

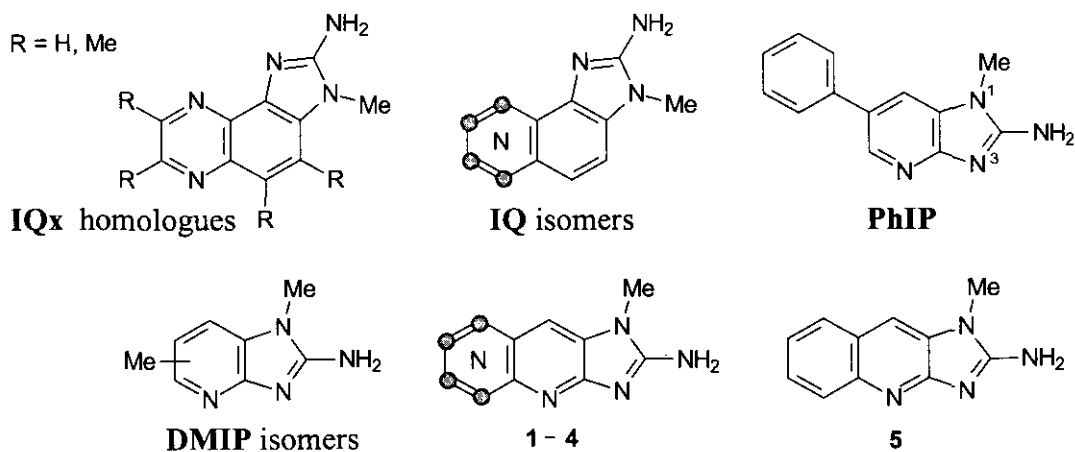
SYNTHESIS OF IMIDAZONAPHTHYRIDINES AND -QUINOLINES

Spiros Grivas^{a,b} and Peter Schuisky^a

^aDepartment of Chemistry, Swedish University of Agricultural Sciences, Box 7015, SE-750 07 Uppsala, Sweden; ^bDepartment of Organic Chemistry, Södertörn University College, Karolinska Institute, CNT, Novum Research Park, SE-141 57 Huddinge, Sweden

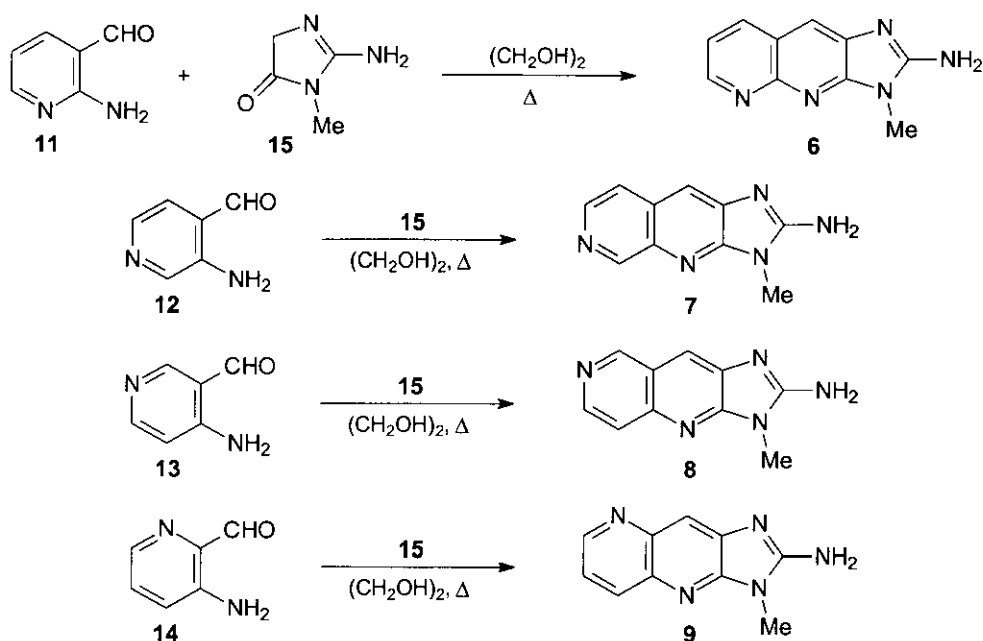
Abstract — Four 2-amino-3-methylimidazo[4,5-*b*][1,*x*]naphthyridines, *x* = 5–8 (6–9) have been obtained from aromatic aldehydes (11–14) and 2-amino-1-methyl-2-imidazolin-5-one (15) in one step. The *N*¹- and *N*³-methyl isomers of 2-aminoimidazo[4,5-*b*]quinoline (5 and 10) were prepared from 2-nitrobenzaldehyde *via* the isolated *E*-isomers of imidazolin-5-one (17) and imidazolin-4-one (20).

The imidazo[4,5-*f*]quinoxalines^{1a} (**IQx** homologues), -quinolines^{1b} (**IQ** isomers), imidazo[4,5-*b*]pyridines^{1c} (**PhIP** and **DMIP** isomers) and related linear compounds, such as 1–5,^{1d,e} belong to a group of mutagenic heterocyclic amines to which we are continuously exposed since they are present in airborne particles, cigarette smoke condensate, and in cooked food.^{1,2} Some of them have been connected with cardiovascular diseases and found to be carcinogenic in rodents and nonhuman primates.^{1,2}

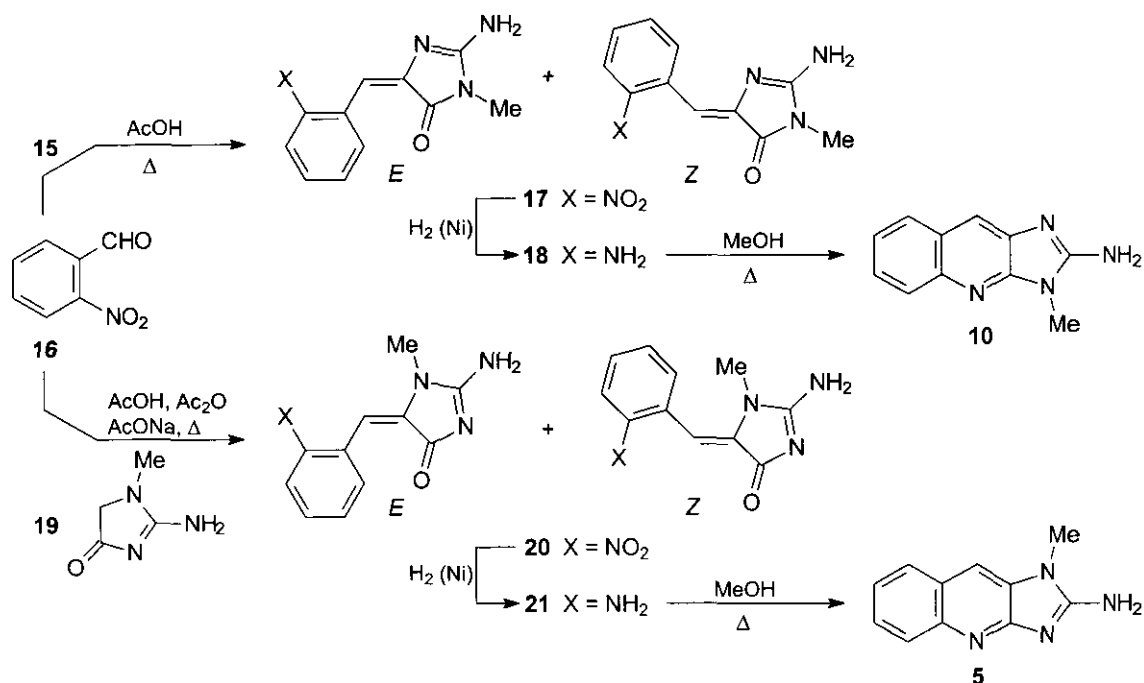


Methods that provide exclusively the *N*¹- and the *N*³-methyl isomer are desirable because apart from the possible separation difficulties after a methylation step, the two compounds can have very different biological activities. For example, the 3-methyl isomer of **PhIP** was found to be much less active than **PhIP** itself in the Ames test.^{1f} Thus, any contamination by the other isomer

would give wrong biological activity results. In connection with previous structure-activity studies³ we needed the imidazonaphthyridines (6-9) and -quinoline (10). We also wished to compare the outcome of the condensation between isocreatinine⁴ (15) and aromatic aldehydes (11-14) to that previously reported^{1d} from the Friedländer reaction of creatinine (19) with these aldehydes. We now report that the desired 6-9 can be prepared in 35-45% yield by heating isocreatinine with 11-14 in ethylene glycol. Under similar conditions, their isomers (1-4) were obtained in 65-85% yield from 11-14 and creatinine.^{1d} Thus, the *N*¹- and the *N*³-methyl isomers of these imidazonaphthyridines can be prepared free from each other.



For the synthesis of the imidazoquinoline (5)^{1c} and its isomer (10) a different approach was employed. Treatment of both isocreatinine (15) and creatinine (19) with 2-nitrobenzaldehyde (16) in ethylene glycol^{1d,c} or piperidine,⁵ produced neither 17 nor 20. Condensation of isocreatinine with 16 under Perkin conditions⁶ i.e., reflux in a mixture of sodium acetate, acetic acid and its anhydride, gave *N*-acetylated products. However, their reaction in acetic acid alone afforded the expected 17 in 13% yield. On the other hand, reaction of creatinine with 16 under Perkin conditions did furnish 20 (24%) with no formation of *N*-acetylated products. Flash chromatography of the geometrical isomers on silica gel, reduction (H₂/Raney Ni) of (*E*)-17 to 18 and of (*E*)-20 to 21, and subsequent cyclization of the crude amines by heating in methanol afforded 10 in 50% yield from (*E*)-17, and 5 in 75% yield from (*E*)-20. The condensation of creatinine with 16 in acetic acid gave no 20. Similarly, treatment of both isocreatinine and creatinine with 16 in acetic anhydride gave no 17 or 20. Interestingly, upon standing at 8 °C in the presence of moisture, (*Z*)-20 was converted into the 2-hydroxy analogue (22, not shown). No such spontaneous hydrolysis of 17 or (*E*)-20 could be detected.



Numerous *E*- and *Z*-isomers of arylideneimidazolones and -imidazolidinediones have been synthesized and distinguished by X-Ray crystallography, UV-, IR-, and NMR spectroscopy.^{5,7} One of the most unambiguous, general and efficient differentiation methods is to look at the long range ($^3J_{\text{CH}}$) coupling between the carbonyl carbon and the olefinic hydrogen, since the *E*-isomers have a $^3J_{\text{CH}}$ which can be twice as large as that of the *Z* isomers,^{7,8} (see experimental part).

EXPERIMENTAL

Organic solvents were of analytical grade and used as purchased. Evaporations were performed at reduced pressure below 40 °C. The reactions and purifications were monitored by TLC (UV detection) on aluminium sheets coated with silica gel 60 F₂₅₄ (Merck); solvent mixtures A: CHCl₃-MeOH-aq. 25% NH₃, 4:1:0.03 and B: CHCl₃-MeOH-aq. 25% NH₃, 7:1:0.03 by volume ratios. Flash and 'dry flash' chromatography⁹ were performed on silica gel (35–60 μ, Grace). Melting points (uncorrected) were determined on a Mettler FP62. EI mass spectra (direct insertion, 70 eV) were obtained on a Jeol JMS-SX/SX102A. All ¹H and ¹³C NMR spectra were recorded in [²H₆]DMSO on a Bruker DRX 400 at 30 °C and referenced to the solvent (δ 2.50 and 39.5) unless otherwise stated. Assignments were done using HMBC and HMQC experiments; the $^3J_{\text{CH}}$ constants for differentiation of the geometrical isomers were obtained by HMBC experiments. FTIR (KBr) spectra were recorded on a Perkin Elmer 1760X.

Materials.—Compounds (11–14) were prepared as previously reported^{1d} and 15 via methylation of glycoyamidine.⁴

2-Amino-1-methylimidazo[4,5-b]quinoline (5).—Compound (*E*)-**20** (100 mg, 0.41 mmol) was dissolved in methanol (30 mL) and ethyl acetate (40 mL). Raney nickel (*ca.* 1.5 mL) was added, and the mixture was hydrogenated under ambient conditions for 15 min (TLC: A). The catalyst was filtered off on a celite bed and the solvents removed. The crude **21** [δ_{H} 3.18 (Me, s), 5.1 (2 NH₂, br s), 6.06 (H-6, s), 6.45 (H-4', app. t, *J* 7.4), 6.63 (H-3', app. d, *J* 8.0), 6.95 (H-5', app. t, *J* 7.6), 7.78 (H-6', app. d, *J* 7.9)] was immediately dissolved in methanol (70 mL) and heated at reflux overnight, under nitrogen and in the presence of molecular sieves. After removal of the solvent the residue was recrystallized from aqueous ethanol to give **5** (60 mg; 75% from (*E*)-**20**) which was identical with an authentic sample;^{1c} δ_{C} 28.7 (Me), 109.1 (C-9), 122.3 (C-7), 124.3 (C-8a), 125.7 (C-6), 127.2 (C-5), 127.5 (C-8), 129.5 (C-3a), 144.6 (C-4a), 158.8 (C-9a), 161.5 (C-2).
Condensation of 11–14 with 15.—The appropriate aldehyde (100 mg, 0.82 mmol) and **15** (140 mg, 1.24 mmol) in ethylene glycol (1 mL) were heated at 140 °C under nitrogen. After a few min the mixture became clear and within 1.5 h the reaction was complete (TLC: B). The solvent was removed, and the crude product was flash chromatographed on silica gel (B). Recrystallization (aq. MeOH) gave pure product.

2-Amino-3-methylimidazo[4,5-b][1,8]naphthyridine (6): yield 40%; mp >300 °C. *Anal.* Calcd for C₁₀H₉N₃: C, 60.3; H, 4.6; N, 35.2. Found: C, 60.2; H, 4.6; N, 35.1; MS, *m/z* 199 (M⁺, 100%); δ_{H} 3.63 (Me, s), 7.38 (H-7, dd, *J* 8.1 and 4.3), 7.5 (NH₂, br s), 7.80 (H-9, s), 8.32 (H-8, dd, *J* 8.1 and 1.9), 8.75 (H-6, dd, *J* 4.0 and 1.6); δ_{C} 27.2 (Me), 115.5 (C-9), 118.7 (C-7), 120.8 (C-8a), 136.4 (C-8), 137.0 (C-9a), 148.1 (C-6), 150.8 (C-4a), 152.6 (C-3a), 159.5 (C-2).

2-Amino-3-methylimidazo[4,5-b][1,7]naphthyridine (7): yield 36%; mp >300 °C. *Anal.* Calcd for C₁₀H₉N₃: C, 60.3; H, 4.6; N, 35.2. Found: C, 60.1; H, 4.5; N, 35.2; MS, *m/z* 199 (M⁺, 100%); δ_{H} 3.61 (Me, s), 7.63 (H-8, d, *J* 5.9), 7.8 (NH₂, br s), 7.91 (H-9, s), 8.42 (H-7, d, *J* 5.8), 9.12 (H-5, s); δ_{C} 28.2 (Me), 107.7 (C-9), 120.1 (C-8), 122.1 (C-8a), 130.8 (C-9a), 142.9 (C-7), 147.8 (C-4a), 150.5 (C-5), 151.5 (C-3a), 163.1 (C-2).

2-Amino-3-methylimidazo[4,5-b][1,6]naphthyridine (8): yield 43%; mp >300 °C. *Anal.* Calcd for C₁₀H₉N₃: C, 60.3; H, 4.6; N, 35.2. Found: C, 60.3; H, 4.5; N, 35.0; MS, *m/z* 199 (M⁺, 100%); δ_{H} 3.61 (Me, s), 7.5 (NH₂, br s), 7.72 (H-5, d, *J* 5.8), 7.89 (H-9, s), 8.42 (H-6, d, *J* 5.7), 9.18 (H-8, s); δ_{C} 27.9 (Me), 115.1 (C-9), 120.1 (C-5), 143.3 (C-6), 145.1 (C-8a), 145.4 (C-4a), 152.0 (C-8), 152.3 (C-9a), 153.9 (C-3a), 160.3 (C-2); MS, *m/z* 199 (M⁺, 100%).

2-Amino-3-methylimidazo[4,5-b][1,5]naphthyridine (9): yield 45%; mp >300 °C. *Anal.* Calcd for C₁₀H₉N₃: C, 60.3; H, 4.6; N, 35.2. Found: C, 60.1; H, 4.6; N, 35.1; MS, *m/z* 199 (M⁺, 100%); δ_{H} 3.63 (Me, s), 7.37 (H-6, dd, *J* 8.0 and 4.2), 7.4 (NH₂, br s), 7.79 (H-9, s), 8.30 (H-5, dd, *J* 8.1 and 1.9), 8.73 (H-7, dd, *J* 4.2 and 1.9); δ_{C} 27.2 (Me), 115.6 (C-9), 118.7 (C-6), 120.9 (C-8a), 136.4 (C-9a), 137.3 (C-5), 148.2 (C-7), 150.8 (C-4a), 152.7 (C-3a), 159.7 (C-2).

2-Amino-3-methylimidazo[4,5-b]quinoline (10).—Reduction of (*E*)-**17** as described under compound **5** afforded crude **18** [δ_{H} 2.99 (Me, s), 5.9 (2 NH₂, br s), 6.21 (H-6, s), 6.46 (H-4', app. t, *J* 7.0), 6.58 (H-3', app. d, 7.9), 6.86 (H-5', td, *J* 6.9 and 1.2), 7.79 (H-6', app. d, *J* 7.5)] which on cyclization afforded **10** in 50% yield (mp >300 °C) from (*E*)-**17**. *Anal.* Calcd for C₁₁H₁₀N₄: C, 66.6; H, 5.1; N, 28.3. Found: C, 66.6; H, 5.1; N, 28.2; MS, *m/z* 198 (M⁺, 100%); δ_{H} 3.71 (Me, s),

7.41 (H-7, ddd, J 8.1, 6.9 and 1.2), 7.54 (H-6, ddd, J 8.5, 6.9 and 1.5), 7.83 (H-9, s), 7.88 (H-8, dd, J 8.2 and 1.4), 7.96 (H-5, dt, J 8.5 and 0.5); δ_c (^{13}C]methanol) 27.4 (Me), 118.9 (C-9), 123.5 (C-8a), 124.5 (C-7), 127.4 (C-6), 127.5 (C-5), 128.7 (C-8), 142.8 (C-4a), 144.2 (C-9a), 150.5 (C-3a), 159.6 (C-2).

2-Amino-1-methyl-4-(2-nitrobenzylidene)-2-imidazolin-5-one (17).—Compounds (15) (550 mg, 4.9 mmol) and (16) (680 mg, 4.5 mmol) in acetic acid (6.5 mL) were heated under nitrogen at 100 °C for 60 min. The solvent was removed and the residue was 'dry flash' chromatographed on silica gel (B). Fractions containing each isomer were then flash chromatographed on silica gel (A). Recrystallization (aq. MeOH) yielded pure isomers.

(E)-17: yield 5%; mp 228–230 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_3$: C, 53.6; H, 4.1; N, 22.8; O, 19.5. Found: C, 53.5; H, 4.0; N, 22.7; MS, m/z 246 (M^+ , 14%); δ_H 3.13 (Me, s), 6.61 (H-6, s), 7.48 (H-4', app. dd, J 7.8 and 1.3), 7.73 (H-5', app. t, J 7.4), 7.96 (H-3', app. dd, J 8.1 and 1.1), 8.0 (NH₂, br s), 8.98 (H-6', dd, J 8.1 and 1.2); δ_c 26.9 (Me), 103.3 (C-6), 125.3 (C-3'), 128.5 (C-4'), 130.7 (C-1'), 132.7 (C-6'), 133.5 (C-5'), 145.9 (C-4), 149.4 (C-2'), 162.8 (C-2), 170.6 (C-5, $^3J_{\text{CH-6}}$ 8.6).

(Z)-17: yield 8%; mp 212.0–213.5 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_3$: C, 53.6; H, 4.1; N, 22.8; O, 19.5. Found: C, 53.5; H, 4.1; N, 22.6; MS, m/z 246 (M^+ , 16%); δ_H 3.07 (Me, s), 6.55 (H-6, s), 7.41 (H-4', app. dd, J 7.2 and 1.3), 7.66 (H-5', app. t, J 7.4), 7.90 (H-3', dd, J 8.2 and 1.3), 8.0 (NH₂, br s), 8.91 (H-6', dd, J 8.0 and 1.3); δ_c 25.7 (Me), 102.1 (C-6), 124.1 (C-3'), 127.3 (C-4'), 129.6 (C-1'), 131.5 (C-6'), 132.3 (C-5'), 144.5 (C-4), 148.2 (C-2'), 161.6 (C-2), 169.4 (C-5, $^3J_{\text{CH-6}}$ 4.5).

2-Amino-1-methyl-5-(2-nitrobenzylidene)-2-imidazolin-4-one (20).—Compounds (16) (1.95 g, 12.9 mmol) and (19) (1.55 g, 13.72 mmol) in a mixture of acetic acid (15 mL), acetic anhydride (4.6 mL) and sodium acetate (5.12 g) were heated at reflux under nitrogen for 60 min (TLC: B). The mixture was poured on ice-water and the precipitate was filtered off. This was crystallized (aq. MeOH) to give **(E)-20**. The solvents of the first mother liquor were removed and the residue was crystallized (MeOH) to yield **(Z)-20**.

(E)-20: yield 11%; mp 258–259 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_3$: C, 53.6; H, 4.1; N, 22.8; O, 19.5. Found: C, 53.5; H, 4.1; N, 22.7; MS, m/z 246 (M^+ , 27%); δ_H 3.18 (Me, s), 6.41 (H-6, s), 7.51 (H-4', td, J 7.9 and 1.4), 7.63 (H-5', td, J 7.5 and 1.2), 7.76 (H-3', dd, J 8.0 and 0.6), 7.9 (NH, br s), 8.01 (H-6', dd, J 8.2 and 1.2), 8.4 (NH, br s); δ_c 28.7 (Me), 107.2 (C-6), 124.8 (C-6'), 129.3 (C-1'), 129.9 (C-4'), 133.3 (C-5'), 133.9 (C-3'), 136.6 (C-5), 148.8 (C-2'), 168.3 (C-2), 175.2 (C-4, $^3J_{\text{CH-6}}$ 7.8).

(Z)-20: yield 13%; mp 263–264 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_3$: C, 53.6; H, 4.1; N, 22.8; O, 19.5. Found: C, 53.5; H, 4.1; N, 22.6; MS, m/z 246 (M^+ , 30%); δ_H 3.08 (Me, s), 6.63 (H-6, s), 7.57 (H-4', td, J 7.3 and 1.1), 7.69 (H-5', td, J 7.4 and 1.1), 7.72 (H-3', d, J 7.1), 8.07 (H-6', d, J 8.2), 8.1 (NH, br s); δ_c 25.8 (Me), 108.7 (C-6), 124.2 (C-6'), 128.4 (C-1'), 129.0 (C-4'), 131.3 (C-5), 132.3 (C-5'), 132.8 (C-3'), 147.6 (C-2'), 153.5 (C-4, $^3J_{\text{CH-6}}$ 3.8), 162.4 (C-2).

2-Hydroxy-1-methyl-5-(2-nitrobenzylidene)-2-imidazolin-4-one (22): mp 258.5–260.5 °C. *Anal.* Calcd for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_4$: C, 53.4; H, 3.7; N, 17.0; O, 25.9. Found: C, 53.3; H, 3.7; N, 16.9; MS, m/z 247 (M^+ , 21%); δ_H 3.08 (Me, s), 6.62 (H-6, s), 7.56 (H-4', app. t, J 7.4), 7.65–7.75 (H'-5 and H-6', m), 8.07 (H-3', d, J 8.1), 11.3 (OH, br s); δ_c 25.8 (Me), 108.8 (C-6), 124.2 (C-3'), 128.9 (C-1'),

129.2 (C-4'), 131.5 (C-5), 132.8 (C-5' or C-6'), 132.9 (C-6' or C-5'), 147.7 (C-2'), 153.6 (C-2), 162.5 (C-4); FTIR (KBr): 3203, 3076, 1764, 1728, 1650, 1519, 1439, 1365, 1337, 1121, 1066 cm⁻¹.

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