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Antiplatelet Aggregation Activity of 4-phenyl-1,8-naphthyridine derivatives: Synthesis and Evaluation

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ABSTRACT

A new series of 4-phenyl-1,8-naphthyridine derivative, substituted in position 6 and 7 were prepared and tested for their inhibitory effects on platelet aggregation by ADP, the most promising agent among them was2-(4'-methoxybenzylamine)-6-amino-7-(piperidin-1-yl)-4-phenyl-1,8-naphthyridine designated as**14**. The specificity of the inhibitory effects of **14** is presented by cycloalkyl amino moiety of the agent. Moreover, platelet aggregation induced by agonists other than ADP e.g., arachidonic acid, and collagen, was inhibited completely by compound **14**. The analogues designated **12** and **13** showed a higher activity than that of **8**-**11** derivatives. Compounds **13** and **14** increased cAMP levels and significantly inhibited platelet aggregation.

INTRODUCTION

According to the World Health Organization, cardiovascular disease will be a leading cause of death in developed and developing countries by 2015. Cardiovascular and thromboembolic events are already the major cause of death in the world [1]. Hemostasis is a widely studied topic due to the pathogenic nature of thrombotic and bleeding disorders [2, 3]. The inappropriate activation of the hemostatic system contributes to the development of severe pathophysiological disorders, including the thromboembolic disorders, such as atherothrombosis and venous thromboembolism [4]. In general, antithrombotic drugs, including antiplatelet agents (e.g., clopidogrel, aspirin, tirofiban), are the primary treatment option for this disease. However, they can lead to serious adverse reactions in some patients, including bleeding, neutropenia, thrombocytopenia and drug resistance [5-7].

Several 1,8-naphthyridines derivative was prepared and demonstrate a good antiplatelet activity [8, 9], in our laboratories. We also prepared and test the antiplatelet activity of some 1,8-naphthyridnes substituted with different types of cycloamines groups [10, 11] .

In this paper, we reported the synthesis of 4-phenyl-1,8-naphthyridine derivatives carrying p-methoxybenzylamine in position 2 and piperidyl, methoxy or ethoxy groups in position 7 and tested *in vitro* for their inhibitory activity on human platelet aggregation.

MATERIALS AND METHODS

Biochemical Evaluation

Human blood samples were drawn from antecubital vein and anticoagulated with 3.8% sodium citrate (9:1 v/c).

Platelet rich plasma (PRP) was prepared in accordance with the method described by Miceli et al., [12], and the platelet count was adjusted to about 280.000cell/µl.

Platelet aggregation was measured turbidimetrically in accordance with the method described by Born and Cross[13], using an aggregometer (Daichii model PA-3220). ADP (3.0 µM), arachidonate sodium (0.7mM) and collagen (2.0µg/mL) were used as aggregating agent. Arachidonate

sodium, ADP, Papaverine, ASA, Ibuprofen and Indomethacin (Sigma chemicals) and collagen from bovine tendon, (Menarini Diagnostic) were used in this study.

The products at different concentrations, ranging from 10 to 0.1µM, were added to PRP and incubated for 10min. at 37°C before addition of the aggregating agent.

To express the aggregation of platelet, the transmittance of PRP itself was set at 100%. The aggregation rate was also evaluated from the slope of the experimental plot of aggregation as a function of time. The tested substances were dissolved in DMSO and were diluted with H_2O to the experimental concentration.

The DMSO solution of compounds **12**, **13** and **14** were diluted with H_2O and few drops of 0.1M HCl. The pH was then set to 7.4 with $NaHCO_3$. Compounds **4**, **5** and **7** were insoluble under their experimental conditions.

The final DMSO concentration was 0.5% v/v. Control aggregation was studied in the presence of DMSO at the same concentration used for treated platelet. Both adenylate cyclase and intracellular cAMP levels were measured by a radioimmunoassay technique using commercially available test (Rianen cAMP [^{125}I] radioimmunoassay kit, P-ATP, NEN-Du Pont).

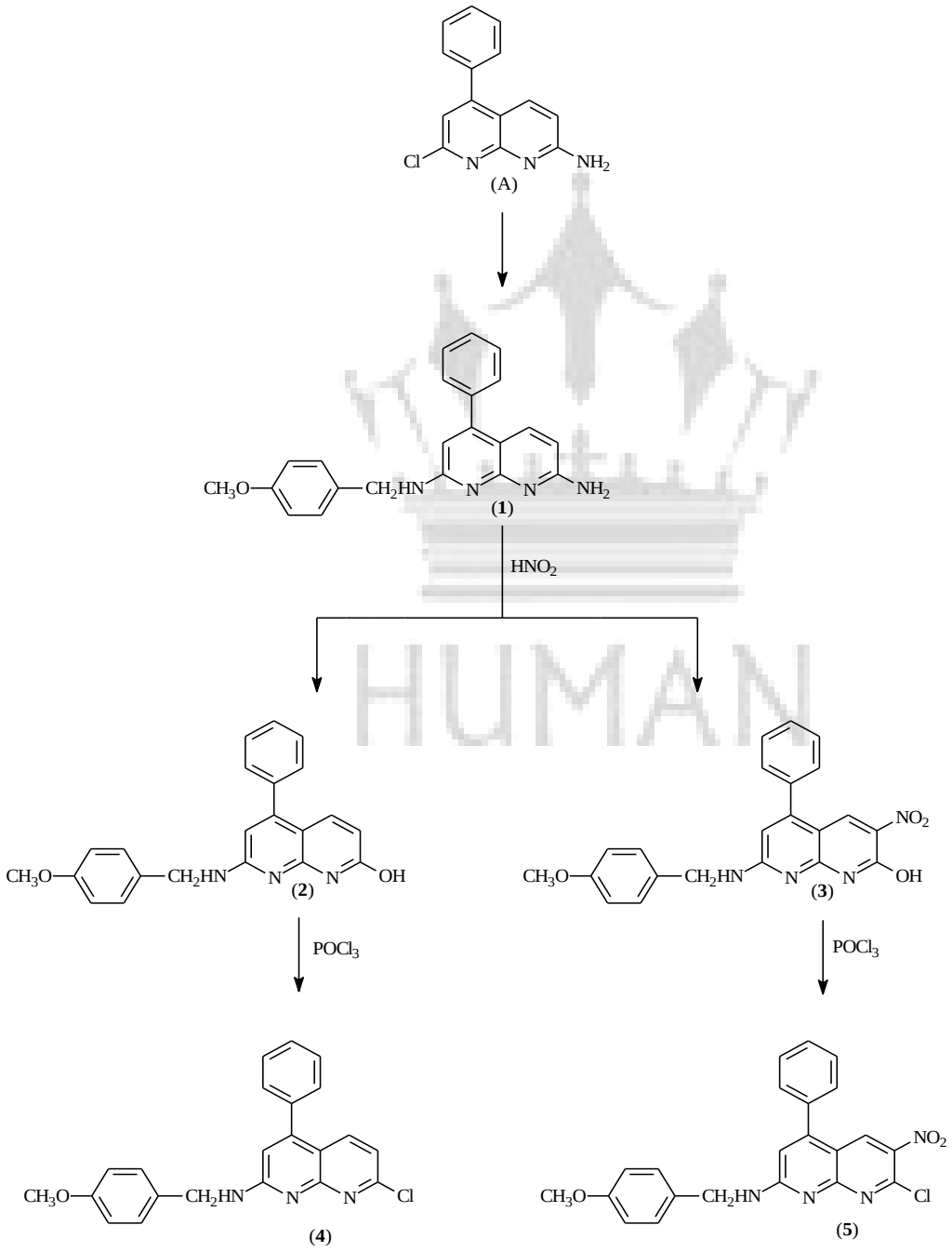
Adenylate cyclase was measured in platelet plasma membranes, prepared in accordance with the method described by Kahn and Sinha[14], while cAMP levels were measured in intact platelets. 200ml of PRP was centrifuged at 200g for 30min. the supernatant was gently decanted and the soft pellet containing intact platelet was suspended in 12ml of Tyrode's buffer (pH 7.5).

The final number of platelets was adjusted to ca. 10^8/mL for each sample, 300µL aliquots of this suspension were at 30°C with the phosphodiesterase inhibitor 3-isobutyl-1-methylxantine (0.5 µM) in absence and the presence of 1mM EGTA. 10min. later, the compounds to be tested were added were required to a final volume of 500µl. Incubation was stopped after 10min. by the addition of 1ml of 3% perchloric acid. Samples were sonicated and centrifuged at 30000g for 15min. The supernatant was neutralized with an excess (about 100mg) of $CaCO_3$). The samples were then centrifuged twice at 30000g for 15 min to remove the excess of $CaCO_3$ and the 100µl aliquots of the supernatant were assayed for their cAMP. Cyclic AMP was measured in triplicate determination using the above mentioned RIA kit.

Chemistry

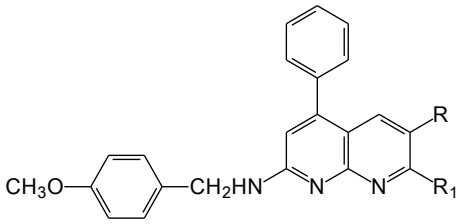
The 7-amino-2-chloro-4-phenyl-1,8-naphthyridine (**A**) [15]was treated with 4-methoxybenzylamine, in accordance with the method described by Park et al., [16], to obtain 7-amino-2-(4'-methoxybenzylamine)-4-phenyl-1,8-naphthyridine (**1**), scheme (1), table (1).

Scheme: **1**



Diazotization of the 7-amino derivative (**1**) was affected with nitrous acid at -5 °C to get the 7-hydroxy -2-(4'-methoxybenzylamine)-4-phenyl-1,8-naphthyridine (**2**) and 7-hydroxy-6-nitro-2-(4'-methoxybenzylamine)-4-phenyl-1,8-naphthyridine (**3**), scheme (1), table (1) .

Table 1. Physical data of 1.8-naphthyridine derivatives



Comp. No.	R	R1	Yield %	M.P. [a]	Mol. formula	Analysis (calcd/found %) C	H	N	Cl
1	H	NH_2	83	193-195 [b]	$C_{22}H_{20}N_4O$	74.14 74.05	5.66 5.68	15.72 15.78	- -
2	H	OH	42	181-183 [c]	$C_{22}H_{19}N_3O_2$	73.93 73.90	5.36 5.39	11.76 11.71	- -
3	NO_2	OH	31	161-163 [c]	$C_{22}H_{18}N_4O_4$	65.66 65.59	4.51 4.48	13.92 13.87	- -
4	H	Cl	75	174-176 [b]	$C_{22}H_{18}N_3OCl$	70.30 70.25	4.83 4.81	11.18 11.21	9.43 9.39
5	NO_2	Cl	82	162-164[b]	$C_{22}H_{17}N_4O_3Cl$	62.79 62.83	4.07 4.09	13.31 13.29	8.42 8.45
6	H	OCH_3	91	152-154[b]	$C_{23}H_{21}N_4O_2$	74.37 74.41	5.70 5.68	11.31 11.28	- -
7	NO_2	OCH_3	85	145-147 [b]	$C_{23}H_{20}N_4O_4$	66.34 66.36	4.84 4.81	13.45 13.41	- -
8	H	OCH_2CH_3	77	138-140 [b]	$C_{24}H_{23}N_3O_2$	74.78 74.74	6.01 5.97	10.90 10.87	- -
9	NO_2	OCH_2CH_3	82	128-130 [b]	$C_{24}H_{22}N_4O_4$	66.97 66.94	5.15 5.18	13.02 12.98	- -
10	H	Pip	72	192-194 [b]	$C_{27}H_{28}N_4O$	76.39 76.42	6.65 6.62	13.20 13.17	- -
11	NO_2	Pip	76	184-186 [d]	$C_{27}H_{27}N_5O_3$	69.07 69.14	5.80 5.78	14.92 14.87	- -

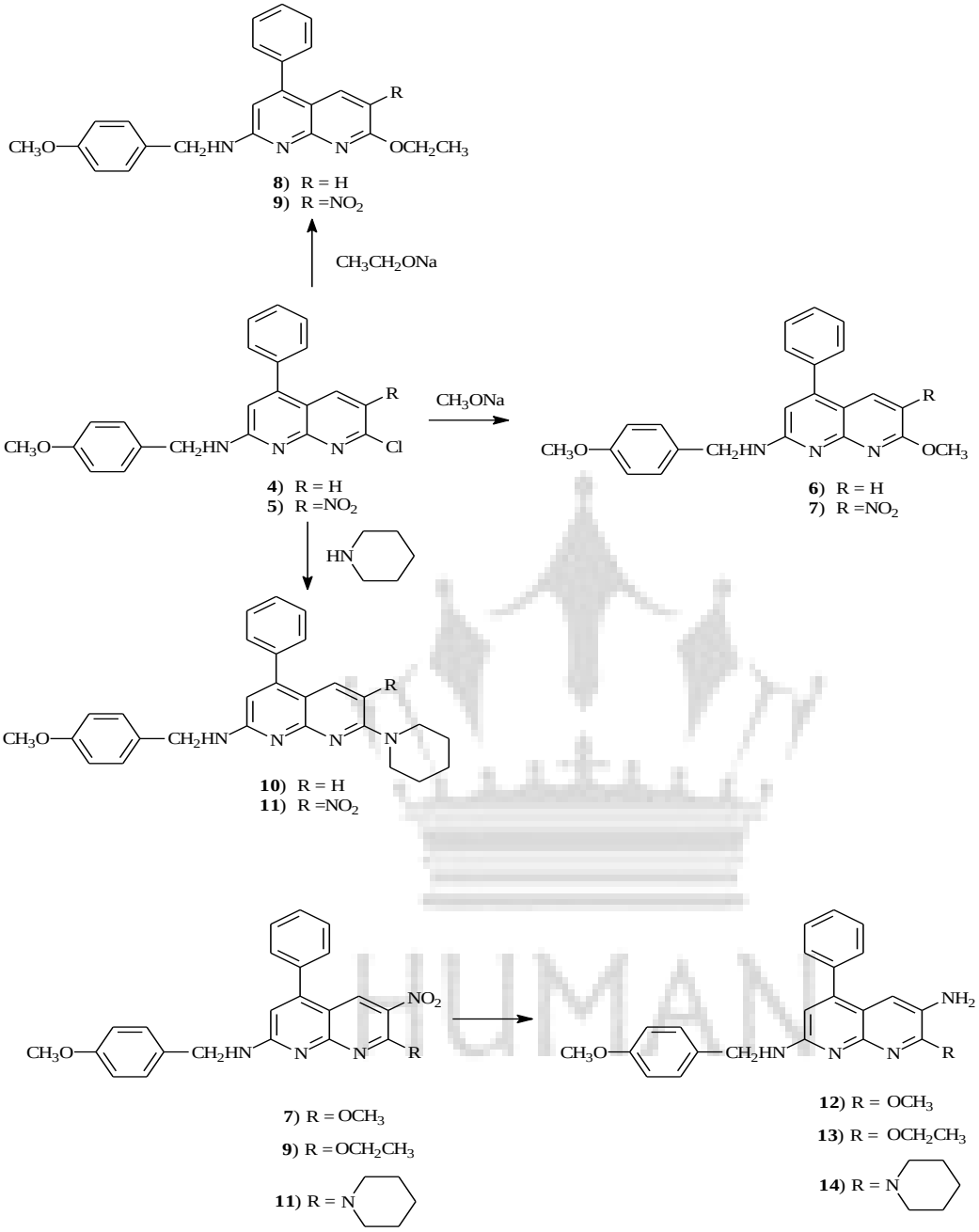
12	NH_2	OCH_3	59	152-154 [d]	$C_{23}H_{22}N_4O_2$	71.48 71.53	5.74 5.71	14.50 14.46	- -
13	NH_2	OCH_2CH_3	88	140-142 [d]	$C_{24}H_{24}N_4O_2$	71.98 72.00	6.04 6.01	13.99 14.01	- -
14	NH_2	Pip	81	174-176 [b]	$C_{27}H_{29}N_5O$	73.78 73.76	6.65 6.63	15.93 15.91	- -

[a] recrystallization solvent, [b] toluene, [c] separated by flash chromatography with EtOAc as solvent

[d] petroleum ether 100-140°C, Pip: Piperidine

Introduction of lipophilic groups, such as methoxy, ethoxy or piperidine in position 7 of the 1,8-naphthyridine nucleus was obtained by the treatment of 7-hydroxy derivative (**2**) and (**3**) with phosphoryl chloride to obtain the relative 7-cholor derivatives (**4**) and (**5**), scheme (1), and table (1) . Which were subsequently treated with sodium methoxide to obtain the relative 7-methoxy compounds (**6**) and (**7**), scheme (2), and table (1).

Scheme 2:



The 7-chloro derivatives (**4**) and (**5**) were treated with sodium ethoxide to obtain the relative 7-ethoxy derivatives (**8**) and (**9**), scheme (2), and table (1).

To study the influence of cycloamines in position 7, the 7-chloro derivatives (**4**) and (**5**) were treated with piperidine to obtain the 7-piperidine derivatives (**10**) and (**11**), scheme (2), and table (1).

The 6-nitro derivatives (**7**), (**9**) and (**11**) were reduced with palladium to 6-amino derivatives (**12**), (**13**) and (**14**), scheme (2), and table (1).

Preparation of 7-amino-2-(4'-methoxybenzylamine)-4-phenyl-1,8-naphthyridine (1):

To a mixture of 2-chloro derivative (**A**) (2.0g, 7.82 mmole) and 4-methoxybenzylamine (3.55ml, 27mmole) was added pyridine (35ml) under N_2.

The mixture was heated to reflux for 48h and then cooled to room temperature, the pyridine was removed and the compound was obtained by column chromatography followed by recrystallization, table (1 and 2).

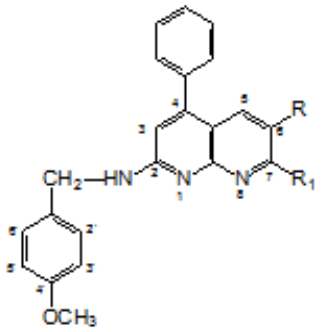
Preparation of 7-hydroxy-2-(4'-methoxybenzylamine)-4-phenyl-1,8-naphthyridine (2) and 7-hydroxy-6-nitro-2-(4'-methoxybenzylamine)-4-phenyl-1,8-naphthyridine (3):

To a solution of 1.0 mmole of 7-amino derivative (**1**) in 5ml of concentrated sulfuric acid, sodium nitrite was added portionwise at -5°C, after standing at room temperature for 1 hour crushed ice was added and then concentrated ammonium hydroxide until pH about 5, the solid was collected by filtration and purified to give compound (**2**) and (**3**), table (1 and 2)

Preparation of the 7-chloro-2-(4'-methoxybenzylamine)-4-phenyl-1,8-naphthyridine (4) and 7-chloro-2-(4'-methoxybenzylamine)-6-nitro-4-phenyl-1,8-naphthyridine (5):

A mixture of the appropriate hydroxyl-1,8-naphthyridine (**2**) or (**3**) (10 mmole) and $POCl_3$ (15ml) was heated at 90°C for 45min. After cooling, the solution obtained was treated with ice and H_2O and alkalinized with conc. NH_4OH. The solid obtained (compound **4** or **5**) was washed with H_2O and purified by crystallization, table (1 and 2).

Table 2. ^{1}H-NMR Chemical shifts (δ PPM/TMS)



Comp. No.	H_3 (s)	H_5	H_6 (d)	C_6H_5 (m)	-NH- (t)	$-CH_2-$ (t)	4 $-OCH_3$ (s)	$-OCH_3$ (s)	Pip(m)	$-OCH_2CH_3$	Others (d) $H_{2'}$ $H_{3'}$ $H_{5'}$ $H_{6'}$ $-NH_2$ (brs)
1	7.35	6.17(d)	7.38	7.61	7.21	3.23	3.52	-	-	-	7.82 7.72 7.18 6.73 -
2	7.36	6.31(d)	7.68	7.42	7.08	3.35	3.59	-	-	-	7.66 7.65 7.11 6.83 -
3	7.48	8.23(s)	-	7.55	7.17	3.32	3.44	-	-	-	7.84 7.75 7.18 6.87 -
4	7.85	6.31(d)	7.53	7.58	7.29	3.35	3.36	-	-	-	7.64 7.61 7.28 6.82 -
5	7.81	8.17(s)	-	7.51	7.35	3.41	3.45	-	-	-	7.61 7.77 7.24 7.14 -
6	7.42	6.20(d)	7.29	7.62	7.25	3.43	3.43	3.74	-	-	7.74 7.73 7.12 6.73 -
7	6.83	8.51(s)	-	7.51	7.21	3.43	3.55	3.69	-	-	7.81 7.71 7.33 6.97 -
8	7.62	5.84(d)	7.75	7.57	7.33	3.48	3.48	-	-	3.91(t),1.35(q)	7.93 7.47 7.39 6.91 -
9	7.72	8.33(s)	-	7.69	7.41	3.22	3.51	-	-	3.81(t),1.38(q)	7.77 7.82 7.20 6.84 -
10	7.27	6.62(d)	7.65	7.71	7.39	3.29	3.56	-	1.43, 3.68	-	7.47 7.52 7.14 6.69 -
11	7.18	8.11(s)	-	7.65	7.28	3.18	3.57	-	1.36, 3.75	-	7.72 7.65 7.19 6.71 -
12	7.28	8.25(s)	-	7.71	7.18	3.28	3.45	3.84	-	-	7.62 7.58 7.14 6.58 5.14
13	7.32	8.41(s)	-	7.73	7.25	3.33	3.61	-	-	3.88(t),1.41(q)	7.58 7.47 7.12 6.48 5.51
14	7.35	8.58(s)	-	7.42	7.35	3.18	3.57	-	1.29, 3.63	-	7.72 7.63 7.24 6.85 5.33

General procedure for the preparation of 7-methoxy and 7-ethoxy derivatives 6, 7, 8 and 9:

A solution of 5 mmole of freshly prepared sodium methoxide(in case of preparation of compounds **6** and **7**) or sodium ethoxide(in case of preparation of compounds **8** and **9**) and 0.5 mmole of the chloro derivatives **4** or **5** in 5ml of anhydrous methanol was refluxed for 2.5 hours. The reaction mixture was evaporated to dryness in vacuo and the crude residue was treated with H_2O, neutralized with 10% hydrochloric acid and the solid precipitate collected by filtration and purified by crystallization to obtain **6**, **7** or **8** and **9**, table (1 and 2).

Preparation of 2-(4'-methoxybenzylamine)-7-(piperidin-1-yl)-4-phenyl-1,8-naphthyridine (10) and 2-(4'-methoxybenzylamine)-6-nitro-7-(piperidin-1-yl)-4-phenyl-1,8-naphthyridine (11):

A mixture of 7-chloro-2-(4'-methoxybenzylamine)-4-phenyl-1,8-naphthyridine (**4**) or 7-chloro-2-(4'-methoxybenzylamine)-6-nitro-4-phenyl-1,8-naphthyridine (**5**) (1 mmole) and piperidine (2 mmole) was heated in a sealed tube at 140°C for 12 hours, the resulting crude residue was treated with water and the solid was collected by filtration and purified by crystallization to obtain piperidine derivatives (**10**) or (**11**), table (1 and 2).

Preparation of 6-amino derivatives (12), (13) and (14):

A solution of 1.1 mmoles of 6-nitro derivatives (**7**), (**9**) or (**11**) in glacial acetic acid was hydrogenated in the presence of 30mg of 10% palladium on charcoal at room temperature and at atmospheric pressure for 3 hrs. The catalyst was filtered and the solvent evaporated to dryness in vacuo to give compound (**12**), (**13**) or (**14**), which was purified by crystallization, table (1 and 2).

Instruments and Analyses:

All compounds were roundly checked for their structure by IR and ^{1}H NMR spectroscopy. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were measured with a Genesis Series FTIR ATI Mattson.

The ^{1}H NMR spectra were determined in DMSO-d_6 or $CDCl_3$ with TMS as the internal standard, on a Varian CFT-20 NMR spectrometer.

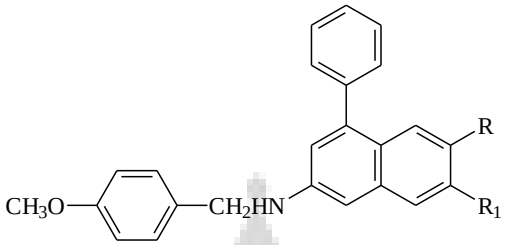
Analytical TLC was carried out on E.Merch 0.20mm precoated silica gel glass plate (60 F254) and the location of spots was detected by illumination with UV Lamp.

Elemental analysis of all compounds synthesized for C, H, N and Cl were within ±0.40% of theoretical value and were performed in our analytical laboratory.

RESULTS AND DISCUSSION

Compounds **1-3**, **6** and **8-14** were subjected to a preliminary screening estimating the effects of a fixed concentration (10µM) on the platelet aggregation induced by 0.7m Marachidonate (table 3).

Table 3. Preliminary screening for inhibition of arachidonate induced (0.7mM) platelet rich plasma (PRP) aggregation by tested compounds at a concentration of 10µM



Comp. No.	R	R_1	Solvent used	A	B
1	H	NH_2	DMSO	15 ± 2	21 ± 2
2	H	OH	DMSO	35 ± 2	32 ± 2
3	NO_2	OH	DMSO	22 ± 2	18 ± 2
4	H	Cl	Not sol	n.t	n.t
5	NO_2	Cl	Not sol	n.t	n.t
6	H	OCH_3	Not sol	39 ± 2	41 ± 2
7	NO_2	OCH_3	Not sol	n.t	n.t
8	H	OCH_2CH_3	DMSO	58 ± 2	49 ± 2
9	NO_2	OCH_2CH_3	DMSO	80 ± 3	75 ± 2
10	H	Pip	DMSO	60 ± 3	60 ± 2
11	NO_2	Pip	DMSO	85 ± 3	80 ± 2
12	NH_2	OCH_3	DMSO-HCl	100 ± 0	100 ± 0
13	NH_2	OCH_2CH_3	DMSO-HCl	100 ± 0	100 ± 0
14	NH_2	Pip	DMSO-HCl	100 ± 0	100 ± 0

It was thus possible to determinate the inhibition of the maximum aggregation due to the agonist and the speed of aggregation or "slope" which gave the amount of platelet aggregating in the time unit whose levels, were expressed as a percentage.

In accordance with the inhibition values observed, the compounds tested were subdivided into two different groups: from 0 to 50% as inactive to moderately active and from 51% onward the really active.

The activity of compounds **4**, **5** and **7** could not be determined because of their insolubility by the procedures used. Compounds **1, 2, 3** and **6** displayed a poor activity.

The IC_{50} for the dose-dependent inhibition of platelet aggregation induced by arachidonate was evaluated for compounds **8-14**. As shown in table 4, all compounds exhibited a very low IC_{50} and some were similar to the values of the reference compounds.

With the aim of excluding a possible selective inhibition of the membrane enzyme phospholipase A_2, the inhibition of aggregation induced by collagen at concentration of 2.0µg/ml was evaluated for compounds **8-14**. The results obtained confirm high inhibitory activities for these compounds that were similar to the values seen in the arachidonate patterns (table 4).

Table 4. Inhibition of platelet rich plasma (PRP) aggregation induced by 0.7mM arachidonate and 2.0µg/ml collagen

Compound	IC_{50} (µM)			
	Arachidonate		Collagen	
	A	B	A	B
8	11.6 ± 1	12.2 ± 2	9.8 ± 1.0	5.0 ± 1.0
9	10.8 ±1	11.8 ± 2	8.7 ± 1.0	7.6 ± 1.0
10	18 ± 2	20 ± 2	14.0 ± 1.0	12.5 ± 1.0
11	6.1 ± 0.6	5.1 ± 0.5	4.8 ± 1.0	4.3 ± 1.0
12	5.5 ± 0.5	12.0 ± 2	5.8 ±1.0	4.2 ±1.0
13	5.2 ± 0.5	11.1 ± 1	4.8 ± 1.0	4.2 ± 1.0
14	3.3 ± 0.5	17.7 ± 2	3.6 ± 1.0	3.2± 1.0
ASA	30.0 ±2	36.0 ±3.1	42.0 ± 5.6	54.0 ± 5.2
PAP	16.0 ± 0.3	20.9 ± 2.0	66.0 ± 1.5	-
Ibu[a]	4.2 ± 0.5	-	6.2 ± 0.4	-
Indo	1.5 ± 0.5	1.8 ± 0.4	1.9 ± 0.6	1.6 ± 0.5

IC_{50} of compounds calculated % inhibition of maximal aggregation (A) and % of aggregation rate (B) induced by 0.7mM arachidonate and 2.0µg/ml collagen. Values are mean ± SE of at least three independent experiment; ASA, acetylsalicylic; PAP, papaverine; Ibu, Ibuprofen; indo, indomethacin. [a]Value obtained from (Vane and Ferreira)[17].

The collagen-induced aggregation made it possible to evaluate the latency time of aggregation that is the time expressed in seconds between the addition of the agonist and the start of aggregation of platelet.

The parameter expressed the delay of platelet aggregation activation mechanism. On the basis of results for this parameter, compared with a mean basal value of 57s, the compounds **12**, **13** and **14** delay the start of aggregation by 360s as evidenced by evaluation a concentration of 10µM and by time lag ranging from 120 to 195 at the 5.0 µM concentration (table 5).

Table 5.Effects of compounds tested on latency time (sec) of collagen-induced aggregation (2.0µg/ml)

Compound	10µM	5µM
11	360 ± 0	168 ± 8
12	360 ± 0	120 ± 10
13	360 ± 0	195 ± 11
14	360 ± 0	180 ± 9
Basal value	75 ± 5	

Values are mean ± SE of at least three independent experiments, the basal value is the mean of latency times of aggregation without the test compounds.

Further studies on the effects of compound **12**, **13** and **14** on platelet aggregations necessitated determination of their dose-effect curve versus the major physiological agonist ADP. The results obtained showed that analogue **14** exhibited a significant biological activity (table 6).

Table 6. IC_{50} (µM) of active compounds in ADP- induced platelet aggregation (3.0µM)

Compound	IC_{50}	IC_{50}
	Inhibition of maximal aggregation value	Inhibition of aggregation rate
12	26.1 ± 4	28.6 ± 5
13	21.3 ± 3.5	23.5 ± 4
14	18.1 ± 3	16.9± 3
Pap	121.0 ± 5.5	104.0 ± 6.1

Values are mean ±SE of at least three independent experiments; Pap, Papaverine.

The study of intracellular events due to treatment of intact platelets with the compounds **13** and **14** showed an increase in cAMP levels independently of the activation of adenylate cyclase (table 7).

Table 7. Percentage increase of cAMP levels in intact platelet

Compound	(µM)	% increase
13	10	64± 4.4
	20	87 ± 6.2
14	10	27 ± 2.2
	20	52 ± 4.7

A probability level $p < 0.05$ was considered statistically significant (Students 't'-test). Values are mean ±SE of at least three independent experiments, each performed in triplicate. The basal value of cAMP was 18.72 ± 0.33 pmol x 10^8 cells.

On the basis of the results, we concluded that the reduction of nitro group to amino group as in compounds **12**, **13** and **14** increases the inhibition of aggregations induced by arachidonate,

collagen and ADP and in general, derivative with piperidinyl substituent in position 7 were most potent on all subtypes.

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