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Synthesis of a New 4-(Pyridin-3-yl)pyrimidine Derivatives for Anticancer Activity

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Abstract : This study is focused on the synthesis of urea and amide derivatives particularly, since the amide moiety is an essential binding group at the binding site. Urea derivatives **3-7** and **13-14** were obtained by reaction of 2-aminopyrimidines and other amines with diverse isocyanates in pyridine as a solvent under reflux. The urea derivatives were obtained in low yield because of the highly electron deficient nature of the amino group of the 2-aminopyrimidine. Amide derivatives **8-10** were obtained in moderate yields by reaction of compound **1** with aryl chloride derivatives. Also, arylamine **11** was synthesized by Buchwald-Hartwig amination in moderate yields. Most of the compound did not show good activity against A375P melanoma cells, compared with Sorafenib as control compound.

Keywords : Anticancer activity, 4-(pyridin-3-yl)pyrimidine derivatives, A375P melanoma cells, B-Raf.

1. Introduction

Protein kinases are functional proteins that play a key role in signal transduction and communication within the cell. These kinases work by phosphorylation of other functional proteins inside the cell, leading to their activation and subsequent transduction of signal[1-2]. Raf kinases are serine/threonine kinases that forms the initiating part of the RAF-RAS-MEK-ERK signaling pathway [3-5]. There are three isoforms of Raf; Raf 1 (C-Raf), A-Raf and B-Raf. Mutated B-Raf was found in about 66% of malignant melanomas, and at lower frequencies in many other human cancers[6-7]. The most frequent mutation of B-Raf is V600B, which arises from the replacement of the valine residue at position 600 in the kinase loop with a glutamic acid. This substitution results in a constitutively active enzyme that is about 500 times as active as the wild type[7]. These facts have made B-Raf be an important therapeutic target for several human cancers. Consequently, intensive works have been made to develop potent and selective inhibitors for B-Raf kinase. 4-(Pyridin-3-yl)pyrimidin-2-amine is a popular scaffold in a large number of kinase inhibitors and anticancer agents[8-11].

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Imatinib[10] and Nilotinib[11] are two popular kinase inhibitors, based on this scaffold, which have been approved as drugs for the treatment of chronic myelogenous leukemia.

In this study, we have utilized this 4-(pyridin-3-yl)pyrimidin-2-amine scaffold to synthesize a number of new derivatives in order to be evaluated as inhibitors for B-Raf kinase. A variety of chemical groups (benzyl, aryl, benzoyl and arylurea) have been inserted into the amino group of the scaffold, in order to test the activity of the resulted classes of compounds as inhibitors for B-Raf kinase with the aim of finding a potential potent lead. After synthesis of the title compounds, we measured antiproliferative activities of the compounds against A375P melanoma cell.

2. Experimental

2.1. General

^{1}H-NMR (300 MHz) was recorded on a Bruker Avance 300 spectrometer with TMS as an internal reference. The IR spectra were recorded on Perkin Elmer Spectrum GX spectrometer. Melting points were taken on a Thomas-Hoover capillary melting apparatus and were uncorrected. Column chromatography was performed on Merck silica gel 60 (230-400 mesh). TLC was carried out using glass sheets precoated with silica gel 60 F254 prepared by E. Merck. All the commercially available reagents were obtained from Aldrich and Tokyo Kasei Chemical and generally used without further purification.

2.2. Synthesis of the compounds 1-14

2.2.1. 1-(3,5-Bis(trifluoromethyl)phenyl) -3-(4-(pyridin-3-yl)pyrimidin-2-yl) urea (3)

4-Pyridin-3-ylpyrimidin-2-amine (**1**) (50 mg, 0.29 mmoles) was dissolved in 5 ml of pyridine, followed by 3,5-bis(trifluoromethyl) phenylisocyanate (50.2 μℓ, 0.29 mmoles) and the mixture refluxed for 22 hr. After the completion of reaction, the mixture was cooled to room temperature and evaporated under reduced pressure. The residue was solidified by methanol, filtered by suction filtration, and dried under vacuum to obtain the pure product, 82 mg (66 %); mp 248.8 - 249.8 °C; ^{1}H-NMR (DMSO-d_6) δ 7.60 (dd, 1H, J = 4.5, J = 7.2 Hz), 7.75 (s, 1H), 7.84 (d, 1H, J = 5.2 Hz), 8.33 (s, 2H), 8.55 (d, 1H, J = 7.5 Hz), 8.77 - 8.84 (m, 2H), 9.37 (s, 1H), 10.62 (s, 1H), 11.99 (s, 1H); IR (KBr): 3436, 1717, 1577, 1474, 1448, 1393, 1338, 1285, 1239, 1164, 1135 cm^{-1}.

2.2.2. 1-(4-(Pyridin-3-yl)pyrimidin-2-yl) -3-(3-(trifluoromethyl)phenyl)urea (4)

4-Pyridin-3-yl-pyrimidine-2-amine (**1**) (30 mg, 0.17 mmoles) was dissolved in 5 ml of pyridine, followed by 3-trifluoromethylphenylisocyante (48.8 μℓ, 0.35 mmoles) and the mixture refluxed for 34 hr. After the completion of reaction, the mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified over silica column using ethyl acetate as mobile phase to obtain the pure product, 4 mg (6.4 %); mp 214.0 - 215.0 °C; ^{1}H-NMR (DMSO-d_6) δ 7.42 (d, 1H, 5.3 Hz), 7.57 - 7.65 (m, 2H), 7.79 - 7.83 (m, 2H), 8.10 (s, 1H), 8.53 - 8.55 (m, 1H), 8.78 (dd, 1H, J = 1.4, 4.7 Hz), 8.81 (d, 1H, J = 5.3 Hz), 9.37 (s, 1H), 10.47 (s, 1H), 11.71 (s, 1H); IR (KBr): 3438, 3068, 2927, 2853, 1709, 1616, 1592, 1571, 1453, 1344, 1261, 1150, 1109, 1073 cm^{-1}.

2.2.3. 1-(2,3-Dichlorophenyl)-3-(4- (pyridine-3-yl)pyrimidine-2-yl) urea (5)

4-Pyridin-3-ylpyrimidine-2-amine (**1**) (50 mg, 0.29 mmoles) was dissolved in 5 ml of pyridine, followed by 2,3-dichlorophenylisocyanate (38.3 μℓ, 0.29

mmoles) and the mixture refluxed for 20 hr. After the completion of reaction, the mixture was cooled to room temperature to induce precipitation. The precipitation was filtered by suction filtration, washed with cool pyridine and dried under vacuum to obtained the pure product, 7 mg (6.3 %); mp 247.9 - 248.9 °C; ^{1}H-NMR (DMSO-*d6*) δ 7.36 - 7.42 (m, 2H), 7.61 (dd, 1H, *J* = 4.4, 7.6 Hz), 7.82 (d, 1H, 5.7 Hz), 8.36 (dd, 1H, *J* = 2.4, 4.7 Hz), 8.52 (d, 1H, *J* = 8.0 Hz), 8.78 (d, 1H, *J* = 3.3 Hz), 8.85 (d, 1H, *J*= 5.1 Hz), 9.34 (s, 1H), 10.61 (s, 1H), 12.12 (s, 1H); IR (KBr): 3436, 2927, 1719, 1623, 1589, 1452, 1250, 1130, 1117, 1101 cm^{-1}.

2.2.4. 1-(4-Chlorophenyl)-3-(4-(pyridin-3-yl)pyrimidin-2-yl)urea (6)

4-Pyridin-3-ylpyrimidin-2-amine (**1**) (50 mg, 0.29 mmoles) was dissolved in 5 ml of pyridine, followed by 4-chlorophenylisocyanate (37.2 μℓ, 0.29 mmoles) and the mixture refluxed for 24 hr. After the completion of reaction, mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified over silica column using ethyl acetate as mobile phase to obtain the pure product, 5 mg (5.3 %); mp 221.4 - 222.4 °C; ^{1}H-NMR (DMSO-*d6*) δ 7.52 (dd, 4H, *J* = 8.5 Hz), 7.62 - 7.65 (m, 1H), 7.80 (d, 1H, *J* = 5.3 Hz), 8.50 - 8.53 (m, 1H), 8.78 - 8.80 (m, 2H), 9.35 (s, 1H), 10.37 (s, 1H), 11.50 (s, 1H); IR (KBr): 3436, 1702, 1612, 1589, 1564, 1548, 1492, 1455, 1340, 1116, 805 cm^{-1}.

2.2.5. 2,6-Difluoro-*N*-(4-(pyridin-3-yl)pyrimidin-2-ylcarbamoyl)benzamide (7)

4-Pyridin-3-ylpyrimidin-2-amine (**1**) (50 mg, 0.29 mmoles) was dissolved in 5 ml of pyridine, followed by 2,6-difluorobenzoylisocyanate (53.2 mg, 0.29 mmoles) and stirred at room temperature under nitrogen atmosphere for 30 min. After the completion of reaction, the mixture was evaporated under reduced pressure and purified over silica column using ethyl acetate as mobile phase to obtain the pure product, 28 mg (27.3 %); mp 235.1 - 236.1 °C; ^{1}H-NMR (DMSO-*d6*) 7.24 (t, 2H, *J* = 8.2 Hz), 7.57 - 7.64 (m, 2H), 7.91 (d, 1H, *J* = 5.3 Hz), 8.49 - 8.52 (m, 1H), 8.76 (dd, 1H, *J* = 1.4, 4.8 Hz), 9.35 (d, 1H, *J* = 1.7 Hz), 10.88 (s, 1H), 12.12 (s, 1H); IR (KBr): 3448, 1728, 1688, 1627, 1597, 1564, 1508, 1471, 1450, 1373, 1340, 1288, 1245, 1025, 797 cm^{-1}.

2.2.6. *N*-(4-(Pyridin-3-yl)pyrimidin-2-yl)-3,5-bis(trifluoromethyl)benzamide (8)

To a stirred solution of 4-pyridin-3-ylpyrimidin-2-amine (**1**) (100 mg, 0.58 mmoles) in 7 ml of pyridine, 3,5-bis(trifluoromethyl)benzoyl chloride (105 μℓ, 0.58 mmoles) was added dropwise over a period of 30 min. The reaction mixture refluxed for 1 hr under nitrogen atmosphere. After the completion of reaction, the mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified over silica column using ethyl acetate as mobile phase to obtain the pure product, 157 mg (65.7 %); mp 127.4 - 128.4 °C; ^{1}H-NMR ($CDCl_3$) 7.40 - 7.50 (m, 2H), 8.03 (s, 1H), 8.31 (d, 1H, *J* = 7.1 Hz), 8.52 (s, 2H), 8.60 - 8.73 (m, 2H), 9.27 (s, 1H), 10.9 (s, 1H); ^{13}C-NMR ($CDCl_3$) 112.83, 121.04, 124.05, 124.65, 125.60, 126.16, 128.54, 130.04, 131.40, 131.85, 132.30, 132.74, 135.78, 136.51, 147.98, 151.35, 158.03, 159.14, 162.34, 163.14, 163.86; IR (KBr): 3436, 1698, 1592, 1536, 1439, 1418, 1280, 1247, 1184, 1137 cm^{-1}.

2.2.7. 4-Chloro-*N*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzamide (9)

To a stirred solution of 4-pyridin-3-ylpyrimidin-2-amine (**1**) (100 mg, 0.58 mmoles) in 8 ml of pyridine, 4-chlorobenzoyl chloride (75 μℓ, 0.58 mmoles) was added dropwise over a period of 30 min. The reaction mixture refluxed for 24 hr under

nitrogen atmosphere. After the completion of reaction, the mixture was cooled to room temperature and evaporated under reduced pressure. The reside was purified over silica column using ethyl acetate as mobile phase to obtain the pure product, 20 mg (11 %); mp 179.9 - 180.9 °C; ^{1}H-NMR ($CDCl_3$) 7.41 - 7.47 (m, 2H), 7.85 (d, 4H, J = 8.4 Hz), 8.42 (d, 1H, J = 8.0 Hz), 8.73 - 8.75 (m, 1H), 8.78 (d, 1H, 5.22), 8.92 (s, 1H), 9.23 (s, 1H); IR (KBr): 3436, 1698, 1634, 1592, 1533, 1489, 1443, 1401, 1270, 1092, 811 cm^{-1}.

2.2.8. 3-Morpholino-*N*-(4-(pyridin-3-yl) pyrimidin-2-yl)-5-(trifluoromethyl) benzamide (10)

2.2.8.1. 1*H*-Benzo[1,2,3]triazole-1-yl-3 -morpholino-5-(trifluoromethyl) benzoate

3-Morpholino-5-(trifluoromethyl)benzoic acid (50 mg, 0.18 mmoles) and 1-hydroxybenzotriazole (49.1 mg, 0.36 mmoles) were dissolved in 5 ml of dichloromethane and added 1-ethyl-3-(3 -dimethylaminopropyl)carbodiimide (34.8 mg, 0.18 mmoles) in an ice bath. The reaction mixture was stirred at rt for 3 hr under N_2 atmosphere. After the completion of reaction, the reaction mixture was evaporated under reduced pressure, dissolved in dichloromethane and washed well with 2 % aqueous HCl solution, aqueous saturated $NaHCO_3$ solution and brine. The organic layer was separated and dried over anhydrous $MgSO_4$, and then evaporated till dryness. The crude product was further purified over silica column using ethyl acetate as mobile phase to obtain the pure product. 43 mg (61 %); ^{1}H-NMR ($CDCl_3$) 3.31 - 3.34 (m, 4H), 3.88 - 3.91 (m, 4H), 7.44 - 7.49 (m, 3H), 7.54 - 7.59 (m, 1H), 7.86 (s, 1H), 7.96 (s, 1H), 8.09 (d, 1H, J = 8.3 Hz).

2.2.8.2. 3-Morpholino-*N*-(4-(pyridin-3 -yl)pyrimidin-2-yl)-5-(trifluoromethyl) benzamide (10)

1*H*-Benzo[1,2,3]triazole-1-yl-3-morpholino -5-(trifluoromethyl)benzoate (43 mg, 0.11 mmoles) and 4-pyridin-3-ylpyrimidin-2-amine (1) (18.8 mg, 0.11 mmoles) were dissolved in 5 ml of xylene and refluxed for 24 hr under N_2 atmosphere. After the completion of reaction, the reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was purified over silica column using the mixed solvent of ethyl acetate and hexane (1 : 2) as mobile phase to obtain the pure product, 15 mg (32 %); mp 212.4 - 213.4 °C; ^{1}H-NMR ($CDCl_3$) 3.29 - 3.30 (m, 4H), 3.88 - 3.89 (m, 4H), 7.44 - 7.48 (m, 1H), 7.53 (d, 1H, J = 5.1 Hz), 7.58 (s, 1H), 7.68 (s, 1H), 8.45 (d, 1H, J = 7.8 Hz), 8.73 - 8.79 (m, 2H), 9.23 - 9.29 (m, 2H); IR (KBr): 3437, 2925, 1690, 1590, 1529, 1439, 1297, 1246, 1170, 1122, 1023, 809, 698 cm^{-1}.

2.2.9. 1-(3-Morpholino-4-yl-5-trifluoromethylphenyl)-3-[4-(6-phenylpyridin-3-yl)pyrimidin-2-yl]urea (13)

3-Morpholino-5-(trifluoromethyl)benzoic acid (50 mg, 0.18 mmoles) in 5 ml of toluene was added *N*,*N*-diisopropylethylamine (34.8 μℓ, 0.18 mmoles). Diphenylphosphorylazide (39.3 μℓ, 0.18 mmoles) was added to the flask and heated under reflux for 4 hr under nitrogen atmosphere. 4-(6-Phenylpyridin-3-yl) pyrimidin-2-amine (2) (31.3 mg, 0.18 mmoles) was added to the reaction mixture while heating and refluxed for 24 hr under N_2 atmosphere. After the completion of reaction, the reaction mixture was cooled to room temperature to induce solid in solution, and filtered by suction filtration. The solid was recrystallized by methanol to give the pure compound, 45 mg (48 %); mp 263.6 - 264.6 °C; ^{1}H-NMR (DMSO-d_6) δ 3.10 - 3.30 (m, 4H), 3.65 - 3.98 (m, 4H), 6.94 (s, 1H), 7.22 (s, 1H), 7.51 - 7.58 (m, 3H), 7.63 (s, 1H), 7.85 (d, 1H, J = 5.3 Hz), 8.19 - 8.22 (m, 3H), 8.62 (dd, 1H, J = 2.0, 8.4 Hz), 8.82 (d,

1H, J = 5.2 Hz), 9.47 (s, 1H), 10.43 (s, 1H), 11.74 (s, 1H); IR (KBr): 3437, 3151, 2961, 1703, 1586, 1571, 1545, 1480, 1409, 1295, 1244, 1161, 1106, 1009, 830, 723, 561 cm^{-1}.

2.2.10. 3-Morpholino-N-(4-(6-phenylpyridin-3-yl)pyrimidin-2-yl)-5-(trifluoromethyl) benzamide (14)

1H-Benzo[1,2,3]triazole-1-yl-3-morpholino-5-(trifluoromethyl)benzoate (50 mg, 0.13 mmoles) and 4-(6-phenylpyridin-3-yl) pyrimidin-2-amine (2) (31.6 mg, 0.13 mmoles) were dissolved in 7 ml of xylene and refluxed for 24 hr under N_2 atmosphere. After the completion of reaction, the reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue was precipitated by the mixed solvent of ethylacetate and hexane (1:1) and filtered by suction filtration. The filtrate was evaporated under vacuum and purified over silica column using the mixed solvent of dichloromethane and methanol (50 : 1) as mobile phase to obtain the pure product, 20.9 mg (31.8 %); mp 269.4 - 267.4 °C; ^{1}H-NMR ($CDCl_3$) δ 3.29 - 3.33 (m, 4H), 3.88 - 3.91 (m, 4H), 7.27 (s, 1H), 7.54 - 7.59 (m, 5H), 7.71 (s, 1H), 7.95 (d, 1H, J = 8.40 Hz), 8.11 - 8.14 (m, 2H), 8.65 - 8.69 (m, 1H), 8.79 (d, 1H, J = 5.22 Hz), 9.07 (s, 1H), 9.38 (m, 1H); IR (KBr): 3436, 1702, 1590, 1509, 1431, 1406, 1376, 1248, 1165, 1121, 999, 697 cm^{-1}.

2.2.11. The syntheses of compound 1, 2, 11 and 12

The synthetic procedure of the compound **1**, **2**, **11** and **12** is explained in literature[14].

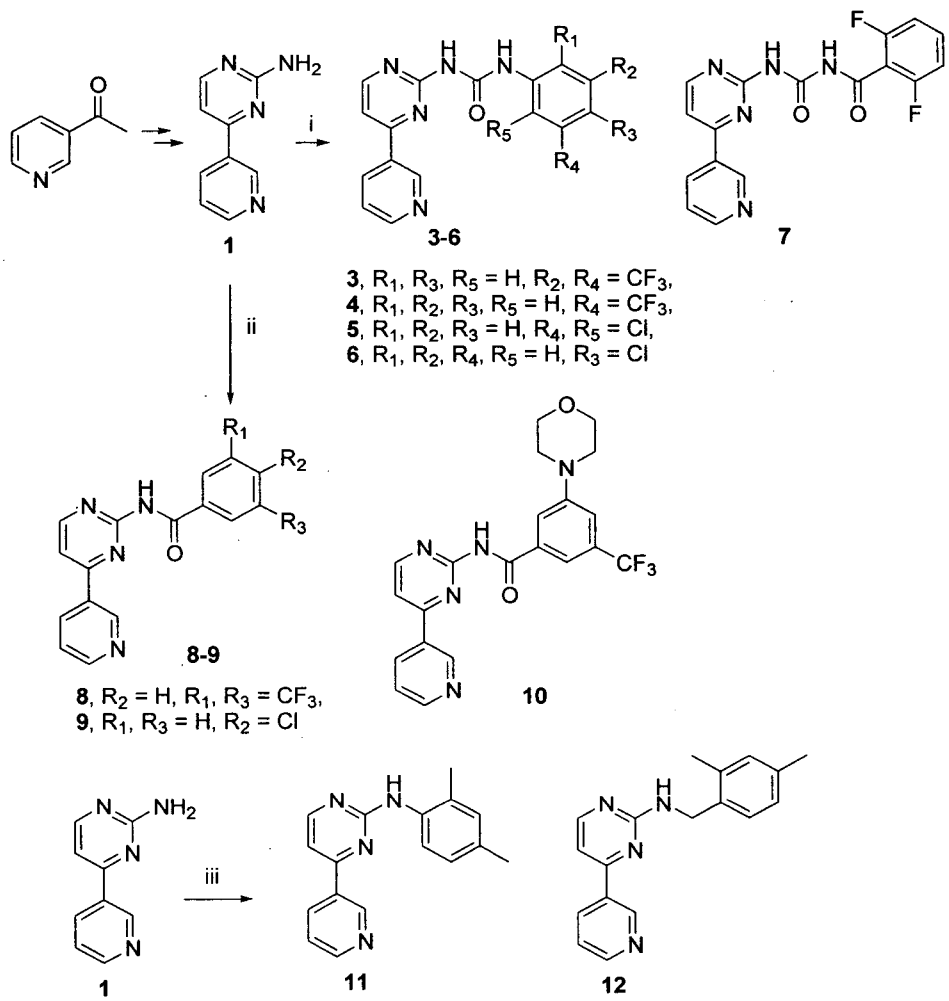
2.3. The antiproliferative activity of the tested compounds against A375P melanoma cells

A375P Cell culture and antiproliferative activity of tested compound on A375P: A375P cells were purchased from American Type Culture Collection (ATCC, Rockville, MD, US) and maintained in DMEM medium (Welgene, Daegu, Korea) supplemented with 10% FBS (Welgene) and 1% penicillin/streptomycin (Welgene) in a humidified atmosphere with 5% CO_2 at 37°C. A375P cells were taken from culture substrate with 0.05% trypsin-0.02% EDTA and plated at a density of 5 × 10^3 cells/well in 96 well plates and then incubated at 37°C for 24 hours in a humidified atmosphere with 5% CO_2 prior to treatment of various concentration (three fold serial dilution, 12 points) of test compounds. The A375P cell viability was assessed by the conventional 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction assay. MTT assays were carried out with CellTiter 96® (Promega) according to the manufacturer's instructions. The absorbance at 590 nm was recorded using EnVision2103 (Perkin Elmer; Boston, MA, US). The IC_{50} was calculated using GraphPad Prism 4.0 software.

3. Results and Discussion

As shown in Scheme 1, the 4-(pyridin-3-yl)pyrimidin-2-amine scaffold was synthesized according to literature procedures, starting by the fusion of 3-acetylpyridine with 1.4 equivalents of *N,N*-dimethylformamide dimethylacetal to yield 3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one in a good yield of 82%[12]. By refluxing 3-(dimethylamino)-1-(pyridin-3-yl) prop-2-en-1-one with guanidine hydrochloride in absolute ethanol and in the presence of sodium ethoxide, the amine **1** was obtained in 73% yield[13]. Urea derivatives **3-7** were prepared by refluxing the amine **1** with different arylisocyanates in pyridine under N_2 atmosphere.

The resulted urea derivatives were obtained in low to moderate yields, 66% (**3**), 6% (**4**), 6% (**5**), 5% (**6**) and 27% (**7**). For benzoylation with simple benzoyl chlorides,

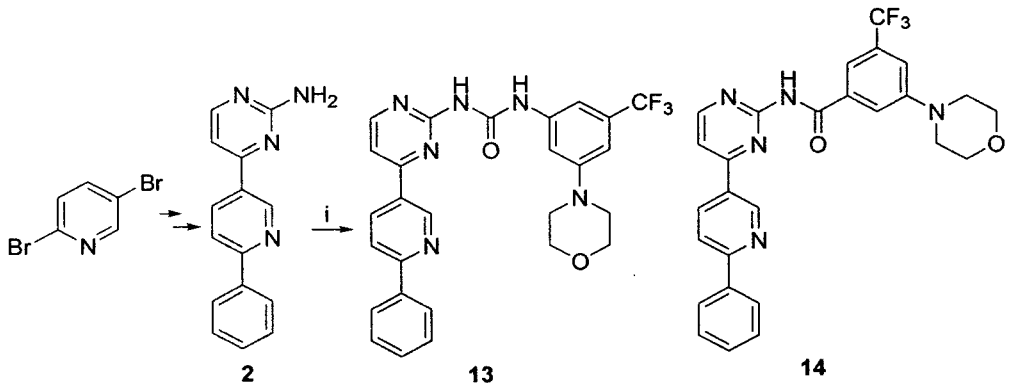


Reaction conditions and yields: i) Ar-NCO, N_2, pyridine, 66% (**3**), 6% (**4**), 6% (**5**), 5% (**6**), 27% (**7**), ii) ArCOCl, pyridine, reflux, N_2, 19% (**8**), 11% (**9**), 32% (**10**), iii) 2,4-dimethylphenylbromide, dichlorobis(triphenylphosphine)Pd(II), Xantphos, Nao-*t*Bu, toluene, N_2, reflux, 8h, 31% (**11**); 2,4-dimethylbenzylbromide, K_2CO_3, 130 °C, 15h, 39% (**12**),

Scheme 1. Synthesis of the title compounds

the amine was refluxed in pyridine with the appropriate benzoyl chloride under nitrogen atmosphere. The benzoyl derivatives **8** and **9** were obtained in 19% and 11% yields, respectively. For the synthesis of compound **10**, a different benzoylating agent, *1H*-benzo[1,2,3]triazole-1-yl-3-morpholino-5-(trifluoromethyl)benzoate, was used.

This agent was prepared in 61% yield by the reaction of 3-morpholino-5-(trifluoromethyl)benzoic acid with 1-hydroxybenzotriazole in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and dichloromethane. By refluxing *1H*-benzo[1,2,3]triazol-1-yl-3-morpholino-5-(trifluoromethyl) benzoate with the amine **1** in xylene under N_2 atmosphere, compound **10** was obtained in 32% yield. The arylation of the amine **1** with 2,4-dimethylphenyl bromide was carried out



Reaction conditions and yields: i) diphenylphosphorylazide, 3-morpholino-5-trifluoro methylbenzoic acid, *N,N*-diisopropylethylamine, toluene, N_2, 4h, 48% (**13**); 1H-benzo[1,2,3]triazole-1-yl-3-morpholino-5-(trifluoromethyl)benzoate, xylene, N_2, 24h, 32% (**14**)

Scheme 2. Synthesis of compounds **13** and **14**

in toluene under N_2 atmosphere, using $Pd(PPh_3)_2Cl_2$ as a catalyst, Xantphos as a ligand, and NaO-*t*-Bu as a base[14]. The *N*-aryl derivative **11** was obtained in yield of 31%. Also, Benzylation of the amine **1** with 2,4-dimethylbenzylbromide gave compound **12** in a moderate yield of 39% by heating in the presence of K_2CO_3 and DMF[14].

As shown in Scheme 2, compound **2** was synthesized in 4 steps using 2,5-dibromopyridine as the starting compound. 2,5-Dibromopyridine was converted into 5-acetyl-2-bromopyridine in 51% yield, by lithiation of 2,5-dibromopyridine in diethylether at -78 °C under nitrogen atmosphere, followed by acetylation at 5-position by *N,N*-dimethylacetamide.

1-(6-phenylpyridin-3-yl)ethanones was obtained by Suzuki coupling of 5-acetyl-2-bromopyridine with phenyl boronic acid in a mixed solvent of acetonitrile and water (1:1, v/v) at 78 °C under nitrogen atmosphere, and in the presence of dichlorobis(triphenylphosphine)Pd(II) and Na_2CO_3 in final yields of 67%[14]. The target **13** and **14** were synthesized according to above-mentioned method for the synthesis of urea and amide. Using 4-pyridin-3-yl-pyrimidin-2-ylamine moiety as active pharmacophore, 12 compounds were totally synthesized and Figure 1 showed the structure of the synthesized compounds.

All the synthesized compounds were screened for antiproliferative activity against A375P melanoma cells in accordance with above-mentioned method. By the way, the synthesized compounds generally did not show good solubility to organic solvent (in case of DMSO) and not dissolve in water, Therefore bioavailability of the compounds for A375P melanoma cells think to be very low. As a result, the maximum activity against A375P melanoma cells was very low and antiproliferative activity was also very low, compared with Sorafenib (IC_{50} = 6.1 μM) as control compounds[7].

4. Conclusion

We synthesized and evaluated a number of 4-(pyridin-3-yl)pyrimidin-2-amine derivatives in 4-5 steps for the screening of anticancer activity. Most of the synthesized compounds did not show good solubility in

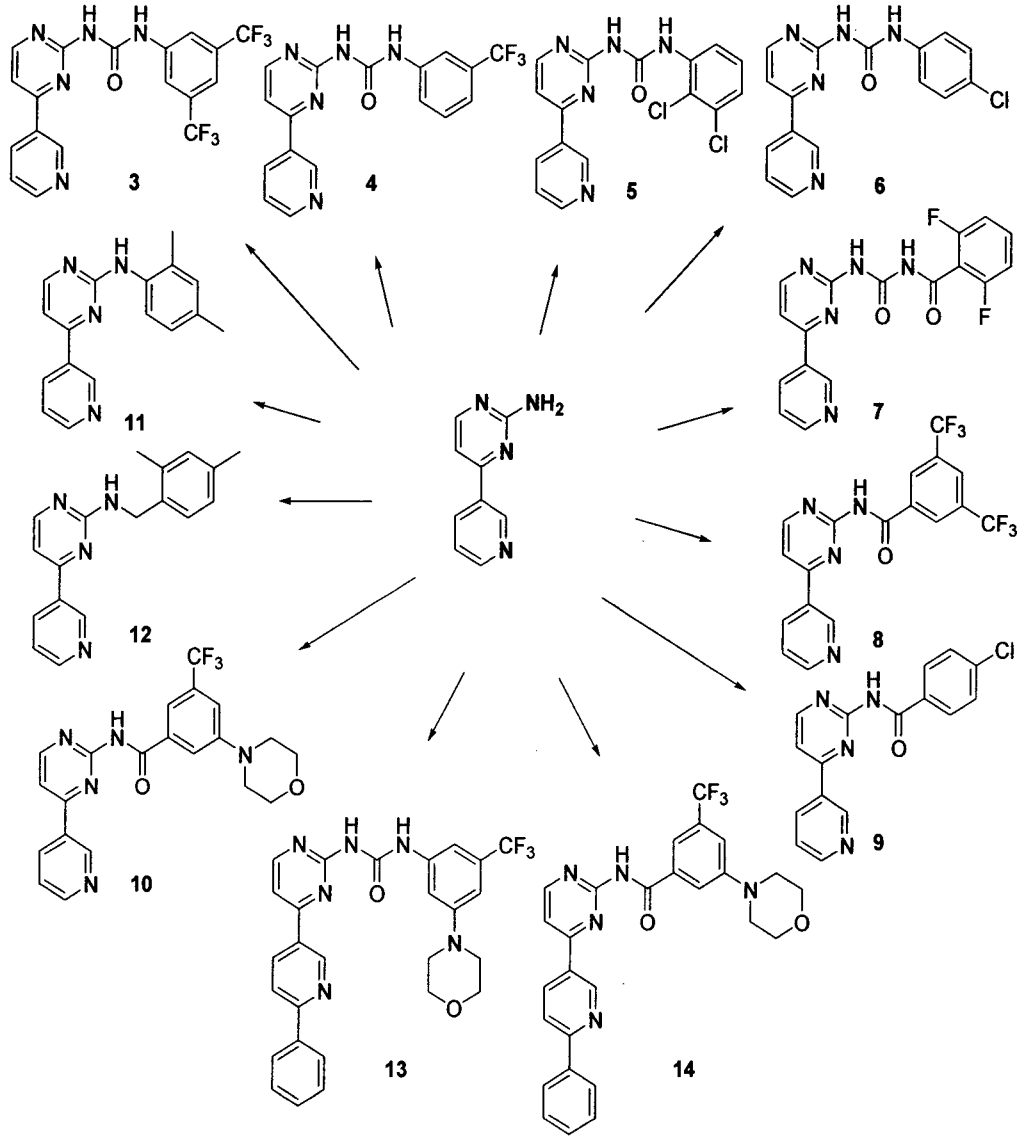


Figure 1. The title compounds

dimethylsulfoxide and water. Therefore, the compounds did not show good activities against A375P melanoma cells because of low solubility in dimethylsulfoxide and lack bioavailability. By optimization of the synthesized derivatives and synthesis of some new hydrophilic compounds, we will prepare highly potent anticancer compounds that can show IC_{50} values below 10 nM and maximum activity over 80%.

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