Supporting Information.

Design, synthesis and biological evaluation of pyrazolo[3,4-*d*]pyrimidines active in vivo on the Bcr-Abl T315I mutant

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Table of Contents

N-(3-Bromophenyl)-1-[2-chloro-2-(4-fluorophenyl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine ***(2f)***. White solid (299 mg, 67%). Mp: 172-175 °C. ^{1}H NMR: δ 4.61-4.74 and 4.82-4.98 (2m, 2H, CH_2N), 5.33-5.44 (m, 1H, CHCl), 6.87-7.03 and 7.21-7.46 (2m, 8H Ar), 7.69 (s, 1H, H-3), 8.34 (s, 1H, H-6). IR cm^{-1}: 3108 (NH). MS: *m/z* 447 $[M+1]^+$. Anal. ($C_{19}H_{14}N_5BrClF$) C, H, N.

N-(3-Bromophenyl)-1-(2-chloro-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (***2g***). White solid (305 mg, 71%). Mp: 214-216 °C. ^{1}H NMR: δ 4.62-4.78 and 4.85-4.98 (2m, 2H, CH_2N), 5.25-5.41 (m, 1H, CHCl), 6.99-7.52 (m, 10H, 9Ar + H-3), 8.27 (s, 1H, H-6). IR cm^{-1}: 3096 (NH). MS: *m/z* 429 $[M+1]^+$. Anal. ($C_{19}H_{15}N_5BrCl$) C, H, N.

1-(2-Chloro-2-phenylethyl)-N-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine ***(2h)***. White solid (246 mg, 67%). Mp: 159-160 °C. ^{1}H NMR: δ 460-4.75 and 4.82-4.97 (2m, 2H, CH_2N), 5.28-5.39 (m, 1H, CHCl), 7.01-7.44 (m, 10H, 9Ar + H-3), 8.26 (s, 1H, H-6). IR cm^{-1}: 3146 (NH). MS: *m/z* 368 $[M+1]^+$. Anal. ($C_{19}H_{15}N_5ClF$) C, H, N.

1-(2-Chloro-2-phenylethyl)-N-(phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine ***(2i)***. White solid (224 mg, 64%). Mp: 178-180 °C. ^{1}H NMR: δ 4.61-4.74 and 4.85-4.98 (2m, 2H, CH_2N), 5.39-5.50 (m, 1H, CHCl), 7.12 (s, 1H, H-3), 7.16-7.47 (m, 10H Ar), 8.33 (s, 1H, H-6). IR cm^{-1}: 3144 (NH). MS: *m/z* 350 $[M+1]^+$. Anal. ($C_{19}H_{16}N_5Cl$) C, H, N.

1-[2-(4-Bromophenyl)-2-chloroethyl]-N-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine ***(2j)***. White solid (244 mg, 57%). Mp: 190-191 °C. ^{1}H NMR: δ 5.02-5.08 (m, 2H, CH_2N), 5.95-6.01 (m, 1H, CHCl), 7.14-7.45 and 7.67-7.82 (2m, 9H Ar), 8.10 (s, 1H, H-3), 8.17 (s, 1H, H-6). IR cm^{-1}: 3301 (NH). MS: *m/z* 429 $[M+1]^+$. Anal. ($C_{19}H_{15}N_5BrCl$) C, H, N.

1-[2-(4-Bromophenyl)-2-chloroethyl]-N-(3-chlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine ***(2l)***. White solid (243 mg, 51%). Mp: 142-143 °C. ^{1}H NMR: δ 4.62-4.73 and 4.77-4.83 (2m, 4H, CH_2N + CH_2Ar), 5.55-5.65 (m, 1H, CHCl), 7.16-7.43 (m, 9H, 8Ar + H-3), 7.95 (s, 1H, H-6). IR cm^{-1}: 3243 (NH). MS: *m/z* 477 $[M+1]^+$. Anal. ($C_{20}H_{16}N_5BrCl_2$) C, H, N.

1-[2-(4-Bromophenyl)-2-chloroethyl]-N-(2-chlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine ***(2m)***. White solid (186 mg, 39%). Mp: 163-164 °C. ^{1}H NMR: δ 4.68-4.77 and 4.84-4.89 (2m, 4H, CH_2N + CH_2Ar), 5.42-5.45 (m, 1H, CHCl), 7.19-7.39 (m, 9H, 8Ar + H-3), 7.88 (s, 1H, H-6). IR cm^{-1}: 3230 (NH). MS: *m/z* 477 $[M+1]^+$. Anal. ($C_{20}H_{16}N_5BrCl_2$) C, H, N.

1-[2-(4-Bromophenyl)-2-chloroethyl]-N-(4-chlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (***2n***). White solid (258 mg, 54%). Mp: 167-169 °C. ^{1}H NMR: δ 4.77-4.85 and 4.91-5.01 (2m, 4H, CH_2N + CH_2Ar), 5.77-5.84 (m, 1H, CHCl), 7.21-7.54 (m, 8H Ar), 7.95 (s, 1H, H-3), 8.01 (s, 1H, H-6). IR cm^{-1}: 3239 (NH). MS: *m/z* 477 $[M+1]^+$. Anal. ($C_{20}H_{16}N_5BrCl_2$) C, H, N.

1-[2-(4-Bromophenyl)-2-chloroethyl]-N-(2,5-dichlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine ***(2o)***. White solid (210 mg, 41%). Mp: 128-132 °C (dec). ^{1}H NMR: δ 4.66-4.72 and 4.89-4.94 (2m, 4H, CH_2N + CH_2Ar), 5.62-5.71 (m, 1H, CHCl), 7.12-7.19 and 7.28-7.35 (2m, 7H Ar), 8.04 (s, 1H, H-3), 8.17 (s, 1H, H-6). IR cm^{-1}: 3285 (NH). MS: *m/z* 512 $[M+1]^+$. Anal. ($C_{20}H_{15}N_5BrCl_3$) C, H, N.

1-[2-(4-Bromophenyl)-2-chloroethyl]-N-(3,4-dichlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine ***(2p)***. White solid (328 mg, 64%). Mp: 163-165 °C. ^{1}H NMR: δ 4.79-4.82 and 5.01-5.06 (2m, 4H, CH_2N + CH_2Ar), 5.55-5.68 (m, 1H, CHCl), 7.04-7.55 and 7.62-7.79 (2m, 7H Ar), 8.04 (s, 1H, H-3), 8.19 (s, 1H, H-6). IR cm^{-1}: 3252 (NH). MS: *m/z* 512 $[M+1]^+$. Anal. ($C_{20}H_{15}N_5BrCl_3$) C, H, N.

1-[2-(4-Bromophenyl)-2-chloroethyl]-N-(4-fluorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine ***(2q)***. White solid (309 mg, 67%). Mp: 178-179 °C. ^{1}H NMR: δ 4.80-4.84 and 5.00-5.09 (2m, 4H, CH_2N + CH_2Ar), 5.87-5.91 (m, 1H, CHCl), 7.16-7.21 and 7.38-7.45 (2m, 8H Ar), 8.02 (s, 1H, H-3), 8.07 (s, 1H, H-6). IR cm^{-1}: 3205 (NH). MS: *m/z* 461 $[M+1]^+$. Anal. ($C_{20}H_{16}N_5BrClF$) C, H, N.

1-[2-(4-Bromophenyl)-2-chloroethyl]-N-(2,5-difluorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine ***(2r)***. White solid (278 mg, 58%). Mp: 165-167 °C. ^{1}H NMR: δ 4.68-4.75 and 4.95-5.01 (2m, 4H, CH_2N + CH_2Ar), 5.63-5.74 (m, 1H, CHCl), 7.13-7.21 and 7.32-7.48 (2m, 7H Ar), 8.05 (s, 1H, H-3), 8.17 (s, 1H, H-6). IR cm^{-1}: 3295 (NH). MS: *m/z* 479 $[M+1]^+$. Anal. ($C_{20}H_{15}N_5BrClF_2$) C, H, N.

*1-[2-(4-Bromophenyl)-2-chloroethyl]-N-(3,4-difluorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2s**).* White solid (374 mg, 78%). Mp: 160-161 °C. ^{1}H NMR: δ 4.72-4.78 and 5.04-5.09 (2m, 4H, CH_2N + CH_2Ar), 5.61-5.72 (m, 1H, CHCl), 7.12-7.56 and 7.68-7.81 (2m, 7H Ar), 8.07 (s, 1H, H-3), 8.21 (s, 1H, H-6). IR cm^{-1}: 3247 (NH). MS: *m/z* 479 $[M+1]^+$. Anal. ($C_{20}H_{15}N_5BrClF_2$) C, H, N.

*N-(4-Bromobenzyl)-1-[2-(4-bromophenyl)-2-chloroethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2t**).* White solid (292 mg, 56%). Mp: 175-177 °C. ^{1}H NMR: δ 4.79-4.86 and 4.91-5.01 (2m, 4H, CH_2N + CH_2Ar), 5.78-5.87 (m, 1H, CHCl), 7.22-7.55 (m, 8H Ar), 7.98 (s, 1H, H-3), 8.04 (s, 1H, H-6). IR cm^{-1}: 3207 (NH). MS: *m/z* 522 $[M+1]^+$. Anal. ($C_{20}H_{16}N_5Br_2Cl$) C, H, N.

*N-(2-Bromobenzyl)-1-[2-(4-bromophenyl)-2-chloroethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2u**).* White solid (386 mg, 74%). Mp: 174-175 °C. ^{1}H NMR: δ 4.72-4.79 and 4.87-4.92 (2m, 4H, CH_2N + CH_2Ar), 5.44-5.49 (m, 1H, CHCl), 7.21-7.42 (m, 9H, 8Ar + H-3), 7.94 (s, 1H, H-6). IR cm^{-1}: 3233 (NH). MS: *m/z* 522 $[M+1]^+$. Anal. ($C_{20}H_{16}N_5Br_2Cl$) C, H, N.

*N-(3-Bromobenzyl)-1-[2-(4-bromophenyl)-2-chloroethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2v**).* White solid (355 mg, 68%). Mp: 145-148 °C. ^{1}H NMR: δ 4.70-4.78 and 4.88-4.94 (2m, 4H, CH_2N + CH_2Ar), 5.43-5.47 (m, 1H, CHCl), 7.22-7.40 (m, 9H, 8Ar + H-3), 7.96 (s, 1H, H-6). IR cm^{-1}: 3206 (NH). MS: *m/z* 522 $[M+1]^+$. Anal. ($C_{20}H_{16}N_5Br_2Cl$) C, H, N.

*1-[2-(4-Bromophenyl)-2-chloroethyl]-N-(3-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2w**).* White solid (341 mg, 72%). Mp: 133-135 °C. ^{1}H NMR: δ 3.65 (s, 3H, OCH_3), 4.72-4.78 and 4.84-4.89 (2m, 4H, CH_2N + CH_2Ar), 5.35-5.41 (m, 1H, CHCl), 6.90-7.22 (m, 9H, 8Ar + H-3), 7.99 (s, 1H, H-6). IR cm^{-1}: 3203 (NH). MS: *m/z* 473 $[M+1]^+$. Anal. ($C_{21}H_{19}N_5OBrCl$) C, H, N.

*N-[3,5-Bis(trifluoromethyl)benzyl]-1-[2-(4-bromophenyl)-2-chloroethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2x**).* White solid (324 mg, 56%). Mp: 147-154 °C (dec). ^{1}H NMR: δ 4.83-4.95 and 4.99-5.06 (2m, 4H, CH_2N + CH_2Ar), 5.42-5.61 (m, 1H, CHCl), 7.28-7.52 and 7.87-7.91 (2m, 7H Ar), 7.97 (s, 1H, H-3), 8.42 (s, 1H, H-6). IR cm^{-1}: 3258 (NH). MS: *m/z* 579 $[M+1]^+$. Anal. ($C_{22}H_{15}N_5BrClF_6$) C, H, N.

*1-[2-Chloro-2-(4-methylphenyl)ethyl]-N-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2y**)*.

White solid (217 mg, 60%). Mp.: 150-154 °C. ^{1}H NMR: δ 2.30 (s, 3H, CH_3), 4.68-4.73 and 4.92-4.98 (2m, 2H, CH_2N), 5.47-5.51 (m, 1H, CHCl), 7.11-7.17 and 7.30-7.33 (2m, 6H Ar), 7.45-7.47 (m, 4H, 3 Ar + H-3), 8.39 (s, 1H, H-6). IR cm^{-1}: 3234 (NH). MS: *m/z* 364 $[M+1]^+$. Anal. ($C_{20}H_{18}ClN_5$) C, H, N.

*1-[2-Chloro-2-(4-iodophenyl)ethyl]-N-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2z**)*.

White solid (332 mg, 70%). Mp: 130-133 °C. ^{1}H NMR: δ 4.70-4.75 and 4.87-4.93 (2m, 2H, CH_2N), 5.42-5.46 (m, 1H, CHCl), 7.14-7.16 and 7.32-7.36 (2m, 5H Ar), 7.45-7.47 and 7.63-7.65 (2m, 5H, 4Ar +H-3), 8.39 (s, 1H, H-6). IR cm^{-1}: 3144 (NH). MS: *m/z* 476 $[M+1]^+$. Anal. ($C_{19}H_{15}ClIN_5$) C, H, N.

Table S1.

Compd	**Elemental analysis (%, calculated, found)**		
	C%	**H%**	**N%**
2e	56.73 56.68	3.51 3.81	17.41 17.35
2f	51.09 51.18	3.16 3.44	15.68 15.50
2g	53.23 52.98	3.53 3.71	16.34 16.29

2h	62.04 61.90	4.11 4.35	19.04 19.00
2i	65.24 65.42	4.61 4.84	20.02 20.06
2j	53.23 53.44	3.53 3.62	16.34 16.08
2k	54.26 54.06	3.87 4.07	15.82 15.62
2l	50.34 50.37	3.38 3.67	14.68 14.39
2m	50.34 50.31	3.38 3.55	14.68 14.55
2n	50.34 50.44	3.38 3.51	14.68 14.75
2o	46.95 46.73	2.96 2.83	13.69 13.59
2p	46.95 46.99	2.96 3.27	13.69 13.88
2q	52.14 52.36	3.50 3.73	15.20 15.38
2r	50.18 50.15	3.16 3.14	14.63 14.47

2s	50.18 50.50	3.16 3.49	14.63 14.93
2t	46.05 46.14	3.09 3.40	13.43 13.55
2u	46.05 45.90	3.09 3.24	13.43 13.22
2v	46.05 46.21	3.09 3.39	13.43 13.51
2w	53.35 53.60	4.05 3.98	14.81 14.88
2x	45.66 45.56	2.61 2.83	12.10 12.27
2y	66.02 66.07	4.99 5.10	19.25 19.30
2z	47.97 48.03	3.18 3.30	14.72 14.84
5d	54.74 54.90	3.94 4.03	18.24 18.45
5e	37.26 37.32	2.16 2.19	13.37 13.40
8a	58.65 58.83	3.87 3.91	19.54 19.62

8b	39.17 39.10	2.02 1.96	14.06 14.15
9a	58.24 58.35	4.54 4.67	19.40 19.42
9b	38.98 39.02	2.52 2.44	13.99 14.05

Table S2.

Cpd	2z60	3dk7
1b	-50.52	-46.07
2a	-48.9	-41.4
2b	-53.2	-35.8
2c	-41.73	-45.73
2d	-44.01	-43.77
2e	-47.01	-39.9
2f	-43.04	
2g	-45.05	
2h	-42.11	
2i	-44.12	
2j	-46.8	
2k	-41.77	

2l	-54.18	
2m	-53.61	
2n	-50.47	
2o	-49.02	
2p	-51.37	
2q	-50.29	
2r	-43.18	
2s	-49.02	
2t	-49.31	
2u	-47.4	
2v	-52.57	
2w	-50.02	
2x	-45.61	