}N_3O_2S_2$ requires C, 67.04; H, 5.42; N, 8.38%]; δ_H (300 MHz, $CDCl_3$) 8.96 (1 H, s, NH), 6.71–7.46 (11 H, m Ar), 4.60–4.67 (2 H, m, 4a-CH and 4-CH), 3.58 (1 H, d, *J* 12.3 Hz, 2′-CH_2), 3.50 (1 H, d, *J* 15.3 Hz, 6′-CH_2), 3.12–3.20 (1 H, m, 7-CH_2), 2.96 (1 H, dd, *J* 15.3, 2.4 Hz, 6′-CH_2), 2.55–2.62 (1 H, m, 7-CH_2), 1.94 (4 H, s, N-CH_3 and 5-CH_2), 1.96 (1 H, d, *J* 12.3 Hz, 2′-CH_2), 1.84–1.91 (2 H, m, 6-CH_2), 1.69–1.79 (1 H, m, 5-CH_2); δ_C (75 MHz, $CDCl_3$) 197.5, 180.0, 141.9, 140.4, 138.3, 132.8, 130.5, 129.7, 129.5, 128.9, 127.8, 126.8, 126.0, 125.7, 123.9, 120.9, 109.4, 74.7, 69.8, 67.3, 56.6, 55.2, 48.4, 48.1, 44.6, 28.3, 25.2.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(1-naphthylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(1-naphthyl)hexahydro-1*H*-pyrrolizine (3l). Obtained as white solid (0.54 g, 92%), m.p. 109–110 ^{o}C; [Found: C, 81.56; H, 6.08; N, 7.21. $C_{40}H_{35}N_3O_2$ requires C, 81.47; H, 5.98; N, 7.13%]; δ_H (300 MHz, $CDCl_3$) 8.75 (1 H, s, NH), 6.75–8.57 (19 H, m Ar), 5.27 (1

H, d, *J* 10.5 Hz, 4-CH), 5.00–5.09 (1 H, m, 4a-CH), 3.67 (1 H, d, *J* 12.0 Hz, 2′-CH_2), 3.53–3.61 (1 H, m, 7-CH_2), 3.09 (1 H, d, *J* 14.7 Hz, 6′-CH_2), 2.64–2.74 (2 H, m, 6′-CH_2 and 7-CH_2), 2.03–2.10 (2 H, m, 5-CH_2), 1.91 (4 H, s, N-CH_3 and 6-CH_2), 1.66–1.73 (1 H, m, 6-CH_2), 1.59 (1 H, d, *J* 12.0 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 199.1, 178.9, 142.4, 136.6, 134.8, 134.2, 134.0, 133.7, 133.2, 132.5, 131.2, 129.2, 128.9, 128.7, 128.4, 127.4, 127.0, 126.7, 126.3, 126.1, 125.4, 125.3, 125.1, 124.9, 121.5, 109.6, 77.3, 75.0, 68.9, 68.2, 58.1, 56.8, 48.0, 44.9, 28.1, 24.9.

Spiro[2.3″]oxindole-spiro[3.3′]-1′-methyl-5′-(2-furylmethylidene)tetrahydro-4′(1*H*)-pyridinone-4-(2-furyl)hexahydro-1*H*-pyrrolizine (3m). Obtained as white solid (0.44 g, 95%), m.p.146–147 ^oC; [Found: C, 71.73; H, 5.20; N, 8.84. $C_{28}H_{27}N_3O_4$ requires C, 71.62; H, 5.08; N, 8.95%]; δ_H (300 MHz, $CDCl_3$) 9.12 (1 H, s, NH), 6.20–7.44 (11 H, m Ar), 4.55–4.67 (1 H, m, 4a-CH), 4.41 (1 H, d, *J* 10.8 Hz, 4-CH), 3.56–3.60 (2 H, m 2′-CH_2 and 6′-CH_2), 3.12–3.24 (1 H, m, 7-CH_2), 3.02 (1 H, d, *J* 16.2, 6′-CH_2), 2.57–2.64 (1 H, m, 7-CH_2), 2.13 (4 H, s, N-CH_3 and 5-CH_2), 1.65–2.05 (4 H, m, 2′-CH_2, 6-CH_2, and 5-CH_2).

Synthesis of 4-aryl-5-phenylpyrrolo(spiro[2.3″]-oxindole)-spiro[3.3′]-1′-methyl-5′-(arylidene)piperidin-4′-ones (4).

General procedure. A mixture of **1** (1 mmol), isatin **2** (0.147 g, 1 mmol) and phenylglycine (0.151 g, 1 mmol) in methanol (10 mL) was 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 to obtain pure **4**. The yield, melting point and NMR spectroscopic data of **4a–f** and **4k–m** agree well with those reported by our group earlier.[17]

4-(2-Methylphenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methyl-5′-(2-methylphenylmethylidene)piperidin-4′-one (4g). Obtained as white solid (0.53 g, 95%), m.p. 166–167 ^oC; [Found: C, 80.36; H, 6.30; N, 7.70. $C_{37}H_{35}N_3O_2$ requires C, 80.26; H, 6.37; N, 7.59%]; δ_H (300 MHz, $CDCl_3$) 7.94 (1 H, br s, 1″-NH), 6.69–7.56 (18 H, m, Ar-H), 5.51 (1

H, d, *J* 9.9 Hz, 5-CH), 4.91 (1 H, d, *J* 9.9 Hz, 4-CH), 3.37 (1 H, d, *J* 12.9 Hz, 2′-CH_2), 3.21 (1 H, d, *J* 15.0 Hz, 6′-CH_2), 2.94 (1 H, dd, *J* 15.0, 2.7 Hz, 6′-CH_2), 2.18 (3 H, s, Ar-CH_3), 2.14 (3 H, s, Ar-CH_3), 2.01 (3 H, s, N-CH_3), 1.82 (1 H, d, *J* 12.9 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 199.3, 180.0, 141.5, 141.3, 138.0, 136.9, 136.2, 134.2, 132.9, 130.1, 129.3, 128.7, 128.4, 128.3, 127.4, 126.8, 126.4, 125.7, 125.4, 122.3, 109.1, 73.3, 65.9, 65.0, 58.4, 57.2, 53.1, 45.4, 21.0, 20.1.

4-(2-Methoxyphenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methyl-5′-(2-methoxyphenylmethylidene)piperidin-4′-one (4h). Obtained as white solid (0.55 g, 94%), m.p. 190–191 ^oC; [Found: C, 75.80; H, 6.14; N, 7.11. $C_{37}H_{35}N_3O_4$ requires C, 75.88; H, 6.02; N, 7.17%]; δ_H (300 MHz, $CDCl_3$) 7.78 (1 H, br s, 1″-NH), 6.67–7.68 (18 H, m, Ar-H), 5.51 (1 H, d, *J* 9.9 Hz, 5-CH), 4.92 (1 H, d, *J* 9.9 Hz, 4-CH), 3.85 (3 H, s, Ar-OCH_3), 3.68 (3 H, s, Ar-OCH_3), 3.26 (1 H, d, *J* 15.0 Hz, 6′-CH_2), 2.97 (1 H, d, *J* 15.0 Hz, 6′-CH_2), 1.98 (3 H, s, N-CH_3), 1.96 (1 H, d, *J* 12.3 Hz, 2′-CH_2).

4-(3-Fluorophenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methyl-5′-(3-fluorophenylmethylidene)piperidin-4′-one (4i). Obtained as white solid (0.54 g, 96%), m.p. 159–161 ^oC; [Found: C, 74.76; H, 5.29; N, 7.40. $C_{35}H_{29}F_2N_3O_2$ requires C, 74.85; H, 5.20; N, 7.48%]; δ_H (300 MHz, $CDCl_3$) 8.02 (1 H, br s, 1″-NH), 6.78–7.67 (18 H, m, Ar-H), 5.53 (1 H, d, *J* 9.9 Hz, 5-CH), 4.95 (1 H, d, *J* 9.9 Hz, 4-CH), 3.30 (1 H, d, *J* 12.9 Hz, 2′-CH_2), 3.20 (1 H, d, *J* 15.0 Hz, 6′-CH_2), 2.93 (1 H, d, *J* 15.0 Hz, 6′-CH_2), 2.00 (3 H, s, N-CH_3), 1.80 (1 H, d, *J* 12.9 Hz, 2′-CH_2).

4-(2,4-Dichlorophenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methyl-5′-(2,4-dichlorophenylmethylidene)piperidin-4′-one (4j). Obtained as white solid (0.63 g, 95%), m.p. 189–190 ^oC; [Found: C, 63.27; H, 4.00; N, 6.40. $C_{35}H_{27}Cl_4N_3O_2$ requires C, 63.36; H, 4.10; N, 6.33%]; δ_H (300 MHz, $CDCl_3$) 8.01 (1 H, br s, 1″-NH), 6.93–7.71 (18 H, m, Ar-H), 5.55 (1 H, d, *J* 9.3 Hz, 5-CH), 5.07 (1 H, d, *J* 9.3 Hz, 4-CH), 3.16 (1 H, d, *J* 15.0 Hz, 6′-CH_2),

2.96–3.01 (2 H, m, 2′-CH_2 and 6′-CH_2), 1.97 (3 H, s, N-CH_3), 1.93 (1 H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.4, 178.6, 141.4, 140.5, 136.7, 135.9, 135.1, 134.8, 134.1, 133.5, 133.0, 131.8, 131.4, 130.5, 129.7, 129.0, 128.8, 128.6, 127.9, 127.6, 127.5, 127.1, 126.7, 126.5, 122.7, 109.1, 74.3, 65.3, 64.0, 57.8, 57.1, 53.3, 45.6.

Synthesis of 1-methyl-4-arylpyrrolo-(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(arylidene)piperidin-4′-ones (5).

General procedure. A mixture of **1** (1 mmol), isatin **2** (0.147 g, 1 mmol) and sarcosine (0.089 g, 1 mmol) were 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 to obtain pure **5**. The physical and spectroscopic data of **5a–d** agree well with those reported in the literature.[20]

1-Methyl-4-(4-fluorophenyl)pyrrolo-(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(4-fluorophenylmethylidene)piperidin-4′-one (5e). Obtained as white solid (0.45 g, 91%), m.p. 178–179 ^oC; [Found: C, 72.19; H, 5.39; N, 8.47. $C_{30}H_{27}F_2N_3O_2$ requires C, 72.13; H, 5.45; N, 8.41%]; δ_H (300 MHz, $CDCl_3$) 8.56 (1 H, s, NH), 6.67–7.39 (13 H, m, Ar), 4.80 (1 H, dd, *J* 10.8, 10.8 Hz, 4-CH), 3.89 (1 H, t, *J* 10.8 Hz, 5-CH_2), 3.25–3.35 (3 H, m, 5-CH_2, 2′-CH_2 and 6′-CH_2), 2.91 (1 H, dd, *J* 14.1, 2.1 Hz, 6′-CH_2), 2.15 (3 H, s, 1-N–CH_3), 2.05 (3 H, s, 1′-N–CH_3), 1.67 (1 H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.4, 177.9, 142.0, 136.4, 133.9, 133.1, 131.8, 131.2, 130.7, 128.7, 127.6, 127.5, 121.8, 115.3, 114.9, 108.9, 75.6, 66.0, 57.0, 56.8, 56.6, 44.7, 44.6, 34.6.

1-Methyl-4-(2-chlorophenyl)pyrrolo-(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(2-chlorophenylmethylidene)piperidin-4′-one (5f). Obtained as white solid (0.48 g, 90%), m.p. 200–202 ^oC; [Found: C, 67.75; H, 5.09; N, 7.81. $C_{30}H_{27}Cl_2N_3O_2$ requires C, 67.67; H, 5.11; N, 7.89%]; δ_H (300 MHz, $CDCl_3$) 8.53 (1 H, s, NH), 7.61 (1 H, s, C═CH), 6.71–8.00 (12 H, m, Ar), 5.12 (1 H, t, *J* 8.7 Hz, 4-CH), 3.96 (1 H, t, *J* 9.0 Hz, 5-CH_2), 3.48 (1 H, t, *J* 9.0

Hz, 5-CH_2), 3.14 (1 H, d, *J* 14.7 Hz, 6′-CH_2), 2.90–3.01 (2 H, m, 2′-CH_2 and 6′-CH_2), 2.12 (3 H, s, 1-N–CH_3), 1.92 (3 H, s, 1′-N–CH_3), 1.82 (1 H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 197.3, 177.8, 142.0, 136.9, 135.8, 134.9, 134.6, 134.0, 133.6, 130.7, 129.9, 129.7, 129.2, 128.5, 127.9, 127.8, 126.6, 126.5, 126.1, 122.7, 108.9, 77.2, 63.6, 57.8, 57.7, 57.0, 45.4, 42.1, 34.7.

1-Methyl-4-(2-methylphenyl)pyrrolo-(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(2-methylphenylmethylidene)piperidin-4′-one (5g). Obtained as white solid (0.45 g, 91%), m.p. 180–181 ^oC; [Found: C, 78.10; H, 6.84; N, 8.64. $C_{32}H_{33}N_3O_2$ requires C, 78.18; H, 6.77; N, 8.55%]; δ_H (300 MHz, $CDCl_3$) 8.85 (1 H, s, NH), 7.51 (1 H, s, C═CH), 6.76–7.85 (12 H, m, Ar), 4.99 (1 H, t, *J* 9.6 Hz, 4-CH), 4.02 (1 H, t, *J* 9.6 Hz, 5-CH_2), 3.42 (1 H, t, *J* 8.4 Hz, 5-CH_2), 3.28 (1 H, d, *J* 12.9 Hz, 2′-CH_2), 3.18 (1 H, d, *J* 14.7 Hz, 6′-CH_2), 2.89 (1 H, dd, *J* 14.7, 2.4 Hz, 6′-CH_2), 2.31 (3 H, s, Ar-CH_3), 2.15 (3 H, s, Ar-CH_3), 2.14 (3 H, s, 1-N–CH_3), 1.96 (3 H, s, 1′-N–CH_3), 1.68 (1 H, d, *J* 12.9 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.5, 178.0, 142.3, 138.0, 137.8, 137.1, 137.0, 134.3, 133.0, 130.2, 130.1, 129.3, 128.6, 128.3, 127.8, 127.3, 126.5, 125.7, 125.3, 122.3, 109.1, 76.9, 64.2, 58.4, 57.2, 45.3, 41.6, 34.7, 21.2, 20.1.

1-Methyl-4-(2-methoxyphenyl)pyrrolo-(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(2-methoxyphenylmethylidene)piperidin-4′-one (5h). Obtained as white solid (0.50 g, 96%), m.p. 197–199 ^oC; [Found: C, 73.47; H, 6.30; N, 8.09. $C_{32}H_{33}N_3O_4$ requires C, 73.40; H, 6.35; N, 8.02%]; δ_H (300 MHz, $CDCl_3$) 8.79 (1 H, s, NH), 7.69 (1 H, s, C═CH), 6.69–7.62 (12 H, m, Ar), 4.90 (1 H, dd, *J* 10.8, 10.5 Hz, 4-CH), 4.11 (1 H, t, *J* 9.9 Hz, 5-CH_2), 3.82 (3 H, s, Ar-OCH_3), 3.72 (3 H, s, Ar-OCH_3), 3.34 (1 H, t, *J* 8.1 Hz, 5-CH_2), 3.22 (1 H, d, *J* 14.4 Hz, 6′-CH_2), 3.02 (1 H, d, *J* 12.3 Hz, 2′-CH_2), 2.90 (1 H, d, *J* 14.7 Hz, 6′-CH_2), 2.14 (3 H, s, 1-N–CH_3), 1.93 (3 H, s, 1′-N–CH_3), 1.82 (1 H, d, *J* 12.3 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 197.3, 178.0, 158.1, 158.0, 142.3, 133.1, 132.6, 130.1, 129.8, 128.5, 128.1, 127.6, 127.4, 127.3,

124.5, 122.0, 120.3, 119.7, 110.5, 109.8, 108, 7, 77.0, 63.8, 57.0, 56.7, 55.8, 55.3, 54.8, 45.3, 39.3, 34.8.

1-Methyl-4-(3-fluorophenyl)pyrrolo-(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(3-fluorophenylmethylidene)piperidin-4′-one (5i). Obtained as white solid (0.47 g, 94%), m.p. 175–177 ^{o}C; [Found: C, 72.07; H, 5.37; N, 8.49. $C_{30}H_{27}F_2N_3O_2$ requires C, 72.13; H, 5.45; N, 8.41%]; δ_H (300 MHz, $CDCl_3$) 8.77 (1 H, s, NH), 6.65–7.29 (13 H, m, Ar), 4.81 (1 H, dd, *J* 11.1, 10.8 Hz, 4-CH), 3.90 (1 H, dd, *J* 11.1, 11.1 Hz, 5-CH_2), 3.29–3.37 (3 H, m, 5-CH_2, 2′-CH_2 and 6′-CH_2), 2.92 (1 H, dd, *J* 15.0, 2.7 Hz, 6′-CH_2), 2.16 (3 H, s, 1-N–CH_3), 2.05 (3 H, s, 1′-N–CH_3), 1.71 (1 H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.2, 177.9, 164.1, 160.9, 142.1, 140.9, 137.1, 136.1, 134.3, 129.8, 129.6, 129.5, 128.9, 127.6, 127.4, 125.5, 125.0, 121.9, 116.3, 116.0, 115.5, 113.7, 109.0, 75.5, 66.3, 56.8, 56.7, 56.2, 45.0, 44.7, 34.5.

1-Methyl-4-(2,4-dichlorophenyl)pyrrolo-(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(2,4-dichlorophenylmethylidene)piperidin-4′-one (5j). Obtained as white solid (0.58 g, 96%), m.p. 215–217 ^{o}C; [Found: C, 59.82; H, 4.29; N, 6.91. $C_{30}H_{25}Cl_4N_3O_2$ requires C, 59.92; H, 4.19; N, 6.99%]; δ_H (300 MHz, $CDCl_3$) 8.63 (1 H, s, NH), 7.50 (1 H, s, C═CH), 6.71–8.00 (10 H, m, Ar), 5.05 (1 H, t, *J* 8.4 Hz, 4-CH), 3.86 (1 H, t, *J* 9.0 Hz, 5-CH_2), 3.47 (1 H, t, *J* 8.4 Hz, 5-CH_2), 3.10 (1 H, d, *J* 14.7 Hz, 6′-CH_2), 2.89–2.96 (2 H, m, 2′-CH_2 and 6′-CH_2), 2.10 (3 H, s, 1-N–CH_3), 1.94 (3 H, s, 1′-N–CH_3), 1.80 (1 H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 197.0, 177.8, 142.0, 136.3, 135.6, 135.5, 134.9, 134.4, 133.5, 132.9, 132.0, 131.7, 130.5, 129.6, 128.9, 128.7, 127.8, 127.0, 126.6, 126.3, 122.6, 109.0, 77.0, 63.5, 57.8, 57.7, 56.9, 45.4, 41.7, 34.7.

1-Methyl-4-(2-thienyl)pyrrolo-(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(2-thienyl-methylidene)piperidin-4′-one (5k). Obtained as white solid (0.46 g, 96%), m.p. 196–198 ^{o}C; [Found: C, 65.61; H, 5.37; N, 8.87. $C_{26}H_{25}N_3O_2S_2$ requires C, 65.66; H, 5.30; N, 8.83%]; δ_H (300 MHz, $CDCl_3$) 7.94 (1 H, s, NH), 6.82–7.61 (11 H, m, Ar), 5.05 (1 H, dd, *J* 11.1, 10.8

Hz, 4-CH), 3.89 (1 H, dd, *J* 10.8, 10.8 Hz, 5-CH_2), 3.48 (1 H, d, *J* 12.6 Hz, 2′-CH_2), 3.32–3.43 (2 H, m, 5-CH_2 and 6′-CH_2), 3.01 (1 H, d, *J* 15.6 Hz, 6′-CH_2), 2.17 (3 H, s, 1-N–CH_3), 2.15 (3 H, s, 1′-N–CH_3), 1.95 (1 H, d, *J* 12.6 Hz, 2′-CH_2).

1-Methyl-4-(1-naphthyl)pyrrolo-(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methyl-5′-(1-naphthylmethylidene)piperidin-4′-one (5l). Obtained as white solid (0.46 g, 92%), m.p. 224–225 ^{o}C; [Found: C, 80.89; H, 5.97; N, 7.49. $C_{38}H_{33}N_3O_2$ requires C, 80.97; H, 5.90; N, 7.45%]; δ_H (300 MHz, $CDCl_3$) 8.82 (1 H, s, NH), 7.97 (1 H, s, C═CH), 6.77–8.35 (18 H, m, Ar), 5.70 (1 H, t, *J* 9.6 Hz, 4-CH), 4.22 (1 H, t, *J* 9.6 Hz, 5-CH_2), 3.53 (1 H, t, *J* 8.1 Hz, 5-CH_2), 3.39 (1 H, d, *J* 12.6 Hz, 2′-CH_2), 3.05 (1 H, d, *J* 14.7 Hz, 6′-CH_2), 2.68 (1 H, dd, *J* 14.7, 2.4 Hz, 6′-CH_2), 2.22 (3 H, s, 1-N–CH_3), 1.85 (3 H, s, 1′-N–CH_3), 1.56 (1 H, d, *J* 12.6 Hz, 2′-CH_2); δ_C (75 MHz, $CDCl_3$) 198.2, 177.9, 142.5, 136.6, 134.8, 134.7, 133.8, 133.2, 132.5, 131.2, 128.9, 128.8, 128.7, 128.4, 128.0, 127.4, 127.3, 127.0, 126.5, 126.2, 126.1, 125.4, 125.3, 125.1, 124.9, 124.8, 124.5, 122.4, 109.3, 76.9, 64.9, 58.7, 57.9, 56.9, 45.0, 40.1, 34.8.

MIC determination

All compounds were screened for their *in vitro* antimycobacterial activity against MTB, MDR-TB and MC^2 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 duplicate.[19] The MDR-TB clinical isolate was obtained from Tuberculosis Research Center, Chennai, India, and was resistant to isoniazid, rifampicin, ethambutol and ofloxacin. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth.

Cytotoxicity

All the compounds were further examined for toxicity (IC_{50}) in a mammalian Vero cell line upto concentration of 62.5 μg/mL[21] by serial dilution method. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation assay.

***In vivo* studies**

One compound was tested for efficacy against MTB at a dose of 25 mg/kg in six-week-old female CD-1 mice six per group. In this model, the mice were infected intravenously through caudal vein approximately 10^7 viable *Mycobacterium tuberculosis* ATCC 35801. Drug treatment by intra peritoneal route began after 10 days of inoculation of the animal with microorganism and continued for 10 days. After 35 days post infection the spleens and right lungs were aseptically removed and ground in a tissue homogenizer, the number of viable organisms was determined by serial 10-fold dilutions and subsequent inoculation onto 7H10 agar plates. Cultures were incubated at 37°C in ambient air for 4 weeks prior to counting. Bacterial counts were measured, and compared with the counts from negative controls (vehicle treated) in lung and in spleen (Table 2).