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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of new pyridazinone derivatives as platelet aggregation inhibitors

Sridhar Thota · Ranju Bansal

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Abstract This paper describes the synthesis and the antiplatelet activity of a series of 6-(4-(substituted-amino)phenyl)-4,5-dihydro-3(2*H*)-pyridazinones. Antiplatelet activity was determined by using the tail transaction bleeding test. All of the newly synthesized pyridazinone derivatives exhibited significant platelet aggregation inhibitory activity. The compounds **IIIc** and **IIIh** displayed two times more platelet aggregation inhibitory effect compared with standard drug aspirin.

Keywords Pyridazinone derivatives · Platelet aggregation inhibitors · 3(2*H*)-pyridazinones

Introduction

Increasing evidence clearly indicates that enhanced platelet activation plays a critical role in the initiation and development of atherothrombotic diseases (Marcus and Safier, 1993; Ruggeri, 2002). Accordingly, to prevent and treat thrombosis and vascular diseases, antiplatelet therapy may be a potential strategy (Ruggeri, 2002; Cherng *et al*., 2006). Aspirin, the primary antiplatelet therapy in use today, has been shown to reduce the risk of arterial thrombosis in placebo-controlled clinical trials. Despite the proven efficacy of aspirin, there are reasons to believe that substantial improvements in antiplatelet therapy can be made. Among these is the fact that aspirin and the other currently available orally administered antiplatelet agents, such as ticlopidine and clopidogrel, are selective platelet inhibitors and thus inhibit some but not all agonist-induced pathways of platelet activation and recruitment (Grotemeyer *et al*., 1993). However, some drawbacks of these drugs, such as

S. Thota · R. Bansal (✉)
University Institute of Pharmaceutical Sciences, Panjab University,
Chandigarh 160014, India
e-mail: ranju29in@yahoo.co.in

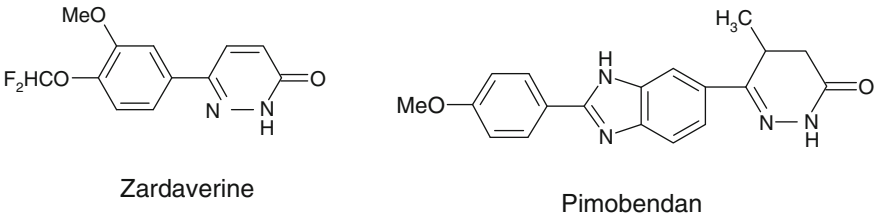


Fig. 1 Structures of pyridazinone type platelet aggregation inhibitors

aspirin resistance and the risk of neutropenia, bleeding, and thrombocytopenia, were occasionally observed. Therefore, to develop safer and effective antiplatelet agents with a broad mechanism of action may be a promising approach for the prevention and treatment of atherothrombosis (Sotelo *et al*., 2002).

6-Aryl-3(2*H*)-pyridazinones have attracted particular attention because of their diversified biological activities, most of them related to the cardiovascular system. Several compounds, such as imazodan, zardaverine, and pimobendan (Fig. 1), have been developed as potent antiplatelet and cardiotonic agents through phosphodiesterase III inhibition (Curran and Ross, 1974). In recent years the potent platelet inhibitory activity of several other 6-phenyl-4,5-disubstituted-3(2*H*)-pyridazinones also has been reported (Dal *et al*., 1991). Because of easy functionalization of various ring positions, 6-aryl-3(2*H*)-pyridazinone has emerged as an attractive synthetic building block for the preparation of compounds of diverse biological interest (Sotelo *et al*., 2000). The search for more potent and safer pyridazinones as platelet aggregation inhibitors continues, and in the process a new series of pyridazinone derivatives possessing substituted amino phenyl group has been synthesized in our laboratory, which we report herein. The structures of these compounds were established by using various spectral and elemental analyses. The newly synthesized compounds were evaluated for antiplatelet activity using tail transaction bleeding test.

Materials and methods

Chemistry

Melting points were determined via an *MP1-Veego* instrument (Veego Instruments, Mumbai, India), uncorrected. All instrumental analysis was performed in the central instrumental laboratory of Panjab University. Infrared (IR) spectra were recorded on a Perkin-Elmer spectrum RX 1, FT-IR spectrophotometer (Huenenberg, Switzerland): KBr pellets; υ_{max} in cm^{-1}. ^{1}H-nuclear magnetic resonance (^{1}H-NMR) was measured with a Bruker AC-300F (300 MHz) instrument (Bruker AG, Fällanden, Switzerland). All chemical shifts were reported as δ (ppm) values. Me_4Si as the internal standard: *J* in Hz. Elemental analyses were performed on a Perkin-Elmer-2400 apparatus. The purity of the compounds was established by TLC and elemental analyses (TLC: plates; E. Merck, Darmstadt, Germany) were prepared

according to Stahl (activated at 110°C for 30 min; AcOEt as a solvent; visualization by I_2 vapors). Materials obtained from the commercial suppliers were used without further purification. Anhydrous Na_2SO_4 was used as a drying agent.

The starting compound 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one (**I**) was prepared according to literature method (Burpitt *et al*., 1988).

Synthesis of 6-(4-(substituted-amino)phenyl)-4,5-dihydro-3(2*H*)-pyridazinones IIIa–h Appropriate aldehyde **IIa–h** (1.58 mmol) was added to stirred solution of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one (**I**) (1.58 mmol) in methanol (15 ml) with constant stirring. The reaction mixture was further stirred at room temperature overnight. The suspension obtained was cooled in ice and sodium borohydride (0.39 g) added in small amounts with constant stirring for a period of 30 min and the solution obtained was further stirred for 2 hr. Ice cold water was added to it and the precipitated material was filtered off, washed with ice cold water, dried, and recrystallization from a mixture of methanol and chloroform resulted into the formation of desired pyridazinones **IIIa–h**. The structures of these compounds were elucidated by using various spectral and elemental analyses.

6-(4-(3,4-Dimethoxybenzylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one (IIIa). Yield: 44.91%; m.p. 137–138°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 3370 (NH), 3085 (CH, aromatic), 2929 (CH, aliphatic), 1661 (CO), 1600 (C=C, aromatic); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.58 (t, 2H, 4-CH_2, $J = 7.42$ Hz), 2.94 (t, 2H, 5-CH_2, $J = 7.4$ Hz), 3.87 (s, 6H, 2x-OCH_3), 4.30 (s, 3H, NH–CH_2), 6.62 (d, 2H, Ar–H, $J_o = 8.84$ Hz), 6.91 (m, 3H, Ar–H), 7.58 (d, 2H, Ar–H, $J_o = 8.80$ Hz) and 8.36 (s, 1H, –N*H*). Anal. calcd. for $C_{19}H_{21}N_3O_3$: C: 67.24, H: 6.24, N: 12.38%; found; C: 67.08, H: 6.13; N: 12.13%.

6-(4-(3,4,5-Trimethoxybenzylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one (IIIb). Yield: 62.09%; m.p. 134–135°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 3360 (NH), 3069 (CH, aromatic), 2928 (CH, aliphatic), 1661 (C=O), 1600 (C=C, aromatic); ^{1}H-NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.58 (t, 2H, 4-CH_2, $J = 7.46$ Hz), 2.95 (t, 2H, 5-CH_2, $J = 7.42$ Hz), 3.84 (s, 9H, 3x-OCH_3), 4.31 (s, 3H, NH–CH_2), 6.58 (s, 2H, Ar–H), 6.65 (dd, 2H, Ar–H, $J_o = 6.88$ Hz, $J_m = 1.90$ Hz), 7.58 (dd, 2H, Ar–H, $J_o = 6.84$ Hz, $J_m = 1.90$ Hz) and 8.36 (s, 1H, –NH, pyridazinone). Anal. calcd. for $C_{20}H_{23}N_3O_4$: C: 65.03, H: 6.27, N: 11.37%; found; C: 65.06, H: 6.14; N: 11.31%.

6-(4-(2-Hydroxybenzylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one (IIIc). Yield: 31.25%; m.p. 197–198°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 3410 (OH), 3192 (NH), 3043 (CH, aromatic), 2931 (CH, aliphatic), 1656 (C=O, pyridazinone), 1606 (C=C, aromatic); ^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 2.50 (t, 2H, 4-CH_2, $J = 8.14$ Hz), 2.88 (t, 2H, 5-CH_2, $J = 8.16$ Hz), 4.34 (d, 2H, NH–CH_2, $J = 5.72$ Hz), 5.26 (t, 1H, NH–CH_2, $J = 5.78$ Hz), 6.65 (d, 2H, Ar–H, $J_o = 8.8$ Hz), 6.78 (t, 1H, Ar–H, $J_o = 7.36$ Hz), 6.87 (d, 1H, Ar–H, $J_o = 7.96$ Hz), 7.07 (t, 1H, Ar–H, $J_o = 7.84$ Hz), 7.21 (d, 1H, Ar–H, $J_o = 7.42$ Hz), 7.53 (d, 2H, Ar–H, $J_o = 8.7$ Hz), 9.06 (s, 1H, –OH) and 9.94 ppm (s, 1H, –NH, pyridazinone). Anal. calcd. for $C_{17}H_{17}N_3O_2$: C: 69.14, H: 5.8, N: 14.23%; found; C: 68.97, H: 5.53; N: 13.89%.

6-(4-(3-Methoxy-4-hydroxybenzylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one (IIId). Yield: 56.04%; m.p. 195–197°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 3402 (OH), 3207 (NH), 3060 (CH, aromatic), 2921 (CH, aliphatic), 1646 (C=O, pyridazinone), 1599 (C=C, aromatic); ^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 2.53 (t, 2H, 4-CH_2, $J = 7.42$ Hz), 2.92 (t, 2H, 5-CH_2, $J = 7.44$ Hz), 3.86 (s, 3H, –OCH_3), 4.27 (d, 2H, NH–CH_2, $J = 5.08$ Hz), 4.75 (t, 1H, NH–CH_2, $J = 5.58$ Hz), 6.62 (d, 2H, Ar–H, $J_o = 7.02$ Hz), 6.80 (m, 3H, Ar–H), 7.31 (s, 1H, –OH), 7.56 (dd, 2H, Ar–H, $J_o = 6.96$ Hz, $J_m = 1.88$ Hz) and 9.27 ppm (s, 1H, –NH, pyridazinone). Anal. calcd. for $C_{17}H_{19}N_3O_3$: C: 65.16, H: 6.11, N: 13.41%; found; C: 64.84, H: 5.76; N: 12.98%.

6-(4-(4-Fluorobenzylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one (IIIe). Yield: 47.36%; m.p. 198–200°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 3361 (NH), 3091 (CH, aromatic), 2925 (CH, aliphatic), 1654 (C=O, pyridazinone), 1609 (C=C, aromatic); ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.58 (t, 2H, 4-CH_2, $J = 8.12$ Hz), 2.91 (t, 2H, 5-CH_2, $J = 8.12$ Hz), 4.34 (s, 3H, NH–CH_2), 6.62 (dd, 2H, Ar–H, $J_o = 6.9$ Hz, $J_m = 1.8$ Hz), 7.03 (m, 2H, Ar–H), 7.32 (m, 2H, Ar–H), 7.56 (dd, 2H, Ar–H, $J_o = 6.9$ Hz, $J_m = 1.9$ Hz) and 8.36 ppm (s, 1H, –NH, pyridazinone). Anal. calcd. for $C_{17}H_{16}N_3OF$: C: 68.67, H: 5.42, N: 14.13%; found; C: 68.54, H: 5.37; N: 14.10%.

6-(4-(Pyridin-3-ylmethylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one (IIIf). Yield: 42.07%; m.p. 203–204°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 3297 (NH), 3033 (CH, aromatic), 2916 (CH, aliphatic), 1658 (C=O, pyridazinone), 1605 (C=C, aromatic); ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.57 (t, 2H, 4-CH_2, $J = 7.46$ Hz), 2.92 (t, 2H, 5-CH_2, $J = 7.41$ Hz), 4.42 (m, 3H, NH–CH_2), 6.64 (dd, 2H, Ar–H, $J_o = 6.8$ Hz, $J_m = 2.0$ Hz,), 7.57 (dd, 2H, Ar–H, $J_o = 6.8$ Hz, $J_m = 1.9$ Hz), 7.67 (d, 1H, pyridine, $J_o = 7.8$ Hz), 8.34 (s, 1H, pyridine), 8.55 (m, 1H, pyridine, CH–N), 8.63 ppm (d, 1H, pyridine, CH–N, $J_m = 1.8$ Hz). Anal. calcd. for $C_{16}H_{16}N_4O$: C: 68.55, H: 5.75, N: 19.99%; found; C: 68.24, H: 5.58; N: 19.77%.

6-(4-(Pyridin-4-ylmethylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one (IIIg). Yield: 39.6%; m.p. 205–206°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 3205 (NH), 3056 (CH, aromatic), 2917 (CH, aliphatic), 1670 (C=O, pyridazinone), 1598 (C=C, aromatic); ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 2.56 (t, 2H, 4-CH_2, $J = 7.54$ Hz), 2.91 (t, 2H, 5-CH_2, $J = 7.52$ Hz), 4.43 (m, 3H, NH–CH_2), 6.58 (dd, 2H, Ar–H, $J_o = 6.9$ Hz, $J_m = 1.9$ Hz), 7.28 (s, 1H, pyridine), 7.56 (dd, 2H, Ar–H, $J_o = 6.8$ Hz, $J_m = 2.04$ Hz), 8.37 (s, 1H, pyridine) and 8.56 ppm (s, 2H, pyridine, CH–N–CH). Anal. calcd. for $C_{16}H_{16}N_4O$: C: 68.55, H: 5.75, N: 19.99%; found; C: 67.91, H: 5.60; N: 19.84%.

6-(4-(1*H*-Indol-3-ylmethylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one (IIIh). Yield: 61.79%; m.p. 204–205°C. Spectroscopic analysis: IR (KBr) υ_{max}/cm^{-1}: 3224 (NH), 3059 (CH, aromatic), 2926 (CH, aliphatic), 1665 (C=O, pyridazinone), 1609 (C=C, aromatic); ^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): δ 2.49 (t, 2H, 4-CH_2 $J = 7.54$ Hz), 2.89 (t, 2H, 5-CH_2 $J = 7.5$ Hz), 4.48 (d, 2H, NH–CH_2, $J = 4.92$ Hz), 5.09 (t, 1H, NH–CH_2, $J = 5.01$ Hz), 6.68 (d, 2H, Ar–H, $J_o = 8.8$ Hz), 7.05 (t, 1H, indole, $J_o = 7.92$ Hz), 7.14 (t, 1H, indole, $J_o = 7.16$ Hz), 7.21 (s, 1H, indole, $J_m = 2.28$ Hz), 7.41 (d, 1H, indole, $J_o = 8.08$ Hz), 7.56 (d, 2H,

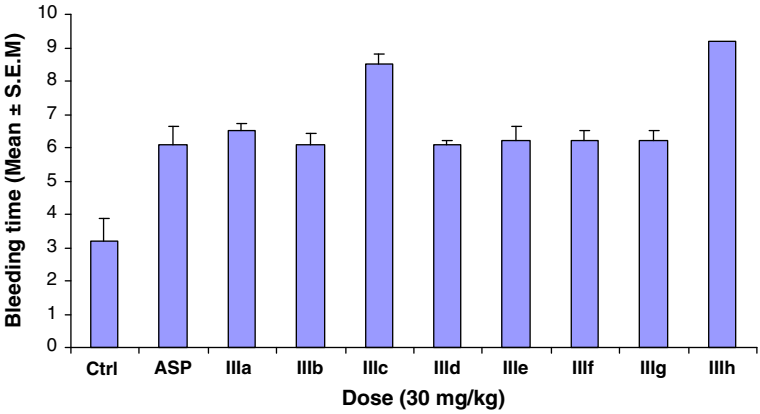


Fig. 2 Effect of compounds **IIIa–h (RB-341-348)** (30 mg/kg., p.o.) on bleeding time in mice. Ctrl = control ($n = 5$); ASP = aspirin 30 mg/kg ($n = 5$). [a]$P < 0.05$ vs. control

Ar–H, $J_o = 8.76$ Hz), 7.62 (d, 1H, indole, –CH–NH, $J_o = 7.76$ Hz), 10.03 (s, 1H, –NH, pyridazinone), 10.32 (s, 1H, NH, indole). Anal. calcd. for $C_{19}H_{18}N_4O$: C: 71.68, H: 5.70, N: 17.6%; found; C: 71.43, H: 5.47; N: 17.4%.

Biological activity

Antiplatelet activity was determined by using the tail transaction bleeding test as reported (Wang *et al*., 2004; Takao *et al*., 1998). Bleeding time of male mice (Laca strain) weighing 20–24 g was determined by administering compounds **IIIa–h** and aspirin (standard drug) suspended in carboxy methyl cellulose orally at various doses 7.5, 15, 30, 60 mg/kg or vehicle control. After 1 hr, 3 mm of the tails of the mice under light diethylether anesthesia were transected and blood was dripped on filter paper. The duration of bleeding was recorded. Bar diagrams (Fig. 2) were prepared by using MS Excel to represent the effect of the newly synthesized 6-aminophenylpyridazinone derivatives **IIIa–h** (7.5–60 mg/kg, p.o.) on bleeding time in mice in comparison to vehicle control and standard drug.

The bleeding time, observed from the mice treated with various pyridazinones at different doses, was compared with standard drug aspirin and with vehicle control. The results obtained have been summarized in Table 1.

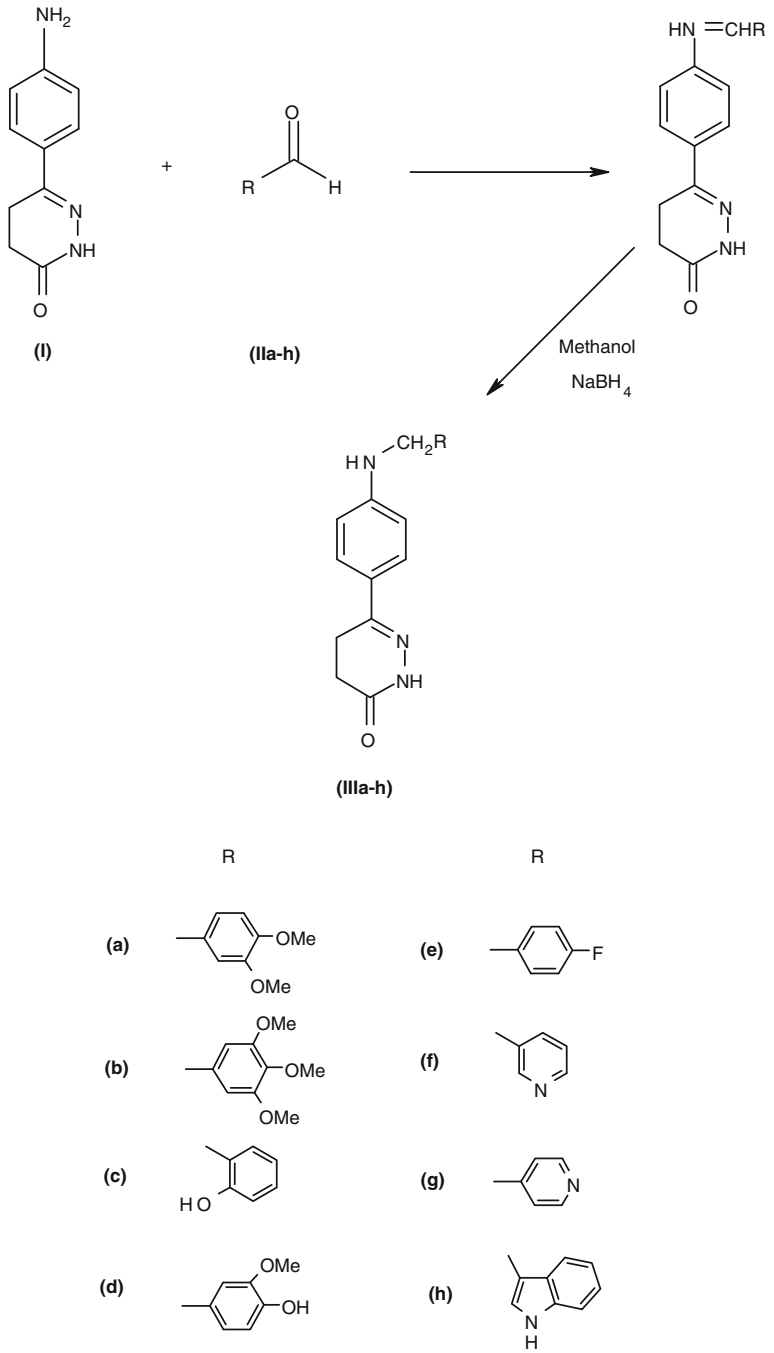
Results and discussion

The compounds **IIIa–h** were synthesized according to Scheme 1. Condensation of 6-(4-aminophenyl)-4,5-dihydropyridazin-3(2*H*)-one (**I**) with various substituted aldehydes **IIa–h** in methanol at room temperature gave corresponding Schiff bases, which on subsequent reduction with sodium borohydride resulted into the formation of desired pyridazinones **IIIa–h**. The structures of these compounds were elucidated using various spectral and elemental analyses.

Table 1 Platelet aggregation inhibitory activity of compounds **IIIa–h**

Sr. No	Compound No. (code)	Concentration (mg/kg body weight)	Bleeding time mean ± SEM
1	**IIIa (RB-341)**	7.5	4.2 ± 0.314
		15	5.6 ± 0.184
		30	6.5 ± 0.542
		60	7.1 ± 0.221
2	**IIIb (RB-342)**	7.5	4.4 ± 0.342
		15	5.2 ± 0.326
		30	6.1 ± 0.227
		60	6.5 ± 0.156
3	**IIIc (RB-343)**	7.5	4.4 ± 0.512
		15	7.4 ± 0.413
		30	8.5 ± 0.341
		60	9.2 ± 0.616
4	**IIId (RB-344)**	7.5	4.1 ± 0.318
		15	5.2 ± 0.282
		30	6.1 ± 0.303
		60	7.3 ± 0.347
5	**IIIe (RB-347)**	7.5	3.8 ± 0.262
		15	4.9 ± 0.323
		30	6.2 ± 0.113
		60	7.0 ± 0.532
6	**IIIf (RB-345)**	7.5	4.1 ± 0.286
		15	5.5 ± 0.321
		30	6.2 ± 0.427
		60	6.6 ± 0.338
7	**IIIg (RB-346)**	7.5	4.3 ± 0.411
		15	5.3 ± 0.306
		30	6.2 ± 0.317
		60	7.0 ± 0.328
8	**IIIh (RB-348)**	7.5	5.5 ± 0.265
		15	8.3 ± 0.412
		30	9.2 ± 0.315
		60	9.7 ± 0.614
	Aspirin	7.5	4.2 ± 0.324
		15	5.3 ± 0.511
		30	6.1 ± 0.674
		60	6.6 ± 0.210
	Control	–	3.2 ± 0.218

The benzylamino substituted pyridazinones **IIIa–e** exhibited characteristic amide C=O stretching bands of pyridazinone ring system at $\sim$1660 cm^{-1}. In the NMR spectra of these compounds, pyridazinone C_4 and C_5 protons resonated as triplets



Scheme 1 General synthesis of pyridazinone derivatives **IIIa–h**

at $\sim\delta$ 2.58 and 2.94 ppm, respectively. Protons of the NHCH_2 were found as a doublet at $\sim\delta$ 4.3 ppm and N*H*CH_2 gave a triplet at varied positions. 2-Unsubstituted N–*H* signal was observed at $\sim\delta$ 9.0 ppm for all the compounds. While methoxy protons of **IIIa**, **IIIb**, and **IIId** were seen at $\sim\delta$ 3.80, the hydroxy proton of **IIIc** was found at δ 9.06 and those of **IIId** at 7.31 ppm. In case of pyridyl substituted derivatives **IIIf** and **IIIg**, the infrared bands appeared in the region $\sim$3300 cm^{-1} due to N-H stretching vibrations along with the characteristic amide C=O stretching band of pyridazinone ring system near 1660 cm^{-1}. Pyridyl protons attached to nitrogen appeared at downfield positions compared with the other aromatic protons.

The 6-(4-(1*H*-indol-3-yl)methylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one (**IIIh**) exhibited the infrared band at 3224 cm^{-1} due to N-H stretching vibrations. Characteristic amide C=O stretching band of pyridazinone ring system was again observed at 1665 cm^{-1}. Pyridazinone C_4 and C_5 protons resonated as triplets at δ 2.51 and 2.91 ppm, respectively. Protons of the NHCH_2 were found as a doublet at 4.48 ppm and N*H*CH_2 gave a triplet at 5.09 ppm. Signals for protons of indole ring were found in the aromatic region. Singlets for the -N*H* of pyridazinone and indole appeared at δ 10.03 and 10.32 ppm, respectively.

All of the newly synthesized pyridazinone derivatives exhibited significant platelet aggregation inhibitory activity. The compounds (6-(4-(2-hydroxybenzylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one **IIIc** and 6-(4-(1*H*-indol-3-ylmethylamino)phenyl)-4,5-dihydropyridazin-3(2*H*)-one **IIIh** were found to be more than twice as potent as standard drug aspirin as shown in Fig. 2. They produced the antiplatelet effect better than aspirin (30 mg/kg) at only half of the dose, i.e., 15 mg/kg.

These results show that the introduction of aryl-amino substituent at *para* position of 6-phenylpyridazinone results in significant platelet aggregation inhibitory activity. Pharmacological evaluation of these compounds allows us to describe the antiplatelet activity of a range of 4-substituted-amino phenylpyridazinones.

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