Eur. J. Med. Chem. (1990) 25, 137–142

Original paper

Synthesis of new 2-, 3-, and 4-substituted azidoquinolines**: inhibitors of human blood platelet aggregation *in vitro*

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(Received January 6, 1989; accepted June 5, 1989)

Summary – A series of 2-, 3- and 4-substituted azidoquinoline derivatives were synthesized and tested for their ability to inhibit human platelet aggregation *in vitro* triggered by adenosine diphosphate (15 μM), collagen (5 μg/ml), platelet activating factor (10 μM), or the stable prostaglandin H_2 mimetic, U46619 (4 μM). The most active compounds (IC_{50} 2.5–68.3 μM) were the geminal 3,3-diazides (**4f** and **4g**) and the 4-azido-3-nitroquinolines (**6f** and **6g**).

Résumé – **Etude de l'action antiagrégante plaquettaire de dérivés substitués en 2-, 3- et 4- d'azidoquinoléines nouvelles.** *Cette note décrit la préparation d'une série de dérivés substitués en 2, 3, et 4 d'azidoquinoléines. L'action inhibitrice de l'agrégation plaquettaire induite par ADP, collagène, PAF et U46619 a été la plus forte pour les composés 3,3-diazido quinoléines (**4f** et **4g**) et 4-azido-3-nitroquinoléines (**6f** et **6g**).*

human blood platelets / platelet aggregation / platelet activating factor (PAF) / thromboxane / azidoquinolines

Introduction

A major physiological function of blood platelets is their involvement in the coagulation process [1, 2]. On the other hand a direct correlation exists between the function of blood platelets and the development of vascular diseases in humans such as myocardial infarction, stroke, and transient ischemic attacks [3–6]. Moreover, enhanced platelet interaction with the arterial wall, platelet adhesion and aggregation as well as release of mitogens are discussed as early events in the process of atherosclerosis.

Human blood platelets can be stimulated by pathways involving i) adenosine diphosphate (ADP), ii) arachidonic acid (including the stimulation with collagen or thrombin), or iii) the platelet-activating factor (PAF) [7]. Since thromboxane A_2 (TXA_2), unlike lipoxygenase metabolites such as hydroxyeicosatetraenoic acids, is the most potent platelet aggregating agent [8, 9], much effort has been directed towards the preparation of thromboxane synthetase inhibitors or thromboxane receptor antagonists [10–15]. Many reports have been produced concerning the platelet inhibitory effect of various heterocyclic systems *in vivo* and *in vitro* [16–23]. However, quinolines are poorly represented among the platelet aggregation inhibitory compounds. We thought that substitution of quinoline systems by highly azido groups could result in a more potent biological behaviour.

In the present study, we focused on the preparation of various substituted azidoquinolines which were evaluated *in vitro* against aggregation induced by ADP, collagen, PAF, and respectively, by U46619, a non physiological prostaglandin H_2 (PGH_2) mimetic.

Chemistry

The synthesis of 2-azido-4-chloroquinolines **2** (Table I), 3-azido-quinolines-2,4-diones **4** (Table II), and 4-azido-2-quinolines **6** (Table III) was performed by reacting the corresponding chloroquinoline derivatives **(1, 3, 5)** with sodium azide in dimethylformamide (DMF). Nucleophilic substitution of the chlorine in compound **1** takes place in a regioselective reaction yielding only the 2-azido isomers **2** [24–28]. Chloroquinolines **(1, 3, 5)** were in turn prepared by treating the appropriate 4-hydroxyquinolones **(1, 3, 5)** with phosphoryl chloride ($POCl_3$) or sulfuryl chloride (SO_2Cl_2) in dioxane as shown in Scheme 1. In the case of **2b** (R = phenyl, Table I) and **5d–h** (R = phenyl- or nitro-

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**Organic Azides in Heterocyclic Synthesis, Part 10.

Table I. 2,4-Dichloroquinolines **1** and 2-azido-4-chloro quinolines **2.**

Compd	R	React. temp. (°C)	Yield	mp (°C) solvent	Formula[a] mol weight	IR (KBr)
1a	H	105		61[b]		
1b	Phenyl	105		90[c]		
2a	H	40	78%	72	$C_9H_5ClN_4$	2100s, 1610w, 1570m
				EtOH	204.6	
2b	Phenyl	40		138[c]		

[a]Analyses: C, H, N. [b]Prepared according to [40, 41]. [c]Prepared according to [24].

group, Table III), the reaction temperature must be kept below 60°C to avoid ring closure and decomposition reactions to indoles or furazanes [29, 30].

Results and Discussion

Platelet rich plasma (PRP) incubated with azidoquinolines (0.320 μM−1 mM) over a 6 min period produced neither spontaneous platelet aggregation nor differences in lactate dehydrogenase activity to controls (data not shown).

The concentrations of the compounds required to inhibit platelet aggregation by 50% (IC_{50}) were calculated by plotting percent inhibition *versus* the log molar concentration of the compound. Only the IC_{50} values for the biologically most potent compounds (**4f, g** and **6f, g**) to inhibit platelet aggregation were summarized in Table IV. All other compounds tested were found to have IC_{50} values more than 500 μM after stimulation of blood platelets with ADP (15 μM), collagen (5 μg/ml PRP), and PAF (10 μM).

Table IV displays that platelet aggregation induced with ADP or PAF result in similar IC_{50} values for compound **4f, g** and **6f, g**. The ADP-induced stimulation of platelets in the presence of azidoquinolines **4f, g** and **6f, g** (40–200 μM) resulted in an inhibition of the second wave of aggregation with a concomitant low inhibition of the first wave of aggregation; lower dose of these azidoquinolines (> 40 μM) resulted only in an inhibition of the second burst of aggregation.

The PAF stimulated pathway which induces increased production of inositol triphosphate, diacylglycerol and Ca^{2+} influx is inhibited in a dose-related manner. Platelet inhibitory activity of azidoquinolines (0.32−8.0 μM) was overcome by raising PAF concentrations from 0.032 to 20 μM.

U46619 (15(S)-hydroxy-11α,9α-(epoxymethano) prosta-5Z,13E-dienoic acid) induces platelet aggregation by interaction at a thromboxane/endoperoxide membrane receptor leading to the suppression of adenylate cyclase [31]. IC_{50} values for U46619 triggered platelet aggregations (final concentrations 4 μM) are ranging from 47.6 to 67.5 μM for **4f, g** and **6f, g**. These experiments were performed after blocking cyclo-oxygenase activity with aspirin in PRP for 15 min at 37°C to exclude formation of cyclic endoperoxides and TXA_2.

In contrast to U46619-induced platelet aggregation, collagen triggered platelet aggregation increased platelet thromboxane production by mobilizing the arachidonic acid cascade and decrease platelet cyclic AMP levels in parallel. According to Table IV, IC_{50} values for collagen stimulated aggregation (5 μg collagen/ml PRP) ranged between 45.2 ± 4.6 and 68.3 ± 5.9 μM for compounds **4f, g** and **6f, g**, respectively. The concomitant formation of malondialdehyde (MDA, a cyclo-oxygenase breakdown product in about equimolar concentrations to TXA_2) was measured after collagen-induced stimulation (38 μg/ml PRP) in the presence of azidoquinolines **4f, g** (Fig. 1), observing that the increase of concentration of azidoquinolines **4f** (line A), and **4g** (line B), determined a concomitant decrease in nmol MDA/1×10^9 platelets. Similar results were obtained for compounds **6f** and **6g** (data not shown).

To follow cyclo-oxygenase activity of human blood platelets in the presence of azidoquinolines **4f, g** and **6f, g**, lysed platelets were incubated with sodium arachidonate (62 μM final concentration) at 37°C. Figure 2 displays the time course of the inhibitory effect of azidoquinolines on MDA production.

Figure 3 displays the [^{14}C]-5-hydroxytryptamine release [32] during collagen triggered aggregation (5 μg/ml PRP) in the presence of azidoquinolines **4f, g** and **6f, g** at different concentrations (1.6−200 μM).

On the basis of the results obtained, some structural features appear of importance for the platelet aggregation inhibitory activity of the azidoquinoline derivatives tested. In particular, the most potent azidoquinolines are characterized by the presence of a geminal azido group (3,3-diazidoquinoline-2,4-diones, **4f** and **4g**) or a nitro group (4-azido-3-nitro-2-quinolones, **6f** and **6g**) at the 3-position. The weak inhibitory effect of these compounds towards collagen and U46619-induced platelet aggregation suggests that they do not act on the arachidonic acid pathway and on the TXA_2/PGH_2 receptor of human blood platelets.

Experimental protocols

Chemistry

Melting points were determined in open capillaries on a Gallenkamp Melting point Apparatus MFB-595 and are uncorrected. The ^{1}H NMR were obtained on a Varian EM 360 (60 MHz, TMS as an internal standard, DMSO−d_6 as solvent). The IR were recorded on a Perkin Elmer 298 using KBr-pellets. Analytical TLC was performed on Merck TLC aluminium sheets silica gel 60 F_{254}. Elemental analyses (C, H, N) were performed on a C, H, N-automat Carlo Erba 1106 and the determined values are within 0.4% of the theoretical.

General method for the synthesis of 2.4-dichloro-quinolines ***1*** *and 4-chloro-2 (1H)-quinolinones* ***5***

A solution of the corresponding 4-hydroxy-2(1*H*)-quinolone [33] (10 mmol) in 30 ml of $POCl_3$ was refluxed for 3 h. The excess of $POCl_3$

Table II. 3-Chloroquinoline-2,4 (1*H*, 3*H*)-diones **3a–g, k** and **3h–j*** and 3-azidoquinoline-2,4 (1*H*, 3*H*)-diones **4a–g** and **4h–j***

Compd.	R	R′	X	Temp. (°C) yield	mp (°C) solvent	Formula[a] mol. weight	IR(KBr) (cm^{-1}) ^1H NMR (δ/ppm)
3a	Phenyl	6-chloro	NH	50	193[b]		
3b	Phenyl	H	NH	50	181[b]		
3c	Phenyl	7-methyl	NH	50	218	$C_{16}H_{12}ClNO_2$	3100–2920m, 1710s, 1675s, 1615m
				89%	EtOH	285.7	
3d	Ethyl	H	N-methyl	50	74	$C_{12}H_{12}ClNO_2$	3080–2940m, 1705s, 1670s, 1610w
				68%	Hexane	237.7	
3e	Ethyl	7-methyl	NH	50	139	$C_{12}H_{12}ClNO_2$	3240–2940m, 1710s, 1680s, 1615w
				97%	EtOH	237.7	1.0 (t, J = 7 Hz, Me), 2.3 (s, 7–Me), 2.5 (q, J = 7 Hz, CH_2), 6.8–7.1 (m, 2 ArH), 7.8 (dd, H at C–5), 10.5 (s, b, NH)
3f	Chloro	H	NH	50	174[c]		
3g	Chloro	H	N-*n*-butyl	50	76	$C_{13}H_{13}Cl_2NO_2$	2980m, 1710s, 1665s, 1595s
				80%	MeOH	286.2	
3h	*n*-Butyl	–	–	50	155	$C_{16}H_{18}ClNO_2$	3060–2850m, 1700s, 1675s, 1605m
				81%	EtOH	291.8	
3i	Phenyl	–	–	50	156[d]		
3j	Benzyl	–	–	50	143[d]		
3k	Nitro	H	N-methyl	50	234[e]		
4a	Phenyl	6-chloro	NH	50	113[d]		
4b	Phenyl	H	NH	50	166[d]		
4c	Phenyl	7-methyl	NH	10	180	$C_{16}H_{12}N_4O_2$	2110s, 1710s, 1680s, 1615m
				96%	EtOH	292.3	2.3 (s, 6–Me), 6.8–7.5 (m, 7 aromat. H), 7.8 (d, J = 2 Hz, H at C–5)
4d	Ethyl	H	N-methyl	10	51	$C_{12}H_{12}N_4O_2$	2100s, 1705s, 1670m, 1610m
				78%	MeOH	244.3	1,2 (t, Me, J = 7 Hz), 2.4 (q, CH_2, J = 7 Hz), 3.7 (s, N–Me), 7.0–7.5 (m, 3 arom. H), 7.9 (dd, J = 2+7 Hz, H at C–5)
4e	Ethyl	7-methyl	NH	10	121	$C_{12}H_{12}N_4O_2$	2110s, 1700s, 1670sh, 1610m
				75%	EtOH	244.3	1.2 (t, Me, J = 7 Hz), 2.3 (s, 7–Me), 2.4 (q, CH_2, J = 7 Hz), 7.0–7.5 (m, 3 arom. H), 7.9 (dd, J = 2+7 Hz, H at C–5)
4f	Azido	H	NH	10	115[d]		
4g	Azido	H	N-*n*-butyl	10	72	$C_{13}H_{13}N_7O_2$	2990–2930m, 2100s, 2115s, 1705s, 1690s, 1600s
				80%	EtOH	299.3	0.9 (t, Me), 1.1–1.8 (m, 2 CH_2), 4.2 (q, N–CH_2), 7.1–7.7 (m, 3 arom. H), 8.0 (dd, H at C–5)
4h	*n*-Butyl	–	–	10	86	$C_{16}H_{18}N_4O_2$	2980m, 2110s, 1705s, 1665s, 1590m
				76%	EtOH	298.3	
4i	Phenyl	–	–	10	93[d]		
4j	Benzyl	–	–	10	148[d]		

[a]Analyses: C, H, N. [b]Prepared according to [25]. [c]Prepared according to [26]. [d]Prepared according to [26–28]. [e]Prepared according to [42].
*Compds. **3h–j, 4h–j** are considered as 1,8-trimethylene-bridged quinolines, actually belong to the 1*H*, 5*H*, benzo[i, j]quinolizine system.

Table III. 4-Chloroquinoline-2 (1*H*)-ones **(5b–i)**, 4-azidoquinoline-2 (1*H*)-ones **(6b–i)**, 4-chlorocoumarin **5a** and 4-azidocoumarin **6a**.

Compd.	R	R′	X	Temp. (°C)	mp (°C) (recryst.)
5a	H	H	O	90	94[b]
5b	H	H	N-methyl	90	115[c]
5c	Chloro	H	N-methyl	90	127[d]
5d	Phenyl	H	N-phenyl	90	166[e]
5e	Phenyl	H	N-methyl	90	106[e]
5f	Nitro	H	N-phenyl	90	81[d]
5g*	Nitro	–	–	90	148[d]
5h	Ethyl	H	N-methyl	90	131[d]
5i	Chloro	H	N-phenyl	90	181[d]
6a	H	H	O	90	118[d]
6b	H	H	N-methyl	90	130[d]
6c	Chloro	H	N-methyl	60	164[d]
6d	Phenyl	H	N-phenyl	60	127[f]
6e	Phenyl	H	N-methyl	60	92[f]
6f	Nitro	H	N-phenyl	50	90[d]
6g*	Nitro	–	–	50	85[a] (MeOH)
6h	Ethyl	H	N-methyl	95	82[d]
6i	Chloro	H	N-phenyl	70	80[d]

[a]Analyses: C, H, N. [b]Prepared according [43]. [c]Prepared according [44]. [d]Prepared according [29]. [e]Prepared according to [45]. [f]Prepared according to [30].
*Compds. **5g, 6g** considered as 1,8-trimethylene-bridged quinolines, actually belong to the 1*H*, 5*H*, benzo[i, j]quinolizine system.

was removed *in vacuo* and the residue digested with ice water (100 ml) and neutralized with 2 N sodium hydroxide. After filtration the crude product was recrystallized from the appropriate solvent [29, 30] (Table I, III).

*General method for the synthesis of 3-chloro-quinoline-2,4(1*H*, 3*H*)-diones **3***

To a solution of the corresponding 4-hydroxy-2-quinolone [33] (10 mmol) in 30 ml of dioxane at 50°C, 3 ml of SO_2Cl_2 was added in 3 portions after a period of 10 min. The mixture was poured on crushed ice (50 g). The resulting precipitate was washed with 200 ml of water and recrystallized from the appropriate solvent (Table II).

*General method for the synthesis of 2-azido-4-chloroquinolines **2**, 3-azido-quinoline-2,4 (1*H*, 3*H*)-diones **4**, and 4-azido-2 (1*H*)-quinolinones **6***

A suspension of the corresponding chloroquinolines **1, 3** or **5,** (0.01 mol) and sodium azide (0.02 mol) in 30 ml of DMF was stirred for 3 h at the temperature given in Tables I, II or III. The reaction mixture was diluted with 100 ml of water and the resulting precipitate was collected by filtration. The crude product was washed with water and recrystallized from the appropriate solvent (Tables I–III).

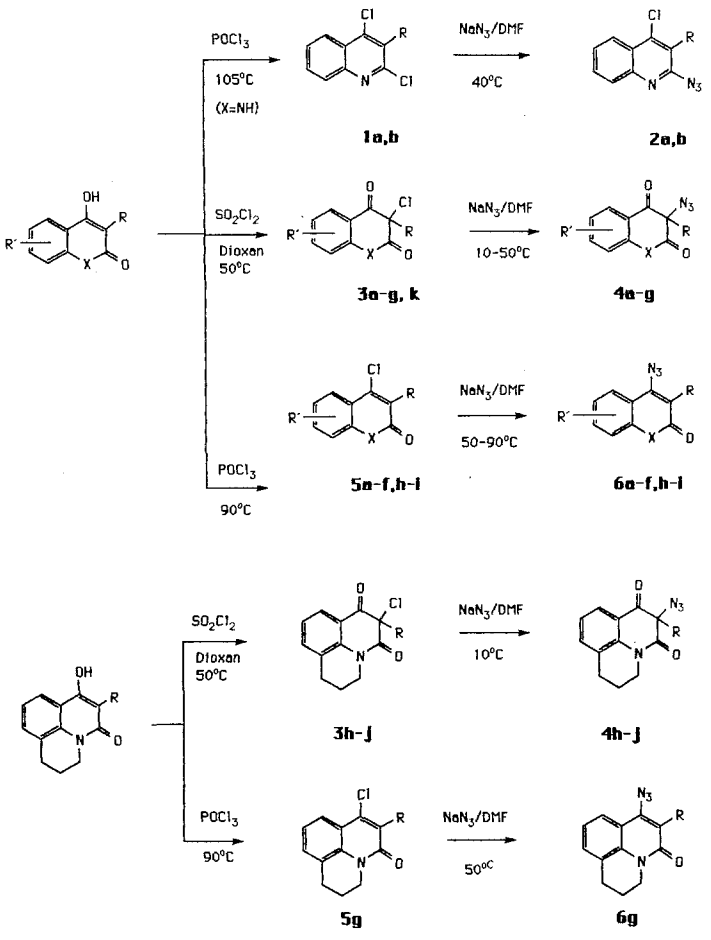
Biological evaluations

In vitro *assay for human platelet aggregation*

Blood was obtained from normal human nonsmoking volunteers (20–25 yrs) who reported to be free of medication for at least 14 d. PRP was prepared by centrifugation at 200 *g* of the citrated blood sample for 10 min and at 37°C [34–37]. Platelet poor plasma (PPP) was obtained by centrifugation at 27,000 *g* for 20 min. The platelet count was determined on a Thrombocounter-C System (Coulter electronics LTD., UK) and adjusted to 300,000 / μl with autologous PPP.

Platelet aggregation studies were performed according to Born [38] with the use of a dual-channel aggregation module-Elvi 840 (Elvi Logos, Milan, Italy) coupled with an Omniscribe recorded [34, 39]. All compounds were freshly dissolved in DMSO before use and added to 500 μl PRP in a volume of 1 μl. Plasma samples were preincubated exactly 1 min before addition of aggregating agents. DMSO was included in the control samples of PRP where appropriate. Aggregations were terminated after 6 min.

Final concentrations of trigger substances were: 5 μg collagen / ml PRP, 15 μM ADP and 10 μM PAF. ADP and PAF were dissolved in 0.25% (w / v) human serum albumin in 0.9% (w / v) phosphate buffered saline (pH 7.3), U46619 was stored at concentrations of 10 mg / ml ethanol at −20°C and diluted to a final concentration of 4 μM with 0.9% NaCl saline.



Scheme 1.

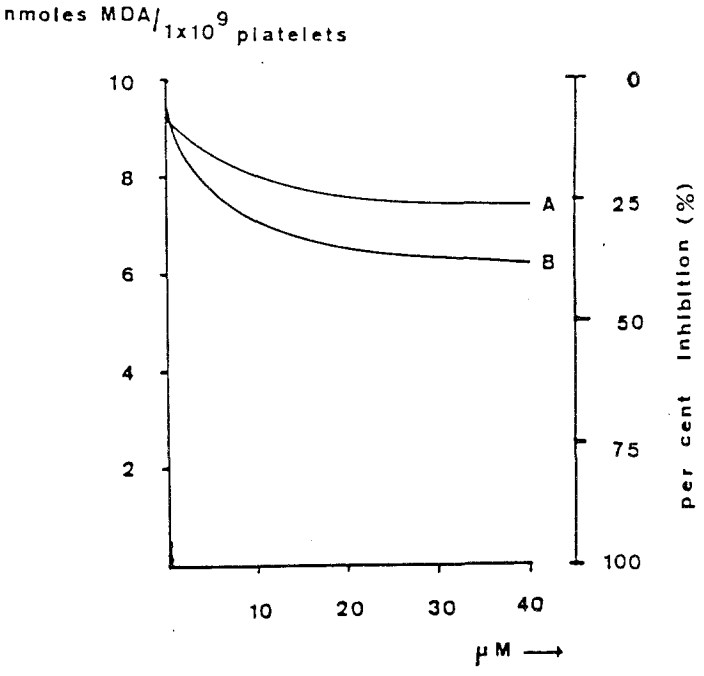


Fig. 1. Displays the inhibitory effect of azidoquinolines **4f** (A) and **4g** (B) at various concentrations (0.32–40 μM) on the formation of MDA. MDA released from platelets after stimulation of 0.5 ml PRP with collagen (38 μg / ml PRP) for 6 min at 37°C is given in nmol / 1×10^9 platelets. The percentage inhibition (%) of formation of MDA by compounds **4f** and **4g** can be deduced on the right secondary axis. Values are given as means of duplicate determinations of 3 series of experiments (maximum standard deviation ±5.6%). Measurement of MDA was performed by the thiobarbituric acid method as described [39].

Table IV. IC_{50} values (given in μM) for the biologically most potent compounds **4f, g** and **6f, g.**

Stimulat.	4f	4g	6f	6g
ADP 15 μM	2.5±0.4	2.3±0.5	4.6±1.1	5.8±0.9
PAF 10 μM	2.7±0.3	7.2±1.2	10.3±1.9	14.6±0.8
Coll 5 μg	45.2±4.6	47.7±3.9	60.5±6.8	68.3±5.9

Assay for cell lysis
Lactate dehydrogenase activity was assayed with the LDH UV Test (Boeringer Mannheim, FRG) in PRP.

Assay for determination of MDA
MDA was quantitated colorimetrically by use of the thiobarbituric acid method after termination of platelet stimulation by the addition of chloroacetic acid as described previously [39].

[^{14}C]-Serotonin secretion
Extent of secretion was estimated by measurement of the percentage release of [^{14}C]-serotonin after incubation of PRP with 5-hydroxy-(side chain-2-^{14}C)-tryptamine creatine sulphate (Amersham, UK) for 30 min and worked up as described [35, 39].

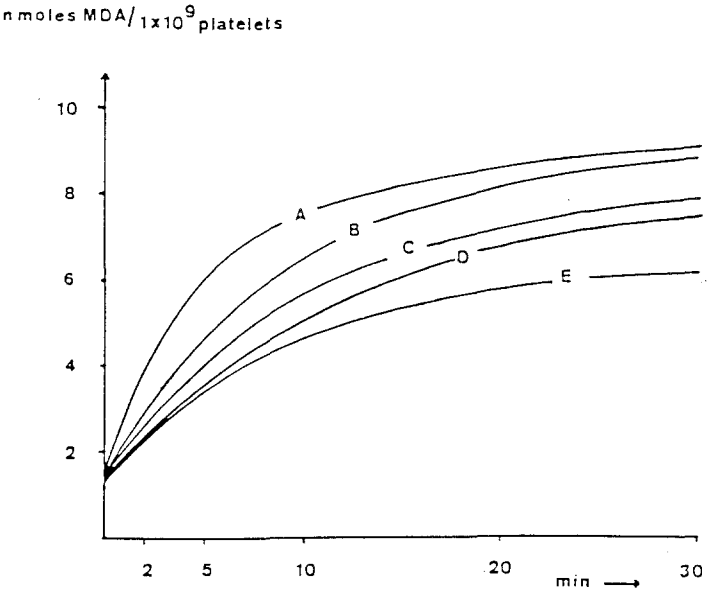


Fig. 2. Time course of formation of nmol MDA / 1×10^9 platelets after incubation with azidoquinolines (40 μM): A (control); B **(6f)**; C **(6g)**; D **(4f)**; E **(4g)**. To study cyclo-oxygenase activity, platelets were frozen several times and incubated with sodium arachidonate (62 μM) at 37°C. Measurement of MDA was performed by the thiobarbituric acid method as described [39]. Values are given as means of duplicate determinations of 3 series of experiments (maximum standard deviation ±4.7%).

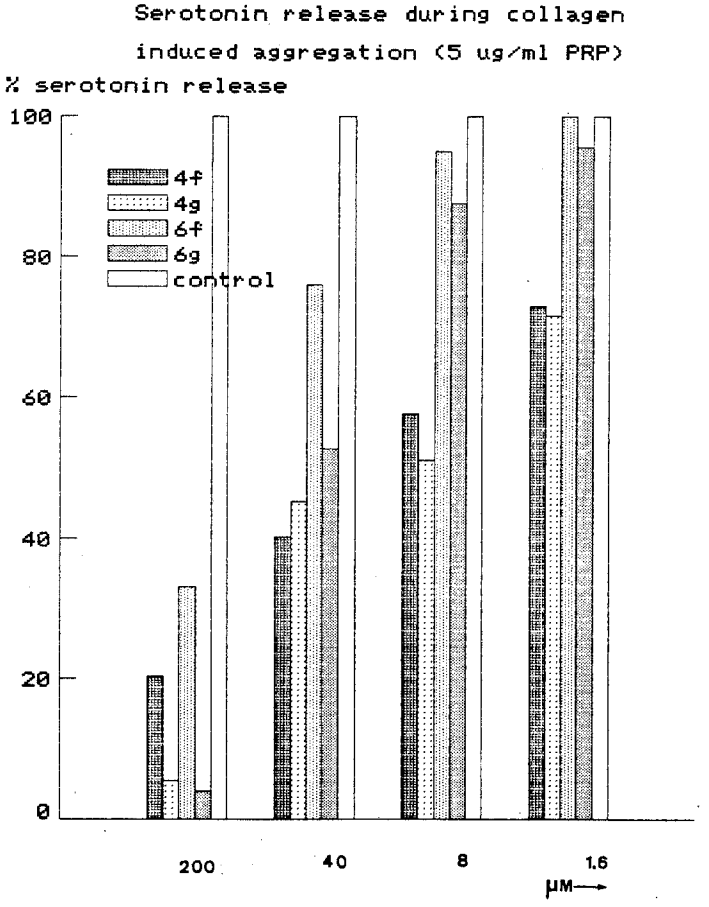


Fig. 3. Displays the serotonin release after collagen triggered (5 μg/ml PRP) platelet aggregation in the presence of azidoquinolines **4f, g** and **6f, g**, at different concentrations (1.6–200 μM). PRP was incubated with 5-hydroxy-(side chain-2-^{14}C)tryptamine creatine sulfate at least 15 min prior to aggregation and worked up as described [35, 39]. Values are given as means of duplicate determinations of 3 series of experiments (maximum standard deviation ±4.9%).

Materials

Collagen was from Hormonchemie Munich (FRG), ADP (equine muscle grade), was from Sigma Munich (FRG), PAF was from Bachem AG, Bubendorf (Switzerland), U46619 was a kind gift from Dr. J.E. Pike (Upjohn Co., MI). All other materials were from Merck (FRG) as analytical grade reagents.

Acknowledgments

This work was supported by grants from the Fonds zur Förderung der Wissenschaftlichen Forschung (grant No. S46 and 6882M) and the F. Lanyar Foundation, University of Graz.

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