Hypolipidemic Activity of Phthalimide Derivatives. 1. N-Substituted Phthalimide Derivatives

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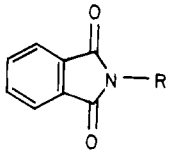
The general lipid-lowering action of the N-substituted phthalimide derivatives reported herein, as well as the activity of potassium phthalimide, implicates the phthalimide moiety as possessing hypolipidemic activity in rodents. Compounds containing substituents with chain lengths of four carbon or oxygen atoms showed the best hypolipidemic activity in the series tested. Tests involving 1-*N*-phthalimidobutan-3-one demonstrated a dose-dependent hypolipidemic action free of estrogenic side effects, with no apparent deposition of cholesterol in body organs, and with a high therapeutic index. Further work on the hypolipidemic activity of phthalimido, as well as other imido compounds, is underway.

A number of compounds which are structurally related to phthalimide have recently been shown to have hypocholesterolemic and/or hypotriglyceridemic effects in rodents. These include phthalate esters which are industrial plasticizers,[1] 2-phenoxyalkanoic acid esters of *N*-hydroxyimides,[2] 1-(*p*-chlorophenyl)-1-(β-hydroxy-*p*-chlorophenethyl)-2,3-dihydroisoindoline,[3] and ethyl 2,2-dimethyl-*p*-(*N*-isoindol-1-one)phenoxyacetate.[4]

Preliminary data from our laboratory indicated that potassium phthalimide (**1**) possessed hypolipidemic activity in mice. Subsequently, a series of N-substituted phthalimides including alkyl (**2–9**), methyl ketone (**10–14**), carboxylic acid (**15–19**), and acetate ester (**20–23**) substituents of various chain lengths were synthesized.

Synthesis. The N-substituted phthalimide derivatives



2–9, R = $(CH_2)_nCH_3$; n = 0–7
10–14, R = $(CH_2)_nC(=O)CH_3$; n = 1–5
15–19, R = $(CH_2)_nCOOH$; n = 1–5
20–23, R = $(CH_2)_nCH(OH)CH_3$; n = 1–4

reported were synthesized utilizing either Gabriel reaction conditions[5] or by reaction of the appropriate amino compound with phthalic anhydride and subsequent ring closure.[6,7] 1-*N*-Phthalimidobutan-3-one (**11**) was prepared by Michael reaction of methyl vinyl ketone with phthalimide.[8] 1-*N*-Phthalimidohexan-5-one (**13**) and 1-*N*-phthalimidoheptan-6-one (**14**) were synthesized first by alkylation of acetoacetic ester with the appropriate *N*-(bromoalkyl)phthalimide and then ester hydrolysis and decarboxylation of the acetoacetylalkylphthalimido product.[9] Acetate esters, with the exception of *N*-phthalimidobutan-1-one acetate, were prepared by acetylation of the corresponding *N*-phthalimido alcohols.

Results and Discussion

The phthalimide analogues significantly reduced serum cholesterol and triglycerides levels after dosing 16 and 14 days, respectively, in mice.

The data support the idea that the phthalimide nucleus itself possesses hypolipidemic activity in this species. With respect to serum cholesterol levels in the *N*-alkyl series, chain lengths of four (**5**) and five (**6**) (Table I) carbon atoms afforded the best activity with 46 and 42% reduction, respectively. In the methyl ketone series, chain lengths of three to six carbon atoms (**10–13**) resulted in the best activity with 33–37% reduction of serum cholesterol levels. Of the acid derivatives, the propionic analogue (**16**) demonstrated the best activity with 45% reduction, whereas in the ester series the methyl acetate derivative (**20**) showed the best reduction, i.e., 38%. It is interesting to note that carbon chain lengths of four atoms or an oxygen substituted for one of the carbons resulted in compounds which had the best reduction activity of each series, viz., *N*-alkyl (**5**), methyl ketone (**11**), acid (**16**), and ester (**20**).

The serum triglyceride levels were reduced to a greater degree with derivatives of the ketone and acid series. In the ketone series, the propanone (**10**), butanone (**11**), and pentanone (**12**) analogues were most effective with 52, 42, and 41% reduction, respectively. In the acid series, the propionic (**16**), butyric (**17**), valeric (**18**), and caproic (**19**) derivatives were significantly active with 42, 41, 46, and 49% reduction, respectively. The only N-1 ester substituent which showed significant activity in lowering serum triglycerides was the methyl acetate analogue (**20**), which demonstrated 43% reduction. With the exception of the *N*-alkyl series, side-chain length equivalent to four carbons resulted in the best inhibitory activity against triglycerides in the acid, ester, and ketone series.

In vitro acetyl coenzyme A synthetase activity was also significantly inhibited by the phthalimide derivatives. In the *N*-alkyl series, chain lengths of 1 (**2**), 3 (**4**), and 5 (**6**) resulted in the best inhibitory activity, whereas the even numbered chains containing 2 (**3**) and 4 (**5**) carbon atoms afforded minimal activity. In the ketone series, the propanone (**10**) and butanone (**11**) resulted in 42 and 47% inhibition, with the pentanone (**12**) and hexanone (**13**) being somewhat less active. In the acid series, the propionic (**16**), butyric (**17**), and caproic (**19**) analogues possessed the best activity at 43, 36, and 41% inhibition, respectively. In the ester series, only the methyl acetate derivative (**20**) was significantly active. Linear-regression analysis showed that there was a positive correlation between the inhibition of acetyl coenzyme A synthetase activity and the lowering of serum triglyceride with a coefficient of correlation of 0.808 at a 0.001 probability level.

Selecting 1-*N*-phthalimidobutan-3-one (**11**) as a representative analogue of the series, a number of other parameters were examined. It can be shown that the lowering of serum cholesterol is dose dependent in mice (Table II) and that this compound is also active in rats. Compound **11** at 10 (mg/kg)/day caused 41% reduction of serum cholesterol and serum triglyceride levels of rats after 16 days of dosing. Compound **11** at 8.6 μmol caused a 23% inhibition of HMGCoA reductase activity, the regulatory enzyme of cholesterol synthesis (Table III). Compared to clofibrate, only 20% of the concentration of compound **11** was required to cause the same magnitude

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Table I. Effects of Phthalimide Analogues on Serum Lipids in Mice[a] ($N = 6$)

no.	compound	% control: serum cholesterol 9th day	% control: serum cholesterol 16th day	% control: serum triglycerides	% control: in vitro AcCoA synthetase	obsd mp or bp, °C (mmHg)	lit. mp or bp, °C (mmHg)	lit. ref
1	potassium phthalimide	63 ± 6[e]	78 ± 3[d]	88 ± 4[d]	78 ± 6[e]			
2	*N*-methylphthalimide	74 ± 4[e]	74 ± 8[d]	68 ± 8[e]	66 ± 12[e]	137-139	133.5-134	26
3	*N*-ethylphthalimide	83 ± 4[e]	76 ± 2[e]	87 ± 5[d]	82 ± 5[e]	77-78.5	79	26
4	*N*-*n*-propylphthalimide	96 ± 4	74 ± 5	81 ± 9[d]	67 ± 3[e]	63.5-65	64.5	27
5	*N*-*n*-butylphthalimide	72 ± 10[e]	54 ± 6[e]	82 ± 16	82 ± 7[d]	110-116 (0.12)	100-104 (0.03)	6
6	*N*-*n*-pentylphthalimide	76 ± 5[e]	58 ± 3[e]	75 ± 16[c]	68 ± 6[e]	114-115 (0.028)	175 (14)	28
7	*N*-*n*-hexylphthalimide	96 ± 5	66 ± 4[e]	84 ± 8[d]	71 ± 12	118-122 (0.07)	140-146 (0.04)	6
8	*N*-*n*-heptylphthalimide	99 ± 7	72 ± 4[e]	84 ± 6[d]	71 ± 5[e]	34-35	40	29
9	*N*-*n*-octylphthalimide	101 ± 7	82 ± 3[d]	77 ± 4[e]	76 ± 7[e]	47-48	50-51	30
10	1-*N*-phthalimidopropan-2-one	80 ± 16[b]	67 ± 12[e]	48 ± 10[e]	58 ± 7[e]	124-127	122.9-123.5	31
11	1-*N*-phthalimidobutan-3-one	67 ± 11[e]	63 ± 7[e]	58 ± 7[e]	53 ± 12[e]	114-116	111-113	8
12	1-*N*-phthalimidopentan-4-one	71 ± 6[e]	63 ± 5[e]	59 ± 13[e]	62 ± 3[e]	73.5-75	74.5-75.5	11
13	1-*N*-phthalimidohexan-5-one	65 ± 9[e]	65 ± 7[e]	77 ± 5[e]	68 ± 6[e]	65-67	66-68	9
14	1-*N*-phthalimidoheptan-6-one	71 ± 6[e]	75 ± 12[c]	88 ± 5[d]	85 ± 3[e]	71.5-74	71-72	32
15	2-*N*-phthalimidoacetic acid	76 ± 7[e]	68 ± 7[e]	72 ± 9	72 ± 12[e]	199-202	191-192	33
16	3-*N*-phthalimidopropionic acid	74 ± 7[e]	55 ± 11[e]	58 ± 10[e]	57 ± 7[e]	152-153	151	34
17	4-*N*-phthalimidobutyric acid	80 ± 7[e]	68 ± 6[e]	59 ± 14[e]	64 ± 12[e]	117-118	117.5	35
18	5-*N*-phthalimidovaleric acid	83 ± 9[d]	77 ± 4[d]	54 ± 5[e]	76 ± 8[e]	118.5-120	118.5-119.5	36
19	6-*N*-phthalimidocaproic acid	81 ± 6[e]	67 ± 3[e]	51 ± 12[e]	59 ± 9[e]	108	107-108	37
20	*N*-phthalimidomethyl acetate	61 ± 9[e]	62 ± 4[e]	57 ± 25[e]	62 ± 10[e]	119-121	118	38
21	*N*-phthalimidoethyl acetate	93 ± 13	95 ± 1[e]	82 ± 7[d]	81 ± 6[e]	89-90	88.5	39
22	*N*-phthalimidopropan-1-ol acetate	102 ± 4	66 ± 2[e]	89 ± 9	84 ± 2[h]	63.5-65		
23	*N*-phthalimidobutan-1-ol acetate	93 ± 9	66 ± 5[e]	88 ± 7[b]	83 ± 2[e]	58.5-60.5	59.5	40
24	1% carboxymethylcellulose	100 ± 2[f]	100 ± 11[g]	100 ± 6[h]	100 ± 6[i]			

[a] N = number of mice per test group = 6. [b] $p = 0.25$. [c] $p = 0.10$. [d] $p = 0.005$. [e] $p = 0.001$. [f] 115 mg %. [g] 118 mg %. [h] 138 mg %. [i] 10.8 mg/g wet tissue.

Table II. Serum Lipid Level[a] after Administering Test Compounds

	% control, $\bar{x}$ ± SD: 9th day of dosing	16th day of dosing
serum cholesterol levels		
CF_1 male mice, ip ($N = 8$)		
11, 10 (mg/kg)/day	73 ± 9[d]	66 ± 5[d]
11, 20 (mg/kg)/day	67 ± 9[d]	63 ± 9[d]
11, 30 (mg/kg)/day	66 ± 7[d]	54 ± 6[d]
clofibrate,[e] 20 (mg/kg)/day	98 ± 12	96 ± 15
1% CMC, control	100 ± 8	100 ± 7
control value (mg %)	113	128
Holtzman male rats, po ($N = 6$)		
11, 1 (mg/kg)/day	82 ± 10[c]	
11, 10 (mg/kg)/day	70 ± 8[d]	59 ± 8[d]
clofibrate,[e] 10 (mg/kg)/day	97 ± 15	106 ± 9
1% CMC, control	100 ± 8	100 ± 7
control value (mg %)	73	77
serum triglycerides levels		
Holtzman male rats ($N = 6$)		
11, 10 (mg/kg)/day		59 ± 13[d]
1% CMC, control		100 ± 11
control value (mg %)		151

[a] In milligram percent. [b] $p = 0.025$. [c] $p = 0.01$. [d] $p = 0.001$. [e] Ethyl 2-(*p*-chlorophenoxy)-2-methylpropionate (ATROMID-S), Ayerst.

Table III. In Vitro Effects of Test Compounds on Regulatory Enzyme for Lipid Synthesis

compd ($N = 6$)	% control: HMGCoA reductase act., ± SD
11 (8.6 μmol)	76 ± 2[a]
clofibrate (41 μmol)	76 ± 3[a]
1% CMC	100 ± 3[b]

[a] $p = 0.001$. [b] 1 142 065 dpm/g wet weight of liver.

of inhibition of HMGCoA reductase activity. However, a major effect of 11 appears to be on AcCoA synthetase activity, which was inhibited 50% at one-fourth of the concentration required to inhibit HMGCoA reductase activity 26%. Compound 11 did not suppress the appetite of the animal and thereby reduced serum lipids (Table IV). Similarly, there was no pronounced change in the body weight of animals over this period. Examination of liver homogenates demonstrated that compound 11 caused no marked alteration of nucleic acid, glycogen, protein, or lipid content of liver cells (Table V). When [^{14}C]cholesterol was administered after 16 days of dosing with compound 11, it was obvious that there was a substantial reduction in the deposition of labeled cholesterol in the liver (79%), kidney (40%), and heart (49%) (Table VI). In the presence of the drug, a larger percentage of labeled cholesterol was deposited in the large intestine and feces after 24 h, whereas in the control a larger percentage was concentrated in the stomach and small intestine, suggesting that 11 accelerates the removal of cholesterol through the feces. LD_{50} studies showed that the therapeutic index of this drug was quite high, since at 2 g/kg no deaths were recorded. The limits of solubility of the drug has been reached at this concentration. There was no evidence that the weight of any of the major organs was altered after drug treatment (Table VII). This is not true of phthalate esters, the plasticizers, which have been reported to cause a large increase in liver weight.[10] A number of hypolipidemic agents also possess estrogenic characteristics. With 11 there was no decrease in the size of the vas deferens, vesicular, or testes (Table VII) after a 16-day

Table IV. Effects of Compound 11 on Food Intake and Body Weight

compound (N = 6)	av. daily food intake, g/rat: 1-8 days, $\bar{x}$ ± SD	av. daily food intake, g/rat: 9-16 days, $\bar{x}$ ± SD	rat body wt, g: 0 day, $\bar{x}$ ± SD	rat body wt, g: 9th day, $\bar{x}$ ± SD	rat body wt, g: 16th day, $\bar{x}$ ± SD
11	39.4 ± 3.8	39.5 ± 4.6[a]	317 ± 9	338 ± 9 (106%)	348 ± 15 (110%)
1% CMC	34.9 ± 5.2	34.7 ± 3.7	325 ± 7	341 ± 14 (105%)	362 ± 5 (116%)

[a] p = 0.025.

Table V. Percent of Control of RNA, DNA, Protein, Glycogen, and Lipid Levels of Rat Liver Treated 16 Days with 11 at 10 (mg/kg)/day

compd (N = 6)	DNA, $\bar{x}$ ± SD	RNA, $\bar{x}$ ± SD	lipid, $\bar{x}$ ± SD	glycogen, $\bar{x}$ ± SD	protein, $\bar{x}$ ± SD
11	104 ± 11	108 ± 19	100 ± 5	94 ± 6	99 ± 5
1% CMC	100 ± 18	100 ± 6	100 ± 7	100 ± 8	100 ± 3

Table VI. ^{14}C Content of Tissues after 16-Days Dosing with 11 and 24 h after Administration of [^{14}C]Cholesterol

tissue (N = 6)	control, 1% CMC: dpm/g of tissue	control, 1% CMC: total dpm	treated with 11: dpm/g of tissue	treated with 11: total dpm	treated with 11: % control
liver	31425	386525	6655	82522	21.3
kidney	7630	17778	4413	10591	59.5
heart	4916	3849	2018	1968	51.1
chyme	2774	11318	1378	2864	25.3
stomach	166617	324903	17320	45754	14.1
small intestine	35671	363130	1819	18754	5.2
large intestine & feces	3808	18010	1212	60646	336.7

treatment at 10 (mg/kg)/day, nor did the drug demonstrate uterotropic effects in ovariectomized immature females at 20 mg/kg. Furthermore, compound 11 caused no hypertrophy of the adrenal as was seen with many hypercholesteremic agents.

Experimental Section

Chemistry. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer 297 spectrophotometer. NMR data were obtained using a JEOL FX-60 spectrophotometer. *N*-Phthalimidoacetic acid was obtained from Aldrich Chemical Co. and recrystallized from water. Potassium phthalimide and *N*-(hydroxyethyl)phthalimide were obtained from Eastman Kodak Co. Elemental analyses were conducted by M-H-W Laboratories, Phoenix, Ariz., and were within ±0.4% of theory.

Method A. According to the procedure of Abdel-Monem et al.,[11] 0.11 mol of methyl *p*-toluenesulfonate, ethyl iodide, 1-bromopentane, chloroacetone, or 5-chloro-2-pentanone was added to 0.1 mol of potassium phthalimide in DMF and heated to 100 °C for 8 h to afford compound **2** (41%), **3** (63%), **6** (51%), **10** (50%), or **12** (12%).

Method B. Equimolar amounts of phthalic anhydride and a primary amine were mixed in toluene and heated according to the method of Sterk et al.[6] to synthesize compounds **4** (79%), **5** (88%), **7** (83%), **8** (61%), **9** (85%), **15** (90%), **16** (39%), **17** (75%), **18** (70%), and **19** (70%).

1-*N*-Phthalimidobutan-3-one (11). This compound was prepared according to the method of Irai, Shima, and Murata[8] in 80% yield.

1-*N*-Phthalimidohexan-5-one (13) and 1-*N*-Phthalimidoheptan-6-one (14). These compounds were prepared according to the method of Baker and Querry.[9] Distillation in vacuo gave oils which after solidification were recrystallized from ether. **13**: 45% yield; bp 176–186 °C (0.05 mmHg); mp 65–67 °C (Et_2O). **14**: 48% yield; bp 166–176 °C (0.25 mmHg); mp 71.5–74 °C (Et_2O).

Synthesis of *N*-Alkanol Acetates. The acetates were prepared from the corresponding alcohols with acetic anhydride in pyridine. *N*-(Hydroxymethyl)phthalimide[12] (94% yield), *N*-(hydroxyethyl)phthalimide (Eastman Kodak Co.), and 3-*N*-phthalimido-1-propanol[13] (90% yield) were esterified with acetic anhydride in pyridine to give compounds **20–22**, respectively. Anal. ($C_{13}H_{13}NO_4$) C, H. *N*-Phthalimidobutan-1-ol acetate (**23**) was prepared by method B from 4-bromobutyl acetate[14] and potassium phthalimide by keeping the mixture at 190–200 °C for 10 h, with a 44% yield. All compounds synthesized are listed in Table VII with observed and literature physical constants.

Table VII. Percent of Total Body Weight after 16 Days of Treatment

organ (N = 6)	control, 1% CMC	11	% control
liver	3.38 ± 0.15	3.56 ± 0.31	105
kidney	0.64 ± 0.11	0.70 ± 0.09	109
heart	0.22 ± 0.07	0.23 ± 0.04	105
brain	0.29 ± 0.06	0.30 ± 0.09	103
spleen	0.12 ± 0.05	0.16 ± 0.10	133
lung	0.44 ± 0.12	0.46 ± 0.10	105
chyme	1.31 ± 0.38	0.81 ± 0.47	62
feces	1.16 ± 0.33	1.01 ± 0.37	87
stomach	0.52 ± 0.23	0.58 ± 0.25	112
small intestine	2.81 ± 0.44	2.98 ± 0.56	106
large intestine	1.31 ± 0.19	1.41 ± 0.66	108
epididymis/vas deferens	0.50 ± 0.04	0.52 ± 0.09	104
vesicular glands	0.29 ± 0.06	0.35 ± 0.08	121
testes	0.93 ± 0.13	1.06 ± 0.15	114
adrenals	0.037 ± 0.014	0.027 ± 0.012	73

Biological. Animals and Diet. CF_1 male mice (≃30 g) and male Holtzman rats (≃140 g) were fed Wayne Blox rodent lab chow with water ad libitum for the duration of the experiment. Drugs were suspended in 1% CMC (carboxymethylcellulose)–H_2O and homogenized. Doses were calculated on weekly weights of the animals.[15]

Serum Hypolipidemic Activity. Compounds were tested at 20 (mg/kg)/day and administered intraperitoneally to male mice at 11:00 a.m. On days 9 and 16, the blood was collected by tail-vein bleeding. The blood samples were collected between 8:00 and 9:30 a.m. in alkali-free nonheparinized microcapillary tubes which were centrifuged for 3 min to obtain the serum.[15] Duplicate 25-μL samples of nonhemolyzed serum were used to determine the milligram percent serum cholesterol levels by a modification of the Liebermann–Burchard reaction.[16] Using a separate group of mice, which were bled on day 14, serum triglyceride levels (in milligram percent) were measured using duplicate samples of 50 μL.[17] A dose–response curve was obtained for compound 11 at 10, 20, and 30 (mg/kg)/day for the suppression of serum cholesterol levels in male mice.

Using Holtzman male rats, compound 11 was administered at 1 and 10 (mg/kg)/day, ip. Serum cholesterol levels were measured on days 9 and 16 and serum triglyceride levels on day 16.

Effects on Lipid Distribution. The average weight increase (in grams) and food consumption (in grams/day) was determined over the 16-day period for rats (≃325 g) treated at 10 (mg/kg)/day.[15] On day 16, 4 μCi of [26-^{14}C]cholesterol (58 mCi/mmol) was injected intraperitoneally. Rats were sacrificed 24-h later, and a number of organs were excised and weighed. Aliquots of these tissues were homogenized in water (10%), combusted using a Packard Tri-Carb sample oxidizer, and analyzed for ^{14}C content using a scintillation counter.[18,19] The radioactive counts were corrected for quenching and are expressed as disintegrations per minute/gram of wet tissue. Aliquots of liver were homogenized (10%) in 0.25 M sucrose plus 0.001 M EDTA, pH 7.2. The DNA, RNA, protein, lipid, and glycogen were extracted and quantitated

by the method of Shibko et al.[20]

Enzymatic Assays. In vitro effects of test compounds on fatty acid synthesis (AcCoA synthetase enzymatic activity) were tested at 2.4 μmol concentrations by the method of Goodridge.[21] Compound 11 was also tested at 8.6 μmol for its effects on in vitro cholesterol synthesis by using the radioactive incorporation of [^{14}C]acetate into cholesterol as described by Haven et al.[22] and extracted according to the method of Wada et al.[23]

Acute Toxicity Studies. LD_{50} studies in CF_1 male mice (≃30 g) were carried out by the method of Litchfield and Wilcoxon[24] over the range of 50 μg to 2 g/kg for compound 11.

Uterotropic activity of compound 11 was determined in ovariectomized immature Holtzman female rats (≃50 g). Ovaries were removed by the method of Emmens.[25] Three days after operating, animals were dosed at 20 (mg/kg)/day ip for the next 3 days. 17-β-Ethinylestradiol at 10 (μg/kg)/day was used as a standard. On the 4th day, the animals were sacrificed, and the uteri were removed, trimmed, and weighed.[25] The uteri for the control was 68 ± 8 mg, for the ethinylestradiol standard 184 ± 9 mg, and after treatment with compound 11, 52 ± 7 mg.

In Tables I–VII, the probable significant level (p) was determined between experimental groups and the control by the Student's t test; the number of animals per group is expressed as N; the mean of the percentage of the control and the standard deviation are expressed as $\bar{x}$ ± SD.

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Synthesis and Biological Evaluation of 9,11-Azo-13-oxa-15-hydroxyprostanoic Acid, a Potent Inhibitor of Platelet Aggregation

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The synthesis of a prostaglandin endoperoxide analogue, 9,11-azo-13-oxa-15-hydroxyprostanoic acid (AOHP), is described. AOHP was found to block effectively both the thromboxane synthetase and the PGH_2/TxA_2 receptors in human platelets. It inhibits the platelet aggregation induced by arachidonic acid, 9,11-methanoepoxy-PGH_2, PGH_2, and TxA_2 but does not affect the ADP-induced aggregation in aspirinated platelet-rich plasma. Some of the intermediates for the synthesis of AOHP also are effective in inhibiting platelet aggregation.

Over the past several years prostaglandins have received considerable attention with regard to their divergent effects on platelet aggregation.[2,3] The greatest attention has been focused on the physiologic antagonists thromboxane A_2

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