# Codeine derivatives as inhibitors of the morphine glucuronidation.

**Abstract**

The invention relates to ester derivatives of codeine at position 6 capable of altering the morphine metabolism. In particular, they are capable of inhibiting the formation of morphine-3-glucuronide (M3G) and capable of reducing, by means of said inhibition, the neuro-excitatory manifestations (alldynia and hyperalgesia) associated with the phenomenon of morphine tolerance. The pharmacological effect shown by these new derivatives resides in modifying the morphine metabolism, in particular decreasing the formation of M3G, in liver cells and mammalian microglia, thus making the effect of morphine more effective and lasting. Among the derivatives of the invention, pivaloyl codeine is considered the most promising compound.

## Keywords

- **CODEINE**
- **MORPHINE**
- **GLUCURONIDATION**
- **ALLODYNA**
- **HYPERALGESIA**
- **ESTERS OF CODEINE**
- **PIVALOYL CODEINE**

## Area

- **PHARMACEUTICAL**

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## Patent Type

Patent for invention.

## Co-Ownership

Sapienza Università di Roma 90%,
Nicoletti Rosario 10%

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## Industrial & Commercial Reference

Pharmaceutical industry, pain killers sector.

## Time to Market

Until now in vitro studies with primary hepatocytes have been conducted, therefore it will be necessary to perform all the in vivo studies and human testing.

## Availability

Cession, Licensing, Research, Development, Experimentation, Collaboration.

## Pubbllicazioni

Codeine derivatives as inhibitors of the morphine glucuronidation.

Technical Description
The invention relates to ester derivatives of codeine at position 6 of general formula (I), able to modify the metabolism of morphine, in particular to inhibit the formation of morphine-3-glucuronide (M3G). The experimental data obtained allow to predict that the codeine derivatives of the invention cause a concentration-dependent decrease in the enzymatic conversion of morphine due to their inhibitory action on its glucuronidation, the main mechanism for removing morphine from the bloodstream.

The technical problem solved by the invention is therefore to provide novel codeine derivatives capable of solving the problems associated with the opioids administration, particularly to reduce or eliminate the problems of hyperalgesia and allodynia following the administration of such opioids.

Technologies & Advantages
Morphine is used in cases of intense pain of various nature. Repeated exposure to this analgesic, like other opioid analgesics, causes the tolerance phenomenon, consisting in the progressive decrease of the analgesic effect, with the consequent need to increase the dose administered to maintain the pain-relief effect. Tolerance contributes to paradoxical phenomena such as hyperalgesia (a pathological increase in pain sensitivity) and allodynia (pain due to a stimulus that normally does not cause pain).

A metabolic derivative of morphine, morphine-3-glucuronide (M3G), which does not interact with morphine receptors, but instead activates the glutamate-mediated system mediated by NMDA receptors. This causes neuro-excitatory effects that contribute to the appearance of hyperalgesia and allodynia in cases of prolonged administration of morphine.

In humans, morphine is metabolised by at least 60% in M3G.

The modulation of morphine M3G glucuronidation is thus an interesting and promising pharmacological route to reduce the excitatory phenomena caused by the metabolism of morphine.

Applications
The codeine derivatives of the invention are capable of in vitro inhibiting the formation of M3G at least as much as codeine, if not more than codeine.

These derivatives are able to counteract the phenomena of hyperalgesia and allodynia related to opioid tolerance, as they can significantly reduce or even eliminate the phenomenon of tolerance in morphine-treated patients.

Since morphine has a great potential for pain relieving and can still give relief to thousands of patients suffering from chronic or acute pain of intense degree, it is important to find molecules that can mitigate or eliminate the development of tolerance by becoming effective compounds in enhancing the therapeutic effects of morphine itself.