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SUPPLEMENTARY MATERIAL TO

Synthesis, computational and pharmacological evaluation of novel *N*-{4-[2-(4-aryl-piperazin-1-yl)ethyl]phenyl}-arylamides

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1-(4-(2-methoxyphenyl)piperazin-1-yl)-2-(4-nitrophenyl)ethan-1-one (**2b**): Yield: 74%, oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 8.25-8.15 (*m*, 2H, ArH), 7.50-7.41 (*m*, 2H, ArH), 7.09-6.84 (*m*, 4H, ArH), 3.87 (*s*, 5H, 3H OCH_3 and 2H CH_2), 3.83 (*d*, *J* = 5.1, 2H piperazine), 3.71-3.60 (*m*, 2H, piperazine), 3.06-2.95 (*m*, 4H, piperazine). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 167.91, 152.12, 146.89, 142.67, 140.28, 129.90 (2C), 123.73 (3C), 120.00, 118.32, 111.25, 55.32, 50.75, 50.26, 46.23, 43.11, 40.94.

1-(4-(2,3-dichlorophenyl)piperazin-1-yl)-2-(4-nitrophenyl)ethan-1-one (**2c**): Yield: 74%, oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 8.26-8.16 (*m*, 2H, ArH), 7.51-7.40 (*m*, 2H, ArH), 7.24-7.11 (*m*, 2H, ArH), 6.89 (*dd*, J_1 = 7.2, J_2 = 2.4, 1H, ArH), 3.86 (*d*, *J* = 6.7, 4H piperazine), 3.72-3.60 (*m*, 2H, CH_2), 2.98-2.89 (*m*,4H, piperazine). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 168.88, 150.92, 148.10, 142.53, 134.23, 130.81 (2C), 127.60, 125.38, 123.88 (3C), 118.74, 52.03, 50.15, 46.27, 42.63, 40.27.

1-(2-methoxyphenyl)-4-(4-nitrophenethyl)piperazine (**3b**): Yield: 72%, oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 8.21-8.10 (*m*, 2H, ArH), 7.44-7.35 (*m*, 2H, ArH), 7.08-6.84 (*m*, 4H, ArH), 3.87 (*s*, 3H, OCH_3), 3.13 (*t*, *J* = 4.9, 4H piperazine), 2.99-2.91 (*m*, 2H, CH_2), 2.82-2.65 (*m*, 6H, 4H piperazine and CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 152.22, 148.36, 146.48, 141.12, 128.98 (2C), 124.14, 123.01 (2C), 120.96, 118.16, 111.13, 59.48, 55.29, 53.29 (2C), 50.54 (2C), 33.90.

1-(2,3-dichlorophenyl)-4-(4-nitrophenethyl)piperazine (**3c**): Yield: 72%, oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 8.22-8.12 (*m*, 2H, ArH), 7.46-7.33 (*m*, 2H, ArH), 7.22-7.10 (*m*, 2H, ArH), 7.01-6.92 (*m*, 1H, ArH), 3.09 (*t*, *J* = 4.7, 4H piperazine), 2.99-2.92 (*m*, 2H, CH_2), 2.75-2.68 (*m*, 6H, 4H piperazine and CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 151.14, 147.73, 146.54, 134.05 (2C), 129.54 (2C), 127.48, 124.67, 124.13 (2C), 118.60, 59.34, 53.17(2C), 52.03 (2C), 34.08.

4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)aniline (**4b**): Yield: 93%, oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.07-6.81 (*m*, 6H, ArH), 6.68-6.56 (*m*, 2H, ArH), 3.86 (*s*, 3H, OCH_3), 3.14 (*s*, 4H, piperazine), 2.83-2.68 (*m*, 6H, 4H piperazine and CH_2), 2.66-2.57 (*m*, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 152.71, 144.46, 141.24, 131.00, 130.09 (2C), 123.38, 120.91, 118.14, 115.20 (2C), 103.92, 59.84, 54.48, 52.88 (2C), 51.00 (2C), 33.70.

4-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)aniline (**4c**): Yield: 89%, oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.18-8.12 (*m*, 2H, NH_2), 7.38 (*d*, *J* = 8.4, 2H, ArH), 7.29-7.21 (*m*, 2H, ArH), 6.93 (*d*, *J* = 8.2, 2H, ArH), 6.86 (*t*, *J* = 7.3, 1H, ArH), 3.28-3.16 (*m*, 4H, piperazine), 2.96-2.92 (*m*, 2H, CH_2), 2.76-2.61 (*m*, 6H, 4H piperazine and CH_2). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 151.18, 148.23, 146.52, 129.54 (2C), 127.85 (2C), 123.64, 119.46 (2C), 116.09 (2C), 59.42, 53.54 (2C), 49.14 (2C), 33.43.

2-hydroxy-N-*(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)nicotinamide* (**5b**): Yield: 69%, oil. IR (ATR): 3257, 2933, 2832, 1673, 1593, 1239, 1115, 1022, 752, cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 8.71 (*d*, *J* = 9.4, 1H, ArH), 7.65 (*d*, *J* = 8.5, 1H, ArH), 7.57 (*d*, *J* = 8.5, 1H, ArH), 7.26-7.21 (*m*, 3H, ArH), 7.04-6.99 (*m*, 1H, ArH), 6.97-6.91 (*m*, 2H, ArH), 6.87 (*d*, *J* = 9.6, 1H, ArH), 6.59 (*t*, *J* = 6.8, 1H, ArH), 3.87 (*s*, 3H, OCH_3), 3.15 (*s*, 4H, piperazine), 2.88-2.66 (*m*, 8H, 4H piperazine and $2CH_2$). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 163.70, 160.59, 151.61, 145.49, 139.81, 137.71, 136.34, 136.09, 129.15 (2C), 122.98, 121.86, 120.97, 120.67, 120.11, 118.21, 110.67, 108.08, 60.38, 54.94 (2C), 53.31 (2C), 50.43, 32.81. (+)ESI-HRMS *m/z*: calculated for $[C_{25}H_{28}N_4O_3+H^+]$ 433.22342, observed 433.22197.

N-*(4-{2-[4-(2,3-dichlorophenyl)piperazin-1-yl]ethyl}phenyl)benzamide* (**5c**): Yield: 88%, oil. IR (ATR): 3113, 2958, 2814, 1675, 1599, 1268, 1114, 961, 778, cm^{-1}. ^1H NMR (500 MHz, DMSO-d6, δ): 8.44 (*dd*, J_1 = 7.2, J_2 = 2.1, 1H, ArH), 7.78 (*dd*, J_1 = 6.2, J_2 = 2.3, 1H, ArH), 7.58 (*d*, *J* = 8.3, 2H, ArH), 7.28-7.25 (*m*, 2H, ArH), 7.21 (*d*, *J* = 8.1, 2H, ArH), 7.13-7.11 (*m*, 1H, ArH), 6.55 (*t*, *J* = 6.7, 1H, ArH), 2.97 (*s*, 4H piperazine), 2.72 (*t*, *J* = 7.8, 2H, CH_2), 2.60-2.55 (*m*, 6H, 4H piperazine and CH_2). ^{13}C NMR (126 MHz, DMSO-d6, δ): 162.95, 161.76, 151.60, 144.85, 140.41, 136.74, 136.23, 133.01, 129.56 (2C), 128.83, 126.40, 124.71, 120.52, 120.04, 119.95 (2C), 107.28, 60.00, 53.12 (2C), 51.32 (2C), 32.53. (+)ESI-HRMS *m/z*: calculated for $[C_{24}H_{24}Cl_2N_4O_2+H^+]$ 471.13491, observed 471.13342.

6-hydroxy-N-*(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)nicotinamide* (**6b**): Yield: 86%, oil. IR (ATR): 3118, 2944, 2814, 1673, 1539, 1238, 1133, 1028, 751, cm^{-1}. ^1H NMR (500 MHz, DMSO-d6, δ): 9.90 (*s*, 1H, OH), 8.17 (*d*, *J* = 2.7, 1H, ArH), 7.94 (*dd*, J_1 = 9.6, J_2 = 2.6, 1H, ArH), 7.58 (*d*, *J* = 8.5, 2H, ArH), 7.17 (*d*, *J* = 8.6, 2H, ArH), 6.93-6.89 (*m*, 2H, ArH), 6.84-6.82 (*m*, 2H, ArH), 6.38 (*d*, *J* = 9.7, 1H, ArH), 3.75 (*s*, 3H, OCH_3), 2.94 (*s*, 4H, piperazine), 2.71 (*t*, *J* = 7.8, 2H, CH_2), 2.56-2.52 (*m*, 6H, 4H piperazine and 2H CH_2). ^{13}C NMR (126 MHz, DMSO-d6, δ): 162.74, 152.93, 141.68, 139.72, 138.34, 137.34, 135.99, 129.12 (2C), 123.18, 121.91 (2C), 120.67 (2C), 119.53, 118.71, 113.03, 112.32, 60.27, 56.23, 53.36 (2C), 51.01 (2C), 32.58. (+)ESI-HRMS *m/z*: calculated for $[C_{25}H_{28}N_4O_3+H^+]$ 433.22342, observed 433.22182.

N-*(4-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)phenyl)-6-hydroxynicotinamide* (**6c**): Yield: 92%, oil. IR (ATR): 3281, 2921, 2809, 1651, 1518, 1255, 1131, 790, cm^{-1}. ^1H NMR (500 MHz, DMSO-d6, δ): 9.90 (*s*, 1H, OH), 8.17 (*s*, 1H), 7.94 (*dd*, J_1 = 9.7, J_2 = 2.7, 1H, ArH), 7.58 (*d*, *J* = 8.2, 2H, ArH), 7.30-7.27 (*m*, 2H, ArH), 7.18 (*d*, *J* = 8.3, 2H, ArH), 7.12 (*dd*, J_1 = 6.8, J_2 = 2.9, 1H, ArH), 6.38 (*d*, *J* = 9.6, 1H, ArH), 3.35 (*s*, 4H, piperazine), 2.97 (*s*, 4H, piperazine), 2.71 (*t*, *J* = 7.7, 2H, CH_2), 2.60-2.55 (*m*, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d6, δ): 162.74, 151.62, 139.71, 138.35, 137.72, 135.93, 132.42, 129.12 (2C), 128.84

(2C), 125.94, 124.72, 120.68 (2C), 119.97, 119.53, 113.03, 60.48, 53.14 (2C), 51.34 (2C), 32.56. (+)ESI-HRMS *m/z*: calculated for [$C_{24}H_{24}Cl_2N_4O_2$+H^+] 471.13491, observed 471.13327.

2-(4-hydroxyphenyl)-N-*(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-phenyl)acetamide* (**7b**): Yield: 91%, oil. IR (ATR): 3300, 2953, 2835, 1656, 1513, 1243, 1115, 1022, 754, cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d6, δ): 10.00 (*s*, 1H, OH), 7.50 (*d*, *J* = 8.5, 2H), 7.14 (*dd*, J_1 = 13.6, J_2 = 8.5, 4H), 6.95-6.88 (*m*, 2H), 6.87-6.85 (*m*, 2H), 6.71 (*d*, *J* = 8.5, 2H), 3.76 (*s*, 3H, OCH_3), 3.48 (*s*, 2H, CH_2), 2.96 (*s*, 4H, piperazine), 2.72-2.65 (*m*, 2H, CH_2), 2.57 (*s*, 4H, piperazine), 2.55-2.51 (*m*, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d6, δ): 169.84, 156.44, 152.38, 141.68, 137.63, 135.56, 130.37 (2C), 129.21 (2C), 126.60, 122.74, 121.25, 119.52 (2C), 118.30, 115.48 (2C), 112.32, 60.27, 55.71, 53.36 (2C), 50.43(2C), 42.92, 32.55. (+)ESI-HRMS *m/z*: calculated for [$C_{27}H_{31}N_3O_3$+H^+] 446.24382, observed 446.24189.

3-hydroxy-N-*(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)benz-amide* (**8b**): Yield: 75%, oil. IR (ATR): 3402, 2956, 2828, 1674, 1518, 1239, 1116, 1022, 750, cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d6, δ): 10.10 (*s*, 1H, OH), 7.68 (*d*, *J* = 8.1, 2H, ArH), 7.38 (*d*, *J* = 7.6, 1H, ArH), 7.32-7.29 (*m*, 2H, ArH), 7.21-7.17 (*m*, 2H, ArH), 6.98-6.88 (*m*, 5H, ArH), 3.79 (*s*, 3H, OCH_3), 2.97 (*s*, 4H, piperazine), 2.75-2.70 (*m*, 2H, CH_2), 2.58-2.55 (*m*, 6H, 4H piperazine and 2H CH_2). ^{13}C NMR (126 MHz, DMSO-d6, δ): 167.43, 159.40, 154.00, 143.29, 139.13, 138.53, 137.68, 131.40, 130.72 (2C), 124.35, 122.86, 122.37 (2C), 121.16, 120.14, 119.91, 116.54, 113.93, 61.88, 57.95, 54.98 (2C), 52.05 (2C), 35.40. (+)ESI-HRMS *m/z*: calculated for [$C_{26}H_{29}N_3O_3$+H^+] 432.22817, observed 432.22637.

4-hydroxy-N-*(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)benz-amide* (**9b**): Yield: 69%, oil. IR (ATR): 3195, 2962, 2829, 1679, 1501, 1244, 1146, 1026, 747, cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d6, δ): 10.09 (*s*, 1H, OH), 8.24 (*s*, 1H, ArH), 7.49 (*d*, *J* = 8.2, 2H, ArH), 7.18 (*d*, *J* = 8.4, 2H, ArH), 7.10 (*d*, *J* = 8.1, 1H, ArH), 6.94-6.87 (*m*, 6H, ArH), 3.76 (*s*, 3H, OCH_3), 2.96 (*s*, 4H, piperazine), 2.73-2.70 (*m*, 2H, CH_2), 2.58-2.53 (*m*, 6H, 4H piperazine and 2H CH_2). ^{13}C NMR (126 MHz, DMSO, δ): 164.49, 161.38, 153.99, 143.27, 138.18, 137.70, 131.57, 131.00 (2C), 124.36, 122.86 (2C), 121.15 (2C), 119.91 (2C), 119.68, 116.82, 113.93, 61.81, 57.32, 55.61 (2C), 52.85 (2C), 34.14. (+)ESI-HRMS *m/z*: calculated for [$C_{26}H_{29}N_3O_3$+H^+] 432.22817, observed 432.22709.

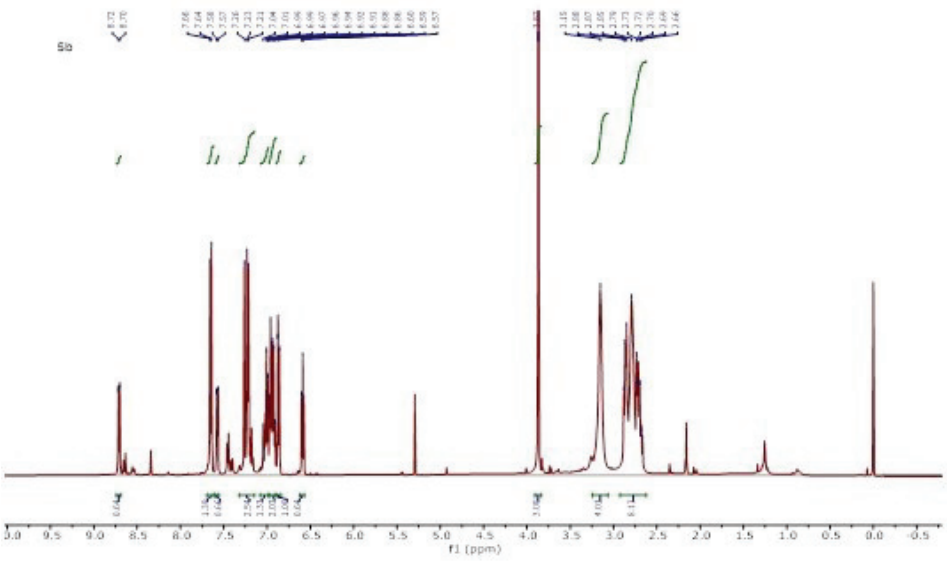


Fig. S-1. ^{1}H-NMR spectrum for 2-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)nicotinamide (**5b**)

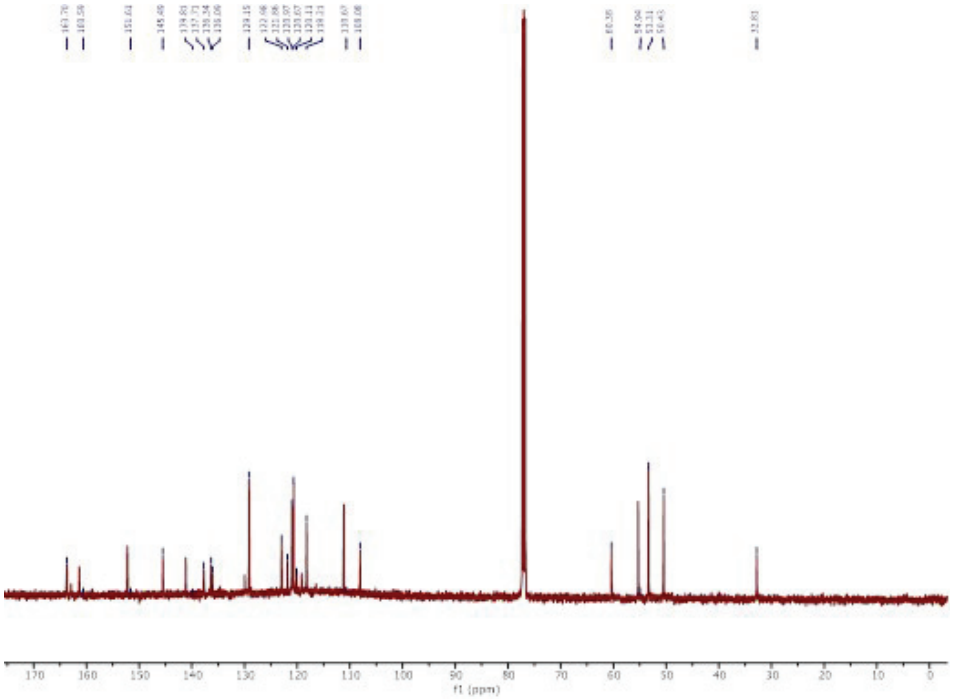
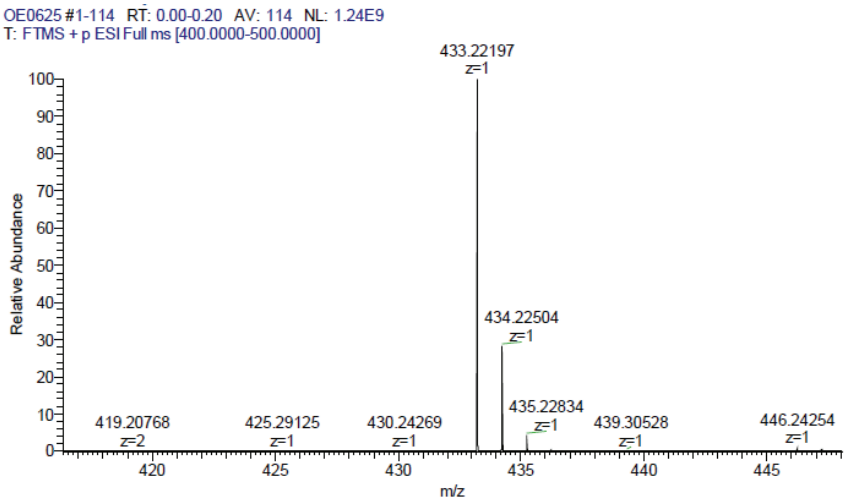


Fig. S-2. ^{13}C-NMR spectrum for 2-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)nicotinamide (**5b**)



Exact mass	Observed mass	Observed ion type	Error (ppm)
433.22342	433.22197	$[M+H]^+$	3.35

Fig. S-3. HRMS spectrum for 2-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)nicotinamide (**5b**)

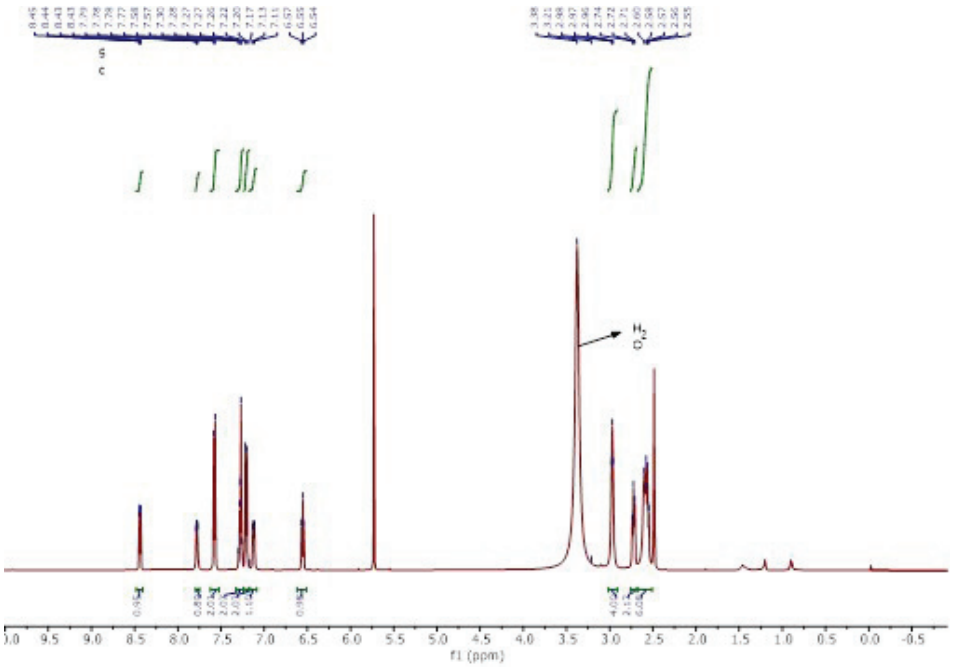


Fig. S-4. ^{1}H-NMR spectrum for *N*-(4-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)phenyl)-2-hydroxynicotinamide (**5c**)

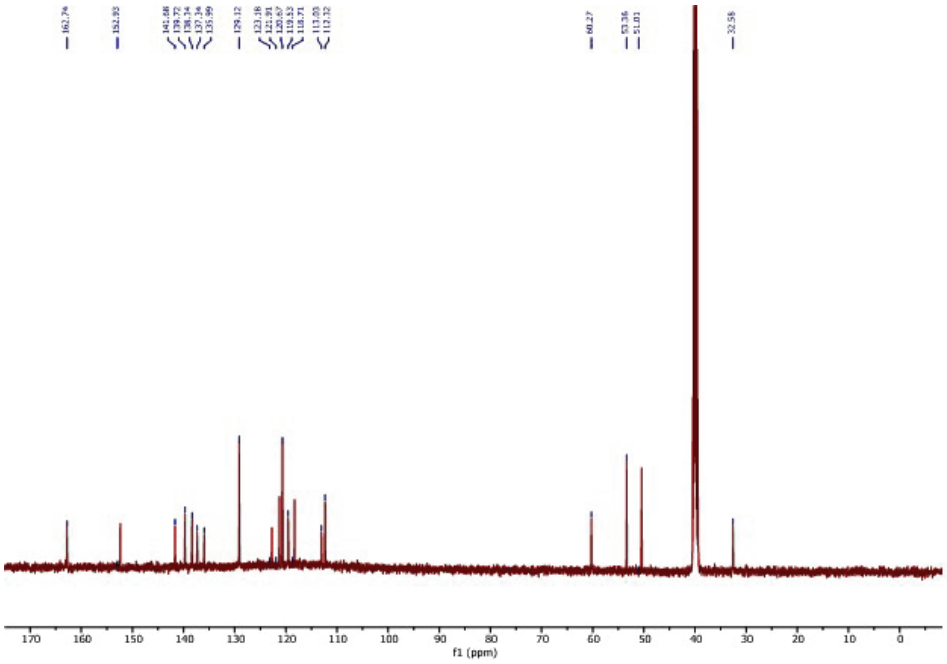
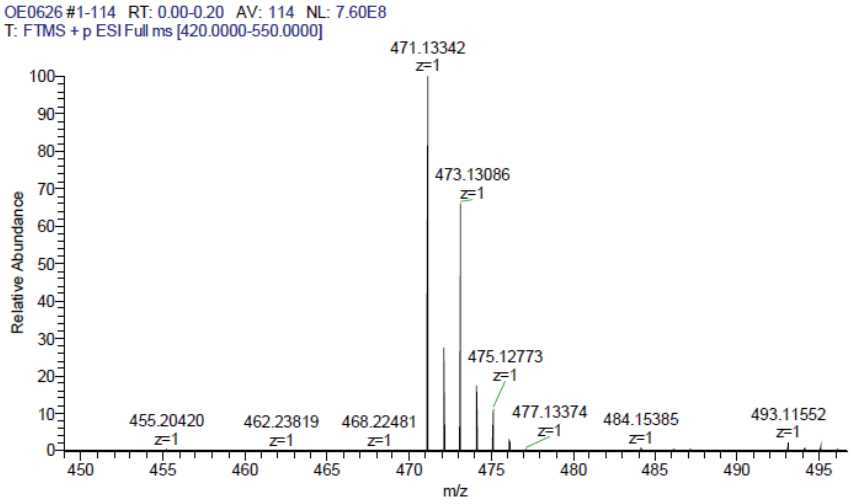


Fig. S-5. ^{13}C-NMR spectrum for *N*-(4-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)phenyl)-2-hydroxynicotinamide (**5c**)



Exact mass	Observed mass	Observed ion type	Error (ppm)
471.13491	471.13342	$[M+H]^+$	3.16

Fig. S-6. HRMS spectrum for *N*-(4-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)phenyl)-2-hydroxynicotinamide (**5c**)

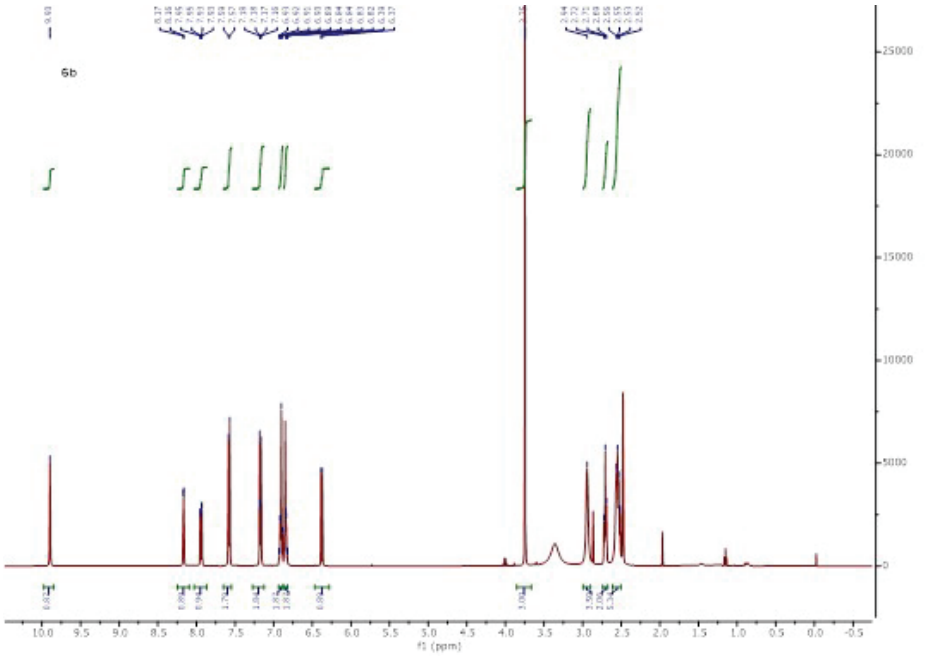


Fig. S-7. ^{1}H-NMR spectrum for 6-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)nicotinamide (**6b**)

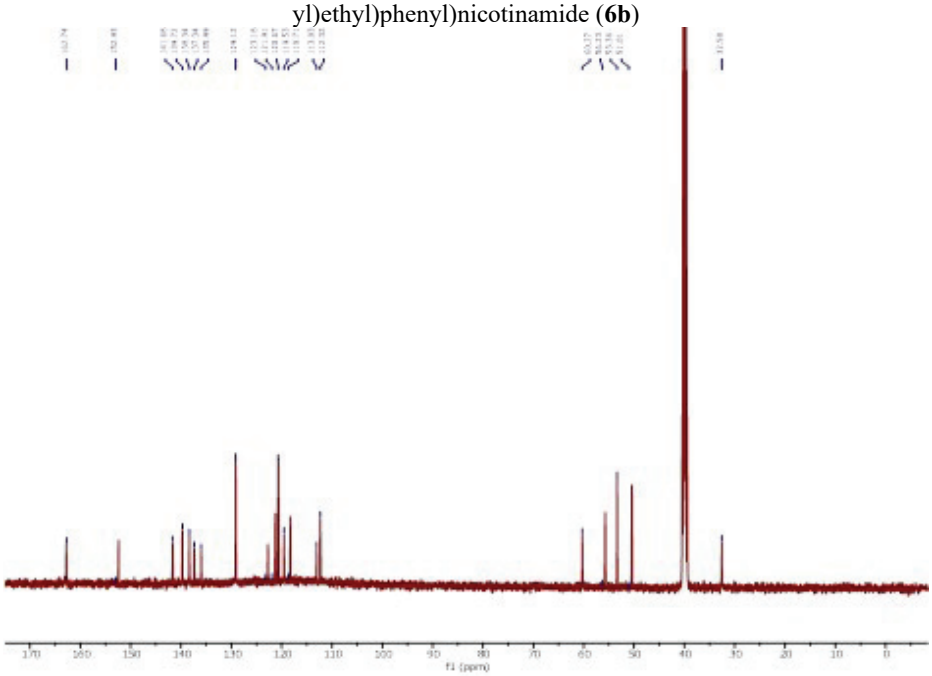
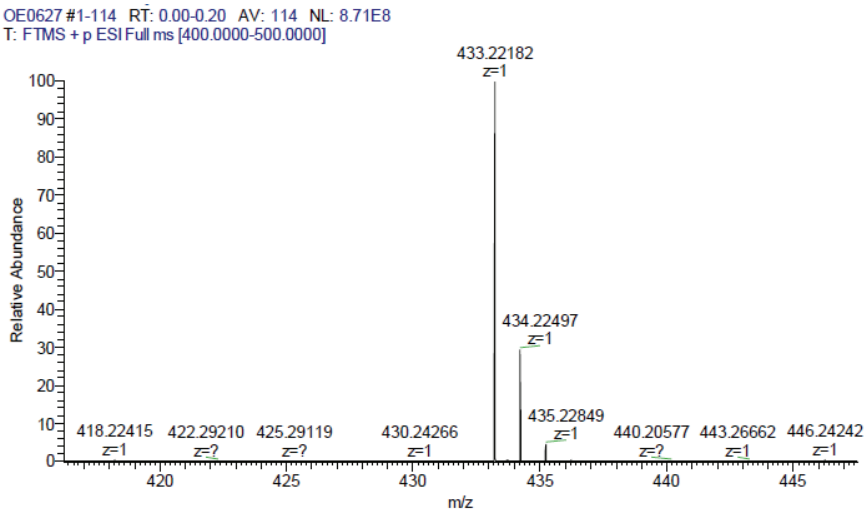


Fig. S-8. ^{13}C-NMR spectrum for 6-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)nicotinamide (**6b**)



Exact mass	Observed mass	Observed ion type	Error (ppm)
433.22342	433.22182	$[M+H]^+$	3.69

Fig. S-9. HRMS spectrum for 6-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)nicotinamide (**6b**)

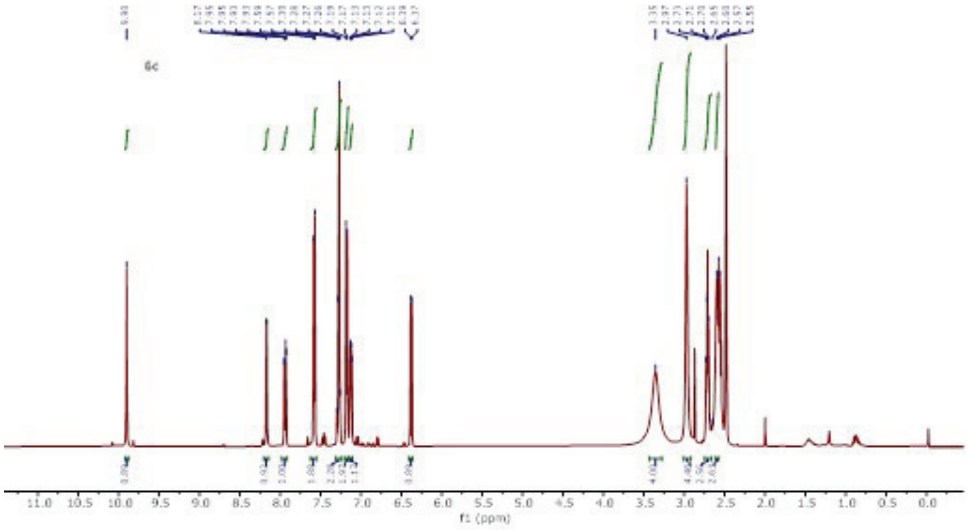


Fig. S-10. ^{1}H-NMR spectrum for *N*-(4-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)phenyl)-6-hydroxynicotinamide (**6c**)

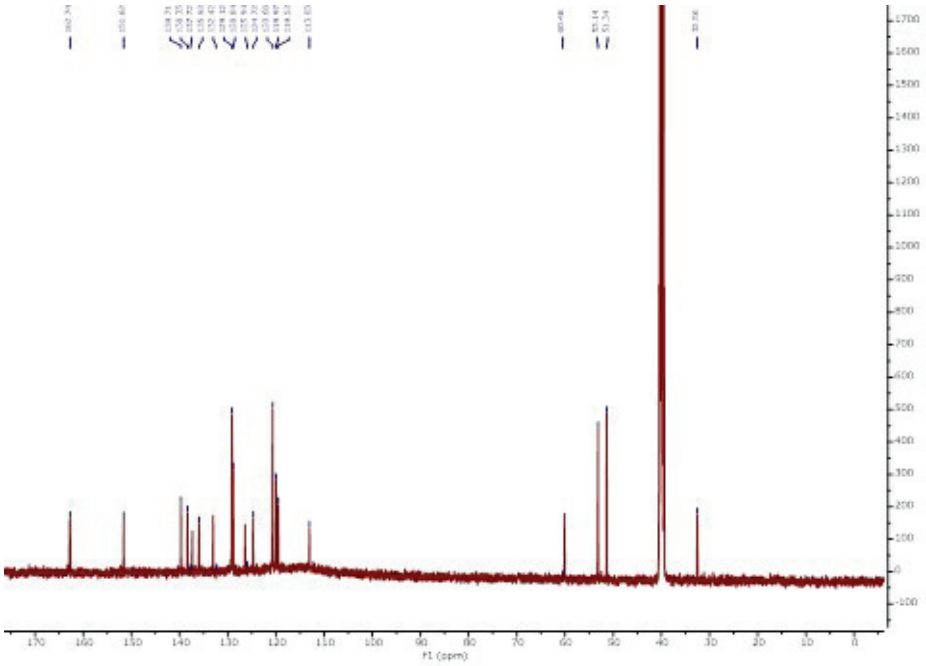
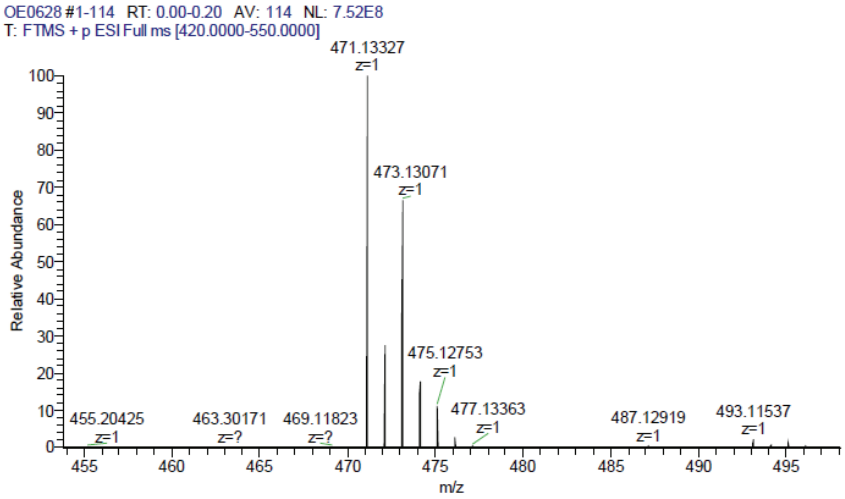


Fig. S-11. ^{13}C-NMR spectrum for *N*-(4-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)phenyl)-6-hydroxynicotinamide (**6c**)



Exact mass	Observed mass	Observed ion type	Error (ppm)
471.13491	471.13327	$[M+H]^+$	3.48

Fig. S-12. HRMS spectrum for *N*-(4-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)phenyl)-6-hydroxynicotinamide (**6c**)

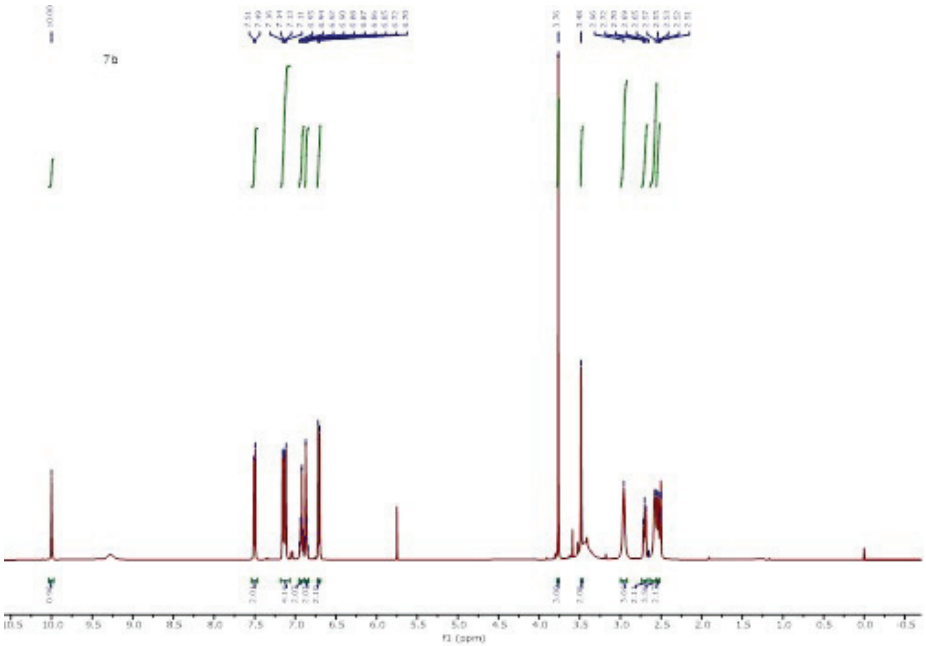


Fig. S-13. ^{1}H-NMR spectrum for 2-(4-hydroxyphenyl)-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)acetamide (**7b**)

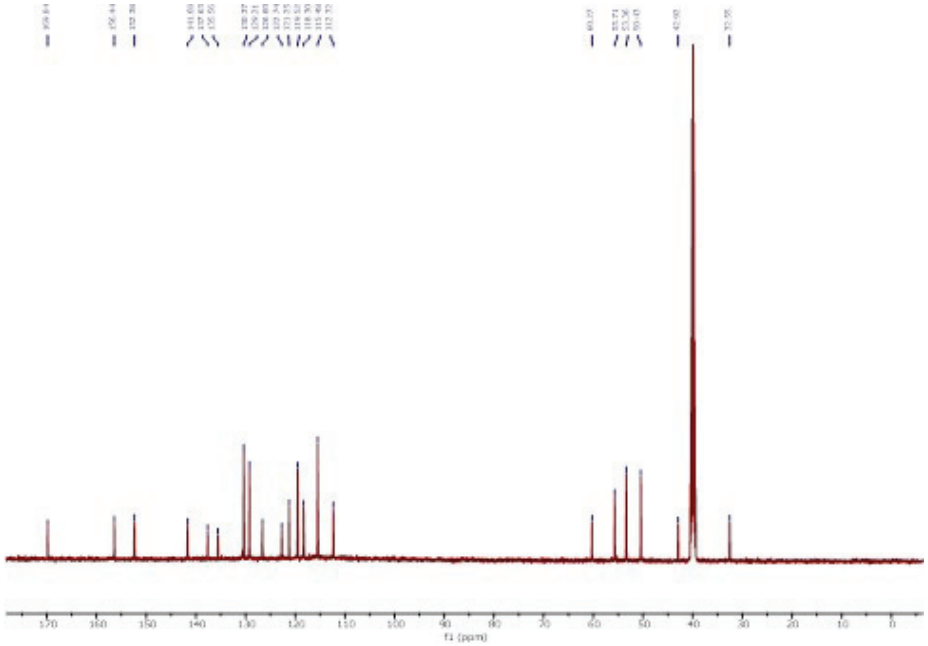
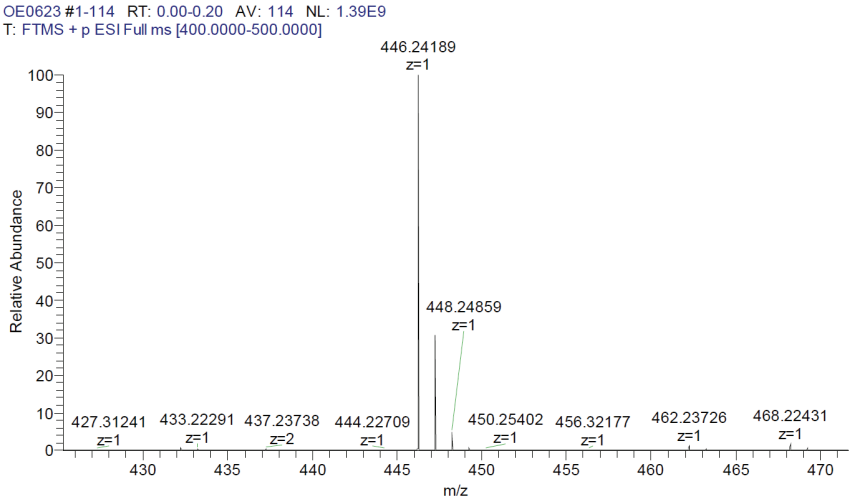


Fig. S-14. ^{13}C-NMR spectrum for 2-(4-hydroxyphenyl)-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)acetamide (**7b**)



Exact mass	Observed mass	Observed ion type	Error (ppm)
446.24382	446.24189	$[M+H]^+$	4.32

Fig. S-15. HRMS spectrum for 2-(4-hydroxyphenyl)-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)acetamide (**7b**)

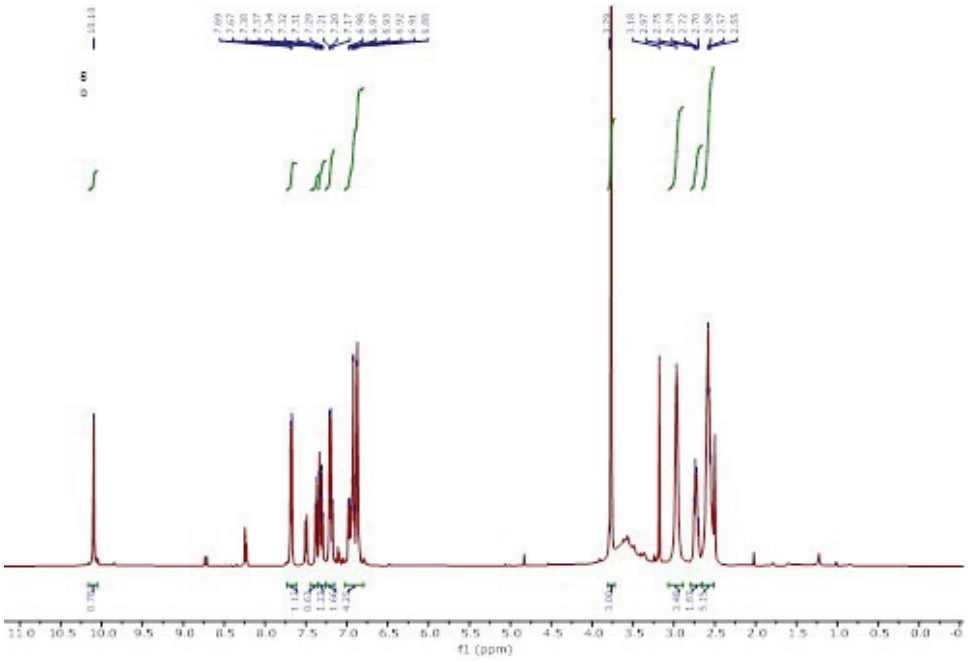


Fig. S-16. ^{1}H-NMR spectrum for 3-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)benzamide (**8b**)

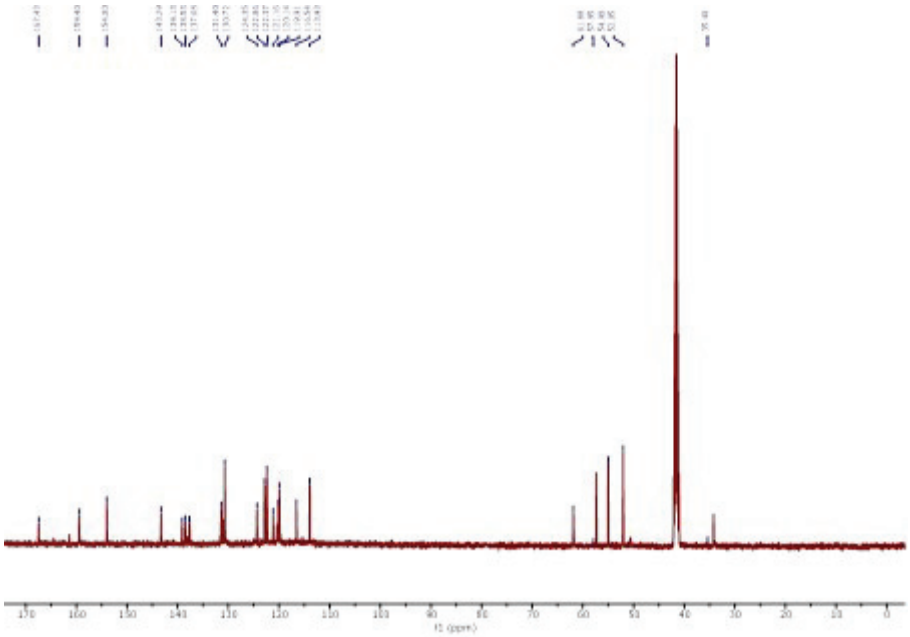
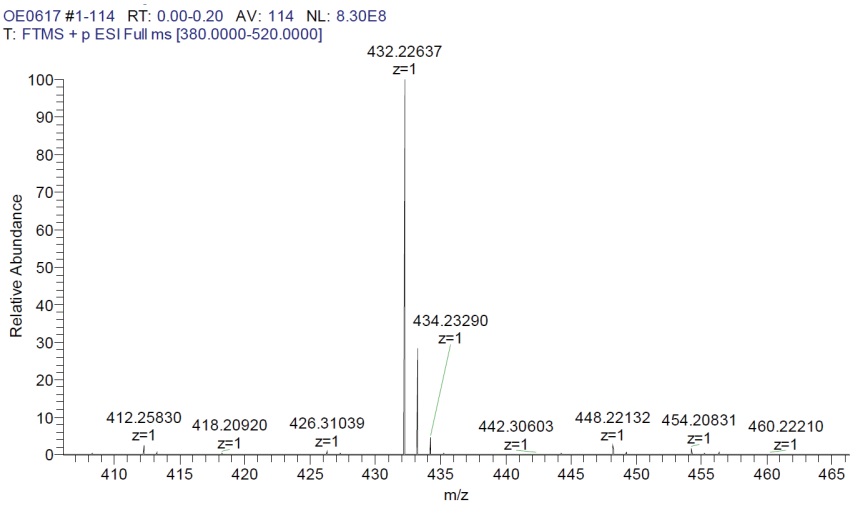


Fig. S-17. ^{13}C-NMR spectrum for 3-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)benzamide (**8b**)



Exact mass	Observed mass	Observed ion type	Error (ppm)
432.22817	432.22637	$[M+H]^+$	4.16

Fig. S-18. HRMS spectrum for 3-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)benzamide (**8b**)

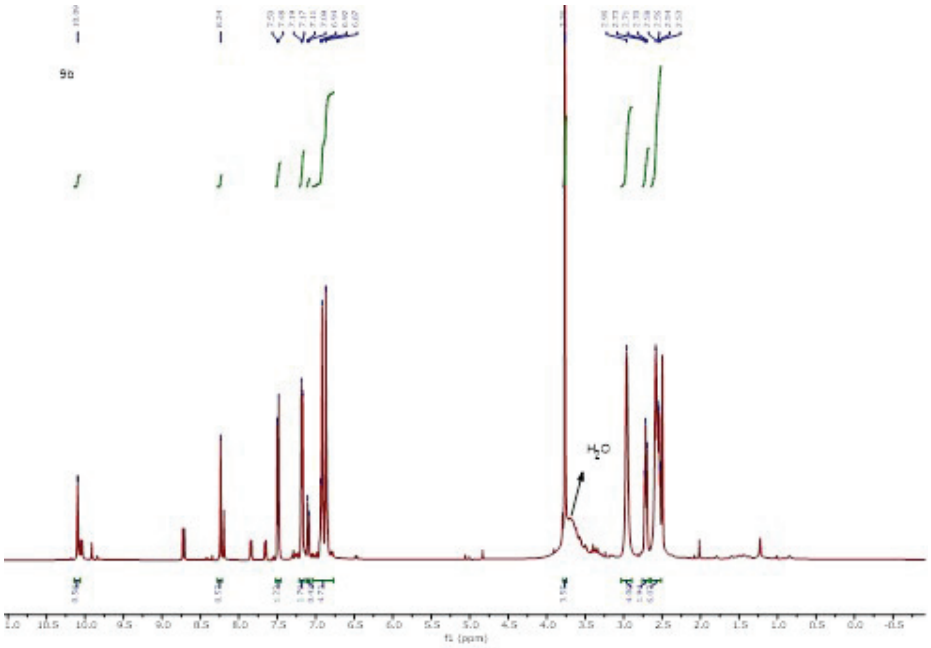


Fig. S-19. ^{1}H-NMR spectrum for 4-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)benzamide (**9b**)

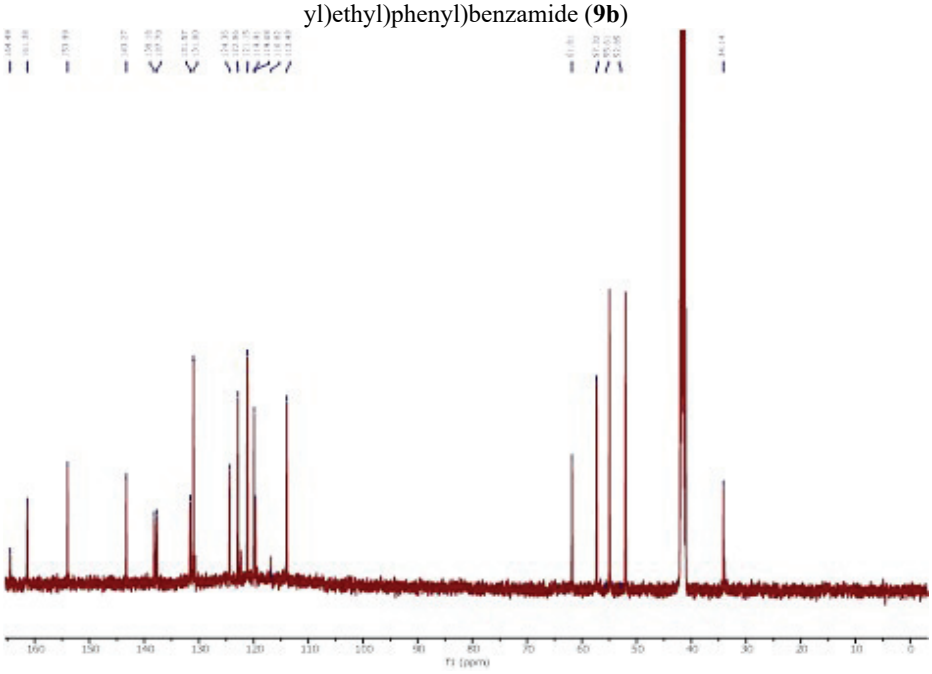
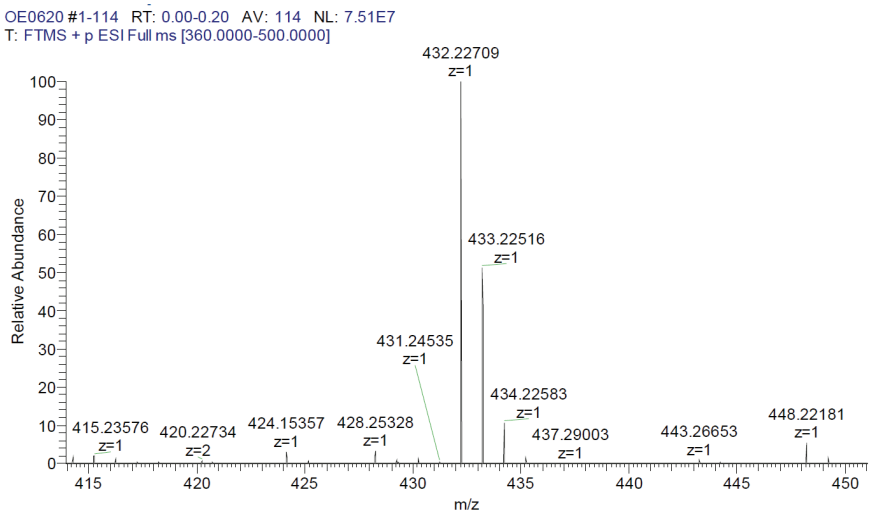


Fig. S-20. ^{13}C-NMR spectrum for 4-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)benzamide (**9b**)



Exact mass	Observed mass	Observed ion type	Error (ppm)
432.22817	432.22709	$[M+H]^+$	2.50

Fig. S-21. HRMS spectrum for 4-hydroxy-*N*-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)benzamide (**9b**)

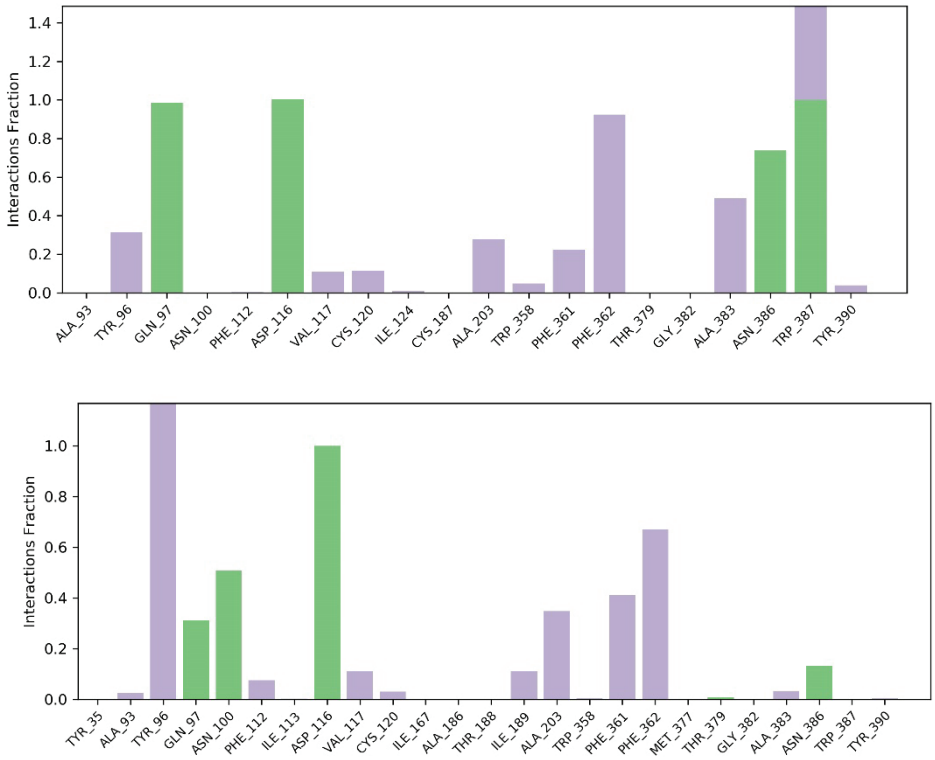


Fig. S-22. Diagram of key receptor – **5a** (top) and **6a** (bottom) interactions observed during 100ns molecular dynamics. Aromatic interactions are shown in violet, while hydrogen bonds are green. Interactions maintained for 20% or more of total MD time are considered crucial.

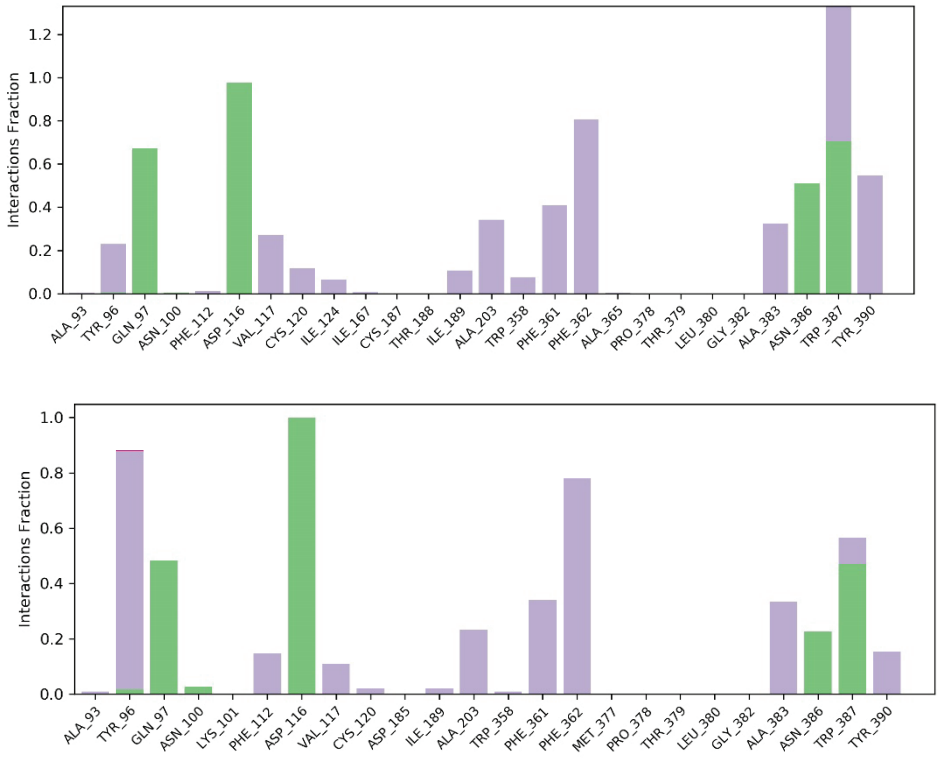


Fig. S-23. Diagram of key receptor – **5b** (top) and **5c** (bottom) interactions observed during 100ns molecular dynamics. Aromatic interactions are shown in violet, while hydrogen bonds are green. Interactions maintained for 20% or more of total MD time are considered crucial.

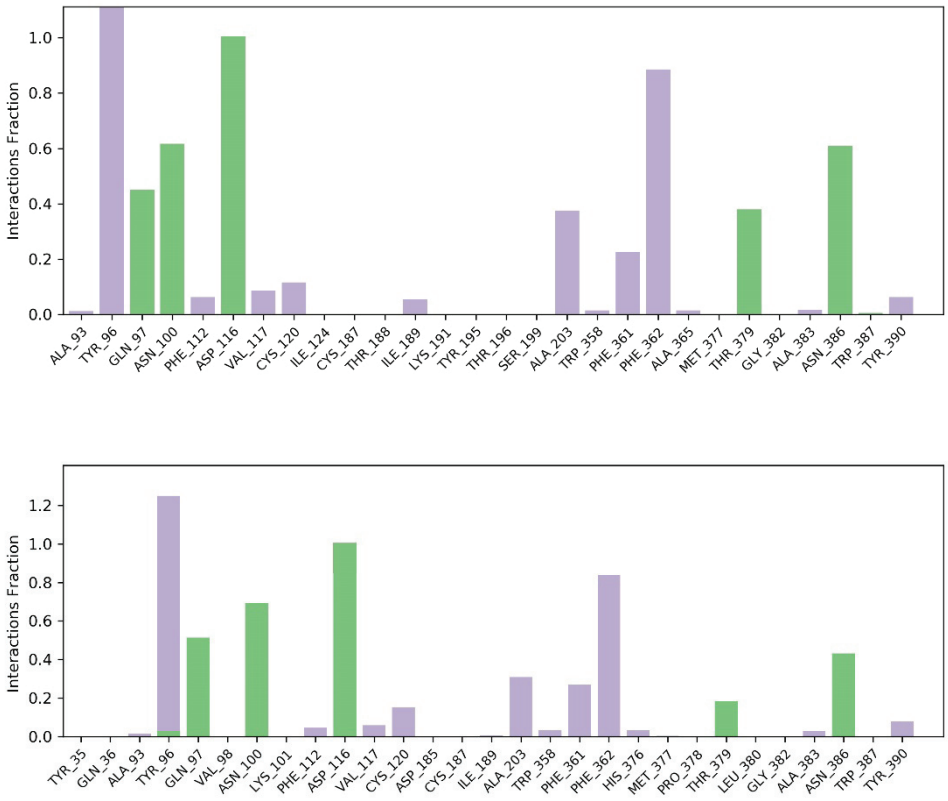


Fig. S-24. Diagram of key receptor – **6b** (top) and **6c** (bottom) interactions observed during 100ns molecular dynamics. Aromatic interactions are shown in violet, while hydrogen bonds are green. Interactions maintained for 20% or more of total MD time are considered crucial.

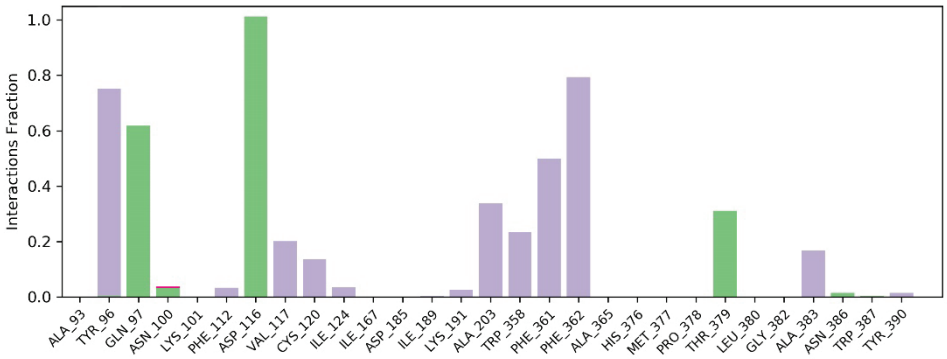
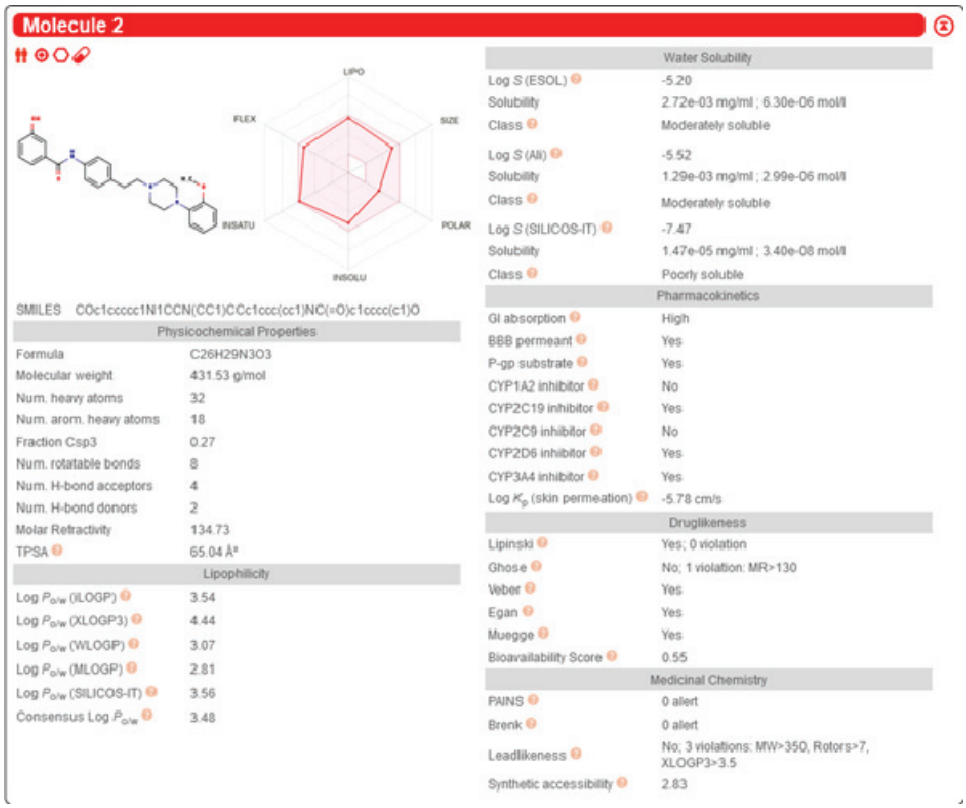


Fig. S-25. Diagram of key receptor – **7b** interactions observed during 100ns molecular dynamics. Aromatic interactions are shown in violet, while hydrogen bonds are green. Interactions maintained for 20% or more of total MD time are considered crucial.



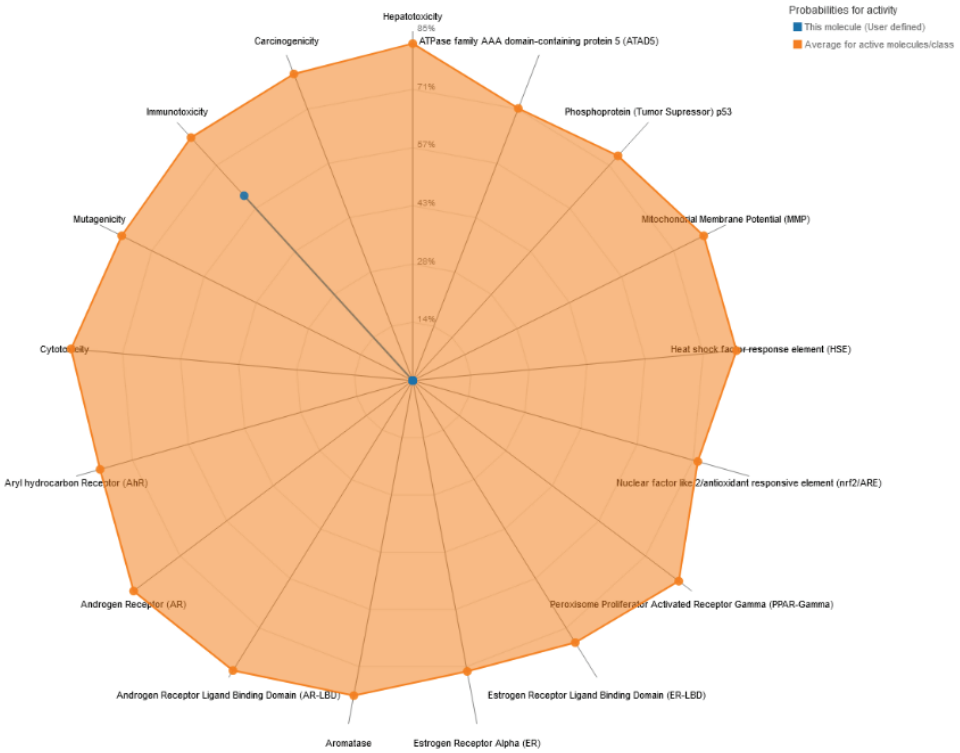


Fig. S-26. ADMET of 3-hydroxy-N-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)benzamide (**8b**).

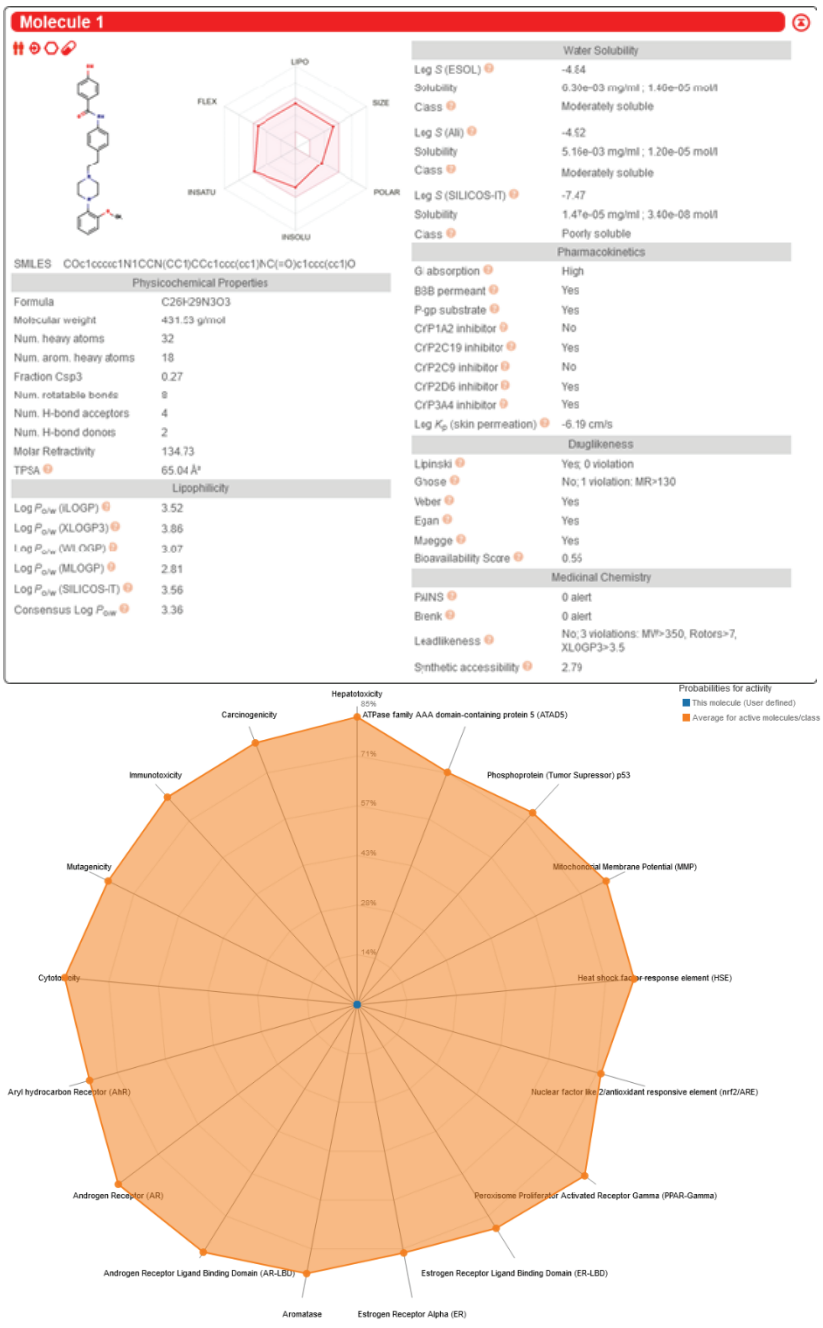
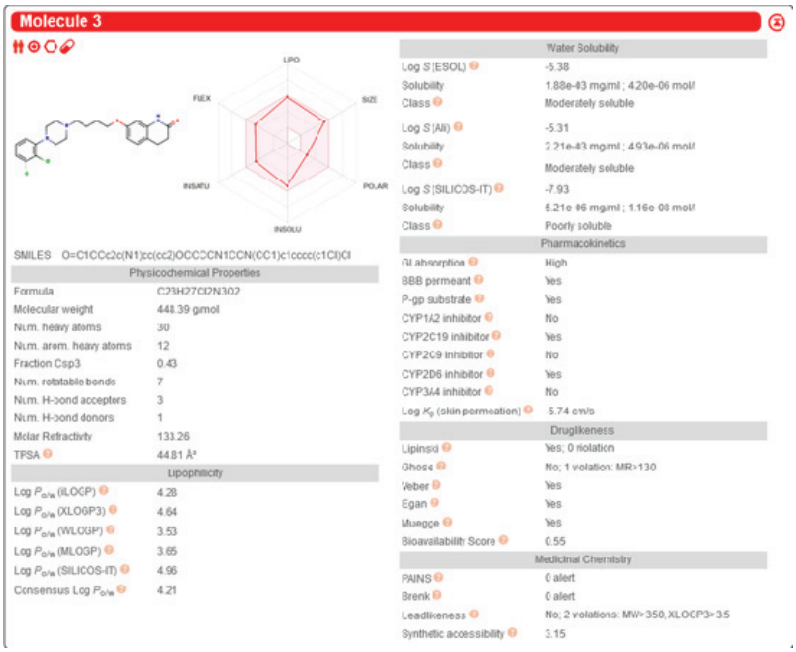


Fig. S-27. ADMET of 4-hydroxy-N-(4-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)phenyl)benzamide (**9b**).



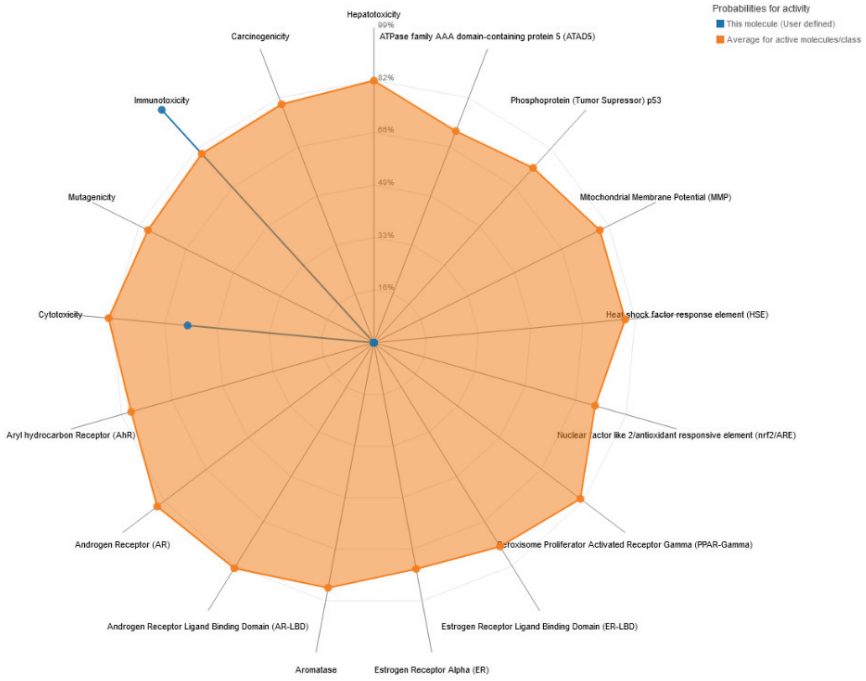


Fig. S-28. ADMET of aripiprazole.