α-METHYLDOPA, α-METHYLDOПAMINE AND α-METHYLNORADRENALINE: SUBSTRATES FOR THE THERMOLABILE FORM OF HUMAN PLATELET PHENOL SULPHOTRANSFERASE

GABRIEL MWALUKO & RICHARD WEINSHILBOUM
The Clinical Pharmacology Unit, Departments of Pharmacology and Internal Medicine, The Mayo Foundation/Mayo Medical School, Rochester, Minnesota 55905, USA

1 Sulphate conjugation catalyzed by phenol sulphotransferase (PST) is an important pathway in the catabolism of α-methyldopa (MD). Variations in PST activity in an easily obtained tissue such as the human platelet might reflect individual differences in the sulphate conjugation of MD in other organs and tissues. There are at least two forms of human platelet PST, a thermolabile form for which dopamine is a substrate and a thermostable form for which low concentrations of phenol can serve as a substrate.

2 MD, α-methyldopamine (MDA) and α-methylnoradrenaline (MNA) were tested as substrates for human platelet PST. All three were substrates for the thermolabile form of the enzyme and none were substrates for the thermostable form of PST. Apparent Michaelis-Menten (Km) values for MD, MDA and MNA were 5.5, 0.014 and 0.28 mm, respectively. Apparent Km values for 3' -phosphoadenosine-5' -phosphosulphate, the sulphate donor for the reaction, were 0.08, 0.13 and 0.10 μM, respectively, for the three catechol substrates. The pH optima for the reaction were 7.5 for MD and 6.5 for both MDA and MNA.

3 When platelet homogenates from 20 individual subjects were tested, there were significant correlations between PST activities measured with dopamine and those measured with MD, MDA and MNA (r = 0.54, 0.98 and 0.93, P <0.02, <0.001, and <0.001, respectively), but not between activities measured with low concentrations of phenol and those measured with MD, MDA and MNA (r = 0.021, 0.045 and 0.046, respectively). These results were also compatible with the conclusion that MD, MDA and MNA were substrates for the thermolabile form of platelet PST.

4 These observations will make it possible to test the hypothesis that variations in the activity of the thermolabile form of platelet PST may reflect individual differences in the sulphate conjugation of MD, MDA and MNA.

Introduction

α-Methyldopa (MD) is a widely used antihypertensive drug. Sulphate conjugation catalyzed by phenol sulphotransferase (E.C. 2.8.2.1, PST) is an important metabolic pathway for MD (Myhre et al., 1972; Saavedra et al., 1975; Stenboek et al., 1977) as it is for many other phenolic and catechol drugs and neurotransmitters (Richter, 1940; Axelrod et al., 1959; Levy et al., 1975). There are wide individual variations in the dose of MD required to lower blood pressure in hypertensive patients, and the degree of sulphate conjugation of MD varies 5 fold among individuals (Dollery & Harrington, 1962; Saavedra et al., 1975). These observations have raised the possibility that one factor which may play a role in variations in the therapeutic effect of the drug and/or in the occurrence of adverse reactions to it might be individual differences in the metabolism of MD and its amine metabolites, metabolites that are thought to play an important role in the anti hypertensive actions of MD (Hennig, 1975).

PST activity is present in several human tissues including the platelet (Hart et al., 1979; Anderson & Weinshilboum, 1980; Anderson et al., 1981; Rein et al., 1981a). There are 4-5 fold individual variations in the activity of platelet PST when 3-methoxy-4-hydroxyphenyglycol (MHPG) is used as a substrate, and relative platelet PST activities are directly related to relative PST activities in the kidney (Anderson et al., 1981; Weinshilboum & Anderson, 1981). Therefore, it is possible that individual differences in platelet PST activity may reflect variations in the sulphate conjugation of MD and its metabolites by other
tissues. However, Rein et al. (1981b) have recently suggested, and results of experiments conducted in our laboratory have confirmed (Reiter & Weinsilboum, 1981, 1982), that there are at least two forms of human platelet PST. One form is ther-

molable. Its activity can be measured with dopamine as a substrate. The other form of the enzyme is ther-

molable, and low concentrations of phenol can serve as a substrate for that form of the enzyme (Reiter & Weinsilboum, 1981, 1982). Some com-

pounds, including phenol itself at high concentrations and paracetamol can serve as substrates for both the ther-

molable and thermostable forms of the enzyme (Reiter & Weinsilboum, 1981, 1982). Although sulphate conjugation of MD catalyzed by PST is a major catabolic pathway for MD (Myhre et al., 1972; Saavedra et al., 1975; Stenboek et al., 1977), it is not known whether MD and its amine metabolites are substrates for one or both forms of platelet PST. The present study was designed to determine whether MD, α-methyldopamine (MDA) and α-methylnor-

 adrenaline (MNA) were substrates for the thermo-

lable, the thermostable or both forms of human platelet PST. All three of these compounds were found to be substrates for platelet PST, and they were substrates for the thermostable form of the enzyme. These observations will make it possible to test the hypothesis that individual variations in the activity of the thermostable form of human platelet PST might reflect variations in the sulphate conjugation of MD, MDA and MNA in man.

Methods

Blood samples

Blood samples were obtained from randomly selected adult white blood donors at the Mayo Clinic Blood Bank, Rochester, Minnesota. The conditions under which these samples were obtained have been described (Anderson et al., 1981).

Platelet preparation

Platelets were isolated and processed as described previously (Anderson & Weinsilboum, 1980; Anderson et al., 1981). Fresh pooled platelet homogenates from four to eight subjects were used for all experiments except those in which platelets from twenty individual subjects were studied. Platelet counts were performed with a Coulter model ZBI cell counter. In preparation for the PST assay, 1 ml of platelet-rich plasma was placed in a 16 × 75 mm plastic tube and was centrifuged at 16,000 g for 10 min at 4°C. The supernatant was discarded. When MD was used as substrate, 2 ml of 10 mM Tris-HCl buffer, pH 7.5, was added to the tube containing the pellet. When other substrates were studied, 2 ml of 5 mM potassium phosphate buffer, pH 7.5, was added. The pellet was then homogenized for 15 s with a Polytron tissue homogenizer.

PST assay

Two methods of assay were used to measure PST activity, one for MDA, MNA, dopamine and phenol, and the other for MD. When MDA, MNA, dopamine and phenol were used as substrates, plate-

let PST activity was assayed by the method of Foldes & Meek (1973) as modified by Anderson & Weinsilboum (1980) and Anderson et al. (1981). The assay involved the incubation of diluted platelet homogenates in the presence of 35S-3′-phospho-

adenosine-5′-phosphosulphate (PAPS), the sulphate donor, and one of the sulphate acceptor substrates. Pargyline, a monoamine oxidase inhibitor (Fuentes & Neff, 1975), at a final concentration of 1 mM was included in the reaction mixture in all experiments in which MDA, MNA and dopamine were used as sub-

strates. The final concentrations of MD, MDA and MNA used in the assay were 12 mM, 47 μM and 0.75 mM, respectively. After 30 min of incubation the reaction was terminated by the precipitation of protein and PAPS with barium hydrox-

ide and zinc sulphate. The aqueous supernatant contain-

ing the radioactive product was aspirated and was placed in a liquid scintillation counting vial containing Instagel (Packard Instrument Co., Inc.). Radio-

activity was measured in a Beckman LS-7500 liquid scintillation counter.

When MD was used as a substrate, the PST assay was performed exactly as described above up to the point at which the reaction was terminated. Com-

pounds such as MD that contain carboxylic acid residues are precipitated by the barium hydroxide used to terminate the Foldes & Meek (1973) assay (Baranczyk-Kuzma et al., 1981). Precipitation of the reaction product may give the impression that such acidic compounds are poor substrates for PST. To avoid this artifact, PST activity measured with MD as a substrate was assayed by a modification of the method described by Baranczyk-Kuzma et al. (1981). This approach avoids the use of barium hydroxide to precipitate the PAPS and instead uses ion exchange chromatography to separate radioactive PAPS from the radioiodelabeled product of the reaction. Specifically, the reaction was terminated at the end of the 30 min incubation period by placing the reaction tubes in ice-cold water. The contents of the tubes were then poured onto 7 × 30 mm Ectoela cellulose ion exchange columns formed in 6 inch disposable plastic transfer pipettes. The Ectoela cellulose had initially been equilibrated with 0.5 M ammonium bicarbon-

ate. After the columns were formed, they were washed with 0.005 M ammonium bicarbonate prior to
sample application. After sample application, radioactively labeled MD-sulphate was eluted with 3 ml of 0.005 M ammonium bicarbonate, and this 'wash' was collected in a liquid scintillation counting vial. Instagel, 10 ml, was added to the vial, and radioactivity was measured in a Beckman LS-7500 liquid scintillation counter. Figure 1 shows the elution pattern from a column with MD as substrate. In this case, the procedure was altered so that the column was eluted with increasing concentrations of ammonium bicarbonate ranging from 0.005 M to 0.2 M. One ml fractions were collected. The radioactive peak for the reaction product was well separated from the large, late peak which represented the elution of 35S-PAPS (Figure 1). The major modification of the procedure described by Baranczyk-Kuzma et al. (1981) was alteration of the elution conditions so that 35S-MD sulphate was eluted in the initial fractions, a change that made it possible to assay a large number of samples.

'Blanks' for both assay procedures were samples to which no substrate had been added. One unit of enzyme activity represented the formation of 1 nmol of sulphate conjugated product per hour of incubation at 37°C. Results were expressed per 10⁹ platelets. It has previously been shown that this method for the expression of results is more reproducible than is one based on mg of platelet protein (Anderson et al., 1981; Weinshilboum & Anderson, 1981).

**Thermal stability assays**

Pooled platelet homogenates in phosphate buffer were diluted 1:1 (vol:vol) in 5 mM potassium phosphate buffer, pH 7.5, containing 0.0625% bovine serum albumin (BSA). One ml aliquots were placed in 10 × 75 mm plastic tubes covered with Parafilm. The tubes were incubated for 15 min in a shaker water bath at various temperatures. An aliquot of the same homogenate was kept at 4°C as a control. The heated tubes were placed at 4°C immediately after thermal treatment. No substrate or other constituent of the enzyme reaction mixture was present during thermal treatment. After heating, each sample was diluted an additional 64 fold (final dilution 128 fold), and 200 µl aliquots were used to measure PST activity. When MD was to be the substrate, the final dilution was performed with 0.0625% BSA in 10 mM Tris-HCl buffer, pH 7.5. When the other substrates were used, dilution was performed with 0.0625% BSA in 5 mM potassium buffer, pH 7.5. Values for blank samples were determined for each incubation temperature studied.
Kinetic analysis

Michaelis-Menten ($K_m$) values were estimated by the method of Wilkinson (1961) with a Fortran program written by Cleland (1963). A Control Data Corporation Cyber 170/720 computer was used for these calculations.

Materials

MD and BSA were purchased from Sigma Chemical Company, St. Louis, Missouri. MDA was a gift of Dr. Neal Castagnoli, University of California Medical School, San Francisco, California. MNA was purchased from Regis Chemical Company, Morton Grove, Illinois, and pargyline hydrochloride was obtained from Saber Laboratories, Inc., Morton Grove, Illinois. $^{35}$S-PAPS (2.0–4.5 Ci/mmol) was purchased from New England Nuclear Corporation, Boston, Massachusetts. Dithiothreitol (Cleland’s reagent) and 3,4-dihydroxyphenylethylamine (dopamine) were purchased from Calbiochem, San Diego, California. Phenol was obtained from Fisher Scientific Company, Fairlawn, New Jersey. Ecteola cellulose (Cellex E) was purchased from BioRad Laboratories, Richmond, California.

Results

Effect of enzyme quantity and incubation time on PST activity

PST activity in a pooled platelet homogenate increased in a linear fashion for all three of the α-methylcatechol compounds with increasing quantities of diluted homogenate varying from dilutions of 2 to 256 fold. A final dilution of 128 fold, a value well within the linear range, was chosen for use in the assays. With all three substrates there was also a linear increase in product formed with increasing time of incubation for up to 50 min. Thirty minutes was chosen as the standard incubation time for all subsequent experiments.

Effect of pH on PST activity

Platelet PST activity was measured at various pH values in the presence of each of the three α-methylcatechol substrates. Three separate buffer systems were used in these experiments: 16 mM sodium acetate; 8 mM postassium phosphate; and 16 mM Tris-HCl. The concentrations indicated were those present in the final reaction mixtures. pH values were measured at room temperature in the presence of all components of the reaction mixture. The pH optima found were approximately 7.5 for MD, and approximately 6.5 for MDA and MNA. There was no evidence of a ‘second peak’ of activity at higher pH values for any of the three substrates. A Tris-HCl buffer that resulted in a reaction pH of 7.5 was used for the assay of MD and a potassium phosphate buffer that resulted in a reaction pH of 6.5 was used with MDA and MNA.

Effect of substrate concentrations on PST activity

PST activity in a pooled platelet homogenate was measured with varying concentrations of MD, MDA and MNA. Apparent $K_m$ values were estimated from these data (Table 1). Previous studies from our laboratory have yielded estimates of apparent $K_m$ values for dopamine, a substrate for the thermolabile form of the enzyme, of 15 to 20 μM and of 15 to 16 μM for low concentrations of phenol, a substrate for the thermostable form of the enzyme (Reiter & Weinshilboum, 1981, 1982).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Concentration (μM)</th>
<th>Apparent $K_m$ (mM)</th>
<th>Catechol substrate (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol</td>
<td>0.0625</td>
<td>0.73</td>
<td>–</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0.060</td>
<td>0.18</td>
<td>–</td>
</tr>
<tr>
<td>MD</td>
<td>12.0</td>
<td>0.082</td>
<td>–</td>
</tr>
<tr>
<td>MDA</td>
<td>0.047</td>
<td>0.13</td>
<td>–</td>
</tr>
<tr>
<td>MNA</td>
<td>0.750</td>
<td>0.10</td>
<td>–</td>
</tr>
<tr>
<td>MD</td>
<td>–</td>
<td>–</td>
<td>5.5</td>
</tr>
<tr>
<td>MDA</td>
<td>–</td>
<td>–</td>
<td>0.014</td>
</tr>
<tr>
<td>MNA</td>
<td>–</td>
<td>–</td>
<td>0.28</td>
</tr>
</tbody>
</table>

PST activities with either MD, MDA or MNA as the sulphate acceptor substrates were also measured with various concentrations of PAPS, the sulphate donor for the reaction. These data were used to calculate apparent $K_m$ values for PAPS (Table 1). Apparent $K_m$ values for PAPS were also calculated with phenol, a substrate for the thermostable form of the enzyme at the 62.5 μM concentration used, and with dopamine, a substrate for the thermolabile form of platelet PST. The higher apparent $K_m$ value for PAPS with phenol than was found for dopamine confirms an observation that we made previously (Reiter & Weinshilboum, 1981, 1982). It is of interest that apparent $K_m$ values for PAPS measured with MD, MDA and MNA as sulphate acceptors were closer to that for dopamine than to that found with phenol as a substrate.
The coefficient of variation for the assay procedure performed with MD, MDA and MNA as substrates was determined with a pooled platelet homogenate. The homogenate was divided into 10 separate aliquots, and each aliquot was assayed with all three substrates. The coefficients of variation were 7.5%, 5.8% and 8.8% for MD, MDA and MNA, respectively.

Comparison of column with precipitation assay

The PST assay procedure developed by Foldes & Meek (1973) has been shown to be inappropriate for use with compounds such as MD because the reaction product is precipitated by the barium acetate, barium hydroxide and zinc sulphate used to precipitate PAPS (Baranczyk-Kuzma et al., 1981). Therefore, ion exchange columns of Ecteola cellulose were used in the assay of MD sulphotransferase activity in these studies. An experiment was performed to compare directly these two different assay procedures with MD as substrate. PST activity was assayed with both assay procedures in platelet preparations from 20 individual subjects. The average activity was 0.078 ± 0.014 units per 10⁶ platelets with the Foldes & Meek (1973) 'precipitation' assay and was 0.43 ± 0.04 units per 10⁶ platelets with the ion exchange column assay. The apparent PST activity measured by the Foldes & Meek (1973) assay with MD as a substrate was only 18% of that found when the procedure of Baranczyk-Kuzma et al. (1981) was used.

The purpose of this experiment was to determine whether MD, MDA and MNA were substrates for the thermostable, the thermostable or both forms of human platelet PST. Aliquots of a pooled platelet homogenate were incubated for 15 min at seven temperatures ranging from 37° to 49°C. PST activity was measured with 60 μM dopamine, a substrate for the thermostable form of the enzyme, and with 62.5 μM phenol, a substrate for the thermostable activity. The concentrations of dopamine and phenol used were based on the results of previous experiments performed in this laboratory (Reiter & Weinshilboum, 1981, 1982). Half of the dopamine sulphate conjugating activity was inactivated at approximately 40°C while half of the phenol sulphate conjugating activity was inactivated by pre-incubation at approximately 44.8°C (Figure 2). These results were virtually identical with those that we have reported previously (Reiter & Weinshilboum, 1981, 1982). PST activity was measured in the same homogenates with MD, MDA and MNA as substrates (Figure 2). None of the three α-methylcatechol compounds was a substrate for the thermostable activity which catalyzed the sulphate conjugation of 62.5 μM phenol. MDA and MNA had thermal inactivation curves that could be super-imposed on that of 60 μM dopamine (Figure 2). With the exception of the first point in its thermal inactivation curve, MD also behaved as if it were a substrate for the same thermostable activity that catalyzed the sulphate conjugation of dopamine (Figure 2). When
the experiment was repeated, identical results were obtained. These results were compatible with the conclusion that MD, MDA and MNA were not substrates for the thermostable form of platelet PST. In addition, it appeared that all or most of the sulphate conjugation of these compounds was catalyzed by the thermostable form of the enzyme.

**PST activity in individual subjects**

All of the previously described experiments were performed with pooled platelet preparations. There is at least a 5 fold individual variation in human platelet PST activity (Anderson & Weinshilboum, 1980; Anderson et al., 1981; Weinshilboum & Anderson, 1981). Advantage was taken of the natural individual variance in platelet PST to further test the hypothesis that MD, MDA and MNA were substrates for the thermostable form of the enzyme, a form for which dopamine serves as a substrate. PST activity was measured in platelet preparations from 20 individual subjects. Phenol (62.5 μM), dopamine (60 μM), MD (12 mM), MDA (47 μM) and MNA (0.75 mM) were all used as substrates for these assays. Average enzyme activities in samples from female and from male subjects for all five substrates are shown in Table 2. There were no significant differences between the two sexes in the enzyme activities measured in this small population sample. The average age of the female subjects studied was 35.8 ± 1.5 years (mean ± s.e. mean, n = 10), while that of the male subjects was 36.0 ± 1.8 years (n = 10). However, the major reason for performing the experiment was not to measure average enzyme activity levels but rather to study correlations of the variance of the activity in individual samples when different substrates were used.

We previously demonstrated that there was not a significant correlation between relative PST activities in individual platelet samples when the enzyme activities in the same samples were measured with both phenol and dopamine as substrates (Reiter & Weinshilboum, 1981, 1982). That observation was confirmed in these 20 samples (r = 0.045, P > 0.05, Figure 3). One interpretation of this observation is that the thermostable and the thermostable forms of human platelet PST activity are regulated independently. If that is correct, and if MD, MDA and MNA are substrates primarily or entirely for the thermostable form of the enzyme, then it would be expected that there would be a significant correlation among activities measured with α-methylcatechol compounds and those measured with dopamine, but not among the activities measured with α-methylcatechols and those determined with phenol. That is exactly what was found (Figures 4 and 5). Even though the correlation coefficients were significant between activities measured with each of the α-methylcatechol compounds and those measured with dopamine, the r value was not as great for MD as for MDA and MNA. Whether this observation was merely a reflection of the fact that a different assay procedure was used to measure MD sulphate conjugation, or was a reflection of a true biological characteristic of the platelet enzyme system was unclear. However, it was clear that MDA, MNA and MD were, like dopamine, entirely or primarily substrates for the thermostable form of human platelet PST.

**Table 2** Human platelet PST activity in male and female subjects. Platelet PST activity was measured with five substrates in platelet samples from 10 male and 10 female subjects. Enzyme activities are expressed as units per 10⁶ platelets.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Concentration (mM)</th>
<th>Female Activity</th>
<th>Male Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol</td>
<td>0.0625</td>
<td>0.33 ± 0.01</td>
<td>0.35 ± 0.01</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0.060</td>
<td>0.84 ± 0.02</td>
<td>0.79 ± 0.02</td>
</tr>
<tr>
<td>MD</td>
<td>12.0</td>
<td>0.38 ± 0.03</td>
<td>0.44 ± 0.03</td>
</tr>
<tr>
<td>MDA</td>
<td>0.047</td>
<td>0.98 ± 0.02</td>
<td>0.96 ± 0.02</td>
</tr>
<tr>
<td>MNA</td>
<td>0.750</td>
<td>0.63 ± 0.02</td>
<td>0.65 ± 0.02</td>
</tr>
</tbody>
</table>

**Discussion**

There are large individual variations in clinical response to and in the metabolism of MD. PST plays an important role in the metabolism of MD. The fact that PST activity can be measured in an easily obtained human tissue, the platelet, raises the possibility that measurement of platelet PST activity might make it possible to estimate one factor, variation in PST activity, which may play a role in individual differences in MD catabolism. To test this hypothesis would require determination of whether MD and
Figure 3  Correlation of PST activities in platelet preparations from 20 individual subjects. Each value represents the mean of three determinations.

Figure 4  Correlation of PST activities in platelet preparations from 20 individual subjects. Each value represents the mean of three determinations.

Figure 5  Correlation of PST activities in platelet preparations from 20 individual subjects. Each value represents the mean of three determinations.
related compounds were capable of serving as substrates for platelet PST. The recent suggestion that there are at least two forms of platelet PST (Rein et al., 1981b; Reiter & Weinsilboum, 1981, 1982) made it necessary to determine not only whether MD, MDA and MNA were substrates for platelet PST but, also, whether the reaction was catalyzed by the thermostable or the thermolabile form of the enzyme. The results of the experiments described here showed that MD, MDA and MNA were substrates for platelet PST. Apparent $K_m$ values were 5.5, 0.014 and 0.28 mM for MD, MDA and MNA, respectively. Apparent $K_m$ values for the sulphate donor, PAPS, were 0.082, 0.13 and 0.10 µM for MD, MDA and MNA, respectively. Thermal stability studies performed with a pooled platelet homogenate indicated that MD, MDA and MNA were substrates for the thermodabile form of the enzyme. These results were confirmed when samples from 20 individual subjects were studied. The lesser degree of correlation between activities measured with MD and those measured with dopamine, a model substrate for the thermodabile form of the enzyme, as compared with MDA and MNA may be related either to the use of a different assay procedure for MD or may represent a true biological characteristic of the system.

It has been suggested by Rein et al. (1981b) that the two forms of platelet PST be referred to as the 'P' or 'phenol' form and as the 'M' or 'monoamine' form. The thermodabile and thermodabile forms described in this and in our previous studies (Reiter & Weinsilboum, 1981, 1982) are probably analogous to the 'P' and 'M' forms, respectively. Since phenol can serve as a substrate for both forms of the enzyme, and since nonmonoamines such as MHPG can serve as substrates for the thermodabile form, the 'P' and 'M' nomenclature that has been suggested may be somewhat misleading. No matter what nomenclature is ultimately used to describe the apparent multiple forms of human platelet PST, the occurrence of these different activities will have to be taken into account in future clinical pharmacological studies of sulphate conjugation in man. It must now be determined whether other tissues such as brain, liver and intestine contain analogous forms of PST, whether the regulation of the platelet enzyme activity reflects regulation of the relative PST activity in these other tissues, and whether such differences represent a functionally significant factor that plays a role in individual variations in human drug metabolism. Finally, the results of the experiments described here have laid the groundwork that will make it possible to proceed with testing the hypothesis that individual variations in platelet PST activity might be of value in predicting at least a portion of individual variance in the sulphate conjugation of α-methylcatechol compounds in man.

We thank Luanne Wussow, Joel Dunnette and Dr Christoph Reiter for their assistance with these studies.

This work was supported in part by a grant from Merck, Sharp and Dohme Division of Merck and Co., Inc. and by NIH grants NS 11014 and GM 28157. Dr Mwaluko is a Fogarty International Fellow on leave from the Muhimbili Medical Centre, University of Dar es Salaam, Dar es Salaam, Tanzania. Dr Weinsilboum is a Burroughs Wellcome Scholar in Clinical Pharmacology.

References


LEVY, G., KHANNA, N.N., SODA, D.M., TSUKUKI, O. &
MD, MDA, MNA AS SUBSTRATES FOR PLATELET PST


(Received December 8, 1981, accepted February 18, 1982)