

NITROIMIDAZOLES VIII [1]. SYNTHESSES, ANTI-BACTERIAL AND ANTIFUNGAL ACTIVITIES OF 2-PYRIDYL-NITROIMIDAZOLES

A. Shafiee, A. Lavasani, B. Pirouzzadeh, M. Mafakhari and F. Kamal

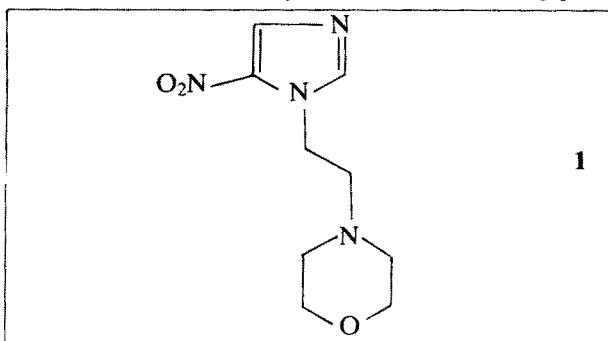
Department of Chemistry, College of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Starting from 2-(2-pyridyl) imidazole a series of substituted imidazoles (2-5) were prepared. From the reaction of 2-(3-pyridyl)-4-(or 5) nitroimidazole (15) with dimethyl sulfate in alkaline medium 1-methyl-2-(3-pyridyl)-4-nitroimidazole (6) was prepared. Reaction of compound 15 with diazomethane gave 1-methyl-2-(3-pyridyl)-5-nitroimidazole (7) in addition to 6. The antibacterial and antifungal activities of compounds 5, 6, and 7 against a number of microorganisms were determined.

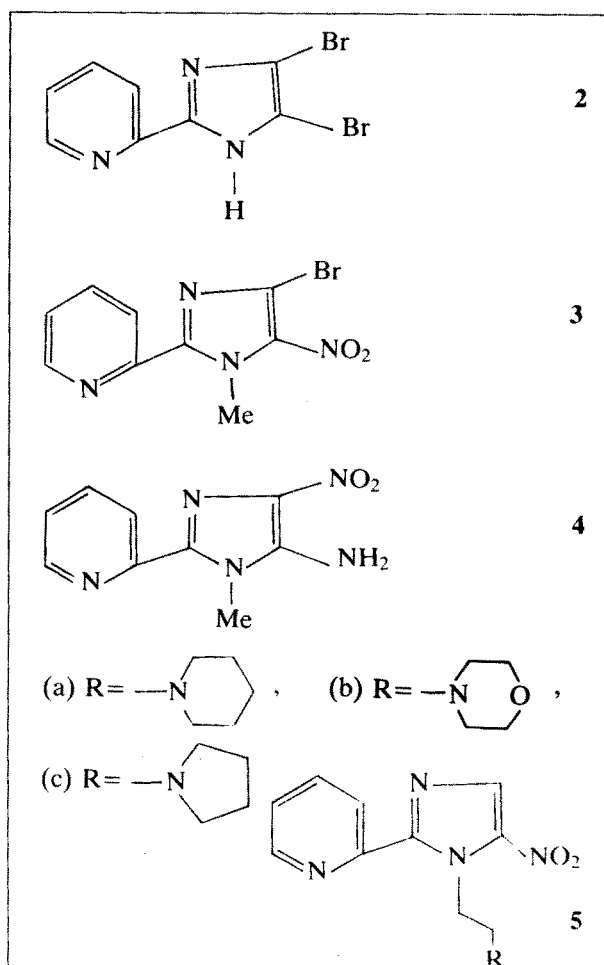
Introduction

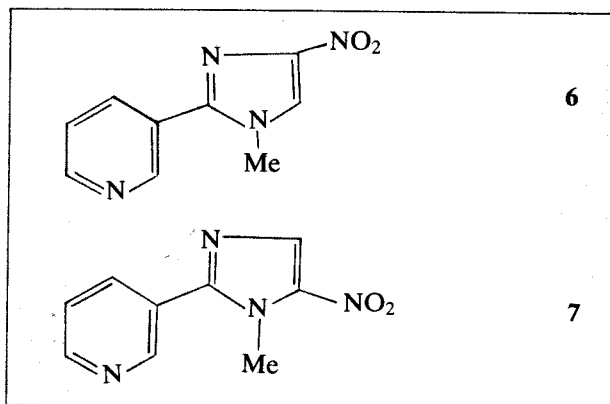
The considerable biological importance of the group of compounds incorporating an imidazole nucleus has stimulated much work on this heterocycle [2-4]. The syntheses of 1-methyl-2-(2-pyridyl)-nitroimidazoles and 1-methyl-2-(2-oxazolyl)-5-nitroimidazole as possible effective drugs against tropical diseases has recently been reported [5,6]. Since Nimorazole (1) is an effective drug against *T. vaginalis*, *Entamoeba histolytica* and *G. lamblia* [7] we



have decided to synthesize 2-(2-pyridyl)-4, 5-dibromimidazole (2), 1-methyl-2-(2-pyridyl)-4-bromo-5-nitroimidazole (3), 1-methyl-2-(2-pyridyl)-4-nitro-5-aminoimidazole (4), 1-(2-dialkylaminoethyl)-2-(2-pyridyl)-5-nitroimidazole (5), 1-methyl-2-(3-pyridyl)-4-nitroimidazole (6) and 1-methyl-2-(3-pyridyl)-5-nitroimidazole (7) as possible effective drugs against tropical diseases [8].

Key words: 2-pyridyl - Nitroimidazoles, Antibacterial Activity of Nitroimidazoles, Antifungal Activity of Nitroimidazoles.





Results and Discussion

Bromination of 2-(2-pyridyl) imidazole (8)[9] with bromine in chloroform afforded compound 2. Nitration of compound 8 with nitric acid-sulfuric acid afforded 2-(2-pyridyl) - 4 - (or 5) nitroimidazole (9) and 2 - (2 - pyridyl) - 4, 5 - dinitroimidazole (12). N Methylation of compound 9 with diazomethane gave 1-methyl-2-(2-pyridyl)-5-nitroimidazole (11)[5].

Bromination of compound 11 with bromine in chloroform did not give compound 3. However bromination in acetic acid afforded the desired compound 3 in moderate yield. Reduction of compound 12 with sodium dithionite in methanol resulted in the reduction of only one of the nitro group. The position of the amino group could be established through the uv spectrum of the compound. In compound 11 the maximum absorption is at 325 nm while in the corresponding 4-nitro isomer the maximum lies at 297 nm [5]. In compound 4 there is no absorption at 325 nm region and exists a maximum absorption at 297 nm. This demonstrates that the nitro group at position 5 is reduced. In addition because of the linear conjugation system between the amino and pyridyl ring there exists a maximum absorption at 380 nm.

Reaction of compound 9 with NaH in THF and subsequent reaction with 2-dialkylaminoethyl chloride yielded compound 5 and 1-(2-dialkylaminoethyl)-2-(2-pyridyl)-4-nitroimidazole (13) Assignment of structures of compounds 5 and 13 were made by spectroscopic data. In the uv spectra of compounds 5a and 13a, because of the linear conjugated system of compound 5a over the branched conjugated system in compound 13a, the position of the main absorption maximum in 5a would be in a higher wavelength than in 13a. In fact compound 5a had a distinct maximum at 328nm whereas 13a had a maximum at 306 nm. In addition compound 5a exhibited a maximum at 234 nm [10].

It has been reported that in nmr spectrum, the δ value of 1-methyl in the 5-nitroimidazoles is greater than the 4-nitroimidazoles because of the greater de-

shielding effect of the 5-nitro group as compared with 4-position [5,11], in compound 5 the N-CH₂ group appeared 0.43 ppm lower field relative to N-CH₂ group in 13.

2-(3-pyridyl)-4-(or 5) nitroimidazole (15) was prepared according to previous reports [4]. N-Methylation of compound 15 in the presence of a base yielded compound 6, whereas N-methylation with diazomethane gave compound 6 and 7.

In the present work the antibacterial and antifungal activities of compounds 5, 6 and 7 were determined. None of the compounds showed significant antifungal activity. The antibacterial activity of these compounds are summarized in Table 1.

Table 1- Antibacterial activity of compounds 5, 6 and 7. The amount of compound in a disk in μg ; average zone size, mm.

Compound NO.	Microorganisms*	Concentration		Furazolidone (10 μg)
		10	30	
5a	<i>B. subtilis</i>	8	13	21
5b	"	8.5	14	21
7	"	17	22	21
5a	<i>E. Coli</i>	-	7.5	25

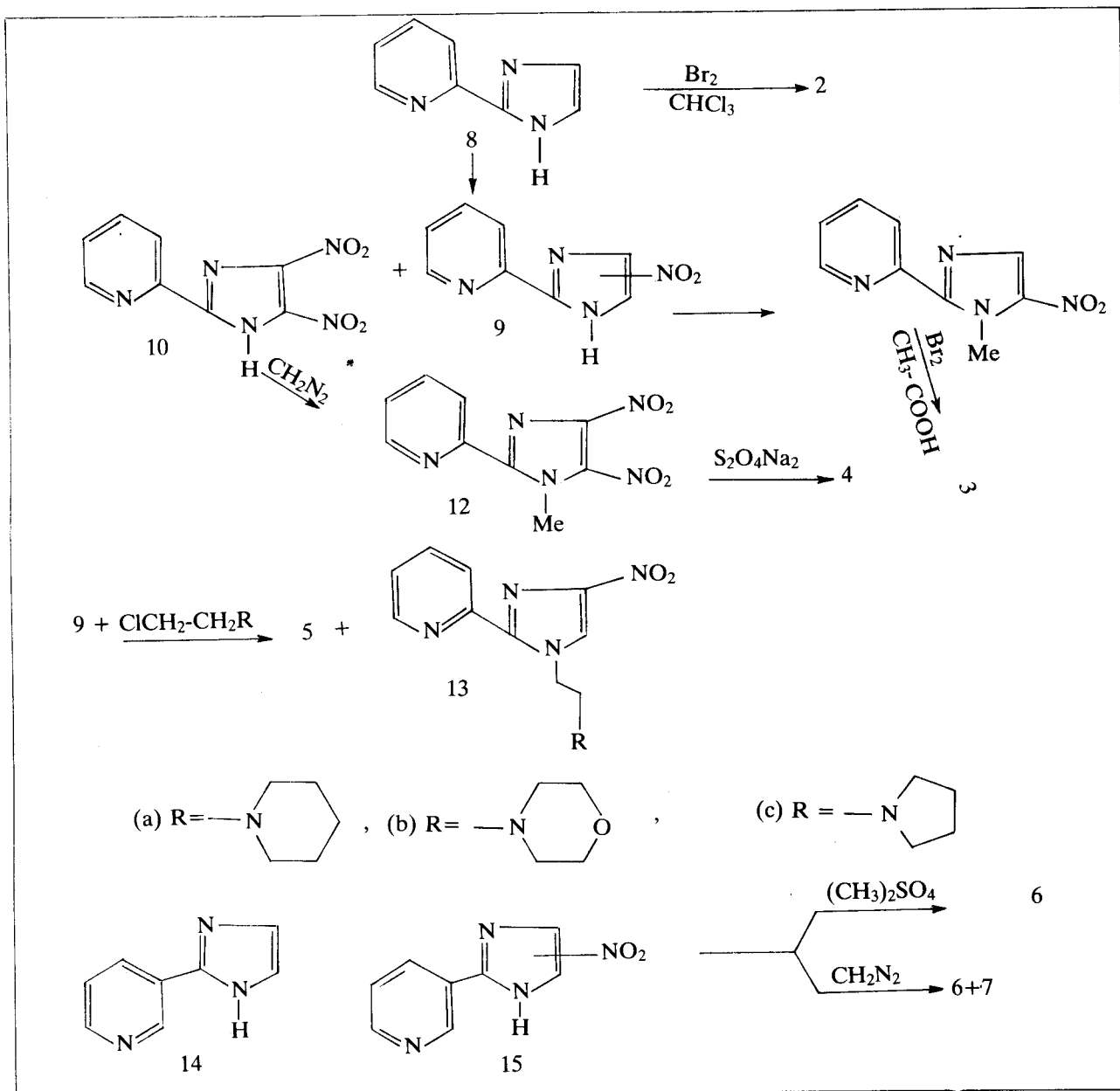
* The antibacterial activity against other microorganisms was not significant. The antibacterial activity of compound 6 was insignificant.

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained using a Perkin-Elmer Model 267 spectrograph (potassium bromide disks). The NMR spectra were recorded on a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS - 311 spectrometer at 70 ev.

2-(2-Pyridyl)-4,5-dibromoimidazole (2)

To a stirring solution of compound 8 (5.7 g, 0.03 mol) in chloroform (11 ml) at 5-10°C a solution of bromine (2.2 ml) in chloroform (11 ml) was added dropwise. After the disappearance of bromine colour, the solvent was evaporated and extracted with ether. The residue was crystallized from chloroform to give 2 g (22%) of 2: mp 214 - 215°C; NMR (DMSO-d₆): 8.90 (q, 1H, H₆), 8.30 (m, 2H, H₄ and H₅) and 7.60 (m, 1H, H₃); ms: m/e (%) 305(M⁺, 80), 303(100), 301(80), 278(12), 276(24), 274(14), 224(24), 222(25), 197(25), 195(27), 143(70), 105(71), 90(21), 78 (62) and 64 (15) Anal. Calcd for C₈H₅N₃Br₂:



Scheme 1

C,31.68; H,1.65; N,13.86. Found: 31.85; H,1.73; N,13.94.

1-Methyl-2-(2-pyridyl)-4-bromo-5-nitroimidazole
(3)

To a stirring solution of 1-methyl-2-(2-pyridyl)-5-nitroimidazole (11, 714 mg, 3.5 mmol) in acetic acid (5 ml) a solution of bromine (0.09 ml) in acetic acid (5 ml) was added. The solution was refluxed for 48 hrs. The precipitate was filtered and crystallized from methanol-water (2:1) to give 248 mg (25%) of 3; mp 229-230°C; IR: 3050, 1585, 1485

(aromatic), 1530 and 1365 cm^{-1} (NO_2); ms: m/e (%) 284(M^+ , 11), 282(10), 267(33), 265(33), 237(16), 235(16), 122(16), 120(18), 106(10), 105(19), 104(22) and 78(100).

Anal. Calcd for $\text{C}_9\text{H}_7\text{BrN}_4\text{O}_2$: C, 38.16; H,2.47; N,19.76.

Found: C, 38.02; H,2.39; N,19.67.

1-Methyl-2-(2-pyridyl)-4-nitro-5-aminoimidazole
(4)

To a stirring solution of sodium dithionite (1.41 g, 8 mmol) and sodium carbonate (0.64 g, 6 mmol) in water (27 ml) 249 mg, 1 mmol) in methanol (14

ml) was added dropwise. After the addition was complete, it was stirred for another 10 minutes. The solvent was evaporated. To the residue methanol (15 ml) was added and filtered. The solvent was evaporated. The residue was purified by preparative tlc on silica gel using chloroform-methanol (8:2) as the eluent. The desired compound was crystallized from methanol to give 57 mg (26%) of **4**; mp 266-268°C; UV (methanol): λ_{\max} 380, 295 and 245 nm; IR: 3445, 3425 and 1640 (NH₂), 3160, 1580 and 1480 (aromatic), 1535 and 1345 cm⁻¹ (NO₂); ms: m/e (%) 219(M⁺, 100), 202(19), 173(19), 157(21), 146(14), 144(17), 119(61), 105(46), 78(43), 64(31) and 57(39).

Anal. Calcd for C₉H₉N₅O₂: C, 49.32; H, 4.11; N, 31.96.

Found: C, 49.15; H, 4.01; N, 31.79.

1-(2-Piperidinoethyl)-2-(2-pyridyl)-5-nitroimidazole (5a)

To a stirring solution of compound **9** (1.9 g, 0.01 mol) in dry THF (250 ml), a 80% suspension of sodium hydride in parafin (0.33 g, 0.011 mol) was added. After stirring for two minutes, THF was evaporated, dry toluene (120 ml) and 2-piperidinoethyl chloride (1.475 g, 0.01 mol) were added. The mixture was refluxed at 110°C for 50 hrs. The precipitate was filtered (starting material, 675 mg). The solvent was evaporated and the residue was crystallized from methanol-ether (2:1) to give 1.04 g (53% based on reacted starting material) of **5a**; mp 94-95°C; UV (methanol): λ_{\max} 328 (log ϵ = 4.32), 234 nm (log ϵ = 4.27); NMR(CDCl₃): 8.65 (d, 1H, H₆ pyridine), 8.23 (dd, 1H, H₄ pyridine), 8.05 (s, 1H, H₄), 7.83 (dt, 1H, H₅ pyridine), 7.42 (dt, 1H, H₃ pyridine), 5.27 (t, 2H, CH₂-N imidazole), 2.75 (t, 2H, CH₂N), 2.42 (m, 4H, CH₂N) and 1.36 (m, 6H, CH₂); ms: m/e (%) 301 (M⁺, 6), 284(20), 255(92), 145(17), 111(24), 98(48), 78(15), 55(26), 43(37), 42(21), 41(90) and 40(100).

Anal. Calcd for C₁₅H₁₉N₅O₂: C, 59.80; H, 6.31; N, 23.26. Found: C, 59.72; H, 6.43; N, 23.14.

The TLC of the mother liquid had two spots near each other (chloroform/ethyl acetate, 80:20). The lower spot was compound (**5a**) and the upper spot was the corresponding 4-nitro isomer (**13a**). The solvent was evaporated. In the UV spectrum of the mixture in addition to λ_{\max} at 328 and 234 another distinct maximum was observed at 306 nm. The latter absorption results from the 4-nitro isomer. These two spots could not be separated through PLC.

1-(2-Morpholinoethyl)-2-(2-pyridyl)-5-nitroimidazole (5b)

This compound was prepared from **9** and 2-morpholinoethyl chloride similar to **5a** in 36% yield; mp 102- 104°C (water); UV: (methanol): λ_{\max} 328 (log ϵ = 4.19) and 234nm (log ϵ = 4.10; NMR (CDCl₃): 8.70 (d, 1H, H₆ pyridine), 8.26 (td, 1H, H₄ pyridine), 8.03 (s, 1H, H₄), 7.87 (dt, 1H, H₅ pyridine), 7.4 (dt, 1H, H₃ pyridine), 5.26 (t, 2H, CH₂N imidazole), 3.46 (t, 4H, CH₂O), 2.70 (t, 2H, CH₂N) and 2.36 (t, 4H, CH₂N); ms: m/e (%) 303 (M⁺, 4), 257 (50), 113 (96), 105 (16), 100 (100), 83 (11), 78 (15), 70 (10), 56 (34) and 42 (14).

Anal. Calcd for C₁₄H₁₇N₅O₃: C, 55.45; H, 5.61; N, 23.10.

Found: C, 55.39; H, 5.72; N, 23.15.

1-(2-Pyrrolidinoethyl)-2-(2-pyridyl)-5-nitroimidazole (5c)

This compound was prepared from **9** and 2-pyrrolidinoethyl chloride similar to **5a** in 20% yield; mp 31-32°C (ether); UV (methanol): λ_{\max} 326 (log ϵ = 4.21) and 234 nm (log ϵ = 4.11); NMR(CDCl₃): 8.70 (d, 1H, H₆ pyridine), 8.23 (td, 1H, H₄ pyridine), 8.05 (s, 1H, H₄), 7.42 (dt, 1H, H₃ pyridine), 5.27 (t, 2H, CH₂N imidazole), 2.74 (t, 2H, CH₂N) and 2.41 (m, 4H, CH₂N) and 1.38 (m, 4H, CH₂); ms: m/e (%) 287 (M⁺, 2), 241(8), 143 (11), 118 (14), 105 (57), 97 (18), 84 (77), 78 (83), 69 (32), 55 (59), 53 (54) and 42 (100).

Anal. Calcd for C₁₄H₁₇N₅O₂: C, 58.54; H, 5.92; N, 24.39.

Found: C, 58.63; H, 6.01; N, 24.43.

1-Methyl-2-(3-pyridyl)-4-nitroimidazole (6)

To a stirring solution of compound **15** (570 mg, 3 mmol) in dry acetone (100 ml), potassium carbonate (414 mg, 3 mmol) and diethyl sulfate (189 mg, 1.5 mmol) was added. The mixture was refluxed overnight. Dimethyl sulfate (189 mg, 1.5 mmol) was added and heating was continued for 12 hrs. The solvent was evaporated. To the residue, water (10 ml) was added and extracted with chloroform. The solvent was evaporated and the residue was crystallized from methanol to give 100 mg (16%) of **6**; mp 152-153°C; UV (methanol): λ_{\max} 298 (log ϵ = 3.90); NMR (CDCl₃): 8.2-7.27 (m, 4H, pyridine), 7.93 (s, 1H, H₅ imidazole) and 3.90 (s, 3H, CH₃); ms: m/e (%) 204 (m⁺, 93); 187 (8), 117 (25), 106 (82), 78 (100) and 51 (19).

Anal. Calcd for C₉H₈N₄O₂: C, 52.94; H, 3.92; N, 27.45.

Found: C, 52.83; H, 4.05; N, 27.56.

1-Methyl-2-(3-pyridyl)-5-nitroimidazole (7)

A suspension of 2-(3-pyridyl)-4 (or 5)-nitroimidazole (**15**, 5.7 g, 0.03 mol) with excess diazomethane in dry ether (400 ml) was stirred at room temperature for 5 days. The mixture was fil-

tered. The solvent was removed *in vacuo* and the residue purified by preparative TLC on silica gel using chloroform methanol (9:1) as the eluent.

The faster moving fraction was crystallized from methanol-water (2:1) to give 0.61 g (10%) of **7**; mp 130-131°C; UV(methanol): λ_{\max} 314($\epsilon=9772$); NMR (CDCl₃): 8.25-7.30 (m, 4H, pyridine), 8.20 (s, 1H, H₄) and 4.03 (s, 3H, CH₃); ms: m/e (%): 204 (M⁺, 97), 174 (98), 155 (91), 143 (23), 117 (100), 106 (54), 90 (51), 78 (60), 63 (50) and 51 (33).

Anal. Calcd for C₉H₈N₄O₂: C, 52.94; H, 3.92; N, 27.45.

Found: C, 52.83; H, 3.80; N, 27.46.

Antibacterial and Antifungal Assay-all compounds were tested against *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538 p), *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella Paratyphi B*, *Candida albicans*, *Aspergillus niger*, *Penicillium sp*, *Microsporium canis* and *Microsporium gypseum*.

Antibacterial assay: Compounds **5**, **6** and **7** were dissolved in methanol. They were diluted to 1 mg/1ml concentration. To standard paper disk of 6 mm. diameter the latter solution was added until the desired amount of compound was absorbed by the disk (see table 1). The disks were placed on inoculated assay medium surface. Furazolidone was used for comparison.

Acknowledgement

This work was partially supported by the International Organization of Chemical Sciences in Development (IOCD).

References

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