

**Theses of doctoral (PhD) dissertation**

**Synthesis of alkynylated chromones with Sonogashira reaction**

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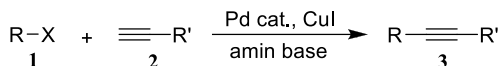
University of Debrecen

Doctoral School of Chemistry

Debrecen, 2015.

## 1. Introduction and the aims of the dissertation

The palladium-catalyzed transformations became widely used reactions in the organic synthetic chemistry. We have investigated the Sonogashira reaction which allows the coupling of terminal alkynes with aryl of vinyl halides (Scheme 1).

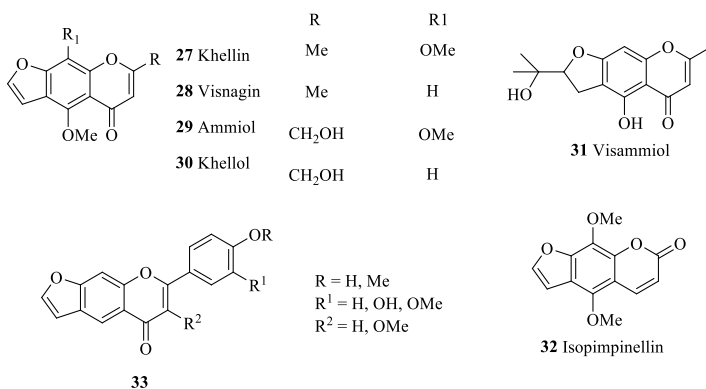


R = aryl, vinyl

R' = aryl, alkenyl, alkyl, SiR<sub>3</sub>    X = I, Br, OTf

**Scheme 1** The Sonogashira reaction

Previously our research group successfully optimized the cross-coupling of 3-bromochromone (**40**) and phenylacetylene (**15**). Optimal conditions were found as follows: triethylamine as base and solvent, 2,5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst and 1,5 mol% CuI co-catalyst at temperature 70 °C. Our aims were to study the Sonogashira reaction of variously substituted bromochromones and –flavones with different terminal acetylenes.



**Scheme 2** Naturally occurring tricyclic oxygen heterocycles

With the optimal conditions in our hand we extended our investigations to chromones with orto-hydroxy functionality adjacent to the halogen atom. Such a reaction would allow the synthesis of naturally occurring compounds or their related derivatives with the same skeleton (Scheme 2).

## **2. Applied methods**

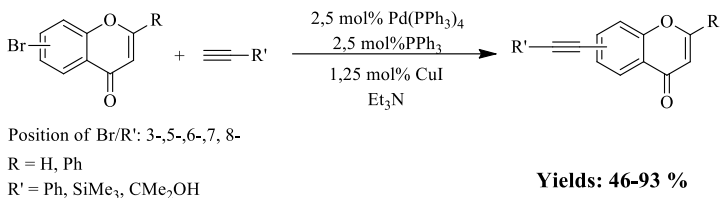
The micro, semimicro and macro methods of modern synthetic organic chemistry were applied in our synthetic work. Reactions were monitored by thin layer chromatography, the isolation and purification of the crude products were carried out by either crystallization or by column chromatography. Melting point determination, 1D or 2D NMR, IR and MS spectroscopy were applied to identify and characterize the prepared compounds.

## **3. New results**

### **3.1 Sonogashira reaction of bromosubstituted chromones and flavones**

The optimized conditions were successfully used in the coupling of bromochromones carrying the halo substituent in their ring A or B and for bromoflavones, too. The desired products were isolated with good to excellent yields (Scheme 3), thus, we demonstrated the usefulness of Sonogashira reaction in the field of bromochromones and bromoflavones. In one case, however, in the reaction of 5-bromochromone (**61**) and phenylacetylene (**15**) only the homocoupling product was obtained (Scheme 3). Instead of the expensive and more unstable  $\text{Pd}(\text{PPh}_3)_4$  catalyst we

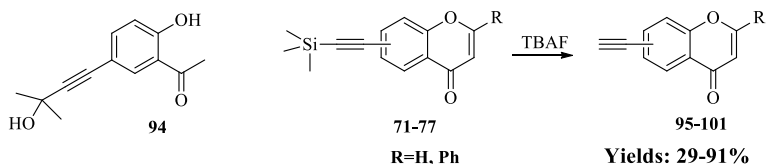
successfully used Pd-C. This latter catalyst worked well in the cross-coupling, although the yields were usually somewhat lower.



**Scheme 3.** Extension of the Sonogashira reaction

### 3.2 Syntesis of ethynylchromones and ethynylflavones

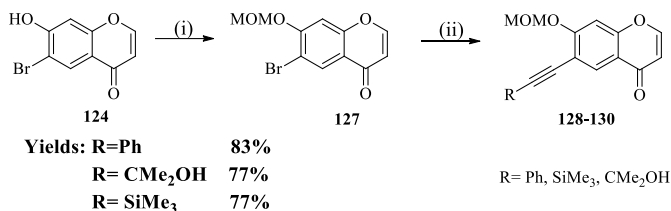
Another aim of our research group was to prepare ethynyl bridged chromones by reactions where ethynylchromones as terminal alkynes are coupled with bromochromones. To synthesize ethynylchromones by Sonogashira reactions terminal acetylenes with a protecting group should be used followed by a deprotection. In our experiments (trimethylsilyl)acetylene (**18**) and 2-methyl-3-butyn-2-ol (**75**) were applied as protected alkynes. In the latter case strong base and high temperature is needed to cleave an acetone unit and many molecules do not tolerate these conditions. In our experiments no reaction was observed or 2'-hydroxyacetophenone **80** was formed by ring opening of chromone. Trimethylsilyl protecting group was successfully removed with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) and seven, hitherto unknown ethynylchromone or flavone was prepared by this method (Scheme 4).



**Scheme 4.** Removal of trimethylsilyl protecting group

### 3.3 Sonogashira reaction of 6-bromo-7-hydroxychromone

Extension of the Sonogashira reaction to 6-bromo-7-hydroxychromone (**91**) required the protection of the free hydroxy group as in the lack of blocking a ring-closure takes place according to the literature. We pointed out that acetyl group is not stable under the conditions of the cross-coupling, therefore, we considered the use of methoxymethyl (MOM) protecting group.



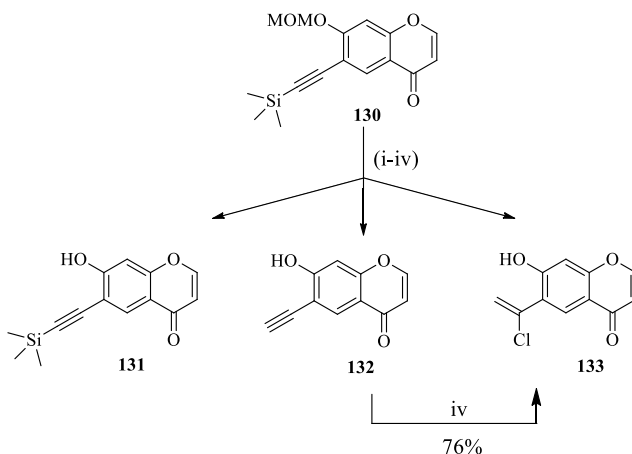
*Reaction conditions:* (i) 1.2 equiv. MOM-Cl, 1.2 equiv. K<sub>2</sub>CO<sub>3</sub>, abs. acetone (80 %), (ii) Alkyne / Pd(PPh<sub>3</sub>)<sub>4</sub> / CuI / Et<sub>3</sub>N / 70°C

**Scheme 5.** Sonogashira reaction of 6-bromo-7-hydroxychromone (**124**)

This protecting group proved to be stable under the conditions of the coupling and Sonogashira products **128-130** were obtained in good yields. The cleavage of the protecting group was not observed in any case (Scheme 5).

### 3.4 Removal of the protecting group from 6-substituted 7-(methoxymethoxy)chromones and ring-closure of the products

For the synthesis of naturally-occurring tricyclic systems a free phenolic hydroxylic group in *ortho* position is needed which can be performed by the cleavage of the MOM protecting group. This was done in the case of **130** [(trimethylsilyl)ethynyl]chromone (Scheme 6). Amberlyst 15 was found to be the optimal reagent leading to the expected compound in good yields. By using other reagents and conditions various secondary reactions (desilylation, addition of hydrogen chloride to the ethynyl group) was observed.

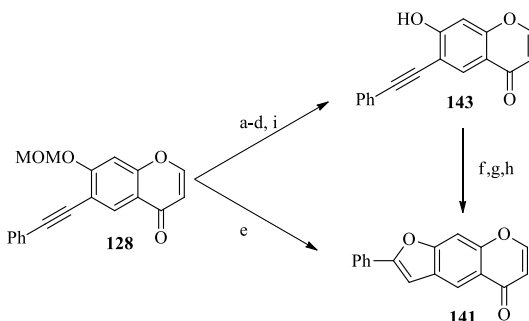


Entry	Conditions	Product (yield, %)		
		<b>131</b>	<b>132</b>	<b>133</b>
1	i	88	0	0
2	ii	38	29	0
3	iii	9	64	0
4	iv	41	23	13
5	MeOH/cat. cc. HCl	No reaction		

**Conditions:** (i) Amberlyst 15 H<sup>+</sup>, iPrOH, reflux (ii) 50 % AcOH-H<sub>2</sub>O, (cat.) cc. H<sub>2</sub>SO<sub>4</sub>, 50 °C (iii) 50 % AcOH-H<sub>2</sub>O, (cat.) cc. H<sub>2</sub>SO<sub>4</sub>, reflux (iv) 1,4-dioxane, 2N HCl, 80 °C

**Scheme 6.** Removal of the MOM protecting group from trimethylsilyl derivative **130**

Removal of the protecting group has also been performed in case of 6-(2-phenylethynyl)-7-(methoxymethoxy)chromone (**128**) and studies on the ring-closure of the obtained product **143** were also done. Use of acidic resin resulted in the formation of the expected product **143** in good yields (74%). Similar result was achieved using silica doped sodium hydrogen sulfate as heterogeneous catalyst (Scheme 7).



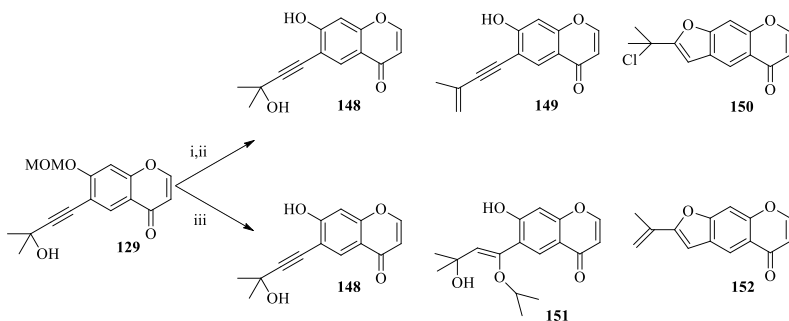
**Conditions:** (a) Amberlyst 15 H<sup>+</sup>, iPrOH, reflux (b) 1,4-dioxane, 2N HCl, 50°C, (c) NaHSO<sub>4</sub>.SiO<sub>2</sub>, DCM, RT, 24h, (d) Montmorillonit K10, abs. DCM, RT, 24h, (e) 1,4-dioxane, 2N HCl, 80°C, (f) 10 equiv. KOH, abs. toluene, 60°C, 5h, (g) 10 M/M % CuI, Et<sub>3</sub>N, 70°C, (h) Et<sub>3</sub>N, 70 °C

**Scheme 7.** Removal of the protecting group from phenyl derivative

In the presence of triethylamine (TEA), copper(I)iodide on 70 °C the cyclic derivative **141** was obtained good yields. To clarify the role of copper(I)iodide the reaction was repeated without this compound simply in

hot TEA and phenylfurochromone **141** was isolated in excellent yield. Thus, we proved that the ring-closure is initiated by the basic medium. By the attack of the base on the phenolic hydroxy group a deprotonation takes place and the formed phenolate attacks the  $\beta$  carbon of the triple bond.

Deprotection of (3-hydroxy-3-methyl-1-butynyl)chromone **129** was also studied under three different conditions (Scheme 8). Three different products were isolated in each case. Desired product **148** was obtained in low yield even in the presence of Amberlyst 15 but two new and hitherto unknown tricyclic derivatives were identified. To prove their structure 2D NMR measurements were performed.

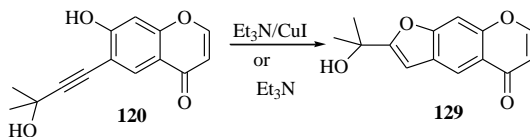


*Conditions:* (i) 1,4-dioxane, 2N HCl, RT, (ii) 1,4-dioxane, 2N HCl, 80°C, (iii) Amberlyst 15 H<sup>+</sup>, iPrOH, reflux

**Scheme 8.** Removal of the protecting group from butynyl derivative **129**

Ring closure of compound **148** was performed in TEA in the presence and in the lack of copper(I)iodide, the yields were 76% and 93%, respectively. Here we found again that the presence of copper(I)iodide is not necessary to the ring-closure and better yields could be achieved in sole TEA.

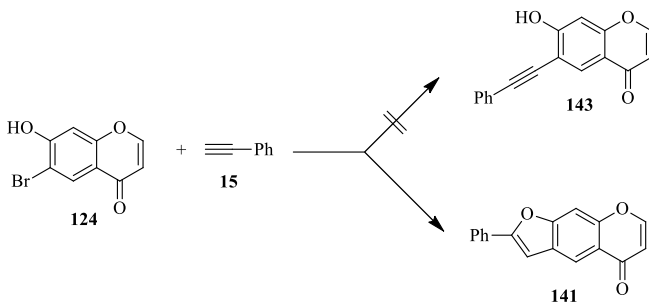




**Scheme 9.** Ring-closure of 6-(3-hydroxy-3-methyl-1-butynyl)-7-hydroxychromone (**120**)

### 3.7. Direct Sonogashira reaction of 6-bromo-7-hydroxychromone (**124**)

We also tested the direct cross-coupling reaction of the non-protected 6-bromo-7-hydroxychromone (**124**) with phenylacetylene (**15**) by using several Sonogashira conditions available from literature and our optimized methodology and ring-closed product **141** was obtained (Scheme 10).



**Conditions A:** 2,5 mol%  $\text{Pd}(\text{PPh}_3)_4$ , 2,5 mol %  $\text{PPh}_3$ , 1,25 mol%  $\text{CuI}$ ,  $\text{Et}_3\text{N}$ , 24 h; **Conditions B:** 20 mol% DABCO, 10 mol %  $\text{CuI}$ , 2 ekv.  $\text{Cs}_2\text{CO}_3$ , DMF,  $140^\circ\text{C}$ ; **Conditions C:** 10 mol%  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ , 10 mol%  $\text{CuI}$ ,  $\text{Et}_3\text{N}$ , 24h,  $80^\circ\text{C}$

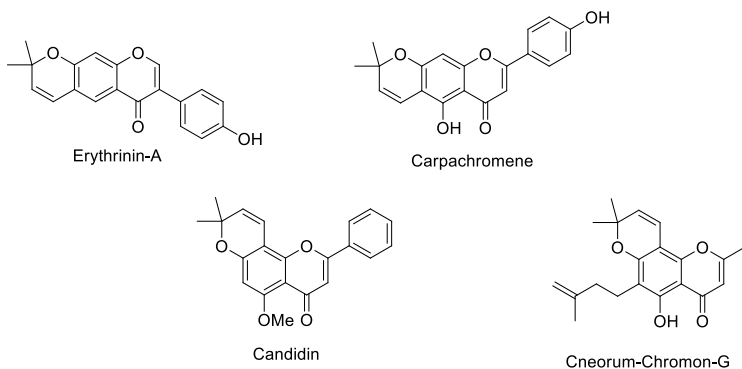
**Scheme 10.** Cross-coupling of 6-bromo-7-hydroxychromone (**124**)

Similar results were achieved in the reaction of 2-methyl-3-butyn-2-ol (**89**) but while the former reagent gave a moderate (47%) yield the latter one resulted in a poor (16%) yield, only.

Altogether this one-pot reactions is time and cost efficient in comparison with the four-step sequences since their overall yields are very similar, 46% and 17%, respectively.

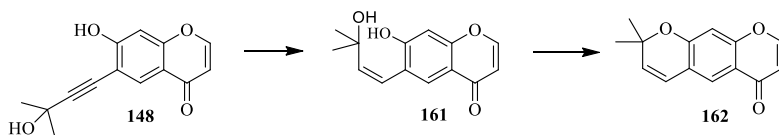
### 3.8 Reduction of (8-phenylethynyl)chromones

We also aimed at the synthesis of tricyclic systems with oxygen-containing and 6-membered heterocycles. Some of these derivatives are available from natural sources and possess biological activity. Representative examples are shown by Scheme 11.



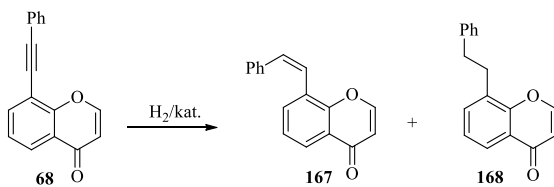
**Scheme 11.** Naturally occurring tricyclic systems

The synthesis of the afore-mentioned compounds, in principle, can be performed by the Sonogashira reaction of hydroxychromones, subsequent partial reduction and ring closure (Scheme 12).



**Scheme 12.** Possible synthetic route to tricyclic compounds with two six-membered rings

We investigated the reduction of chromones bearing (2-phenylethynyl) groups in various positions under catalytic hydrogenation conditions by using either homogeneous or heterogeneous catalysts. In the heterogeneous reductions we applied Lindlar catalyst in the presence of various additives which decreased its activity. We found that the reduction is strongly depends on the additive, the solvent and the position of the substituent. During the homogeneous catalysis  $\{[\text{RuCl}_2(\text{mtppps})_2]_2\}$  catalyst was used in water/organic solvent two-phase system. A strong position dependence was observed in this case, too. The use of these two catalytic methods resulted partially reduced product **167** with the requested *cis* stereochemistry in case of 8-(2-phenylethynyl)chromone (**68**) only (Scheme 13). In the reduction of other substrates considerable amount of „overreduced” alkane was also detected even at lower conversion.



**Scheme 13.** Reduction of (8-phenylethynyl)chromone

## Documented scientific results

*Scientific papers published (accepted for publication) in peer reviewed journals.*

### Publications connected with the thesis

1. T. Patonay, I. Pazurik, **A. Ábrahám**: C-Alkynylation of Chromones and Flavones by Sonogashira Reaction

*Austr. J. Chem.*, **2013**, 66, 646-654, doi.org/10.1071/CH13006

2. K. Kónya, Sz. Fekete, **A. Ábrahám**, T. Patonay:  $\alpha$ -Azido ketones, Part 7. Synthesis of 1,4-disubstituted triazoles by the “click” reaction of various terminal acetylenes with phenacyl azides or  $\alpha$ -azidobenzo(hetera)cyclanones

*Mol. Divers.* **2012**, 16, 91. doi:10.1007/S11030-012-9360-7

### Lectures

1. Patonay Tamás, **Ábrahám Anita**, Fekete Szabolcs, Tóth Veronika: Újabb eredmények az  $\alpha$ -azido-ke-tonok kémiájában.

MTA Heterociklusos Kémiai Munkabizottság előadóü-lése, 2006. június 7-9, Balatonszemes.

2. **Ábrahám Anita**, Patonay Tamás: A-gyűrűben szubsztituált 3-aminokromonok előállítása és reaktivitása.

MTA Flavanoidkémiai Munkabizottság előadóü-lése, 2006. december 1, Budapest.

3. Patonay Tamás, **Ábrahám Anita**, Fekete Szabolcs, Pazurik István, Vasas Attila: Palladium-catalyzed Cross-coupling Reactions in the Field of Chromonoids and Flavanoids.

21st International Congress for Heterocyclic Chemistry, 2007. július 15-20, Sydney, Ausztrália.

4. **Ábrahám Anita**, Pazurik István, Patonay Tamás: Brómszubsztituált kromonszármazékok Sonogashira-reakciói.

MTA Heterociklusos Kémiai Munkabizottság előadóülése, 2007. szeptember 13, Balatonszemes.

5. **Ábrahám Anita**, Patonay Tamás: Alkinilezett-hidroxikromonok előállítás és gyűrűzárási reakciói.

MTA Heterociklusos Kémiai Munkabizottság előadóülése, 2008. május 22-24, Balatonszemes.

6. **Ábrahám Anita**, Patonay Tamás: Oxigéntartalmú heterociklusok Sonogashira - reakciója: Természetben előforduló triciklusos rendszerek kiépítése.

Kisfaludi Előadóülés, Richter Gedeon Centenárium előadóülés, Budapest, 2009. március 9.

7. **Ábrahám Anita**, Patonay Tamás: Furokromonok előállítása Sonogashira intermedierek ciklizációjával. Heterociklusos Munkabizottsági Ülés 2009. május 20-22.

8. **Ábrahám Anita**, Papp Gábor, Kiss-Szikszai Attila, Joó Ferenc, Patonay Tamás: Kromonok Sonogashira termékeinek ciklizációja és redukciója.

MTA Flavanoidkémiai Munkabizottság előadóülése, Budapest, 2009. december.07.

## Posters

1. **Ábrahám Anita**, Pazurik István, Patonay Tamás: Sonogashira reakciók oxigéntartalmú heterociklusok körében.

Centenárium Vegyészkonferencia 2007. április 29, Sopron.

2. **Ábrahám Anita**, Patonay Tamás: Sonogashira Reactions in the Field of Oxygen Heterocycles: from Model Compounds to Natural Products. 3<sup>rd</sup> German-Hungarian Workshop "Synthesis, Isolation and Biological Activity of Natural Products", 2008. május 15-17, Paderborn, Németország.

3. **Ábrahám Anita**, Patonay Tamás: Szomszédos helyzetben védett hidroxil-csoportot tartalmazó bróm-kromonok Sonogashira-reakciója MKE Vegyészkonferencia, 2008. június 4-6, Hajdúszoboszló.

4. *Ábrahám Anita*, Patonay Tamás: Synthesis of Furochromones from Sonogashira's Intermediates of Chromones.  
16th European Symposium on Organic Chemistry, 2009. július 12-16,  
Prága, Csehország.

5. *Ábrahám Anita*, Papp Gábor, Kiss-Szikszai Attila, Joó Ferenc, Patonay Tamás: New Synthetic Routes to Tricyclic Chromonoid Systems.  
International Conference: Natural and Artificial Ecosystems in the Somes-Cris-Mures-Tisa River Basin, 2010. május 7-8, Arad, Románia

6. Patonay Tamás, *Ábrahám Anita*, Vasas Attila, Nagy Gergő Zoltán:  
Synthesis of Naturally Occurring Chromone Derivates by Palladium-Catalyzed Cross-Coupling reaction.  
XIV<sup>th</sup> Conference on Heterocycles in Bio-organic Chemistry. 2011.  
szeptember 4-8, Brno, Csehország.



Candidate: Anita Ábrahám  
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Doctoral School: Doctoral School of Chemistry

Registry number: DEENK/189/2015.PL  
Subject: Ph.D. List of Publications

### List of publications related to the dissertation

#### Foreign language scientific article(s) in international journal(s) (2)

1. Patonay, T., Pazurik, I., **Ábrahám, A.**: C-Alkynylation of Chromones by Sonogashira Reaction.  
*Aust. J. Chem.* **66** (6), 646-654, 2013. ISSN: 0004-9425.  
DOI: <http://dx.doi.org/10.1071/CH13006>  
IF: 1.644
2. Kónya, K., Fekete, S., **Ábrahám, A.**, Patonay, T.: [alpha]-Azido ketones. Part 7: synthesis of 1,4-disubstituted triazoles by the "click" reaction of various terminal acetylenes with phenacyl azides or [alpha]-azidobenzo(hetera)cyclanones  
*Mol Divers.* **16** (1), 91-102, 2012. ISSN: 1381-1991.  
DOI: <http://dx.doi.org/10.1007/s11030-012-9360-7>  
IF: 2.861

**Total IF of journals (all publications): 4,505**

**Total IF of journals (publications related to the dissertation): 4,505**

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

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