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Metabolism of *cis*-Δ^4-15(*S*)-15-Methylprostaglandin $F_{1\alpha}$ Methyl Ester in the Rat

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The metabolic transformation and excretion of tritium-labeled *cis*-Δ^4-15(*S*)-15-methylprostaglandin $F_{1\alpha}$ methyl ester (**1**) have been investigated in rats after chronic and single dose oral administration. Three metabolites have been identified from a partially purified urinary extract. They were the *cis*-Δ^4-15-methylprostaglandin $F_{1\alpha}$ (**2**), 15-methyl-2,3-dinorprostaglandin $F_{1\alpha}$ (**3**), and 15-methyl-2,3,4,5-tetranorprostaglandin $F_{1\alpha}$ (**4**). The excretion of the drug-related species was significantly slower than that of the natural prostaglandin $F_{2\alpha}$. The slow excretion rate and the presence of unchanged *cis*-Δ^4-15-methylprostaglandin $F_{1\alpha}$ in urine suggested that the metabolically protected prostaglandin could persist in the body and, therefore, exhibit longer duration of action.

Although natural prostaglandins possess many potent and diverse biological activities, they usually have a short duration of action due to their rapid metabolism and excretion. PGE_2 and $PGF_{2\alpha}$ administered intravenously in humans disappear from the peripheral circulation in a few seconds.[1] The bulk of the administered drug is excreted usually within a few hours.[2] The administered prostaglandins are completely degraded into various metabolites before excretion.

Studies of prostaglandin metabolism in this laboratory[3,4] and others[5-7] have defined the major routes of metabolism involved: (a) oxidation of the C-15 hydroxyl group, (b) reduction of the C-13 double bond, (c) β-oxidation of the carboxyl acid side chain, (d) ω-hydroxylation and oxidation, and (e) reduction of the C-15 keto back to hydroxyl groups. Urinary metabolites isolated from natural prostaglandin treated animals or human subjects usually reflect the combined results of several degradative reactions. The urinary metabolite patterns vary depending on animal species used and physiological state, as well as the dosage or route of administration.[8]

The major catabolic pathways that cause the rapid disappearance of active prostaglandins are the prostaglandin 15-hydroxyl dehydrogenase and the β-oxidation system. Both enzyme systems are widely distributed in various tissues and organs. The lung is especially enriched in prostaglandin 15-hydroxyl dehydrogenase and is believed to be the primary site for the removal of circulating PG.

Many chemical modifications of PG have been designed to circumvent these metabolic pathways and prolong the duration of their pharmacological actions. The 15-methyl and 16,16-dimethyl analogues of PGE_2 and $PGF_{2\alpha}$[9,10] which are not substrates of prostaglandin 15-hydroxyl dehydrogenase are more potent and longer in duration than natural PG. Green et al.[11] reported that shifting the Δ^5 double bond of $PGF_{2\alpha}$ to the Δ^4 position considerably retards the degradative action of the β-oxidation system. The Δ^4-$PGF_{2\alpha}$ is still a substrate of prostaglandin dehydrogenase and is degraded to the 15-keto derivatives in the same way as the naturally occurring Δ^5 compound.

Recently, Johnson and Nidy[12] reported the *cis*-Δ^4-15-methyl analogue of $PGF_{2\alpha}$. This compound is slightly less active than $PGF_{2\alpha}$ as a pressor agent in the rat in stimulating gerbil colon smooth muscle but four times more active than $PGF_{2\alpha}$ as an abortifacient in hamsters. The compound is not a substrate for prostaglandin 15-hydroxyl dehydrogenase and should partially resist β-oxidation. In this communication we will describe the excretion and metabolism of this compound in the rat.

Experimental Section

Materials. [11-^{3}H]-*cis*-Δ^4-15(*S*)-15-Methylprostaglandin $F_{1\alpha}$ methyl ester was kindly synthesized by Dr. E. W. Yankee. The specific activity of the final product was 154 μCi/mg and the radioactive purity was greater than 93%. The reference compounds, *cis*-Δ^4-15(*S*)-15-methylprostaglandin $F_{1\alpha}$ methyl ester, *cis*-Δ^4-15(*S*)-15-methylprostaglandin $F_{1\alpha}$, 15(*S*)-15-methyl-2,3-dinorprostaglandin $F_{1\alpha}$, and 15(*S*)-15-methyl-2,3,4,5-tetranorprostaglandin $F_{1\alpha}$ lactone, were made available by members of the Experimental Chemistry Unit of The Upjohn Company.

Silicic acid (SilicAR CC-4) was obtained from Mallinckrodt Chemical Works, St. Louis, Mo. Sephadex LH-20 was purchased from Pharmacia Fine Chemicals, Inc. (Piscataway, N.Y.). The prepacked preparative silica gel 60 column was purchased from EM Laboratories, Inc. (Elmsford, N.Y.). Amberlite XAD-2 resin was purchased from Rohm and Hass (Philadelphia, Pa.). Bis(trimethylsilyltrifluoroacetamide) with 1% trimethylsilane and Trisil Z were obtained from Pierce Chemical Co. (Rockford, Ill.). Glass redistilled solvents were purchased from Burdick and Jackson Laboratories, Inc. (Muskegon, Mich.).

Methods. Drug Administration and Sample Collection. A. Single Dose Oral Administration. Four female Sprague–Dawley rats (Upjohn strain) weighing approximately 200 g were fasted overnight. Each rat was given a single 0.28-mg dose of [^{3}H]-*cis*-Δ^4-15(*S*)-15-methylprostaglandin $F_{1\alpha}$ methyl ester (**1**) (1.24×10^7 dpm) in distilled water via a gastric tube. The rats were housed in stainless steel metabolism cages with free access to food and water. Urine and feces samples were collected at appropriate intervals for a total of 54 h.

B. Accumulation of Metabolites. Fifteen rats were housed in metabolism cages for 17 days. Each morning the rats were administered a 0.25-mg oral dose of **1** containing 1×10^7 dpm of radioactivity. Urine samples were collected daily, pooled, and stored at −70 °C.

Extraction and Chromatographic Methods. The unchanged drug and metabolites were isolated from urine using the Amberlite XAD-2 column procedure as described previously.[4] The recovery of radioactivity was greater than 95%. The crude extract was partially purified by silicic acid column chromatography (200 g, SilicAR CC-4 column) with ethyl acetate–heptane (8:2) as solvent. The bulk of the radioactivity was readily eluted with this solvent. A small amount of polar components was eluted with ethyl acetate–methanol (9:1). The overall radioactivity recovery was approximately 95%.

The separation of radioactivity components in the partially purified urine extract was carried out by reversed phase partition column chromatography. Sephadex LH-20 was used as the solid support, and the solvent mixture C-38 consisting of isooctyl alcohol–chloroform–methanol–water (15:15:114:86) was the partition system. Sephadex LH-20 (60 g) was shaken with 60 mL

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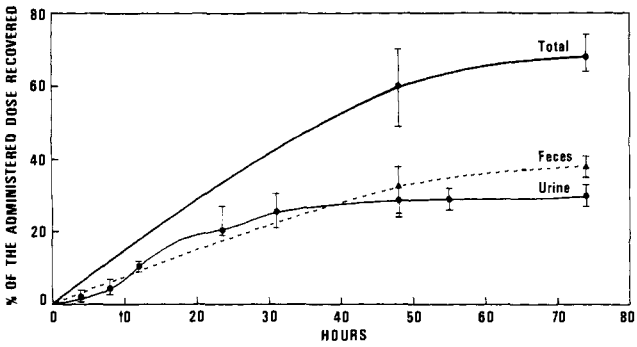

Figure 1. Excretion of [11-^{3}H]-*cis*-Δ^4-15-methylprostaglandin $F_{1\alpha}$ methyl ester.

of the stationary phase for 4 h and then swelled in 100 mL of the mobile phase for 5 h before being packed into a 55 × 2.2 cm column. The partially purified urine extract, suspended in the mobile phase, was loaded on the top of the column. Elution was carried out with the mobile phase, collecting 9-mL fractions. Fractions containing material under the same radioactivity peaks were combined, evaporated to dryness, and treated with ethereal diazomethane.

Methyl esters of various metabolites were purified on silica gel 60 prepacked columns 31 × 2.8 cm (EM Laboratories) with a methylene chloride–acetone step gradient from 7:3 to 4:6.

Gas–Liquid Chromatography and Mass Spectrometry. Gas chromatography (GC) was performed on a Hewlett-Packard Model 402 GC equipped with a flame ionization detector and a Nuclear Chicago radioactivity monitor for simultaneous measurement of retention time and radioactivity. The column was a 4-ft 3.8% UCW-98 on GasChrom Q (80–100 mesh) operated at 200 °C. The carrier gas flow was 40 mL/min and the retention time was standardized with a standard fatty acid methyl ester (C-14 to C-24) mixture.[13]

Mass spectrometry was performed with a combined GC–MS (LKB-9000) equipped with a 4-ft 3.8% UCW-98 column operated at 200 °C. The electronic energy was set at 70 eV and the trap current at 60 μA. The flash heater and the separator were kept at 220–230 °C.

Preparation of Derivatives for GC–MS. The methods used to prepare the methyl ester and *O*-methoxime derivatives of PG metabolites have been described.[4] The trimethylsilyl derivatives were prepared by treating the sample with a 1:1 mixture of bis(trimethylsilyltrifluoroacetamide) containing 1% TMCS and dry pyridine. The mixture was heated at 50 °C for 1 h, evaporated with a stream of nitrogen, and dissolved in a small aliquot of chloroform (50 μL) before injection. Alternatively, the samples were treated with 0.1 mL of Trisil Z, heated at 50 °C for 1 h, and used directly.

Measurement of Radioactivity. Radioactivity was determined with a Packard Tri-Carb 3375 liquid scintillation spectrometer. Quenching was corrected by the external standard method. Urine samples were counted directly by mixing 0.2-mL aliquots with 15 mL of diotol counting solvent. Feces were weighed and homogenized with water. Aliquots of the homogenate were weighed, dried, and combusted in a Packard Model 603 auto oxidizer before counting.

Results

Excretion. Figure 1 shows the urinary and fecal excretion of total radioactivity after oral administration of a single 0.28-mg dose of tritium-labeled drug. In the three rats, only 20.9 ± 5.5% of the administered dose was recovered from the urine within 24 h. A total of 68 ± 5.4% of the dose was recovered from the rats excreta in 74 h, 30 ± 2.9% from the urine and 38 ± 3% from the feces.

At this high dose, side effects from the drug were apparent. During the first 1–3 days of chronic administration, the rats generally appeared depressed. Several animals experienced diarrhea and fecal stained abdominal area was most common. The severity of the side effects subsided after 3 days of drug administration in most animals. No incidence of mortality was observed. The urine samples contaminated with loose fecal material were excluded from further analysis.

The daily administration of massive doses was primarily intended to accumulate enough urinary excretion products for subsequent analyses. The rats showed some distress symptoms at the beginning of the dosing period but quickly built tolerance and recovered. We have no reason to believe that the state of the animal was drastically impaired by the large dose of the drug.

Separation of Urinary Metabolites. Radioactive rat urine was quantitatively extracted with Amberlite XAD-2. The crude extract was partially purified by silicic acid column chromatography, followed by reverse phase partition chromatography.

Identification of Compound 2. The most nonpolar fraction obtained from the reverse phase partition fractionation contained approximately 20% of the total urinary radioactivity. After methylation and purification on a silica gel column, this material was converted to its Me_3Si ether derivative and analyzed on a GC equipped with a radioactivity detector. One major area of radioactivity was found with a retention time corresponding to a *C* value of 24.2. This value was identical with that of the Me_3Si derivative of the parent **1**, and subsequent mass spectra confirmed this structure (Figure 2A).[17] Another area of radioactivity occurred at a region below C-20. This area was contaminated with a large amount of urinary material and a clean mass spectrum could not be obtained. At present, the compound(s) have not been identified.

Identification of Compounds 3 and 4. The major fraction II eluted from the reverse phase column contained 35% of the total urinary radioactivity. After treatment with ethereal diazomethane, this fraction was separated on a small silica gel column into two fractions. Each was converted to their Me_3Si ether derivative and analyzed on GC (IIA, nonpolar, and IIb, polar).

Gas chromatographic separation of the polar fraction yielded two peaks of radioactivity that appeared at retention times corresponding to *C* 20.8 and *C* 22.9, respectively. The mass spectrum (Figure 2B)[17] of the *C* 22.9 peak showed prominent ions at *m/e* 557 ($M^+ - 15$), 501 ($M^+ - 61$), 411 [$M^+ - (71 + 90)$], and 321 [$M^+ - (2 \times 90 + 71)$]. The spectrum resembled that of the unchanged drug except most prominent ions were shifted 26 mass units lower, indicating the loss of two CH from the analogous fragment ions. The presence of the 217 ion indicated that the five-member ring has not been modified, and the intense ion generated after the loss of the 5-carbon fragment at the ω end ($M^+ - 71$) suggested that the bottom chain remained intact. The ion at *m/e* 295 might be formed by the α-cleavage between C-14 and C-15 and the loss of a trimethylsilanol molecule. Therefore, we concluded that this compound was 7,9,13-trihydroxy-13-methyldinorprosta-11-enoic acid (**3**). Compound **3** was subsequently prepared by total synthesis. The authentic compound had identical GC–MS characteristics as the isolated material, thus conclusively proving its identity.

The low *C* value of the other radioactive GC peak suggested that it was a further degraded compound, probably a 16-carbon metabolite. The molecular ion was not observed (Figure 3A).[17] The highest ion was found at *m/e* 473, which was interpreted as the loss of the 5-carbon fragment at the ω end. Successive loss of two trimethylsilanols from the $M^+ - 71$ peak gave two intense ions at *m/e* 383 and 293. The presence of these three major ions appeared to be analogous to the *m/e* 501, 411, and 321 fragment in compound **3**. The difference, 28 mass

units, corresponded to the loss of two CH_2's from the carboxylic acid side chain. The fragment at m/e 267 which was analogous to the m/e 295 ion in compound **3** suggested that the original C-13 double bond and the C-15 methyl were not modified, and the m/e 217 ion indicated an intact dihydroxylated five-membered ring. These results demonstrated that this compound was 5,7,11-trihydroxy-11-methyltetranorprosta-9-enoic acid.

The authentic compound, 15(*S*)-15-methyl-2,3,4,5-tetranorprostaglandin $F_{1\alpha}$, was obtained in lactone form. The compound was dissolved in 0.05 M Tris HCl, pH 8.5, for 18 h to hydrolyze the lactone. The pH was readjusted to 3.0 and the compounds were quickly extracted with ether. Diazomethane was immediately added to convert the free acid to the methyl ester. After conversion to the Me_3Si derivative, the compound was analyzed by GC–MS. Two peaks emerged. The fast-running major peak has an identical mass spectrum as the tetranor metabolite **4** obtained from the urine extract. The minor peak which emerged later showed a mass spectrum of the δ-lactone.

GC analysis of the nonpolar fraction showed an area of radioactivity at *C* 22.0. Its mass spectrum (Figure 3B)[17] showed the base peak ion at m/e 369 while other major fragments occurred at m/e 279 and 189, indicating successive loss of two trimethylsilanol groups. Other ions were found at m/e 425, 335, 299, and 143. Both the retention time and the MS were compatible with compound **5**, as they resembled closely the reported retention time and mass spectrum of 5,7,11-trihydroxytetranorprostanoic acid δ-lactone previously isolated as a metabolite of $PGF_{2\alpha}$ in the monkey. A comparison with the authentic compound confirmed the proposed structure.

The lactone formation was a well-known property of tetranorprostaglandin F metabolites.[3,4] In aqueous solvent, the tetranorprostaglandin F compound will rapidly form an equilibrium mixture of lactone and free acids. The ratio of lactone to acid depends on the acidity of the medium. In the present study, the lactone was apparently formed during the initial acidification of the urine and separated from the tetranor metabolites (methyl ester) by the final silica gel column chromatography.

Discussion

The pattern of metabolism of the natural PG has been well delineated.[2] As a result of these studies, structural modifications have been proposed which would retard the PG metabolism, thereby enhancing their duration of action. In this study we have investigated the metabolism of a PG analogue, in which both the 15-dehydrogenation and the β-oxidation have been blocked or retarded.

An important feature observed was the slow excretion rate of this compound. When tritium-labeled $PGF_{2\alpha}$ was given to rats orally, the majority of the radioactivity was excreted within 24 h. Urinary excretion was essentially completed within 6 h. In contrast, only 21% of the total administered was excreted in the first 24 h, with the remainder being excreted in a spread of several days. The route of excretion was also altered. Orally administered $PGF_{2\alpha}$ is mainly excreted via the urine (71%) while **1** is evenly excreted between the urine and feces. The prominent fecal excretion may be attributed to extensive biliary excretion which may return to the liver for further metabolism via the enterohepatic recirculation. The slow excretion cannot be explained by inefficient absorption since we have demonstrated that it is absorbed as fast as $PGF_{2\alpha}$ in an isolated segment of rat jejunum.[14]

The effect of the metabolic protection was clearly reflected in the pattern of the metabolites. The major metabolite obtained from $PGF_{2\alpha}$-treated rats is the 5,7-dihydroxy-11-ketotetranorprosta-1,16-dienoic acid. Essentially no dinor or the intact carbon-20 PG was found in the urine. In this case, the Δ^4-15-methyl analogue formed no 15-keto derivative as it is not a substrate of the prostaglandin 15-hydroxyl dehydrogenase. Figure 4 shows the summary of metabolites found in this study. The major metabolite was the compound **4** tetranor derivative. But the appearance of dinor and intact carbon-20 compounds in the urine clearly indicated that **1** is more resistant to β-oxidation.

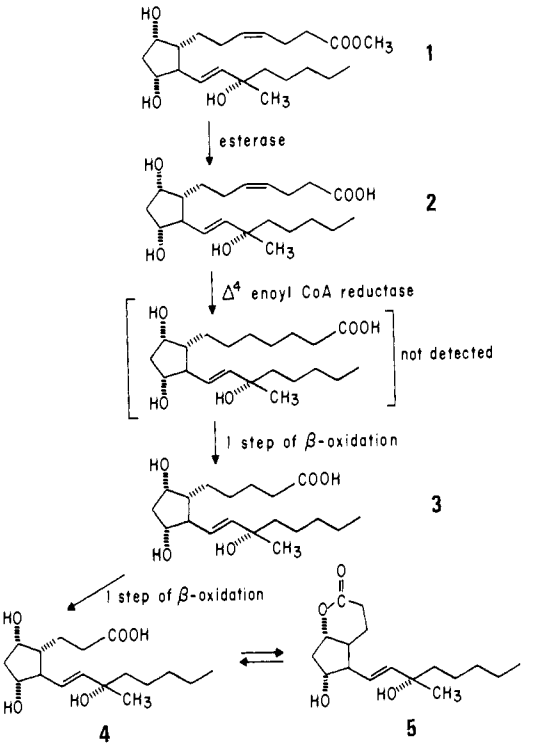

Figure 4. Proposed metabolic pathway of *cis*-Δ^4-15-methylprostaglandin $F_{1\alpha}$ methyl ester in the rat.

It should be pointed out that both the slow excretion rate and the appearance of unchanged drug in the urine suggested the unchanged drug must be circulated through the animal and thereby should result in longer duration of action. The finding that **1** is a potent abortifacient agent in the hamster could be partially due to its resistance to metabolism.

Green and Samuelsson have studied the metabolism of intravenously administered *cis*-Δ^4-$PGF_{1\alpha}$. This compound lacks the protection of the 15-methyl substitution and is a substrate of prostaglandin 15-hydroxyl dehydrogenase. It was excreted rapidly with 35–54% of the total administered radioactivity cleared from the body in 14 h. The pattern of metabolites showed 10–20% unchanged drug, 11–18% dinor metabolite, and 8–15% tetranor metabolite. Apparently this compound is degraded less extensively by the β-oxidation system than our observations with the Δ^4-15-methyl analogue **1**. This difference could be due to the rapid excretion of their unprotected analogue.

The term "intact C-20 compound" has been used indiscriminately in this report. The administered drug is the methyl ester. When the radioactivity was recovered from the urine, we could not distinguish the ester from the free acid because all compounds were converted to the methyl ester before GC–MS analysis. However, both rat plasma and intestine contain powerful esterases which hydrolyze the PG esters readily.[15] We have observed that under in vitro conditions *cis*-Δ^4-15-methylprostaglandin

$F_{1\alpha}$ methyl ester could be completely hydrolyzed by the undiluted rat plasma in less than 1 min.[14] Therefore, we do not expect any of the originally administered ester to survive the action of the hydrolases and appear in the urine.

The mechanism for the formation of the tetranor metabolite from the *cis*-Δ^4-PG has been discussed by Green and Samuelsson.[11] They postulated that the reaction sequence included one step of β-oxidation followed by the hydration of the Δ^2-cis double bond to form the 3-D(−)-hydroxyl compound. The 3-D(−) compound is then epimerized by the action of D(−)-β-hydroxyacyl CoA epimerase of the 1(+) antipode which, in turn, can enter another cycle of β-oxidation. This mechanism, however, cannot explain the presence of the dinorprostaglandin of the F_1 series in which the carboxylic side chain is fully saturated. Furthermore, in this study we could not detect any dinor metabolites with an unsaturated top side chain. All dinor metabolites found by Green and Samuelsson from the *cis*-Δ^4-$PGF_{1\alpha}$ also lost the Δ^4 double bond.

From the study of the substrates specificity of bovine liver acyl CoA dehydrogenase, Kunau[16] reported that polyunsaturated fatty acids with the Δ^4 double bond were very poor substrates for the first enzyme of the β-oxidation system. The Δ^4 double bond has to be reduced before further chain shortening can take place. An enzyme, 4-enoyl-CoA reductase, which catalyzed the hydrogenation reaction has been found in mammalian liver. Our results suggest that the Δ^4-prostaglandins may also follow this metabolic pathway. It would be of interest to test whether Δ^4-prostanoate is a substrate of the Δ^4-enoyl-CoA reductase.

Acknowledgment. I thank R. Johnson, E. Nidy, E. W. Yankee, and J. Sih of The Upjohn Company for providing the necessary compounds for this study. I also thank J. C. McGuire for his invaluable assistance.

Supplementary Material Available: Figure 2 (mass spectra of the methyl ester, Me_3Si ether derivatives of **2** and **3**) and Figure 3 (mass spectra of the methyl ester, Me_3Si derivatives of **4** and **5**) (2 pages). Ordering information is given on any current masthead page.

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Notes

Antineoplastic Agents. Structure–Activity Relationship Study of Bis(substituted aminoalkylamino)anthraquinones

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A structure–activity relationship study was conducted on a number of bis(substituted aminoalkylamino)anthraquinones. These compounds were prepared by the condensation of substituted or unsubstituted leucoquinizarin with appropriate amines, followed by air oxidation. Both the position and the nature of the center nitrogen atom of the side chain are vital to the antineoplastic activity. The possible mode of action of these aminoquinones was discussed. 1,4-Dihydroxy-5,8-bis[[2-(hydroxyethyl)amino]ethyl]amino-9,10-anthracenedione (DHAQ) was found to possess potent inhibitory activity against both the P-388 leukemia system (T/C of 299 at 0.5 mg/kg with 4/6 cures) and the B-16 melanoma system (T/C of 503 at 1 mg/kg with 7/10 cures).

The mode of action of many chemotherapeutic agents, including certain antineoplastic drugs, has been claimed to be due to their ability to intercalate between the base pairs of the DNA double helix. The molecular complex formation was earlier postulated to explain the biological activity of chloroquine[1,2] and acridine.[3] Although some investigators consider drug–DNA intercalation just a late subterminal event rather than the prime mode of action, other workers accept it as a convenient working hypothesis and have used it to explain the activity of many anticancer agents, including actinomycin D,[4,5] daunorubicin,[6] adriamycin,[7] anthramycin,[8] and coralyne.[9,10] Among these agents, both daunorubicin and adriamycin are recognized as very promising drugs and the latter, particularly, shows good inhibitory activity against leukemia as well as many solid tumors.[11] However, these drugs (or their metabolites) cause severe and irreversible cardiotoxicity which could be fatal if the accumulated dose of these drugs exceeds a limited amount.[12] The amino sugar portion of these drugs has been proposed as responsible for this toxicity.[13] It was

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