

K₂CO₃: A MILD AND EFFICIENT CATALYST FOR THE SYNTHESIS OF PYRAN ANNULATED HETEROCYCLIC SYSTEMS BY GRINDING METHOD UNDER SOLVENT-FREE CONDITIONS

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Abstract: The potassium carbonate was applied as a green and efficient catalyst for the one-pot synthesis of pyran annulated heterocyclic systems, via the condensation between aromatic aldehydes, malononitrile and dimedone/1-naphthole by a grinding method at room temperature and solvent-free conditions. Short reaction times, environmentally friendly procedure and excellent yields are the main advantages of this procedure which makes it more economic than other environmentally synthetic methods.

Keywords: Potassium carbonate; pyran annulated heterocyclic systems; grinding method

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Introduction

Use of solvents is the major environmentally problematic aspects of organic synthesis. The solvent has to be produced in another chemical process, which also consumes energy and resources. Within the reaction, the vast amount of solvent has to be heated or cooled; consuming large amounts of energy, and has to be removed after completion of the reaction from the reaction mixture. It is believed that solvent-free organic synthesis and transformations are industrially useful and largely green. Green chemistry, also called sustainable chemistry, stimulates researchers to design the products and processes that reduce or eliminate the use and generation of hazardous substances¹. Avoiding the use of solvents in organic synthesis has led in some cases to improved results and milder synthetic procedures, and the solvent-free reactions are more important for practical synthetic processes in industry².

4*H*-Pyrans and 4*H*-pyran-annulated heterocyclic scaffolds represent an outstanding structural motif well distributed in naturally occurring compounds³⁻⁵ with a broad spectrum of considerable biological activities that embrace antimicrobial,⁶ anti-inflammatory,⁷ antihyperglycemic and antidyslipidemic,⁸ anti-HIV⁹⁻¹¹ and antimalarial^{12,13}.

Moreover, functionalized 4*H*-pyran derivatives have played increasing roles in synthetic approaches to promising compounds in the field of medicinal,^{14,15} agrochemical, cosmetics, and pigment industries¹⁶ (Figure 1).

The one-pot synthesis of pyran annulated heterocyclic systems from condensation of aromatic aldehydes and malononitrile with dimedone/1-naphthol have been reported in the presence of different catalysts such as: Fe₃O₄@SiO₂-Imid-PMAⁿ,¹⁷ [PVPH]HSO₄,¹⁸ PhB(OH)₂,¹⁹ [DABCO-

PDO][CH₃COO],²⁰ NH₄Al(SO₄)₂·12H₂O,²¹ TFE,²² CTBr,²³ MW,²⁴ (S)-proline²⁵ and HAP²⁶. Each of these methods has its own merit, with at least one of the limitations of low yields, long reaction time, effluent pollution, harsh reaction conditions and tedious work-up procedures. Thus, in view of the diverse therapeutic activity of pyrans and in continuation to our ongoing endeavor²⁷⁻²⁹ aimed at developing environmentally benign methodologies using green catalysts, we report herein the synthesis of tetrahydrobenzopyran and 2-aminobenzochromene derivatives in the presence of K₂CO₃ as a green catalyst by grinding at room temperature (Scheme 1).

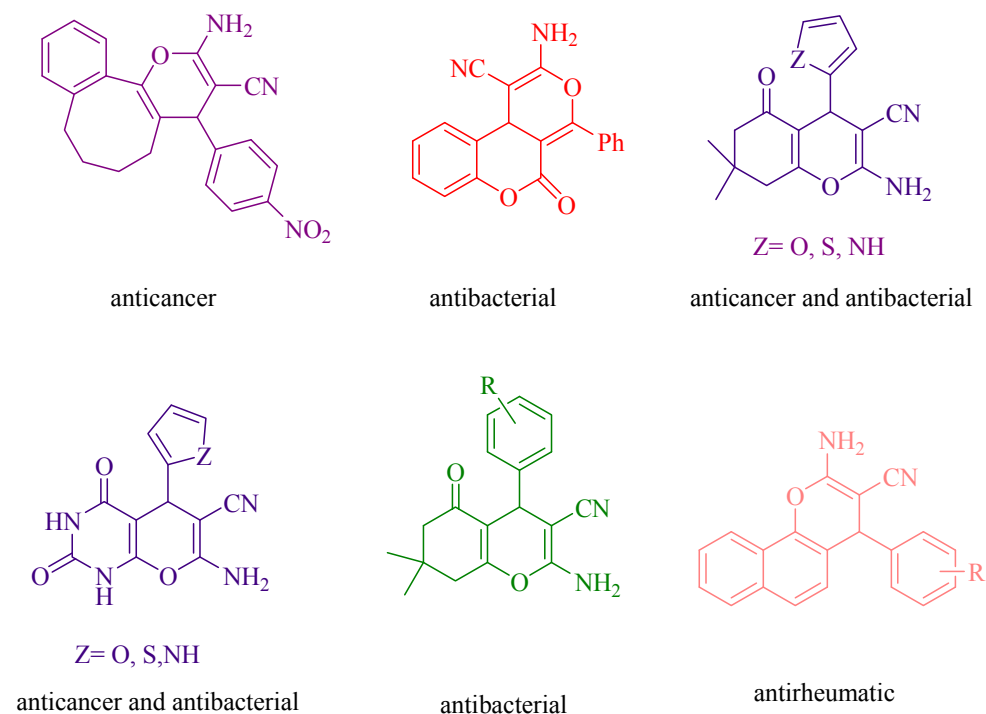
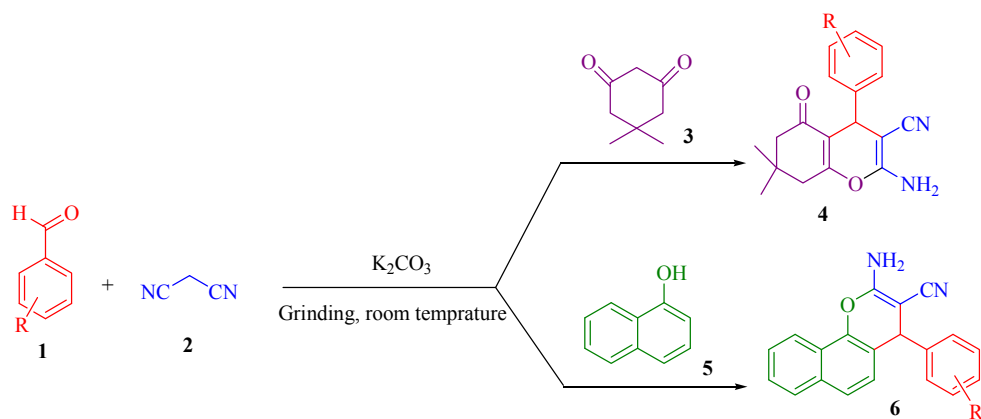


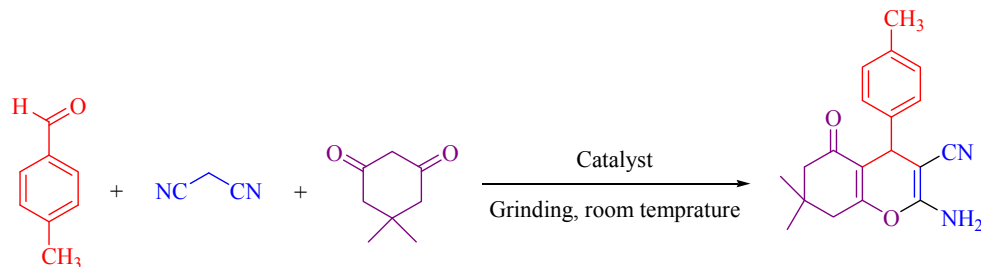
Figure 1. Some important drug-like pyrans heterocycles.



Scheme 1. Synthesis of tetrahydrobenzopyran and 2-aminobenzochromene derivatives in the presence of K_2CO_3 as a green catalyst by grinding at room temperature.

Results and Discussion

Initially, the reaction of 4-methylbenzaldehyde (1.0 mmol), malononitrile (1.0 mmol) and dimedone (1.0 mmol) was chosen as a model system (Scheme 2). The reaction was performed in the presence of different catalysts and different amounts of K_2CO_3 by grinding at room temperature (Table 1). As can be seen in Table 1 the best result was obtained in the presence of 20 mol % of K_2CO_3 . Next, the same reaction was repeated with 1-naphthole, in this case 20 mol% of K_2CO_3 was the best result, respectively.



Scheme 2. The optimized reaction conditions for the synthesis of tetrahydrobenzopyrans.

Table 1. Optimization of the reaction conditions for the synthesis of tetrahydrobenzopyrans.

Entry	Catalyst (mol %)	Grinding time (min)	Isolated yields (%)
1	-	60	-
2	K ₂ HPO ₄ (10 mol%)	30	68
3	Na ₂ CO ₃ (10 mol%)	45	65
4	K ₂ CO ₃ (10 mol%)	20	80
5	K ₂ CO ₃ (15 mol%)	12	89
6	K ₂ CO ₃ (20 mol%)	7	94
7	K ₂ CO ₃ (25 mol%)	7	94

Using the optimized reaction condition in the hand (Table 1, Entry 6), a variety of tetrahydrobenzopyran and 2-aminobenzochromene derivatives (Scheme 1) were synthesized and the results are summarized in Table 2. A variety of aromatic aldehydes with *ortho*, *meta* and *para* substituents were examined. In all cases electron donating and electron withdrawing groups were tolerated very well and gave excellent yields in shorter reaction times (Table 2).

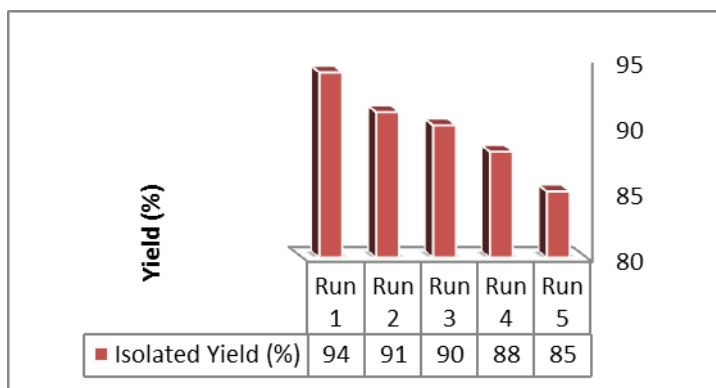
Table 2. Synthesis of tetrahydrobenzopyran and 2-aminobenzochromene derivatives.

Entry	Ar	1,3-dicarbonyl	Product	Time (min)	Isolated Yield (%)	M.p observed (°C)	M.p reported (°C)
1	4-Me C ₆ H ₄	3	4a	7	94	210-212	212-215 [19]
2	C ₆ H ₅	3	4b	20	95	230-232	228-230 [19]
3	2-NO ₂ C ₆ H ₄	3	4c	15	90	227-230	224-226 [25]
4	3-NO ₂ C ₆ H ₄	3	4d	13	88	210-212	208-210 [19]
5	2-Cl C ₆ H ₄	3	4e	15	82	210-212	208-210 [20]

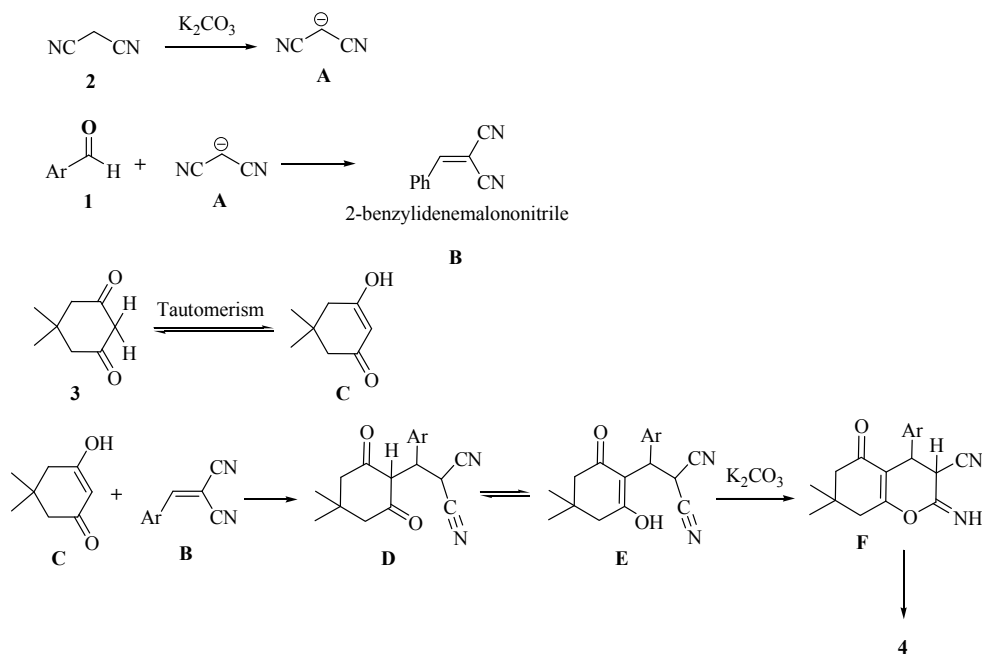
Table 2. Continued

6	4-NO ₂ C ₆ H ₄	3	4f	16	87	182-184	183-185 [19]
7	4-Cl C ₆ H ₄	3	4g	15	85	208-210	210-212 [25]
10	2,4-(Cl) ₂ C ₆ H ₃	3	4h	15	94	120-122	115-117 [25]
11	4-OMeC ₆ H ₄	3	4i	6	95	205-207	213-215 [19]
12	thiophene- 2- carbaldehyde	3	4j	20	90	212-214	210-212 [22]
13	4-OH C ₆ H ₄	3	4k	10	83	206-208	204-206[25]
14	4-Me C ₆ H ₄	5	6a	8	94	210-212	212-215 [26]
15	C ₆ H ₅	5	6b	20	95	208-210	210-211 [26]
16	3-NO ₂ C ₆ H ₄	5	6c	13	88	210-211	212-214 [26]
17	3-Cl C ₆ H ₄	5	6d	50	82	227-229	229-230 [24]
18	4-NO ₂ C ₆ H ₄	5	6e	16	87	238-240	239-241[26]
19	4-Cl C ₆ H ₄	5	6f	8	94	229-230	231-232 [26]

Recovery of the catalysts is important in green organic synthesis. Thus, we also for recyclability of the catalysts investigated the recycling of K₂CO₃ under grinding and solvent-free conditions using a selected model reaction of dimedone, 4-methylbenzaldehyde and malononitrile in the presence of K₂CO₃ as homogeneous catalyst (Figure 2).

**Figure 2.** Results of recycling over five consecutive recycling experiments.

We propose the possible following mechanism to account for the condensation of **1**, **2**, and **C** (Scheme 3). The step 1 can be regarded as a fast Knoevenagel condensation. In this mechanism, K₂CO₃ is an effective catalyst for the formation of the arylidenemalononitrile (**B**). K₂CO₃ also catalyzes the formation of intermediate (**D**), which affords the products **4** *via* tautomerization.



Scheme 3. Proposed mechanism for the formation of tetrahydrobenzopyrans.

For efficiency of the present work in comparison with the reported results in the literature, some of the results has been accumulated in Table 3. The results show that K₂CO₃ is a more efficient catalyst with respect to the reaction time and yield.

Table 3. Comparison of the efficiency of K_2CO_3 with other reported catalysts in literature.

Entry	Product	Catalysts	Conditions	Time	Yield (%)	Ref
1	4a	PhB(OH) ₂	5 mol %, EtOH/H ₂ O Reflux	30 min	65	[19]
2	4a	Na ₂ SO ₄	30 mol%, EtOH/H ₂ O	25 min	84	[30]
3	4a	NaOAc	5 mol%, EtOH, H ₂ O, 50°C	20 min	89	[31]
4	4k	A-Alum	20 mol%, solvent free or reflux, 100 °C	110 min	85	[32]
5	4a	RHPrBPCI	H ₂ O, reflux	30 min	84	[33]
6	4a	{[HMIM]C(CN) ₃ }	0.5 mol%, solvent-free, r.t	8 min	96	[34]
7	4k	[DABCO-PDO][CH ₃ COO]	10 mol%, H ₂ O, 60 °C	30 min	92	[20]
8	4a	NH ₄ Al(SO ₄) ₂ .12H ₂ O	0.2 g, EtOH, 80 °C	130 min	90	[21]
9	4a	TFE	TFE, Reflux	5h	88	[22]
10	4a	Pectin	0.05 g, H ₂ O:EtOH, r.t	35 min	82	[27]
11	4a	K ₂ CO ₃	Grinding/ solvent-free/r.t	7 min	93	This work
12	6b	<i>p</i> -Toluenesulfonic acid	CH ₃ CN/ Reflux	5 h	90	[35]
13	6a	Nano MgO	MeOH/r.t	60 min	96	[8]
14	6a	K ₂ CO ₃	Grinding/ solvent-free/r.t.	8	94	This work

Experimental

Chemicals were purchased from Merck (Darmstadt, Germany), and Fluka (Buchs, Switzerland), and used without further purification. Melting points were taken on an Electrothermal 9100 apparatus. IR spectra were obtained on a JASCO FT/IR-460 plus spectrometer. The ¹H NMR spectra

were recorded on a Bruker DRX-400 Avance instrument with CDCl₃ as solvent and using TMS as internal reference at 400 MHz respectively.

General Procedure for the synthesis of tetrahydrobenzopyran and 2-aminobenzochromene derivatives

Aromatic aldehydes **1** (1.0 mmol), malononitrile **2** (1.0 mmol), dimedone or 1-naphthol (1.0 mmol), and K₂CO₃ (20 mol %) are added to a mortar. The mixture is ground by mortar and pestle at room temperature (25 °C) for 7-20 min (Table 2). The solid product is obtained from an intermediate melt and then is laid up at room temperature. Then, 5 mL of water was added to the mixture and filtered for separation of the crude product. The separated product was washed twice with water (2×5 mL). The solid crude product subsequently recrystallized from hot ethanol to give the pure solid. In order to recover the catalyst, since K₂CO₃ is soluble in water, the filtrate was extracted with diethyl ether. The aqueous layer was separated, and its solvent was evaporated under reduced pressure and K₂CO₃ was recovered and reused. Selected spectroscopic data of some products is given below:

2-amino-5,6,7,8-tetrahydro-4-(4-methyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (4a)

mp 210-212 IR (KBr) v/cm⁻¹ 3467, 3325, 2955, 2190, 1676, 1247; ¹H NMR (400 MHz, DMSO-d₆): δ 1.06 (s, 3H, CH₃), 1.12 (s, 3H, CH₃), 2.26 (dd, 2H, CH₂, *J*= 16.4 Hz, *J*= 22.0), 2.38 (s, 3H), 2.46 (s, 2H, CH₂), 4.37 (s, 1H, CH), 4.59 (s, 2H, NH₂), 7.10 (d, 2H, Ar, *J*= 8.0 Hz), 7.17 (d, 2H, Ar, *J*= 8.0 Hz).

2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4H-chromene-3-carbonitrile (4b)

mp 230-232 IR (KBr) ν/cm^{-1} 3360, 3285, 2960, 2190, 1686, 1209; ^1H NMR (400 MHz, CDCl_3) δ 1.07 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.23 (dd, 2H, CH_2 , $J=16.4$, $J=22.0$ Hz), 2.78, (s, 2H, CH_2), 4.43 (s, 1H, CH), 4.55 (s, 2H, NH_2), 7.21, 7.35 (m, 5H, Ar).

2-amino-5,6,7,8-tetrahydro-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (4f)

mp 182-184 IR (KBr) ν/cm^{-1} 3285, 3160, 2960, 2185, 1675, 1209; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 0.98 (s, 3H, CH_3), 1.029 (s, 3H, CH_3), 2.12 (d, 1H, CH_2 , $J=16.0$ Hz), 2.27 (d, 1H, CH_2 , $J=16.0$ Hz), 2.51 (d, 2H, CH_2 , $J=12.0$ Hz), 4.36 (s, 1H, CH), 7.14 (s, br, NH_2), 7.44 (d, 2H, Ar, $J=8.0$ Hz), 8.12 (d, 2H, Ar, $J=8.0$ Hz).

2-amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (4i)

mp 205-207 IR (KBr) ν/cm^{-1} 3465, 3320, 2955, 2190, 1676, 1247; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 0.95 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.09 (d, 1H, CH_2 , $J=18.0$ Hz), 2.25 (d, 1H, CH_2 , $J=18.0$ Hz), 3.37 (s, 1H, CH_2), 3.72 (s, 3H, OCH_3), 4.13 (s, 1H, CH), 6.85 (d, 2H, Ar, $J=8.0$ Hz), 6.97 (br, NH_2), 7.06 (d, 2H, Ar, $J=8.0$ Hz).

2-amino-5,6,7,8-tetrahydro-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (4k)

IR (KBr, cm^{-1}): 3275, 3170, 2950, 2285, 1675, 1219; ^1H NMR (400 MHz, CDCl_3): δ (ppm) : 1.07 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 2.21-2.27 (dd, 2H, CH_2 , $J=16.0$ Hz, 20.0), 2.42-2.53 (dd, 2H, CH_2 , $J=16.0$ Hz, $J=20.0$ Hz), 4.36 (s, 1H, CH), 4.55 (s, 2H, NH_2), 5.27 (s, 1H, OH), 6.71- 7.29 (m, 4H, Ar).

2-amino-4-phenyl-4H-benzo[h]chromene-3-carbonitrile (6b)

IR (KBr, cm⁻¹): 3454, 3318, 2205, 1656, 1600, 1572; ¹H NMR (400 MHz, CDCl₃): 4.90 (s, 1H, CH), 7.10 (s 2H, NH₂), 7.07-7.12 (m, 6H, Ar), 7.56-7.66 (m, 3H, Ar), 7.94 (d, *J*= 8.4 Hz, 1H, Ar), 8.23 (d, *J*= 8.4 Hz, 1H, Ar).

2-amino-4-(3-chlorophenyl)-4H-benzo[h]chromene-3-carbonitrile (6d)

IR (KBr, cm⁻¹): 3465, 3340, 2220, 1644, 1660, 1580, ¹H NMR (400 MHz, CDCl₃): 5.13 (s, 1H, CH), 7.10 (s, 2H, NH₂), 7.13 (d, *J*= 8.4 Hz, 1H, Ar), 7.32-7.35 (m, 4H, Ar), 7.23 (s, 1H, Ar), 7.56-7.67 (m, 3H, Ar), 7.90 (d, *J*= 8.4 Hz, 1H, Ar), 8.25 (d, *J*= 8.4 Hz, 1H, Ar).

2-amino-4-(4-nitrophenyl)-4H-benzo[h]chromene-3-carbonitrile (6e)

IR (KBr, cm⁻¹): 3450, 3325, 2196, 1645, 1575, ¹H NMR (400 MHz, CDCl₃): 5.14 (s, 1H, CH), 7.11 (s, 2H, NH₂), 7.15 (d, *J*= 8.4 Hz, 1H, Ar), 7.50-7.71 (m, 3H, Ar), 7.52 (d, 2H, Ar), 7.90 (d, 1H, *J*= 8.4 Hz, Ar), 8.15 (d, 2H, Ar), 8.27 (d, 1H, *J*= 8.4, Ar).

Conclusions

In conclusion, we have described a highly efficient procedure for the preparation of pyran annulated heterocyclic systems by a three-component condensation *via* a one-pot grinding method using K₂CO₃ as catalyst under solvent-free conditions. Moreover, the procedure offers several advantages including operational simplicity, high yields, minimal environmental impact, cleaner reaction, and low cost, which make it a useful and attractive process for the synthesis of these compounds.

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