The Synthesis and Anti-inflammatory Properties of a New Sulindac Analogue Synthesized from Natural Safrole

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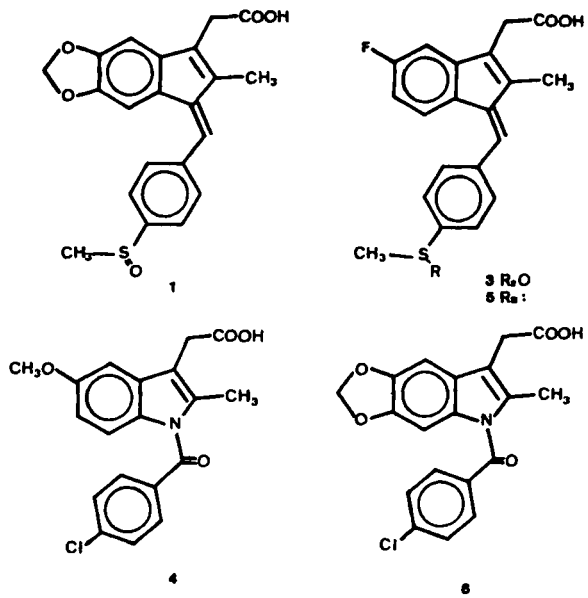
Abstract □ The synthesis of the new sulindac (3) analogue (*Z*)-5,6-methylenedioxy-2-methyl-1-(*p*-methylsulfinylbenzylidene)-3-indenyl acetic acid (1) from natural safrole (2), an abundant natural product occurring as the principal chemical constituent of Sassafraz oil, is described. The principal feature of this route is shortness, stereoselectivity, and high overall yield. The new analogue is produced in a yield of ~30% from the natural product. The results include the anti-inflammatory activity of 1 as well as that for its corresponding sulfide (12), a synthetic precursor of 1 that may be an important metabolic product of 1 by analogy to 3 itself. The anti-inflammatory profiles of these derivatives, measured in the carrageenan-induced rat paw edema test, indicated a 50% effective dose of 42 mg/kg for 1 and of 23 mg/kg for 12, confirming the structure–activity relationships of these agents. These results indicate that the new analogue 1 could represent a prodrug with a similar therapeutic profile to that of the pharmaceutical product 3.



A research area of continuous development is that of nonsteroidal anti-inflammatory agents (NSAIAs).[1] Among the acidic NSAIAs, the 2-arylacetic acids represent an important pharmaceutical class of drugs with anti-inflammatory (AI), analgesic, and antipyretic properties.[2] The AI activity of these classical agents has been attributed to inhibition of inflammatory prostaglandin production arising from the arachidonic acid cascade via a cyclooxygenase (CO)-dependent pathway.[3] This mechanism of action is also responsible for the irritating properties of these acids at the gastrointestinal tract level.[2] Many 2-arylacetic acid derivatives are synthesized as prodrugs to reduce the undesirable effects noted when the drugs are used orally.[4] Sulindac (3),[5] a representative of the indenylacetic acid group, is a well-tolerated NSAIA that is primarily used in the clinic[6] and was developed as a bioisostere of indomethacin (4).[5] This therapeutic agent has a reduced gastrointestinal irritating effect because of its reversible prodrug character.[7] In fact, this *S*-oxide of the benzylidene-3-indenylacetic acid derivative 3 is reduced in vivo to the bioactive sulfide metabolite 5.[7]

As part of a research program to synthesize bioactive compounds from abundant Brazilian natural products as inexpensive starting materials, we have previously described[8] the synthesis of an indomethacin analogue (6) from natural safrole (2).[9] In this paper we describe the synthesis of 1, an indene isostere of 4 (analogue to 3), using the same natural product (2) that was isolated in very high yield from Sassafraz oil (*Ocotea pretiosa*).[10]

The known structure–anti-inflammatory activity relationships of NSAIAs belonging to the 2-arylacetic acid group, as well as the presumed receptor topography,[5] show that the minimal structural requirements for AI activity include an aromatic ring as a planar flat area, a second structural unit to interact with a cavity present in the receptor surface, and an acidic function near the planar area close to a cationic site.[5,11] The receptor is the main enzymatic complex CO responsible for the bioformation of prostaglandins.[5] This presumed interaction between NSAIAs and CO is less dependent on the type and position of substituents in the aromatic planar unit of the NSAIA molecule. The nature of substituents can interfere in the drug distribution process by controlling the physicochemical characteristics of the drug and then influencing the time of action of the agent. With these structure–activity relationships principles in mind, the structure of the new analogue (1) was designed with all the minimal structural features required for AI activity. In fact, the presence of the methylenedioxy unit from the natural product used in the synthesis could improve the lipophilic character of 1.

Results and Discussion

An obvious synthetic approach to the new analogue (1) indicates the methylenedioxyindenylacetic acid derivative (11) as an intermediate. Compound 11 could be easily prepared from the methylenedioxyindanone derivative (8) by exploring the known ketone nucleophilic reactivity. This rationale indicates that the initial synthetic goal must be the transformation of the allyl moiety of the natural product 2 into a cyclic unit representing the indane system of 8, which could then be transformed into 9 by a simple C-monoalkylation.[12]

Initially we attempted the synthesis of the indane derivative (8) with a π-allyl palladium complex,[13] directly prepared from 2, as an intermediate in the oxidative intramolecular cyclization process, by using the known electrophilic C-6 reactivity of 2.[14] Unfortunately, despite several attempts,[15]

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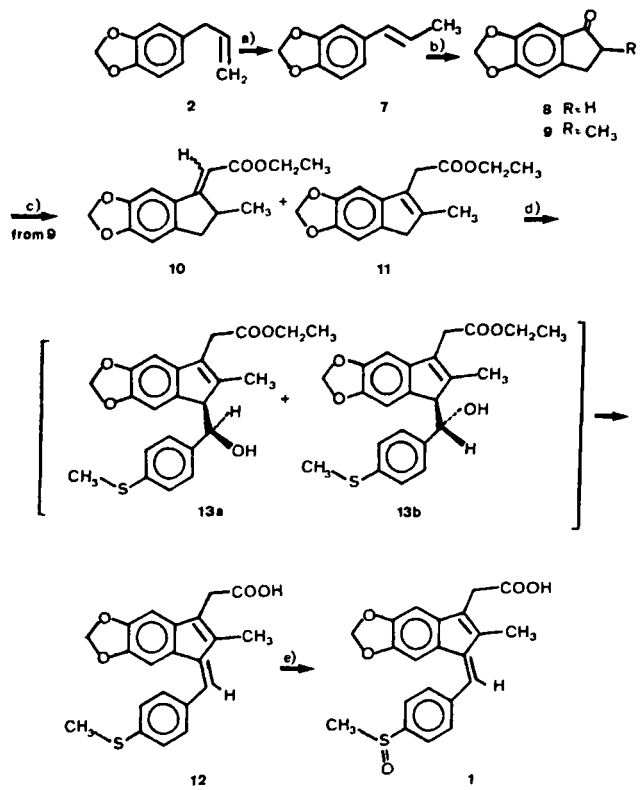
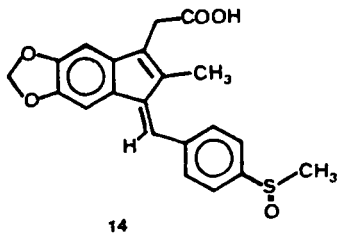
the only product isolated was the corresponding 3,4-methylenedioxypropiophenone in very low yield.[16]

On the other hand, the well-known indanone synthesis starting from allylbenzenes[17] consists of a minimum of three steps and was considered too long. For this reason, we turned our attention to the Witiak method,[18] using a Vielsmaier–Haack reaction on activated styrenes. For instance, applying this reaction on **2**, we and others[19,20] obtained products distinct from indanones in very low yields. Meanwhile, previous results from our laboratory[21] indicated that **2** could be isomerized in almost quantitative yield to the corresponding styrene derivative (**7**), assuring the preparation of **9** from this derivative. In fact, treatment of 3,4-methylenedioxystyrene (**7**) under modified Witiak conditions[18] (see *Experimental Section*) furnished the desired methylindanone (**9**) directly in >85% yield from **2**. Then, we submitted this crystalline intermediate to a synthetic sequence similar to that used by Shen and co-workers in the synthesis of **3**[5] (Scheme I). The next step in the planned synthetic route involved a Reformatsky reaction to promote two-carbon homologation of **9**, introducing the acetic acid framework present in **1**. Treatment of **9** under classical Reformatsky conditions[22] with ethyl bromoacetate furnished an isomeric olefin mixture (**10**, **11**), as shown by NMR analysis, in a ratio of 2:1. Subsequent careful chromatographic purification of this mixture furnished the major isomeric component as the less mobile one, which was characterized as the exoisomer **10**. This compound was obtained as a mixture of the (*E*) and (*Z*) isomers in a 4:1 ratio as shown by analysis of the relative area of the C-7 aromatic proton signals, which were shifted in the less favored (*Z*)-isomer (**10b**) that occurs at 8.40 ppm. Several attempts to isolate the tertiary benzylic carbinol intermediate failed,[23] even when sonication conditions were employed in this process,[24] ending any further



Scheme I—Synthesis of **1** from **2**. Key: (**a**) 3 N KOH, *n*BuOH, reflux, 3 h (98%); (**b**) dimethylformamide, $POCl_3$, 120 °C, 3 h; NaOH, MeOH:H_2O (85%); (**c**) $BrCH_2CO_2Et$, Zn°, catalysis, C_6H_6, 5 h (81%); (**d**) MeONa, MeOH, reflux; $MeSC_6H_4CHO$, 12 h; H_2O, reflux, 1 h (82%); (**e**) $NaIO_4$, MeOH, H_2O (96%).



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attempts to verify the possible regiodehydration in favor of the desired endo-olefin product (**11**). Fortunately, we were able to effect the isomerization of the major exo-olefin (**10**) to the desired endo-isomer (**11**). Because the next step in the planned synthetic sequence was an aldol condensation with a functionalized aromatic aldehyde, we thought that by working at the adequate thermodynamic conditions we could accomplish the exo–endo (**10**-to-**11**) isomerization before the aldol condensation step in a one-pot process. Given the theoretical differences in the kinetic acidities between the hydrogen at C-1 at the benzylic position and the α-ester hydrogens at C-3 in **11**, we started the synthetic scheme with the intent of preparing **12**. Fortunately, when a mixture of olefins (**10**:**11**) was carefully treated with sodium methoxide in methanol at reflux, followed by careful addition of *p*-thiomethylbenzaldehyde, refluxing for 12 h, and water addition, the acid **12** was obtain as the only product in 82% yield, without any evidence of the formation of other diastereoisomeric unsaturated products or contamination with any Canizaro products.[25] These surprising results represent a formal stereospecific process, involving only the indenyl anion formed from **11**. These results also suggest that the dehydration step of the carbinol intermediates (**13**) occurs more rapidly in one of the two possible enantiomeric pairs by a probable Elcb or E2 mechanism elimination of hydroxide that is stereocontrolled by a C-2 methyl group. On the other hand, epimerization at the benzylic stereogenic center of the carbinol intermediate **13a**, the precursor of the double-bond (*E*)-isomer **12**, could be favored by a lower steric interaction with the C-2 methyl group. This, in turn, would result in the greater thermodynamic stability observed in the desired (*E*)-isomer.[25] This process could also be rationalized by considering that the less stable carbinol intermediate **13b**, precursor of the double-bond (*Z*)-isomer, could suffer a retrograde reaction more rapidly than the other enantiomeric pair, followed by recondensation, and thereby favoring also the formation of the (*E*)-isomer. Indeed, this process represents a high-yield, regiostereoselective, four-step, one-pot procedure comprised of ene-isomerization, aldol condensation, aldol–adduct dehydration, and ester hydrolysis, to furnish the desired (*E*)-indenylacetic acid derivative (**12**) in 80% yield. Finally, the synthesis of the new analogue (**1**) was completed by sodium periodate oxidation of the sulfide (**12**) to furnish the corresponding sulfoxide (**1**) in near quantitative yield (Scheme I).

The (*E*)-configuration of the double bond in **12** was determined by careful examination of the signal attributed to C-2 methyl protons in the proton nuclear magnetic resonance (^1H NMR) spectrum. These protons appear at 2.20 ppm as a nice singlet, providing very strong evidence for the assigned configuration.[7,25] In fact, this chemical shift is identical to that observed in **3** [i.e., a 0.4 ppm downfield shift to the (*Z*)-isomer (**14**)[8,25]].

The AI profiles of **1** and **12** were measured with the classical model of carrageenan-induced rat paw edema test, with **3** and **4** as standards.[26] The 50% effective dose (ED_{50}) observed for derivatives **1** and **12** (Figure 1) indicate an AI profile similar to that of **3**, including a better AI activity measured for the precursor sulfide (**12**) "vis-à-vis" the corresponding sulfoxide (**1**),[27] thus mimicking the biological behavior of **3**.[8] These results indicate a prodrug character of **1** similar to that observed for **3**.

Conclusions

The synthetic route described here represents a very useful approach to different sulindac analogues possessing a methylenedioxy moiety in the aromatic ring of the indenylacetic acid subunit, as in 1. The method has a key, "one-pot multireaction" step with an aldol condensation step that permits utilization of a variety of different functionalized aromatic aldehydes. The results confirm that 2, an abundant natural compound, represents a readily available material that can be used in the synthesis of planned bioactive analogues of therapeutically useful drugs.

Experimental Section

The ^{1}H NMR spectra, unless otherwise stated, were determined in deuterochloroform containing ~1% tetramethylsilane as an internal standard with Bruker HP 80 SY or Varian T-60 spectrometers at 80 or 60 MHz, respectively. The IR spectra were obtained with a Perkin-Elmer 397 spectrophotometer and sodium chloride plates for neat liquids and potassium bromide plates for solids. The UV spectra were determined in ethanol solution on a Beckman DV-6 or Varian UV-vis 634-S spectrophotometer. The mass spectra were obtained with a Varian MAT-SS-100 MS computer system. Satisfactory analytical data (+ 0.4% for C, H) were obtained for 1 and 12.

The progress of all reactions was monitored by thin-layer chromatography (TLC) that was performed on 2.0 × 6.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under UV light and sprayed with concentrated sulfuric acid for spot visualization. For column chromatography, Merck silica gel (70–230 mesh) was used. Solvents used in the reactions were generally redistilled prior to use and stored over 3–4 Å molecular sieves. Reaction mixtures were generally stirred under a dry nitrogen atmosphere. The usual workup means that the organic extracts, prior to concentration and under reduced pressure, were treated with a saturated aqueous sodium chloride solution, referred to as brine, dried over anhydrous magnesium or sodium sulfate, and filtered.

Isomerization of 2 to 7[10]—To 80.0 g (0.49 mmol) of 2 was added 100 mL of a 3 N solution of potassium hydroxide in *n*-butyl alcohol and the reaction mixture was stirred at room temperature for 3 h. The mixture was poured into a solution of 12 mL of concentrated HCl, and 52 mL of ice water. After neutralization with additional concentrated HCl, the organic layer was extracted with three 35-mL portions of ethyl acetate. After usual workup, a white oily residue was obtained and distilled to furnish 78.4 g (96–98%) of the styrene derivative (7) as a colorless oil. An analytical sample showed spectroscopic data identical with those reported.[27]

2-Methyl-5,6-(methylenedioxy)-1-indanone (9)—A modification of an earlier procedure[18] was used. To 14.5 mL (185 mmol) of dry dimethylformamide was added in a dropwise manner with vigorous stirring 3.5 mL (37.03 mmol) of recently distilled $POCl_3$. The mixture was stirred in an ice bath for 30 min, then the resulting rose pale solution was put in an oil bath at 110 °C and the olefin (7, 5.0 g, 0.03 mmol) was added. The mixture was stirred at this temperature for 3 h, then cooled to room temperature and poured into 200 mL of ice water. The aqueous layer was extracted with two 25-mL portions of ethyl ether to remove the unreacted olefin (7). The aqueous layer was made basic by addition of 7 N aqueous sodium hydroxide solution and stirred at room temperature overnight. Finally, the aqueous layer was treated with three 50-mL portions of ethyl ether, and the organic layers were combined and submitted to the usual workup to provide a pale brown viscous oil as product. Chromatographic purification on a silica gel column with ethyl acetate as eluant gave 5.0 g (85%) of indanone (9) as a pale yellow solid: mp 63 °C (lit. 63.5 °C)[18] ^{1}H NMR: 7.09 (s, 1, Ar), 6.79 (s, 1, Ar), 6.04 (s, 2, OCH_2O), 2.34–3.55 (m, 3H), and 1.25 ppm (d, 3, J = 7 Hz, CH_3).

Ethyl (*E,Z*)-2-methyl-(5,6-methylenedioxy)-1-indenylidene acetate (10) and Ethyl 2-methyl-(5,6-methylenedioxy)-1-indenyl acetate (11)[28]—A mixture of 1.01 g (5.27 mmol) of 9 and 1.8 g (15.8 mmol) of ethyl bromoacetate in 37 mL of dry benzene was added to a catalytic amount of iodine and 2.74 g (42.10 mol) of activated Zn powder. The reaction mixture was carefully warmed until the reaction started and then was stirred at reflux for 5 h under dry nitrogen atmosphere. The cooled reaction mixture was stirred 30 min after addition of 40 mL of 1:1:1 mixture of acetic acid, methanol, and water. The aqueous layer was extracted with two 25-mL portions of ethyl ether. The combined organic solutions were worked up as usual to furnish an oily residue as product. The residue was purified on 25 g of silica gel in a chromatographic column with 3% ethyl acetate:n-hexane as eluant. The faster moving compound [major TLC spot had a retardation factor (R_f) of 0.4, 5% ethyl acetate:*n*-hexane] consisted of 0.79 g (53%) of a isomeric mixture of (*E,Z*)-10: mp 93–96 °C; UV:λ_{max} (MeOH) 340 nm (ϵ 18 000); ^{1}H NMR (CCl_4): 8.40 (s, 0.2, Ar), 6.90 (s, 0.8, Ar), 6.65 (s, 1, Ar), 5.92 (s, 2.8, OCH_2O, vinylic-H), 5.75 (s, 0.2, vinylic-H), 3.75–4.22 (m, 3), 3.08 (dd, 1, J = 8, 16 Hz), 2.41 (d, 1, J = 16 Hz), and 1.10–1.40 ppm (m, 6, two CH_3); MS: *m/z* 260 (M^+, 100%), 231 (45%), 215 (55%), 187 (63%), and 157 nm (30%). The lesser moving compound (minor TLC spot had an R_f of 0.34, 5% ethyl acetate:*n*-hexane) corresponded to the endoisomer 11: 0.38 g (28%); mp 83–84 °C; UV:λ_{max} (MeOH) 285 (ϵ 7800) and 235 nm (ϵ 10 000); ^{1}H NMR (CCl_4): 6.76 (s, 1, Ar), 6.70 (s, 1, Ar), 5.95 (s, 2, OCH_2O), 4.12 (q, 2, J = 8 Hz, OCH_2), 3.30 (s, 2, CH_2-COO), 3.10 (s, 2, benzylic-H), 2.05 (s, 3, C2-CH_9), and 1.10 ppm (t, 3, J = 8 Hz, OCH_2CH_9); MS: *m/z* 260 (M^+, 100%), 187 (80%), 173 (30%).

(*Z*)-2-Methyl-(5,6-methylenedioxy)-1-(*p*-methylthiobenzylidene)-3-*i*-*n*-denylacetic acid (12)—To a solution of 0.46 g (1.78 mmol) of olefin mixture (10:11) in 4 mL of methanol containing sodium methoxide (~7.4 mmol) was added 0.3 g (1.96 mmol) of *p*-thiomethylbenzaldehyde dissolved in 3 mL of methanol. The initially pale pink reaction mixture was stirred overnight at reflux. Then, ~10 mL of water was added to the reaction vessel and gentle reflux was continued for 1 h. At this time, the reaction mixture became very turbid, and a copious amount of precipitate was obtained by cooling the reaction mixture in an ice bath. The slurry of red-brown solids was filtered, the filtrate was stirred with methanol, adjusting the pH of this solution to 2 with concentrated HCl, and a dark-orange precipitate was obtained. This cake was filtered and washed with water, and the resulting product was crystallized with a mixture of ethyl acetate and *n*-pentane to produce 0.588 g (82%) of 12 as orange crystals; mp 185–186 °C; UV:λ_{max} (MeOH) 347 (ϵ 30 000) and 316 nm (ϵ 30 000); ^{1}H NMR (DMSO-d_6): 7.20–7.45 (br. d, 4, Ar), 7.10 (s, 1, Ar), 6.75 (s, 1, Ar), 6.70 (s, 1, Ar), 5.90 (s, 2, OCH_2O), 3.20–3.80 (br s, 1H, exchangeable with D_2O), 3.45 (s, 2, CH_2CO), 2.50 (s, 3, SCH_3), and 2.18 ppm (s, 3, C2-CH_3); MS: *m/z* 366 (M^+, 100%), 274 (50%), 259 (50%), 215 (30%).

Anal.—Calcd for $C_{21}H_{18}O_4S$: C, 68.85; H, 4.92. Found: C, 69.12; H, 4.63.

(*Z*)-2-Methyl-(5,6-methylenedioxy)-1-(*p*-methylsulfinylbenzylidine)-3-indenylacetic acid (1)—To a methanolic solution of 0.12 g (0.29 mmol) of the acid 12 was added in a dropwise manner an aqueous solution of sodium periodate (0.23 g; 1.08 mmol). The reaction mixture was vigorously stirred for 8 h and then diluted with four 25-mL portions of $CHCl_3$. The combined organic solution were worked up as usual to afford 0.11 g (96%) of the sulfoxide 1, which showed a nicely resolved TLC spot (R_f of 0.41; 6:3.9:0.2 solution of benzene:dioxane:acetic acid). This material was recrystallized from warm ethyl acetate to furnish orange-red crystals: mp 193–194 °C; UV: λ_{max} (MeOH) 335 (ϵ 18 500) and 302 nm (ϵ 32 000); ^{1}H NMR (DMSO-d_6): 7.80 (s, 4, Ar), 7.20 (s, 1, Ar), 6.75 (s, 1, Ar), 6.63 (s, 1, Ar),

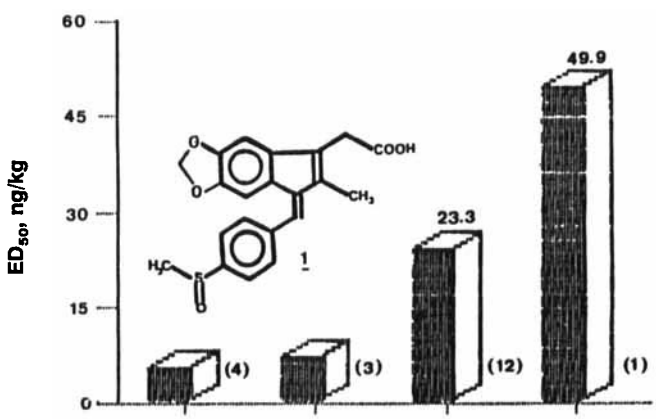

Figure 1—The AI activity of 1 and 12, expressed in ED_{50} (mg/kg) as measured by the carrageenan-induced rat paw edema test (compound numbers in parentheses).

5.85 (s, 2, OCH_2O), 3.20–3.80 (br s, 1, exchangeable with D_2O), 3.45 (s, 2H), 2.80 (s, 3, SCH_9), and 2.15 ppm (s, 3, C2-CH_3).

Anal.—Calcd for $C_{21}H_{18}O_5S$: C, 65.97; H, 4.71; Found: C, 65.82; H, 4.54.

Biological Assays—The AI activity was measured as described previously[29] by comparison with the AI activity of indomethacin and sulindac in the carrageenan-induced rat paw edema test. Edema was measured plethysmographically 3 h after intraplantar injection (0.05 mL) of a stabilized 2% solution of carrageenan in saline into one hindpaw. Five animals were used. The test compounds were administered orally as stabilized propylene glycol solutions 2 h before injection of carrageenan at three different concentrations (5, 10, and 50 mg/kg). The percent inhibition of responses observed in saline-treated control animals were analysed by the *t* test for unpaired samples ($p < 0.05$) and are expressed as means ± standard errors of the mean (SEM). The ED_{50} value is expressed with a >95% of confidence interval.

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