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잠재적 항암작용이 있는 6-Allylthio-3-aminopyridazine 유도체의 합성

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Synthesis of Potential Anticancer 6-Allylthio-3-aminopyridazine Derivatives

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요 약. 항암작용이 기대되는 일련의 새로운 6-allylthio-3-aminopyridazine 유도체를 allylthiolation, amination을 이용하여 합성하였다. 피리다진 핵은 hydrazine monohydrate와 maleic anhydride의 축합반응으로 제조하였다. 3,6-Dichloropyridazine은 3,6-dihydroxypyridazine을 $POCl_3$에 가하여 합성하였다. 6-Allythio-3-chloropyridazine은 3,6-dichloropyridazine에 allylmercaptan과 sodium hydroxide을 이용하여 얻었다. Morpholine, piperazine, pyrazole, imidazole, pyrrolidine, piperidine, perhydroazepine 및 perhydroazocine와 같은 질소 친핵체를 갖는 hetero환을 피리다진 환의 3번 위치에 도입시켜 6-allylthio-3-aminopyridazine 합성하였다. 이 과정은 아민 친핵체의 친핵성 치환반응으로 *n*-buthanol에서 NH_4Cl를 가하고 24~48시간 동안 환류시켜 진행하였다.

주제어: 아미노화반응, 치환반응, 아미노피리다진, 헤테로사이클로피리다진

ABSTRACT. A series of new 6-allylthio-3-aminopyridazine derivatives was synthesized through allylthiolation, amination and expected for anti-tumor activity. The pyridazine nucleus was obtained by condensing hydrazine monohydrate with maleic anhydride. 3,6-Dichloropyridazine was synthesized from 3,6-dihydroxypyridazine by treating with $POCl_3$. 6-Allylthio-3-chloropyridazine was prepared from the reaction of 3,6-dichloropyridazine with allylmercaptan and sodium hydroxide. The heterocycles with nitrogen nucleophile such as morpholine, piperazine, pyrazole, imidazole, pyrrolidine, piperidine, perhydroazepine, and perhydroazocine were introduced into 3-position of pyridazine ring. The substitution reaction of 6-allylthio-3-chloropyridazine with heteroamines was performed by refluxing for 24~48 h in *n*-buthanol with NH_4Cl.
Keywords: Amination, Substitution, Aminopyridazines, Heterocyclopyridazines

INTRODUCTION

Aminopyridazines constitute an important pharmacophoric moiety present in many drugs acting on various pharmacological targets.[1-5] In particular, the aminopyridazine nucleus is found in dopaminergic, seretoninergic, cholinergic, and GABAergic ligands, as well as in monoamine oxidase and acetylcholine esterase inhibitors.

Other pyridazine derivatives **A** at the 3-position of the 6-allylthiopyridazine introduced by oxygen or sulfur and nitrogen have been synthesized.[6] 3-Alkoxy-6-allylthiopyridazines and 3-alkylthio-6-allylthiopyridazines showed especially good hepatoprotective and antitumor activities (*Fig.* 1).[6] The allylthio group was considered a pharmacophore, a key structural component for biological activity.

The isosteric replacement of the exo oxygen (or sulfur) of compound **A** by a nitrogen atom yielded the aminopyridazines (*Fig.* 1). We have recently

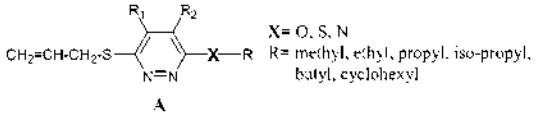
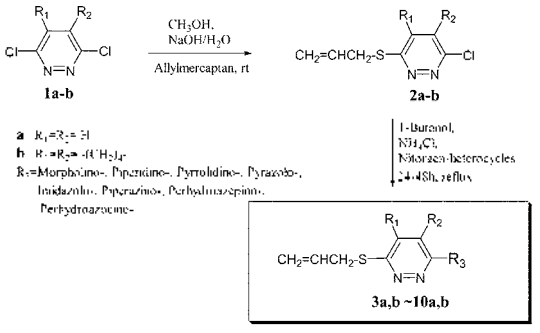


Fig. 1. Reported Alkoxy (or alkylthio)-allylthiopyridazines.

reported the synthesis of *N*-acylated 3-amino-6-chloropyridazine derivatives through amination and acylation.[7] Kwon *et al.* reported the synthesis of 3-allylthio-6-heterocyclylaminopyridazines and their antitumor activities.[8] We became interested in synthesis of 3-aminopyridazines through coupling of pyridazinyl chloride with secondary amines known to give new heterocyclic pyridazines.

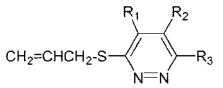
Activated aryl halides react well with ammonia and with primary and secondary amines to give the corresponding arylamines. The reaction of aryl halide with a secondary amine is not only important for the synthesis of tertiary amines, but is also essential for the preparation of a number of pharmaceuticals. Many reports have been published on the nucleophilic amination of aryl halides.[10]

Even though the synthetic pathway for 3-aminopyridazines were developed by Wermuth *et al.*,[4] Contreras *et al.*,[2,5b] Parrot *et al.*,[9] the synthesis of 6-allylthiopyridazines has not been reported until now. We applied a general method of preparing aminopyridazines from pyridazinyl halides and secondary amines.[4] The key intermediates in these preparation are pyridazinyl chlorides **2a-b**, which can be readily obtained from the corresponding 3,6-dichloropyridazine **1a-b** by reaction with allylmercaptan. Condensation of the pyridazinyl chlorides **2a-b** with various secondary amines gave the final products **3-10** (*Table* 1). The tetrahydrophthalazine **1b** was prepared according to the literature.[6a]



Scheme 1. Synthetic Routes for Target Compounds **3~10**.

Table 1. Synthesis of 3-allylthio-6-heterocyclopyridazine (**3a, b~10a,b**)



Comp. No.	R_1	R_2	Amine (R_3)	Mp(°C)	Yield (%)
3a	H	H	—N O	32~34	53
3b	-(CH$_2$)$_4$-			92~97	54
4a	H	H	—N NH	26~28	43
4b	-(CH$_2$)$_4$-			Oil	75
5a	H	H	—N N	93~94	31
6a	H	H	—N N	93~94	33
7a	H	H	—N	53~56	54
7b	-(CH$_2$)$_4$-			28~30	74
8a	H	H	—N	25~26	47
8b	-(CH$_2$)$_4$-			29~31	34
9a	H	H	—N	Oil	45
9b	-(CH$_2$)$_4$-			Oil	28
10a	H	H	—N	Oil	31
10b	-(CH$_2$)$_4$-			Oil	5

EXPERIMENTAL

Chemicals were supplied by Aldrich, Sigma, Merck, and Tokyo Kasei. Melting points were determined in open capillary tubes on a Büchi 535 melting point apparatus and uncorrected. The NMR spectra were recorded using Bruker 300 MHz NMR spectrometer. Chemical shift values were reported in parts per million on the scale in deuteriochloroform or dimethyl-d_6 sulfoxide with tetramethylsilane as the internal standard. The NMR spin multiplicities were indicated by the symbols: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer using NaCl discs and pellets. The Mass fragmentations were recorded using Agi-

lent 6890 GC and 5973 MS. Low and high-resolution FABMS (positive ion mode) mass spectra were determined on a JEOL 700 mass spectrometer.

General procedure for the synthesis of compounds 2a-b

Sodium hydroxide (2 g, 50 mmol) was dissolved in methanol (50 mL) and then mixed with allyl mercaptane (4 mL, 50 mmol). To this mixture was added 3,6-dichloropyridazine (7.5 g, 50 mmol). The reaction solution was stirred at room temperature for 30 min-1h. The solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate, washed with water and brine, and dried over Na_2SO_4. After solvent evaporation, the residue was purified by recrystallization in ethanol.

6-Allylthio-3-chloropyridazine (2a). Yield: 95%. mp: 47-52 °C, R_f 0.50 (hexanes: ethyl acetate, 2:1). Recrystn. Solvent *dil*-ethanol. ^{1}H NMR ($CDCl_3$) δ 7.29(s, 2H, pyridazine), 6.03-5.94 (m, 1H, =CH), 5.36(d, *J*=16.8 Hz, 1H, CH_2=), 5.16(d, *J*=9.3 Hz, 1H, CH_2=), 3.98(d, *J*=6.9 Hz, 2H, SCH_2). ^{13}C NMR ($CDCl_3$) δ 1621.27, 153.70, 128.27, 127.32(pyridazine), 132.41, 118.80, 33.09(allyl). FT-IR (NaCl) cm^{-1} 3447, 3060, 1564, 1420, 1265, 1034. GC-MS *m/z* (%) 188.6(M+) 171.1(100), 173.0(51.9), 73.1(27.8), 118.1(22.4), 153.1(21.7).

1-Allylthio-4-chloro-5,6,7,8-tetrahydrophthalazine (2b). Yield: 92%. mp 40-43 °C. R_f 0.56 (hexanes: ethyl acetate, 3:1). Recrystn. Solvent *dil*-ethanol. ^{1}H NMR ($CDCl_3$) δ 6.06-5.97(m, 1H, =CH), 5.35(d, *J*=16.8 Hz, 1H, CH_2=), 5.14(d, *J*=9.9 Hz, 1H, CH_2=), 3.99(d, *J*=7.2 Hz, 2H, SCH_2), 2.68(s, 2H, CH_2), 2.54(s, 2H, CH_2), 1.84(s, 2H×2, CH_2×2). ^{13}C NMR($CDCl_3$) δ 161.23, 155.19, 135.62, 134.66 (pyridazine), 138.05, 118.81, 33.06(allyl), 26.32, 25.33, 21.63, 21.44(-CH_2-×4). FT-IR (NaCl) cm^{-1} 3452, 3053, 1549, 1265, 738. GC-MS *m/z*(%) 225.1(M+) 227.1(100.0), 207.1(88.9), 226.0(75.4), 39.2(48.3).

General procedure for the synthesis of compounds 3-10

A solution of 3-allylthio-6-chloropyridazine (0.75 g, 4 mmol) and the appropriate amine (12 mmol) and ammonium chloride (0.21g, 4 mmol) in *n*-butanol (10 mL) were refluxed for 24-48 h. The solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate, washed with water and brine, and dried over Na_2SO_4. After solvent evaporation, the residue was purified by column chromatography on silica gel.

6-Allylthio-3-morpholinopyridazine (3a). Yield: 53%. mp 32-34 °C. R_f 0.38(hexanes: ethyl acetate, 1:1). ^{1}H NMR($CDCl_3$) δ 7.14(d, *J*=9.5 Hz, 1H, pyridazine), 6.82(d, *J*=9.5 Hz, 1H, pyridazine), 6.02-5.96(m, 1H, =CH), 5.29(d, *J*=16.9 Hz, 1H, CH_2=), 5.11(d, *J*=9.9 Hz, 1H, CH_2=), 3.93(d, *J*=6.9 Hz, 2H, SCH_2), 3.84(t, *J*=4.8 Hz, 2H×2, CH_2×2, morpholine), 3.57-3.54(m, 2H×2, CH_2×2, morpholine). ^{13}C NMR ($CDCl_3$) δ 158.75, 152.13, 128.39, 118.19(pyridazine), 133.93, 113.95, 33.77(allyl), 66.88, 46.00(morpholine). FT-IR (NaCl) cm^{-1} 2963, 2852, 1632, 1428, 1241. GC-MS *m/z*(%) 237.3(M+) 222.2(100.0), 237.1(18.2), 223.1(13.8), 204.2(12.1), 236.2(7.0).

1-Allylthio-4-morpholino-5,6,7,8-tetrahydrophthalazine (3b). Yield: 54%. mp 93-97 °C. R_f 0.28 (hexanes: ethyl acetate, 1:1). ^{1}H NMR($CDCl_3$) δ 6.10-6.01(m, 1H, =CH), 5.33(d, *J*=16.3 Hz, 1H, CH_2=), 5.13(d, *J*=10.0 Hz, 1H, CH_2=), 3.99(d, *J*=6.9 Hz, 2H, SCH_2), 3.85(t, *J*=4.5 Hz, 2H×2, CH_2×2, morpholine), 3.23(t, *J*=4.5 Hz, 2H×2, CH_2×2, morpholine), 2.59(t, *J*=6.0 Hz, 2H, CH_2), 2.53(t, *J*=6.3 Hz, 2H×2, CH_2), 1.88-1.74(m, 2H×2, CH_2×2). ^{13}C NMR ($CDCl_3$) δ 160.90, 157.11, 134.12, 130.71(pyridazine), 136.37, 118.12, 32.88(allyl), 67.39, 50.65(morpholine), 25.48, 25.22, 22.07, 21.99(-CH_2-×4). FT-IR (NaCl) cm^{-1} 2952, 2856, 1635, 1421, 1254. GC-MS *m/z* (%) 291.4(M+) 276.2(100.0), 291.2(22.3), 277.2(20.2), 258.2(10.3), 234.1(8.1).

6-Allylthio-3-piperazinopyridazine (4a). Yield: 18.1%. mp 26-28 °C. R_f 0.07 (hexanes: ethyl acetate: methanol, 1:1:0.5). ^{1}H NMR ($CDCl_3$) δ 7.10(d, *J*=9.5 Hz, 1H, pyridazine), 6.47(d, *J*=9.3 Hz, 1H, pyridazine), 6.05-5.94(m, 1H, =CH), 5.28(d, *J*=16.9 Hz, 1H, CH_2=), 5.10(d, *J*=9.9 Hz, 1H, CH_2=), 3.91(d, *J*=6.9 Hz, 2H, SCH_2), 3.56(t, *J*=5.0 Hz, 2H×2, CH_2×2, piperazine), 2.99(t, *J*=5.0 Hz, 2H×2, CH_2×2, piperazine), 1.98(s, 1H, NH). ^{13}C NMR

($CDCl_3$) δ 158.86, 151.41, 128.33, 118.10(pyridazine), 134.03, 114.06, 33.83(allyl), 46.76, 46.06(piperazine). FT-IR (NaCl) cm^{-1} 3054, 2986, 1422, 1265. GC-MS *m/z*(%) 236.35(M+) 168.1(100.0), 221.1(91.9), 180.1(48.5), 236.1(36.5), 194.1(15.3).

1-Allylthio-4-piperazino-5,6,7,8-tetrahydrophthalazine (4b). Yield: 66%. Oil. R_f 0.03 (hexanes: ethyl acetate: methanol, 1:1:0.5). ^1H NMR ($CDCl_3$) δ 6.12-5.99(m, 1H, =CH), 5.32(d, *J*=17.2 Hz, 1H, CH_2=), 5.12(d, *J*=9.9 Hz, 1H, CH_2=), 3.99(d, *J*=6.9 Hz, 2H, SCH_2), 3.18(t, *J*=8.0 Hz, 2H×2, CH_2×2, piperazine), 3.03(t, *J*=4.8 Hz, 2H×2, CH_2×2, piperazine), 2.59(t, *J*=5.8 Hz, 2H, CH_2), 2.52(t, *J*=6.4 Hz, 2H, CH_2), 2.16(s, 1H, NH), 1.89-1.80(m, 2H, CH_2), 1.77-1.69(m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 161.40, 156.73, 134.18, 130.86(pyridazine), 136.20, 118.04, 32.85(allyl), 51.60, 46.52(piperazine), 29.04, 28.83, 25.46, 25.21(-CH_2-×4). FT-IR(NaCl) cm^{-1} 2940, 2839, 1636, 1404, 1257. GC-MS *m/z*(%) 290.4(M+) 275.2(100.0), 222.1(42.1), 234.1(36.3), 290.2(33.9), 276.2(18.0).

6-Allylthio-3-pyrazolopyridazine (5a). Yield: 31%. mp 93-94 °C. R_f 0.26(hexanes: ethyl acetate, 10:1). ^1H NMR($CDCl_3$) δ 8.71(d, *J*=2.4 Hz, 1H, pyrazole), 8.04(d, *J*=9.2 Hz, 1H, pyridazine), 7.78(d, *J*=1.2 Hz, 1H, pyrazole), 7.45(d, *J*=9.2 Hz, 1H, pyridazine), 6.52(t, *J*=2.1 Hz, 1H, pyrazole), 6.11-5.97(m, 1H, =CH), 5.37(d, *J*=16.9 Hz, 1H, CH_2=), 5.18(d, *J*=10.0 Hz, 1H, CH_2=), 4.02(d, *J*=6.8 Hz, 2H, SCH_2). ^{13}C NMR ($CDCl_3$) δ 160.25, 152.87, 129.11, 127.41(pyridazine), 133.12, 118.92, 33.56(allyl), 143.16, 117.85, 109.17(pyrazole). FT-IR (NaCl) cm^{-1} 3053, 2986, 1582, 1444, 1265. GC-MS *m/z* (%) 218.2(M+) 203.0(100.0), 218.0(17.9), 96.0(17.8), 69.0(12.3), 204.0(12.0).

6-Allylthio-3-imidazolopyridazine (6a). Yield: 33%. mp 93-94 °C. R_f 0.50 (hexanes: ethyl acetate: methanol, 1:1:0.5). ^1H NMR ($CDCl_3$) δ 8.37(s, 1H, imidazole), 7.71(s, 1H, imidazole), 7.48(d, *J*=9.2 Hz, 1H, pyridazine), 7.40(d, *J*=9.2 Hz, 1H, pyridazine), 7.25(s, 1H, imidazole), 6.09-5.96(m, 1H, =CH), 5.38(d, *J*=16.3 Hz, 1H, CH_2=), 5.19(d, *J*=10.0 Hz, 1H, CH_2=), 4.03(d, *J*=6.8 Hz, 2H, SCH_2). ^{13}C NMR ($CDCl_3$) δ 161.14, 150.16, 132.82, 131.74(pyridazine), 135.00, 129.23, 33.55(allyl), 119.18, 117.29, 116.34 (imidazole). FT-IR (NaCl) cm^{-1} 3053, 2984, 1636, 1431, 1265. GC-MS *m/z* (%) 218.2(M+) 203.1(100.0), 204.1(12.7), 185.1(9.5), 96.0(9.1), 218.1(7.0).

6-Allylthio-3-pyrrolidinopyridazine (7a). Yield: 55%. mp 53-56 °C. R_f 0.39 (hexanes: ethyl acetate, 1:1). ^1H NMR ($CDCl_3$) δ 7.06(d, *J*=9.3 Hz, 1H, pyridazine), 6.53(d, *J*=9.3 Hz, 1H, pyridazine), 6.02-5.99(m, 1H, =CH), 5.25(d, 1H, *J*=17.1 Hz, CH_2=), 5.08(d, *J*=10.1 Hz, 1H, CH_2=), 3.90(d, *J*=6.6 Hz, 2H, SCH_2), 3.50(t, *J*=5.2 Hz, 2H×2, CH_2×2, pyrrolidine), 2.08-1.97(m, 2H×2, CH_2×2, pyrrolidine), ^{13}C NMR ($CDCl_3$) δ 156.38, 148.91, 128.35, 117.82(pyridazine), 134.36, 113.29, 34.12(allyl), 47.02, 25.79(pyrrolidine), FT-IR (NaCl) cm^{-1} 2970, 2864, 1636, 1452, 1265. GC-MS *m/z* (%) 221.3(M+) 206.2(100.0), 221.1(20.2), 188.2(14.8), 207.1(13.3), 70.1(11.1).

1-Allylthio-4-pyrrolidino-5,6,7,8-tetrahydrophthalazine (7b). Yield: 75%. mp 28-30 °C. R_f 0.25 (hexanes: ethyl acetate, 5:1). ^1H NMR($CDCl_3$) δ 6.13-5.99(m, 1H, =CH), 5.31(d, *J*=17.0 Hz, 1H, CH_2=), 5.10(d, *J*=9.9 Hz, 1H, CH_2=), 3.97(d, *J*=6.9 Hz, 2H, SCH_2), 3.51(t, *J*=7.2 Hz, 2H×2, CH_2×2, pyrrolidine), 2.59(t, *J*=5.3 Hz, 2H, CH_2), 2.51(t, *J*=5.7 Hz, 2H, CH_2), 1.95-1.91(m, 2H×2, CH_2×2, pyrrolidine), 1.84-1.79(m, 2H, CH_2), 1.74-1.69(m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 159.53, 153.39, 134.56, 127.38(pyridazine), 135.73, 117.78, 32.96(allyl), 50.42, 25.89(pyrrolidine), 26.95, 25.48, 22.42, 21.82(-CH_2-×4). FT-IR(NaCl) cm^{-1} 2940, 2865, 1635, 1410, 1291. GC-MS *m/z*(%) 275.4(M+) 260.2(100.0), 275.2(20.3), 261.2(18.2), 242.2(10.0), 70.1(7.7).

6-Allylthio-3-piperidinopyridazine (8a). Yield: 47%. mp 25-26 °C. R_f 0.36(hexanes: ethyl acetate, 3:1). ^1H NMR($CDCl_3$) δ 7.06(d, *J*=9.4 Hz, 1H, pyridazine), 6.83(d, *J*=9.4 Hz, 1H, pyridazine), 6.02-5.96(m, 1H, =CH), 5.27(d, 1H, *J*=16.8 Hz, CH_2=), 5.09(d, *J*=9.9 Hz, 1H, CH_2=), 3.91(d, *J*=6.9 Hz, 2H, SCH_2), 3.57(s, 2H×2, CH_2×2, piperidine), 1.65(s, 2H×3, CH_2×3, piperidine), ^{13}C NMR ($CDCl_3$) δ 158.70, 150.33, 158.24, 117.95(pyridazine), 134.66, 114.11, 33.85(allyl), 46.74, 25.66, 24.88 (piperidine). FT-IR (NaCl) cm^{-1} 2933, 2852, 1635, 1430, 1248. GC-MS *m/z*(%) 235.3(M+) 220.2(100.0), 235.2(20.8), 84.2(14.7), 221.2(14.6), 202.2(13.3).

1-Allylthio-4-piperidino-5,6,7,8-tetrahydrophthalazine (8b). Yield: 34.5%. mp 29-31 °C. R_f 0.14 (hexanes: ethyl acetate, 10:1). ^{1}H NMR ($CDCl_3$) δ 6.13-5.99(m, 1H, =CH), 5.32(d, *J*=17.6 Hz, 1H, CH_2=), 5.12(d, *J*=9.9 Hz, 1H, CH_2=), 3.99(d, *J*=6.9 Hz, 2H, SCH_2), 3.13(t, *J*=5.1 Hz, 2H×2, CH_2×2, piperidine), 2.60-2.49(m, 2H×2, CH_2×2), 1.87-1.81(m, 2H, CH_2), 1.76-1.62(m, 2H×3+2H, CH_2×3+CH_2). ^{13}C NMR($CDCl_3$) δ 162.20, 156.26, 134.36, 131.07 (pyridazine), 135.97, 117.97, 32.87(allyl), 51.56, 26.57, 25.04(piperidine), 25.25, 24.82, 22.19, 22.11(-CH_2-×4). FT-IR (NaCl) cm^{-1} 2934, 2857, 1636, 1403, 1254. GC-MS *m/z*(%) 289.4(M+) 274.2(100.0), 289.2(22.16), 275.2(20.4), 84.2(11.7), 256.2(9.9).

6-Allylthio-3-perhydroazepinopyridazine (9a). Yield: 45%. Oil. R_f 0.18 (hexanes: ethyl acetate, 5:1). ^{1}H NMR ($CDCl_3$) δ 7.05(d, *J*=9.5 Hz, 1H, pyridazine), 6.67(d, *J*=9.5 Hz, 1H, pyridazine), 6.08-5.94(m, 1H, =CH), 5.26(d, *J*=16.9 Hz, 1H, CH_2=), 5.09(d, *J*=9.9 Hz, 1H, CH_2=), 3.91(d, *J*=6.9 Hz, 2H, SCH_2), 3.67(t, *J*=5.9 Hz, 2H×2, CH_2×2, perhydroazepine), 1.81-1.78(m, 2H×2, CH_2×2, perhydroazepine), 1.59-1.52(m, 2H×2, CH_2×2, perhydroazepine). ^{13}C NMR($CDCl_3$) δ 157.42, 148.88, 128.43, 117.89(pyridazine), 134.32, 112.26, 34.08(allyl), 48.10, 27.93, 27.38(perhydroazepine). FT-IR (NaCl) cm^{-1} 2930, 2855, 1636, 1429, 1265. GC-MS *m/z*(%) 249.3(M+) 234.2(100.0), 249.2(22.3), 235.2(15.7), 216.2(10.5), 206.1(9.6).

1-Allylthio-4-perhydroazepino-5,6,7,8-tetrahydrophthalazine (9b). Yield: 28%. Oil. R_f 0.11 (hexanes: ethyl acetate, 10:1). ^{1}H NMR ($CDCl_3$) δ 6.10-5.99(m, 1H, =CH), 5.31(d, *J*=16.9 Hz, 2H, CH_2=), 5.11(d, *J*=9.1 Hz, 1H, CH_2=), 3.99(d, *J*=6.9 Hz, 2H, SCH_2), 3.43(t, *J*=5.7 Hz, 2H×2, CH_2×2, perhydroazepine), 2.56-2.49(m, 2H×2, CH_2×2), 1.85-1.67(m, 2H×4+2H×2, perhydroazepine×4+CH_2). ^{13}C NMR ($CDCl_3$) δ 162.52, 154.52, 134.02, 129.59 (pyridazine), 135.68, 117.56, 32.57(allyl), 52.71, 28.99, 27.18(perhydroazepine), 26.26, 25.11, 22.00, 21.57(-CH_2-×4). FT-IR (NaCl) cm^{-1} 2931, 2862, 1636, 1424, 1265. HRMS (FAB, M+H) Caled for $C_{15}H_{22}N_3S$ 303.5, found 304.2607.

6-Allylthio-3-perhydroazocinopyridazine (10a). Yield: 31%. Oil. R_f 0.15 (hexanes: ethyl acetate, 10:1). ^{1}H NMR ($CDCl_3$) δ 7.06(d, *J*=9.5 Hz, 1H, pyridazine), 6.66(d, *J*=9.5 Hz, 1H, pyridazine), 6.06-5.95(m, 1H, =CH), 5.26(d, *J*=16.9 Hz, 1H, CH_2=), 5.09(d, *J*=9.9 Hz, 1H, CH_2=), 3.91(d, *J*=6.9 Hz, 2H, SCH_2), 3.66(t, *J*=5.7 Hz, 2H×2, CH_2×2, perhydroazocine), 1.82-1.74(m, 2H×2, CH_2×2, perhydroazocine), 1.60-1.50(m, 2H×2, CH_2×3, perhydroazocine). ^{13}C NMR ($CDCl_3$) δ 156.64, 148.46, 127.93, 117.51(pyridazine), 133.95, 112.13, 33.75(allyl), 49.17, 27.03, 26.49(perhydroazocine). FT-IR (NaCl) cm^{-1} 3053, 2986, 1635, 1421, 1265. GC-MS *m/z*(%) 263.4(M+) 248.2(100.0), 263.2(21.7), 249.2(17.1), 180.1(10.1), 230.2(7.2).

1-Allylthio-4-perhydroazocino-5,6,7,8-tetrahydrophthalazine (10b). Yield: 5%. Oil. R_f 0.7 (hexanes: ethyl acetate, 3:1). ^{1}H NMR($CDCl_3$) δ 6.12-5.99(m, 1H, =CH), 5.31(d, *J*=17.7 Hz, 1H, CH_2=), 5.11(d, *J*=9.9 Hz, 1H, CH_2=), 3.99(d, *J*=7.0 Hz, 2H, SCH_2), 3.49(t, *J*=5.8 Hz, 2H×2, CH_2×2, perhydroazocine), 2.58-2.49(m, 2H×2, CH_2×2), 1.85-1.64(m, 2H×5+2H×2, perhydroazocine + CH_2×2). ^{13}C NMR($CDCl_3$) δ 160.58, 153.08, 132.99, 128.26 (pyridazine), 134.56, 116.53, 31.59(allyl), 51.03, 26.74, 26.48, 23.88(perhydroazocine), 25.39, 24.17, 21.00, 20.48(-CH_2-×4). FT-IR(NaCl) cm^{-1} 2928, 2863, 1636, 1411, 1264. HRMS(FAB, M+H) Caled for $C_{18}H_{27}N_3S$ 317.52, found 318.2657.

RESULTS AND DISCUSSION

A series of 6-allylthio-3-heterocyclopyridazines **3a,b~10a,b** were prepared by allylthiolation and nucleophilic substitution. The heterocycles with a nitrogen nucleophile such as morpholine, piperazine, pyrazole, imidazole, piperidine, pyrrolidine, perhydroazepine and perhydroazocine were introduced into the 3-position of the pyridazine ring (*Scheme* 1). Here, we present our results concerning the substitution reaction of 3-chloro-6-allylthiopyridazine by nitrogen heterocycle, which produced 6-allylthio-3-heterocyclopyridazines.

For the synthesis of pyridazine **3**, 6-allylthio-3-chloropyridazine **2** was converted to 6-allylthio-3-aminopyridazine **3** by nucleophilic aromatic substitution with nitrogen heterocycle in the presence of ammonium

chloride. The ammonium chloride assisted coupling of various nitrogen heterocycles with 6-allylthio-3-chloropyridazine **2** resulted in nucleophilic substitution. The amination reactions of 3-chloropyridazine **2** with a range of amines are found in *Table* 1.

The nucleophilic displacement of chlorine in 6-allylthio-3-chloropyridazine **2** requires prolonged reaction time at the reflux temperature of *n*-butanol. A typical reaction was that a mixture of nitrogen heterocycle (12 mmol), 6-allylthio-3-chloropyridazine (4 mmol), and ammonium chloride (4 mmol) in *n*-butanol were stirred under reflux for 24~48 h. The reaction was carried out using 1: 3 equivalents of 6-allylthio-3-chloropyridazine: nitrogen heterocycle.

In the proposed mechanism of substitution reaction of amine nucleophile, the secondary amine added to the pyridazine nucleus to form a tertiary ammonium intermediate and proton transfer from nitrogen to chloride produced a hydrochloride. A molecule of hydrochloride was eliminated due to nucleophilic addition at the carbon of the pyridazine nucleus and new C-N bond formed. For additional amination, halides **2** were converted to compounds **3-10** by eliminating hydrochloride.

The mono-allylthiolation from 3,6-dichloropyridazines **1a-b** to 6-allylthio-3-chloropyridazine **2a,b** gave high yields. Reactions of dichloropyridazines with allylmercaptan occurred in yields of more than 91%. Pyridazine halide and piperazine were reacted in the presence of ammonium chloride in *n*-butanol to form the corresponding amine products relatively in good yields (*Table* 1, entry **4b**). Similarly, perhydroazepine and perhydroazocine were converted into corresponding aminopyridazine derivatives in somewhat lower yields (*Table* 1, entries **9b** and trace amount of **10b**) because steric hindrance between tetrahydrophthalazine ring and the large (seven- or eight-membered) heterocyclic ring.

The formation of C-N bond in aminopyridazines was accomplished using NH_4Cl for 24~48h in *n*-butanol. Pyridazines were identified by NMR, IR, GC-MS, and HRMS. The pyridazine NMR peak of **3a,b-10a,b** appeared at 6.47-6.89 and 7.05-7.14 ppm, and the allyl peak appeared at 5.08-5.19, 5.25-5.38, and 5.94-6.09 ppm. The pyridazine ^{13}C NMR peak appeared at 118, 128, 152, and 158 ppm. The allylthio ^{13}C NMR peak appeared at 33, 113, and 133 ppm.

In conclusion, we synthesized new 6-allylthio-3-heterocyclopyridazine derivatives in order to discover a potential antitumor candidate. The refluxing of 6-allylthio-3-chloropyridazines and the corresponding nucleophilic heterocycle such as morpholine, piperazine, pyrazole, imidazole, piperidine, pyrrolidine, perhydroazepine and perhydroazocine for about 24~48h produced the target compound. The resulted compound will be tested about antitumor activity.

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