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Antimycobacterial Activity of 1-Substituted Indolizines

Indolizine derivatives were tested as antimycobacterials against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using the Microplate Alamar Blue Assay. The most active compounds examined carry an α-hydroxybenzyl substituent in the indolizine 1-position. MICs against *Mycobacterium tuberculosis* for these compounds were 6.25 µg/mL

Key Words: Indolizines; Tuberculosis; Antimycobacterial

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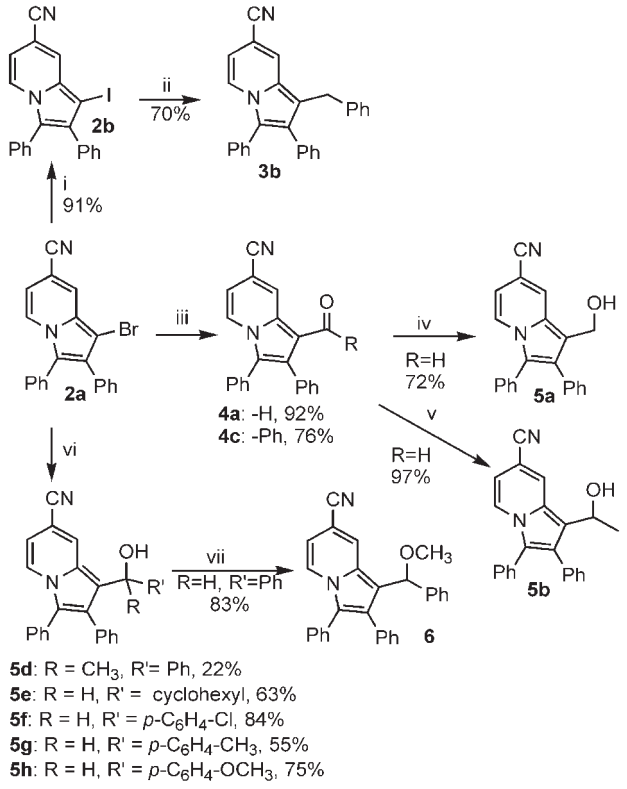
Introduction

Tuberculosis (TB) is the major cause of death from a single infectious agent among adults in developing countries, and in the industrial world there has been an unfortunate revival of the disease. Human immunodeficiency virus (HIV) infections have further increased TB morbidity and mortality. Multi-drug resistant tuberculosis (MDR-TB) defined as resistance to the two most important drugs, isoniazid (INH) and rifampin (RMP), is a growing problem among HIV-infected patients. Ca. 1/3 of the world's population is infected with *Mycobacterium tuberculosis*, including those carrying dormant infections. It has been estimated that ca. 30 million people will die from tuberculosis in the next 10-year period [1].

In recent years, our screening of a number of heterocyclic compounds for antimycobacterial activity has resulted in identification of certain purine derivatives as potent inhibitors of *M. tuberculosis* [2–4]. We are now reporting antimycobacterial activity for 1-substituted indolizines, some of them previously studied as potential antioxidants [5–7].

Results and discussion

The syntheses of the novel compounds are outlined in Scheme 1. The 1-benzylindolizine **3b** was formed by Negishi coupling, essentially as previously reported for the synthesis of **3a**, but when the reaction was performed with the bromide **2a**, a substantial amount of the indolizine **1** was formed and the isolated yield of compound **3b** was low. The more reactive iodide **2b**, on the other hand, gave the desired benzylindolizine **3b** in 70% yield. Reaction of the bromide **2a** with butyllithium followed by trapping with DMF, acid chlorides, aldehydes, or ketones gave the indolizinyl aldehyde and ketones **4** or alcohols **5d–5h**, generally in high yields.



Scheme 1. Reagents and conditions: i, 1. BuLi, THF, –78 °C, 2. I_2; ii, $PhCH_2ZnBr$, $(Ph_3P)_4Pd$, dioxane, 100 °C; iii, 1. BuLi, THF, –78 °C, 2. DMF or PhCOCl; iv, $NaBH_4$, EtOH; iv, CH_3Li, THF, –78 °C; vi, 1. BuLi, THF, –78 °C, 2. RCOR'; vii, NaH, CH_3I, THF.

Reaction of the aldehyde **4a** with sodium borohydride or methyllithium gave the alcohols **5a** and **5b**. The hydroxy group in compound **5c** was alkylated to give the ether **6**. The syntheses of compounds **1**, **2a**, **3a**, **3c**, **4b**, and **5c** (Figure 1) have been reported before [6].

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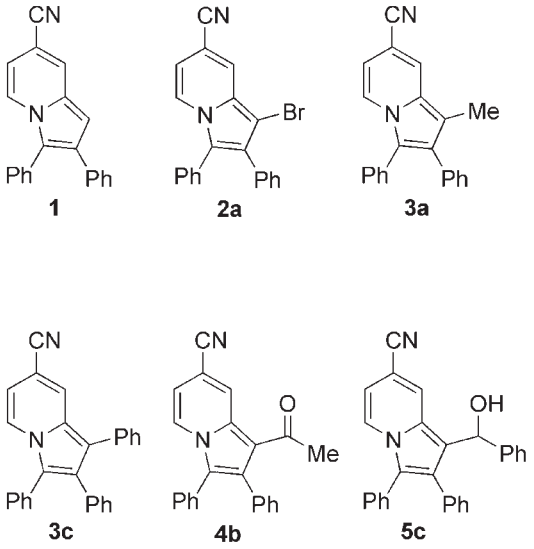

Figure 1. Structure of previously reported compounds.

The indolizines **1**–**6** were tested as antimycobacterials against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA) [8], and the results are summarized in Table 1.

The parent indolizine **1** exhibited essentially no inhibitory activity against *Mycobacterium tuberculosis*. Moderate activity was found when an alkyl substituent **3a** and **3b**, or acyl substituent, compounds **4**, was introduced. The 1-arylindolizine **3c** was inactive. Active compounds was, however, found among the indolizines **5** carrying a 1-hydroxyalkyl substituent in the 1-position. The most effective compound was the benzaldehyde adduct **5c** and the *para* substituted analogs **5f** and **5g**. Introducing a methyl group in the α-position **5d**, or on the hydroxy group **6**, resulted in a small decrease in activity against *M. tuberculosis*.

Compound **5c** and related structures are, to the best of our knowledge, the first antimycobacterial indolizines reported. The need for new antituberculosis drugs, especially due to the growing problem with multi-drug resistant tuberculosis, makes the indolizine **5c** an interesting lead compound. Synthesis of both enantiomers of **5c** as well as further structure optimization of antimycobacterial indolizines are in progress.

Acknowledgements

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Table 1. Antimycobacterial activity for indolizines **1**–**6**.

Compds	Substituent in the indolizine 1-position	% Inhibition of *M.tuberculosis* at 6.25 μg/mL	MIC, *M. tuberculosis* (μg/mL)
1	H	9	n.d.[a]
2a	Br	69	n.d.
3a	CH_3	41	n.d.
3b	CH_2Ph	43	n.d.
3c	Ph	8	n.d.
4a	CHO	35	n.d.
4b	$COCH_3$	21	n.d.
4c	COPh	33	n.d.
5a	CH_2OH	67	n.d.
5b	$CH(OH)CH_3$	78	n.d.
5c	CH(OH)Ph	100	6.25
5d	$C(CH_3)(OH)Ph$	71	n.d.
5e	CH(OH)-cyclohexyl	90	>6.25
5f	CH(OH)-*p*-C_6H_4-Cl	95	6.25
5g	CH(OH)-*p*-C_6H_4-CH_3	90	6.25
5h	CH(OH)-*p*-C_6H_4-OCH_3	87	n.d.
6	$CH(OCH_3)Ph_3$	74	n.d.

[a] Not determined.

contract with the US National Institute of Allergy and Infectious Diseases. We are thankful for all help provided by Dr. Cecil Kwong and his co-workers. The Norwegian Research Council is gratefully acknowledged for partial financing of Bruker Avance NMR instruments used in this study.

Experimental

The ^{1}H NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument, or at 200 MHz with a Bruker Avance DPX 200 or a Varian Gemini 200 instrument and the ^{13}C NMR spectra were recorded at 125, 75, or MHz using the above mentioned spectrometers. Mass spectra were recorded at 70 eV ionising voltage with a VG Prospec instrument, and are presented as *m*/*z* (% rel. int.). Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected. THF and dioxane were distilled from Na/benzophenone, and DMF was distilled from BaO. All other reagents were commercially available and used as received. Synthesis of compounds **1**, **2a**, **3a**, **3c**, **4b**, and **5c** have been reported before [6].

1-Iodo-2,3-diphenyl-7-indolizinecarbonitrile (**2b**)

n-Butyllithium (0.784 mL of a 1.32 M solution in hexane, 1.05 mmol) was added dropwise to a stirred solution of compound **2a** (373 mg, 1.0 mmol) in dry THF (20 mL) at –78 °C under N_2. After 30 min, iodine (508 mg, 2.0 mmol) in THF (5 mL) was added and the resulting mixture was stirred for 1.5 h. EtOAc (75 mL), diethyl ether (75 mL) and saturated aqueous ammonium chloride (50 mL) were added to the cold reaction mixture. The phases were separated and the organic layer was washed with water (3 × 75 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The product was purified by flash chromatography, eluting with hexane followed by EtOAc-hexane (1:39). Yield 383 mg (91 %), yellow powdery crystals. – Mp 226–228 °C. – R_f = 0.47 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 6.57 (dd, 1 H, *J* = 7.4 and 1.7 Hz, H-6), 7.21–7.39 (m, 10 H, Ph), 7.89 (dd, 1 H, *J* = 1.7 and 0.9 Hz, H-8), 7.97 (dd, 1 H, *J* = 7.4 and 0.9 Hz, H-5). – ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) = 63.3, 101.0, 111.1, 118.7, 123.3, 127.1, 127.2, 127.5, 128.1, 128.8, 129.1, 129.2, 130.4, 130.6, 131.7, 133.3, 133.7. – MS (EI): 420 (M^+, 100), 293 (31), 292 (38), 264 (7), 146 (12). – HRMS: Calcd. for $C_{21}H_{13}N_2I$: 420.0124; found 420.0123.

1-Benzyl-2,3-diphenyl-7-indolizinecarbonitrile (**3b**)

A solution of benzylmagnesium chloride (0.50 mL of a 2.0 M solution in THF, 1.0 mmol) was added dropwise to a stirred solution of zinc bromide (0.90 mL of a 1.49 M solution in THF, 1.3 mmol) in dry THF (3 mL) at –78 °C under N_2. When the addition was complete, the resulting mixture was stirred for 1 h at –78 °C and at ambient temperature for 30 min. Tetrakis-(triphenylphosphine)palladium(0) [generated *in situ* from tris-(dibenzylideneacetone)dipalladium chloroform adduct (13 mg, 13 µmol) and triphenylphosphine (26 mg, 0.1 mmol)] in dry dioxane (1 mL) and compound **2b** (210 mg, 0.50 mmol) in dry dioxane (3 mL) were added and the reaction mixture was stirred for 48 h at 100 °C. After cooling to ambient temperature, EtOAc (50 mL) and diethyl ether (50 mL) were added and the mixture was washed with saturated ammonium chloride solution (50 mL) and water (3 × 50 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The product was purified by flash chromatography, eluting with EtOAc-hexane (1:99). Yield 136 mg (70 %), yellow powdery crystals. – Mp 186–187 °C. – R_f = 0.44 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.17 (s, 2 H, CH_2), 6.50 (dd, *J* = 7.4 and 1.7 Hz, 1 H, H-6), 7.02–7.44 (m, 15 H, Ph), 7.70 (dd, 1 H, *J* = 1.7 and 0.9 Hz, H-8), 8.04 (dd, *J* = 7.4 and 0.9 Hz, 1H, H-5). – ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) = 30.6, 98.6, 110.6, 116.7, 119.9, 122.8, 125.6, 126.3, 126.6, 127.4, 128.5, 128.6, 128.7, 129.0, 129.3, 129.4, 130.4, 130.7, 131.1, 131.3, 134.3, 141.4. – MS (EI): 384 (M^+, 100), 307 (48), 153 (6). – HRMS: Calcd. for $C_{20}H_{28}N_2$: 384.1626; found 384.1637.

1-Formyl-2,3-diphenyl-7-indolizinecarbonitrile (**4a**)

n-Butyllithium (1.25 mL of a 1.32 M solution in hexane, 1.65 mmol) was added dropwise to a stirred solution of compound **2a** (560 mg, 1.5 mmol) in dry THF (30 mL) at –78 °C under N_2. After 1 h, dry DMF (0.58 mL, 7.5 mmol) was added and the resulting mixture was stirred for additional 2 h before the reaction mixture was heated to room temperature. EtOAc (100 mL), diethyl ether (100 mL), and saturated aqueous ammonium chloride (100 mL) were added to the cold reaction mixture. The phases were separated and the organic layer washed with water (100 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:29) followed by (1:19), (1:9) and finally (1:4). Yield 445 mg (92 %), yellow crystals. – Mp 205–207 °C. – R_f = 0.29 (SiO_2, EtOAc-hexane, 1:4). -^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.82 (dd, *J* = 7.3 and 1.8 Hz, 1 H, H-6), 7.15–7.30 (m, 7 H, Ph), 7.35–7.40 (m, 3 H, Ph), 8.06 (dd, *J* = 7.3 and 0.9, 1 H, H-5), 8.83 (dd, *J* = 1.8 and 0.9 Hz, 1 H, H-8), 9.90 (s, 1 H, CHO). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 106.4, 114.0, 114.6, 117.9, 118.1, 123.5, 126.6, 127.0, 127.9, 128.4, 129.3, 129.3, 130.6, 131.0, 131.2, 132.2, 133.9, 186.5. – MS (EI): 322 (M^+, 100), 321 (80), 293 (29), 292 (22), 161 (6), 146 (11). – HRMS: Calcd. for $C_{22}H_{14}N_2O$: 322.1106; found 322.1097.

1-Benzoyl-2,3-diphenyl-7-indolizinecarbonitrile (**4c**)

n-Butyllithium (0.416 mL of a 1.32 M solution in hexane, 0.55 mmol) was added dropwise to a stirred solution of compound **2a** (199 mg, 0.50 mmol) in dry THF (20 mL) at –78 °C under N_2. After 1 h, benzoyl chloride (0.290 mL, 351 mg, 2.5 mmol) was added and the resulting mixture was stirred for additional 2 h before the reaction mixture was heated to ambient temperature. EtOAc (100 mL), diethyl ether (100 mL), and saturated aqueous ammonium chloride (100 mL) were added to the cold reaction mixture. The phases were separated and the organic layer washed with water (100 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:29) followed by (1:19), (1:9), and finally (1:4). Yield 151 mg (76 %), yellow crystals. – Mp 215–216 °C. – R_f = 0.34 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 6.70 (dd, *J* = 7.3 and 1.8 Hz, 1 H, H-6), 6.80–6.95 (m, 5 H, Ph), 6.95-7.10 (m, 2 H, Ph), 7.10–7.25 (m, 3 H, Ph), 7.40–7.30 (m, 3 H, Ph), 7.45–7.55 (m, 2 H, Ph), 8.01 (dd, *J* = 7.3 and 1.0 Hz, 1 H, H-5), 8.38 (dd, *J* = 1.8 and 1.0 Hz, 1 H, H-8). – ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) = 104.3, 112.6, 115.8, 118.3, 123.2, 126.5, 126.8, 127.6, 128.9, 129.0, 129.3, 129.1, 129.5, 130.8, 130.9, 131.7, 131.8, 132.8, 133.2, 192.1. – MS (EI): 398 (M^+, 100), 321 (61), 293 (25), 292 (18), 199 (9), 105 (7). – HRMS: Calcd. for $C_{28}H_{18}N_2O$: 398.1419; found 398.1410. – Anal: Found: C, 84.18; H, 4.65; N, 6.72. $C_{28}H_{18}N_2O$ requires C, 84.40; H, 4.55; N, 7.03 %.

1-(Hydroxymethyl)-2,3-diphenyl-7-indolizinecarbonitrile (**5a**)

Compound **4a** (148 mg, 0.46 mmol) and sodium borohydride (26 mg, 0.69 mmol) was dissolved in absolute ethanol (50 mL) and stirred at ambient temperature for 48 h. Saturated aqueous

ammonium chloride (1 mL) was carefully added to the resulting mixture before it was evaporated *in vacuo*. EtOAc (100 mL), diethyl ether (100 mL), and saturated aqueous ammonium chloride (100 mL) were added to the residue. The phases were separated and the organic layer washed with water (100 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:29) followed by (1:19), (1:9), (1:4), and finally (1:1). Yield 107 mg (72%), yellow crystals. – Mp. 204–206 °C. – R_f = 0.31 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.7 (br s, 1H, –OH), 4.88 (s, 2H, CH_2), 6.55 (dd, *J* = 7.4 and 1.8 Hz, 1H, H-6), 7.20–7.30 (m, 5H, Ph), 6.95–7.10 (m, 2H, Ph), 7.30–7.43 (m, 3H, Ph), 8.00 (dd, *J* = 7.4 and 1.0 Hz, 1H, H-5), 8.07 (dd, *J* = 1.8 and 1.0 Hz, 1H, H-8). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 55.3, 99.4, 110.6, 116.1, 119.1, 122.5, 124.9, 125.9, 127.2, 128.3, 128.5, 129.1, 129.5, 129.8, 130.3, 130.4, 130.5, 133.2. – MS (EI): 324 (*M*$^+$, 100), 307 (100), 305 (15), 292 (12), 229 (5), 203 (7), 153 (16). – HRMS: Calcd. for $C_{22}H_{16}N_2O$: 324.1263; found 324.1271.

1-(1-Hydroxyetyl)-2,3-diphenyl-7-indolizinecarbonitrile (**5b**)

Methyllithium (0.309 mL of a 1.6 M solution in hexane, 0.495 mmol) was added dropwise to a stirred solution of compound **4a** (145 mg, 0.45 mmol) in dry THF (20 mL) at –78 °C under N_2. The reaction mixture was stirred at –78 °C for 4 h before saturated aqueous ammonium chloride (1 mL) was added dropwise. The reaction mixture was heated to ambient temperature and EtOAc (100 mL), diethyl ether (100 mL), and saturated aqueous ammonium chloride (100 mL) were added. The phases were seperated and the organic layer washed with water (100 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:29) followed by (1:19), (1:9), and finally (1:4). Yield 148 mg (97%), yellow crystals. – Mp 197–198 °C. – R_f = 0.35 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 1.68 (d, *J* = 13.0 Hz, 3H, CH_3), 2.12 (br d, *J* = 2.2 Hz, 1H, OH), 5.27 (dq, *J* = 13.0 and 2.2 Hz, 1H, CH), 6.58 (dd, *J* = 7.4 and 1.8 Hz, 1H, H-6), 7.15–7.45 (m, 10H, Ph), 8.05 (dd, *J* = 7.4 and 1.0 Hz, 1H, H-5), 8.39 (dd, *J* = 1.8 and 1.0 Hz, 1H, H-8). – MS (EI): 338 (*M*$^+$, 42), 323 (100), 320 (78), 319 (82), 293 (7), 242 (9), 215 (10), 152 (8). – HRMS: Calcd. for $C_{23}H_{18}N_2O$: 338.1419; found 338.1429.

1-[1-Hydroxy-1-phenylethyl]-2,3-diphenyl-7-indolizinecarbonitrile (**5d**)

n-Butyllithium (0.42 mL of a 1.32 M solution in hexane, 0.56 mmol) was added dropwise to a stirred solution of compound **2a** (187 mg, 0.50 mmol) in dry THF (10 mL) at –78 °C under N_2. After 30 min, acetophenone (0.177 mL, 1.50 mmol) was added and the resulting mixture was stirred for additional 1.5 h. EtOAc (50 mL), diethyl ether (50 mL), and saturated aqueous ammonium chloride (30 mL) were added to the cold reaction mixture. The phases were separated and the organic layer was washed with water (3 × 30 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:29) followed by (1:9). Yield 47 mg (22%), yellow powdery crystals. – Mp 170–171 °C, – R_f = 0.33 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.77 (s, 3H, CH_3), 2.31 (s, 1H, OH), 6.49 (dd, *J* = 7.3 and 1.4 Hz, 1H, H-6), 6.86 (m, 2H, Ph), 7.04–7.18 (m, 5H, Ph), 7.2–7.4 (m, 8H, Ph), 7.91 (br d, 1H, *J* = 7.3 Hz, H-5), 8.31 (br s, 1H, H-8). – ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 32.6, 76.4, 99.3, 110.4, 120.0, 122.9, 124.1, 126.1, 127.4, 127.5, 127.6, 127.9, 128.0, 128.6, 128.6, 129.1, 129.8, 130.1, 130.7, 131.5, 135.3, 148.8, one signal was hidden. – MS (EI): 414 (*M*$^+$, 4), 397 (27), 396 (100), 319 (18), 291 (8), 159 (6). – HRMS: Calcd. for $C_{29}H_{22}N_2O$: 414.1732; found 414.1718. – Anal: Found: C, 81.16; H, 5.43; N, 6.29. $C_{29}H_{22}N_2O$ requires C, 84.03; H, 5.35; N, 6.76%.

1-[1-Hydroxycyclohexylmethyl]-2,3-diphenyl-7-indolizinecarbonitrile (**5e**)

The compound was prepared as described for compound **5d** and purified by flash chromatography eluting with EtOAc-hexane (1:39) followed by (1:9). Yield 257 mg (63%), yellow powdery crystals. – Mp 204–206 °C. – R_f = 0.28 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (500 MHz, CDCl3): δ (ppm) = 0.67–0.71 (m, 1H, c-hex), 0.96–1.28 (m, 4H, c-hex), 1.56–1.59 (m, 3H, c-hex), 1.72–1.78 (m, 2H, c-hex), 1.96 (d, *J* = 2.5 Hz, 1H, OH), 2.04 (m, 1H, c-hex), 4.66 (dd, *J* = 8.5 and 2.5 Hz, 1H, CH), 6.52 (dd, *J* = 7.4 and 1.8 Hz, 1H, H-6), 7.13–7.33 (m, 10H, Ph), 7.99 (dd, *J* = 7.4 and 0.9 Hz, 1H, H-5), 8.23 (dd, *J* = 1.8 and 0.9 Hz, 1H, H-8). – ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 25.8, 26.0, 26.2, 29.6, 29.7, 45.6, 73.0, 98.5, 110.2, 119.3, 119.4, 122.4, 125.8, 127.0, 127.1, 127.9, 128.1, 128.2, 128.9, 129.8, 130.2, 130.4, 130.7, 133.9. – MS (EI): 406 (*M*$^+$, 13), 388 (19), 324 (36), 323 (100), 307 (10), 294 (7), 217 (5). – HRMS: Calcd. for $C_{28}H_{26}N_2O$: 406.2045; found 406.2055.

1-[1-Hydroxy(4-chlorophenyl)methyl]-2,3-diphenyl-7-indolizinecarbonitrile (**5f**)

The compound was prepared as described for compound **5d** above and purified by flash chromatography, eluting with EtOAc-hexane (1:29) followed by (1:9). Yield 183 mg (84%), yellow crystals. – Mp 186–188 °C. – R_f = 0.25 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.26 (d, *J* = 3.4 Hz, 1H, OH), 6.12 (d, *J* = 3.4 Hz, 1H, CH), 6.54 (dd, *J* = 7.4 and 1.7 Hz, 1H, H-6), 7.10–7.39 (m, 14H, Ph), 7.92 (br s, 1H, H-8), 8.01 (br d, *J* = 7.4 Hz, 1H, H-5). – ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 69.3, 99.9, 111.1, 119.3, 119.5, 123.1, 126.3, 126.9, 127.8, 128.2, 128.8, 128.9, 129.0, 129.5, 129.9, 130.6, 130.7, 131.0, 133.6, 133.7, 142.4. – MS (EI): 436/434 (*M*$^+$, 35/100), 418 (25), 417 (43), 323 (50), 293 (19), 292 (20), 139 (12), 195 (17), 77 (11). – HRMS: Calcd. for $C_{28}H_{19}ClN_2O$: 434.1186; found 434.1311. – Anal: Found: C, 77.00; H, 4.73; N, 6.05. $C_{28}H_{19}ClN_2O$ requires C, 77.33; H, 4.40; N, 6.44%.

1-[1-Hydroxy(4-methylphenyl)methyl]-2,3-diphenyl-7-indolizinecarbonitrile (**5g**)

The compound was prepared as described for compound **5d** above and purified by flash chromatography, eluting with EtOAc-hexane (1:29) followed by (1:9). Yield 115 mg (55%), yellow crystals. – Mp 158–160 °C. – R_f = 0.23 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.34 (s, 4H, OH and CH3), 6.11 (s, 1H, CH), 6.51 (dd, *J* = 7.3 and 1.3 Hz, 1H, H-6), 7.12–7.37 (m, 14H, Ph), 7.97 (br s, 1H, H-8), 8.06 (br d, *J* = 7.3 Hz, 1H, H-5). – ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 21.1, 69.3, 98.9, 110.4, 119.5, 112.4, 125.3, 125.6, 125.8, 126.9, 127.1, 127.8, 128.1, 128.3, 128.9, 129.1, 129.7, 130.1, 130.2, 130.6, 133.4, 137.1, 140.6. – MS (EI): 414 (*M*$^+$, 100), 413 (10), 398 (24), 397 (48), 323 (39), 321 (10), 295 (15), 91 (7), 91 (6). – HRMS: Calcd. for $C_{29}H_{22}N_2O$: 414.1732; found 414.1725.

1-[1-Hydroxy(4-methoxyphenyl)methyl]-2,3-diphenyl-7-indolizinecarbonitrile (**5h**)

The compound was prepared as described for compound **5d** above and purified by flash chromatography, eluting with EtOAc-hexane (1:29) followed by (1:9). Yield 162 mg (75%), yellow crystals. – Mp 111–112 °C. – R_f = 0.25 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.42 (s, 1H, OH), 3.79 (s, 3H, OCH_3), 6.11 (s, 1H, CH), 6.51 (dd, *J* = 7.2

and 1.5 Hz, 1H, H-6), 6.84 (m, 2H, Ph), 7.12–7.36 (m, 12H, Ph), 7.99–8.02 (m, 2H, H-5 and H-8). – ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 55.2, 69.3, 98.9, 110.4, 113.8, 119.3, 119.5, 122.4, 125.6, 127.0, 127.2 (2 C), 127.6, 128.1, 128.3, 128.9, 129.6, 130.0, 130.2, 130.6, 133.4, 135.8, 158.8. – MS (EI): 430 (M^+, 100), 414 (63), 413 (73), 323 (19), 321 (13), 305 (11), 294 (11), 292 (17), 135 (8). – HRMS: Calcd. for $C_{29}H_{22}N_2O_2$: 430.1681; found 430.1677.

1-[Methoxyphenylmethyl]-2,3-diphenyl-7-indolizinecarbonitrile (**6**)

Sodium hydride (26 mg, 1.1 mmol) was added to a stirred solution of compound **5c** in dry THF (15 mL) at ambient temperature, under N2 and the resulting mixture was stirred for 30 min, before iodomethane (156 mg, 1.1 mmol) was added dropwise. After stirring of 36 h, the reaction was quenched with saturated aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (50 mL) and diethyl ether (50 mL) and the organic layer was washed with water (3 × 30 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:29). Yield 172 mg (83%), yellow crystals. – Mp 68–70 °C. – R_f = 0.46 (SiO_2, EtOAc-hexane, 1:4). – ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.34 (s, 3H, OCH_3), 5.53 (s, 1H, CH), 6.50 (dd, J = 7.4 and 1.8 Hz, 1H, H-6), 7.97 (dd, J = 7.4 and 0.7 Hz, 1H, H-5), 7.07–7.11 (m, 2H, Ph), 7.20–7.31 (m, 13H, Ph), 8.02 (br s, 1H, H-8). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 57.4, 79.3, 99.5, 110.9, 118.0, 119.8, 122.9, 126.2, 126.9, 127.4, 127.6, 127.8, 128.1, 128.6, 128.7, 128.8, 129.4, 130.2, 130.6, 131.1, 131.3, 134.1, 142.3. – MS (EI): 414 (M^+, 35), 384 (45), 383 (17), 383 (100), 337 (15), 307 (10), 305 (25), 292 (15), 298 (8), 191 (9), 105 (8), 77 (5), 28 (32). – HRMS: Calcd. for $C_{29}H_{22}N_2O$: 414.1732; found 414.1757.

Activity against mycobacteria [8]

The primary screening was conducted at 6.25 μg/mL against *Mycobacterium tuberculosis* H_{37}Rv (ATCC 27294) in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA). Compounds exhibiting fluorescence were tested in the BACTEC 460-radiometric system, and compounds demonstrating at least 90% inhibition in the primary screen were retested at lower concentrations against *M. tuberculosis* H_{37}Rv to determine the actual minimum inhibitory concentration (MIC) in the MABA. MIC for rifampin was 0.25 μg/mL.

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