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An optimized and very detailed, grams scale synthesis of CTEP, through a complete characterization of all the isolated and purified intermediates

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Abstract: Glutamate is the major excitatory neurotransmitter in the brain. 2-Chloro-4-[2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazol-4-ylethynyl]pyridine (**5**) (CTEP) is the first reported negative allosteric modulator of the metabotropic glutamate receptor 5 (mGlu5NAM) with a biological half-life of 48 hours in rodents and therefore considered an ideal tool for chronic studies in rats and mice. In this work an optimized protocol for the synthesis and purification of CTEP is reported. Through the developed new work up scrupulously described in detail, CTEP was obtained in 63 % yield, with a significant improvement in comparison with the methods reported in literature (27%) and in a tripled overall yield (27% versus 9%). Furthermore, all the intermediates between which the unreported multifunctional and appealing compound **8** as well as the final compound **5** were isolated, purified and fully characterized by IR, NMR (^{1}H NMR and ^{13}C NMR), melting point, except for the oily **7**, and Elemental analysis.

Keywords: Acetylene-type mGlu5 NAMs; optimization; isolation; purification; NMR; characterization; conformational investigation.

1. Introduction

Glutamate is the major excitatory neurotransmitter in the brain and mediates its effects through both ionotropic (iGluR) and metabotropic glutamate receptors (mGluR). mGluRs are G-protein-coupled receptors widely expressed in the nervous system; on the basis of the sequence homology, G-protein coupling and ligand selectivity, mGluRs can be classified into three groups (namely group I, II and III). Group I includes metabotropic glutamate receptor 5 that represents an attractive drug target. In particular antagonists of mGluR5 have potential for the treatment of different diseases such as anxiety,[1-3] obsessive-compulsive disorders,[4] autism,[4] intellectual disability (ID),[4] Parkinson's dyskinesia,[2] depression[2,3] and fragile X syndrome (FXS).[2,4-6]

2. Background

The first class of mGluR5 antagonists were glutamate analogs targeting the orthosteric binding site.[7] They enabled the scientists to understand the pharmacology of the receptor but were affected by a low capability to penetrate the brain and low selectivity towards the different receptor subtypes.

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The negative allosteric modulators (NAMs) are a recently identified class of compounds structurally unrelated to glutamate, endowed with high subtype selectivity and a great lipophilic nature which facilitates brain penetration. Except for **3**, compounds **1-5** (Figure 1) are NMAs sharing the acetylene substructure. In particular, **1**[8] and **2**[9] are two potent, brain-penetrant NMAs, but lacking of drug-like properties and therefore not suitable for clinical trials.[10]

The compound **3** is another strong and selective mGlu5 antagonist widely studied in the seventies as a non-benzodiazepine anxiolytic but characterized by an erratic bioavailability and limited tolerability.[11] Derivative **4** is characterized by a long lasting action, high target selectivity and in vivo potency, without any genotoxic or teratogenic effects.[12] CTEP (**5**) is the first reported strong, orally bioavailable, long half-life acting mGlu5 receptor inhibitor.[13] An oral CTEP administration every 48 hours induces a continuous block of the receptors and allows the evaluation of the therapeutic potential of mGlu5 inhibitors where a chronic inhibition is required.

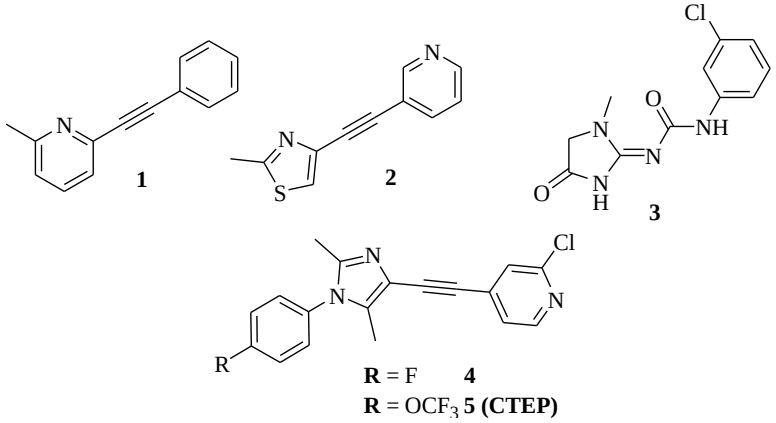
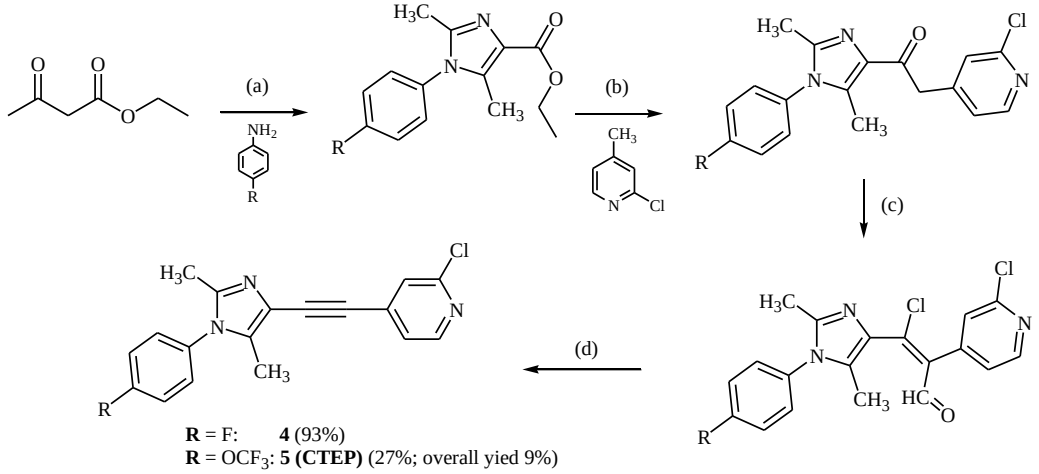


Figure 1. mGlu5 NAMs: **1**, **2**, **3**, **4** and **5 (CTEP)**

As reported in the literature,[12] CTEP (**5**) as well as **4** can be prepared from acetoacetic ester in scales of hundreds of grams (Scheme1).



Reagent and condition: (a) (i) $NaNO_2$, AcOH, H_2O; (ii) *p*-R-aniline, PPTS, toluene; (iii) $MeC(OEt)_3$, *p*-TsOH, Pd/C, 1 bar of H_2; (b) KHMDS, toluene; (c) Vilsmeier salt, DCM; (d) *t*-BuO^-K^+, H_2O, THF.

Scheme 1. Synthesis of compounds **4** and **5**.[12]

In the procedure suggested in the previous work, aiming only at obtaining the final products for pharmacological studies, only one of the intermediates (namely, compound **9**) and the final compounds **4** and **5** have been isolated and purified by crystallization. The characterizations are limited to ^{1}H NMR peaks list and ESI-MS; no ^{13}C NMR and IR data, no melting point or Elemental

analysis are provided. Furthermore, while the final yield of **4** is more than good (93%), the reported yields for **9** and **5**, which is currently the most attractive compound among the mGlu5 receptor inhibitors, were only 44% and 27% (overall yield 9%), respectively. All the other compounds were not isolated but obtained as concentrated solutions of the reaction mixture or as crude products in the form of dark brown oils or unstable tan solids and as such used in the next reaction step accumulating impurities.

In this paper we report an optimized synthetic procedure for the production of **5** on a grams scale and of excellent quality. We adopted the same type of reactions used in the previously published article[12] but making use of an innovative work up along the synthesis. In comparison with the procedure reported in the literature, our developed synthetic and purification protocols, allowed to obtain **10** as crystals with high degree of purity as assessed by melting point and Elemental analysis.

Besides, it enabled us to increase the yield of **9**, to isolate and crystallize **11** enhancing its yield, to double the yield of **5** prepared from **11** and to triple its overall yield, thus making **5** more easily available at low costs. Since it is known that the degree of purity of a synthetic product is influenced by the quality of the substrates from which it derives, all the reaction intermediates were isolated and purified using unreported procedures. Compounds **7**-**11** as well as **5** were fully characterized by melting point (except for the oily **7**), IR, NMR (^{1}H and ^{13}C) and Elemental analysis. A meticulous NMR structural analysis conducted with particular care to the conformational investigation of compounds containing double bonds was exposed. The isolation and purification of the unreported multifunctional and appealing intermediate **8** (80% yield) was achieved and described.

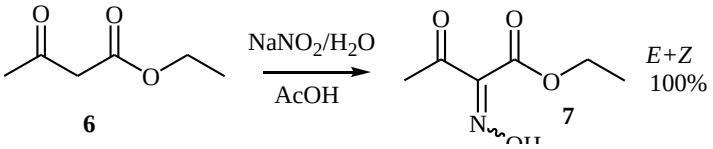
Many new details on how to proceed along the synthesis were scrupulously reported. An innovative and faster isolation procedure of the crude **9** together with a different way to crystallize the final product **5**, were displayed.

3. Experimental

The general experimental procedure, the synthesis of compounds **7**-**11** and **5** and their complete characterization (spectral data, melting points, Elemental analysis) are given in Supporting information file.

4. Present Study

The acetoacetic ester **6** was treated with an aqueous solution of $NaNO_2$ in the presence of acetic acid (AcOH) for 1 hour at room temperature monitoring the progress of the reaction by IR spectroscopy. The strongly orange solution was then quenched with water and extracted with ethyl acetate (AcOEt) to afford the oxime derivative **7** as a yellowish oil (yield 100% versus 91.5%[14]) (Scheme 2) and was completely characterized.



Scheme 2. Synthesis of oxime derivative **7**

NMR spectroscopy (DMSO-d_6) and Elemental analysis confirmed the chemical identity and purity of the derivative **7**. The ^{1}H NMR ($CDCl_3$) data collected for derivative **7** were consistent with the NMR analysis (carried out in the same solvent) reported in the literature[14] for the same compound intended as major geometric isomer. In fact, the NMR analysis acquired both in $CDCl_3$ and in DMSO-d_6 showed that compound **7** was not obtained as a single isomer but as a mixture of geometrical isomers being the *E* form the prevalent one. The stereochemical assignment was made on the basis of the δ value of the signal of the C=NOH group in the ^{13}C NMR. Literature data reported that the signal for *E* isomer is positioned at lower fields [151.15 ppm ($CDCl_3$) and 150.71 ppm (DMSO-d_6) in our case] compared to that of the *Z* form [149.87 ppm ($CDCl_3$) and 149.71 ppm (DMSO-d_6)][15,16] (Figure 2).

The *E/Z* ratio was instead calculated from ^{1}H NMR spectrum by comparing the values of the integrals of the signals of the C<u>H</u>$_3$C=O group at 2.43 (*Z*) and 2.42 (*E*) ppm respectively ($CDCl_3$) and at 2.38 (*Z*) and 2.36 (*E*) ppm respectively (DMSO-d_6) (Figure 3).

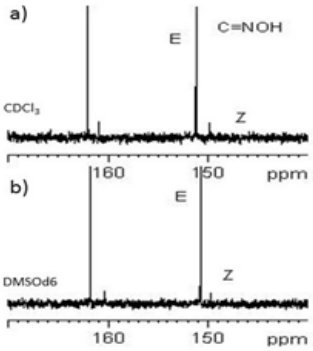


Figure 2. Peaks of the <u>C</u>=NOH group in the ^{13}C NMR spectrum of **7** in $CDCl_3$ (a) and in DMSO-d_6 (b)

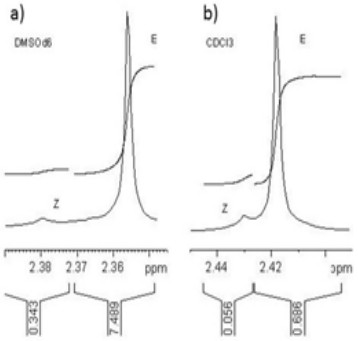
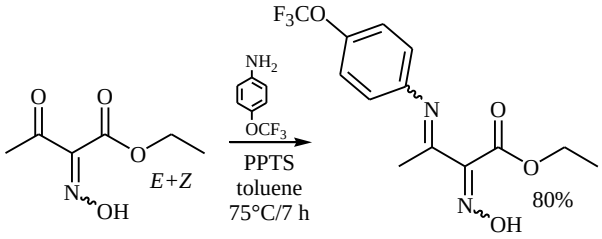


Figure 3. Peaks of the C<u>H</u>$_3$CO group in the ^{1}H NMR spectrum of **7** in DMSO-d_6 (a) and in $CDCl_3$ (b)

To the *E,Z* mixture of oximes **7** dissolved in freshly dried toluene, *p*-trifluoromethoxyaniline and PPTS were added. The reaction flask containing the pale yellow solution was fitted with a Dean-Stark trap and heated at 75 °C under reduced pressure for 7 hours (Scheme 3) removing the azeotropic mixture distilled and restoring the initial volume of toluene five times.



7 **8**

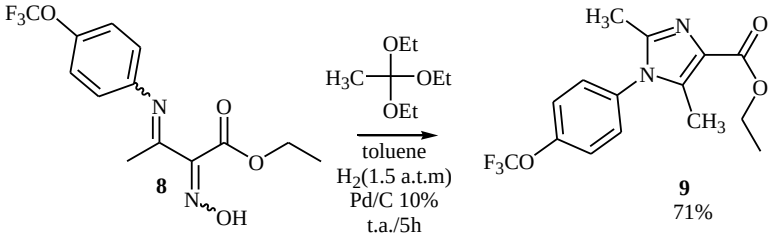
PPTS = Pyridinium *p*-toluensuphonate

Scheme 3. Synthesis of multifunctional compound **8**

The brown solution obtained was evaporated under reduced pressure to afford a light brown solid which was purified by crystallization from $CHCl_3$/*n*-pentane. The unreported **8** was obtained as off-white solid in 80% yield. The multifunctional and appealing structure of **8** was firstly ascertained by the IR spectrum that showed bands related to all functional groups. Then, as expected, the ^{1}H NMR (DMSO-d_6) spectrum pointed out that **8** was a mixture of four geometric isomers as indicated for example by the presence of multiple peaks (12.65, 12.98, 13.01 and 13.24 ppm) for the OH group.

The relative abundance of the distinct isomers in the mixture (measured by the integration values of the OH signals) varied over time and batch (Table 1, S.5. Supporting information file) and with heating up (Table 2 and Table 3, S.5.) indicating that the four components interconverted over time tending to isomerize to the more stable forms. It was noticeable as the interconversion process towards the two more stable forms was promoted both by short or extended heating up and it was irreversible. About this Table 3 (S.5.) is illuminating. Two samples of **8** initially consisting of a mixture of isomers qualitatively and quantitatively different reach a practically identical composition (equilibrium) after one week if maintained at room temperature, after only a few minutes if heated to 75 ° C and then cooled. A prolonged heating (24 h) did not cause large additional changes but the system seemed only tend towards a single isomeric form (74.3%). The ^{13}C NMR spectrum showed all the characteristic peaks of the structure of **8** including the signal of the CF_3 group (118.45 ppm) even if

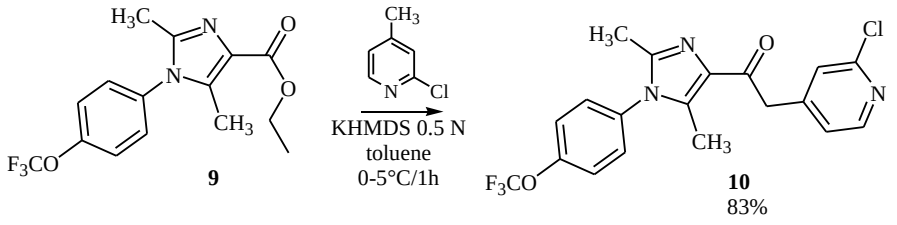
the typical splitting[17] (quartet, $^{1}J_{CF}$ = 200-300 Hz) was not visible because of the low intensity signal but disappeared in the DEPT135 experiment. Elemental analysis and melting point confirmed the structure and the purity of **8**. Compound **8** was condensed under reducing conditions with triethyl orthoacetate to afford the imidazole derivative **9** (Scheme 4).



Scheme 4. Synthesis of imidazole derivative **9**

Briefly, **8** was dissolved in dry toluene and *p*-toluenesulfonic acid (catalytic amount), triethyl orthoacetate and Pd/C 10% were added. The mixture was kept under a stream of hydrogen at 1.5 bar at room temperature for 5 hours monitoring the progress by IR spectroscopy.

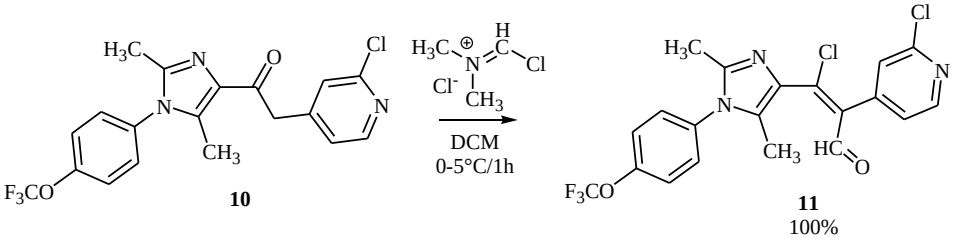
An attempt to prepare **9** reproducing the procedure of literature[12] without isolation of derivative **7**, without isolation and purification of **8** and working at room pressure during the reduction step, led to **9** only in a 13% yield and as a yellow solid with low degree of purity. Our protocol instead allowed the desired product as off-withe crystals in 71% yield versus 44%[12] and with a two degree melting point. A new faster isolation procedure of the crude **9** was explored. Starting from the isolated and purified **8**, the imidazole derivative **9** may be obtained as crystals after simple evaporation of the reaction mixture separated from the catalyst, avoiding the long and tedious treatments with acids, bases and organic solvents suggested.[12] Then simple washings of the obtained solid with petroleum ether enabled to get **9** as white crystalline solid with an increased yield (63%) and with higher degree of purity as assessed by the one degree melting point. The chemical identity of the obtained compound was confirmed by Elemental, IR and NMR analyses. The imidazole ester **9** was condensed with chloropicoline in the presence of the strong base potassium *bis*(trimethylsilyl)amide (KHMDS) to obtain the ketone derivative **10** (Scheme 5).



Scheme 5. Synthesis of ketone derivative **10**

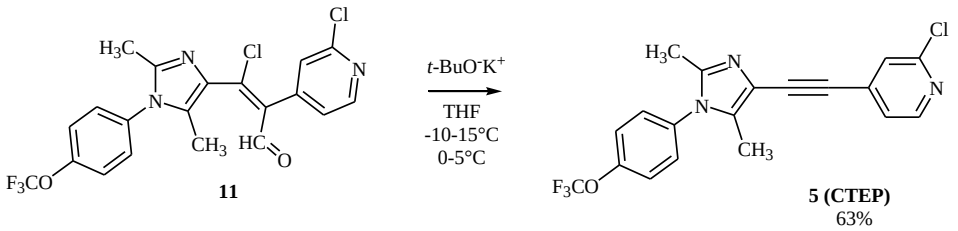
The reaction was complete in 1 hour at 0-5 °C as demonstrated by the IR spectrum The quality of KHMDS dry toluene solution emerged to be critical for the reaction: old or slightly colored KHMDS solutions led to the formation of complex mixtures. **10** was obtained with a high degree of purity with an isolation procedure slightly different from literature[12] and a totally new purification protocol was developed. After neutralization of the reaction mixture with AcOH and hydrolysis, waters were separated and extracted with ethyl acetate (AcOEt) and the organic phase was dried on anhydrous $MgSO_4$. After evaporation of the solvent the crude product was obtained as oil tending to crystallize. The complete crystallization was promoted by treatment with *n*-pentane to get **10** as a pale yellow solid in 83% yield. The IR and NMR spectra as well as Elemental analysis and melting point confirmed the structure and the purity of **10** and the ^{1}H NMR data acquired in $CDCl_3$ were in accordance with literature peaks list.[12] The ketone **10** was then dissolved in dry dichloromethane

(DCM) and added dropwise to a precooled suspension of the Vilsmeier salt (chloromethylene)dimethyliminium chloride to obtain the chloroneal product **11** (Scheme 6).



Scheme 6. Synthesis of chloroneal derivative **11**

The reaction was carried out at 0 °C and reached completion in one hour. In this case the ^{1}H NMR and ^{13}C NMR ($CDCl_3$) spectra acquired on a sample from the reaction mixture were help us to determine the end of the reaction. In literature[12] **11** is not purified and obtained as dark brown oil (yield 83%) and characterization is completely absent. So we developed a new purification protocol. After hydrolysis and extraction, the combined organic phase was dried on anhydrous $MgSO_4$ to remove traces of water then, the solvent was removed and the crude product was obtained as orange oil tending to crystallize. The complete crystallization was promoted by treatment with petroleum ether to get **11** as yellow solid (100% yield). The structure of **11** was confirmed by ^{1}H and ^{13}C NMR spectra in addiction to Elemental analysis and IR. The chloroneal compound **11** was treated with potassium *tert*-butoxide (*t*-BuO^-K^+) in dry tetrahydrofuran (THF) to afford the final product **5** (CTEP) by Grob-type fragmentation (Scheme 7).



Scheme 7. Synthesis of compound **5** (**CTEP**)

The reaction was complete after 1 hour at 0-5°C and was monitored by IR spectroscopy. CTEP was achieved as off-white solid in 63% yield with a 36% yield increase in comparison with the protocol reported in the literature[12] and in a tripled overall yield (27% versus 9%). A new purification procedure was applied in order to avoid the use of water that, in addition to promoting the precipitation of every organic material and impurities, is difficult to be removed. The crude product obtained as dark solid was crystallized from DCM/*n*-pentane obtaining **5** with high degree of purity.

The IR, ^{1}H and ^{13}C NMR spectra, DEPT experiments registered in two different solvents ($CDCl_3$ and DMSO-d_6), Elemental analysis and melting point confirmed the quality of the isolated sample. The ^{1}H NMR spectrum collected in DMSO-d_6 appears to be more resolved than that acquired in $CDCl_3$. The figures of the IR and NMR spectra of all compounds and of the results of NMR structural analysis of the multifunctional compound **8** are available in Supporting information file together with some summary Tables.

4. Conclusion

CTEP is an important negative allosteric modulator of the metabotropic glutamate receptor 5 (mGlu5NAM). Its availability in high amounts and purity could open new horizons in biological and pharmacological studies aiming at better defining and evaluating the activity of this compound in the clinical treatment of some severe neurological disease of our times. With the goal to make this

possible even at low costs the synthesis of **5** on a grams scale was optimized in terms of reaction yield and a detailed description of all the intermediates has been provided. The work-up is innovative. Since it is known that the degree of purity of a synthetic product and its yield are significantly influenced by the quality of the substrates from which it derives we chose of proceeding step by step, isolating, purifying and characterizing exhaustively all the intermediates. This protocol allowed the obtainment in high yield and degree of purity of interesting and almost unreported molecules showing different functional groups. It is worthy of note the obtainment in a crystalline form and in 80% yield of the unreported and appealing intermediate **8** in which an imine group is at once present together with an oxime one. It is open-and-shut the potentiality of this multifunctional compound in a series of chemoselective modifications of each double bond for synthesizing molecules of biological importance. A meticulous NMR structural analysis of all the obtained compounds, with a special interest in the conformational investigation of compounds containing double bonds was exposed in Supporting information file and it could be useful in the design of modified analogues starting from a biological active lead structure. Furthermore this investigation enabled us to detect that **8** is obtained as a mixture of four geometric isomers that can interconvert over time tending to isomerize to the more stable forms. The ^{1}H NMR spectra of different batches were run over time, at 75 °C and at room temperature but after extended heating up the sample and then cooling. This study let us know that the interconversion process was promoted by heating and it was irreversible. More suitable isolation and purification procedures were described for compounds **9** and **5** optimizing their yields which were 71% for **9** (44%)[12] and 63% (overall yield 27%) for **5** (27%)[12] (overall yield 9%). A new purification protocol was provided for compounds **10** and **11**. So, **10** was obtained in a crystalline form instead of dark brown oil, while **11** was obtained as yellow crystals (instead of dark brown oil) and in 100% yield (83%).[12] Except for the oily oxime **7**, all the products were obtained as solids and the melting points were provided. The purity of the reported compound was confirmed also by Elemental analysis.

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/OC

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