
THROMBOLYSIS BY THIENOPYRIDINES AND THEIR CONGENERS

Chair of Pharmacology, Medical College of Jagiellonian University
Cracow, Poland *, Chair of Pharmaceutical Organic Chemistry University Victor Segalen
Bordeaux II, Bordeaux, France **

We propose that anti-platelet thienopyridines, such as ticlopidine or clopidogrel, are thrombolytic owing to endothelial release of prostacyclin (PGI₂) and tissue plasminogen activator (t-PA). In this study we used anaesthetised Wistar rats with extracorporal circulation in which arterial blood superfused thrombi which adhered to a strip of collagen. Weight of thrombi was continuously monitored. When administered intravenously, clopidogrel or its R enantiomer deprived of anti-platelet action, both at doses of 3 mg kg⁻¹, produced lost in weight of thrombi by 14.1 ± 1.3% or 16.0 ± 1.4% (n = 9), and at doses 10 mg kg⁻¹ by 28.3 ± 2.3% or 30.4 ± 1.9% (n = 8), respectively. Maximum of thrombolysis occurred 30—45 min following the drug administration. Ticlopidine at a dose of 30 mg kg⁻¹ reduced weight of thrombi by 33.7 ± 1.7% (n = 32). Thrombolytic action of ticlopidine was accompanied by a rise in 6-keto-PGF₁₀, blood levels from 0.42 ± 0.10 to 1.58 ± 0.29 ng ml⁻¹ and t-PA antigen plasma levels from 4.70 ± 1.00 to 12.90 ± 1.15 ng ml⁻¹ (n = 7). Five out of eleven tested thienopyridine congeners with pyrimidine or pyrimidinone instead of pyridine rings had thrombolytic potencies similar to that of clopidogrel (ED₃₀ at a range of 6.2—11.4 mg kg⁻¹). A substantial increase in thrombolytic potency (ED₃₀ at a range of 0.3—2.1 mg kg⁻¹) was observed for congeners in which thienyl ring was condensed with an additional cyclopentyl, cyclohexyl or cycloheptyl structures or in which thienopyridine complex was replaced for a pyridopyrimidine one. We claim that thienopyridines, independently of their delayed anti-platelet action, do produce immediate thrombolysis in vivo. This new activity emulates capacity of their native, non-metabolised molecules to release prostacyclin and tissue plasminogen activator. We have also shown that structural changes in molecules of thienopyridines may intensify their thrombolytic potency.

Key words: ticlopidine; clopidogrel; thienopyridine and pyridopyrimidine derivatives; vascular endothelium; prostacyclin; tissue plasminogen activator; thrombolysis

INTRODUCTION

Anti-platelet thienopyridines encompass ticlopidine (TP), i.e. [5-(2-chlorophenyl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2c]pyridine hydrochloride (1) and its optically active derivative, clopidogrel (CL) (2).
Thienopyridines successfully compete with aspirin in prevention or treatment of myocardial infarction and of other diseases associated with atherothrombosis (3—5). They are also used in therapy of diabetic vascular complications (6). Beneficial clinical actions of thienopyridines are usually linked with their ex vivo but not in vitro ability to antagonise a subtype of low-affinity platelet ADP receptor, that is sensitive to 2-MeS-ADP-induced activation of Gi protein, followed by inhibition of adenylate cyclase, fall in cyclic-AMP, mobilisation of \([\text{Ca}^{2+}]\) from internal stores, activation of glycoprotein GPIIb/IIIa receptors and formation of stable platelet macroaggregates (7—8). Thienopyridines hardly bind to platelet P2X1 (9) and high affinity P2Y1 purinoceptors (10). A conception that a Gi-coupled P2Y receptor is involved in anti-platelet action of thienopyridines has been recently challenged (11).

Unlike immediate anti-platelet effect of aspirin which is easily detected both ex vivo and in vitro, fine interaction between thienopyridines and platelets seems to occur exclusively in vivo, but not in platelet-rich plasma in vitro. The ex vivo Anti-platelet effect of TP manifests itself fully only a few days after ingestion of the drug. An idea of in vivo hepatic biotransformation of TP or CL to active and unstable metabolites seems obvious and sound (7).

Previously, we reported that in humans, cats and rats ticlopidine (TP) had displayed thrombolytic action (12). We claimed that this action of TP had not depend on its anti-platelet properties, but rather it was mediated by vascular endothelial cells (12—15). Presently, we broaden the scope of investigated thienopyridines by adding clopidogrel (CL) and its R enantiomer (ECL) that is deprived of anti-platelet potency (16). In addition, we provide data on thrombolytic potencies of eleven congeners of thienopyridines, in which either pyridine moiety was replaced by pyrimidine or pyrimidinone rings, or thienyl moiety was condensed with various cyclic structures, or replaced by other heterocyclic rings (17—20); (Table 1).

MATERIALS AND METHODS

Drugs and reagents

Thienopyridines, i.e. ticlopidine (TP), clopidogrel (CL, SR 25990C) or its R enantiomer deprived of anti-platelet properties (ECL, SR25989C) were kindly donated by Sanofi Recherche (Toulouse, France), prostacyclin (PGI₂) and its stable analogue iloprost by Schering Company (Berlin, Germany). Thienopyridine congeners (Table 1) were synthesised in the laboratory of Professor Jean-Pierre Dupin (Bordeaux II University, France).
Table 1

<table>
<thead>
<tr>
<th>number</th>
<th>formula</th>
<th>name</th>
<th>synthesis</th>
<th>ED&lt;sub&gt;30&lt;/sub&gt; mg/kg i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td><img src="formula_1.png" alt="Image" /></td>
<td>2,3-dihydro-3-(phenylmethyl)-thieno [2,3-d] pyrimidin-4(1H)-one</td>
<td>*</td>
<td>10 (n=13)</td>
</tr>
<tr>
<td>II</td>
<td><img src="formula_2.png" alt="Image" /></td>
<td>2,3-dihydro-5,6-dimethyl-3-(phenylmethyl)-thieno [2,3-d] pyrimidin-4(1H)-one</td>
<td>*</td>
<td>6.2 (n=10)</td>
</tr>
<tr>
<td>III</td>
<td><img src="formula_3.png" alt="Image" /></td>
<td>2,3-dihydro-3-(phenylmethyl)-cyclopenta [b] thieno [2,3-d] pyrimidin-4(1H)-one</td>
<td>*</td>
<td>0.6 (n=8)</td>
</tr>
<tr>
<td>IV</td>
<td><img src="formula_4.png" alt="Image" /></td>
<td>2,3,5,6,7,8-hexahydro-3-(phenylmethyl)-benzo [b] thieno [2,3-d] pyrimidin-4(1H)-one</td>
<td>(19)</td>
<td>0.6 (n=23)</td>
</tr>
<tr>
<td>V</td>
<td><img src="formula_5.png" alt="Image" /></td>
<td>2,3-dihydro-3-(phenylmethyl)-cyclohepta [b] thieno [2,3-d] pyrimidin-4(1H)-one</td>
<td>*</td>
<td>2.1 (n=10)</td>
</tr>
<tr>
<td>VI</td>
<td><img src="formula_6.png" alt="Image" /></td>
<td>3-[(2-chlorophenyl)methyl]-2,3,5,6,7,8-hexahydrobenzo [b] thieno [2,3-d] pyrimidin-4(1H)-one</td>
<td>(19)</td>
<td>11.4 (n=16)</td>
</tr>
<tr>
<td>VII</td>
<td><img src="formula_7.png" alt="Image" /></td>
<td>5,6,7,8-tetrahydro-3-(phenylmethyl)-benzo [b] thieno [2,3-d] pyrimidin-4(3H)-one</td>
<td>(19)</td>
<td>1.7 (n=15)</td>
</tr>
<tr>
<td>VIII</td>
<td><img src="formula_8.png" alt="Image" /></td>
<td>3-[(2-chlorophenyl)methyl]-5,6,7,8-tetrahydrobenzo [b] thieno [2,3-d] pyrimidin-4(3H)-one</td>
<td>(19)</td>
<td>0.8 (n=20)</td>
</tr>
<tr>
<td>IX</td>
<td><img src="formula_9.png" alt="Image" /></td>
<td>5,6-dihydro-1-methyl-5-(phenylmethyl)-pyrazolo [3,4-d] pyrimidin-4(7H)-one</td>
<td>*</td>
<td>8.0 (n=6)</td>
</tr>
<tr>
<td>X</td>
<td><img src="formula_10.png" alt="Image" /></td>
<td>1,2,3,4-tetrahydro-3-(phenylmethyl)-pyrido [2,3-d] pyrimidine</td>
<td>(20)</td>
<td>0.3 (n=19)</td>
</tr>
<tr>
<td>XI</td>
<td><img src="formula_11.png" alt="Image" /></td>
<td>3-[(2-chlorophenyl)methyl]-1,2,3,4-tetrahydropyrido [2,3-d] pyrimidine</td>
<td>(20)</td>
<td>9.0 (n=22)</td>
</tr>
<tr>
<td>XII</td>
<td><img src="formula_12.png" alt="Image" /></td>
<td>ticlopidine</td>
<td>-</td>
<td>21.5 (n=43)</td>
</tr>
<tr>
<td>XIII</td>
<td><img src="formula_13.png" alt="Image" /></td>
<td>clopidogrel</td>
<td>-</td>
<td>10.0 (n=36)</td>
</tr>
</tbody>
</table>

* New compound synthesized as described in experimental part
n – number of doses tested

**Chemical synthesis**

Melting points were determined on a Kofer apparatus. IR spectra were recorded on a Shimadzu IR 470 spectrometer as potassium bromide pellets and frequencies (v) are expressed in cm<sup>-1</sup>. ^1H-NMR spectra were obtained on a Varian EM 360 L spectrometer in CDCl<sub>3</sub> with TMS
as the internal standard and chemical shifts are reported in ppm (δ). Synthesis of new compounds were performed according to a previous report (19). Other chemicals were purchased from Sigma Aldrich France.

**Synthesis of 2,3-dihydro-3-(phenylmethyl)-thieno [2,3-d] pyrimidin-4(1H)-one (I)** Ethyl 2-aminothiophene-3-carboxylate (17) has been used to afford 3-(phenylmethyl)-thieno [2,3-d] pyrimidin-4(3H)-one: yield 65%; mp 125°C; ν C = O 1660; δH2 8.06 (s); δ HBenzyL 5.16 (s); δ HArom. 7.33 (m). Dihydrogenation of this latter compound gave compound I: yield 70%; mp 156°C; ν C = O 1610; ν NH 3250; δH2 4.55 (s); δ HBenzyL 4.66 (s); δ HArom. 7.30 (m).

**Synthesis of 2,3-dihydro-5,6-dimethyl-3-(phenylmethyl)-thieno [2,3-d] pyrimidin-4(1H)-one (II)** Ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (18) has been used to afford 5,6-dimethyl-3-(phenylmethyl)-thieno [2,3-d] pyrimidin-4(3H)-one: yield 72%; mp 105°C; ν C = O 1660; δH2 7.96 (s); δ HBenzyL 5.10 (s); δ HArom. 7.30 (m). Dihydrogenation of this latter compound gave compound II: yield 75%; mp 136°C; ν C = O 1610; ν NH 3250; δH2 4.63 (d); δ HBenzyL 4.43 (s); δ HArom. 7.36 (m).

**Synthesis of 2,3-dihydro-3-(phenylmethyl)-cyclopenta [b] thieno [2,3-d] pyrimidin-4(1H)-one (III)** Ethyl 2-aminocyclopenta [b] thiophene-3-carboxylate has been used to afford 3-(phenylmethyl)-cyclopenta [b] thieno [2,3-d] pyrimidin-4(3H)-one: yield 58%; mp 120°C; ν C = O 1665; δH2 8.03 (s); δ HBenzyL 5.20 (s); δ HArom. 7.43 (m). Dihydrogenation of this latter compound gave compound III: yield 65%; mp 156°C; ν C = O 1605; ν NH 3200; δH2 4.60 (s); δ HBenzyL 4.46 (s); δ HArom. 7.36 (m).

**Synthesis of 2,3-dihydro-3-(phenylmethyl)-cyclohepta [b] thieno [2,3-d] pyrimidin-4(1H)-one (IV)** Ethyl 2-aminocyclohepta [b] thiophene-3-carboxylate has been used to afford 3-(phenylmethyl)-cyclohepta [b] thieno [2,3-d] pyrimidin-4(3H)-one: yield 76%; mp 124°C; ν C = O 1660; δH2 8.06 (s); δ HBenzyL 5.20 (s); δ HArom. 7.43 (m). Dihydrogenation of this latter compound gave compound IV: yield 75%; mp 186°C; ν C = O 1610; ν NH 3250; δH2 4.63 (s); δ HBenzyL 4.40 (s); δ HArom. 7.33 (m).

**Synthesis of 5,6-dihydro-1-methyl-5-(phenylmethyl)-pyrazolo [3,4-d] pyrimidin-4(7H)-one (IX)** Ethyl 5-amino-1-methylpyrazol-4-carboxylate has been used to afford 1-methyl-5-(phenylmethyl)-pyrazolo [3,4-d] pyrimidin-4(5H)-one: yield 35%; mp 142°C; ν C = O 1680; δH2 8.16 (s); δ HBenzyL 5.23 (s); δ HArom. 7.40 (m). Dihydrogenation of this latter compound gave compound IX: yield 89%; mp 120°C; ν C = O 1660; ν NH 3150; δH2 4.56 (s); δ HBenzyL 4.43 (d); δ HArom. 7.43 (m).

**Bringing compounds into solution**

Thienopyridines were dissolved with vigorous stirring in saline at 37°C, while their congeners were dissolved _ex tempore_ in dimethyl sulfoxide (DMSO). The investigated compounds were injected intravenously at doses ranging from 30 μg kg⁻¹ to 3 mg kg⁻¹. Any dose of a congener was given in a volume of 15 μL DMSO. DMSO alone injected intravenously at a volume of 20 μL did not produce in rats detectable effect on blood pressure (BP) and on weight of thrombus (THR).

**Thrombolysis in extracorporeal circulation of anaesthetised rats**

_Exp vivo_ model for studying of thrombolytic properties of drugs in cats (21) was adopted to rats (12). Briefly, male Wistar rats body weight 300—350 g were anaesthetised (thiopental 30 mg kg⁻¹ i.p.) and unfractionated heparin at a dose of 800 units kg⁻¹ i.v. was administered. The extracorporeal circulation was established between left carotid artery and left jugular vein, and a collagen strip from rabbit tendon of Achilles was superfused with arterial blood at a rate of 1.5 ml min⁻¹. Its weight was continuously monitored by an auxotonic Harvard transducer.
Because of deposition of thrombi (21, 22) the strip gained in weight by 80—120 mg during the first 20 min of superfusion and stayed at that level during next 3—5 hours of the experiment. Mean arterial blood pressure (BP) was monitored from right carotid artery by a Harvard pressure transducer, and right femoral vein was prepared for drug administration. In the above system dispersion of thrombi occurred after intravenous administration of prostacyclin or iloprost (0.1—1.0 μg kg\(^{-1}\)), glyceryl trinitrate (30—100 μg kg\(^{-1}\)), metacholine hydrochloride (10 μg kg\(^{-1}\)) or kallikrein (100 units kg\(^{-1}\)) whereas aspirin at doses of 5—50 mg kg\(^{-1}\) did not evoke thrombolysis. Streptokinase (3—30 megaunits kg\(^{-1}\)) produced biphasic thrombogenic/thrombolytic response (13).

Thrombolytic potencies of thienopyridines and their congeners were calculated by measuring per cent lost in weight of thrombi at the maximum response next to intravenous injections of various doses of tested compounds (Fig. 1 and Fig. 2). These measurements were used to calculate regression line with confidence intervals at 95% (Fig. 3). Then the effective dose that resulted 30% of thrombolysis was computed (ED\(_{30}\) in mg kg\(^{-1}\)).

![Diagram of thrombolytic responses to intravenous injections of thienopyridines](image)

**Fig. 1.** Original tracing of thrombolytic responses to intravenous injections of thienopyridines (ticlopidine, clopidogrel or its enantiomer) in three Wistar rats with extracorporeal circulation in which thrombi (THR) that adhered to collagen strips, were superfused with arterial blood.

**Blood assays of 6-keto-PGF\(_{1α}\) and t-PA antigen**

Blood samples (500 μl) were collected into Eppendorff tubes with indomethacin to yield its final concentration of 10 μM, and then stored at -70°C not longer than for a week. 6-Keto-PGF\(_{1α}\) was assayed using the enzyme immunoassay kit (Cayman Chemical Co., Ann Arbor, MI) and t-PA antigen was assayed using the enzyme immunoassay kit (Biopool TintElize t-PA antigen, Umea, Sweden). All results were expressed in ng ml\(^{-1}\). Experimental protocol was approved and experiments carried out in accordance with recommendations from the Declaration of Helsinki.
Fig. 2. Original tracing of thrombolytic (THR) responses and blood pressure (BP) responses in two rats which received intravenous injections of a range of doses of two most potent thienopyridine congeners (compounds IV and X, see Table 1).

![Thrombolysis in rats by ticlopidine](image)

Regression line with confidence intervals at 95%

- N=6
- n=24
- ED$_{30}$=20 194 μg/kg i.v.

Fig. 3. Calculation of thrombolytic potency of ticlopidine. Regression line with confidence intervals at 95% was used for computing ED$_{30}$. N — number of rats, n — number of doses of ticlopidine. The above principle was used to calculate ED$_{30}$ for all thienopyridines and for their congeners (Table 1).
**Statistical analysis**

Arithmetical means are given with s.e. of a mean. Differences inside group were assessed by unpaired Student's t test. Data for multiple observations over time (i.e. assays of 6-keto PGF$_{1\alpha}$ and t-PA antigen) were analysed by two-way ANOVA. P values less than 0.05 were assumed to denote a significant difference.

**RESULTS**

**Thrombolysis in extracorporal circulation of anaesthetised rats**

Thienopyridines (TP, CL, ECL) at a range of doses from 3 to 30 mg kg$^{-1}$ i.v. produced thrombolytic effect with maximum at 30—45 min (Fig. 1). TP (30 mg kg$^{-1}$), CL (10 mg kg$^{-1}$) and ECL (10 mg kg$^{-1}$) showed similar potencies in reducing initial weight of the thrombus by maximum of 33.7 ± 1.7% (n = 32), 28.3 ± 2.3% (n = 9) and 30.4 ± 1.9% (n = 8), respectively. A qualitative difference between patterns of thrombolysis by TP (30 mg kg$^{-1}$) and CL (10 mg kg$^{-1}$) was their duration that lasted 166 ± 4 min (n = 15) and 84 ± 6 min (n = 9), respectively (Fig. 1). Thienopyridines at the above doses hardly influenced mean arterial blood pressure. TP-induced time-dependent increase in blood 6-keto-PGF$_{1\alpha}$ and in plasma t-PA antigen levels. One hour after administration of TP at a dose 30 mg kg$^{-1}$ blood plasma levels of 6-keto-PGF$_{1\alpha}$ rose from 0.42 ± 0.10 ng ml$^{-1}$ to 1.58 ± 0.29 ng ml$^{-1}$, while t-PA antigen plasma levels rose from 4.70 ± 1.00 ng ml$^{-1}$ to 12.90 ± 1.15 ng ml$^{-1}$. Thrombolytic potencies of the investigated thienopyridine congeners (Fig. 2) are indicated in Table 1.

**DISCUSSION**

Clinical efficacy of thienopyridines (ticlopidine — TP, clopidogrel — CL) in patients with atherothrombosis (1—3) had been associated with a delayed antagonistic action of their metabolites on a subtype of platelet ADP receptors (7, 9—10). Such a mechanism can hardly explain immediate fibrinolytic or thrombolytic effects of thienopyridines observed by us ex vivo in humans, cats (12) and rats (13—14); (present data). Indeed, anti-platelet drugs may impair thrombus growth and platelet-collagen adhesion (23), however, in our ex vivo model (21;22) thienopyridines were injected intravenously to rats well after platelet-fibrin thrombus had been formed over collagen strip in the extracorporal circulation. Likewise, there are other good reasons to believe that ex vivo dispersion of thrombi by thienopyridines is not associated with their direct anti-platelet properties. Firstly, in our animal models TP and CL
dispersed thrombi without a delay that is so characteristic for their *ex vivo* anti-platelet action. Secondly, enantiomer of CL (ECL, SR 25989 C), inactive as anti-platelet agent (16), was equally potent as CL itself in inducing thrombolysis. Thirdly, thrombolysis by TP was timely associated with the release of PGI₂ and t-PA, both of which abide endothelial cells rather than blood platelets. Fourthly, pretreatment of rats with a high dose of aspirin (50 mg kg⁻¹) not only abolished TP-induced release of PGI₂ and t-PA but it also erased thrombolytic activity of TP, thus pointing to endothelial PGI₂ as to a major player in thrombolysis by TP (14). Moreover, pretreatment with a low, “platelet-selective”, dose of aspirin (1 mg kg⁻¹) not only augmented release of PGI₂ and t-PA, but also enhanced efficacy of TP to dissipate thrombi (14). Promotion of antithrombotic activity of TP by low doses of aspirin was reported (Herbert et al., 1996) as well as synergism in fibrinolytic response to rt-PA and thienopyridines (24—25).

So, our hypothesis is that thienopyridines are thrombolytic because of their ability to stimulate vascular release of PGI₂, t-PA and, possibly, NO. Unlike release of t-PA in response to venous stasis (26), the TP-induced discharge of t-PA from arterial endothelium seems to be triggered by endogenous PGI₂. Lowering of functional fibrinogen levels, that occurs 4 weeks after TP therapy (27), is unlikely to contribute to TP-induced thrombolysis in our acute experiments. Klein-Soyer et al. (16) reported that human endothelial cells grown in presence of ECL increased their production of t-PA and thrombospondin-1. Our data on equal thrombolytic potencies of CL and ECL (Fig. 1) point out to a distinct possibility that anti-platelet and thrombolytic properties of thienopyridines are coded in different regions of their molecules.

A coupled release of endothelial PGI₂ and EDRF(NO) in response to any stimulus seems to be a rule (28—29). This rule is also obeyed by ticlopidine that stimulates simultaneous release of 6-keto-PGF₁α and nitrite from cultured endothelial cells harvested from human umbilical vein and from bovine aorta (15). An open possibility is that thienopyridines activate endothelial NOS-3 and COX-1 through an increase in free cytoplasmic calcium level [Ca²⁺]i (15). TP and CL at doses of 10 mg kg⁻¹ were reported to hamper vasoconstrictor responses to platelet-rich plasma or endothelins in arterial preparations excised from rats, rabbits (30) or dogs (31). Interestingly, these authors suspected thienopyridines to combat vasoconstriction through their metabolites which supposedly modulated esoteric “ADP receptors on the vessel wall”. We put it forward that thienopyridines may moderate vasoconstrictor responses through releasing endothelial NO.

Not only the mechanism of anti-platelet action of thienopyridines, but also their stimulatory effect on vascular endothelium makes them so different from aspirin (32). Aspirin has a potential to inhibit synthesis of prostanoids, both in platelets and in endothelial cells while thienopyridines like some ACE inhibitors (33) are endowed with a capacity to stimulate the secretory function
of vascular endothelium. Hence clinical compatibility between ACE inhibitors and thienopyridines in the treatment of patients with intermittent claudication (34) or chronic heart failure (35) that does not show up when thienopyridines are replaced by aspirin.

Another issue of this study refers to a possibility of increasing thrombolytic potency of thienopyridines by changing their chemical structure (Table I) (17—20). Replacement of pyridine ring with pyrimidine or pyrimidinone moieties (compounds I, II, VI, IX, XI) leaved thrombolytic potencies of such compounds at the level of that for thienopyridines. When within these pyrimidine or pyrimidinone analogues an additional cycloalkane ring was condensed with their thienyl ring (compounds III, IV, V, VII) then their thrombolytic activities became 10—30 times higher than that of ticlopidine. A 70-fold increase in thrombolytic potency as compared to ticlopidine was recorded for pyridopyrimidine analogue of ticlopidine (compound X) that was also deprived of chlorine substitution in the phenyl ring. Presence or absence of chlorine substitution in the phenyl ring seems to modify thrombolytic activity of the thienopyridine analogues (compounds VII vs VIII and X vs XI). The above chemical-pharmacological exercise opens a new possibility for seeking thienopyridine congeners with augmented thrombolytic potencies.

Acknowledgements: The authors thank Dr Magdalena Łomnicka for statistical calculations. This research was funded by the State Committee for Scientific Research Grant No 4 P05A 050 19.

REFERENCES

4. Easton JD. What have we learned from recent Anti-platelet trials?. [Review] [21 refs]. Neurology 1998; 51(3 Suppl 3): S36—S38.


Received: October 3, 2000
Accepted: October 18, 2000

Author's address: R. J. Gryglewski, Chair of Pharmacology Jagiellonian University, Medical College, Grzegórzecka 16, Cracow 31-531, Poland.