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Delta agonist hydroxy bioisosteres: The discovery of 3-((1-benzylpiperidin-4-yl){4-[(diethylamino)carbonyl]phenyl}amino)benzamide with improved delta agonist activity and in vitro metabolic stability

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ABSTRACT

We have investigated phenol replacements in a series of diaryl amino piperidine delta opioid agonists. From this study we have demonstrated that the hydroxy functional group can be replaced with a primary amide group, giving enhanced activity at the delta receptor, increased selectivity versus mu and kappa as well as improved in vitro metabolic stability.

Three main opioid receptor subtypes have been shown to exist—mu, delta, and kappa.[1] Current analgesics such as morphine act at the mu receptor and while they produce pronounced analgesia they are also associated with undesired side effects such as tolerance, addiction, and respiratory depression. Initial investigation of the delta receptor demonstrated that analgesia was produced without the unwanted side effects of mu receptor agonists[2] and recently Adolor published information on their development delta agonist, ADL5859, for pain management.[2d] The delta receptor has been implicated in additional therapeutic areas. For example, a recent report from Pfizer[3] demonstrated that peripheral delta agonists are effective in models of irritable bowel syndrome while a report from Johnson and Johnson[4] showed antidepressant and anxiolytic effects in rodent models with a series of 4-phenyl-4-[1H-imidazol-2-yl]-piperdine delta agonists.

Within our own contributions to the development of non-peptidic delta agonists, the previous Letter[5] highlighted the discovery of *N*,*N*-diethyl-4-[(3-hydroxyphenyl)(piperidin-4-yl)amino] benzamide derivatives **1** as potent and selective delta agonists (Fig. 1).

One of the most interesting compounds in this series, phenol **2** (Fig. 1), displayed potent agonism at the delta receptor and good selectivity over the mu and kappa receptors, yet had suboptimal metabolic stability as measured in human and rat liver microsomes. In this Letter, we report our studies aimed at improving metabolic stability in this scaffold by investigating replacements for the metabolically labile phenol group. Approaches to replace the phenol group of several mu opioid ligands have been documented with varying degrees of success in the literature.[6] In this study, we demonstrate that the hydroxy functional group in our delta agonists can be replaced with a primary amide group, giving enhanced activity at the delta receptor, increased selectivity versus mu and kappa as well as improved in vitro metabolic stability.

Syntheses of analogs where the hydroxy group is replaced with alternative functional group are shown in Schemes 1–4. For all derivatives, the diethyl amide and benzyl group were kept constant and much of the chemistry relied on palladium mediated N-arylation.[7]

Synthesis of aldehyde **4** was achieved using an acetal as a masked aldehyde as shown in Scheme 1. Synthesis of acetal **3** was achieved via arylation of 1-benzylpiperidin-4-amine with 2-(3-bromophenyl)-1,3-dioxolane and BINAP[8] as the phosphine ligand followed by a second arylation using 4-bromo-*N*,*N*-diethylbenzamide and xantphos[9] as the ligand. The use of xantphos was essential for a good conversion to acetal **3** (79% yield) as BINAP afforded poorer yields for the second arylation (~30%). Cleavage of the acetal **3** under acidic conditions afforded aldehyde **4**, which was then converted to secondary alcohol **5** and ketone **6**.

Primary amine **8** was synthesized in two steps as shown in Scheme 2. Arylation of 1-benzylpiperidin-4-amine with 3-bromobenzonitrile followed by a second arylation with 4-bromo-*N*,*N*-diethylbenzamide was performed in a two-step, one pot reaction

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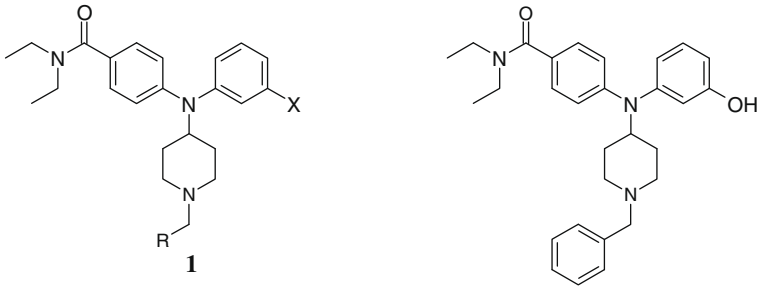
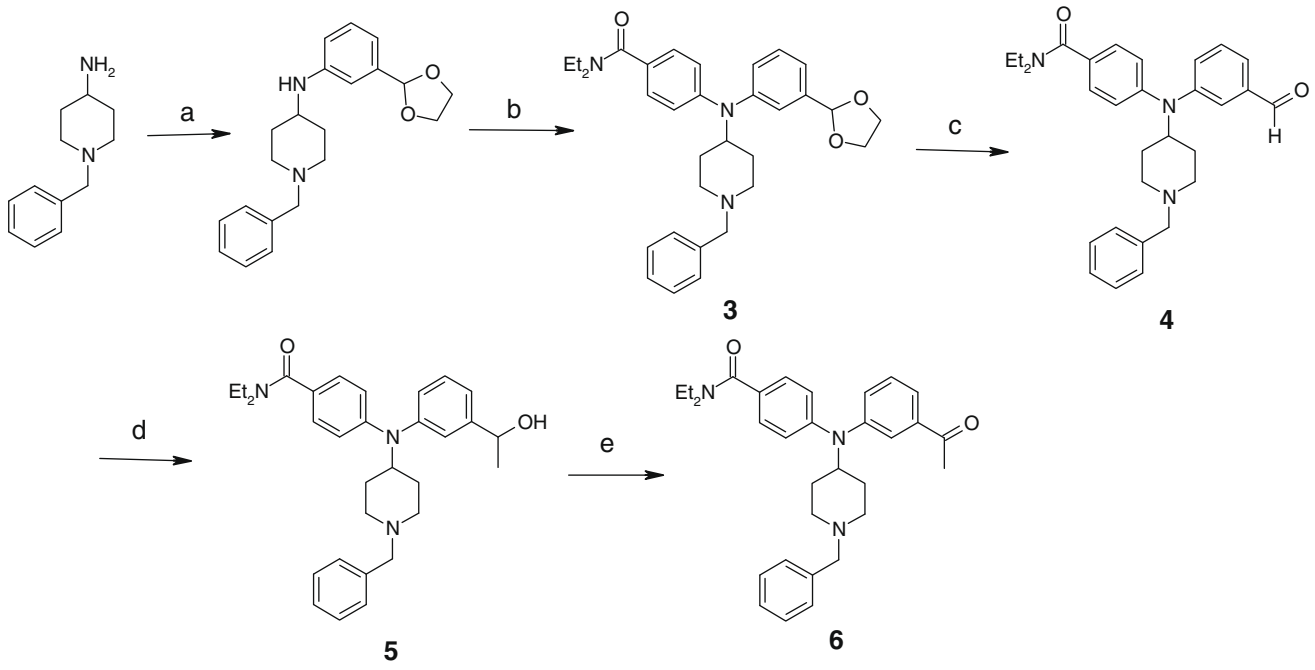
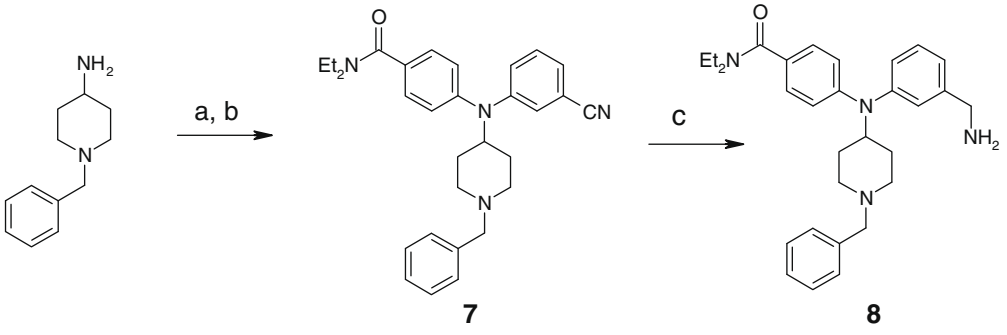


Figure 1.



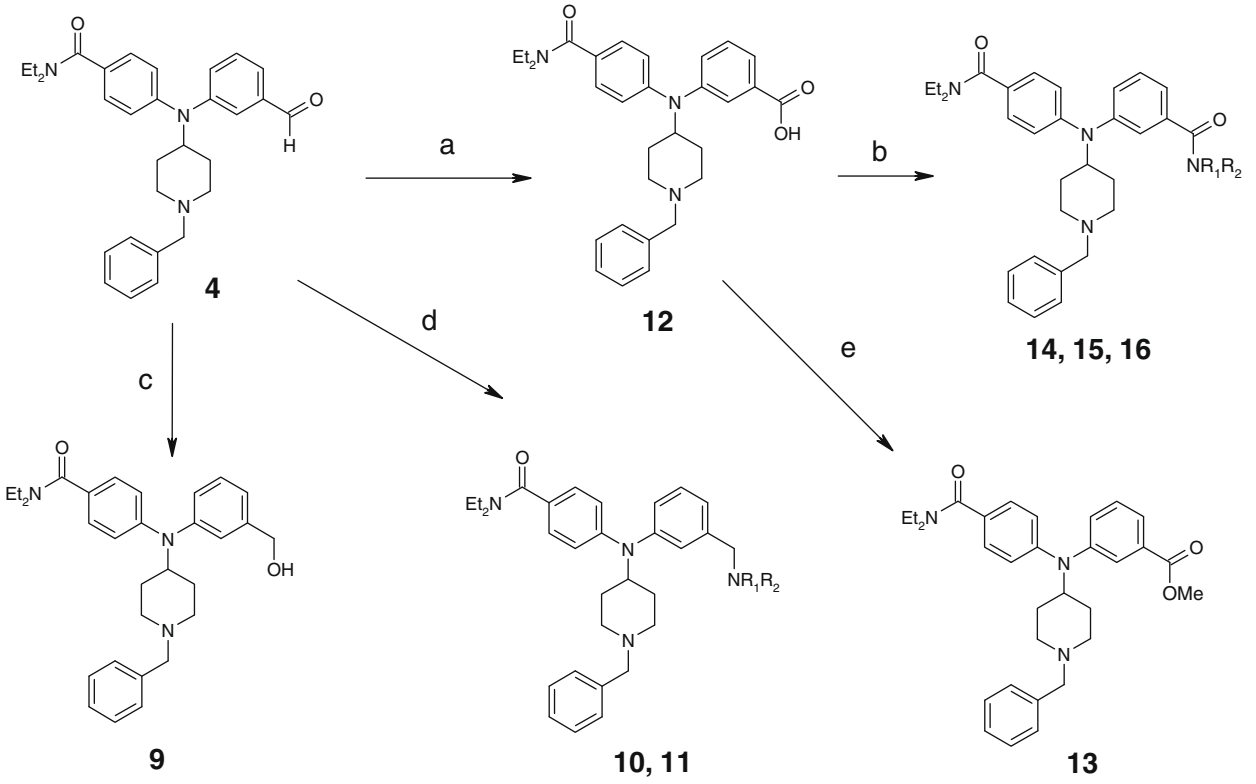
Scheme 1. Reagents and conditions: (a) 2-(3-bromophenyl)-1,3-dioxolane, $Pd_2(dba)_3$, BINAP, NaO^{t}Bu, toluene, 80 °C, 91%; (b) 4-bromo-*N*,*N*-diethylbenzamide, xantphos, $Pd_2(dba)_3$, NaO^{t}Bu, toluene, 110 °C, 79%; (c) HCl, THF, 86%; (d) MeMgBr, THF, −78 °C to rt, 77%; (e) TPAP, NMO, CH_2Cl_2, 65%.



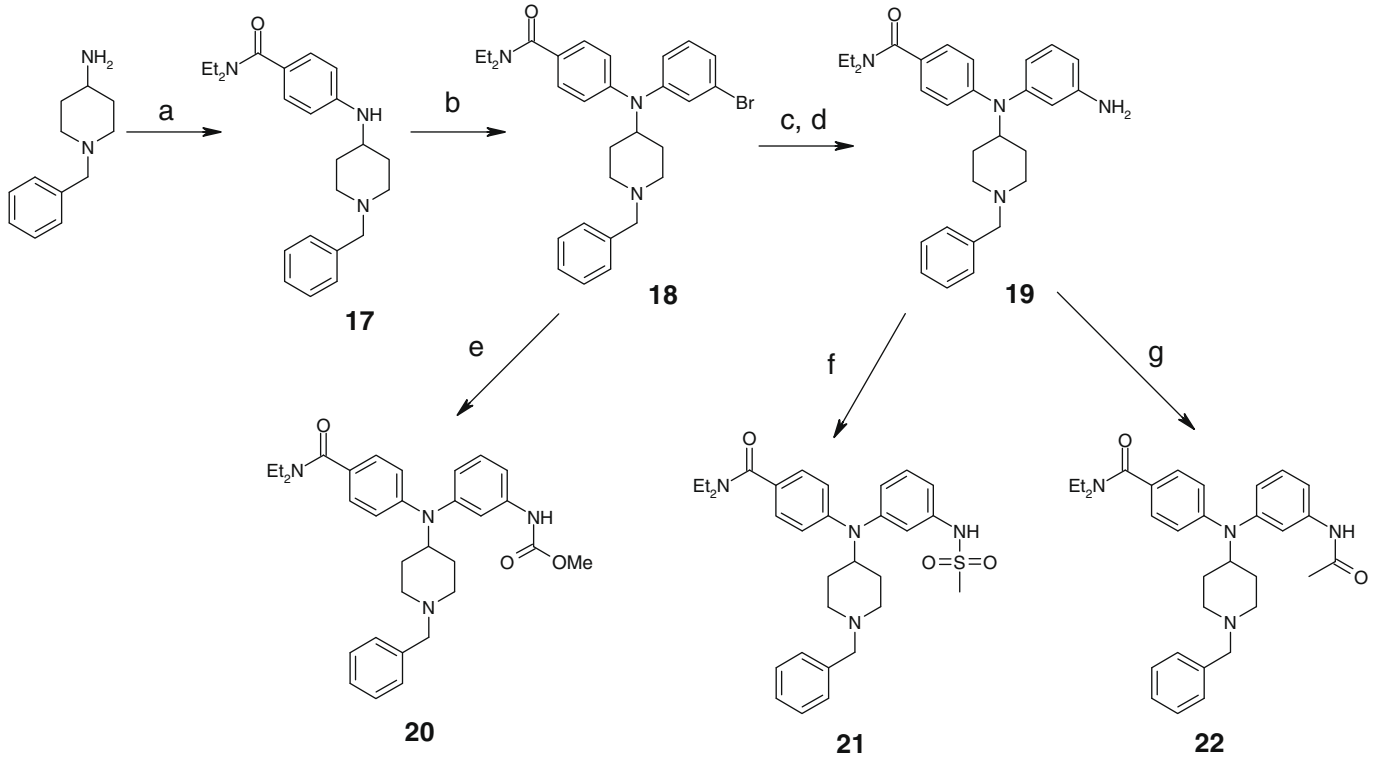
Scheme 2. Reagents and conditions: (a) 3-bromobenzonitrile, $Pd_2(dba)_3$, BINAP, NaO^{t}Bu, toluene, 80 °C; (b) 4-bromo-*N*,*N*-diethylbenzamide, NaO^{t}Bu, toluene, 110 °C, 93% over two steps; (c) $CoCl_2$, $NaBH_4$, MeOH, 41%.

to afford the bis arylated adduct **7** in 93% overall yield. The success of BINAP for the double arylation is in contrast to the synthesis described above in Scheme 1, which required xantphos as phosphine ligand for the second arylation. Reduction of the nitrile group was achieved using $CoCl_2$ and sodium borohydride.[10]

Alcohol, amine, amide, and ester derivatives were synthesized from aldehyde **4** as shown in Scheme 3 using standard chemical transformations. Amino derivatives **19–22** were synthesized as shown in Scheme 4 and once again made use of N-arylation chemistry. Arylation of 1-benzylpiperidin-4-amine with 4-bromo-



Scheme 3. Reagents and conditions: (a) $NaOCl_2$, NaH_2PO_4, ^tBuOH, H_2O, 27%; (b) R_1R_2NH, pyBOP, $^iPr_2NEt$, DMF, 48–65%; (c) $NaBH_4$, MeOH, 64%; (d) R_1R_2NH, $NaCNBH_3$, MeOH, 32–44%; (e) $TMSCHN_2$, MeOH, 58%.



Scheme 4. Reagents and conditions: (a) 4-bromo-*N*,*N*-diethylbenzamide, $Pd_2(dba)_3$, BINAP, NaO^tBu, toluene, 80 °C, 77%; (b) 1,3-dibromobenzene, xantphos, $Pd_2(dba)_3$, NaO^tBu, toluene, 110 °C, 68%; (c) benzophenone imine, $Pd_2(dba)_3$, BINAP, NaO^tBu, toluene, 80 °C; (d) HCl, THF, 81% over two steps; (e) methyl carbamate, xantphos, $Pd_2(dba)_3$, NaO^tBu, toluene, 110 °C, 23%; (f) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 38%; (g) AcCl, NEt_3, CH_2Cl_2, 66%.

N,*N*-diethylbenzamide and BINAP as the ligand gave mono aryl adduct **17** in 77% yield. Subsequent arylation with 1,3-dibromobenzene required xantphos as the ligand and gave bromide **18** in 68% yield. With bromide **18** in hand, arylation with methyl carbamate[11] gave **20**, while arylation with benzophenone imine[12] followed by treatment with acid afforded aniline **19**. Synthesis of sulfonamide **21** and acetate **22** was achieved under standard conditions from aniline **19**.

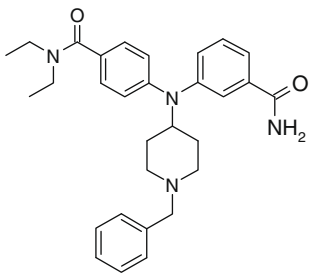
Binding affinities for analogs were determined as described in the previous Letter[5] and data is reported in Table 1. Data for phenol **2** is included for comparison.

Amines (**8**, **10**, **11**), alcohols (**5**, **9**) ester **13**, and acid **12** showed a significant loss in binding affinity at the delta receptor compared to phenol **2** and were not pursued further. Amino derivatives **19–22**, however, possessed delta agonist potencies in the range 1–7 nM and demonstrated that replacement of the hydroxy group of **2** was possible. It is of interest to note that a report in the literature demonstrated the hydroxy group of some mu ligands could not be replaced by a sulfonamide isostere.[6c] This is not the case in our series of delta agonists, although sulfonamide **21** was eight times less potent an agonist than phenol **2**. Carbamate **20** had a similar profile to phenol **2** with a slightly enhanced binding affinity at mu.

Primary amide **14** was the most interesting analog synthesized, showing improved selectivity (972 vs 210 for mu and 2500 vs 1771 for kappa) over phenol **2** and a twofold improvement in delta agonist potency as determined in the [^{35}S] GTPγS binding assay. SAR around **14** showed the primary amide group was optimal for delta activity as mono-methylation caused a 67-fold drop in delta binding affinity (compound **15**) and dimethylation a 379-fold drop (compound **16**). Regioisomers of amide **14** were synthesized (schemes not shown) and data shown in Table 2. The *meta* position of the primary amide functional group was optimal as both *ortho* and *meta* analogs showed a >100-fold drop in delta binding affinity.

Metabolic stability of amino analogs **20–22** and primary amide **14** was assessed and data shown in Table 3 along with data for phe-

Table 2
Binding affinity of primary amide regioisomers



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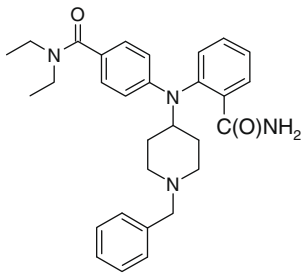

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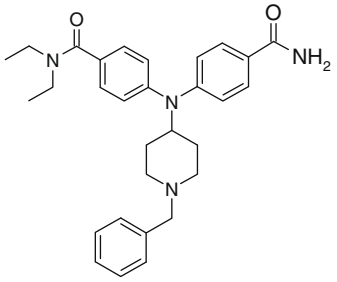

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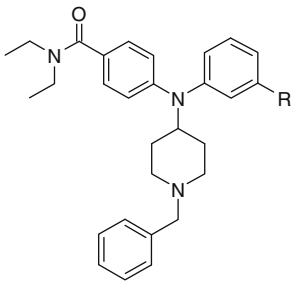
Compound	Binding affinities (K_i nM)			Selectivity ratios	
	δ	μ	κ	μ/δ	κ/δ
12	0.29 ± 0.02	282 ± 96	725 ± 86	972	2500
23	38.1 ± 4.5	5036 ± 427	>10,000	132	262
24	32.0 ± 2.3	486 ± 68	6176 ± 265	15	193

Table 1
Binding affinity and δ agonist activity of OH replacements



Compound	R	Binding affinities (K_i nM)			Selectivity ratios		δ Agonist activity	
		δ	μ	κ	μ/δ	κ/δ	EC_{50} (nM)	E_{max} (%)
2	OH	0.42 ± 0.03	88 ± 11	744 ± 127	210	1771	0.56 ± 0.07	100 ± 2
4	CHO	3.40 ± 0.14	1188 ± 212	4796 ± 534	349	1411	17.0 ± 1.7	109 ± 5
5	$CHOHCH_3$	80.6 ± 1.9	3750 ± 727	4742 ± 2954	47	59		
6	$COCH_3$	1.70 ± 0.38	1541 ± 148	4542 ± 648	906	2671	7.93 ± 0.80	116 ± 1
8	CH_2NH_2	447 ± 56	831 ± 53	2928 ± 305	2	7		
9	CH_2OH	11.7 ± 0.7	3809 ± 377	6666 ± 733	326	570	133 ± 38	103 ± 10
10	$CH_2NH(CH_3)$	435 ± 70						
11	$CH_2N(CH_3)_2$	34.3 ± 3.3	4162 ± 378	1747 ± 130	121	51	277 ± 38	112 ± 5
12	CO_2H	1369 ± 13						
13	CO_2CH_3	60.3 ± 7.6	7104 ± 1592	5543 ± 1993	118	92		
14	$CONH_2$	0.29 ± 0.02	282 ± 96	725 ± 86	972	2500	0.30 ± 0.03	101 ± 4
15	$CONHCH_3$	19.4 ± 2.7	4711 ± 1663	>10,000	243	>515	151 ± 53	100 ± 4
16	$CON(CH_3)_2$	110 ± 15						
19	NH_2	2.01 ± 0.30	2879 ± 448	4249 ± 1201	1432	2114	19.2 ± 3.2	109 ± 9
20	$NHCO_2CH_3$	0.41 ± 0.02	75 ± 11	576 ± 151	183	1405	1.08 ± 0.11	102 ± 1
21	$NHSO_2CH_3$	1.37 ± 0.03	462 ± 79	3556 ± 412	337	2596	4.53 ± 0.87	98 ± 3
22	$NHCOCH_3$	1.79 ± 0.24	1017 ± 246	>10,000	568	>5587	6.94 ± 0.96	96 ± 5

Table 3
In vitro metabolic stability for selected compounds

Compound	Mean Clint (μl/min/mg)	
	Human	Rat
2	286	384
14	71	62
20	200	
21	96	
22	139	

nol **2**. Phenol **2** shows a high intrinsic clearance of 286 μl/min/mg when incubated with human liver microsomes while all other analogs in Table 3 show improved metabolic stability. Of all the analogs presented in Table 3, primary amide **14** is not only more metabolically stable than phenol **2** but is a more potent delta agonist, demonstrating the primary amide to be a suitable replacement for the hydroxy group in our series of delta agonists.

To summarize, we have continued our work in the amino piperidine series of delta agonists and shown that the hydroxy group can be successfully replaced with a primary amide functional group. A similar modification has been successfully reported in a series of mu ligands[6a] around the same time as our initial discovery.[13] The amide derivative **14** not only shows improved delta potency and selectivity versus mu and kappa but it is also metabolically more stable as determined in human liver microsomes. Further developments in the amide series of delta agonists will be reported in due course.

Acknowledgment

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