Synthesis of New TGX-221 Analogs

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TGX-221 is a potent phosphoinositide 3-kinase (PI3K)β inhibitor that has great therapeutic potential to treat prostate cancer. Chemical modification of TGX-221 at positions 2 and 9 was made. Five new TGX-221 analogs with different heterocyclic substituents of morpholine, 1-methylpiperazine, aniline, and thiazole-2-amine at positions 2 and 9 were synthesized. Parallel synthetic methods were employed in S_N2 replacement reactions at positions 2 and 9 of TGX-221.

Key words: TGX-221, Heterocyclic Substituent, Parallel Synthesis, S_N2 Reaction, Microwave Reaction

Introduction

TGX-221 {7-methyl-2-morpholino-9-(1-(phenylamino)ethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one} is a potent phosphoinositide 3-kinase (PI3K)β inhibitor [1 – 4]. Its key chemical features include a pyridopyrimidinone nucleus (I), a morpholinyl substituent at position 2 (II) and a 1-phenylaminoethyl moiety at position 9 (III) as shown in Fig. 1 [2]. Following on earlier reports of the PI3Kβ-inhibiting ability of TGX-221, structural modifications on TGX-221 were carried out. On the core structure of TGX-221, replacement of the pyridopyrimidinone nucleus was made [5 – 8]. Two families of imidazopyrimidinones and triazolopyrimidinones were generated [5, 6]. Both series of the compounds were found to display high clearance in metabolism [7, 8]. Therefore two series of pyrazolopyrimidines and thiazolopyrimidinones were synthesized in an attempt to improve clearance [7, 8]. On the side fragment of TGX-221, a hydroxyethyl moiety was added to the aniline group at position 9 to produce analogs [9, 10].

In this paper chemical modifications of TGX-221 at positions 2 and 9 were undertaken. The group at position 2 was replaced by 1-methylpiperazine and morpholine. The moiety at position 9 was substituted with thiazole-2-amine, 1-methylpiperazine and aniline. Five new TGX-221 analogs were synthesized. Parallel synthetic methods were employed in S_N2 replacement reactions.

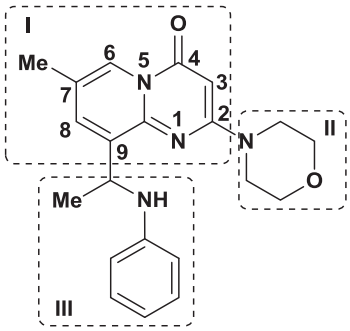


Fig. 1. Chemical structure of TGX-221.

Results and Discussion

The synthesis of TGX-221 analogs was initiated from 2-amino-3-bromo-5-methylpyridine and malonyl dichloride to generate the scaffold of 9-bromo-2-hydroxy-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1**). The hydroxyl group at position 2 of compound **1** was substituted with morpholine or 1-methylpiperazine. Subsequent replacement at position 9 of the resulting compounds was made with 1-methyl-

piperazine, aniline or thiazole-2-amine. The synthetic procedures are illustrated in Scheme 1.

Compound **1** was formed through a nucleophilic cyclization reaction by treatment of malonyl dichloride with a solution of 2-amino-3-bromo-5-methylpyridine in dichloromethane (CH_2Cl_2). The hydroxyl group in compound **1** was substituted with morpholine and 1-methylpiperazine through parallel synthesis to produce compounds **2** and **5**, respectively. The bromo group in compound **2** was transformed to an acetyl group to afford compound **3** through an intramolecular Heck reaction. Using the same method compound **6** was generated from compound **5**. The ketone group in compound **3** was reduced to the secondary alcohol by sodium borohydride ($NaBH_4$) to afford compound **4**. Compound **7** was obtained in the same manner from compound **6**.

Parallel synthesis was employed for the S_N2 reaction to replace the secondary alcohol in compounds **4** and **7** with thiazole-2-amine, 1-methylpiperazine and aniline to yield five compounds of TGX-221 analogs, as shown in Scheme 1. Analogs **TGX-221a** and **TGX-221b** were generated from compound **4**; analogs **TGX-221c**, **TGX-221d** and **TGX-221e** were synthesized from compound **7**. The new TGX-221 analogs were characterized by ^{1}H and ^{13}C NMR spectra and high-resolution mass spectrometry.

A series of pyridopyrimidinone was reported in the patent by Jackson and co-workers [1]. In their patent, pyridinyl and morpholino groups were used as substituents at position 2 of the pyridopyrimidinone nucleus [1]. Some substituents, such as benzyl, 4-hydroxyphenylamino, pyridin-4-yl-ethyl and thiophene-2-yl-methyl were employed at position 9 [1]. The hydroxylethyl moiety was added to the aniline group at position 9 of TGX-221 [9, 10]. In our work, modifications of TGX-221 at positions 2 and 9 were undertaken. All analogs contain amino-substituted heterocyclic moieties as substituents. 1-Methylpiperazine and morpholine rings were used as substituents at position 2. Thiazole-2-amine, 1-methylpiperazine and aniline were selected as substituents at position 9. Combination of the substituents generated five new TGX-221 analogs. Four analogs with the 1-methylpiperazine group are particularly attractive, since 1-methylpiperazine possesses a protonatable nitrogen atom which will enable the formation of more water-soluble acid addition salts, such as hydrochlorides.

We developed a synthetic procedure for TGX-221 analogs which is different from the previous synthetic method for a series of pyridopyrimidinone in Jackson's patent [1]. In our work, a microwave synthesizer was used to speed up the S_N2 replacement reactions from compound **1** to compounds **2** and **5**. We employed two reaction steps to achieve the formation of the final compounds *via* compounds **3** and **6**, which made methylation and S_N2 replacement reactions to proceed easily. Our synthesis is facile, proceeds from commercially available materials, is easily scaled up, and very manageable in relation to the synthesis of analogs. Morpholine and 1-methylpiperazine groups at position 2 are installed by a nucleophilic displacement reaction. 1-Methylpiperazine, aniline and thiazole-2-amine moieties at position 9 are installed by a S_N2 reaction.

Conclusion

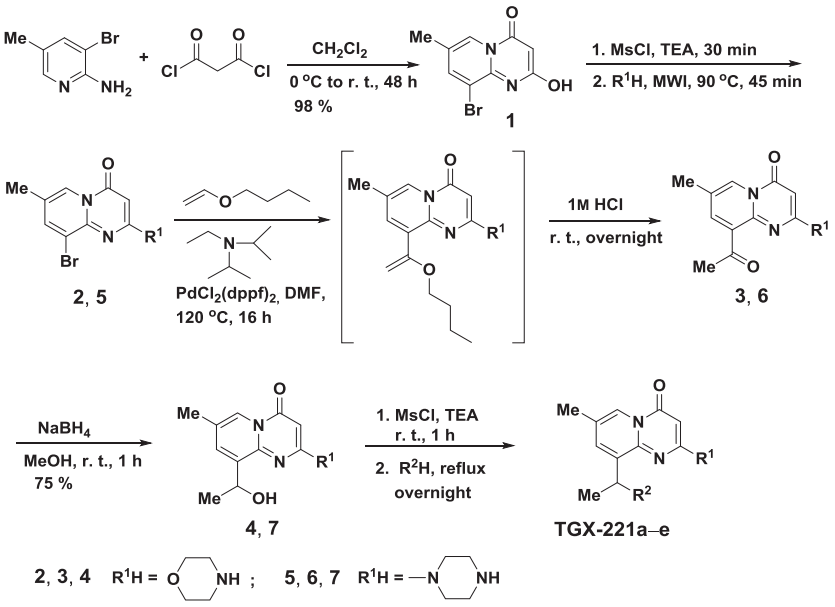
Chemical modification of TGX-221 was carried out. 9-Bromo-2-hydroxy-7-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one was synthesized as the scaffold. Five new TGX-221 analogs were synthesized. Parallel synthetic methods were developed for S_N2 replacement of the hydroxyl group at positions 2 and 9 of the scaffold.

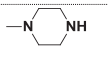
Experimental Section

Reactions that required an inert atmosphere were carried out under argon with flame-dried glassware. Column chromatography was carried out by employing silica gel (230 – 400 mesh). Thin-layer chromatography (TLC) was performed on a silica gel w/uv254 uniplate™. Parallel synthesis was conducted on Mettler Toledo MiniBlock and MiniBlock XT. Anhydrous organic solvents were purchased. Melting points were determined using a Barnstead International MET-TEMP® capillary Melting Point Apparatus, Model 1001D-120VAC. IR spectra were measured with a Perkin Elmer™ Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer (400 and 100 MHz, respectively), or a 500 MHz spectrometer (500 and 125.5 MHz, respectively). Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra (HRMS) were obtained on a double-focusing mass spectrometer.

*Procedures for the synthesis of intermediates **1–7***

Compounds **1**, **2**, and **3** were synthesized following the procedures given in refs. [1, 2].



Entry	R^1H	R^2H	Yield (%)
TGX-221a			67
TGX-221b			69
TGX-221c			75
TGX-221d			72
TGX-221e			55

Scheme 1. Synthesis of TGX-221 analogs.

*9-Bromo-2-hydroxy-7-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (**1**)*

To a solution of 2-amino-3-bromo-5-methylpyridine (2.25 g, 12 mmol) in CH_2Cl_2 (25 mL) was added malonyl dichloride (1.25 mL, 12.5 mmol) at 0 °C. The mixture was stirred at room temperature for 48 h. The yellow solid was collected by filtration, washed with CH_2Cl_2 (3×25 mL), and dried under reduced pressure. Compound **1** was obtained as a yellow solid with a yield of 88 % (2.75 g). M. p. 209 – 211 °C. – ^{1}H NMR ([D$_6$]DMSO, 400 MHz): $\delta = 8.74$ (s, 1H, 8-CH), 8.29 (s, 1H, 6-CH), 5.55 (s, 1H, 3-CH), 2.35 (s, 3H, 7-CH_3) ppm. – HRMS ((+)-ESI): $m/z = 254.9793$ (calcd. 254.9769 for $C_9H_8BrN_2O_2$, $[M+H]^+$).

*9-Bromo-7-methyl-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (**2**)*

To a suspension of compound **1** (1.275 g, 5 mmol) in CH_2Cl_2 (30 mL) were added triethylamine (1.4 mL, 10 mmol) and methanesulfonyl chloride (0.54 mL, 7 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. Morpholine (1.25 mL, 12.5 mmol) was added, and the mixture was heated in a microwave synthesizer at 90 °C for 45 min. The mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3×100 mL). The organic layer was washed with water and dried over Na_2SO_4. After concentration under reduced pressure, the dark-yellow residue was purified through a silica flash column using EtOAc/hexane

2 : 1 as an eluent to give compound **2** as a pale-yellow solid with a yield of 45 % (0.65 g). M. p. 198 – 199 °C. – ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.69$ (s, 1H, 8-CH), 7.85 (s, 1H, 6-CH), 5.59 (s, 1H, 3-CH), 3.82 (m, 4H, 2 O-CH_2), 3.75 (m, 4H, 2 N-CH_2), 2.33 (s, 3H, 7-CH_3) ppm. – HRMS ((+)-ESI): $m/z = 324.0348$ (calcd. 324.0348 for $C_{13}H_{15}BrN_3O_2$, $[M+H]^+$).

*9-Acetyl-7-methyl-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (**3**)*

Compound **2** (650 mg, 2 mmol) in DMF (10 mL) was mixed with *N*,*N*-diisopropylethylamine (1.5 mL), butyl vinyl ether (1.6 mL) and dichloro-1,1′-bis(diphenylphosphino)ferrocene palladium(II) (70 mg, 0.066 mmol) at room temperature under argon for 30 min until a homogeneous solution was formed. The solution was heated to 120 °C for 16 h. After cooling, the solution was poured into 100 mL of 1 M HCl aqueous solution at 0 °C. The mixture was stirred at room temperature overnight and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with water and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification of the resulting residue through a silica flash column using EtOAc/hexanes 3 : 1 as an eluent afforded compound **3** as a yellow solid with a yield of 60 % (389 mg). M. p. 207 – 208 °C. – ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.88$ (s, 1H, 8-CH), 7.86 (s, 1H, 6-CH), 5.65 (s, 1H, 3-CH), 3.84 – 3.79 (m, 4H, 2 O-CH_2), 3.67 – 3.62 (m, 4H, 2 N-CH_2), 2.75 (s, 3H, CH_3), 2.35 (s, 3H, 7-CH_3) ppm. – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 199.17 (11-C=O), 160.17 (4-C=O), 158.21 (2-C), 147.30 (10-C), 141.07 (8-C), 133.29 (6-C), 128.40 (9-C), 121.98 (7-C), 81.37 (3-C), 66.56 (O-CH_2), 44.55 (N-CH_2), 31.35 (CH_3), 17.87 (7-CH_3) ppm. – HRMS ((+)-ESI): $m/z = 288.1347$ (calcd. 288.1348 for $C_{15}H_{18}N_3O_3$, $[M+H]^+$).

*9-(1-Hydroxyethyl)-7-methyl-2-morpholino-4H-pyrido-[1,2-a]pyrimidin-4-one (**4**)*

Sodium borohydride (52.2 mg, 1.38 mmol) was added to a suspension of compound **3** (198 mg, 0.69 mmol) in CH_2Cl_2 (5 mL) and methanol (10 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. Water was added and the mixture extracted with chloroform (3 × 30 mL). The organic layer was washed with water and dried over Na_2SO_4. After concentration under reduced pressure, the residue was crystallized in EtOAc/hexane (1:1) to obtain compound **4** as a colorless solid with a yield of 75 % (150 mg). M. p. 218 – 219 °C. – ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.57$ (s, 1H, 8-CH), 7.51 (d, $J = 2$ Hz, 1H, 6-CH), 5.58 (s, 1H, 3-CH), 5.22 (q, $J = 6$ Hz, 1H, O-CH), 4.66 (s, 1H, OH), 3.80 (m, 4H, 2 O-CH_2), 3.59 (m, 4H, 2 N-CH_2), 2.29 (s, 3H, 7-CH_3), 1.57 (d, $J = 6$ Hz, 3H, CH_3) ppm. – ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 160.21$ (4-C=O), 158.69 (2-C), 147.45 (10-C), 137.22 (8-C), 135.47 (6-C), 129.77 (9-C), 117.80 (7-C), 81.39 (3-CH), 66.57 (O-CH_2), 49.23 (O-CH), 44.63 (N-CH_2), 22.11 (CH_3), 18.29 (7-CH_3) ppm. – HRMS ((+)-ESI): $m/z = 290.1513$ (calcd. 290.1505 for $C_{15}H_{20}N_3NO_3$, $[M+H]^+$).

*9-Bromo-7-methyl-2-(4-methylpiperazin-1-yl)-4H-pyrido-[1,2-a]pyrimidin-4-one (**5**)*

To a suspension of compound **2** (600 mg, 2.35 mmol) in CH_2Cl_2 (30 mL) was added triethylamine (1.5 mL, 7.06 mmol), followed by methanesulfonyl chloride (0.4 mL, 4.7 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. 1-Methylpiperazine (1.1 mL, 7.06 mmol) was added, and the mixture was heated in a microwave synthesizer at 90 °C for 45 min. The mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with water and dried over Na_2SO_4. After concentration under reduced pressure, the dark-yellow residue was purified through a silica flash column using 1 % MeOH/CH_2Cl_2 as an eluent to give compound **5** as a pale-yellow solid with a yield of 43 % (0.45 g). M. p. 201 – 202 °C. – ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.70$ (s, 1H, 8-CH), 7.84 (s, 1H, 6-CH), 5.62 (s, 1H, 3-CH), 3.76 (m, 4H, 2 N-CH_2), 2.53 (s, 3H, N-CH_3), 2.37 (s, 3H, 7-CH_3), 2.33 (m, 4H, 2 N-CH_2) ppm. – HRMS ((+)-ESI): $m/z = 337.0637$ (calcd. 337.0664 for $C_{14}H_{18}BrN_4O$, $[M+H]^+$).

*9-Acetyl-7-methyl-2-(4-methylpiperazin-1-yl)-4H-pyrido-[1,2-a]pyrimidin-4-one (**6**)*

Compound **5** (328 mg, 1.0 mmol) in DMF (10 mL) was mixed with *N*,*N*-diisopropylethylamine (0.8 mL), butyl vinyl ether (0.4 mL, 4 mmol) and dichloro-1,1′-bis(diphenylphosphino)ferrocene palladium(II) (70 mg, 0.05 mmol) at room temperature under argon for 30 min until a homogeneous solution was formed. The solution was heated to 120 °C for 1 h in a microwave synthesizer. After cooling, the solution was poured into 100 mL of a 1 M HCl aqueous solution at 0 °C. The mixture was stirred at room temperature overnight and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with water and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification of the resulting residue through a silica flash column using 1 % MeOH/$CHCl_3$ as an eluent afforded compound **6** as a yellow solid with a yield of 60 % (192 mg). M. p. 206 – 208 °C. – ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.89$ (s, 1H, 8-CH), 7.86 (s, 1H, 6-CH), 5.68 (s, 1H, 3-CH), 3.70 (m, 4H, 2 N-CH_2), 2.81 (m, 3H, N-CH_3), 2.53 (s, 4H, 2 N-CH_2), 2.38 (s, 3H, 7-CH_3), 2.37 (s, 3H, CH_3) ppm. – HRMS ((+)-ESI): $m/z = 301.1654$ (calcd. 301.1664 for $C_{16}H_{21}N_4O_2$, $[M+H]^+$).

*9-(1-Hydroxyethyl)-7-methyl-2-(4-methylpiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**7**)*

Sodium borohydride (100 mg, 1.32 mmol) was added to a suspension of compound **6** (200 mg, 0.66 mmol) in CH_2Cl_2 (5 mL) and methanol (10 mL) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. Water was added and extracted with chloroform (3 × 30 mL). The organic layer was washed with water and dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by column chromatography with 2% MeOH/$CHCl_3$ as an eluent to obtain compound **7** as a colorless solid with a yield of 78% (156 mg). M. p. 215–216 °C. – IR: ν = 3423 (HN), 2925 (CH_3), 1667 (C=C), 1643 (N=C) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.64 (s, 1H, 8-CH), 7.48 (s, 1H, 6-CH), 5.64 (s, 1H, 3-CH), 5.20 (q, J = 6.0 Hz, 1H, 11-CH), 3.65 (t, J = 4.0 Hz, 4H, 2 N-CH_2), 2.50 (t, J = 4.2 Hz, 4H, 2 N-CH_2), 2.35 (s, 3H, N-CH_3), 2.33 (s, 3H, 7-CH_3), 1.62 (d, J = 6.4 Hz, 3H, CH_3) ppm. – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.09 (4-C=O), 158.13 (2-C), 147.45 (10-C), 137.13 (8-C), 135.33 (6-C), 129.25 (9-C), 117.69 (7-C), 81.42 (3-CH), 66.56 (O-CH), 54.66 (N-CH_2), 46.11 (N-CH_2), 44.22 (N-CH_3), 22.22 (CH_3), 18.29 (7-CH_3) ppm. – HRMS ((+)-ESI): m/z = 303.1910 (calcd. 303.1921 for $C_{16}H_{23}N_4O_2$, $[M+H]^+$).

*General procedure for the parallel synthesis of **TGX-221a–e***

Parallel synthesis was carried out in five reactors on a Mettler Toledo MiniBlock for the S_N2 reaction to replace the secondary alcohol in compounds **4** and **7** with thiazole-2-amine, 1-methylpiperazine and aniline. Triethylamine and methanesulfonyl chloride were added to the solution of compounds **4** and **7** in CH_2Cl_2 at 0 °C, respectively. The mixtures were stirred at room temperature for 1 h. When the methylation reactions were completed, thiazole-2-amine, 1-methylpiperazine and aniline were added to the obtained solutions of methylated compounds **4** and **7**, respectively. After the mixtures were refluxed for 24 h, the solutions were diluted with CH_2Cl_2 (30 mL). The organic layer was washed with water and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification of the resulting residue through a silica flash column using MeOH/CH_2Cl_2 as an eluent produced the five analogs **TGX-221a–e**.

*7-Methyl-2-morpholino-9-(1-(thiazol-2-ylamino)ethyl)-4H-pyrido[1,2-a]pyrimidin-4-one (**TGX-221a**)*

Compound **4** (35 mg, 0.121 mmol), triethylamine (0.47 mL, 3.63 mmol), methanesulfonyl chloride (0.05 mL, 0.609 mmol), thiazole-2-amine (242 mg, 2.42 mmol), and CH_2Cl_2 (5 mL). **TGX-221a**: a pale-yellow solid. Yield: 67% (22 mg). M. p. 212–213 °C. – IR: ν = 3274 (HN), 2925 (CH_3), 1728 (C=O), 1667 (C=C), 1641 (N=C) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.69 (s, 1H, 8-CH), 7.58 (s, 1H, 6-CH), 7.12 (d, J = 4.6 Hz, 1H, thiazole-CH), 6.75 (d, J = 7.3 Hz, 1H, NH), 6.48, (d, J = 4.6 Hz, 1H, thiazole-CH), 5.66 (s, 1H, 3-CH), 5.27 (m, 1H, N-CH), 3.82 (t, J = 4.0 Hz, 4H, 2 O-CH_2), 3.66 (t, J = 4.0 Hz, 4H, 2 N-CH_2), 2.31 (s, 3H, CH_3), 1.69 (d, J = 6.8 Hz, 3H, 7-CH_3) ppm. – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.31 (thiazole-2-C), 160.13 (4-C=O), 158.87 (2-C), 147.47 (10-C), 139.02 (thiazole-5-C), 135.97 (thiazole-4-C), 135.39 (8-C), 124.38 (6-C), 122.24 (9-C), 107.06 (7-C), 81.49 (3-C), 66.52 (O-CH_2), 52.62 (N-CH), 44.67 (N-CH_2), 21.33 (CH_3), 18.21 (7-CH_3) ppm. – HRMS ((+)-ESI): m/z = 372.1442 (calcd. 372.1494 for $C_{18}H_{22}N_5O_2S$, $[M+H]^+$).

*7-Methyl-9-(1-(4-methylpiperazin-1-yl)ethyl)-2-morpholino-4H-pyrido[1,2-a]pyrimidin-4-one (**TGX-221b**)*

Compound **4** (35 mg, 0.121 mmol), triethylamine (0.47 mL, 3.63 mmol), methanesulfonyl chloride (0.05 mL, 0.609 mmol), 1-methylpiperazine (242 mg, 2.42 mmol), and CH_2Cl_2 (5 mL). **TGX-221b**: a pale-yellow solid. Yield: 69% (24 mg). M. p. 210–211 °C. – IR: ν = 3286 (HN), 2925 (CH_3), 1666 (C=C), 1645 (N=C) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.68 (s, 1H, 8-CH), 7.70 (s, 1H, 6-CH), 5.65 (s, 1H, 3-CH), 4.37 (m, 1H, 11-CH), 3.81 (t, J = 4.0 Hz, 4H, O-CH_2), 3.64 (t, J = 4.0 Hz, 4H, N-CH_2), 2.59 (m, 8H, N-CH_2), 2.43 (s, 3H, N-CH_3), 2.30 (s, 3H, CH_3), 1.36 (d, J = 6.4 Hz, 3H, 3-CH_3) ppm. – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.23 (4-C=O), 158.17 (2-C), 146.68 (10-C), 137.22 (8-C), 123.39 (6-C), 122.24 (9-C), 113.28 (7-C), 81.49 (3-C), 66.52 (O-CH_2), 54.62 (N-CH_2), 49.23 (N-CH), 46.10 (N-CH_2), 44.23 (N-CH_2), 42.22 (N-CH_3), 21.33 (CH_3), 18.21 (7-CH_3) ppm. – HRMS ((+)-ESI): m/z = 372.2301 (calcd. 372.2400 for $C_{20}H_{30}N_5O_2$, $[M+H]^+$).

*7-Methyl-2-(4-methylpiperazin-1-yl)-9-(1-(phenylamino)-ethyl)-4H-pyrido[1,2-a] pyrimidin-4-one (**TGX-221c**)*

Compound **7** (150 mg, 0.5 mmol), triethylamine (0.4 mL, 3 mmol), methanesulfonyl chloride (0.2 mL, 2.2 mmol), aniline (1.0 mL, 10.0 mmol), and CH_2Cl_2 (20 mL). **TGX-221c**: a pale-yellow solid. Yield: 75% (120 mg). M. p. 214–215 °C. – IR: ν = 3269 (HN), 2925 (CH_3), 1728 (C=O), 1665 (C=C), 1645 (N=C) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.67 (s, 1H, 8-CH), 7.60 (s, 1H, 6-CH), 7.15 (d, J = 6.6 Hz, 2H, aniline-CH), 6.68 (d, J = 7.3 Hz, 1H, aniline-CH), 6.48, (d, J = 6.6 Hz, 2H, aniline-CH), 5.68 (s, 1H, 3-CH), 5.15 (m, 1H, 11-CH), 3.81 (m, 4H, 2 N-CH_2), 2.72 (m, 4H, 2 N-CH_2), 2.41 (s, 3H, N-CH_3), 2.28 (s, 3H, 7-CH_3), 1.59 (d, J = 6.0 Hz, 3H, CH_3) ppm. – ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.88 (4-C=O), 159.09 (2-C), 147.45 (10-C), 146.77 (Ar-C), 137.13 (8-C), 135.33 (Ar-

C), 129.25 (Ar-C), 123.79 (6-C), 122.20 (9-C), 117.69 (7-C), 113.24 (Ar-C), 81.42 (3-C), 54.66 (N-CH_2), 49.28 (N-CH), 46.10 (N-CH_2), 44.22 (N-CH_3), 22.12 (CH_3), 18.28 (7-CH_3) ppm. – HRMS ((+)-ESI): $m/z = 378.1951$ (calcd. 378.2224 for $C_{22}H_{28}N_5O$, $[M+H]^+$).

7-Methyl-2-(4-methylpiperazin-1-yl)-9-(1-(thiazol-2-ylamino)ethyl)-4H-pyrido[1,2-a]pyrimidin-4-one ***(TGX-221d)***

Compound **7** (150 mg, 0.5 mmol), triethylamine (0.4 mL, 3.0 mmol), methanesulfonyl chloride (0.2 mL, 2.2 mmol), 2-aminothiazole (960 mg, 9.6 mmol), and CH_2Cl_2 (20 mL). **TGX-221d**: a pale-yellow solid. Yield: 72 % (106 mg). M. p. 210 – 211 °C. – IR: $\nu = 3269$ (HN), 1728 (C=O), 2925 (CH_3), 1665 (C=C), 1645 (N=C) cm^{-1}. – ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.71$ (s, 1H, 8-CH), 7.61 (s, 1H, 6-CH), 7.12 (d, $J = 6.6$ Hz, 1H, thiazole-CH), 6.68 (t, $J = 6.6$ Hz, 1H, thiazole-CH), 6.48, (s, 1H, NH), 5.68 (s, 1H, 3-CH), 5.15 (m, 1H, N-CH), 3.81 (m, 4H, N-CH_2), 3.17 (m, 4H, N-CH_2), 2.64 (s, 3H, N-CH_3), 2.36 (s, 3H, 7-CH_3), 1.69 (d, $J = 6.6$ Hz, 3H, CH_3) ppm. – ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 168.52$ (thiazole-2-C), 160.17 (4-C=O), 158.87 (2-C), 147.49 (10-C), 139.09 (thiazole-4-C), 135.97 (8-C), 135.39 (thiazole-5-C), 124.38 (6-C), 122.24 (9-C), 107.06 (7-C), 81.49 (3-C), 54.68 (N-CH_2), 49.28 (N-CH), 46.19 (N-CH_2), 44.27 (N-CH_3), 22.13 (CH_3), 18.22 (7-CH_3) ppm. – HRMS ((+)-ESI): $m/z = 385.1497$ (calcd. 385.1811 for $C_{19}H_{25}N_6OS$, $[M+H]^+$).

7-Methyl-2-(4-methylpiperazin-1-yl)-9-(1-(4-methylpiperazin-1-yl)ethyl)-4H-pyrido[1,2-a]pyrimidin-4-one ***(TGX-221e)***

Compound **7** (80 mg, 0.27 mmol), triethylamine (1.0 mL, 8.1 mmol), methanesulfonyl chloride (0.1 mL, 1.35 mmol), 1-methylpiperazine (0.54 mL, 5.4 mmol), and CH_2Cl_2 (10 mL). **TGX-221e**: a pale-yellow solid. Yield: 55 % (42 mg). M. p. 217 – 219 °C. – IR: $\nu = 1728$ (C=O), 2930 (CH_3), 1668 (C=C), 1640 (N=C) cm^{-1}. – ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.67$ (s, 1H, 8-CH), 7.73 (s, 1H, 6-CH), 5.67 (s, 1H, 3-CH), 4.39 (m, 1H, 11-CH), 3.75 (m, 4H, N-CH_2), 2.96 (s, 3H, N-CH_3), 2.52 (s, 3H, N-CH_3), 2.37 (m, 12H, N-CH_2), 2.31 (s, 3H, 7-CH_3), 1.65 (m, 3H, CH_3), ppm. – ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 160.22$ (4-C=O), 159.13 (2-C), 147.45 (10-C), 135.33 (8-C), 122.27 (6-C), 117.60 (9-C), 113.28 (7-C), 81.32 (3-C), 56.69 (N-CH_2), 54.67 (N-CH_2), 49.23 (N-CH), 46.18 (N-CH_2), 44.69 (N-CH_2), 42.23 (N-CH_3), 22.11 (CH_3), 18.30 (7-CH_3) ppm. – HRMS ((+)-ESI): $m/z = 385.2558$ (calcd. 385.2716 for $C_{21}H_{33}N_6O$, $[M+H]^+$).

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