*In silico* docking studies and synthesis of new phosphoramidate derivatives of 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole as potential antimicrobial agents

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*4-Nitrophenyl N-4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl-N-(4-fluorobenzyl) phosphor ramidate (4a)*

Brown solid, Yield (%): 94; mp: 135-137 oC; IR (cm-1, υmax): 3385 (NH), 1234 (P=O), 747 (C-Pali); 1H NMR (400 MHz, CDCl3, ppm): *δ* 8.34 (d, 2H, *J* = 6.9 Hz, Ar-H), 8.23 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.91 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.41 (d, 1H, *J* =8.4 Hz, Ar-H), 7.37 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.09 (d, 1H, *J* = 7.4 Hz, Ar-H), 6.83 (s, 1H, Ar-H), 4.11 (t, 1H, *J* = 10.3 Hz, NH), 4.02 (s, 2H, CH2), 3.34 (t, 4H, *J* = 13.6 Hz, N-CH2), 2.71-2.74 (m, 1H, CH2), 1.52 (qt, 4H, *J* = 9.3 Hz, N-CH2); 13C NMR (100 MHz, CDCl3, ppm): *δ* 167.4, 165.2, 160.3, 148.6, 141.1, 138.6, 128.2, 126.4, 123.2, 121.3, 116.3, 115.1, 111.2, 97.6, 47.7, 41.3, 32.5, 28.1; 31P NMR (162 MHz, CDCl3, ppm): -10.3; LC-MS *m/z* (*%*): Calcd. for C25H23F2N4O5P: 528; Found: 529 [M+H]+; Anal. Calcd. for C25H23F2N4O5P: C, 56.82; H, 4.39; and N, 10.60; Found: C, 56.75; H, 4.36; and N, 10.56.

*4-Nitrophenyl N-(4,6-dimethylpyrimidin-2-yl)-P-(4-(6-fluorobenzo[d] isoxazol-3-yl)piperidin-1-yl)phosphoramidate (4b)*

Brown solid, Yield (%): 82; mp: 180-182 oC; IR (cm-1, υmax): 3374 (NH), 1248 (P=O), 744 (C-Pali); 1H NMR (400 MHz, CDCl3): *δ* 8.00 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.52 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.38 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.14 (d, 1H, *J* = 8.3 Hz, Ar-H), 6.79 (s, 1H, Ar-H), 6.73 (s, 1H, pyrimidinyl CH), 4.43 (t, 1H, *J* = 11.1 Hz, NH), 3.55 (t, 4H, *J* = 10.6 Hz, N-CH2), 2.17-2.23 (m, 1H, CH2), 2.61 (s, 6H, CH3), 1.49 (qt, 4H, *J* = 12.1 Hz, N-CH2); 13C NMR (100 MHz, CDCl3, ppm): *δ* 169.3, 168.4, 168.4, 168.0, 166.6, 165.0, 157.2, 146.4, 141.6, 141.1, 128.2, 123.9, 123.1, 117.7, 113.4, 112.0, 97.7, 97.5, 44.6, 43.3, 34.8, 28.4, 25.7; 31P NMR (162 MHz, CDCl3, ppm): *δ* -7.9; LC-MS *(m/z*) (*%*): Calcd. for C24H24F2N6O5P: 528; Found: 528 [M]+. Anal. Calcd. for C24H24F2N6O5P: C, 54.75; H, 4.59; and N, 15.96; Found: C, 54.72; H, 4.56; and N, 15.89.

*4-Nitrophenyl N-(2,4-difluorophenyl)-P-4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)phosp horramidate (4c)*

Pale brown solid, Yield (%): 79; mp: 140-142 oC; IR (cm-1, υmax): 3391 (NH), 1256 (P=O), 785 (C-Pali); 1H NMR (400 MHz, CDCl3, ppm): *δ* 8.13 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.42 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.36 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.11 (d, 1H, *J* = 9.0 Hz, Ar-H), 6.79 (s, 1H, Ar-H), 6.76 (d, 1H, *J* = 9.2 Hz, Ar-H), 6.74 (d, 1H, *J* = 8.4 Hz, Ar-H), 6.54 (d, 1H, *J* = 8.5 Hz, Ar-H), 4.17 (t, 1H, *J* = 6.3 Hz, NH), 3.35 (t, 4H, *J* = 9.2 Hz, N-CH2), 2.81-2.84 (m, 1H, CH2), 1.49 (qt, 4H, *J* = 14.2 Hz, N-CH2); 13C NMR (100 MHz, CDCl3, ppm): *δ* 167.4, 165.2, 159.4, 156.2, 148.6, 141.1, 128.1,126.4, 123.2, 121.3, 118.1, 116.3, 112.3, 111.2, 104.1, 97.6, 47.7, 32.5, 28.1; 31P NMR (162 MHz, CDCl3, ppm): *δ* -11.6; LC-MS *(m/z*) (*%*): Calcd. for C24H20F3N4O5P: 532; Found: 533 [M+H]+; Anal. Calcd. for C24H20F3N4O5P: C, 54.14; H, 3.79; and N, 10.52; Found: C, 54.20; H, 3.72; and N, 10.58.

*4-NitrophenylN-benzo[d]thiazol-2-yl-P-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)phosp horramidate (4d)*

Pale brown solid, Yield (%): 87; mp: 160-162 oC; IR (cm-1, υmax): 3436 (NH), 1254 (P=O), 762 (C-Pali); 1H NMR (400 MHz, CDCl3, ppm): *δ* 8.23 (d, 2H, *J* = 8.3 Hz, Ar-H), 8.16 (d, 1H, *J* = 8.5 Hz, thiazol Ar-H), 8.04 (d, 1H, *J* = 8.3 Hz, thiazol Ar-H), 7.52 (t, 1H, *J* = 8.4 Hz, thiazol Ar-H), 7.48 (t, 1H, *J* = 9.0 Hz, thiazol Ar-H), 7.41 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.35 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.32 (d, 2H, *J* = 12.2 Hz, Ar-H), 6.83 (s, 1H, Ar-H), 4.11 (t, 1H, *J* = 10.3 Hz, NH), 3.34 (t, 4H, *J* = 13.6 Hz, N-CH2), 2.69-2.74 (m, 1H, CH2), 1.52 (qt, 4H, *J* = 9.3 Hz, N-CH2); 13C NMR (100 MHz, CDCl3, ppm): *δ* 173.1, 167.4, 165.2, 152.1, 148.6, 141.1, 130.2, 128.4, 125.3, 124.5, 123.2, 121.3, 118.1, 116.3, 111.2, 97.6, 47.7, 32.5, 28.1; 31P NMR (162 MHz, CDCl3, ppm): *δ* -12.2; LC-MS *(m/z*) (*%*): Calcd. for C25H21FN5O5PS: 553; Found: 554 [M+H]+; Anal. Calcd. for C25H21FN5O5PS: C,54.25; H, 3.82; and N, 12.65; Found: C,54.18; H, 3.79; and N, 12.60.

*4-Nitrophenyl 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl(1H-indol-1-yl)phosphoramidate (4e)*

Yellow solid, Yield (%): 84; mp: 135-137 oC. IR (cm-1, υmax): 3423 (NH), 1252 (P=O), 761 (C-Pali); 1H NMR (400 MHz, CDCl3, ppm): *δ* 8.21 (d, 2H, *J* = 9.6 Hz, Ar-H), 7.93 (d, 1H, *J* = 15.3 Hz, indolyl Ar-H), 7.90 (d, 1H, *J* = 6.0 Hz, indolyl Ar-H), 7.61 (d, 1H, *J* = 8.5 Hz, indolyl Ar-H), 7.44 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.36 (t, 1H, *J* = 8.6 Hz, indolyl Ar-H), 7.33 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.30 (d, 2H, *J* = 8.5 Hz, Ar-H), 6.89 (t, 1H, *J* = 5.0 Hz, indolyl Ar-H), 6.85 (s, 1H, Ar-H), 6.34 (d, 1H, *J* = 7.2 Hz, indolyl Ar-H), 3.32 (t, 4H, *J* = 11.6 Hz, N-CH2), 2.78-2.81 (m, 1H, CH2), 1.48 (qt, 4H, *J* = 9.3 Hz, N-CH2); 13C NMR (100 MHz, CDCl3, ppm): *δ* 167.4, 165.2, 148.6, 141.1, 134.4, 128.5, 125.2, 124.5, 126.4, 123.2, 121.9, 120.6, 120.1, 119.2, 116.3, 111.4, 110.2, 101.4, 97.6, 47.7, 32.5, 28.1; 31P NMR (162 MHz, CDCl3, ppm): *δ* -9.4; LC-MS *(m/z*) (*%*): Calcd. for C26H22FN4O5P: 520; Found: 521 [M+H]+; Anal. Calcd. for C26H22FN4O5P: C,60.00; H, 4.26; and N, 10.77; Found: C,60.06; H, 4.31; and N, 10.83.

*4-Nitrophenyl N-4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl-P-(pyridin-3-yl-methyl)phos phorramidate (4f)*

Brown solid, Yield (%): 78; mp: 170-172 oC. IR (cm-1,υmax): 3435 (NH), 1257 (P=O), 762 (C-Pali); 1H NMR (400 MHz, CDCl3, ppm): *δ* 8.56 (s, 1H, pyridinyl CH), 8.39 (d, 1H, *J* = 6.0 Hz, pyridinyl CH), 8.24 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.81 (d, 1H, *J* = 8.1 Hz, pyridinyl CH), 7.41 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.39 (t, 1H, *J* = 8.0 Hz, pyridinyl CH), 7.33 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.14 (d, 1H, *J* = 10.2 Hz, Ar-H), 6.81 (s, 1H, Ar-H), 4.14 (t, 1H, *J* = 8.6 Hz, NH), 4.06 (s, 2H, CH2), 3.36 (t, 4H, *J* = 12.3 Hz, N-CH2), 2.82-2.85 (m, 1H, CH2), 1.54 (qt, 4H, *J* = 12.2 Hz, N-CH2); 13C NMR (100 MHz, CDCl3, ppm): *δ* 167.4, 163.2, 148.4, 147.2, 145.3, 142.4, 137.3, 134.5, 128.5, 123.3, 122.5, 121.4, 115.6, 112.3, 98.4, 48.5, 43.2, 33.3, 29.2; 31P NMR (162 MHz, CDCl3, ppm): *δ* -10.1; LC-MS *(m/z*) (*%*): Calcd. for C24H23FN5O5P: 511; Found: 511 [M]+; Anal. Calcd. for C24H23FN5O5P: C,56.36; H, 4.53; and N, 13.69; Found: C,56.42; H, 4.47; and N, 13.73.

*4-Nitrophenyl N-4,6-dimethoxypyrimidin-2-yl-P-(4-(6-fluorobenzo[d] isoxazol-3-yl)piperidin-1-yl)phosphoramidate (4g)*

Pale brown solid, Yield (%): 92; mp: 205-207 oC. IR (cm-1,υmax): 3346 (NH), 1252 (P=O), 772 (C-Pali); 1H NMR (400 MHz, CDCl3, ppm): *δ* 8.28 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.45 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.29 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.21 (d, 1H, *J* = 8.4 Hz, Ar-H), 6.79 (s, 1H, Ar-H), 5.67 (s, 1H, pyrimidinyl CH), 4.19 (t, 1H, *J* = 13.2 Hz, NH), 3.78 (s, 6H, OCH3), 3.39 (t, 4H, *J* = 11.6 Hz, N-CH2), 2.76-2.81 (m, 1H, CH2), 1.58 (qt, 4H, *J* = 8.7 Hz, N-CH2); 13C NMR (100 MHz, CDCl3, ppm): *δ* 169.3, 168.1, 164.2, 163.6, 147.3, 142.1, 128.5, 122.4, 122.5, 116.6, 111.5, 98.3, 74.3, 54.5, 48.2, 33.6, 28.4; 31P NMR (162 MHz, CDCl3, ppm): *δ* -9.3; LC-MS *(m/z*) (*%*): Calcd. for C24H24FN6O7P: 558; Found: 559 [M+H]+; Anal. Calcd. for C24H24FN6O7P: C,51.62; H, 4.33; and N, 15.05; Found: C, 51.67; H, 4.38; and N, 15.11.

*4-Nitrophenyl azepan-1-yl(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)phosphoramidate (4h)*

Brown solid, Yield (%): 96; IR (cm-1, υmax): 3456 (NH), 1243 (P=O), 778 (C-Pali); 1H NMR (400 MHz, CDCl3, ppm): *δ* 8.26 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.43 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.35 (d, 2H, *J* = 7.3 Hz, Ar-H), 7.17 (d, 1H, *J* = 8.2 Hz, Ar-H), 6.84 (s, 1H, Ar-H), 3.37 (t, 4H, *J* = 13.3 Hz, N-CH2), 2.74-2.78 (m, 1H, CH2), 2.91 (t, 4H, *J* = 11.6 Hz, CH2), 1.56 (m, 2H, CH2), 1.51 (t, 4H, *J* = 13.3 Hz, N-CH2), 1.46 (qt, 4H, CH2); 13C NMR (100 MHz, CDCl3, ppm): *δ* 167.3, 164.3, 148.2, 142.3, 128.2, 124.3, 122.4, 117.4, 112.3, 98.5, 51.2, 48.5, 33.6, 29.2, 25.4, 23.5; 31P NMR (162 MHz, CDCl3, ppm): *δ* -10.2 ; LC-MS *(m/z*) (*%*): Calcd. for C23H26FN4O5P: 488; Found: 489 [M+H]+; Anal. Calcd. for C23H26FN4O5P: C, 56.56; H, 5.37; and N, 11.47; Found: C, 56.61; H, 5.32; and N, 11.52.

*4-Nitrophenyl methyl ((4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)-tyrosinate phosphor ramidate (4i)*

Brown solid, Yield (%): 92; mp: 180-182 oC. IR (cm-1, υmax): 3358 (NH), 1249 (P=O), 778 (C-Pali); 1H NMR (400 MHz, CDCl3, ppm): *δ* 9.12 (s, 1H, Ar-OH), 8.25 (d, 2H, *J* = 8.2 Hz, Ar-H), 7.43 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.37 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.14 (d, 1H, *J* = 8.5 Hz, Ar-H), 6.93 (d, 2H, *J* = 7.5 Hz, Ar-H), 6.86 (s, 1H, Ar-H), 6.63 (d, 2H, *J* = 9.0 Hz, Ar-H), 4.14 (t, 1H, *J* = 11.1 Hz, NH), 3.86 (qt, 1H, *J* = 7.1 Hz, -CH), 3.62 (s, 3H, COOCH3), 3.54 (d, 2H, *J* = 11.5 Hz, CH2), 3.33 (t, 4H, *J* = 5.6 Hz, N-CH2), 2.76-2.81 (m, 1H, CH2), 1.53 (qt, 4H, *J* = 16.3 Hz, N-CH2); 13C NMR (100 MHz, CDCl3, ppm): *δ* 172.3, 168.1, 164.3, 156.1, 148.2, 142.3, 132.1, 129.1, 128.2, 123.4, 121.6, 116.4, 116.4, 113.1, 97.2, 55.2, 52.2, 47.1, 39.5, 32.2, 28.4; 31P NMR (162 MHz, CDCl3, ppm): *δ* -10.6; LC-MS *(m/z*) (*%*): Calcd. for C28H28FN4O8P: 598; Found: 598 [M]+; Anal. Calcd. for C28H28FN4O8P: C, 56.19; H, 4.72; and N, 9.36; Found: C, 56.12; H, 4.70; and N, 9.34.

*4-Nitrophenyl methyl ((4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)tryptophanate phosp horamidate (4j)*

Pale brown solid, Yield (%): 91; mp: 185-187 oC. IR (cm-1, υmax): 3445 (NH), 1253 (P=O), 772 (C-Pali); 1H NMR (400 MHz, CDCl3, ppm): *δ* 10.82 (s, 1H, NH), 8.26 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.52 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.43 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.33 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.31 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.22 (d, 1H, *J* = 7.3 Hz, Ar-H), 7.16 (d, 1H, *J* = 6.5 Hz, Ar-H), 7.05 (t, 1H, *J* = 13.2 Hz, Ar-H), 6.95 (t, 1H, *J* = 8.6 Hz, Ar-H), 6.86 (s, 1H, Ar-H), 4.14 (t, 1H, *J* = 11.3 Hz, NH), 3.85 (qt, 1H, *J* = 15.3 Hz, -CH), 3.41 (d, 2H, *J* = 6.5 Hz, CH2), 3.65 (s, 3H, COOCH3), 3.37 (t, 4H, *J* = 9.6 Hz, N-CH2), 2.75-2.78 (m, 1H, CH2), 1.54 (qt, 4H, *J* = 10.3 Hz, N-CH2); 13C NMR (100 MHz, CDCl3, ppm): *δ* 172.4, 167.4, 165.2, 148.6, 141.1, 137.2, 128.4, 127.2, 124.2, 123.1, 122.2, 121.9, 119.2, 118.3, 116.3, 113.4, 111.5, 109.4, 97.6, 55.2, 51.1, 47.7, 32.8, 31.1, 28.1; 31P NMR (162 MHz, CDCl3, ppm): *δ* -9.5; LC-MS *(m/z*) (*%*): Calcd. for C30H29FN5O7P: 621; Found: 622 [M+H]+; Anal. Calcd. for C30H29FN5O7P: C, 57.97; H, 4.70; and N, 11.27; Found: C, 57.93; H, 4.76; and N, 11.32.

Table S1: Anti-bacterial activity of the title compounds (4a-j) against gram-positive bacteria.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Compound | *S. aureus*  25 50 75 100 | | | | *B. subtilis*  25 50 75 100 | | | |
| 4a | 19.1 | 29.6 | 40.3 | 62.1 | 18.0 | 31.3 | 39.8 | 49.3 |
| 4b | 25.6 | 36.2 | 50.6 | 69.4 | 23.6 | 39.2 | 49.6 | 54.2 |
| 4c | 18.0 | 30.3 | 41.5 | 63.0 | 16.2 | 34.3 | 43.5 | 47.1 |
| 4d | 26.3 | 38.3 | 51.2 | 70.0 | 24.3 | 39.6 | 48.4 | 56.0 |
| 4e | 17.2 | 27.6 | 39.3 | 60.1 | 16.2 | 30.7 | 39.2 | 48.3 |
| 4f | 16.1 | 25.1 | 36.0 | 59.4 | 15.2 | 32.3 | 42.2 | 49.6 |
| 4g | 15.4 | 23.2 | 34.1 | 58.2 | 19.4 | 34.1 | 38.1 | 46.4 |
| 4h | 24.2 | 37.4 | 49.3 | 68.0 | 23.2 | 39.5 | 50.2 | 55.4 |
| 4i | 26.4 | 38.1 | 51.6 | 70.3 | 22.2 | 41.3 | 49.2 | 54.3 |
| 4j | 25.6 | 38.3 | 50.5 | 71.1 | 24.6 | 40.2 | 50.7 | 56.1 |
| Stda | 28.6 | 41.0 | 55.9 | 74.6 | 26.9 | 44.0 | 52.1 | 58.7 |

aStandard: Norfloxacin was used as a standard.

Table S2: Anti-bacterial activity of the title compounds (4a-j) against gram-negative bacteria.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Compound | *K.pneumoniae*  25 50 75 100 | | | | *S. typhi*  25 50 75 100 | | | | *P. mirabilis*  25 50 75 100 | | | |
| 4a | 29.2 | 43.4 | 58.3 | 69.2 | 28.5 | 45.1 | 60.1 | 68.3 | 30.0 | 44.1 | 59.2 | 70.4 |
| 4b | 34.4 | 54.2 | 65.1 | 78.5 | 36.6 | 55.1 | 67.0 | 79.0 | 35.3 | 55.3 | 66.2 | 79.1 |
| 4c | 26.6 | 45.5 | 59.4 | 70.0 | 27.1 | 47.1 | 58.2 | 71.3 | 29.5 | 45.2 | 60.2 | 69.2 |
| 4d | 35.6 | 53.1 | 66.5 | 76.1 | 36.5 | 55.2 | 68.3 | 78.2 | 36.2 | 56.3 | 67.1 | 77.4 |
| 4e | 28.3 | 44.6 | 58.6 | 71.3 | 27.1 | 46.5 | 59.4 | 70.1 | 29.1 | 45.2 | 58.3 | 70.5 |
| 4f | 29.7 | 48.3 | 60.1 | 69.4 | 30.3 | 45.1 | 58.2 | 68.2 | 28.6 | 47.1 | 60.5 | 68.6 |
| 4g | 29.4 | 47.4 | 59.7 | 71.5 | 29.1 | 44.2 | 58.8 | 71.6 | 28.6 | 48.2 | 60.2 | 70.2 |
| 4h | 35.3 | 54.3 | 66.4 | 76.6 | 36.2 | 56.3 | 67.5 | 77.1 | 36.2 | 55.1 | 66.3 | 77.1 |
| 4i | 36.4 | 55.1 | 66.6 | 77.2 | 37.3 | 54.5 | 68.1 | 77.8 | 35.3 | 56.3 | 68.1 | 78.5 |
| 4j | 36.8 | 56.2 | 68.4 | 78.6 | 37.1 | 56.4 | 69.3 | 79.6 | 37.5 | 57.4 | 67.3 | 77.3 |
| Stda | 39.6 | 58.2 | 72.0 | 84.3 | 39.6 | 58.2 | 72.0 | 84.3 | 39.6 | 58.2 | 72.0 | 84.3 |

aStandard: Norfloxacin was used as a standard.

Table S3: Anti-fungal activity of the title compounds against (4a-j) *A. niger* and *A. flavus.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Compound | *A. niger*  25 50 75 100 | | | | *A. flavus*  25 50 75 100 | | | |
| 4a | 24.2 | 33.4 | 41.1 | 55.1 | 27.5 | 37.2 | 46.4 | 57.1 |
| 4b | 31.3 | 32.2 | 47.4 | 61.2 | 36.6 | 46.2 | 54.2 | 65.1 |
| 4c | --- | 30.1 | 43.3 | 54.3 | 29.1 | 38.2 | 47.3 | 59.4 |
| 4d | 30.9 | 40.3 | 48.6 | 60.4 | 35.6 | 45.3 | 53.4 | 64.6 |
| 4e | 25.1 | 33.3 | 43.5 | 56.2 | 30.3 | 38.4 | 47.7 | 58.3 |
| 4f | 24.3 | 31.6 | 42.4 | 55.5 | 29.4 | 39.1 | 48.3 | 57.1 |
| 4g | 23.4 | 32.4 | 43.1 | 54.6 | 31.2 | 37.4 | 47.5 | 58.4 |
| 4h | 31.5 | 40.2 | 48.1 | 62.2 | 36.3 | 45.3 | 54.6 | 65.1 |
| 4i | 32.0 | 40.8 | 50.3 | 61.4 | 35.5 | 46.6 | 55.1 | 65.6 |
| 4j | 33.1 | 42.1 | 49.2 | 62.1 | 36.7 | 45.1 | 55.7 | 66.1 |
| Stda | 35.8 | 44.6 | 52.9 | 65.2 | 39.0 | 48.5 | 57.3 | 69.5 |

aStandard: Nystatin was used as a standard. “---” indicates no activity.

Table S4: Dock profiles of synthesized compounds (4a-j) and standards against 3V2B protein.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Compound | Binding energy  (K cal mol-1) | Bonding interaction | Bond Length(AO) | Bond Angle (o) | Bond Type |
| **4a** | - 9.4 | Ser 302 CB ….ON | 2.8 | 79.9 | H- acc |
| **4b** | - 7.5 | Ile 342 CZ ….HN | 2.4 | 103.8 | H- don |
| **4c** | - 7.4 | Ser 311 CZ ….ON | 2.3 | 107.1 | H- acc |
| **4d** | - 9.5 | Ile 291 CZ ….ON  Gln 247 CB ….OP  Gly 387 CZ ….ON | 1.9  2.4  2.4 | 120.8  97.9  88.0 | H- acc  H- acc  H- acc |
| **4e** | - 8.1 | Ala 385 CA ….HN  Gly 389 CA ….ON  Gly 387 CZ ….ON  Thr 388 CB ….ON  Thr 388 CB ….ON | 2.3  2.4  2.3  2.3  2.4 | 98.3  107.7  114.0  130.0  78.4 | H- don  H- acc  H- acc  H- acc  H- acc |
| **4f** | - 8.8 | Arg 309 CA ….ON  Gln 427 CB ….OP  Gly 387 CZ ….ON  Ser 302 CB ….ON  Val 424 CB ….HN | 2.3  2.3  1.9  2.5  2.6 | 89.1  121.7  130.2  122.7  81.8 | H- acc  H- acc  H- acc  H- acc  H- don |
| **4g** | -7.4 | Ala 391 CA ….ON  Gly 387 CA ….ON  Ser 302 CB ….ON  Ala 385 CB ….OC  Val 313 CZ ….OC | 2.3  2.2  2.5  2.2  2.1 | 99.7  133.2  96.6  87.4  107.0 | H- acc  H- acc  H- acc  H- acc  H- acc |
| **4h** | -8.4 | Val 313 CB ….OP | 2.4 | 99.7 | H- acc |
| **4i** | -8.7 | Ile 291 CZ ….ON  Ser 302 CZ ….ON | 2.0  2.2 | 123.7  117.2 | H- acc  H- acc |
| **4j** | -7.2 | Asn 308 CB ….ON  Arg 305 CA ….OP  Ser 302 CZ ….ON  Gly 387 CB ….ON | 2.6  2.7  2.4  1.9 | 107.1  90.3  88.7  88.4 | H- acc  H- acc  H- acc  H- acc |
| Norfloxacin | - 5.8 | Thr 303 CB ….HO  Gly 359 CZ ….OH | 1.9  2.5 | 97.0  121.8 | H- don  H- acc |
| Nystatin | - 6.6 | Thr 379 CB ….OH  Thr 379 CB ….OH  Ser 380 CZ ….OC  Gln 295 CA ….OC  Lys 422 CB ….OC | 2.4  2.7  2.3  2.1  2.1 | 77.6  85.5  96.3  104.0  118.7 | H- acc  H- acc  H- acc  H- acc  H- acc |