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SYNTHETIC STUDIES ON ISOQUINOLINE DERIVATIVES WITH MULTIDRUG RESISTANCE (MDR) MODULATING ACTIVITY

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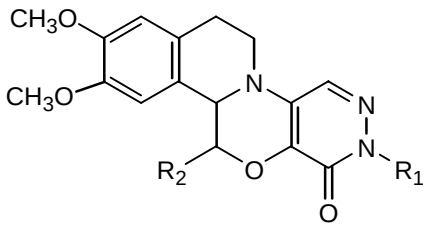
Abstract–Tetrahydropyridazino-1,4-oxazinoisoquinoline derivatives with multidrug resistance (MDR) modulating activity were designed and synthesized. A key step for cyclization of 1,4-oxazine ring was developed using K_2CO_3 and CH_3CN in one-pot. Among prepared compounds, 2-(4-fluorobenzyl)-9,10-dimethoxy-12-methyl-6,7,11*b*,12-tetrahydropyridazino[4',5',5,6][1,4]oxazine-[3,4,-*a*]isoquinolin-1(2*H*)-one (**1f**) exhibited significant MDR reversing activity and low toxicity, which might be as potential MDR agent.

Isoquinoline alkaloids are important because of their occurrence in nature and their physiological proerties.[1] They possess many diverse types of biological activities (*i.e*. bronchodilators,[2] skeletal muscle relaxants,[3] and antiseptics[4]) and have been extensively studied over the past hundred years. Recently there has been a growing interest in developing general and versatile synthetic methods[5] for the synthesis of these heterocyclic systems. Methods available for construction of tetrahydroisoquinoline derivatives include the Pictet-Spengler cyclization,[6] the Bischler-Napieralski cyclization,[7] the Heck-type cyclization,[8] the Parham-type cyclization,[9] the Pomeranz-Fritsch cyclization,[10] and other methods.[11] In addition, 3(2*H*)-pyridazinones have attracted considerable attention as a result of their pharmacological properties.[12] Several potentially useful drugs and pharmacological tools based on this pharmacophore have been developed in recent years, but there is ample scope for further exploration of this system. Several studies have indicated that the NH group adjacent to the carbonyl group in the azine system may

be an essential structural requirement in the binding of 3(2*H*)-pyridazinones to a variety of biological receptors.[13]

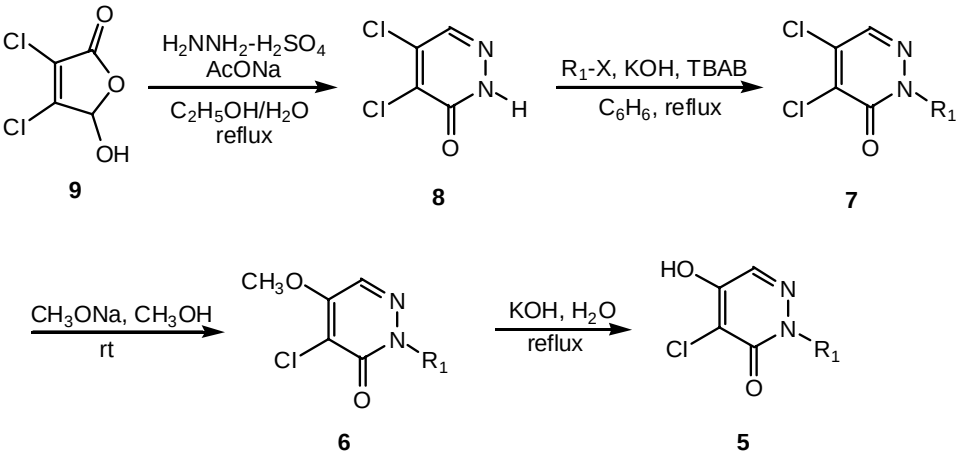
In connection with our research program for the study on the pharmacological characterization of novel isoquinoline derivatives, we designed isoquinoline derivatives (**1**) containing pyridazinone moiety that are expected as MDR modulating active compounds.



Designed Isoquinoline Derivatives (**1**)

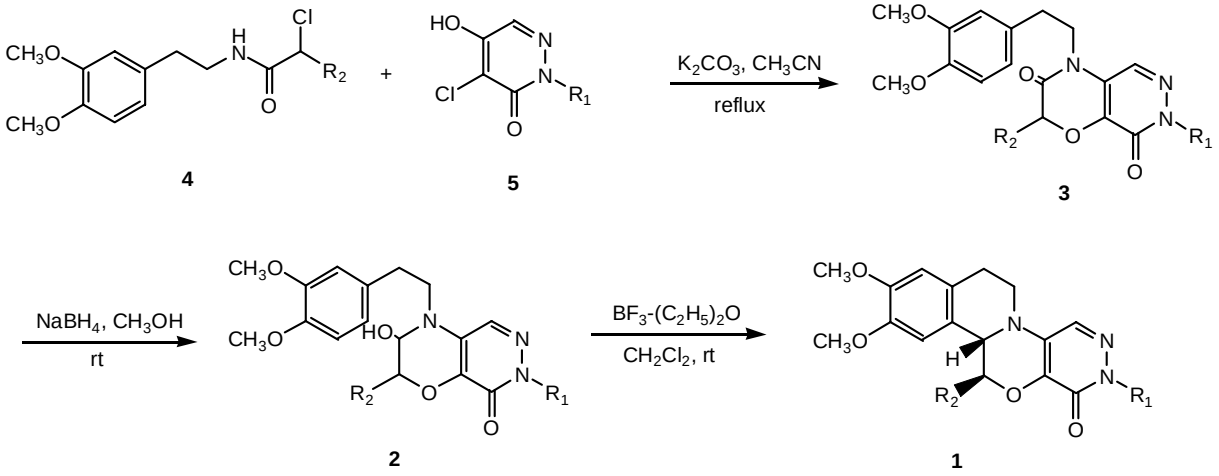
The designed compound (**1**) was obtained from **3** *via* two steps reaction by reduction and the cyclization. The ketone (**3**) was prepared by the cyclization of *N*-substituted 2-chloroacetamides (**4**) with *N*-substituted pyridazinones (**5**). Acetamides (**4**) was easily prepared by reaction of the amine to 2-chloroacetyl chloride. 4-Chloro-5-hydroxy-3(2*H*)-pyridazinones (**5**) was synthesized in four steps from commercially available mucochloric acid (Scheme 2).

Key intermediate (**5**) was obtained as shown in Scheme 1. Treatment of mucochloric acid (**9**) with hydrazine sulfate in ethanol/water (v/v=1:1) in the presence of sodium acetate at reflux gave pyridazinone (**8**) in excellent yields.[14]

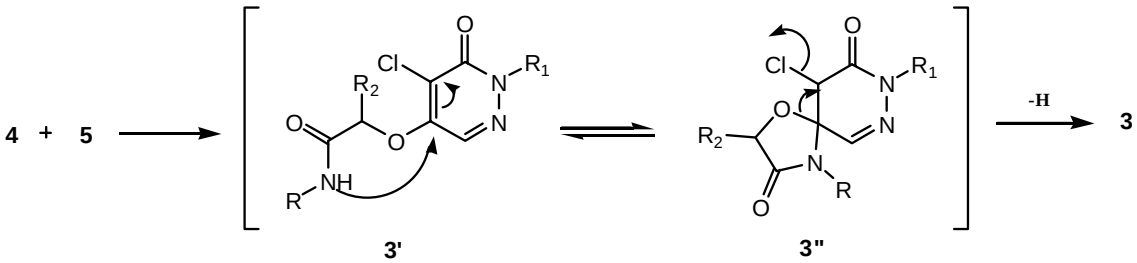


Scheme 1

Two methods (A and B) might be used for synthesis of 2-alkyl-4,5-dichloro-3(2*H*)-pyridazinone (**7**). Reactions of **8** with alkyl halides in the presence of potassium hydroxide and TBAB in benzene obtained *N*-alkylation product (**7**) (method A). Treatment of **8** with alkyl halides in the presence of potassium carbonate in DMF also afforded **7** in high yield (method B). *N*-Alkyl substituted pyridazinones (**7**) were easily transformed into 2-alkyl-4-chloro-5-methoxy-3(2*H*)-pyridazinones (**6**) by treatment of **7** with sodium methoxide in methanol. Hydrolysis of **6** in the present of potassium hydroxide resulted in the formation of 2-alkyl-4-chloro-5-hydroxy-3(2*H*)-pyridazinones (**5**) from mucochloric acid by four steps [15] The structure of **5** was identified by IR, NMR spectra and microanalysis. Reactions of 2-(3,4-dimethoxyphenyl)ethylamine with 2-chloroacetyl chlorides in the presence of potassium carbonate in dichloromethane at room temperature afforded **4** in excellent yields.



Scheme 2

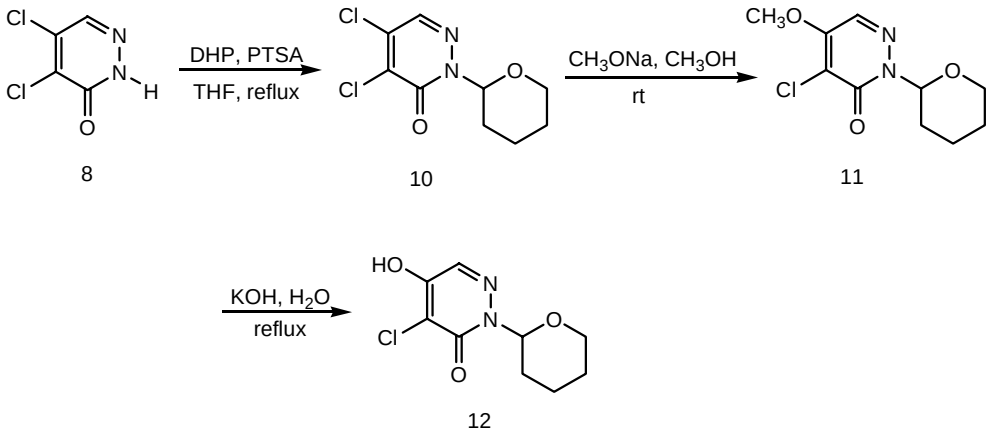


Scheme 3

The compounds (**3**) were synthesized by the reactions of acetamides (**4**) and various 2-alkylpyridazinones (**5**). The cyclization reaction occurred rapidly in the presence of potassium carbonate in acetonitrile at 82 ^{0}C. A possible pathway for formation of **3** is outlined in Scheme 3. Following the initial S_N2 nucleophilic

substitution of the hydroxyl group of **5** intermediate (**3'**) undergoes subsequent intramolecular Michael addition to give the spiro-aminoketal (**3"**). Migration of the spiro-oxygen, possibly assisted by the nitrogen lone pair, with concomitant displacement of the adjacent chloride and subsequent aromatization with loss of a proton evolves **3**. Reduction of **3** in the present of sodium borohydride in methanol at room temperature afforded **2** in good yield. Treatment of **2** with Lewis acids such as boron trifluoride-etherate in dichloromethane gave **1** (Scheme 2). In the Pictet-Spengler cyclyzation of **2** (R_2=Me), two diastereomers would be probably formed, only *trans*-isomer was obtained. The structure was identified by *X*-Ray analysis.

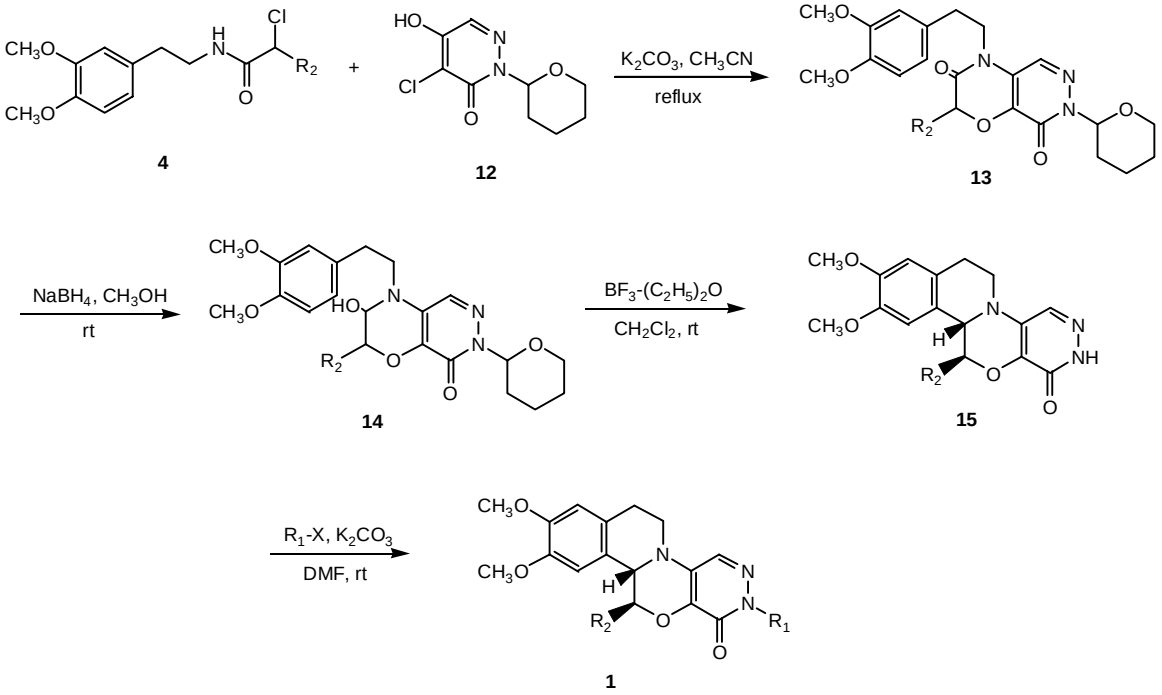
To find out the more effective synthetic method for **1**, we focused the attention on exploring protecting group which was attached to the nitrogen of the pyridazinone (Scheme 4). Our strategy is synthesis of **1** containing *N*-substituted protecting group. Then deprotecting process was carried out in an appropriate reaction conditions and new various substituents were attached to target compound. This method furnished us a convenient approach for the preparation of compounds (**1**) containing various substituents.



Scheme 4

The pyridazinone nitrogen of 4,5-dichloro-3(2*H*)-pyridazinone (**8**) was protected by treatment of **8** with excess dihydropyran and *p*-toluenesulfonic acid in tetrahydrofuran at 66 ^{0}C to give 4,5-dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**10**).[16] The compound (**10**) was followed by methoxide displacement to produce 4-chloro-5-methoxypyridazinone (**11**) which was then demethylated with potassium hydroxide in water at reflux to give pyridazinone (**12**) in good yield. The compound (**12**) was easily transformed into **14** by cyclization and reduction with known procedure shown in Scheme 2. Treatment of **14** with boron trifluoride-etherate in dichloromethane furnished tetracyclic isoquinoline derivative (**15**) in 81% yield. Interestingly, we found that cyclization to form isoquinoline moiety and

deprotection to give N-H group happened simultaneously (Scheme 5). At last, the various substituents were attached to the nitrogen of the pyridazinone moiety of **15** using various alkyl halides



Scheme 5

Table 1. The overall yields of **1**

Entry	R_1	R_2	Overall yield (%)	Entry	R_1	R_2	Overall yield (%)
1a	CH_3	H	18	**1b**	CH_3	CH_3	16
1c	CH_2=$CHCH_2$	H	22	**1d**	CH_2=$CHCH_2$	CH_3	21
1e	*p*-F$PhCH_2$	H	21	**1f**	*p*-F$PhCH_2$	CH_3	20
1g	*p*-Cl$PhCH_2$	H	26	**1h**	*p*-Cl$PhCH_2$	CH_3	22
1i	*p*-Br$PhCH_2$	H	27	**1j**	*p*-Br$PhCH_2$	CH_3	25
1k	*p*-CH_3PhCH_2	H	24	**1l**	*p*-CH_3PhCH_2	CH_3	19
1m	*p*-CH_3OPhCH_2	H	28	**1n**	*p*-CH_3OPhCH_2	CH_3	23
1o	*p*-*t*-$C_4H_9PhCH_2$	H	20	**1p**	*p*-*t*-$C_4H_9PhCH_2$	CH_3	17

The compounds (**1a-1p**) were obtained from **15**. The overall yields of **1** were listed in Table 1. All products were identified by IR, NMR spectra and microanalysis. *X*-Ray analysis of crystal structure of **1c** was shown in Figure 1.

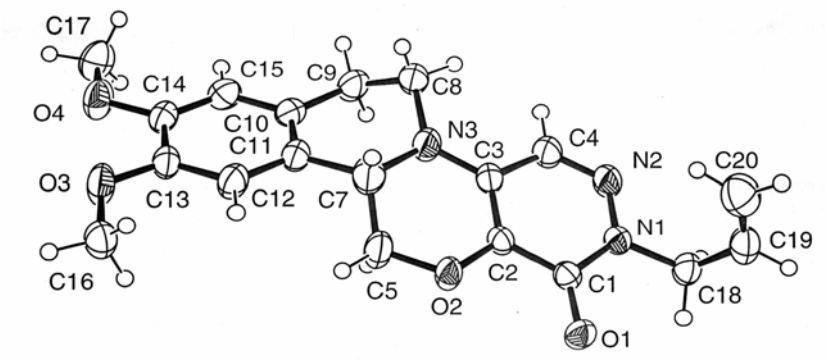


Figure 1. The stereo ORTEP drawing of **1c**

Multidrug resistance (MDR) modulating activity of **1** was examined in the following manner. The modulating efficacy of **1** was compared with verapamil, a standard MDR-modulator. The ability to restore sensitivity to adriamycin was evaluated as an increase of cellular concentration of adriamycin. As shown in Figure 2, CSA-121 (**1f**) modulates MDR in K562 cells as strongly as verapamil.

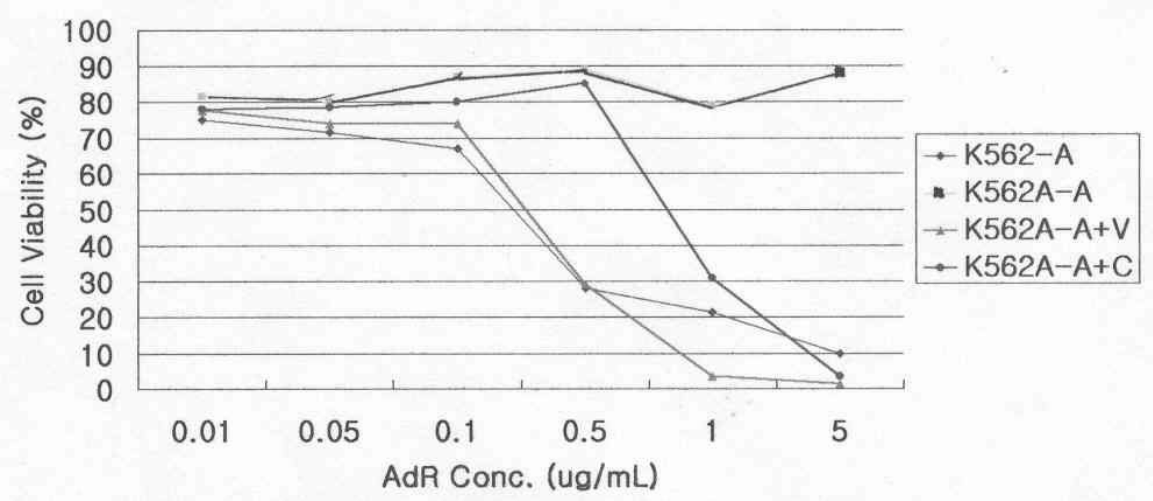


Figure 2. Reversal of MDR in K562 cells by CSA-121 and verapamil
(A: adriamycin; V: verapamil; C: CSA-121.)

In conclusion, new kinds of tetrahydropyridazino-1,4-oxazino-isoquinoline derivatives (**1**) with multidrug resistance (MDR) modulating activity were designed and synthesized. To prepare 1,4-oxazino-isoquinoline derivatives (**1**) more easily and effectively, we developed the modified synthetic method using *N*-THP protecting group. The 16 kinds of isopuinoline derivatives were synthesized using the modified synthetic method and examined the biological activity for MDR modulator. Specially, 2-(4-

fluorobenzyl)-9,10-dimethoxy-12-methyl-6,7,11*b*,12-tetrahydropyridazino[4',5',5,6][1,4]-oxazine[3,4,-*a*]isoquinolin-1(2*H*)-one (**1f**) exhibited a significant MDR reversing activity, which could be developed as a potential MDR-modulator.

EXPERIMENTAL

General Methods. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Varian spectrometer (solvent $CDCl_3$ if not otherwise mentioned). Chemical shifts are reported in parts per million (δ) downfield from TMS. Coupling constants (J values) are given in hertz (Hz). IR spectra were recorded on FTIR Nicolet Impect 410 spectrophotometer. MS spectral data were obtained on a Kratos MS 30 spectrometer using an ionization energy of 70eV. TLC was performed on Merck silica gel plates. Column chromatography was performed on Merck D-6100 silica gel 60 (70~230 mesh, ASTM).

4,5-Dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (10). A mixture of 4,5-dichloro-3(2*H*)-pyridazinone (30 g, 181.8 mmol), dihydropyran (19.4 g, 230.8 mmol), *p*-toluenesulfonic acid monohydrate (2.83 g, 14.9 mmol), and 160 mL of trteahydrofuran was stirred at reflux for 29 h. Additional dihydropyran was added at 6 h (13.3 g, 157.9 mmol) and at 21 h (7.8 g, 92.5 mmol). The reaction mixture was allowed to cool to rt overnight. The mixture was concentrated *in vacuo* to an oily residue. The residue was taken up in 160 mL of ethyl acetate and washed with 2N sodium hydroxide. The organic solution was dried ($MgSO_4$) and concentrated *in vacuo* to give **10** as a black oily solid which was used without further purification in the next step. The product was purified by filtration through silica gel with ethyl acetate followed by evaporation and recrystallization from ethyl acetate/cyclohexane to give a white solid. R_f 0.35 (Hexane/EtOAc, 3/1); mp 75-77 ^{0}C; IR (KBr, cm^{-1}): 3078, 2923, 2853, 1670, 1573, 1460, 1382, 1320, 1235, 1092; ^{1}H NMR ($CDCl_3$): δ 7.85 (s, 1H), 6.01 (d, J = 10.8 Hz, 1H), 4.13 (d, J = 13.5 Hz, 1H), 3.75 (m, 1H), 2.03~2.17 (m, 2H), 1.58~1.76 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 21.2, 24.9, 28.0, 66.7, 73.3, 112.0, 129.7, 132.8, 155.4; Anal. Calcd for $C_9H_{10}N_2O_2Cl_2$: C, 43.40; H, 4.05; N, 11.25. Found: C, 43.28; H, 4.16; N, 11.07.

4-Chloro-5-methoxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (11). A mixture of **10** and 170 mL of methanol was cooled to 0 ^{0}C and 87% potassium hydroxide (11.7 g, 181.7 mmol) was added in portions over approximately 1 h. The mixture was heated to 40 ^{0}C. Following the addition the mixture was allowed to stir an additional 3 h at ambient temperature. The reaction mixture was partitioned with

120 mL of ethyl acetate and 120 mL of water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried ($MgSO_4$). The organic solution was clarified by filtration and concentrated to give a dark semi-solid. The crude material was equally divided and added to two 220 mL flasks. The material was suspended and stirred in 120 mL hexane/ethyl ether (2:1 ratio). The washed material was vacuum filtered on a Buchner funnel and air dried overnight to give 34.1 g (77% over 2 steps) of **11** as a dark solid suitable for further transformations. The product was purified by recrystallization from ethyl acetate/cyclohexane to give a white solid. R_f 0.20 (Hexane/EtOAc, 3/1); mp 116~118 ^{0}C; IR (KBr, cm^{-1}): 3062, 2933, 2860, 1678, 1556, 1400, 1365, 1230, 1116; ^{1}H NMR ($CDCl_3$): δ 7.89 (s, 1H), 6.08 (d, J = 10.8 Hz, 1H), 4.12 (m, 1H), 4.08 (s, 3H), 3.76 (m, 1H), 2.03~2.17 (m, 2H), 1.60~1.72 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 21.5, 25.1, 28.2, 66.8, 68.3, 73.5, 111.4, 129.2, 134.0, 155.2; Anal. Calcd for $C_{10}H_{13}N_2O_3Cl$: C, 49.09; H, 5.36; N, 11.45. Found: C, 49.23; H, 5.33; N, 11.51.

4-Chloro-5-hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (12). **A** mixture of **11** (45 g, 184 mmol) and potassium hydroxide (12.4 g, 220.8 mmol) in water (150 mL) was heated to reflux for 3 h, then the mixture solution was cooled to rt. 1N HCl aqueous solution was added dropwise to cooled solution (pH=5~6). The mixture solution was filtered and residue was washed with water. The crude product was purified by recrystallization from methanol/hexane to give 36.7 g (86.5%) of **12**. R_f = 0.15 (Hexane/EtOAc, 2/1); mp 135~137 ^{0}C; IR (KBr, cm^{-1}): 3397, 2967, 2865, 2569, 1638, 1588, 1410, 1301, 1205, 1092; ^{1}H NMR ($CDCl_3$): δ 7.82 (s, 1H), 7.51 (m, 1H), 6.03 (d, J = 10.5 Hz, 1H), 4.12 (d, J = 13.2 Hz, 1H), 3.75 (m, 1H), 2.03~2.17 (m, 2H), 1.63~1.71 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 21.3, 24.9, 28.2, 66.7, 73.5, 111.5, 129.1, 133.8, 155.3; Anal. Calcd for $C_9H_{11}N_2O_3Cl$: C, 46.87; H, 4.81; N, 12.15. Found: C, 46.95; H, 4.78; N, 12.10.

7-(Tetrahydro-2*H*-pyran-2-yl)-4-(3,4-dimethoxyphenethyl)-2-methyl-2*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8(4*H*,7*H*)-dione (13). **A** mixture of **12** (8.48 g, 36.8 mmol), **4** (10.0 g, 36.8 mmol), and K_2CO_3 (12.2 g, 88.4 mmol) in CH_3CN (100 mL) was heated to reflux for 60 h, monitored by TLC. Then CH_3CN was removed under reduced pressure and CH_2Cl_2/H_2O were added. The phases were separated and aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was separated by flash column chromatography using EtOAc/CH_2Cl_2 (30%) as eluent to afford 10.4 g (65.5%) of **13**. R_f 0.40 (CH_2Cl_2/EtOAc, 2/1); IR (KBr, cm^{-1}): 3020, 2940, 2861, 1702, 1659, 1625, 1532, 1430, 1376, 1315, 1276, 1245, 1110; ^{1}H NMR ($CDCl_3$): δ 7.71 (s, 1H), 6.69~6.80 (m, 3H), 6.10 (d, J = 10.8 Hz, 1H), 4.74~4.87 (m, 1H), 3.96~4.15 (m, 3H), 3.73~3.86 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.87 (t, J = 7.2 Hz, 2H), 2.02~2.12 (m, 2H), 1.61~1.74 (m, 4H), 1.57 (d, J = 4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 16.5, 22.6, 24.7, 28.8, 33.6, 43.0, 55.6, 68.7, 74,3,

76.5, 77.4, 82.6, 111.2, 111.6, 120.7, 124.9, 127.2, 129.1, 134.3, 147.9, 148.9, 155.1, 164.4. Anal. Calcd for $C_{22}H_{27}N_3O_3$: C, 61.53; H, 6.34; N, 9.78. Found: C, 61.51; H, 6.36; N, 9.82.

7-(Tetrahydro-2*H*-pyran-2-yl)-4-(3,4-dimethoxyphenethyl)-3-hydroxy-2-methyl-3,4-dihydro-2*H*-pyridazino[4,5-*b*][1,4]oxazine-8(7*H*)-one (14). A mixture of **13** (4.0 g, 9.2 mmol) in CH_3OH (50 mL) was cooled to 0 ^{0}C and $NaBH_4$ (0.42 g, 11.2 mmol) was added. The reaction mixture was stirred at rt for 2 h and CH_3OH was removed under reduced pressure. CH_2Cl_2 was added to the residue. The mixture was stirred for 10 min, then filtered and washed with CH_2Cl_2. The solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography using EtOAc/CH_2Cl_2 as eluent to afford 3.4 g (85.6%) of **14**. R_f 0.60 (100% CH_3OH); IR (KBr, cm^{-1}): 3310, 3012, 2973, 2860, 1645, 1612, 1530, 1273, 1120; ^{1}H NMR ($CDCl_3$): δ 7.70 (s, 1H), 6.67~6.82 (m, 3H), 6.10(d, J = 10.8 Hz, 1H), 4.42~4.49 (m, 2H), 4.10 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.58~3.82 (m, 4H), 2.88~2.92 (m, 2H), 2.01~2.17 (m, 2H), 1.60~1.71 (m, 4H), 1.45 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 16.2, 22.5, 24.9, 29.0, 33.5, 42.3, 56.1, 63.6, 68.7, 75.5, 82.8, 93.9, 111.5, 120.7, 125.0, 126.7, 130.7, 135.2, 147.8, 148.8, 155.2; Anal. Calcd for $C_{22}H_{29}N_3O_6$: C, 61.24; H, 6.77; N, 9.74. Found: C, 61.30; H, 6.76; N, 9.79.

9,10-Dimethoxy-12-methyl-6.7.11*b*,12-tetrahydropyridazino[4',5',5,6][1,4]oxazine[3,4-*a*]isoquinolin-1(2*H*)-one (15). A solution of **14** (3.0 g, 6.96 mmol) in dry CH_2Cl_2 (50 mL) was cooled to 0 ^{0}C, then BF_3-Et_2O (5 mL, 40 mmol) was added dropwise. The reaction mixture was stirred at rt for 10 h, then saturated $NaHCO_3$ solution was added slowly. The layers were partitioned and the aqueous layer was extracted with CH_2Cl_2. The organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash column chromatography using EtOAc/CH_2Cl_2 as eluent to afford 2.1 g (91.5%) of **15**. R_f 0.12 (CH_2Cl_2/EtOAc, 1/2); IR (KBr, cm^{-1}): 3386, 3053, 2978, 1643, 1417, 1256. ^{1}H NMR ($CDCl_3$): δ 7.65 (s, 1H), 6.83 (s, 1H), 6.64 (s, 1H), 6.21 (s, 1H), 4.18~4.25 (m, 1H), 4.08 (d, J = 5.4 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.75 (m, 1H), 3.31~3.42 (m, 1H), 2.98~3.06 (m, 1H), 2.62~2.73 (m, 1H), 1.51 (d, J = 5.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 20.4, 29.3, 46.8, 48.1, 55.1, 56.8, 72.7, 102.4, 122.6, 125.3, 131.3, 132.0, 136.7, 140.4, 146.7, 147.9, 156.3; Anal. Calcd for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 61.93; H, 5.85; N, 12.82.

2-(4-Fluorobenzyl)-9,10-dimethoxy-12-methyl-6.7.11*b*,12-tetrahydropyridazino[4',5',5,6][1,4]oxazine[3,4-*a*]isoquinolin-1(2*H*)-one (1f). A mixture of **15** (0.20 g, 0.61 mmol), K_2CO_3 (0.17 g, 1.22 mmol) in DMF (10 mL) was stirred at rt for 15 min, then *p*-$FC_6H_4CH_2Br$ (0.14 g, 0.73 mmol) was added dropwise under stirring. The reaction mixture was stirred at rt for 10 h, then saturated NH_4Cl solution was added slowly. To the mixture solution was added CH_2Cl_2.

The layers were partitioned and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash column chromatography using EtOAc/CH_2Cl_2 as eluent to afford 0.25 g (92.1%) of **1f**. R_f 0.60 (CH_2Cl_2/EtOAc, 3/1); mp 228~229 ^{0}C; IR (KBr, cm^{-1}): 3078, 2982, 2926, 2860, 1640; ^{1}H NMR ($CDCl_3$): δ 7.67 (s, 1H), 7.41~7.46 (m, 2H), 6.95~7.00 (m, 2H), 6.73 (s, 1H), 6.61 (s, 1H), 5.17~5.34 (m, 2H), 4.16~4.20 (m, 1H), 4.02 (d, *J* = 5.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.76~3.86 (m, 1H), 3.35~3.41 (m, 1H), 2.88~2.93 (m, 1H), 2.65~2.70 (m, 1H), 1.48 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 17.5, 27.6, 46.2, 55.1, 56.4, 60.3, 71.9, 82.6, 102.8, 114.8, 118.5, 124.1, 129.0, 130.6, 130.9, 133.4, 135.7, 138.5, 139.2, 146.3, 148.5, 157.0; Anal. Calcd for $C_{24}H_{24}N_3O_4F$: C, 65.89; H, 5.53; N, 9.61. Found: C, 65.72; H, 5.55; N, 9.67.

ACKNOWLEDGEMENTS

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