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Synthesis of novel arylaminoquinazolinylurea derivatives and their antiproliferative activities against bladder cancer cell line

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ABSTRACT

A novel series of arylurea and arylamide derivatives **1a–z**, **2a–d** having aminoquinazoline scaffold was designed and synthesized. Their in vitro antiproliferative activities against RT112 bladder cancer cell line and inhibitory activities against FGFR3 kinase were tested. Most compounds showed good antiproliferative activities against RT112 bladder cancer cell line, and arylurea compounds **1a–z** were more potent than arylamide compounds **2a–d**. Among them, eight compounds **1a**, **1d–g**, **1l**, **1y**, and **1z** showed potent activities with GI_{50} values below submicromolar range. Especially, arylurea compounds **1d** and **1g** possessing 2,3-dimethyl and 3,4-dimethyl moieties exhibited superior or similar antiproliferative activity (GI_{50} = 8.8 nM and 30.2 nM, respectively) to AZD4547 (GI_{50} = 29.2 nM) as a reference standard.

Bladder cancer represents the fifth most common neoplasms in developed countries and a major cause of cancer-related morbidity and death. Incidence and mortality rates have remained relatively constant over the past four decades, with an estimated 72,570 new cases and 15,210 deaths predicted for 2013 in the United States alone.[1] About 70% of cases are non-muscle invasive and have a high propensity to recur, giving bladder cancer the highest recurrence rate of any cancer.[2] The other 30% of cases are muscle invasive tumors, for which the 5-year survival is approximately 50%. Their conventional treatment involves surgical resection and intravesical chemo- or immunotherapy.[3]

Fibroblast growth factor receptors (FGFRs) constitute a major class of receptor tyrosine kinases (RTKs) for a large family of fibroblast growth factors (FGFs) and contain an extracellular ligand-binding domain and an intracellular tyrosine kinase domain.[4] Overexpression of each FGFR has been identified and linked to a variety of human cancers, including breast and prostate cancer, as well as multiple myeloma.[5–7] FGFR3 is a member of a structurally related family of tyrosine kinase receptors (FGFR1–4) that orchestrate a diverse variety of cellular activities, including proliferation, differentiation, and survival.[8] Epithelial cancers such as bladder cancer also exhibit deregulation and mutation of FGFR3, but whether this contributes to tumorigenesis in vivo has remained unclear. FGFR3 has long been considered a particularly promising target for novel therapeutic approaches in bladder cancer.[9] Recently, a number of small molecule as receptor tyrosine kinase inhibitors have been developed to target FGFRs and their associated FGFs.[10–14] AZD4547 (AstraZeneca, Phase II/III)[15] is a novel and selective inhibitor of FGFR1, FGFR2, FGFR3 tyrosine kinases, and PD173074 (Pfizer)[16] serves as an important antitumor inhibitor because of their good selectivity towards FGFR1 and FGFR3 (Fig. 1).

Quinazoline is one of the most widespread scaffolds among natural and synthetic bioactive compounds. Several compounds possessing quinazoline scaffold have been recently reported as potential antiproliferative agents.[17–21] In this work, a novel series of arylurea and arylamide derivatives **1a–z**, **2a–d** having an aminoquinazoline scaffold as a hinge region binding motif, based on the structural features of AZD4547 and PD173074, was designed and synthesized (Fig. 1). Their in vitro antiproliferative activities were tested over RT112 bladder cancer cell line[22,23] (FGFR3 high-expressing bladder cancer). And their inhibitory activities against FGFR3 kinase are reported.

Arylaminoquinazolinylureas **1a–z** were synthesized by the pathways illustrated in Scheme 1. Ring closure of 2-amino-3-

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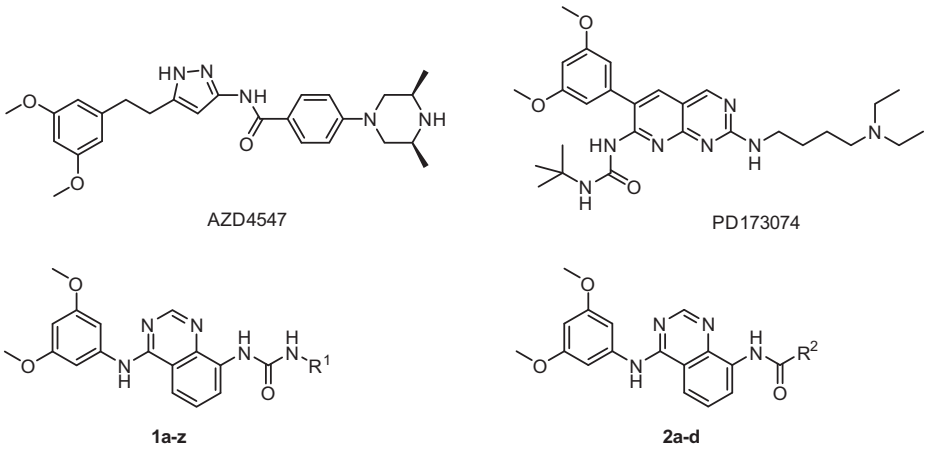
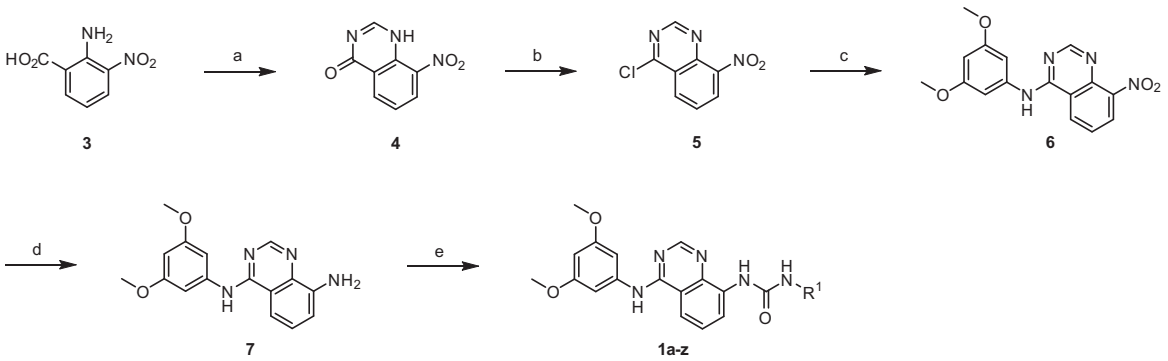


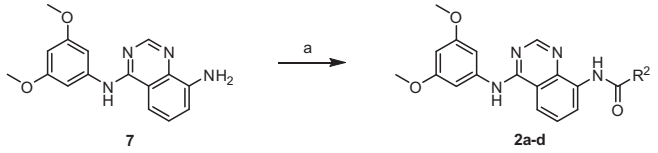
Figure 1. Structures of AZD4547, PD173074, and the lead compounds.



Scheme 1. Reagents and conditions: (a) formamidine acetate, 2-methoxyethanol, 160 °C, 24 h, 51%; (b) DIPEA, $POCl_3$, chlorobenzene, 10–90 °C, 5 h, 60%; (c) 3,5-dimethoxyaniline, Na_2CO_3, *i*-PrOH, 95 °C, 15 h, 79%; (d) Pd/C, H_2, EtOH, rt, 24 h, 87%; (e) R^1NCO, THF, rt, 3 h, **1a**: 62%, **1b**: 22%, **1c**: 45%, **1d**: 32%, **1e**: 79%, **1f**: 24%, **1g**: 19%, **1h**: 26%, **1i**: 33%, **1j**: 47%, **1k**: 32%, **1l**: 39%, **1m**: 42%, **1n**: 32%, **1o**: 29%, **1p**: 42%, **1q**: 33%, **1r**: 52%, **1s**: 43%, **1t**: 49%, **1u**: 41%, **1v**: 45%, **1w**: 67%, **1x**: 22%, **1y**: 52%, **1z**: 46%.

nitrobenzoic acid (**3**) as a starting material with formamidine acetate in 2-methoxyethanol gave 8-nitroquinazolin-4(1*H*)-one (**4**),[24] which was then chlorinated with phosphorus oxychloride in the presence of *N*,*N*-diisopropylethylamine to give 4-chloro-8-nitroquinazoline (**5**). Nucleophilic substitution of the chloro group of **5** with 3,5-dimethoxyaniline was carried out using sodium carbonate in 2-propanol to produce *N*-(3,5-dimethoxyphenyl)-8-nitroquinazolin-4-amine (**6**). Reduction of the nitro group of **6** using palladium over carbon in hydrogen atmosphere gave the compound **7** in good yield. Treatment of **7** with the appropriate aryl isocyanate derivatives afforded the corresponding title compounds **1a**–**z**, respectively.

Synthesis of arylaminoquinazolinylamides **2a**–**d** was carried out by the sequence of reactions shown in Scheme 2. Amide coupling of the amino group of compound **7** with the appropriate carboxylic acid derivatives in the presence of HOBt, EDCI, and triethylamine led to the desired title compounds **2a**–**d**, respectively.



Scheme 2. Reagents and conditions: (a) R^2CO_2H, HOBt, EDCI, Et_3N, DMF, 0–80 °C, 18 h, **2a**: 24%, **2b**: 48%, **2c**: 29%, **2d**: 43%.

The in vitro antiproliferative activity of the newly synthesized compounds against RT112 bladder cancer cell line was tested.[25] The ability of arylaminoquinazolinylureas **1a**–**z** and arylaminoquinazolinylamides **2a**–**d** to inhibit the growth of RT112 cell line is summarized in Tables 1 and 2. AZD4547 was selected as a reference standard in this experiment because of its good selectivity towards FGFR1, FGFR2, FGFR3 tyrosine kinases. Most compounds showed good antiproliferative activities against RT112 bladder cancer cell line. In general, arylaminoquinazolinylureas **1a**–**z** with a terminal urea moiety as a hydrophobic tail region were more potent than arylaminoquinazolinylamides **2a**–**d** having a terminal amide moiety. This may be attributed to that the longer spacer, urea moiety, may geometrically permit appropriate fitting of the molecule at the receptor site. Or the terminal NH group of the urea moiety may form additional hydrogen bond at the binding pocket. Any or both of these effects would enable optimal drug–receptor interaction, and hence higher antiproliferative activity. As shown in Table 1, thirteen compounds showed good potency with GI_{50} values in 1-digit micromolar range (GI_{50} = 1.08–6.23 μM) and eight compounds **1a**, **1d**–**g**, **1l**, **1y**, and **1z** exhibited potent activities with GI_{50} values below submicromolar range (GI_{50} = 8.8–471 nM) against RT112 bladder cancer cell line. The effect of substituents onto aryl nucleus on potency was also investigated. Compounds with electron-donating group were generally found to be more potent than compounds having electron-withdrawing group, except for compounds **1y**,**z** having nitro moiety. Among them, dimethylphenylurea compounds **1d**–**g** showed higher potency compared with compounds bearing the different terminal