Pyridazines. XV. Synthesis of 6-Aryl-5-amino-3(2*H*)-pyridazinones as Potential Platelet Aggregation Inhibitors [1]

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This paper is dedicated to Professor Miha Tišler of the University of Ljubljana, Slovenia, on the occasion of his 71st birthday

Several 3(2*H*)-pyridazinones with amino groups at the 5-position of the pyridazine nucleus have been prepared. The 6-aryl-5-halo-3(2*H*)-pyridazinones obtained from mucochloric and mucobromic acid lead to the corresponding 5-alkylamino-3(2*H*)-pyridazinones, which were tested as platelet aggregation inhibitors.

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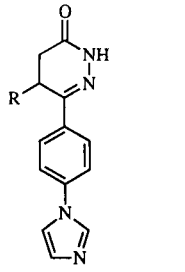
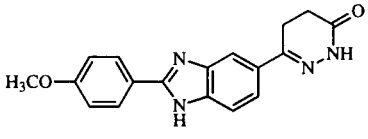
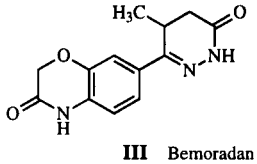
It is known that 6-aryl-3(2*H*)-pyridazinones and their 4,5-dihydro derivatives display several pharmacological activities, all of them related to cardiotonics, such as reduction of blood pressure [2-4], inhibition of platelet aggregation [4-6], positive inotropic activity [7-9], and others. Several pyridazinones such as imazodan **Ia**, CI-930 **Ib** [7], pimobendan **II** [10], bemoradan **III** [11] which are active as cardiotonic agents are structurally related to amrinone (5-amino-3,4'-bipyridine-5'-carbonitrile) the prototype of a series of non glycoside, non catecholamine cardiotonics which have stimulated great interest as promising agents for the treatment of congestive heart failure [12-14].



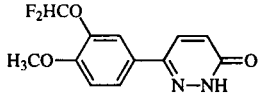
Ia R = H Imazodan
Ib R = CH_3 CI-930



II Pimobendan



III Bemoradan

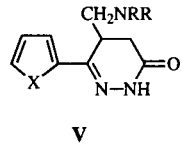


VI Zardaverine

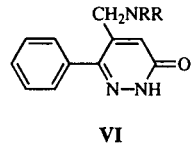
Figure I.

Likewise, 6-arylpyridazinones with nitro and acyl substituents at the 4- and 5-positions show good antiaggregating properties [15]. Moreover, other pyridazinones such as zardaverine **IV** [16,17] bearing dialkoxy groups in the *meta* and *para* positions of the phenyl ring as well as related compounds are mixed PDE III/IV inhibitors, and are being studied as platelet aggregation inhibitors, antiallergics and antiashmatics.

We have previously reported the synthesis of 5-aminomethyl-6-aryl-4,5-dihydropyridazinones **V** and 6-aryl-5-aminomethyl-3(2*H*)-pyridazinones **VI** [18-21]. Some of these compounds show a good *in vitro* inhibitory activity on ADP-induced rat platelet aggregation, **V** (X = S, NRR = *N*-methylpiperazine, IC_{50} = 0.97 μ*M*, X = CH=CH, NRR = *o*-methoxyphenylpiperazine, IC_{50} = 1.22 μ*M*). As a continuation of these previous reports on the chemistry and pharmacology of 6-aryl-5-substituted-3(2*H*)-pyridazinones and 6-aryl-5-substituted-pyridazines [19-23], we retain our interest on the preparation of 6-aryl-3(2*H*)-pyridazinones with amino substituents linked directly to the 5-position.



V

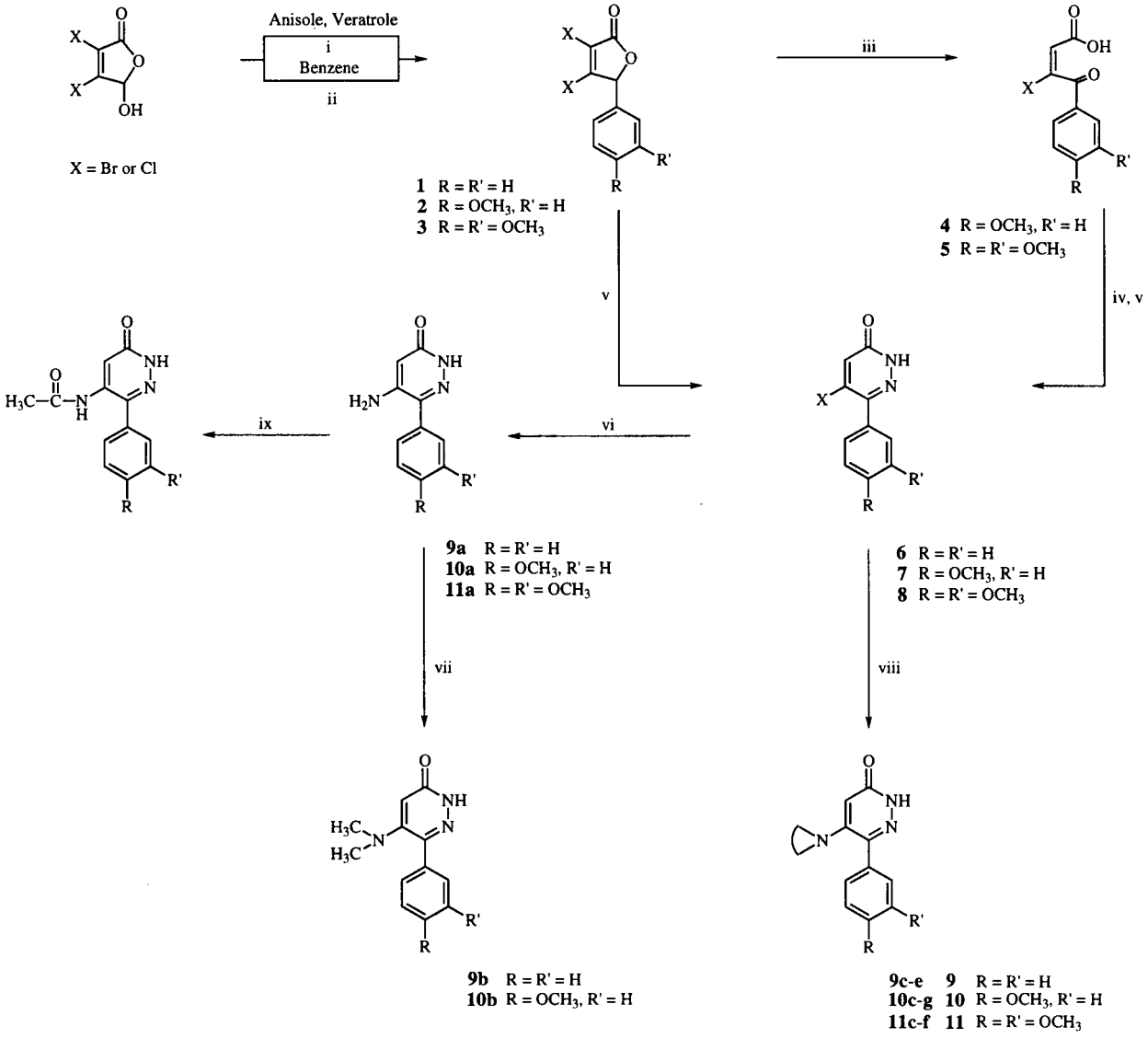


VI

Figure II.

Starting from mucochloric or mucobromic acid the target compounds 5-amino-6-aryl-3(2*H*)-pyridazinones **9-11** were prepared following Scheme I.

Scheme I



Reagents: i, PPA, P_2O_5; ii, $AlCl_3$; iii, MgO; iv, CH_3OH; v, NH_2-NH_2; vi, NH_3-NH_4Cl; vii, HCHO, $NaBH_3CN$; viii, amines, BuOH; ix, $(AcO)_2O$, EtOH.

A Friedel-Crafts reaction of benzene with mucobromic acid in the presence of aluminium chloride gave 4-phenyl-3,3-dibromocrotonolactone **1** in 70% yield as previously described [24]. Similarly, a Friedel-Crafts reaction of phenolic ethers, anisol and veratrol, in the presence of a mixture of ortophosphoric acid and phosphoric anhydride according to the procedure described by Semonsky *et al.* [25] gave crotonolactones **2** and **3** in 70 and 20% yields respectively. This procedure was reinvestigated by us and improved by careful temperature control (50-55°) and vigorous homogenization of the reaction mixture during 10-15 hours. Under these conditions we obtained yields of 60-80% of both dichloro and dibromocrotonolactones (Table I). Reaction of butenolides **1**, **2**, **3** with hydrazine hydrate in diethyleneglycol according to a patent procedures [26] afforded the 6-aryl-5-bromo-3(2*H*)-pyridazinones **6-9** in yields of 40-60%.

Alternatively, treatment of butenolides **2** and **3** with magnesium oxide in dioxane according to Semonsky [27], occurs with simultaneous loss of halogen in the α-position to give the *E*-acrylic acids **4**, **5**, with bromo and H in a *cis* position (^1H nmr s, 6.47 ppm). Esterification in acidic methanol afforded the methyl esters which were cyclocondensed with hydrazine hydrate to yield nearly quantitatively the 5-bromopyridazinones **7**, **8**.

All of the 5-halopyridazinones showed low reactivity toward nucleophilic displacement, in agreement with previously observations in the literature for analogous sys-

tems. We carried out the determination of the favored geometry for compound **6** using the quantum chemical AM1 method in MOPAC. The pyridazinone moiety is essentially planar and forms a dihedral angle, with the phenyl substituent on C-6 (Dihedral angle: 1-2-3-4 = 90.67°). The calculated heat of formation for the favored conformation of compound **6** was 51.17 Kcal/mol. Taking into account the amide-iminol tautomerism in the cyclic amide, in addition we calculated the favored conformation of the enol form and we observed the dihedral angle (-122.60°) and the heat of formation was 46.80 Kcal/mol which demonstrated that this enol is the predominant form in the equilibrium, allowing aromatization of the pyridazine nucleus.

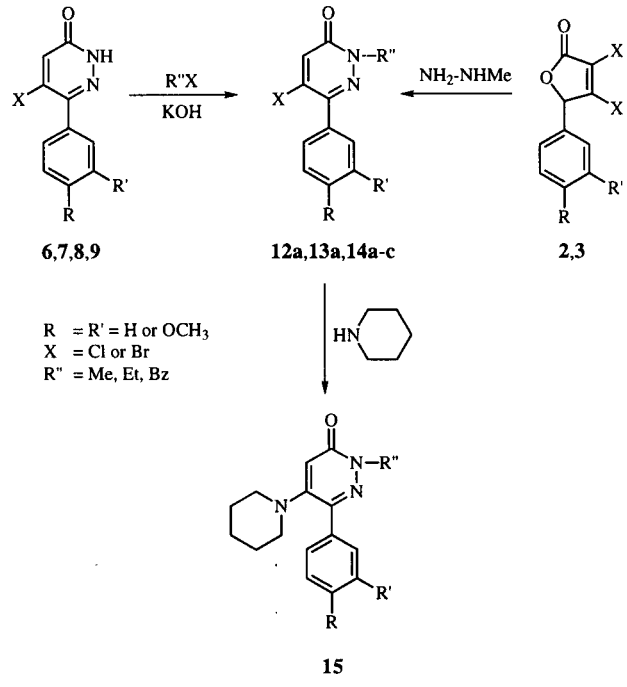
The charge density values for the more relevant atoms are shown in Table III.

The 5-amino-6-aryl-pyridazinones (Table I) were prepared in yields of 20-95% by nucleophilic displacement of 5-bromopyridazinones with the appropiate amines in butanol, or for compounds **9c**, **10c**, **11c** with diethylamine at high pressure in a Parr apparatus. The 5-amino-6-phenyl-3(2*H*)-pyridazinones **9a**, **10a**, **11a** were prepared in 30-65% yields by treatment with concentrated ammonia-ammonium chloride in a Parr reactor. The acetyl derivative was synthesized from **9a** in excellent yields.

These 5-aminopyridazinones showed satisfactory analytical and spectroscopic data. Thus, in addition to the amino and carbonyl signals in the ir spectra at 3200-3500 cm^{-1} and 1680 cm^{-1} respectively, the incorporation of an amino substituent in the 5 position also modified positions 3, 4 and 5 of the pyridazinone due to the charge transfer between the electron donating amino and the electron accepting carbonyl along the olefinic double bonds of the pyridazine ring. This effect is observed in ^1H nmr and ^{13}C nmr and is responsible for δ values (6.5 ppm) found in the ^1H nmr for the H-4, and characteristic values of δ in the ^{13}C nmr spectra for the C-3 (160 ppm) and C-4 (105 ppm) and C-5 (145 ppm). A similar electronic effect has been previously observed in other systems.

It is known that substitution at the nitrogen atom of the hydrazide moiety may change the pharmacological activity of the resulting pyridazinone. As starting materials for further syntheses, we have prepared in good yields 6-alkoxyphenyl-N^2-alkyl-5-halopyridazinones by reaction with alkyl halides in alkaline medium (Table II). Alternatively, *N*-methyl derivatives were also prepared by direct condensation of crotonolactones **2**, **3** with *N*-methylhydrazine in yields no higher than 30% (Scheme II). We have studied the geometry of compound **12a** by AM1 calculations and the heat of formation was 59.02 Kcal/mol. The net atomic charges are shown in Table III.

Scheme II



6,7,8,9 **12a,13a,14a-c** **2,3**

15

The effects of compounds **9a-9e**, **10a-10f** and **11a-11c** on platelet aggregation were measured on rat platelet rich plasma according to the turbidimetric method of Born [29].

All compounds showed only weak activities. The most active derivatives were **10a** and piperazino compounds **10e and 11e** with IC_{50} no lower than 10 m*M*. Despite these pharmacological data, aminopyridazinones can be used as promising starting compounds for further syntheses of fused heterocyclic systems. New studies addressing this point are still in progress.

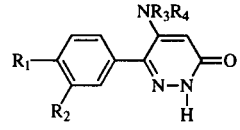
EXPERIMENTAL

Melting points were determined on a Gallemkap melting point apparatus and are uncorrected. Infrared spectra (ir) were measured on Perkin-Elmer 1640FTIR spectrophotometer and were performed in potassium bromide pellets. The ^1H nmr spectra were taken on a Bruker WM250 MHz and AMX300 MHz spectrometer using tetramethylsilane as an internal standard and chemical shifts are given in δ units. Mass spectra were determined on a Varian MAT-711 instrument. Elemental analyses were performed on a Perkin-Elmer 240B apparatus. Thin layer chromatography was run on aluminium sheets Silicagel 60F-254, 0.2 mm thickness and short-wave length ultraviolet light (254 nm) was used to detect the uv absorbing spots. Molecular modeling was performed using the software package SYBYL (Tripos associates, version 6.1) on a Silicon Graphics terminal.

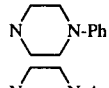
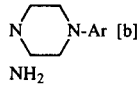
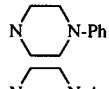
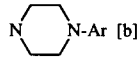
4-Phenyl-2,3-dichlorocrotonolactone (**1**).

Mucochloric acid (66.0 g, 0.40 mole) was added in small portions to a suspension of 80 g (0.06 mole) of anhydrous alu-

Table I

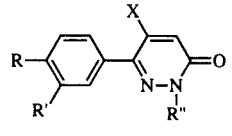


Formula I

Compound	R_1	R_2	NR_3R_4	Yield %	mp (°C)	Solvent of Recrystallization	Formula
9a	H	H	NH_2	65	239-244	ethanol	$C_{10}H_9N_3O$
9c	H	H	NEt_2	35	207-209	ethyl acetate	$C_{14}H_{17}N_3O$
9d	H	H		65	238-240	2-propanol	$C_{15}H_{17}N_3O$
9e	H	H		63	264-267	2-propanol	$C_{14}H_{16}N_4O$
10a	OCH_3	H	NH_2	60	218	ethanol	$C_{11}H_{11}N_3O_2$
10b	OCH_3	H	NMe_2 [a]	70	220	ethanol	$C_{13}H_{15}N_3O_2$
10c	OCH_3	H	NEt_2	40	210	ethyl acetate	$C_{15}H_{19}N_3O_2$
10d	OCH_3	H		95	212-214	ethanol	$C_{16}H_{19}N_3O_2$
10e	OCH_3	H		80	185-188	2-propanol	$C_{15}H_{18}N_4O_2$
10f	OCH_3	H		50	183-185	ethanol	$C_{21}H_{22}N_4O_2$
10g	OCH_3	H	 [b]	90	280	ethanol	$C_{22}H_{24}N_4O_3$
11a	OCH_3	OCH_3	NH_2	30	239-242	ethanol	$C_{12}H_{13}N_3O_3$
11c	OCH_3	OCH_3	NEt_2	20	212-218	ethyl acetate	$C_{16}H_{21}N_3O_3$
11d	OCH_3	OCH_3		45	206-210	2-propanol	$C_{17}H_{21}N_3O_3$
11e	OCH_3	OCH_3		25	209-212	2-propanol	$C_{16}H_{20}N_4O_3$
11f	OCH_3	OCH_3		37	240	ethanol	$C_{22}H_{24}N_4O_3$
11g	OCH_3	OCH_3	 [b]	55	244	ethanol	$C_{23}H_{26}N_4O_4$

[a] Prepared from **10a** with formaldehyde-sodium cyanoborohydride by using the classical Eschweiler-Clark procedure; [b] Ar = 2-methoxyphenyl.

Table II



Formula II

Compound	R	R'	R"	X	Yield %	mp (°C)	Solvent of Recrystallization	Formula
12a	H	H	CH_3	Cl	30	oil		$C_{11}H_{13}ClN_2O$
13a	OCH_3	H	CH_3	Br	64	140-142	cyclohexane	$C_{12}H_{11}BrN_2O_2$
14a	OCH_3	OCH_3	CH_3	Cl	30	135-137	cyclohexane	$C_{12}H_{11}ClN_2O_2$
14b	OCH_3	OCH_3	CH_2-CH_3	Cl	65	111-112	cyclohexane	$C_{14}H_{15}ClN_2O_3$
14c	OCH_3	OCH_3	CH_2-Ph	Cl	50	oil		$C_{19}H_{17}ClN_2O_3$
15	OCH_3	OCH_3	CH_2-CH_3		80	oil		$C_{19}H_{25}N_3O_3$

Table III
Charge Density Values Calculated for the Pyridazine Atoms

	N-1	N-2	C-3	C-4	C-5	C-6
6 (keto)	0.02	-0.26	0.30	-0.18	-0.12	-0.07
6 (enol)	0.00	-0.10	0.06	-0.14	-0.14	-0.05
12a	0.02	-0.22	0.30	-0.18	-0.12	-0.07

minium chloride in 320 ml of benzene. The mixture was energically stirred for 3 hours and then poured into 600 g of ice and 180 ml of concentrated hydrochloric acid. Then the mixture was extracted with benzene and the combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated to give a residue which was recrystallized from methanol, (yield 73%); mp [27] 79-80°; ir: 1760 (CO), 1600 (C=C); ^{1}H nmr (dimethyl sulfoxide-d_6) δ 7.45 (m, 5H, Ph), 6.38 (s, 1H, Ar-CH) ppm.

4-(4'-Methoxyphenyl)-2,3-dibromocrotonolactone (**2**).

This compound was synthesized from mucobromic acid and anisole by using the same procedure as above, mp 99-100°; ir: 1770 (C=O lactone), 1510 (C=C); ^{1}H nmr (deuteriochloroform): δ 7.45 (m, 4H, Ph), 6.38 (s, 1H, Ar-C*H*; 3.77 (s, 3H, OCH_3) ppm; ms: [m/z, (%)] 348 (M^+, 100), 300 (0.54), 269 (88.7), 240.9 (57.28), 2.23 (65.5), 182 (15.8), 135 (83.80), 108 (35.7).

4-(3',4'-Dimethoxyphenyl)-2,3-dibromocrotonolactone (**3**).

This compound was synthesized from mucobromic acid and veratrole by using the same procedure as above, yield 60%, mp 145-147°, (methanol); ir: 1780 (C=O), 1550 (-C=C-), 700-800 (C=C-Br); ^{1}H nmr (deuteriochloroform): δ 6.90 (s, 2H, *o*-Ph), 6.69 (s, 1H, *m*-Ph), 5.80 (s, 1H, Ar-C*H*), 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3) ppm.

(*E*)-3-Bromo-3-(4'-methoxybenzoyl)acrylic Acid (**4**).

A mixture of 40 ml of water, 40 ml of dioxane and 0.77 mg (0.01 mole) of magnesium oxide was heated for 3 minutes and added to a solution of 5.0 g (0.01 mole) of **1** in 10 ml of dioxane. The resulting mixture was refluxed for 75 minutes and then, without cooling, the white suspended solid was filtered and the filtrate evaporated. A 20% sodium hydrogen carbonate solution was added to the residue and the resulting solution filtered and treated with concentrated hydrochloric acid to give a yellow solid which was recrystallized from benzene to give the desired acid **4**, yield 76%, mp 144°, lit [28] mp 144-145°; ir: 3500-3000 (C=C-COOH), 1610 (Ar-CO), 970 (-CH=CH-); ^{1}H nmr (deuteriochloroform): δ 7.75 (d, J = 8.78, 2H, *o*-Ph), 6.85 (d, J = 7.76, 2H, *m*-Ph), 5.15 (s, 1H, OH acid), 6.47 (s, 1H, CO-C*H*=), 3.78 (s, 3H, OCH_3) ppm.

(*E*)-3-Bromo-3-(3,4-dimethoxybenzoyl)acrylic Acid (**5**).

This compound was prepared in 40% yield, mp 138°; ir: 3500-3000 (-C=C-COOH), 1610 (Ar-CO-), 970 (-CH=CH-) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.8 (s, 1H, OH), 6.9 (s, 2H, *o*-Ph), 6.69 (s, 1H, *m*-Ph), 5.8 (s, 1H, =CH-CO, pyridazine), 3.9 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.78 (s, 6H, OCH_3) ppm.

5-Bromo-6-phenyl-3(2*H*)-pyridazinone (**6**).

This compound was prepared according to Reicheneder and Dury [27] by reaction of α,β-dibromo-γ-phenylcrotonolactone (15.89 g, 0.05 mole) with 4.06 ml (0.08 mole) of hydrazine hydrate in ethyleneglycol, yield 67%, mp 230-231°, mp lit [27] 230°; ir: 3200-3000 (NH), 1700-1680 (CO); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.39 (m, 5H, Ph), 7.29 (s, 1H, H pyridazinone), 8.31 (br s, 1H, NH deuterium oxide exchangeable).

5-Bromo-6-(4'-methoxyphenyl)-3(2*H*)-pyridazinone (**7**).

This compound was prepared as previously described for compound **6**, mp 218°; ir: 2832 (NH), 1665 (CO); ^{1}H nmr (deuteriochloroform): δ 3.87 (s, 3H, OCH_3); 6.9 (d, J = 2, 2H, *m*-Ph), 6.8 (s, 1H, H pyridazinone), 7.8 (d, J = 8.7, 2H, *o*-Ph); 10.8 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_9N_2O_2Br$: C, 46.99; H, 3.23; N, 9.97. Found: C, 46.93; H, 3.28; N, 9.92.

5-Bromo-6-(3',4'-dimethoxyphenyl)-3(2*H*)-pyridazinone (**8**).

This compound was prepared as previously described for compound **6**, mp 199-201° (ethanol); ir: 3000 (NH), 1780 (CO), 1100 (C-Br); ^{1}H nmr (deuteriochloroform): δ 3.92 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.9 (d, 1H, J = 8.3, *m*-Ph), 7.09 (d, 1H, J = 2.03, *o*-Ph), 7.16 (s, 1H, H pyridazinone), 7.2 (dd, 1H, J = 8.3, Ph), 11.4 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{11}N_2O_3Br$: C, 46.44; H, 3.55; N, 9.03. Found: C, 46.39; H, 3.58; N, 8.98.

5-Amino-6-(4'-methoxyphenyl)-3(2*H*)-pyridazinone (**10a**).

A suspension of 0.5 g (1.9 mmoles) of **7**, 0.26 g (4.8 mmoles) of ammonium chloride and 50 ml of ammonium hydroxide was heated at 184° and at a pressure of 374 psi for 2.5 hours in a PARR reactor. The solution was concentrated and a solid was filtered and washed with ammonia solution. It was purified by recrystallization from ethanol to give **10a**, yield 50%, mp 218-220°; ir: 3480-3425 (NH_2), 3180 (C=C-NH_2), 1678 (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.5 (s, 1H, -NH), 7.40 (d, 2H, *o*-Ph), 7.03 (d, 2H, *m*-Ph), 5.66 (s, 1H, pyridazine), 5.96 (s, 2H, NH_2), 3.79 (s, 3H, OCH_3) ppm; ms: [m/z, (%)]: 247 (M^+, 100), 216 (14.62), 190 (14.16), 174 (13.6), 145 (5.02), 117 (3.22).

Compound **10a** Hydrochloride.

A saturated solution of dry hydrogen chloride in absolute ethanol was added dropwise to a solution of the amine in a minimum amount of absolute ethanol until cessation of salt formation. The resulting solution was concentrated under reduced pressure and the hydrochloride precipitate recovered by filtration and recrystallized from ethanol-ethyl ether, white prisms, mp 237-240°.

The following compounds were prepared similarly.

5-Amino-6-phenyl-3(2*H*)-pyridazinone (**9a**).

This compound was obtained in 65% yield, mp 244° (methanol), lit [28] 280°.

5-Acetylamino-6-phenyl-3(2*H*)-pyridazinone.

A mixture of 0.4 g (2.1 mmoles) of **9a** and 5 ml of acetic anhydride in 25 ml of ethanol was refluxed for 3 hours. After cooling the mixture was poured into ice forming a white solid which was recrystallized from 2-propanol to yield the acetylamino derivative (88%), mp 279-281°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 13.35 (s, 1H, NH), 10 (s, 1H, NHCO), 8.5 (s, 1H, CH), 7.75 (d, 2H, Ph), 7.45 (t, 3H, Ph), 2.2 (s, 3H, CH_3) ppm; ms [m/z, (%)] 229 (M^+), 189, 158, 130, 102, 77, 58.

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.88; N, 18.34; H, 4.80. Found: C, 62.93; N, 18.30; H, 4.85.

5-Amino-6-(3',4'-dimethoxyphenyl)-3(2*H*)-pyridazinone (**11a**).

This compound was obtained in 50% yield, mp 239-242°; ir: 3500-2932 (C-NH_2), 3149 (C-NH), 1653 (C=O), 833-756 (C-Br) cm^{-1}; ^1H nmr (deuteriochloroform + trifluoroacetic acid): δ 10.7 (s, 1H, NH), 7.16 (dd, 1H, Ph), 7,09 (s, 1H, Ph), 7.05 (d, 1H, Ph), 6.87 (s, 1H, Ar-CH), 3.96 (d, 6H, 2-OCH_3) ppm; ms: [m/z, (%)] 247 (M^+, 100), 216 (14.62), 190 (14.16), 174 (13.60), 145 (5.02), 117 (3.22).

6-(4'-Methoxyphenyl)-5-dimethylamino-3(2*H*)-pyridazinone (**10b**).

A mixture of 0.19 g (0.01 mole) of sodium cyanoborohydride and 0.1 ml of glacial acetic acid was added to a solution of 0.23 g (1 mmole) of **10a**, 0.3 ml (0.01 mole) of 37% formaldehyde in 14 ml of acetonitrile. The mixture was stirred for 2 hours at room temperature, then 0.1 ml of acetic acid was added and the stirring was continued for an additional 30 minutes. The resulting solid was filtered and purified by recrystallization from ethanol to give the desired dimethylamino derivative **10b**, yield 70%, mp 217-220°; ir: 3450-3300 (C-NH), 1670 (C=O), 1400-1000 (C-N); ^1H nmr (deuteriochloroform): δ 11.1 (s, 1H, -NH), 7.49 (d, 2H, H-Ph), 7.41 (s, 1H, CH-CO, pyridazine), 6.97 (d, 2H, H-Ph), 3.86 (s, 3H, OCH_3), 1.23 (d, 6H, $N(CH_3)_2$) ppm.

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 64.01; H, 6.26; N, 17.42.

5-Diethylamino-6-(4'-methoxyphenyl)-3(2*H*)-pyridazinone (**10c**).

A suspension of 1.0 g (3.7 mmoles) of **7**, 5 ml of diethylamine and 20 ml of ethanol was heated at 185° and 200 psi in a PARR reactor for 7 hours. After cooling the solvent was removed *in vacuo* and the residue washed with water. The resulting solid was filtered and recrystallized from ethyl acetate to give **10c**, yield 40%, mp 219°; ir: 3500-3470 (C-N), 1670 (C=O); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.28 (s, 1H, pyridazinone), 7.07 (m, 4H, Ph), 3.77 (s, 3H, -OCH_3), 2.78 (m, 4H, 2-N-(CH_2)-), 1.19 (t, 6H, -N-(CH_2-CH_3)$_2$ ppm.

Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.81; H, 6.80; N, 15.67.

The same procedure was followed for compounds **9c** and **11c** given below.

5-Diethylamino-6-(3',4'-dimethoxyphenyl)-3(2*H*)-pyridazinone (**11c**).

This compound was obtained in a yield of 20%, mp 212-218° (ethyl acetate); ir: 3500-3470 (C-N), 1670 (C=O).

5-Diethylamino-6-phenyl-3(2*H*)-pyridazinone (**9c**).

This compound was obtained in a yield of 35%, mp 207-209° (ethyl acetate).

6-Phenyl-5-piperidinyl-3(2*H*)-pyridazinone (**9d**).

A solution of 0.46 g (1.87 mmoles) of **6** and 1.7 ml (17.2 mmoles) of anhydrous piperidine was refluxed for 7 hours and then cooled to give a solid which was filtered, washed with water, and recrystallized from 2-propanol to give 0.308 g of **9d**, 66% yield, mp 210°; ir: 3500 (C-N, piperidine), 1668 (CO); ^1H nmr (deuteriochloroform + trifluoroacetic acid): δ 1.50 (s, 6H, H3, H4, H5 piperidine), 2.80 (s, 4H, H2, H6 piperidine), 7.6 (m, 5H, Ph), 10.9 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.59; H, 6.67; N, 16.47. Found: C, 70.54; H, 6.72; N, 16.42.

The same procedure was followed for compounds **10d** and **11d** given below.

6-(4'-Methoxyphenyl)-5-piperidinyl-3(2*H*)-pyridazinone (**10d**).

This compound was obtained in a yield of 95%, mp 212° (ethanol); ir: 3500 (CN, piperidine), 1668 (CO); ^1H nmr (deuteriochloroform): δ 1.51 (s, 6H, piperidine), 2.84 (s, 4H, piperidine), 3.85 (s, 3H, OCH_3), 6.18 (s, 1H, H pyridazinone), 7.1 (d, 2H, Ph), 7.6 (d, 2H, Ph), 10.99 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 67.35; H, 6.72; N, 14.73. Found: C, 67.78; H, 6.80; N, 14.85.

6-(3',4'-Dimethoxyphenyl)-5-piperidinyl-3(2*H*)-pyridazinone (**11d**).

This compound had mp 207° (2-propanol); ir: 3000 (CN), 1660 (CO); ^1H nmr (deuteriochloroform): δ 1.50 (s, 6H, piperidine), 2.80 (s, 4H, piperidine), 3.96 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.05 (d, 1H, Ph), 7.09 (s, 1H, Ph), 7.16 (dd, 1H, Ph), 11.2 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 163.3 (C=O, pyridazinone), 155.3 (Cl, Ph), 149.5 (*C*-OCH_3, Ph), 148.8 (*C*-OCH_3, Ph), 143.4 (C-N, pyridazine), 129.1 (-C-N-, pyridazine), 120.3 (*C*-CO, pyridazine), 110.9 (-C-, *o*-Ph), 110.8 (-C-, *m*-Ph), 109.3 (-C-, *o*-Ph), 55.9 (2-*O*CH_3), 50.8 (2-C, piperidine), 25.2 (2C, piperidine), 23.6 (C-, piperidine) ppm.

Anal. Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.76; H, 6.66; N, 13.33. Found: C, 64.32; H, 6.70; N, 13.35.

6-(4'-Methoxyphenyl)-5-piperazinyl-3(2*H*)-pyridazinone (**10e**).

A solution of 0.5 g (1.78 mmoles) of **7** and 6 ml of butanol was heated at 60° and then added 0.46 g (5.34 mmoles) of anhydrous piperazine. The mixture was refluxed and stirred for 16 hours. Then it was cooled and the resulting white solid was filtered and washed with butanol. This solid was recrystallized from ethanol to give 0.35 g of derivative **10e**, yield 68%, mp 186-188°; ir: 3500 (N, piperazinyl), 3193 (C=C-NH), 1654 (C=O); ^1H nmr (deuteriochloroform): δ 7.63 (d, 2H, *o*-Ph), 6.96 (d, 2H, *m*-Ph), 6.19 (s, 1H, pyridazine), 3.85 (s, 3H, OCH_3), 3.05 (s, 1H, NH, piperazine), 2.85 (s, 8H, piperazine) ppm.

Anal. Calcd. for $C_{15}H_{18}N_4O_2$: C, 62.93; H, 6.29; N, 19.58. Found: C, 62.37; H, 6.67; N, 20.04.

6-(3',4'-Dimethoxyphenyl)-5-piperazinyl-3(2*H*)-pyridazinone (**11e**).

This compound was prepared by the same procedure as described above, yield 25% (2-propanol), mp 209-212; ir: 3500 (N, piperazine), 3193 (C=C-NH_2), 1654 (C=O); ^1H nmr (deuteriochloroform): δ 7.63 (d, 2H, *o*-Ph), 6.96 (d, 2H, *m*-Ph), 6.19 (s, 1H, pyridazine), 3.85 (s, 6H, 2-OCH_3), 3.05 (s, 1H, NH, piperazine), 2.85 (s, 8H, piperazine) ppm.

Anal. Calcd. for $C_{16}H_{20}N_4O_3$: C, 60.76; H, 6.36; N, 17.72. Found: C, 60.9; H, 6.80; N, 17.87.

6-(4'-Methoxyphenyl)-5-(N^4-phenyl-N^1-piperazinyl)-3(2*H*)-pyridazinone (**10f**).

This compound was obtained in a yield of 50% (ethanol), mp 183-185°; ir: 3500 (NH piperazine); 3193 (C=C-NH_2), 1654 (C=O); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.24 (m, 3H, H3 and H5-Ph-N4= and H2-Ph), 7.17 (d, 1H, H6-Ph), 7.02 (t, 1H, H5-Ph), 6.90 (d, 1H, H2 and H6-Ph-N4=), 6.77 (m, 1H, H4-Ph-N4=), 6.14 (s, 1H, pyridazinone), 3.76 (d, 3H, -OCH_3), 3.08 (d, 4H, N4-(CH_2)$_2$-), 2.96 (s, 4H, N1-(CH_2)$_2$) ppm.

Anal. Calcd. for $C_{21}H_{22}N_4O_2$: C, 69.3; H, 6.07; N, 15.46. Found: C, 69.92; H, 6.09; N, 15.90.

6-(3',4'-Dimethoxyphenyl)-5-(N^4-phenyl-N^1-piperazinyl)-3(2*H*)-pyridazinone (**11f**).

This compound was obtained in a yield of 31%, mp 240-242° (ethanol); ir: 3500 (N, piperazine), 3193 (C=C-NH_2), 1654 (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.24 (m, 3H, H3 and H5-Ph-N4= and H2-Ph), 7.17 (d, 1H, H6-Ph), 7.02 (t, 1H, H5-Ph), 6.90 (d, 1H, H2 and H6-Ph-N4=), 6.77 (m, 1H, H4-Ph-N4=), 6.14 (s, 1H, pyridazinone), 3.76 (d, 6H, 2-OCH_3), 3.08 (d, 4H, N4-$(CH_2)_2$-), 2.96 (s, 4H, N1-$(CH_2)_2$) ppm.

Anal. Calcd. for $C_{22}H_{24}N_4O_3$: C, 67.00; H, 6.09; N, 14.21. Found: C, 66.65; H, 5.58; N, 13.90.

6-(4'-Methoxyphenyl)-5-[N^4-(*o*-methoxyphenyl)-N^1-piperazinyl]-3(2*H*)-pyridazinone (**10g**).

This compound was obtained in a yield of 90%, mp 284° (ethanol); ir: 3500 (NH, piperazine), 3193 (C=C-NH_2), 1654 (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.23 (d, 1H, *p*-Ph), 7.21 (s, 1H, *m*-Ph), 7.03 (d, 1H, *o*-Ph), 6.92 (m, 2H, H3, H5-*o*-methoxy-Ph-N4=), 6.12 (s, 1H, pyridazinone), 2.77 (m, 9H, 3-OCH_3), 2.93 (s, 8H, piperazine) ppm.

Anal. Calcd. for $C_{22}H_{24}N_4O_3$: C, 67.3; H, 6.12; N, 14.28. Found: C, 67.8; H, 6.01; N, 14.88.

6-(3',4'-Dimethoxyphenyl)-5-[N^4-(*o*-methoxyphenyl)-N^1-piperazinyl]-3(2*H*)-pyridazinone (**11g**).

This compound was obtained in a yield of 55%, mp 243-244° (ethanol); ir: 3500 (N, piperazine); 3193 (C=C-NH_2), 1654 (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.23 (d, 1H, *o*-Ph), 7.21 (s, 1H, *o*-Ph), 7.03 (d, 1H, *m*-Ph), 6.92 (m, 2H, H3, H5, *o*-methoxy-Ph-N4=), 6.84 (m, 2H, H4 and H6, *o*-methoxy-Ph-N4=), 6.12 (s, 1H, pyridazine), 2.77 (m, 9H, 3-OCH_3), 2.93 (s, 8H, piperazine) ppm.

Anal. Calcd. for $C_{23}H_{26}N_4O_4$: C, 65.09; H, 6.13; N, 13.20. Found: C, 64.51; H, 6.16; N, 12.62.

5-Bromo-6-(4'-methoxyphenyl)-2-methyl-3(2*H*)-pyridazinone (**13a**).

A solution of 1.55 g (55 mmoles) of **7** in 45 ml of methanol was added 0.42 g (7.5 mmoles) of potassium hydroxide and 2.12 g (0.015 mmole) of methyl iodide. The mixture was refluxed for 1 hour and then another 2.12 g (0.015 mmole) of methyl iodide was added and the entire mixture was refluxed for 2 additional hours. Then the solvent and the excess of iodide were eliminated and the residue was extracted with hot benzene. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to afford a solid which was purified by recrystallization from cyclohexane and identified as **13a** (63%), mp 139-140°; ir: 1680 (C=O); ^{1}H nmr (deuteriochloroform): δ 7.5 (d, J = 8.3, 2H, *o*-Ph), 7.36 (s, 1H, pyridazine), 6.99 (d, 2H, J = 7.1, *m*-Ph), 3.80 (s, 3H, -CH_3), 3.86 (s, 3H, OCH_3) ppm.

Anal. Calcd. for $C_{12}H_{11}BrN_2O_2$: C, 48.84; H, 3.76; N, 9.49. Found: C, 48.63; H, 3.36; N, 9.49.

5-Chloro-6-(3',4'-dimethoxyphenyl)-2-methyl-3(2*H*)-pyridazinone (**14a**).

To a solution of 0.2 g (0.5 mmole) of lactone **3** in 2 ml of ethyleneglycol and 5 ml of ethanol was added 0.4 ml (7.5 mmoles) of methylhydrazine *via* syringe. The mixture was refluxed for 4 hours and the solvent was eliminated by distillation. The resulting oil was purified by flash chromatography (ethyl acetate), yield 30%; ir: 1680 (CO), 700 (C=C); ^{1}H nmr (deuteriochloroform): δ 7.27 (m, 2H, Ph), 6.9 (s, 1H, C*H*CO, pyridazine), 3.93 (s, 3H, OCH_3); 3.92 (s, 3H, OCH_3), 3.82 (s, 3H, CH_3) ppm.

5-Chloro-6-(3',4'-dimethoxyphenyl)-2-ethyl-3(2*H*)-pyridazinone (**14b**).

This compound was prepared following the same procedure as for **13a** (65%), mp 111-112° (cyclohexane); ir 1680 (C=O), 700 (C=C); ^{1}H nmr (deuteriochloroform): δ 7.15-7.03 (m, 3H, Ph), 6.92 (d, 1H, J = 8.2, *o*-Ph), 6.21 (s, 1H, C*H*CO, pyridazine), 4.18 (c, 2H, J = 7.2, CH_2-CH_3), 3.93 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.82 (s, 3H, CH_3) ppm.

2-Ethyl-6-(3',4'-dimethoxyphenyl)-5-piperidinyl-3(2*H*)-pyridazinone (**15**).

A solution of 0.04 g (0.13 mmole) of **14b** in 3 ml of butanol was added 0.2 ml (2.1 mmoles) of piperidine. The mixture was refluxed for 7 hours. Then the solvent and the excess piperidine were distilled and the residue was washed with water twice and extracted with ethyl acetate (3 x 25 ml), dried over anhydrous sodium sulfate and filtered to afford a yellow oil which did not crystallize on standing, yield 80% of **15**; ir: 1680 (CO), 750 (C=C); ^{1}H nmr (deuteriochloroform): δ 7.27 (m, 2H, H-Ph), 6.92 (d, 1H, J = 8.2, *o*-Ph), 6.21 (s, 1H, C*H*-CO, pyridazine), 4.18 (c, 2H, J = 7.2, CH_2-CH_3), 3.93 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3); 2.8 (s, 4H, piperidine), 1.5 (s, 6H, piperidine), 1.37 (t, 3H, J = 7.2, CH_2-CH_3) ppm.

Compound **15** Hydrochloride.

A saturated solution of dry hydrogen chloride in absolute ethanol was added dropwise to a solution of **15** in absolute ethanol until cessation of salt formation. The resulting solution was concentrated under reduced pressure and the hydrochloride was recovered by filtration and recrystallized from ethanol, white needles mp, 142°.

Anal. Calcd. for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 65.85; H, 7.38; N, 11.74.

6-(3',4'-Dimethoxyphenyl)-5-chloro-2-benzyl-3(2*H*)-pyridazinone (**14c**).

To a solution of 0.2 g (0.75 mmole) of **13** in 5 ml of methanol was added 0.042 g (0.75 mmole) of potassium hydroxide and 0.19 ml (1.5 mmoles) of benzyl chloride. The resulting solution was refluxed for 7 hours and then the solvent and excess of benzyl chloride were distilled. Water was added to the residue and the resulting mixture extracted with ethyl acetate, then dried over anhydrous sodium sulfate and concentrated to afford a white oil which was purified by flash chromatography (100% ethyl acetate), yield 50%; ir: 3500 (N-CH), 1680 (C=O); ^{1}H nmr (deuteriochloroform): δ 7.48 (dd, 2H, H2, H6, Ph), 7.28-7.37 (m, 3H, H3, H4, H5), 7.17 (dd, 1H, *o*-dimethoxyphenyl), 7.12 (s, 1H, CH, pyridazine), 7.05 (d, J = 2.0, 1H, *o*- dimethoxyphenyl), 6.9 (d, J = 8.4, 1H, *m*-dimethoxyphenyl), 5.35 (s, 2H, CH_2), 3.93 and 3.90 (2s, 6H, 2-OCH_3) ppm.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.8; N, 7.85. Found: C, 63.53; H, 5.08; N, 8.03.

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