with Sarcoma 180 and 60–100 mg/kg per day for those with leukemia L1210; each agent was injected intraperitoneally for six consecutive days beginning 24 h after tumor implantation. Determination of the sensitivity of ascitic neoplasms to these agents was based upon the prolongation of survival time afforded by drug treatments.

References and Notes

(1) This work was supported by U.S. Public Health Service Grants CA-02817 and CA-16359 from the National Cancer Institute and a grant from the Bristol-Myers Co.
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Antimycotic Imidazoles. 2. Synthesis and Antifungal Properties of Esters of 1-[2-Hydroxy(mercapto)-2-phenylethyl]-1*H*-imidazoles[1]

Keith A. M. Walker,* Donald R. Hirschfeld, and Michael Marx

Syntex Research, Palo Alto, California 94304.

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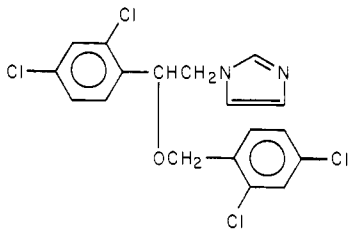
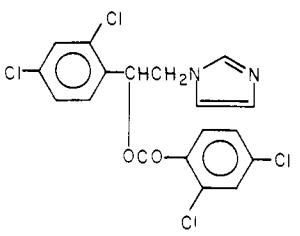
The synthesis of carboxylic and (thio)carbonate esters of 1-[2-hydroxy(mercapto)-2-phenylethyl]-1*H*-imidazoles, some of which are formally related to miconazole and its analogues by replacement of an ether with an ester linkage, is described. In antifungal bioassays a number of compounds display in vitro and, in a few cases, in vivo activities comparable to that of miconazole. In this series lipophilicity within a relatively narrow range is shown to be a necessary, although not sufficient, criterion for in vitro and, in particular, in vivo antifungal activity.

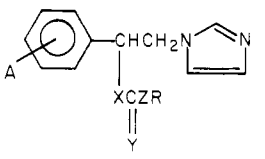
In connection with a program directed toward the development of new broad-spectrum antifungal agents, we became interested in compounds obtained by the formal replacement of the ether linkage in the potent drug, miconazole[2] (I), by an ester function, II (e.g., 6). Since it



I



6



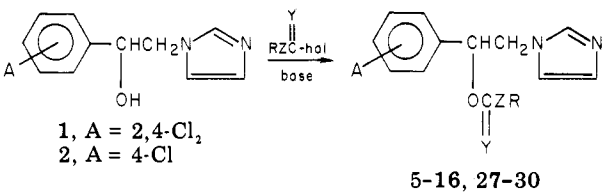
II

5-16, X = Y = O; Z = bond
17-26, X = S; Y = O; Z = bond
27-29, X = Y = Z = O
30, X = Y = O; Z = S
31, 32, X = S; Y = Z = O
33, 34, X = Z = S; Y = O
35-44, X = Y = S; Z = O

has been found by others[2,3] and by ourselves[4] that maximum antifungal activity in 1-phenylethylimidazoles is associated with 2,4-dichloro substitution in the benzene ring, we retained this subunit in the majority of compounds prepared. The nature of the ester linkage was extended beyond simple esters to include carbonates and various thio derivatives (see II).

Chemistry. Phenylethyloxy esters were prepared by standard esterification procedures from the known[2] alcohols 1 and 2 and the corresponding acyl halide (Scheme I). Phenylethylthio esters were obtained by a different route (Scheme II); the xanthates **35–44** were obtained via

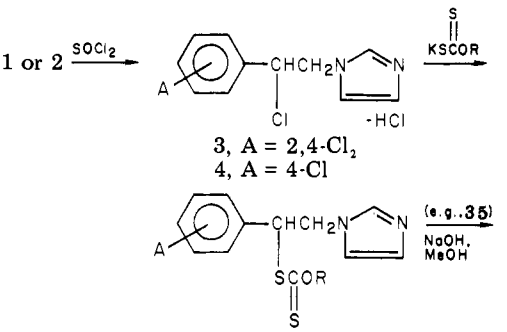
Scheme I



1, A = 2,4-Cl_2
2, A = 4-Cl

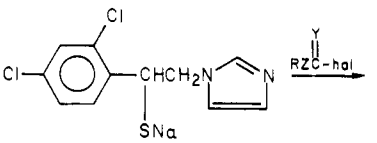
5-16, 27-30

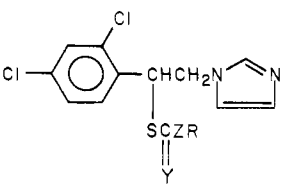
Scheme II



3, A = 2,4-Cl_2
4, A = 4-Cl

35-44

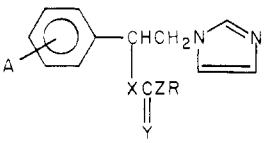




17-26, 31-34

0022-2623/78/1821-1335$01.00/0

Table I. Esters Derived from 1-[2-Hydroxy(mercapto)-2-phenylethyl]-1*H*-imidazoles



compd	A	X	Y	Z	R	formula	mp, °C	solvent[a]	analyses[b]
5	2,4-Cl_2	O	O		4-ClC_6H_4	$C_{18}H_{13}Cl_3N_2O_2 \cdot HNO_3$	195-196.5	C	C, H, N
6	2,4-Cl_2	O	O		2,4-$Cl_2C_6H_3$	$C_{18}H_{12}Cl_4N_2O_2 \cdot HNO_3$	163.5-165 dec	C	C, H, N
7	2,4-Cl_2	O	O		4-*t*-BuC_6H_4	$C_{22}H_{22}Cl_2N_2O_2 \cdot (COOH)_2$	202-205 dec	F	C, H, N
8	2,4-Cl_2	O	O		4-$O_2NC_6H_4$	$C_{18}H_{13}Cl_2N_3O_4 \cdot (COOH)_2$	200-202.5 dec	F	C, H, N
9	2,4-Cl_2	O	O		4-$ClC_6H_4CH_2$	$C_{19}H_{15}Cl_3N_2O_2 \cdot HNO_3$	154-155.5 dec	E	C, H, N
10	2,4-Cl_2	O	O		4-$ClC_6H_4CH{=}CH$	$C_{20}H_{15}Cl_3N_2O_2 \cdot HNO_3$	182-183	C	C, H, N
11	2,4-Cl_2	O	O		*n*-C_6H_{13}	$C_{18}H_{22}Cl_2N_2O_2 \cdot HNO_3$	124-126 dec	E	C, H, N
12	2,4-Cl_2	O	O		*n*-C_7H_{15}	$C_{19}H_{24}Cl_2N_2O_2 \cdot HNO_3$	99-100.5	E	C, H, N
13	2,4-Cl_2	O	O		*n*-$C_{11}H_{23}$	$C_{23}H_{32}Cl_2N_2O_2 \cdot HNO_3$	84.5-86.5	D	C, H, N
14	4-Cl	O	O		2-ClC_6H_4	$C_{18}H_{14}Cl_2N_2O_2 \cdot (COOH)_2$	201-203 dec	G	C, H, N
15	4-Cl	O	O		4-ClC_6H_4	$C_{18}H_{14}Cl_2N_2O_2 \cdot HNO_3$	193-195.5 dec	F	H, N; C[c]
16	4-Cl	O	O		4-$ClC_6H_4CH_2$	$C_{19}H_{16}Cl_2N_2O_2 \cdot (COOH)_2$	158-159.5 dec	F	C, H, N
17	2,4-Cl_2	S	O		4-ClC_6H_4	$C_{18}H_{13}Cl_3N_2OS \cdot HNO_3$	149-150.5 dec	E	C, H, N
18	2,4-Cl_2	S	O		2-ClC_6H_4	$C_{18}H_{13}Cl_3N_2OS \cdot HNO_3$	159-161 dec	C	C, H, N
19	2,4-Cl_2	S	O		4-MeC_6H_4	$C_{19}H_{16}Cl_2N_2OS \cdot HNO_3$	162-164.5 dec	A	C, H, N
20	2,4-Cl_2	S	O		$C_6H_5CH_2$	$C_{19}H_{16}Cl_2N_2OS \cdot HNO_3$	115-116 dec	E	C, H, N
21	2,4-Cl_2	S	O		4-$FC_6H_4CH_2$	$C_{19}H_{15}Cl_2FN_2OS \cdot HNO_3$	125-126.5	A	C, H, N
22	2,4-Cl_2	S	O		4-$ClC_6H_4CH_2$	$C_{19}H_{15}Cl_3N_2OS \cdot HNO_3$	136.5-139 dec	A	C, H, N
23	2,4-Cl_2	S	O		*trans*-$C_6H_5CH{=}CH$	$C_{20}H_{16}Cl_2N_2OS \cdot HNO_3$	139-141 dec	H	C, H, N
24	2,4-Cl_2	S	O		CH_3	$C_{13}H_{12}Cl_2N_2OS \cdot HNO_3$	142-143	A	C, H, N
25	2,4-Cl_2	S	O		*n*-C_5H_{11}	$C_{17}H_{20}Cl_2N_2OS \cdot HNO_3$	122-123.5 dec	E	C, H, N
26	2,4-Cl_2	S	O		*n*-C_7H_{15}	$C_{19}H_{24}Cl_2N_2OS \cdot (COOH)_2$	133.5-134.5 dec	E	C, H, N
27	2,4-Cl_2	O	O	O	*n*-C_6H_{13}	$C_{18}H_{22}Cl_2N_2O_3 \cdot HNO_3$	108-112 dec	B	C, H, N
28	2,4-Cl_2	O	O	O	*n*-C_8H_{17}	$C_{20}H_{26}Cl_2N_2O_3 \cdot HNO_3$	92.5-95.5 dec	E	C, H, N
29	4-Cl	O	O	O	4-ClC_6H_4	$C_{18}H_{14}Cl_2N_2O_3 \cdot (COOH)_2$	152-152.5 dec	G	C, H; N[d]
30	2,4-Cl_2	O	O	S	*n*-C_3H_7	$C_{15}H_{16}Cl_2N_2O_2S \cdot (COOH)_2$	161.5-165 dec	C	C, H, N
31	2,4-Cl_2	S	O	O	*n*-C_4H_9	$C_{16}H_{18}Cl_2N_2O_2S \cdot HNO_3$	112.5-114.5 dec	E	C, H, N
32	2,4-Cl_2	S	O	O	*n*-C_8H_{17}	$C_{20}H_{26}Cl_2N_2O_2S \cdot HNO_3$	99-101	E	C, H, N
33	2,4-Cl_2	S	O	S	C_6H_5	$C_{18}H_{14}Cl_2N_2OS_2 \cdot HNO_3$	157.5-160.5 dec	E	C, H, N
34	2,4-Cl_2	S	O	S	*t*-C_4H_9	$C_{16}H_{18}Cl_2N_2OS_2 \cdot HNO_3$	163-166.5 dec	H	C, H, N
35	2,4-Cl_2	S	S	O	C_2H_5	$C_{14}H_{14}Cl_2N_2OS_2 \cdot HNO_3$	142.5-143 dec	H	C, H, N
36	2,4-Cl_2	S	S	O	*n*-C_3H_7	$C_{15}H_{16}Cl_2N_2OS_2 \cdot HNO_3$	140-141.5	E	C, H, N
37	2,4-Cl_2	S	S	O	*i*-C_3H_7	$C_{15}H_{16}Cl_2N_2OS_2 \cdot HNO_3$	125-126.5 dec	E	C, H, N
38	2,4-Cl_2	S	S	O	*n*-C_4H_9	$C_{16}H_{18}Cl_2N_2OS_2 \cdot HNO_3$	120-121.5 dec	E	C, H, N
39	2,4-Cl_2	S	S	O	*i*-C_4H_9	$C_{16}H_{18}Cl_2N_2OS_2 \cdot HNO_3$	148.5-150 dec	E	C, H, N
40	2,4-Cl_2	S	S	O	*n*-C_5H_{11}	$C_{17}H_{20}Cl_2N_2OS_2 \cdot HNO_3$	118.5-119.5 dec	E	C, H, N
41	2,4-Cl_2	S	S	O	c-C_6H_{11}	$C_{18}H_{20}Cl_2N_2OS_2 \cdot HNO_3$	139.5-140.5 dec	E	C, H, N
42	2,4-Cl_2	S	S	O	*n*-C_8H_{17}	$C_{20}H_{26}Cl_2N_2OS_2 \cdot HNO_3$	107-113 dec	E	C, H, N
43	2,4-Cl_2	S	S	O	$C_6H_5CH_2$	$C_{19}H_{16}Cl_2N_2OS_2 \cdot (COOH)_2$	107-111 dec	E	C, H; N[e]
44	4-Cl	S	S	O	*n*-C_5H_{11}	$C_{17}H_{21}ClN_2OS_2 \cdot (COOH)_2$	151-152.5 dec	A	C, H, N

[a] Recrystallization solvents: A, acetone; B, benzene-hexane; C, EtOAc-EtOH; D, EtOAc-Et_2O; E, EtOAc; F, EtOH; G, MeOH; H, acetone-EtOAc. [b] Unless otherwise stated, the analyses are within ±0.4% of the theoretical values. [c] C: calcd, 50.96; found, 51.46. [d] Analysis performed on free base. [e] N: calcd, 5.46; found, 6.06.

the known[5] chloro compounds **3** and **4** and the appropriate potassium dithiocarbonate salts. Hydrolysis of the ethyl xanthate ester **35** (sodium hydroxide–methanol) produced the sodium thiolate, acylated in situ as above to give the corresponding thiol esters or thiocarbonates, **17–26** or **31–34**. All final products were isolated as the nitrate or oxalate salts (Table I).

Biological Results. Compounds were evaluated in vitro against the following: fungi (broth dilution assay) *Microsporum audouini* (*M.a.*) or *Microsporum gypseum* (*M.g.*), *Epidermophyton floccosum* (*E.f.*), *Trichophyton mentagrophytes* (*T.m.*), *Candida albicans* ATCC 10231 (*C.a.* 1), *Candida albicans* ATCC 14053 (*C.a.* 2), and *Cryptococcus neoformans* (*C.n.*); bacteria (broth microdilution assay[6]) *Staphylococcus aureus* ATCC 12600 (*S.a.*), *Streptococcus faecalis* ATCC 14506 (*S.f.*), *Corynebacterium acnes* ATCC 11828 (*C.ac.*), *Erysipelothrix insidiosa* ATCC 19414 (*E.i.*), and *Pasteurella multocida* ATCC 19427 (*P.m.*). In vivo experiments were conducted using a vaginal *C. albicans* infection in mice according to the method of Wildfeuer.[7] Test compounds were applied as 2% formulations in an aqueous propylene glycol cream[8] for 4 days b.i.d.

Results and Discussion

The test results, summarized in Table II, show that broad-spectrum in vitro antifungal activity, as well as activity against Gram-positive bacteria and *P. multocida*, is retained in a large number of compounds when the ether linkage present in miconazole and its analogues is replaced by an ester group. Furthermore, it is clear that this activity is not limited to the isosteric acyloxy group but extends to carbonates and various sulfur analogues. We have found that the antifungal activity in this series is markedly influenced by lipophilicity. As an index of lipophilicity in this series, R_m values of selected compounds were determined by reverse-phase TLC[9] using miconazole as the standard. The relative lipophilicities were then expressed in terms of ΔR_m [R_m (compound) - R_m (miconazole)], positive values indicating compounds more lipophilic than miconazole.[10] These values are included in Table II. Inspection shows that, in general, compounds differing

Table II. Antifungal and Antibacterial Activities

compd	lowest level of total inhibition (in vitro),[a,b] μg/mL												in vivo vaginal *C.a.* infection in mice[c,d]	ΔR_m (see text)
	M.a.	*M.g.*	*E.f.*	*T.m.*	*C.a.* 1	*C.a.* 2	*C.n.*	*S.a.*	*S.f.*	*C.ac.*	*E.i.*	*P.m.*		
5		100	<0.1	30	300	300	3						1/9	−0.39
6		30	<0.1	30	300	300	3							−0.24
7		10	1	10	10	10	3							+0.16
8	33		0.33	10	>300	>300								−0.54
9		100	<0.1	30	100	100	3							−0.41
10		10	<0.1	10	>300	>300	<1							
11		30	<0.1	30	100	100	3							−0.16
12		10	<0.1	10	30	30	<1						1/8	+0.10
13		>100	1	>100	>300	>300	<1	10	100	>100	10	1		+1.10
14	50		5	10	100	100								−0.49
15	100		100	>100	>100	>100	10							−0.31
16	10		1	10	50	50								−0.42
17		30	<0.1	10	10	10	<1	3	100	>100	>100	1	7/10	−0.03
18		10	<0.1	10	30	30	<1	10	30	>100	100	1		−0.35
19		30	<0.1	10	10	10	<1							−0.09
20		30	<0.1	30	100	100	<1							−0.43
21		30	<0.1	30	100	100	<1							
22		>30	<0.1	30	100	100	<1							
23		30	<0.1	10	10	10	<1							−0.08
24		100	1	100	300	300	10							
25		30	<0.1	30	100	30	1						0/10	−0.05
26		30	<0.1	10	10	10	<1	3	30	100	30	1	1/8	+0.44
27		30	<0.3	30	100	100	30							−0.17
28		10	<0.1	10	300	30	3							+0.40
29	100		10	10	>100	>100								−0.52
30		30	<0.1	30	300	300	3							
31		30	<0.1	10	30	30	<0.3							−0.14
32		30	<0.1	10	>300	>300	<1	1	30	100	10	1		+0.82
33		3	<0.1	10	100	100	<1	10	30	>100	100	3		−0.02
34		10	<0.1	3	30	30	3	3	10	100	100	1		+0.05
35	5		<0.1	<0.1	50	50	1						1/9	−0.27
36		10	<0.1	10	100	30	<0.3						6/8	−0.03
37		10	<0.1	10	100	30	<0.3							−0.14
38		3	<0.1	3	30	10	1						6/9	+0.19
39		3	<0.1	3	30	10	<0.3							+0.17
40		3	<0.1	3	(3)[e]	(3)[e]	<1	3	10	>100	100	1	0/10	+0.37
41		3	<0.1	3	(3)[e]	(3)[e]	<1							+0.43
42		30	1	30	(100)[e]	(100)[e]	<1	>100	1	100	30	1		+1.23
43		10	<0.1	1	30	10	<0.3							−0.21
44		3	0.3	10	30	30	3							+0.22
miconazole		3	<0.1	3	30	30	<0.3	1	10	10	3	<0.1	25/29[f]	0
gentamycin[g]								1	30	1	30	<0.1		

[a] < denotes lowest level tested. [b] > denotes partial growth at this dilution. [c] Compound applied intravaginally in 2% cream formulation. [d] Ratio of (animals cured)/(total number infected). [e] Values for miconazole in this assay were *C.a.* 1, 1 μg/mL; *C.a.* 2, 3 μg/mL. [f] Commercial formulation (2%). [g] Gentamycin was used as the reference standard for the antibacterial assays.

substantially in lipophilicity from miconazole (as estimated by R_m measurements) show reduced in vitro activity (e.g., compounds **5**, **6**, **8**, **13**, and **42**). The most active compounds have R_m values close to miconazole in the case of aromatic esters (e.g., **7**, **17**, **19**, **23**, and **43**) and close to or slightly greater than miconazole for alkyl esters (e.g., compounds **12**, **26**, **31**, **34**, **38**, **39**, and **44**). However, although some differences in activity exist between compounds of similar structure and ΔR_m (e.g., **18** compared with **5** and **6**), the activity of the series as a whole is remarkably constant for different types of esters having the same lipophilicity. Unfortunately, the in vitro data were found to be too imprecise for regression analysis, a finding also reported by others for related compounds.[11] The poor activity of compound **6**, a direct analogue of miconazole, is thus readily explained on the basis of its excessive hydrophilicity. Significant in vivo activity against *C. albicans* was associated only with compounds having an R_m close to that of miconazole (i.e., $\Delta R_m \approx 0$–$+0.2$) (compounds **17**, **36**, and **38**), although this is clearly not the only factor determining in vivo activity (compounds **12** and **25**). None of the compounds tested demonstrated in vivo activity superior to the miconazole standard.

It has thus been shown that formal replacement of the ether linkage in miconazole and analogues by an ester function gives compounds which generally retain broad-spectrum antifungal activity, the most active compounds displaying activity comparable to that of miconazole.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ultraviolet spectra were determined in methanol with a Cary 14 instrument. Infrared spectra were obtained in KBr with a Perkin-Elmer 237B spectrometer. NMR spectra were obtained with Varian A-60 and HA-100 instruments, and mass spectra were determined with a Varian-MAT CH4 spectrometer. Elemental analyses were performed by the Analytical Department of Syntex Research, Institute of Organic Chemistry, and are within ±0.4% of calculated values.

1-[2-(2,4-Dichlorophenyl)-2-(2,4-dichlorophenylcarbonyloxy)ethyl]imidazole Nitrate (6). To a stirred, ice-cold solution of **1** (0.64 g, 0.0025 mol) in 2 mL of Et_3N and 30 mL of dry tetrahydrofuran was added dropwise 2,4-dichlorobenzoyl chloride (0.65 g, 0.0031 mol) in 10 mL of dry tetrahydrofuran. The mixture was stirred overnight at room temperature, the solvent evaporated, and water added. The product was extracted with ether, the extracts were washed and dried ($MgSO_4$), and the nitrate salt was precipitated by dropwise addition of 70% HNO_3. Recrystallization from EtOAc–EtOH gave 0.89 g (72%) of **6**, mp 163.5–165 °C dec.

Compounds **5**, **7**–**16**, and **27**–**30** were prepared in a similar manner (Table I).

1-[2-(2,4-Dichlorophenyl)-2-(ethoxythiocarbonylthio)ethyl]imidazole Nitrate (35). A mixture of **3** (HCl salt, 20.0 g, 0.0641 mol) and anhydrous potassium ethyl xanthate (20.0 g, 0.125 mol) in 300 mL of absolute EtOH was stirred at room temperature for 3 days. After removal of the solvent and addition of water, the product was extracted with ether, the extracts were washed with water and dried ($MgSO_4$), and the ether was evaporated. The resulting oil was chromatographed on silica gel eluting with 15% acetone in CH_2Cl_2, and the pure product was dissolved in ether and treated dropwise with HNO_3. The precipitate was collected and recrystallized from acetone to give 21.0 g (77.2%) of **35**, mp 142.5–143 °C dec.

In a similar manner compounds **36**–**44** were prepared (Table I).

1-[2-(2,4-Dichlorophenyl)-2-(4-chlorophenylcarbonylthio)ethyl]imidazole Nitrate (17). To sodium hydroxide (0.16 g, 0.004 mol) in 40 mL of anhydrous MeOH under N_2 was added **35** (0.42 g, 0.001 mol). After the mixture was stirred for 20 min at room temperature, 1.0 g of anhydrous K_2CO_3 and 0.5 mL of p-ClC_6H_4COCl were added, and the mixture was stirred for 15 min. After evaporation of the solvent and addition of water, the residue was extracted with ether, and the extracts were washed, dried ($MgSO_4$), and treated with HNO_3. The precipitate was collected and recrystallized from ethyl acetate to give 0.36 g (76%) of **17**, mp 149–150.5 °C dec.

Similar reaction of the thiolate derived from **35** with the appropriate acyl halides furnished compounds **18**–**26** and **31**–**34**.

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References and Notes

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(8) The cream contained stearic acid, Span 60, Span 80, Tween 60, propylene glycol, methylparaben, propylparaben, citric acid, and water.
(9) Silica gel plates were impregnated with silicone oil by immersion in a 15% solution of Dow Corning 200 fluid (50 cs) in dichloromethane for 5 min, followed by drying in air. The compounds were eluted with 50% MeCN–45% H_2O–5% AcOH and visualized by UV light where appropriate and by treatment with iodine, followed by spraying with molybdic acid. R_m was calculated as $\ln(1/R_f - 1)$.
(10) Consideration of homologous series reveals that, by the method used, a methylene group is equivalent to ca. 0.20–0.25 ΔR_m units. Most of those ΔR_m values missing from Table II may therefore be estimated using published π values.[12] It is noteworthy that an ortho chlorine substituent, or a benzylic methylene group in the ester function, makes little or no contribution to the lipophilicity (R_m) of these compounds.
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