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Graphical Abstract

Discovery and SAR studies of novel 2-anilinopyrimidine-based selective inhibitors against triple-negative breast cancer cell line MDA-MB-468

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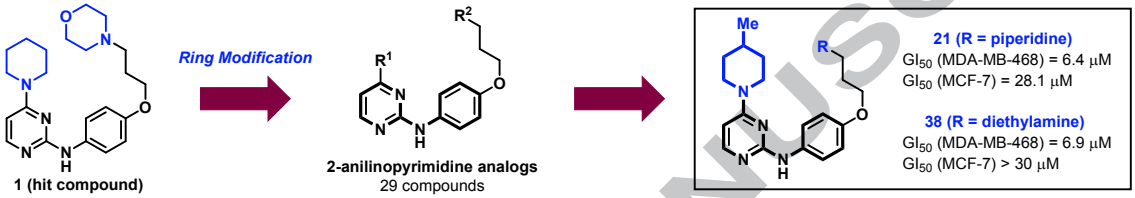

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ABSTRACT

Triple-negative breast cancers (TNBCs) are characterized as an invasive and intractable subtype of breast cancers. Overexpression of epidermal growth factor receptor (EGFR) has been considered to be an important target for TNBC therapy, but efficacies of EGFR inhibitors in clinical trials are elusive. In this study, novel series of 2-anilinopyrimidines were synthesized in an effort to identify selective inhibitors against an EGFR-overexpressing TNBC cell line. Biological evaluation demonstrated that compounds **21** and **38**, with a 4-methylpiperidine group and a high ClogP value, exhibited good potency and selectivity for the TNBC cell line. This study has provided evidence to support further development of 2-anilinopyrimidine-based TNBC selective inhibitors and investigation of the targets of compounds **21** and **38**.

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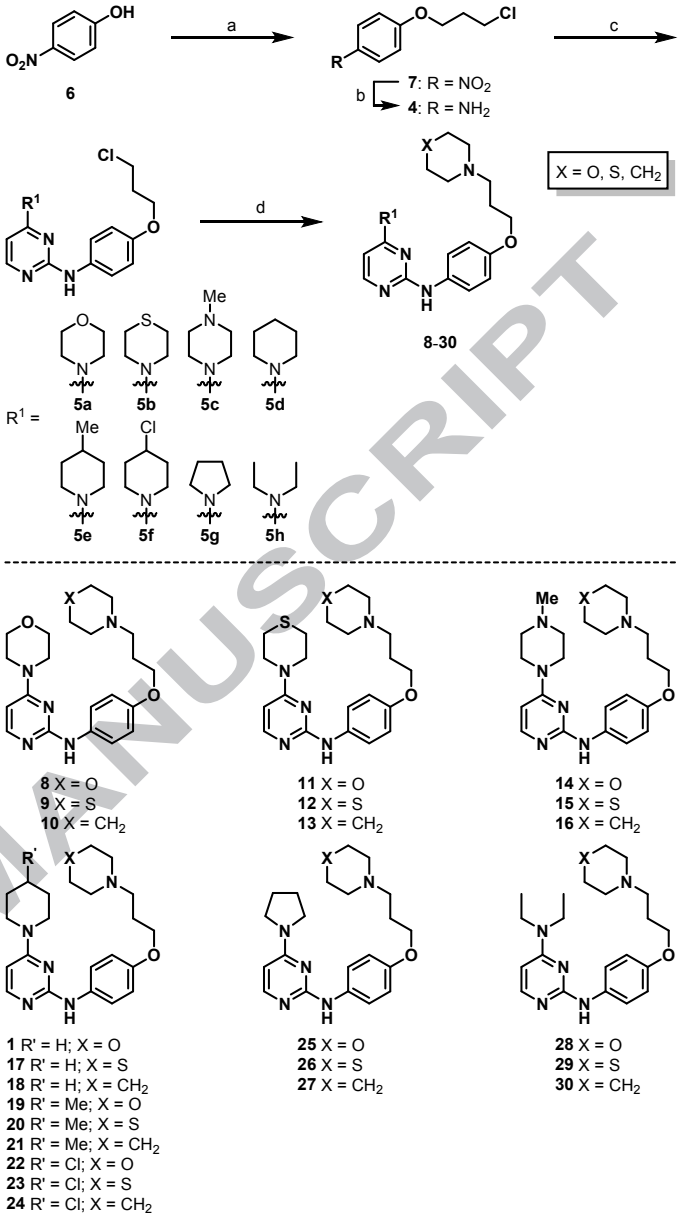
Triple-negative breast cancers (TNBCs) are defined as aggressive mammary tumors that are characterized by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).[1-4] Based on the gene expression (GE) profiles, TNBCs can be subdivided into six subtypes: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR).[3-5] TNBCs account for approximately 15%–20% of all diagnosed breast cancer cases and basal-like type breast cancer constitute approximately 50%–75% of all TNBC tumors.[4-8] Cytotoxic chemotherapy remains the standard treatment for TNBC, but contributes to the improvement of only approximately 20% of patients with TNBC.[1-7] In addition, no approved targeted therapy has been made available for TNBCs.

Numerous molecular-profiling studies have revealed the potential therapeutic targets of TNBCs, which belong to proliferative and survival-dependent pathways.[8-10] In particular, the overexpression of epidermal growth factor receptor (EGFR) in TNBC is well known in comparison with other breast cancer subtypes and has shown to be a negative prognostic factor.[8-13] Furthermore, many EGFR inhibitors have been clinically investigated against TNBC. However, triple-negative and basal-like breast cancers frequently display abnormalities in *PTEN* (the gene encoding the phosphatase and tensin homolog), which counteracts the antitumor activity of anti-EGFR therapies.[14,15] Currently, there is no effective single anti-EGFR agent for the treatment of TNBC.[8-13]

In the context of finding novel EGFR-overexpressing TNBC selective inhibitors, an in-house chemical library was screened in MCF-7 and MDA-MB-468 cell lines using a dose dependent MTT assay. MCF-7 is a representative luminal-type breast cancer cell line, whereas MDA-MB-468 is a unique EGFR-overexpressing TNBC cell line.[16] In particular, MDA-MB-468 exhibits resistance to EGFR tyrosine kinase inhibitors, such as gefitinib and erlotinib, because the lack of PTEN permits a high threshold of Akt activity, independent of receptor tyrosine kinase input.[15,17] Moreover, the cell line has a p53 mutation that can drive cell survival and proliferation through diverse pathways.[18-20] For these reasons, the discovery of potent inhibitors against MDA-MB-468 is challenging and only a limited number of studies have been conducted.[21-25] After cell-based screening of the chemical library, we have identified hit compound **1** (Figure 1A). Interestingly, compound **1** selectively inhibited the proliferation of MDA-MB-468 cells (GI_{50} = 18.3 μM) compared with that of the MCF-7 cells (GI_{50} > 30.0 μM), and had relatively good lead-like properties (MW ≤ 460, rings ≤ 4, hydrogen-bond donors ≤ 5, hydrogen-bond acceptors ≤ 9, and -4 ≤ LogP ≤ 4.2).[26] In addition, the structure of compound **1** contains a 2-anilinopyrimidine backbone, which has widely been investigated in the field of medicinal chemistry.[27-31] Thus, we designed and synthesized a library of novel 2-anilinopyrimidine derivatives through the modification of the piperidine and morpholine rings of **1** and attempted to establish a brief structure-activity relationship (SAR).

Our synthetic strategy for the 2-anilinopyrimidine analogs is outlined in Figure 1B. The overall strategy focused on the modification of both the A and B parts within the final 2-anilinopyrimidines. The efficient synthesis incorporated two simple derivatization processes: the S_NAr reaction of the commercially available **2** with various amines, and the S_N2 reaction of the advanced intermediate **5** with various amines.



Scheme 2. Synthesis of analogs **1**, **8**-**30**. Reagent and conditions: (a) 3-chloro-1-propanol, DIAD, PPh_3, THF, 0 °C, 99%; (b) $SnCl_2 \cdot H_2O$, EtOH, 70 °C, 51%; (c) **3a**-**3h**, 1N HCl in AcOH, MW, 1-butanol, 15-60%; (d) morpholine or thiomorpholine or piperidine, K_2CO_3, KI, DMF, 100 °C, 14-86%.

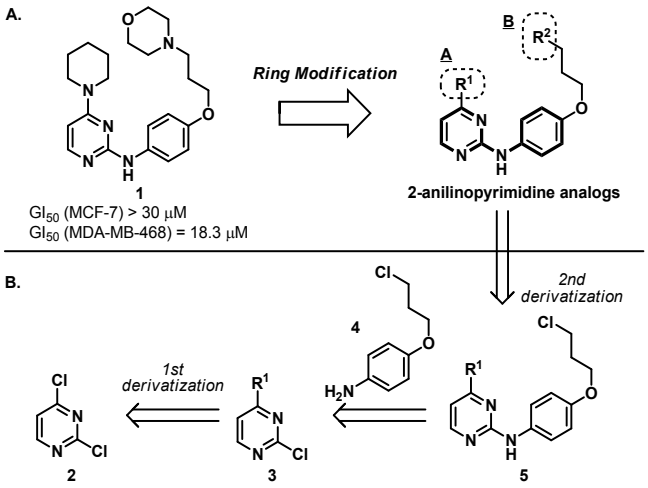


Figure 1. (A) Design of novel 2-anilinopyrimidines; (B) Derivatization

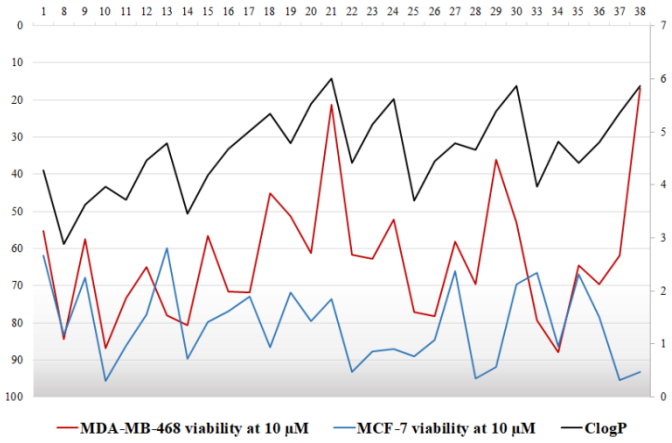
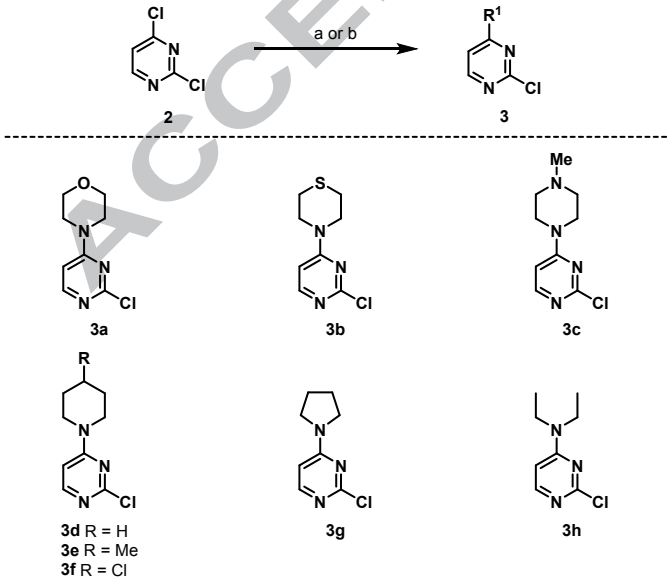


Figure 2. Correlation between the lipophilicity parameter ClogP and cytotoxic activity at 10 μM in MDA-MB-468 cells

The synthesis of novel 2-anilinopyrimidine derivatives commenced with the preparation of 2-chloro-4-aminopyrimidines **3** (Scheme 1). Nucleophilic aromatic substitution of **2** and various cyclic and acyclic amines smoothly afforded the desired aminopyrimidines **3a**–**3e**, **3g**, and **3h**, without the use of a base. However, 4-chloropiperidinopyrimidine **3f** was obtained in the presence of *n*-BuLi.

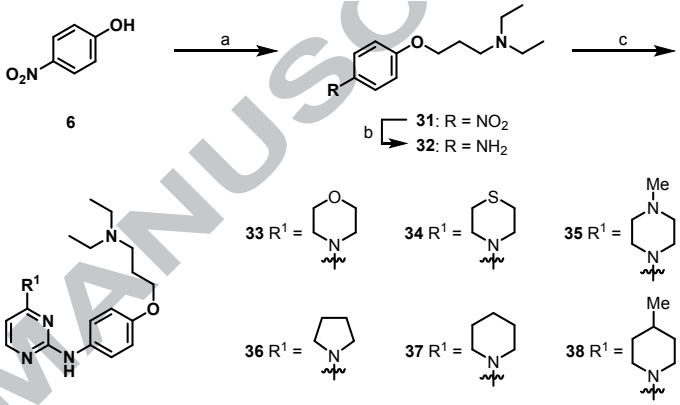
With the 4-substituted 2-chloropyrimidines **3** available, we executed the synthesis of the final analogs (Scheme 2). Mitsunobu reaction of **6** with DIAD and PPh_3, followed by nitro reduction of the resultant chloropropoxybenzene **7** largely provided the chloropropoxyaniline **4**. Unfortunately, our initial attempts to combine aniline **4** and the 2-chloropyrimidines **3a-3h** under conventional conditions were unsuccessful. However, these reluctant couplings achieved under microwave-assisted conditions. The desired 2-anilinopyrimidines **5a-5h** were readily obtained, although the yields of some reactions were unsatisfactory. Finally, simple S_N2 reactions of **5a-5h** with morpholine, thiomorpholine, and piperidine provided the 2-anilinopyrimidine analogs **8-30**.



Scheme 1. Preparation of 2-chloro-4-aminopyrimidines **3a-3h**. Reagent and conditions: (a) morpholine, thiomorpholine, 1-methylpiperazine, piperidine, 4-methylpiperidine, pyrrolidine or diethylamine, EtOH, rt, 17-70%; (b) 4-chloropiperidine, *n*-BuLi, THF, 0 °C, 41%.

[a] Values are the mean ± standard deviation of three experiments.

[b] ClogP values were calculated from ChemDraw Professional 15.1.



Scheme 3. Synthesis of analogs **33-38**. Reagent and conditions: (a) 3-diethylamino-1-propanol, DIAD, PPh_3, THF, 0 °C, 95%; (b) $SnCl_2 \cdot H_2O$, EtOH, 70 °C, 79%; (c) **3a-3e** or **3g**, 1N HCl in AcOH, MW, 1-butanol, 8-33%.

Having established a synthetic procedure, we undertook the synthesis of the acyclic analogs **33-38**, as shown in Scheme 3. Mitsunobu reaction of **6** with 3-diethylamino-1-propanol in the presence of DIAD and the subsequent reduction of the resulting nitrobenzene **31** afforded the diethylaminopropoxyaniline **32**. Finally, the microwave-assisted S_NAr reaction of **32** with **3a-3e** or **3g** under acidic condition successfully provided the desired 2-anilinopyrimidine analogs **33-38**.

With the synthesized compounds in hand, we evaluated their antiproliferative activities on luminal type breast cancer cells MCF-7 and TNBC cells MDA-MB-468 through a dose dependent MTT (3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (Table 1). The results demonstrated that newly synthesized analogs were generally less cytotoxic to MCF-7 cells than gefitinib, when compounds were treated at 10 μM concentration. Interestingly, we observed that antiproliferative effects of 2-anilinopyrimidines in MDA-MB-468 cells relied upon specific molecular features. First, an investigation into the effect of substituents in the A part was conducted. 4-Methylpiperidine analogs **19**, **20**, **21** and **38** exhibited pronounced cytotoxic activity in TNBC cells. In particular, the presence of a methyl group in the 4-position of piperidine, as seen in **19**, resulted in substantially increased antiproliferative activity in TNBC cells and decreased toxicity in MCF-7 cells as compared to hit compound **1**. This result showed that a methyl group in the 4-position of piperidine had an essential role in the selective cytotoxicity on MDA-MB-468 cells. However, the substitution of relatively hydrophilic groups, such as morpholine (**8-10**), thiomorpholine (**11-13**) or *N*-methylpiperazine

Table 1. Cytotoxic activities of 2-anilinopyrmidines against the MCF-7 and MDA-MB-468 cell lines.

Table 2. Growth inhibitory effects and selectivity index (SI) of selected compounds.

Comp.	GI_{50} (μM)[a]		MDA-MB-468 SI[b]
	MCF-7	MDA-MB-468	
18	>30	9.2	>3.3
19	>30	16.3	>1.8
21	28.1	6.4	4.4
24	>30	11.5	>2.6
29	27.3	7.6	3.6
30	18.3	11.4	1.6
38	>30	6.9	>4.3
gefitinib	>30	25.5	>1.2

[a] GI_{50} values are the mean of three experiments and correspond to the concentration of compound that causes a 50% decrease in net cell growth.

[b] SI = GI_{50} for MCF-7 cells/GI_{50} for MDA-MB-468 cells.

(**14**-**16**) in the A part did not lead to potent inhibition against the TNBC cells. The analogs **22**-**24**, bearing 4-chloropiperidine in the same part, were moderately cytotoxic to TNBC cells while the pyrrolidine or acyclic amine substituted analogs **25**-**30** were less active than **1**. From these results, we suggest that the insertion of less polar substituent into the A part led to 2-anilinopyrimidines with promising activity for TNBC cells.

Next, we turned our attention to the effects of substituents in the B part. The results shown in Table 1 demonstrate that the 2-anilinopyrimidines bearing morpholine or thiomorpholine were generally not potent inhibitors of the MDA-MB-468 cell line, with the exception of **29**. However, the piperidine substituted analogs **18**, **21**, **24** and **30** were more cytotoxic to TNBC cells than **1**. This result suggested that the piperidine group in the B part was preferred to other substituents for anti-TNBC activity. The introduction of acyclic amine into the B part (**33**-**37**) resulted in moderate toxicity to TNBC cells. However, for the acyclic amine analog **38**, in which a 4-methylpiperidine group is substituted in the A part, exhibited great potent activity with 16.9% of MDA-MB-468 cells survival even at 10 μM.

The preliminary SAR study guided us to evaluate the relationship between the lipophilicity parameter ClogP and the cytotoxic activity in MDA-MB-468 cells. As displayed in Table 1, the synthesized analogs have wide range of ClogP values from 2.89 to 6.01. Generally, analogs with low ClogP values exhibit low activities. However, the most potent compounds, **21** and **38**, have highest ClogP values with 6.01 and 5.87, respectively. This result showed that the activity of the compounds was strongly dependent on lipophilicity, as depicted in Figure 2. As increased lipophilicity of compounds leads to improved membrane permeability,[32,33] the activity of the analogs might be closely associated with the cell permeability. The SAR study did not reveal any relationship between the activity in MCF-7 cells and lipophilicity or specific structural features. Thus, these results led us to suggest that the target of novel 2-anilinopyrimidines was located intracellularly or intranuclearly in MDA-MB-468 cells specifically.

The aim of our work was not only to discover potent analogs against the TNBC cell line, but also to develop selective inhibitors. The selectivity of potent analogs for TNBC cells was evaluated by dividing the GI_{50} for MCF-7 cells by the GI_{50} values for MDA-MB-468 cells (Table 2). As expected, all selected compounds displayed higher potency than gefitinib against MDA-MB-468 cells. Compound **30** exhibited the lowest selectivity, with an SI of 1.6, whereas the selectivity of compound **18** was more 2-fold greater (SI > 3.3) than **30**. It is assumed that the presence of cyclic amine in the A part was of great importance for the selectivity. Especially, the most potent compounds, **21** (GI_{50} = 6.4 μM) and **38** (GI_{50} = 6.9 μM), showed highly selective activity against TNBC cell line, as indicated by selectivity index (SI > 4.3). This finding supports that the introduction of 4-methylpiperidine in A part led to 2-anilinopyrimidines with promising activity and selectivity for the target TNBC cell line.

In summary, a series of novel 2-anilinopyrimidine-based derivatives were synthesized and evaluated for their in vitro growth inhibition activities in luminal type breast cancer cell line MCF-7 and basal-like TNBC cell line MDA-MB-468. In these newly synthesized compounds, a strong correlation was observed

Comp.	Cell viability at 10 μM (% of untreated control)[a]		ClogP[b]	Comp.	Cell viability at 10 μM (% of untreated control)[a]		ClogP[b]
	MCF-7	MDA-MB-468			MCF-7	MDA-MB-468	
1	61.8 ± 1.0	55.2 ± 1.3	4.27	**23**	87.7 ± 1.4	62.7 ± 1.8	5.14
8	83.2 ± 3.7	84.5 ± 1.4	2.89	**24**	87.1 ± 2.9	52.1 ± 2.5	5.62
9	67.9 ± 2.8	57.4 ± 0.5	3.63	**25**	89.0 ± 3.8	77.1 ± 2.6	3.71
10	95.7 ± 4.0	86.8 ± 1.9	3.96	**26**	84.7 ± 3.7	78.3 ± 0.3	4.45
11	86.1 ± 2.2	73.4 ± 0.7	3.72	**27**	66.1 ± 1.3	58.1 ± 0.9	4.78
12	77.8 ± 4.3	65.0 ± 2.2	4.46	**28**	94.9 ± 3.3	69.7 ± 2.5	4.66
13	60.0 ± 1.4	78.1 ± 4.4	4.79	**29**	91.9 ± 2.5	36.0 ± 2.3	5.39
14	89.6 ± 2.9	80.7 ± 1.0	3.45	**30**	69.7 ± 2.4	53.1 ± 3.2	5.87
15	79.8 ± 2.3	56.5 ± 2.7	4.18	**33**	66.5 ± 1.5	79.4 ± 3.6	3.97
16	76.9 ± 5.0	71.7 ± 2.7	4.67	**34**	86.4 ± 4.5	88.0 ± 4.7	4.81
17	72.9 ± 1.3	71.8 ± 3.9	5.01	**35**	67.0 ± 3.4	64.6 ± 1.3	4.42
18	86.7 ± 2.4	45.1 ± 0.6	5.34	**36**	78.5 ± 1.8	69.7 ± 3.2	4.80
19	71.8 ± 0.9	51.3 ± 1.9	4.79	**37**	95.4 ± 3.4	62.0 ± 5.1	5.36
20	79.5 ± 1.9	61.3 ± 1.2	5.53	**38**	93.2 ± 5.0	16.9 ± 1.2	5.87
21	73.7 ± 4.0	21.3 ± 2.4	6.01	**gefitinib**	70.3 ± 1.5	60.3 ± 1.6	5.45
22	93.3 ± 4.1	61.6 ± 3.7	4.41				

between the lipophilicity parameter ClogP and the antiproliferative activity against the TNBC cell line. The SAR studies and selectivity analysis suggested that the 4-methylpiperidine group in A part turned out crucial for the selective cytotoxicity on MDA-MB-468 cells. Two compounds **21** and **38** showed the most promising potency and the highest SI values for the TNBC cell line. From these observations, investigation of novel lead scaffolds and identification of target of MDA-MB-468 selective inhibitors are underway.

Acknowledgments

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A. Supplementary data

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