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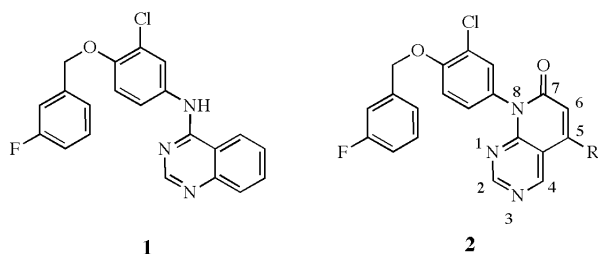
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5-Methoxy and 5-anilino-pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **2a-2f** were obtained by a tandem Michael addition-cyclization reaction of methanol and anilines with pyrimidinylpropynoate **5**. Methoxy derivative **2a** was obtained in 62% yield by treatment of **5** with methanol and potassium carbonate. Anilino derivatives **2b-2f** were prepared in 31-71% yields by reacting **5** with the corresponding anilines in refluxing methanol. This methodology accomplishes Michael-addition and pyridopyrimidinone ring formation in one-pot and affords the desired products in reasonable yield without chromatography. Propynoate **5** did not react with 4-cyanoaniline under these conditions. Reaction of **5** with 2-aminopyridine gave the unexpected arylpyrido[2,3-*d*]pyrimidinone **8** in 58% yield and reaction of **5** with imidazole afforded Michael-adduct **9** in 69% yield. Compounds **2a** and **5** were submicromolar inhibitors of epidermal growth factor receptor (EGFR) tyrosine kinase.

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Introduction.

The benzyloxylanilinoquinazoline substructure **1** is prevalent in a number of potent inhibitors of epidermal growth factor receptor (EGFR) tyrosine kinase and Type I receptor tyrosine kinases (also known as the HER or ErbB family). In addition, a number of dual EGFR/ErbB-2 kinase inhibitors show potential utility as anti-cancer agents [1-4]. As part of a medicinal-chemistry effort targeting analogs of **1**, we wished to synthesize 3-(4-anilino-pyrimidin-5-yl)prop-2-ynoates **5** and 5,8-disubstituted pyrido[2,3-*d*]pyrimidin-7-ones **2** as alkynyl and conformationally constrained versions of **1**, respectively.



Numerous examples of pyrido[2,3-*d*]pyrimidin-7-ones exist in the literature and the majority contain substitution at the 2- and 4-positions [5-8]. Few if any 5,8-disubstituted pyrido[2,3-*d*]pyrimidin-7-ones (*e.g.*, **2**) are reported, and limited examples are known with hydrogen at the 2-, 4- and/or 6-positions [9,10]. Consequently, an efficient synthesis of analogs of **2** was needed. We subsequently found that 5-methoxy and 5-anilino-8-arylpyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **2a-f** are conveniently prepared by

cross-coupling methyl propiolate with iodopyrimidine **4** followed by reaction of the resulting pyrimidinylpropiolate **5** with methanol or anilines [11]. Interestingly, this methodology appears to incorporate the 5-substituent and form the pyridopyrimidinone ring in one pot through a tandem Michael-addition/cyclization mechanism. Herein are described some scope and limitations of the methodology and inhibitory properties of the products against ErbB-2 and EGFR tyrosine kinases.

Results and Discussion.

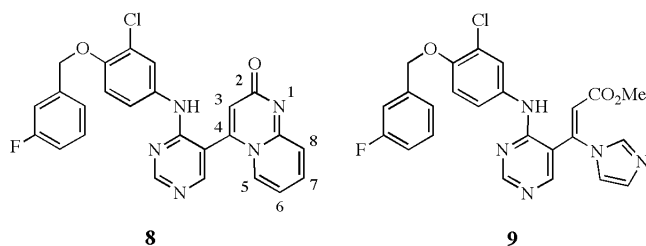
Syntheses of **2a-2f** are outlined in Scheme 1. Preparation of 4-chloro-5-iodopyrimidine (**3**) was accomplished in 2 steps and 37% overall yield employing published procedures [12]. Reaction of **3** with 3-chloro-4-[(3-fluorobenzyl)oxy]aniline [**1**] proceeded in 52% yield to afford anilino-pyrimidine **4**. Coupling of **4** to methyl propiolate [13] provided the pyrimidinylpropynoate **5** in 67% yield.

Reaction of **5** with methanol was investigated under basic conditions. Stirring a methanolic solution of **5** with potassium carbonate for 3 days at room temperature produced methoxypyridopyrimidinone **2a** in 62% yield. The formation and disappearance of a methanol-addition product/Michael adduct ($m/z = 444$, MH⁺) during the course of the reaction was supported by hplc and mass spectrometry. The proton nmr spectrum of the final product **2a** displayed a methine singlet at 6.24 ppm for the C-6 hydrogen, and ir spectroscopy revealed a carbonyl stretch at 1672 cm⁻¹ consistent with the proposed structure.

Addition of anilines to **5** was accomplished in methanol without base. Heating a mixture of **5** and excess aniline in methanol at reflux afforded anilino-pyrido[2,3-*d*]pyrimidi-

none **2b** in 31% yield. The HMBC spectrum of **2b** showed three-bond correlations between the anilino hydrogen ($\delta_{\text{H}} = 9.20$ ppm) and C-6 carbon ($\delta_{\text{C}} = 94.6$ ppm) and also between the C-6 hydrogen ($\delta_{\text{H}} = 5.77$ ppm) and pyrimidine carbon ($\delta_{\text{C}} = 109.0$ ppm) attached to C-5.

Alkoxy-, alkyl-, halo- and acetamido-substituted anilines reacted smoothly with **5** affording pyridopyrimidinones **2c-2f** in 44-71% yields. It is important to note that **5** did not react with 4-cyanoaniline under these conditions, presumably because of the electron-deficient nature of this aniline.



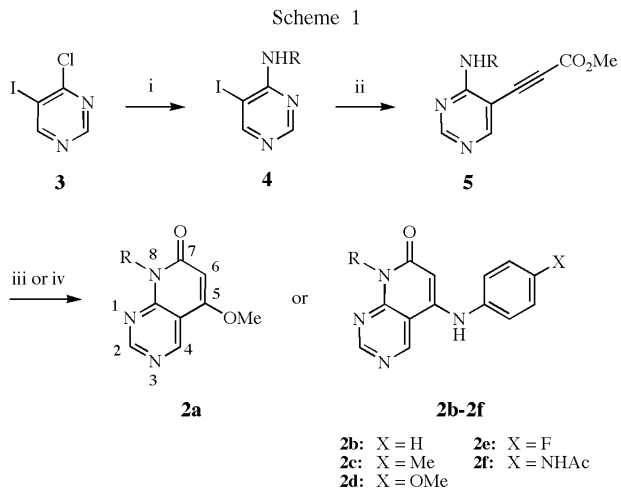
In an effort to improve the solubility of **2a-2f**, replacement of the anilino and methoxy groups in **2a-2f** with aminopyridine and imidazole rings was attempted. However, treatment of **5** with 2-aminopyridine afforded an unanticipated product—namely, arylpyrido[2,3-*d*]pyrimidinone **8** in 58% yield. The C-3 hydrogen in the proton nmr spectrum of **8** ($\delta_{\text{H}} = 6.53$ ppm) appeared *ca.* 1 ppm higher than the C-6 hydrogens of **2b-2f**. Furthermore, HMBC spectroscopy showed three-bond correlations between the anilino hydrogen ($\delta_{\text{H}} = 8.90$ ppm) and the *ortho*-carbons of the chlorinated phenyl ring ($\delta_{\text{C}} = 123.0$ and 125.1 ppm). Similar correlations were observed between the C-5 hydrogen ($\delta_{\text{H}} = 7.81$ ppm) and C-4 carbon ($\delta_{\text{C}} = 145.3$ ppm) of the pyridopyrimidinone ring.

Table 1

ErbB-2 and EGFR Tyrosine Kinase Inhibition Activity of 5-Methoxy and 5-Anilino-pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **2a-2f** and Pyrimidinylpropynoate **5** [a], [b], [c], [d]

Compound	IC ₅₀ (μM)	
	ErbB-2	EGFR
2a	2.34 (N = 2)	0.32 (N = 2)
2b	>20 (N = 1)	1.23 (N = 1)
2c	ND	1.12 (N = 1)
2d	>20 (N = 1)	3.98 (N = 1)
2e	>20 (N = 1)	7.76 (N = 1)
2f	4.86 (N = 3)	1.36 (N = 3)
5	1.26 (N = 2)	0.19 (N = 2)

[a] Mean IC₅₀ values (N > 1); [b] N = number of measurements; [c] ND = not determined; [d] IC₅₀ values for inhibition of ErbB-2 and EGFR by dual kinase inhibitor GW2016 are 9.2 and 10.8 nM, respectively (see reference 16).



R = 3-chloro-4-[(3-fluorobenzyl)oxy]phenyl; i: ArNH₂, Cs₂CO₃, CH₃CN; ii: methyl propiolate, Pd(PPh₃)₄, CuI, K₂CO₃; iii: CH₃OH; K₂CO₃, rt; iv: ArNH₂, CH₃OH, reflux.

Treatment of **5** with imidazole also failed to yield the desired pyridopyrimidinone, and instead gave Michael adduct **9** in 69% yield. No subsequent cyclization to the desired pyridopyrimidinone was observed. Carbon-13 nmr spectroscopy of **9** revealed a 5.4 Hz C-H coupling between the vinylic methine hydrogen and C-5 of the pyrimidine ring, indicating a *cis*-orientation of these atoms and therefore an *anti*-addition of imidazole to **5** [14].

Compounds **2a-2f** and **5** were evaluated for inhibition of ErbB-2 and EGFR tyrosine kinases [15]. The results of these studies are shown in Table 1. Relative inhibitory activities were compared to the known dual kinase inhibitor GW2016 under the same assay conditions [16]. 5-Methoxy analog **2a** and pyrimidinylpropiolate **5** showed IC₅₀s against EGFR in the 190-320nM range and 6-7 fold selectivities over ErbB-2 kinase. The 5-anilino derivative **2b** was less active with an IC₅₀ versus EGFR of 1.23 μM; interestingly, this compound showed greater selectivity over ErbB-2 kinase (>16-fold). Substitution at the 4-position of the anilino ring in **2b** (*e.g.*, **2c-2f**) produced no improvement in the activity of this series. Compounds **8** and **9** were inactive against EGFR and ErbB-2 kinase (IC₅₀s > 20 μM).

In summary, 5-methoxy and 5-anilino-pyridopyrimidinones **2a-2f** proved readily accessible from propiolate **5** by employing the tandem Michael addition-cyclization chemistry shown in Scheme 1. This methodology incorporates the 5-substituent and forms the pyridopyrimidinone ring in one step, affording reasonable yields of the desired products without chromatography. Propiolate **5** did not react with 4-cyanoaniline under the reported conditions and treatment of **5** with 2-aminopyridine or imidazole gave pyridopyrimidinone **8** and Michael adduct **9**, respectively.

Compounds **5** and **2a** are submicromolar inhibitors of EGFR tyrosine kinase.

EXPERIMENTAL

General.

Analytical HPLC analyses were performed on C-18 columns with 10-100% acetonitrile/water as eluent containing 0.1% trifluoroacetic acid. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Proton nmr spectra were recorded at 400 MHz and coupling constants are reported in Hz. Chemical shifts are reported in ppm relative to the residual protonated solvent resonance at 7.24 ppm (deuteriochloroform) or 2.49 ppm (dimethylsulfoxide- d_6). Mass spectral data (ms) are reported in the form m/z (molecular ion, relative intensity).

N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-5-iodopyrimidin-4-amine (**4**).

A mixture of **3** [10] (10 g, 42 mmol) and 3-chloro-4-[(3-fluorobenzyl)oxy]aniline [1] (10.5 g, 42 mmol) in ethanol (500 mL) was heated at reflux for 2.5 hours. The resulting precipitate was collected by filtration and the solid partitioned between ethyl acetate and sodium hydroxide solution. The organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated to an off-white solid which was used without further purification (10 g, 52% yield): ^1H nmr (dimethylsulfoxide- d_6): δ 8.61 (s, 1H), 8.45 (s, 1H), 8.41 (s, 1H), 7.64 (d, 1H, $J=3$), 7.45-7.39 (m, 2H), 7.28-7.24 (m, 2H), 7.17-7.11 (m, 2H), 5.20 (s, 2H); ms: m/z 456 (MH⁺, 100).

Methyl 3-[4-[(3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl)amino]pyrimidin-5-yl]prop-2-ynoate (**5**).

A mixture of **4** (100 mg, 0.219 mmole), methyl propiolate (70 μL , 0.838 mmole), potassium carbonate (61 mg, 0.441 mmole), cuprous iodide (2 mg, 0.011 mmole) and tetrakis(triphenylphosphine)palladium(0) (3 mg, 0.0043 mmole) in tetrahydrofuran (2 mL) was heated at 70 °C for 4 hours. The solvent was evaporated and the crude material then purified by silica gel chromatography eluting with 45% ethyl acetate/hexanes. This afforded **5** as a viscous oil (60 mg, 67% yield): ^1H nmr (deuteriochloroform): δ 8.67 (br s, 1H), 8.54 (br s, 1H), 7.70 (d, 1H, $J=2$), 7.37-7.30 (m, 2H), 7.23-7.16 (m, 3H), 6.99 (dt, 1H, $J=8, 3$), 6.93 (d, 1H, $J=9$), 5.12 (s, 2H), 3.85 (s, 3H); hplc: one major peak (99.9%); hrms: m/z Calcd. for $\text{C}_{21}\text{H}_{16}\text{ClFN}_3\text{O}_3$ (MH⁺): 412.0864; Found: 412.0863.

8-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-5-methoxypyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**2a**).

A mixture of **5** (50 mg, 0.121 mmole) and potassium carbonate (17 mg, 0.121 mmole) in methanol (1 mL) was stirred for 3 days at room temperature. Water was added to the reaction mixture and the resulting precipitate was collected by filtration. The filter cake was washed with methanol and ethyl acetate and dried under high vacuum to yield **2a** as an off-white solid (31 mg, 62% yield): mp 249-251 °C; ^1H nmr (dimethylsulfoxide- d_6): δ 9.10 (s, 1H), 8.91 (s, 1H), 7.50-7.45 (m, 2H), 7.36-7.32 (m, 3H), 7.23 (dd, 1H, $J=9, 3$), 7.19 (dt, 1H, $J=9, 3$), 6.24 (s, 1H), 5.31 (s, 2H), 4.01 (s, 3H); hrms: m/z Calcd. for $\text{C}_{21}\text{H}_{16}\text{ClFN}_3\text{O}_3$ (MH⁺): 412.0864; Found: 412.0870.

Anal. Calcd. for $\text{C}_{21}\text{H}_{15}\text{ClFN}_3\text{O}_3$: C, 61.25; H, 3.67; N, 10.20. Found: C, 60.84; H, 3.69; N, 10.11.

5-Anilino-8-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**2b**).

A solution of **5** (50 mg, 0.121 mmole) and aniline (45 mg, 0.483 mmole) in methanol (2 mL) was heated at reflux for 10 hours. The mixture was diluted with water and the resulting precipitate was collected by filtration. Trituration of the filter cake with methanol and drying under high vacuum afforded **2b** as a beige solid (18 mg, 31% yield): mp 232-235 °C; ^1H nmr (dimethylsulfoxide- d_6): δ 9.47 (s, 1H), 9.20 (s, 1H), 8.86 (s, 1H), 7.47-7.16 (m, 12H), 5.77 (s, 1H), 5.27 (s, 2H); hplc: one major peak (92%); hrms: m/z Calcd. for $\text{C}_{26}\text{H}_{19}\text{ClFN}_4\text{O}_2$ (MH⁺): 473.1180; Found: 473.1190.

Anal. Calcd. for $\text{C}_{26}\text{H}_{18}\text{ClFN}_4\text{O}_2 \cdot \text{H}_2\text{O}$: C, 63.61; H, 4.11; N, 11.41. Found: C, 63.65; H, 3.86; N, 11.14.

8-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-5-[(4-methylphenyl)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**2c**).

This compound was prepared from 4-methylaniline and **5** by the method described for synthesis of **2b** (59% yield): mp 298-299 °C; ^1H nmr (dimethylsulfoxide- d_6): δ 9.49 (s, 1H), 9.16 (s, 1H), 8.87 (s, 1H), 7.48 (dd, 1H, $J=14, 8$), 7.41 (d, 1H, $J=2$), 7.35-7.20 (m, 7H), 7.18 (dd, 2H, $J=8, 3$), 5.68 (s, 1H), 5.30 (s, 2H), 2.33 (s, 3H); hplc: one major peak (99.9%); hrms: m/z Calcd. for $\text{C}_{27}\text{H}_{21}\text{ClFN}_4\text{O}_2$ (MH⁺): 487.1337; Found: 487.1338.

Anal. Calcd. for $\text{C}_{27}\text{H}_{20}\text{ClFN}_4\text{O}_2$: C, 66.60; H, 4.14; N, 11.51. Found: C, 66.74; H, 4.13; N, 11.47.

8-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-5-[(4-methoxyphenyl)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**2d**).

This compound was prepared from 4-methoxyaniline and **5** by the method described for synthesis of **2b** (71% yield): mp 295-298 °C; ^1H nmr (dimethylsulfoxide- d_6): δ 9.48 (s, 1H), 9.12 (s, 1H), 8.87 (s, 1H), 7.47 (dd, 1H, $J=14, 8$), 7.41 (d, 1H, $J=3$), 7.34 (d, 1H, $J=7$), 7.31-7.27 (m, 4H), 7.21-7.16 (m, 2H), 7.05 (d, 2H, $J=9$), 5.53 (s, 1H), 5.30 (s, 2H), 3.78 (s, 3H); hplc: one major peak (99.9%); hrms: m/z Calcd. for $\text{C}_{27}\text{H}_{21}\text{ClFN}_4\text{O}_3$ (MH⁺): 503.1286; Found: 503.1297.

Anal. Calcd. for $\text{C}_{27}\text{H}_{20}\text{ClFN}_4\text{O}_3$: C, 64.48; H, 4.01; N, 11.14. Found: C, 64.46; H, 4.05; N, 11.12.

8-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-5-[(4-fluorophenyl)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**2e**).

This compound was prepared from 4-fluoroaniline and **5** by the method described for synthesis of **2b** (44% yield): mp 268-269 °C; ^1H nmr (dimethylsulfoxide- d_6): δ 9.47 (s, 1H), 9.21 (s, 1H), 8.89 (s, 1H), 7.48 (dd, 1H, $J=14, 8$), 7.42-7.29 (m, 8H), 7.21-7.17 (m, 2H), 5.66 (s, 1H), 5.30 (s, 2H); hplc: one major peak (100%); hrms: m/z Calcd. for $\text{C}_{26}\text{H}_{18}\text{ClFN}_4\text{O}_2$ (MH⁺): 491.1086; Found: 491.1071.

Anal. Calcd. for $\text{C}_{26}\text{H}_{17}\text{ClF}_2\text{N}_4\text{O}_2 \cdot 2\text{H}_2\text{O}$: C, 59.26; H, 4.02; N, 10.63. Found: C, 59.35; H, 3.85; N, 10.58.

N-{4-[(8-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-5-yl)amino]phenyl}acetamide (**2f**).

This compound was prepared from 4'-aminoacetanilide and **5** by the method described for synthesis of **2b** (56% yield): mp 345-347 °C; ^1H nmr (dimethylsulfoxide- d_6): δ 10.04 (s, 1H), 9.48 (s, 1H), 9.16 (s, 1H), 8.87 (s, 1H), 7.68 (d, 2H, $J=9$), 7.48 (dd, 1H, $J=14, 8$), 7.41 (d, 1H, $J=3$), 7.35-7.27 (m, 5H), 7.21-7.17 (m, 2H), 5.66 (s, 1H), 5.30 (s, 2H), 2.04 (s, 3H); hplc: one major peak

(99.9%); hrms: m/z Calcd for $C_{28}H_{22}ClFN_5O_3$ (MH⁺): 530.1395; Found 530.1398.

Anal. Calcd. for $C_{28}H_{21}ClFN_5O_3$: C, 63.46; H, 3.99; N, 13.22. Found: C, 63.60; H, 3.99; N, 13.26.

4-[4-(3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl)amino]pyrimidin-5-yl]-2H-pyrido[1,2-a]pyrimidin-2-one (**8**).

This compound was prepared from 2-aminopyridine and **5** by the method described for synthesis of **2b** (58% yield): mp 276-278 °C; ¹H nmr (dimethylsulfoxide-*d*₆): δ 8.87 (s, 1H), 8.71 (s, 1H), 8.41 (s, 1H), 7.79 (d, 1H, J=7), 7.67 (t, 1H, J=8), 7.62 (d, 1H, J=3), 7.43 (dd, 1H, J=14, 8), 7.32 (dd, 1H, J=9, 2), 7.28-7.22 (m, 3H), 7.16-7.12 (m, 2H), 6.80 (t, 1H, J=7), 6.50 (s, 1H), 5.19 (s, 2H); hplc: one major peak (100%); hrms: m/z Calcd for $C_{25}H_{18}ClFN_5O_2$ (MH⁺): 474.1133; Found: 474.1146.

Anal. Calcd. for $C_{25}H_{17}ClFN_5O_2$: C, 63.36; H, 3.62; N, 14.78. Found: C, 63.50; H, 3.64; N, 14.74.

Methyl (2*Z*)-3-[4-(3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl)-amino]pyrimidin-5-yl]-3-(1*H*-imidazol-1-yl)prop-2-enoate (**9**).

This compound was prepared from imidazole and **5** by the method described for synthesis of **2b**. Purification by silica gel chromatography eluting with 5% methanol/ethyl acetate followed by recrystallization from chloroform provided **9** as a light yellow solid (69% yield): mp 91-94 °C (decomp.); ¹H nmr (dimethylsulfoxide-*d*₆): δ 8.61 (s, 1H), 8.59 (s, 1H), 8.19 (s, 1H), 7.84 (s, 1H), 7.56 (s, 1H), 7.43 (dd, 1H, J=14, 8), 7.28-7.24 (m, 3H), 7.17-7.13 (m, 3H), 6.94 (s, 1H), 6.28 (s, 1H), 5.18 (s, 2H), 3.65 (s, 3H); ms: m/z 480 (MH⁺, 100).

Anal. Calcd for $C_{24}H_{19}ClFN_5O_3 \cdot 0.25H_2O$: C, 59.51; H, 4.06; N, 14.46. Found: C, 59.43; H, 3.99; N, 14.26.

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