**SUPPLEMENTARY INFORMATION**

*Table S1. Observed and predicted activity of wild and T877A mutant AR of bicalutamide derivatives*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| In | Ar (B ring) | X | R (A ring) | Wild (pIC50) | T877A (pIC50) |
| Observed | Predicted | Observed | Predicted |
| Bic | 4-F-Ph | SO2 | 4-CN, 3-CF3 | 4.16 | 4.69 | 4.34 | 4.38 |
| 44e  | 4-CN-Ph | O | 4-CN, 3-CF3 | 4.61 | 4.64 | 4.67 | 4.57 |
| R-Bic | 4-F-Ph | SO2 | 4-CN, 3-CF3 | 4.28 | 4.29 | 4.34 | 4.29 |
| 22c | 3-CF3-Ph | S | 4-CN, 3-CF3 | 5.03 | 4.91 | 5.29 | 5.40 |
| 22d | 2-CF3-Ph | S | 4-CN, 3-CF3 | 5.12 | 5.18 | 5.3 | 5.29 |
| 22h | 4-OCF3-Ph | S | 4-CN, 3-CF3 | 4.39 | 4.59 | 4.36 | 4.36 |
| 22o | 4-CF3-2-Pyridine | S | 4-CN, 3-CF3 | 4.04 | 4.41 | 4.09 | 4.11 |
| 23b# | 4-CF3-Ph | S | 4-NO2, 3-CF3 | 4.67 | 4.85 | 4.54 | 4.61 |
| 23c\* | 3-CF3-Ph | S | 4-NO2, 3-CF3 | 5.06 | 5.19 | 5.19 | 5.53 |
| 23d\* | 2-CF3-Ph | S | 4-NO2, 3-CF3 | 5.35 | 5.35 | 5.32 | 5.43 |
| 24a# | 4-F-Ph | S | 4-CN, 2-CF3 | 4.34 | 4.55 | 4.57 | 4.65 |
| 24c | 3-CF3-Ph | S | 4-CN, 2-CF3 | 4.62 | 4.76 | 4.94 | 4.85 |
| 24d | 2-CF3-Ph | S | 4-CN, 2-CF3 | 4.73 | 4.65 | 4.96 | 4.81 |
| 25a | 4-F-Ph | S | 4-NO2, 2-CF3 | 4.67 | 4.68 | 4.92 | 4.69 |
| 25b# | 4-CF3-Ph | S | 4-NO2, 2-CF3 | 4.76 | 4.73 | 5.06 | 5.09 |
| 25c | 3-CF3-Ph | S | 4-NO2, 2-CF3 | 4.78 | 4.65 | 4.99 | 5.02 |
| 25d | 2-CF3-Ph | S | 4-NO2, 2-CF3 | 4.89 | 4.94 | 4.93 | 4.87 |
| 25f | 3,4-F-Ph | S | 4-NO2, 2-CF3 | --- | --- | 4.08 | 4.66 |
| 25g | 2,4-F-Ph | S | 4-NO2, 2-CF3 | 4.77 | 4.74 | 4.95 | 4.85 |
| 25i# | 3-OCF3-Ph | S | 4-NO2, 2-CF3 | 4.79 | 4.90 | 5.03 | 5.06 |
| 25l | 2-OCF3-Ph | S | 4-NO2, 2-CF3 | 5.27 | 5.22 | 5.48 | 5.42 |
| 25o\* | 4-CF3-2-Pyridine | S | 4-NO2, 2-CF3 | 4.76 | 4.63 | 4.95 | 4.84 |
| 25p | 5-CF3-2-Pyridine | S | 4-NO2, 2-CF3 | 4.76 | 4.93 | 5.25 | 5.17 |
| 26c | 3-CF3-Ph | S | 4-CF3 | 4.7 | 4.62 | 4.64 | 4.73 |
| 26d\* | 2-CF3-Ph | S | 4-CF3 | 5.23 | 5.12 | 5.14 | 4.83 |
| 26i | 3-OCF3-Ph | S | 4-CF3 | 4.72 | 4.77 | 4.85 | 4.88 |
| 27b# | 4-CF3-Ph | O | 4-CN, 3-CF3 | 5.01 | 4.69 | 5.19 | 5.21 |
| 27c# | 3-CF3-Ph | O | 4-CN, 3-CF3 | 5.04 | 4.72 | 5.08 | 4.94 |
| 27d# | 2-CF3-Ph | O | 4-CN, 3-CF3 | 4.77 | 4.55 | 5.01 | 4.98 |
| 27f | 3,4-F-Ph | O | 4-CN, 3-CF3 | 4.59 | 4.58 | 4.72 | 4.77 |
| 27g | 2,4-F-Ph | O | 4-CN, 3-CF3 | 4.41 | 4.42 | 4.42 | 4.60 |
| 27h# | 4-OCF3-Ph | O | 4-CN, 3-CF3 | 4.75 | 4.59 | 4.86 | 4.74 |
| 27i | 3-OCF3-Ph | O | 4-CN, 3-CF3 | 5 | 5.02 | 5 | 5.03 |
| 28b\* | 4-CF3-Ph | O | 4-NO2, 3-CF3 | 4.96 | 5.02 | 4.76 | 5.14 |
| 28c\*,# | 3-CF3-Ph | O | 4-NO2, 3-CF3 | 4.98 | 4.66 | 5 | 4.90 |
| 28d# | 2-CF3-Ph | O | 4-NO2, 3-CF3 | 4.56 | 4.49 | 4.64 | 4.63 |
| 28e | 4-CN-Ph | O | 4-NO2, 3-CF3 | 4.57 | 4.54 | 4.72 | 4.80 |
| 28f\* | 3,4-F-Ph | O | 4-NO2, 3-CF3 | 4.72 | 4.75 | 4.83 | 4.76 |
| 28g | 2,4-F-Ph | O | 4-NO2, 3-CF3 | 4.67 | 4.68 | 4.94 | 4.87 |
| 28h\* | 4-OCF3-Ph | O | 4-NO2, 3-CF3 | 4.7 | 4.72 | 4.75 | 4.91 |
| 28i\* | 3-OCF3-Ph | O | 4-NO2, 3-CF3 | 5.01 | 5.07 | 5 | 5.09 |
| 28l | 2-OCF3-Ph | O | 4-NO2, 3-CF3 | 5.01 | 4.98 | 5.15 | 5.11 |
| 28m\* | 4-CN,2-CF3-Ph | O | 4-NO2, 3-CF3 | 5.07 | 5.05 | 5.24 | 5.44 |
| 28n | 4-CN,3-F-Ph | O | 4-NO2, 3-CF3 | 4.9 | 4.97 | 5.11 | 5.13 |
| 28o | 4-CF3-2-Pyridine | O | 4-NO2, 3-CF3 | --- | --- | 4.43 | 4.51 |
| 29b\* | 4-CF3-Ph | O | 4-CN, 2-CF3 | 4.63 | 4.59 | 4.54 | 4.55 |
| 29c\*,# | 3-CF3-Ph | O | 4-CN, 2-CF3 | 4.66 | 4.53 | 4.81 | 5.03 |
| 29d\* | 2-CF3-Ph | O | 4-CN, 2-CF3 | 4.65 | 4.79 | 4.85 | 4.62 |
| 29e | 4-CN-Ph | O | 4-CN, 2-CF3 | 4.21 | 4.16 | 4.45 | 4.38 |
| 29f | 3,4-F-Ph | O | 4-CN, 2-CF3 | 4.32 | 4.28 | 4.45 | 4.44 |
| 29g | 2,4-F-Ph | O | 4-CN, 2-CF3 | 4.29 | 4.26 | 4.51 | 4.48 |
| 29h\* | 4-OCF3-Ph | O | 4-CN, 2-CF3 | 4.65 | 4.66 | 4.55 | 4.58 |
| 29i\*,# | 3-OCF3-Ph | O | 4-CN, 2-CF3 | 4.24 | 4.66 | 4.19 | 4.21 |
| 29l\*,# | 2-OCF3-Ph | O | 4-CN, 2-CF3 | 4.35 | 4.77 | 4.47 | 4.64 |
| 29m\* | 4-CN,2-CF3-Ph | O | 4-CN, 2-CF3 | 4.75 | 4.64 | 5.02 | 5.24 |
| 29n | 4-CN,3-F-Ph | O | 4-CN, 2-CF3 | 4.11 | 4.07 | 4.1 | 4.10 |
| 30b\* | 4-CF3-Ph | O | 4-NO2, 2-CF3 | 4.73 | 4.82 | 4.86 | 4.62 |
| 30c\* | 3-CF3-Ph | O | 4-NO2, 2-CF3 | 4.71 | 4.80 | 4.88 | 5.08 |
| 31c | 3-CF3-Ph | O | 4-CF3 | 4.72 | 4.81 | 4.74 | 4.96 |
| 31d | 2-CF3-Ph | O | 4-CF3 | 4.93 | 4.87 | 5.15 | 5.03 |
| 31i# | 3-OCF3-Ph | O | 4-CF3 | 5.36 | 5.41 | 5.66 | 5.42 |
| 32b | 4-CF3-Ph | SO2 | 4-CN, 3-CF3 | 4.53 | 4.52 | 4.69 | 4.63 |
| 32c# | 3-CF3-Ph | SO2 | 4-CN, 3-CF3 | 4.4 | 4.41 | 4.82 | 4.76 |
| 32d#,\* | 2-CF3-Ph | SO2 | 4-CN, 3-CF3 | 4.23 | 4.35 | 4.36 | 4.42 |
| 32h,\* | 4-OCF3-Ph | SO2 | 4-CN, 3-CF3 | 4.48 | 4.35 | 4.49 | 4.40 |
| 33b | 4-CF3-Ph | SO2 | 4-NO2, 3-CF3 | 4.5 | 4.46 | 4.74 | 4.67 |
| 33c | 3-CF3-Ph | SO2 | 4-NO2, 3-CF3 | 4.51 | 4.35 | 4.79 | 4.74 |
| 33d | 2-CF3-Ph | SO2 | 4-NO2, 3-CF3 | 4.55 | 4.56 | 4.59 | 4.59 |
| 34a | 4-F-Ph | SO2 | 4-CN, 2-CF3 | 4.18 | 4.17 | 4.03 | 4.05 |
| 34b\* | 4-CF3-Ph | SO2 | 4-CN, 2-CF3 | 4.36 | 4.35 | 4.48 | 4.73 |
| 34c | 3-CF3-Ph | SO2 | 4-CN, 2-CF3 | 4.34 | 4.43 | 4.49 | 4.55 |
| 34d | 2-CF3-Ph | SO2 | 4-CN, 2-CF3 | --- | --- | 4.13 | 4.16 |
| 35a | 4-F-Ph | SO2 | 4-NO2, 2-CF3 | 4.23 | 4.27 | 4.41 | 4.47 |
| 35b | 4-CF3-Ph | SO2 | 4-NO2, 2-CF3 | 4.32 | 4.46 | 4.53 | 4.51 |
| 35c | 3-CF3-Ph | SO2 | 4-NO2, 2-CF3 | 4.41 | 4.37 | 4.77 | 4.79 |
| 35d | 2-CF3-Ph | SO2 | 4-NO2, 2-CF3 | 4.41 | 4.36 | 4.68 | 4.58 |
| 35f\* | 3,4-F-Ph | SO2 | 4-NO2, 2-CF3 | 4.42 | 4.37 | 4.71 | 4.39 |
| 35g | 2,4-F-Ph | SO2 | 4-NO2, 2-CF3 | 4.23 | 4.21 | 4.74 | 4.57 |
| 35i | 3-OCF3-Ph | SO2 | 4-NO2, 2-CF3 | 4.69 | 4.63 | 4.91 | 4.77 |
| 35l | 2-OCF3-Ph | SO2 | 4-NO2, 2-CF3 | 4.28 | 4.22 | 4.75 | 4.83 |
| 35p | 5-CF3-2-Pyridine | SO2 | 4-NO2, 2-CF3 | 4.23 | 4.11 | 4.34 | 4.37 |
| 42b (R) | 4-CF3-Ph | S | 4-CN, 3-CF3 | 5.03 | 4.71 | 4.84 | 4.74 |
| 42c (R)# | 3-CF3-Ph | S | 4-CN, 3-CF3 | 5.05 | 4.94 | 4.84 | 4.86 |
| 42d (R)\* | 2-CF3-Ph | S | 4-CN, 3-CF3 | 5.53 | 5.52 | 5.1 | 4.92 |
| 42g (R) | 2,4-F-Ph | S | 4-CN, 3-CF3 | 4.73 | 4.70 | 4.59 | 4.50 |
| 42h (R) | 4-OCF3-Ph | S | 4-CN, 3-CF3 | 4.75 | 4.74 | 4.7 | 4.72 |
| 45b (R) | 4-CF3-Ph | SO2 | 4-CN, 3-CF3 | 4.5 | 4.37 | 4.75 | 4.69 |
| 45c (R) | 3-CF3-Ph | SO2 | 4-CN, 3-CF3 | 4.39 | 4.56 | 4.88 | 4.92 |
| 45d (R)# | 2-CF3-Ph | SO2 | 4-CN, 3-CF3 | 4.42 | 4.58 | 4.49 | 4.52 |
| 45g (R) | 2,4-F-Ph | SO2 | 4-CN, 3-CF3 | 4.21 | 4.15 | 4.37 | 4.27 |
| 45h (R)#,\* | 4-OCF3-Ph | SO2 | 4-CN, 3-CF3 | 4.5 | 4.66 | 4.72 | 4.83 |
| 46a (R) | 4-F-Ph | SO2 | 4-CN, 2-CF3 | --- | --- | 4.06 | 4.05 |
| 52 | 2-CF3-Ph | S | 4-NO2, 3-CF3 | 5.55 | 5.32 | 6.14 | 6.15 |
| 24a\* | 3,5-CF3-Ph | S | 4-CN, 3-CF3 | 5.56 | 5.81 | 5.63 | 5.60 |
| 25a\* | 3,5-CF3-Ph | S | 4-NO2, 3-CF3 | 5.81 | 5.83 | 5.82 | 5.68 |
| 26a# | 3,5-CF3-Ph | S | 4-CN, 2-CF3 | 5.17 | 5.12 | 5.11 | 5.01 |
| 27a\* | 3,5-CF3-Ph | S | 4-NO2, 2-CF3 | 5.45 | 5.28 | 5.5 | 5.33 |
| 28a | 3,5-CF3-Ph | S | 4-CF3 | 5 | 5.12 | 5.01 | 4.95 |
| 29b\* | 3-CF3-Ph | S | 3,5-CF3 | 5 | 4.97 | 5.05 | 4.97 |
| 29c | 2-CF3-Ph | S | 3,5-CF3 | 5.41 | 5.50 | 5.44 | 5.50 |
| 29d | 3-OCF3-Ph | S | 3,5-CF3 | 5.03 | 5.04 | 5.11 | 5.08 |
| 29e | 2-OCF3-Ph | S | 3,5-CF3 | 5.53 | 5.60 | 5.53 | 5.53 |
| 30a# | 3,5-CF3-Ph | O | 4-CN, 3-CF3 | 5.6 | 5.10 | 5.52 | 5.57 |
| 30f# | 3,5-tBu-Ph | O | 4-CN, 3-CF3 | 5.52 | 5.45 | 5.57 | 5.72 |
| 31a#,\* | 3,5-CF3-Ph | S | 4-NO2, 3-CF3 | 5.77 | 5.85 | 6 | 5.93 |
| 32a# | 3,5-CF3-Ph | O | 4-CN, 2-CF3 | 5.32 | 5.02 | 5.44 | 5.49 |
| 33a\* | 3,5-CF3-Ph | O | 4-NO2, 2-CF3 | 4.82 | 4.96 | 4.62 | 4.83 |
| 34a\* | 3,5-CF3-Ph | O | 4-CF3 | 5.38 | 5.41 | 5.47 | 5.11 |
| 35a | 3,5-CF3-Ph | SO2 | 4-CN, 3-CF3 | 5.2 | 4.93 | 5.54 | 5.59 |
| 36a | 3,5-CF3-Ph | SO2 | 4-NO2, 3-CF3 | 5.48 | 5.15 | 5.67 | 5.61 |
| 38a | 3,5-CF3-Ph | SO2 | 4-NO2, 2-CF3 | 5.14 | 5.11 | 5.51 | 5.49 |
| 39b | 3-CF3-Ph | SO2 | 3,5-CF3 | 5 | 4.82 | 5.02 | 5.04 |
| 39c | 2-CF3-Ph | SO2 | 3,5-CF3 | 5.06 | 5.01 | 5.07 | 5.20 |
| 39d# | 3-OCF3-Ph | SO2 | 3,5-CF3 | 5 | 4.88 | 5.02 | 4.98 |
| 39e | 2-OCF3-Ph | SO2 | 3,5-CF3 | 5 | 5 | 5.09 | 5.15 |
| 41 | 3,5-CF3-Ph | S | 4-CN, 3-CF3 | 6.07 | 5.81 | 6.1 | 5.92 |
| 42 | 3,5-CF3-Ph | SO2 | 4-CN, 3-CF3 | 5.38 | 5.26 | 5.7 | 5.76 |

\*Test set = T877A, #Test set = Wild

*Table S2. Observed and predicted activity of wild and T877A mutant AR of enzalutamide derivatives*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| In | R1 | X | R2 | Wild (pIC50) | T877A (pIC50) |
| Observed  | Predicted  | Observed  | Predicted |
| 61b# | 4-CN, 3-CF3 | O | 4-CF3 | 4.52 |  4.41 | 5.02 | 5.19 |
| 62b# | 4-NO2, 3-CF3 | O | 4-CF3 | 4.13 |  4.42 | 5.67 | 5.60 |
| 62c | 4-NO2, 3-CF3 | O | 3-CF3 | --- | --- | 4.81 | 4.87 |
| 63b | 4-CN, 2-CF3 | O | 4-CF3 | --- | --- | 5.07 | 5.15 |
| 63c | 4-CN, 2-CF3 | O | 3-CF3 | --- | --- | 4.73 | 4.78 |
| 64b | 4-NO2, 2-CF3 | O | 4-CF3 | --- | --- | 5.42 | 5.43 |
| 64c | 4-NO2, 2-CF3 | O | 3-CF3 | 4.87 |  5.05 | 5.39 | 5.18 |
| 65b | 3-CF3 | O | 4-CF3 | 4.14 |  4.26 | 5.22 | 5.24 |
| 65c | 3-CF3 | O | 3-CF3 | 4.12 |  4.20 | 5.24 | 5.09 |
| 71b | 4-CF3 | O | 3-CF3 | --- | --- | 4.78 | 4.90 |
| 71d | 2-CF3 | O | 3-CF3 | --- | --- | 4.54 | 4.80 |
| Enz\*,# | 4-CN, 3-CF3 | S | 3-F, 4-CONHMe | 4.27 | 4.38 | 4.94 | 4.88 |
| 49 | 4-NO2, 3-CF3 | S | 3,5-CF3 | 4.54 | 4.65 | 5 | 5.05 |
| 51 | 4-NO2, 2-CF3 | S | 3,5-CF3 | 4.73 | 4.77 | 5.33 | 5.40 |
| 54# | 3,5-CF3 | S | 3-F, 4-CONHMe | 4.7 | 4.68 | 4.94 | 4.97 |

\*Test set = T877A, #Test set = Wild

*Table S3. Observed and predicted activity of full antagonist of 1-arylmethyl-4-phenylpyrrole derivatives*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| I.D | R1 | X | R2 | R3 | R4 | R5 | Observed (pIC50) | Predicted (pIC50) |
| 1 | H | Bond | Me | CO2Et | NO2 | Me | 6.61 | 6.30 |
| 2 | Me | Bond | Me | CO2Et | NO2 | Me | 6.30 | 6.18 |
| 3\* | Phenyl | Bond | Me | CO2Et | NO2 | Me | 5.36 | 5.38 |
| 4a | Phenyl | CH2 | Me | CO2Et | NO2 | Me | 6.46 | 6.42 |
| 4b\* | Phenyl | CH2 | Me | CO2Me | NO2 | Me | 6.52 | 6.43 |
| 4d | Phenyl | CH2 | Me | CH2OH | NO2 | Me | 5.42 | 5.60 |
| 4e | Phenyl | CH2 | Me | COMe | NO2 | Me | 5.33 | 5.52 |
| 4f | Phenyl | CH2 | Me | H | NO2 | Me | 6.30 | 6.25 |
| 4g | Phenyl | CH2 | Me | CO2Me | H | Me | 5.58 | 5.92 |
| 4h\* | Phenyl | CH2 | Me | CO2Me | CN | Me | 6.56 | 6.32 |
| 4j | Phenyl | CH2 | Me | CN | CN | Me | 7.39 | 7.24 |
| 4l\* | 2-Chloro-5-Methylpyridine | CH2 | Me | CN | CN | Me | 7.34 | 6.97 |
| 4m\* | (5-methylpyridin-3-yl)methanol | CH2 | Me | CN | CN | Me | 7 | 7.27 |
| 4n | (2-chloro-5-methylpyridin-3-yl)methanol | CH2 | Me | CN | CN | Me | 7.60 | 7.46 |
| 4o | (2-chloro-5-methylpyridin-3-yl)methanol | CH2 | H | CN | CN | Me | 6.49 | 6.90 |
| 4p | (2-chloro-5-methylpyridin-3-yl)methanol | CH2 | Me | CN | CN | H | 6.76 | 6.93 |
| 5 | Cyclo-hexyl | CH2 | Me | CO2Et | NO2 | Me | 5.42 | 5.11 |
| 6 | Phenyl | (CH2)2 | Me | CO2Et | NO2 | Me | 5.38 | 5.33 |
| 7\* | Phenyl | C=O | Me | CO2Et | NO2 | Me | 5.61 | 5.95 |
| 8 | Phenyl | SO2 | Me | CO2Et | NO2 | Me | 5.32 | 5.32 |

\*Test set

*Table S4. Observed and predicted activity of full antagonist of 4-arylmethyl-1-phenylpyrazole derivatives*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| I.D | R1 | R2 | X | Observed (pIC50)  | Predicted (pIC50)  |
| 3\* | H | 4- F | CH2 | 6.15 | 6.30 |
| 28b | Cl | 3- CONH2 | CH2 | 6.15 | 6.04 |
| 28c | Cl | 4- CONH2 | CH2 | 6.37 | 6.44 |
| 28d\* | Cl | 4-CONHMe | CH2 | 5.88 | 6.24 |
| 28e | Cl | 4-CONMe2 | CH2 | 5.39 | 5.53 |
| 28f | Cl | 4-CONH*t*Bu | CH2 | 6.01 | 6.24 |
| 28g | Cl | 4-CONH(CH2) 2OH | CH2 | 5.56 | 5.60 |
| 28h\* | Cl | 4-CONHCH2C(CH2) 2 OH | CH2 | 6.22 | 5.71 |
| 33 | Cl | 4-F | Bond | 5.20 | 5.00 |
| 36 | Cl | 4-F | (CH2)2 | 5.95 | 6.10 |

\*Test set

*Table S5. Observed and predicted activity of full antagonist of 4-aryloxy-1-phenylpyrazole derivatives*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| I.D | X | Y | R1 | Observed (pIC50)  | Predicted (pIC50)  |
| 25 | CH | CH | F | 6.17 | 6.06 |
| 29a | CH | CH | N-(2-hydroxy-2-methylpropyl)acetamide | 5.74 | 5.69 |
| 29b | CH | CH | 1-morpholinoethanone | 5.52 | 5.49 |
| 44b | N | CH | N-methylpivalamide | 5.39 | 5.28 |
| 45 | CH | N | N-methylacetamide | 5.14 | 5.18 |

*Table S6. Observed and predicted activity of full antagonist of 3-aryl-3-hydroxy-1-phenylpyrrolidine derivatives*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| I.D | R1 | R3 | R2 | C-3 | Observed (pIC50)  | Predicted (pIC50)  |
| 48 | CONHMe | Cl | *S*-Me | *R* | 7.60 | 7.45 |
| 49 | CONMe2 | Cl | *S*-Me | *R* | 5.76 | 6.18 |
| 50 | CONHMe | Cl | *R*-Me | *S* | 5.19 | 5.06 |
| 51 | Pyrrolidin-2-one | Cl | *S*-Me | *R* | 7.95 | 7.63 |
| 52\* | CONHMe | OMe | *S*-Me | *R* | 7.20 | 7.25 |
| 53 | CONHMe | H | *S*-Me | *R* | 6.39 | 6.39 |
| 54 | CONHMe | F | *S*-Me | *R* | 6.53 | 6.70 |

\*Test set

*Figure S1. Interaction of the hit molecule with helix-12 negative AR*



The A and B ring sites matched with the benzo-oxadiazole rings. The oxygen atom of the oxadiazole in A ring (R11) matched with the acceptor site point. This group forms the essential H-Bond interaction with Arg752, Gln711, and HOH108 (mediated through Gln711). The nitrogen atoms of the oxadiazole ring form H-Bond interactions with HOH108, Met745 (bridged through HOH108), and Gln711. The oxadiazole ring also forms pi-pi interaction with Phe764.