Supporting Information

Development of novel isatin-nicotinohydrazide hybrids with potent activity against susceptible/resistant Mycobacterium tuberculosis and bronchitis causing-bacteria

Zainab M. Elsayed, Wagdy M. Eldehna*, Marwa M. Abdel-Aziz, Mahmoud A. El Hassab, Eslam B. Elkaeed, Tarfah Al-Warhi, Hatem A. Abdel-Aziz, Sahar M. Abou-Seri, Eman R. Mohammed
1. Characterisation details (NMR, IR and elemental analysis) for the target hybrids (5a-m, 9a-c and 14)

*N’-(2-Oxo-1-propylindolin-3-ylidene)nicotinohydrazide 5a.*

Yellow powder, m.p. 141-143 °C; (yield 81%); $^1$H NMR δ ppm: 0.90 (3H, t, $J = 8.0$ Hz, -CH$_2$CH$_3$), 1.63-1.73 (2H, m, N-CH$_2$CH$_3$), 3.73 (2H, t, $J = 8.0$ Hz, N-CH$_2$), 7.16 (1H, t, $J = 8.0$ Hz, H-5 of nicotinic hydrazide), 7.24 (1H, d, $J = 8.0$ Hz, H-7 of 2-indolinone), 7.46 (1H, t, $J = 8.0$ Hz, H-6 of 2-indolinone), 7.60-7.67 (2H, m, H-5 and H-4 of 2-indolinone), 8.25 (1H, d, $J = 8.0$ Hz, H-4 of nicotinic hydrazide), 8.84 (1H, d, $J = 8.0$ Hz, H-6 of nicotinic hydrazide), 9.07 (1H, s, H-2 of nicotinic hydrazide), 13.86 (1H, s, NH); $^{13}$C NMR δ ppm: 11.64 (-CH$_2$C$_3$H$_3$), 20.86 (N-CH$_2$CH$_3$), 41.32 (N-CH$_2$), 110.77, 119.44, 121.37, 123.75, 124.56, 132.46, 135.95, 143.65, 148.98, 153.63, 161.56 (C=O nicotinic hydrazide), 163.78 (C=O 2-indolinone); IR (KBr, $\nu$ cm$^{-1}$) 3452 (NH) and 1706, 1678 (2C=O); Analysis calculated for C$_{17}$H$_{16}$N$_4$O$_2$: C, 66.22; H, 5.23; N, 18.17; found C, 66.45; H, 5.26; N, 18.24.

*N’-(1-Isobutyl-2-oxindolin-3-ylidene)nicotinohydrazide 5b.*

Yellow powder, m.p. 150-152 °C; (yield 76%); $^1$H NMR δ ppm: 0.93 (6H, d, $J = 6.8$ Hz, -CH(CH$_3$)$_2$), 2.07-2.14 (1H, m, -CH(CH$_3$)$_2$), 3.58 (2H, d, $J = 8.0$ Hz, N-CH$_2$), 7.24 (1H, d, $J = 8.0$ Hz, H-7 of indoline-2,3-dione), 7.46 (1H, t, $J = 7.6$ Hz, H-5 of nicotinic hydrazide), 7.23 (1H, d, $J = 8.0$ Hz, H-7 of indoline-2,3-dione), 8.25 (1H, d, $J = 8.0$ Hz, H-6 of 2-indolinone), 7.62-7.67 (2H, m, H-5 and H-4 of 2-indolinone), 8.84 (1H, d, $J = 5.6$ Hz, H-6 of nicotinic hydrazide), 9.07 (1H, s, H-2 of nicotinic hydrazide), 13.84 (1H, s, NH); IR (KBr, $\nu$ cm$^{-1}$) 3369 (NH) and 1697, 1680 (2C=O); Analysis calculated for C$_{18}$H$_{18}$N$_4$O$_2$: C, 67.07; H, 5.63; N, 17.38; found C, 66.82; H, 5.58; N, 17.96.

*Ethyl-2-(3-(2-nicotinoylhydrazono)-2-oxindolin-1-yl)acetate 5c.*

Yellow powder, m.p. 158-160 °C; yield 69%; $^1$H NMR δ ppm: 1.20 (3H, t, $J = 8.0$ Hz, -CH$_2$CH$_3$), 4.16 (2H, q, $J = 8.0$ Hz, -CH$_2$CH$_3$), 4.74 (2H, s, N-CH$_2$), 7.20-7.24 (2H, m, H-5 of nicotinic hydrazide and H-7 of 2-indolinone), 7.48 (1H, t, $J = 8.0$ Hz, H-6 of 2-indolinone), 7.64-7.69 (2H, m, H-5 and H-4 of 2-indolinone), 8.27 (1H, d, $J = 8.0$ Hz, H-4 of nicotinic hydrazide), 8.84 (1H, brs, H-6 of nicotinic hydrazide), 9.08 (1H, s, H-2 of nicotinic hydrazide), 13.59 (1H, s, NH); $^{13}$C NMR δ ppm: 14.47 (-CH$_2$CH$_3$), 41.42 (-CH$_2$CH$_3$), 61.95 (N-CH$_2$), 110.91, 119.30,
121.42, 124.18, 124.53, 128.40, 132.49, 136.10, 143.31, 148.91, 153.67, 161.46 (C=O nicotinic hydrazide), 163.15 (C=O 2-indolinone), 167.88 (C=O ester); IR (KBr, ν cm⁻¹) 3237 (NH) and 1742, 1710, 1686 (3C=O); Analysis calculated for C₁₈H₁₆N₄O₄: C, 61.36; H, 4.58; N, 15.90; found C, 61.51; H, 4.63; N, 15.87.

N’-(1-Benzyl-2-oxindolin-3-ylidene)nicotinohydrazide 5d.

Yellow powder, m.p. 167-169 °C; yield 77%; ¹H NMR δ ppm: 5.04 (2H, s, benzylic protons), 7.09 (1H, d, J= 8.0 Hz, H-7 of 2-indolinone), 7.16 (1H, t, J= 7.6 Hz, H-5 of nicotinic hydrazide), 7.28 (1H, t, J= 8.0 Hz, H-6 of 2-indolinone), 7.34 (2H, t, J= 8.0 Hz, H-3 and H-5 of benzyl moiety), 7.41-7.45 (3H, m, H-2, H-4 and H-6 of benzyl moiety), 7.65-7.68 (2H, m, H-5 and H-4 of 2-indolinone), 8.29 (1H, d, J= 8.0 Hz, H-4 of nicotinic hydrazide), 8.85 (1H, d, J= 5.6 Hz, H-6 of nicotinic hydrazide), 9.10 (1H, s, H-2 of nicotinic hydrazide), 13.80 (1H, s, NH); ¹³C NMR δ ppm: 43.10 (benzylic carbon), 111.09, 119.65, 121.43, 123.98, 124.57, 127.93, 128.16, 128.48, 129.21, 132.36, 136.04, 139.03, 143.32, 149.05, 153.67, 161.58 (C=O nicotinic hydrazide), 163.47 (C=O 2-indolinone); IR (KBr, ν cm⁻¹) 3449 (NH) and 1699, 1680 (2C=O); Analysis calculated for C₂₁H₁₆N₄O₂: C, 70.77; H, 4.53; N, 15.72; found C, 70.49; H, 4.55; N, 15.79.

N’-(5-Chloro-2-oxo-1-propylindolin-3-ylidene)nicotinohydrazide 5e.

Orange powder, m.p. 151-153 °C; yield 82%; ¹H NMR δ ppm: 0.90 (3H, t, J= 8.0 Hz, -CH₂CH₃), 1.62-1.71 (2H, m, N-CH₂CH₂), 3.73 (2H, t, J= 8.0 Hz, N-CH₂), 7.30 (1H, d, J= 8.0 Hz, H-7 of 2-indolinone), 7.53 (1H, d, J= 8.0 Hz, H-6 of 2-indolinone), 7.62 (1H, s, H-4 of of 2-indolinone), 7.65 (1H, t, J= 8.0 Hz, H-5 of nicotinic hydrazide), 8.27 (1H, d, J= 8.0 Hz, H-4 of nicotinic hydrazide), 8.85 (1H, d, J= 8.0 Hz, H-6 of nicotinic hydrazide), 9.08 (1H, s, H-2 of nicotinic hydrazide), 13.75 (1H, s, NH); ¹³C NMR δ ppm: 11.60 (⁻CH₂CH₃), 20.81 (N-CH₂CH₂), 41.48 (N-CH₂), 112.41, 120.88, 121.24, 124.57, 127.95, 128.31, 131.74, 136.16, 142.35, 143.79, 149.11, 153.74, 161.33 (C=O nicotinic hydrazide), 163.16 (C=O 2-indolinone); IR (KBr, ν cm⁻¹) 3450 (NH) and 1704, 1682 (2C=O); Analysis calculated for C₁₇H₁₅ClN₄O₂: C, 59.57; H, 4.41; N, 16.35; found C, 59.78; H, 4.43; N, 16.41.

N’-(5-Chloro-1-isobutyl-2-oxindolin-3-ylidene)nicotinohydrazide 5f.

Orange powder, m.p. 172-174 °C; yield 65%; ¹H NMR δ ppm: 0.91 (6H, d, J= 6.8 Hz, -CH(CH₃)₂), 1.89-2.11 (1H, m, -CH(CH₃)₂), 3.59 (2H, d, J= 8.0 Hz, N-CH₂), 7.27 (1H, d, J= 8.0
Hz, H-7 of 2-indolinone), 7.51 (1H, d, J= 8.0 Hz, H-6 of 2-indolinone), 7.63-7.67 (2H, m, H-4 and H-5 of 2-indolinone), 8.26 (1H, d, J= 8.0 Hz, H-4 of nicotinic hydrazide), 8.84 (1H, d, J= 8.0 Hz, H-6 of nicotinic hydrazide), 9.07 (1H, s, H-2 of nicotinic hydrazide), 13.79 (1H, s, NH); 13C NMR δ ppm: 20.36 (-CH(CH3)2), 27.22 (-CH(CH3)2), 47.23 (N-CH2), 112.59, 116.16, 119.04, 120.83, 124.59, 127.93, 131.68, 134.23, 136.06, 139.96, 142.62, 149.07, 154.42, 161.50 (C=O nicotinic hydrazide), 163.42 (C=O 2-indolinone); IR (KBr, ν cm⁻¹) 3450 (NH) and 1705, 1682 (2C=O); Analysis calculated for C18H17ClN4O2: C, 60.59; H, 4.80; N, 15.70; found C, 60.79; H, 4.75; N, 15.78.

**N’-(5-Bromo-2-oxo-1-propylindolin-3-ylidene)nicotinohydrazide 5g.**

Yellow powder, m.p. 167-168 °C; yield 73%; 1H NMR δ ppm: 0.90 (3H, t, J= 8.0 Hz, -CH2CH3), 1.67 (2H, brs, N-CH2CH2), 3.75 (2H, brs, N-CH2),7.25 (1H, d, J= 8.0 Hz, H-7 of 2-indolinone), 7.66-7.73 (3H, m, H-4 and H-6 of 2-indolinone, H-5 of nicotinic hydrazide), 8.28 (1H, brs, H-4 of nicotinic hydrazide), 8.87 (1H, brs, H-6 of nicotinic hydrazide), 9.08 (1H, s, H-2 of nicotinic hydrazide), 13.73 (1H, s, NH); 13C NMR δ ppm: 11.61 (-CH2CH3), 20.80 (N-CH2CH2), 41.47 (N-CH2), 112.87, 115.55, 121.61, 123.59, 124.58, 126.03, 128.31, 134.57, 137.48, 142.76, 149.02, 153.71, 161.21 (C=O nicotinic hydrazide), 163.83 (C=O 2-indolinone); IR (KBr, ν cm⁻¹) 3449 (NH) and 1694, 1673 (2C=O); Analysis calculated for C17H15BrN4O2: C, 52.73; H, 3.90; N, 14.47; found C, 52.57; H, 3.92; N, 14.51.

**N’-(5-Bromo-1-isobutyl-2-oxindolin-3-ylidene)nicotinohydrazide 5h.**

Orange powder, m.p. 174-175 °C; yield 75%; 1H NMR δ ppm: 0.90 (6H, d, J= 6.8 Hz, -CH(CH3)2), 2.04-2.10 (1H, m, -CH(CH3)2), 3.74 (2H, d, J= 8.0 Hz, N-CH2), 7.21 (1H, d, J= 8.0 Hz, H-7 of 2-indolinone), 7.63-7.67 (2H, m, H-6 of of 2-indolinone and H-5 of nicotinic hydrazide), 7.75 (1H, s, H-4 of 2-indolinone), 8.83 (1H, d, J= 7.6 Hz, H-6 of nicotinic hydrazide), 9.06 (1H, s, H-2 of nicotinic hydrazide), 13.79 (1H, s, NH); IR (KBr, ν cm⁻¹) 3449 (NH) and 1707, 1681 (2C=O); Analysis calculated for C18H17BrN4O2: C, 53.83; H, 4.27; N, 13.96; found C, 53.11; H, 4.23; N, 14.08.

**Ethyl-2-(5-bromo-3-(2-nicotinoylhydrazone)-2-oxindolin-1-yl)acetate 5i.**

Yellow powder, m.p. 206-208 °C; yield 81%; 1H NMR δ ppm: 1.22 (3H, t, J= 8.0 Hz, -CH2CH3), 4.18 (2H, q, J= 8.0 Hz, -CH2CH3), 4.78 (2H, s, N-CH2), 7.04 (1H, d, J= 8.4 Hz, H-5 of
nicotinic hydrazide), 7.21-7.24 (2H, m, H-5 and H-7 of 2-indolinone), 7.47 (1H, t, J= 8.0 Hz, H-6 of 2-indolinone), 7.68 (1H, d, J= 7.6 Hz, H-4 of 2-indolinone), 8.17 (1H, d, J= 8.8 Hz, H-4 of nicotinic hydrazide), 8.77 (1H, s, H-2 of nicotinic hydrazide), 13.52 (1H, s, NH); IR (KBr, ν cm⁻¹) 3230 (NH) and 1741, 1711, 1687 (3C=O); Analysis calculated for C₁₈H₁₅BrN₄O₄: C, 50.13; H, 3.51; N, 12.99; found C, 50.35; H, 3.48; N, 13.06.

6-Methoxy-N’-(2-oxo-1-propylindolin-3-ylidene)nicotinohydrazide 5j.

Orange powder, m.p. 139-141 °C; yield 69%; ¹H NMR δ ppm: 0.91 (3H, t, J= 8.0 Hz, -CH₂CH₃), 1.64-1.73 (2H, m, N-CH₂CH₂), 3.74 (2H, t, J= 8.0 Hz, N-CH₂), 3.97 (3H, s, OCH₃), 7.04 (1H, d, J= 8.0 Hz, H-5 of nicotinic hydrazide), 7.17 (1H, t, J= 8.0 Hz, H-5 of 2-indolinone), 7.25 (1H, d, J= 8.0 Hz, H-7 of 2-indolinone), 7.47 (1H, t, J= 8.0 Hz, H-6 of 2-indolinone), 7.64 (1H, d, J= 8.0 Hz, H-4 of 2-indolinone), 8.16 (1H, d, J= 8.0 Hz, H-4 of nicotinic hydrazide), 8.76 (1H, s, H-2 of nicotinic hydrazide), 13.76 (1H, s, NH); ¹³C NMR δ ppm: 11.65 (−CH₂CH₃), 20.87 (N-CH₂CH₂), 41.31 (N-CH₂), 54.46 (OCH₃), 110.74, 111.50, 119.57, 121.28, 122.09, 123.72, 128.01, 132.27, 138.90, 143.52, 148.41, 154.09, 161.62 (C=O nicotinic hydrazide), 163.18 (C=O 2-indolinone); IR (KBr, ν cm⁻¹) 3449 (NH) and 1694, 1604 (2C=O); Analysis calculated for C₁₈H₁₈N₄O₃: C, 63.89; H, 5.36; N, 16.56; found C, 63.73; H, 5.42; N, 16.59.

N’-(1-Isobutyl-2-oxindolin-3-ylidene)-6-methoxynicotinohydrazide 5k.

Yellow powder, m.p. 154-156 °C; yield 74%; ¹H NMR δ ppm: 0.92 (6H, d, J= 6.8 Hz, -CH(CH₃)₂), 2.07-2.13 (1H, m, -CH(CH₃)₂), 3.57 (2H, d, J= 7.2 Hz, N-CH₂), 3.96 (3H, s, OCH₃), 7.01 (1H, d, J= 8.4 Hz, H-5 of nicotinic hydrazide), 7.15 (1H, t, J= 7.6 Hz, H-5 of 2-indolinone), 7.22 (1H, d, J= 8.0 Hz, H-7 of 2-indolinone), 7.44 (1H, t, J= 8.0 Hz, H-6 of 2-indolinone), 7.62 (1H, d, J= 7.6 Hz, H-4 of 2-indolinone), 8.13 (1H, d, J= 8.8 Hz, H-4 of nicotinic hydrazide), 8.74 (1H, s, H-2 of nicotinic hydrazide), 13.75 (1H, s, NH); ¹³C NMR δ ppm: 20.45 (−CH(CH₃)₂), 27.28 (−CH(CH₃)₂), 47.10 (N-CH₂), 54.46 (OCH₃), 110.99, 111.52, 115.38, 119.51, 121.22, 122.07, 123.72, 132.22, 137.33, 138.86, 143.83, 148.36, 153.37, 161.84 (C=O nicotinic hydrazide), 166.50 (C=O 2-indolinone); IR (KBr, ν cm⁻¹) 3450 (NH) and 1704, 1610 (2C=O); Analysis calculated for C₁₉H₂₀N₄O₃: C, 64.76; H, 5.72; N, 15.90; found C, 64.98; H, 5.68; N, 15.92.

Ethyl-2-(3-(2-(6-methoxynicotinoyl)hydrazono)-2-oxindolin-1-yl)acetate 5l.

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Yellow powder, m.p. 132-133 °C; yield 70%; $^1$H NMR $\delta$ ppm: 1.22 (3H, t, $J= 8.0$ Hz, -CH$_2$CH$_3$), 3.97 (3H, s, OCH$_3$), 4.17 (2H, q, $J= 8.0$ Hz, -CH$_2$CH$_3$), 4.74 (2H, s, N-CH$_2$), 7.02 (1H, d, $J= 8.4$ Hz, H-5 of nicotinic hydrazide), 7.20-7.23 (2H, m, H-5 and H-7 of 2-indolinone), 7.47 (1H, t, $J= 8.0$ Hz, H-6 of 2-indolinone), 7.67 (1H, d, $J= 7.6$ Hz, H-4 of 2-indolinone), 8.16 (1H, d, $J= 8.8$ Hz, H-4 of nicotinic hydrazide), 8.76 (1H, s, H-2 of nicotinic hydrazide), 13.51 (1H, s, NH); $^{13}$C NMR $\delta$ ppm: 14.47 (-CH$_2$CH$_3$), 41.40 (-CH$_2$CH$_3$), 54.44 (OCH$_3$), 61.92 (N-CH$_2$), 110.84, 111.44, 119.39, 121.27, 121.98, 124.11, 132.25, 136.72, 139.00, 143.14, 148.35, 161.49 (C=O nicotinic hydrazide), 166.52 (C=O 2-indolinone), 167.86 (C=O ester); IR (KBr, $\nu$ cm$^{-1}$) 3451 (NH) and 1749, 1684, 1670 (3C=O); Analysis calculated for C$_{19}$H$_{18}$N$_4$O$_5$: C, 59.68; H, 4.75; N, 14.65; found C, 59.84; H, 4.71; N, 14.69.

$N'$-(1-Benzyl-2-oxindol-3-ylidene)-6-methoxynicotinohydrazide 5m.

Yellow powder, m.p. 160-162 °C; yield 83%; $^1$H NMR $\delta$ ppm: 3.96 (3H, s, OCH$_3$), 5.02 (2H, s, benzylic protons), 7.01 (1H, d, $J= 8.8$ Hz, H-5 of nicotinic hydrazide), 7.07 (1H, d, $J= 7.6$ Hz, H-7 of 2-indolinone), 7.13 (1H, t, $J= 8.0$ Hz, 2-indolinone), 7.27 (1H, t, $J= 8.4$ Hz, H-6 of 2-indolinone), 7.33 (2H, t, $J= 7.6$ Hz, H-3 and H-5 of benzyl moiety), 7.40-7.43 (3H, m, H-2, H-4 and H-6 of benzyl moiety), 7.63 (1H, d, $J= 7.6$ Hz, H-4 of 2-indolinone), 8.16 (1H, d, $J= 8.8$ Hz, H-4 of nicotinic hydrazide), 8.77 (1H, s, H-2 of nicotinic hydrazide), 13.71 (1H, s, NH); $^{13}$C NMR $\delta$ ppm: 43.10 (benzylic carbon), 54.43 (OCH$_3$), 111.01, 111.47, 119.71, 121.29, 122.04, 123.91, 127.94, 128.15, 128.96, 129.20, 132.12, 136.05, 137.29, 138.91, 143.13, 148.31, 161.60 (C=O nicotinic hydrazide), 166.51 (C=O 2-indolinone); IR (KBr, $\nu$ cm$^{-1}$) 3449 (NH) and 1694, 1602 (2C=O); Analysis calculated for C$_{22}$H$_{18}$N$_4$O$_5$: C, 68.38; H, 4.70; N, 14.50; found C, 68.17; H, 4.75; N, 14.44.

2-Methyl-$N'$-(2-oxo-1-propylindol-3-ylidene)-6-phenynicotinohydrazide 9a.

Orange powder, m.p. 91-93 °C; yield 76%; $^1$H NMR $\delta$ ppm: 0.89 (3H, t, $J= 8.0$ Hz, -CH$_2$CH$_3$), 1.62-1.71 (2H, m, N-CH$_2$CH$_2$), 2.71 (3H, s, CH$_3$), 3.70 (2H, t, $J= 8.0$ Hz, N-CH$_2$), 7.15-7.23 (2H, m, H-5 and H-6 of 2-indolinone), 7.45-7.56 (5H, m, ArH of phenyl ring), 7.97 (1H, d, $J= 8.0$ Hz, H-7 of 2-indolinone), 8.07 (1H, d, $J= 8.0$ Hz, H-4 of 2-indolinone), 8.16 (2H, d, $J= 8.0$ Hz, H-4 and H-5 of nicotinic hydrazide), 13.31 (1H, s, NH); $^{13}$C NMR $\delta$ ppm: 11.63 (-CH$_2$CH$_3$), 20.85 (N-CH$_2$CH$_2$), 23.88 (CH$_3$), 41.28 (N-CH$_2$), 110.68, 117.82, 119.51, 121.16, 123.65, 127.38, 129.30, 130.21, 132.29, 137.50, 138.17, 143.60, 144.83, 147.01, 151.56, 157.40,
161.33 (C=O nicotinic hydrazide), 163.10 (C=O 2-indolinone); IR (KBr, ν cm⁻¹) 3449 (NH) and 1701, 1693 (2C=O); Analysis calculated for C₂₅H₂₂N₄O₂: C, 72.34; H, 5.57; N, 14.06; found C, 72.39; H, 5.51; N, 14.02.

\(N'-(1-ISOBUTYL-2-OXINDOLIN-3-YLIDENE)-2-MTHYL-6-PHENYLNICOTINOHYDRAZIDE\ 9b.\)

Yellow powder, m.p. 139-141 °C; yield 80%; \(^1\)H NMR δ ppm: 0.91 (6H, d, \(J= 6.8 \) Hz, -CH(CH₃)₂), 2.05-2.12 (1H, m, -CH(CH₃)₂), 2.71 (3H, s, CH₃), 3.56 (2H, d, \(J= 8.0 \) Hz, N-CH₂), 7.16-7.24 (2H, m, H-5 and H-6 of 2-indolinone), 7.44-7.56 (5H, m, ArH of phenyl ring), 7.98 (1H, d, \(J= 8.0 \) Hz, H-7 of 2-indolinone), 8.07 (1H, d, \(J= 8.0 \) Hz, H-4 of 2-indolinone), 8.17 (2H, d, \(J= 8.0 \) Hz, H-4 and H-5 of nicotinic hydrazide), 13.42 (1H, s, NH); \(^{13}\)C NMR δ ppm: 20.41 (-CH(CH₃)₂), 23.88 (-CH(CH₃)₂), 27.24 (CH₃), 56.51 (N-CH₂), 110.91, 117.79, 119.45, 121.13, 123.66, 127.38, 129.30, 130.21, 132.26, 137.36, 138.17, 143.91, 144.93, 147.07, 151.66, 157.47, 161.54 (C=O nicotinic hydrazide), 163.10 (C=O 2-indolinone); IR (KBr, ν cm⁻¹) 3401 (NH) and 1690, 1683 (2C=O); Analysis calculated for C₂₅H₂₂N₄O₂: C, 72.80; H, 5.86; N, 13.58; found C, 72.86; H, 5.81; N, 13.53.

\(ETHYL-2-(3-(2-MTHYL-6-PHENYLNICOTINOYL)HYDRAZONO)-2-OXINDOLIN-1-YL)ACETATE\ 9c.

Yellow powder, m.p. 156-157 °C; yield 73%; \(^1\)H NMR δ ppm: 1.21 (3H, t, \(J= 8.0 \) Hz, -CH₂CH₃), 2.71 (3H, s, CH₃), 4.16 (2H, q, \(J= 8.0 \) Hz, -CH₂CH₃), 4.72 (2H, s, N-CH₂), 7.17-7.22 (2H, m, H-5 and H-6 of 2-indolinone), 7.46-7.57 (5H, m, ArH of phenyl ring), 7.98 (1H, d, \(J= 8.0 \) Hz, H-7 of 2-indolinone), 8.09 (1H, d, \(J= 8.0 \) Hz, H-4 of 2-indolinone), 8.17 (2H, d, \(J= 8.0 \) Hz, H-4 and H-5 of nicotinic hydrazide), 13.14 (1H, s, NH); \(^{13}\)C NMR δ ppm: 14.47 (-CH₂CH₃), 23.88 (CH₃), 41.38 (-CH₂CH₃), 61.92 (N-CH₂), 110.82, 112.38, 117.70, 119.36, 121.17, 124.10, 127.40, 129.33, 130.25, 132.32, 134.07, 138.16, 143.24, 144.93, 147.07, 151.66, 157.50, 161.20 (C=O nicotinic hydrazide), 163.19 (C=O 2-indolinone), 167.89 (C=O ester); IR (KBr, ν cm⁻¹) 3449 (NH) and 1737, 1691, 1616 (3C=O); Analysis calculated for C₂₅H₂₂N₄O₄: C, 67.86; H, 5.01; N, 12.66; found C, 67.82; H, 5.06; N, 12.61.

\(5-BROMO-N-(6-METHOXYPYRIDIN-3-YL)-2,3-DIOXINDOLE-1-CARBOXAMIDE\ 14.

Yellow powder, m.p. 282-284 °C; yield 81%; \(^1\)H NMR δ ppm: 3.82 (3H, s, OCH₃), 6.77 (1H, d, \(J= 8.0 \) Hz, H-7 of indoline-2,3-dione), 6.88 (1H, d, \(J= 8.0 \) Hz, H-6 of indoline-2,3-dione), 7.66 (1H, s, H-4 of of indoline-2,3-dione), 7.73 (1H, d, \(J= 8.0 \) Hz, H-5 of nicotinic hydrazide), 7.81
(1H, d, J= 8.0 Hz, H-4 of nicotinic hydrazide), 8.19 (1H, s, H-2 of nicotinic hydrazide), 8.62 (1H, s, NH); $^{13}$C NMR δ ppm: 53.53 (OCH$_3$), 110.44, 112.67, 120.01, 125.15, 127.36, 130.90, 131.89, 137.63, 138.85, 140.52, 150.03, 153.69 (C=O amid), 159.57 (C=O of position 2 of indoline-2,3-dione), 183.65 (C=O of position 3 of indoline-2,3-dione); IR (KBr, ν cm$^{-1}$) 3279 (NH) and 1730, 1697, 1687 (3C=O); Analysis calculated for C$_{15}$H$_{10}$BrN$_3$O$_4$: C, 47.90; H, 2.68; N, 11.17; found C, 48.03; H, 2.69; N, 11.22.

2. Microplate Alamar Blue Anti-Tuberculcular Assay

Microplate alamar blue assay (MABA) was used to determine MICs of the prepared hybrids (5a-m, 9a-c and 14) against M. tuberculosis ATCC 27294 (Isoniazid-sensitive strain) and Mycobacterium tuberculosis ATCC 35823 (resistant to Isoniazid and Streptomycin). Isoniazid was used as a reference drug against sensitive strain. Preparation of the inoculum was done using fresh Lowenstein Jensen (LJ) medium re-suspended in 7H9-S medium (7H9 broth, 0.1% casitone, 0.5% glycerol, supplemented oleic acid, albumin, dextrose, and catalase (OADC), adjusted to a McFarland tube No. 1, and diluted 1:20; 100 µl was used as inoculum. The examined hybrids were dissolved in DMSO. Drug-free controls containing broth with DMSO were included in the experiment. The final concentration of DMSO in the test medium did not exceed 0.5% (v/v) of the total solution composition, which had no effect on the growth of M. tuberculosis. The 96 wells plates were treated with 100 µl of two-fold serial dilution of each compound. Final concentrations of the examined hybrids in wells were 1000- 0.006 µg/mL. Sterile deionized water (200 µl) was added to all outer-perimeter wells of sterile 96 well plates to decrease evaporation of the medium in the test wells during incubation. A growth control without antibiotic and a sterile control were also set on each plate. The plate was then covered, sealed in plastic bags and incubated at 37 °C in normal atmosphere. After 7 days of incubation, each well was supplied with 30 µl of the Alamar blue solution, and then the plate was re-incubated overnight. Colour change from blue (oxidized state) to pink (reduced) highlighted the growth of bacteria. The MIC was expressed as the minimum concentration of compound which prohibited blue to pink colour change. MIC values were calculated in µg/mL.
3. XTT Susceptibility Antibacterial Assay

Microorganisms: Gram negative bacteria: *Mycoplasma pneumoniae ATCC 15531*, *Haemophilus influenzae ATCC 10211*, *Moraxella catarrhalis ATCC 25238*, *Klebsiella pneumoniae ATCC 43816* and *Bordetella pertussis ATCC 9340*, in addition to *Streptococcus pneumoniae ATCC 1659*, representing Gram positive bacterium. All strains are American type culture collection (ATCC).

Colorimetric broth micro-dilution method using XTT [2,3-bis(2-methoxy-4-nitro-5-sulfo-phenyl)-2H-tetrazolium-5-carboxanilide]-reduction assay \(^{33, 34}\) was adopted to determine the minimum inhibitory concentration (MIC) of examined hybrids against bacteria causing bronchitis. All bacterial strains were cultured overnight at 37 °C in Tryptone Soya Broth (TSB) (Oxoid, UK). XTT (Sigma) was prepared in a saturated solution at 0.5 g/L in Ringer’s lactate. The solution was sterilized through a 0.22-µm-pore-size filter. The compounds were serially diluted in DMSO, and then 50 µL of each dilution at final concentrations of (1000- 0.24 µg/mL) were added to wells in Microtiter plate (96 wells) containing 100 µL TSB. Fifty µL of adjusted microbial inoculum (106 CFU/mL) was added to each well, and then the Microtiter plates were incubated in the dark at 37 °C for 24 h. After incubation, 100 µL of freshly prepared XTT were added, incubated again for 1 h at 37 °C. Colorimetric variation in the XTT assay was measured using a Microtiter plate reader (BioTECK, USA) at 492 NM. The MIC was specified as the extract concentration that produced a 100 % decrease in optical density compared with control growth results. Azithromycin was used as a standard antibacterial.
**Fig. S1.** The 2D diagrams for interactions of compounds 5g and 5h in InhA active site.

**Fig. S2.** the 3D illustrations of the superimposition for the docking poses and the co-crystalized ligands in DprE1 and InhA active sites.
### Table S3. Summarized interactions between compounds 5g and 5h with the DprE1 active site

| Compound | Bond                                                                 | Distance (Å) |
|----------|-----------------------------------------------------------------------|--------------|
| 5g       | Hydrogen bond with Asparagine 385                                     | 2.66         |
| 5g       | Hydrogen bond with Asparagine 385                                     | 2.77         |
| 5g       | Hydrogen bond with Histidine 132                                       | 2.68         |
| 5g       | Hydrogen bond with Histidine 132                                       | 3.04         |
| 5g       | Hydrogen bond with Tyrosine 415                                        | 2.09         |
| 5g       | Non-classical Hydrogen bond with Glycine 133                           | 2.42         |
| 5g       | Non-classical Hydrogen bond with Proline 116                           | 2.95         |
| 5g       | Pi-Pi interaction with Histidine 132                                   | 5.44         |
| 5g       | Pi-Alkyl interaction with Proline 116                                   | 5.17         |
| 5g       | Pi-Alkyl interaction with Valine 365                                    | 4.76         |
| 5g       | Pi-Alkyl interaction with Lysine 367                                    | 4.33         |
| 5g       | Alkyl-Alkyl interaction with Leucine 131                               | 3.75         |
| 5h       | Hydrogen bond with Asparagine 385                                     | 2.75         |
| 5h       | Hydrogen bond with Cysteine 387                                        | 3.72         |
| 5h       | Hydrogen bond with Histidine 132                                       | 2.68         |
| 5h       | Hydrogen bond with Histidine 132                                       | 3.04         |
| 5h       | Hydrogen bond with Tyrosine 415                                        | 2.09         |
| 5h       | Non-classical Hydrogen bond with Glycine 133                           | 2.42         |
| 5h       | Non-classical Hydrogen bond with Proline 116                           | 2.95         |
| 5h       | Pi-Pi interaction with Histidine 132                                   | 5.44         |
| 5h       | Pi-Alkyl interaction with Proline 116                                   | 5.17         |
| 5h       | Pi-Alkyl interaction with Valine 365                                    | 4.75         |
| 5h       | Pi-Alkyl interaction with Lysine 367                                    | 4.39         |
| 5h       | Alkyl-Alkyl interaction with Leucine 131                               | 4.66         |
| 5h       | Alkyl-Alkyl interaction with Valine 121                                 | 4.49         |
| 5h       | Alkyl-Alkyl interaction with Alanine 417                               | 3.87         |
| 5h       | Alkyl-Alkyl interaction with Proline 116                               | 4.45         |
Jun01-2020-abeer.130.fid — WAGDY-MN-5A — PROTON_BSU DMSO {C:\data}:

`1H NMR
Aliphatic Zoom`
$^1$H NMR
$^1$H NMR
Aliphatic Zoom
1H NMR
Aliphatic Zoom

- 3.37 HDO
- 2.50 DMSO
- 1.25
- 1.23
- 1.22

f1 (ppm)
5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0
\[ ^{13}\text{C} \text{NMR} \]
$^{13}$C NMR
\(^1\text{H} \text{NMR}\)
\(^1\text{H NMR}\)

5k

Chemical shifts and peaks are noted on the graph.
\[ ^{13} \text{C NMR} \]
H NMR
Aliphatic Zoom

¹H NMR

5i

1.04
2.104
2.087
2.069
2.121
2.138
2.515 DMSO
3.335 HDO
3.579
3.597
3.964
$^{13}$C NMR

**Wagdy Eldehna-MN-5L-AS-carbon.10.fid — Wagdy Eldehna-MN-5L-AS-carbon**
^1H NMR
$^1$H NMR

[Chemical structure image]

[Graph with peaks and labels]

- 8.18
- 8.17
- 8.09
- 8.07
- 8.00
- 7.98
- 7.56
- 7.55
- 7.52
- 7.50
- 7.47
- 7.44
- 7.42
- 7.22
- 7.16
- 3.58
- 3.56
- 3.39 (HDO)
- 3.52 (DMSO)
- 2.71
- 2.12
- 2.10
- 2.09
- 2.07
- 2.05
- 0.93
- 0.91

- 8.14
- 0.92
- 1.19
- 0.84
- 3.90
- 1.06
- 1.11
- 1.08
- 6.00

f1 (ppm)
