行政院國家科學委員會專題研究計畫　成果報告

新型 Morphine 前驅藥之製備及其製劑研究

計畫類別：個別型計畫
計畫編號：NSC92-2320-B-041-005-
執行期間：92 年 08 月 01 日至 93 年 07 月 31 日
執行單位：嘉南藥理科技大學藥學系

計畫主持人：宋國峻
共同主持人：王志中

報告類型：完整報告

處理方式：本計畫涉及專利或其他智慧財產權，2 年後可公開查詢

中　華　民　國 93 年 11 月 3 日

行政院國家科學委員會補助專題研究計畫成果報告

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計畫主持人：宋國峻教授
共同主持人：王志中教授
計畫參與人員：

本成果報告包括以下應繳交之附件：

□赴國外出差或研習心得報告一份
□赴大陸地區出差或研習心得報告一份
□出席國際學術會議心得報告及發表之論文各一份
□國際合作研究計畫國外研究報告書一份

執行單位：嘉南藥理科技大學藥學系

中　華　民　國　93　年　10　月　31 日

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主持人：宋國峻　嘉南藥理科技大學藥學系

Abstract

The focus of the project is the synthesis and characterization of novel morphine prodrugs. The series of prodrugs synthesized are morphine propionate, morphine pivalate, morphine enanthate and morphine decanoate. Their structure characteristics as well as physicochemical properties are characterized.

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Introduction

Nalbuphine (NA) is a narcotic analgesic used in the treatment of both acute and chronic pain. In order to maintain the blood morphine concentration and to improve the patient compliance and therapeutic effectiveness in pain management, the prodrug approach can be utilized.

The major purpose of this project is to prepare a series of novel morphine prodrugs. The preparation of new morphine prodrugs and deliver them via adequate dosage forms may help to maintain the blood morphine concentration so that the therapeutic efficacy and patient compliance may be improved. This project is a continued effort of previous NSC project in exploring the appropriate medication for pain management. The obtained information from this study may contribute to the design of new narcotic analgesics and their formulations.

Materials and methods

Preparation of prodrugs

Ten grams of morphine HCl was added in 300 mL of flask. Added 141 mL of Dichloromethane into the flask under Ar gas. Add 8.62 mL of TEA into the flask and then stir continuously. Slowly dropped approximately 7 mL of acid chloride and stir continuously for overnight. The acyl chlorides added were propionyl chloride, veleryl chloride, heptanoyl chloride and decanoyl chloride in order to prepare morphine propionate, morphine valerate, morphine enanthate and morphine decanoate, respectively.

Purification

First to dry the DCM using rotorvapor, then added appropriate amount of ethylacetate

into the separation funnel. Use 5% of NaHCO3 to wash two to three times and then wash with MilliQ water for two to three times, collect the organic layer. Use rotorvapor to dry the ethyl acetate. The resultant compound was then added into silica gel column and for further purification. The solvent system for eluting the prodrugs incluing NH4OH, methanol and dichlomethane. The eluting solution was then dried with vacuum pump.

Identification

The various prodrugs were identified with IR, UV as well as Mass spectrascopy. The results are shown in the various Figures in the following section.

HPLC analysis

The chromatographic system consisted of a pump (HITACHI 655-A40), an autosampler (HITACHI L6000), a UV detector (HITACHI L4000) and an integrator (HITACHI D2500). A reverse phase silica column (Lichrospher RP-18, 3.9mm*250mm, 10μm, Merck) was utilized for drug separation, while an acetonitrile-pH 2.2 phosphate buffer system was used as the mobile phase. The flow rate and UV wavelength were 1 ml/min and 212 nm, respectively. The detailed chromatographic condition can be referred to the following result section.

Results and discussion

Figure 1 to Figure 12 show the IR, UV and Mass spectroscopy for the morphine propionate, morphine valerate, morphine enanthate and morphine decanoate, respectively. The results indicate that those synthetic steps and purification condition are appropriate for the preparation of morphine prodrugs. The physiochemical properties of those prodrugs are shown in Table 1.

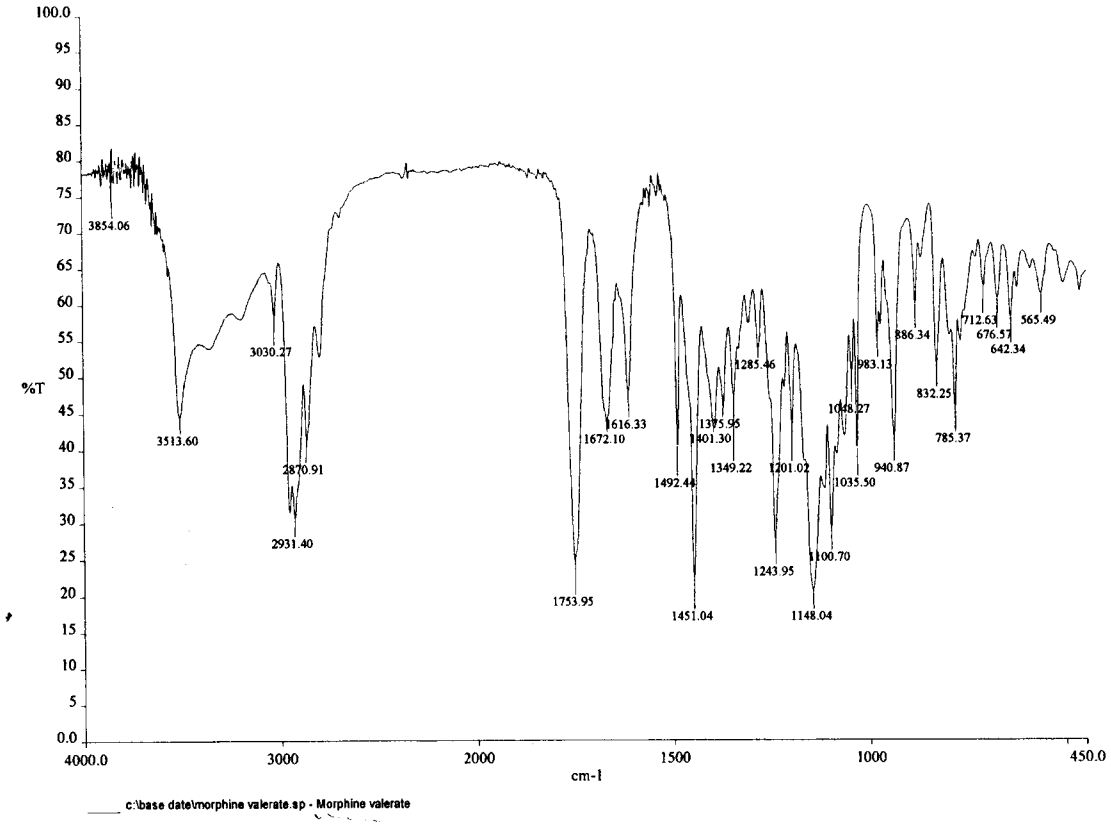
Figure 13 to Figure 17 show the HPLC condition as well as HPLC chromatograms of morphine and morphine prodrugs. The results clearly demonstrate that those chromatographic conditions can be utilized for further studies.

References

1. Banga, A.K., Bose, S., Ghosh, T.K. (1999). *Int. J. Pharm.* **179**: 1-19
2. S.T. Ho eta al., J. Chromatogr. B, 678(1996)289-296.
3. R. C. Etches et al., Anesthesiology, 75(1991) 9-14.
4. Tyle, P. (1986) *Pharm. Res.* **3**: 318-326

Assessment of progress

The results indicate that four prodrugs have been successfully developed. The focus of next year will be the development and evaluation of morphine-prodrug based formulations.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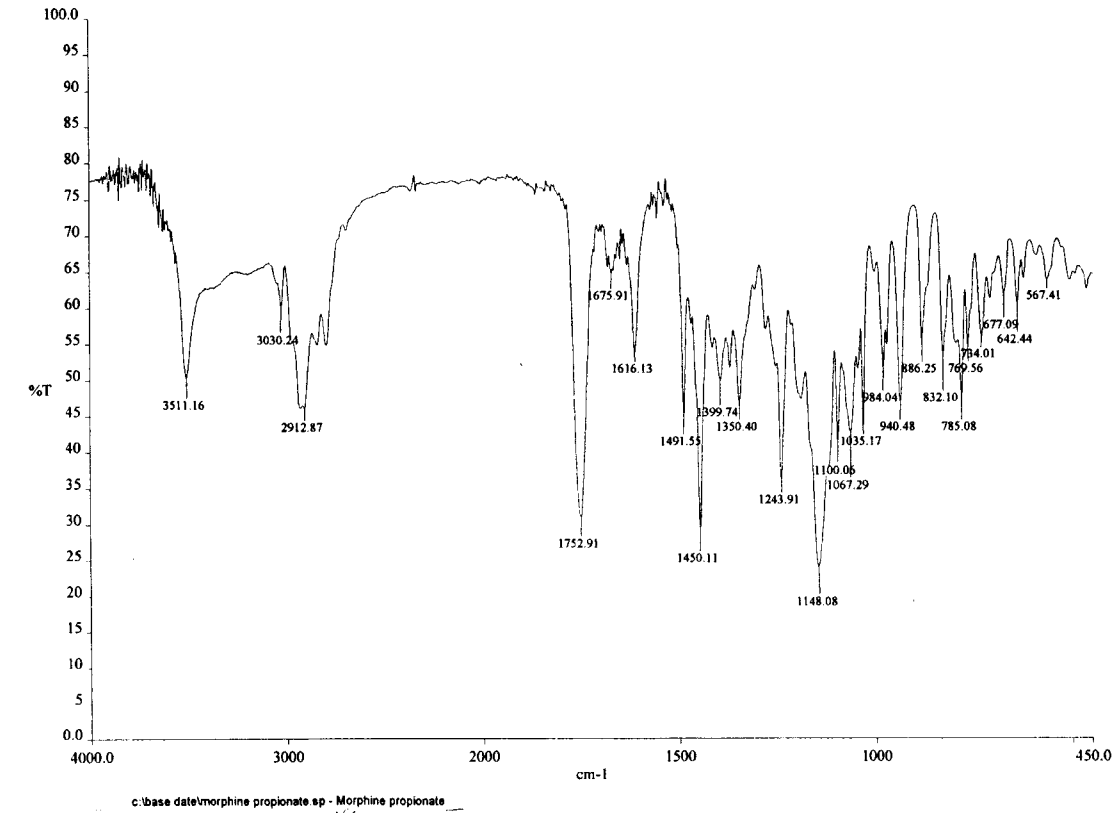
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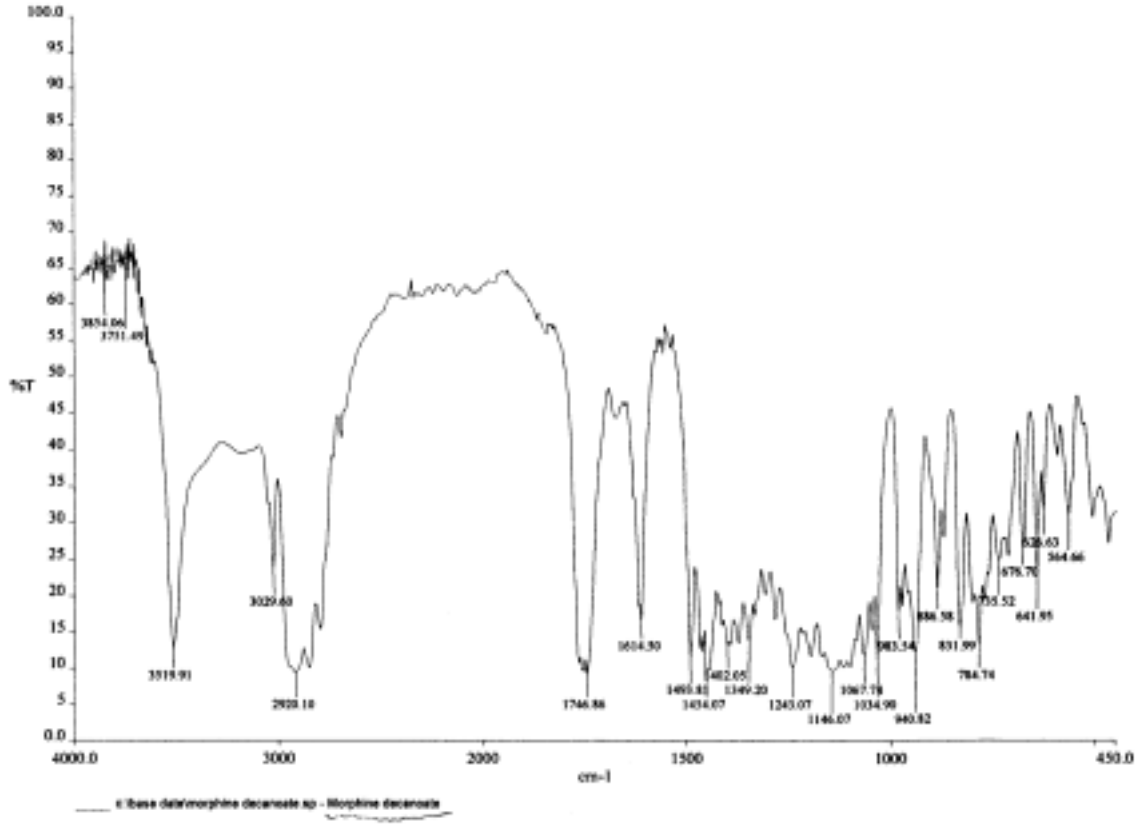
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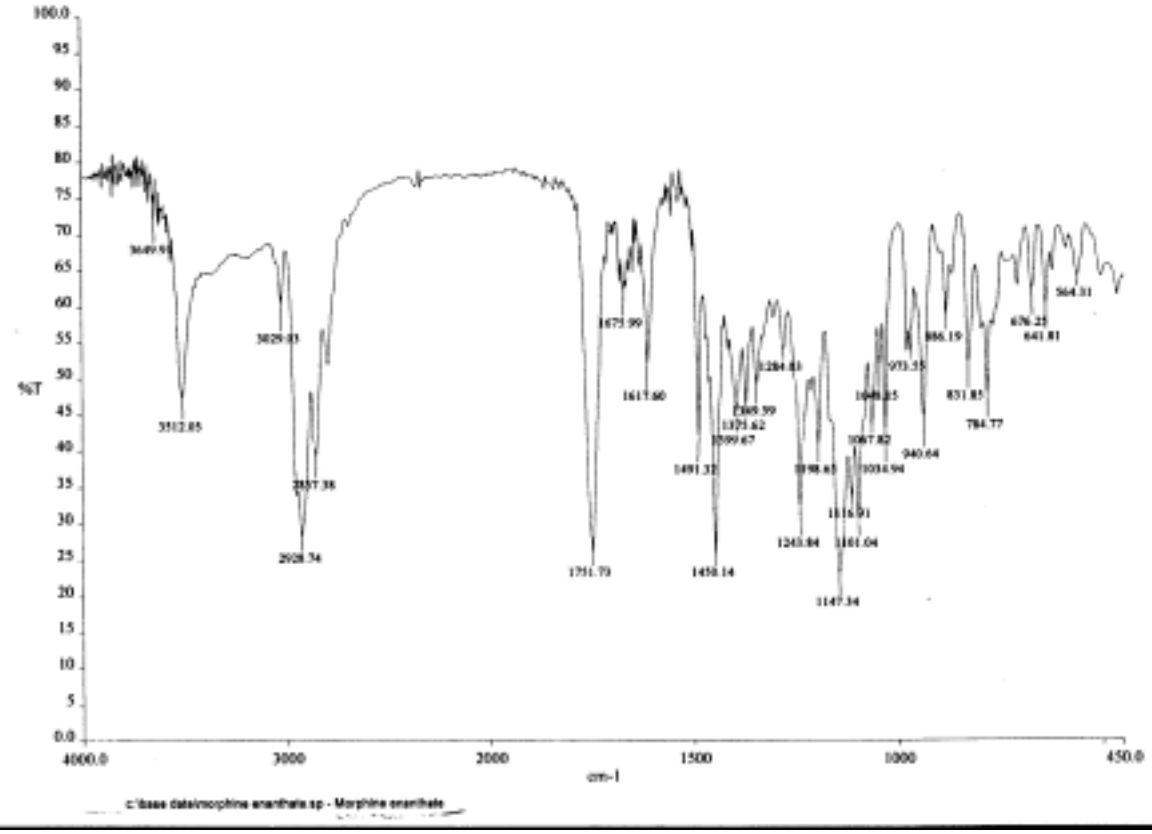
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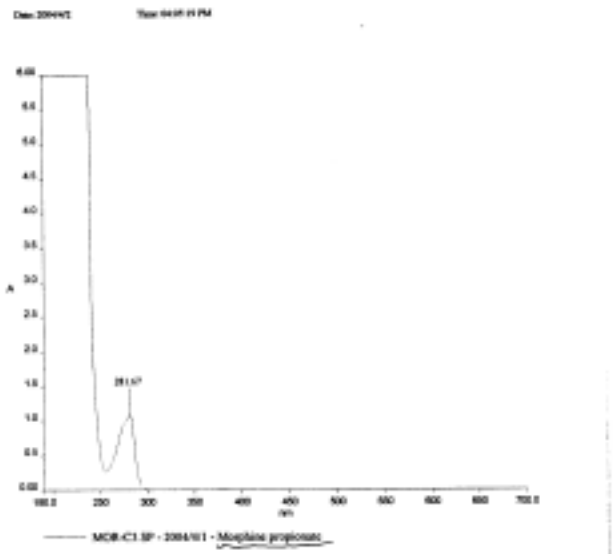

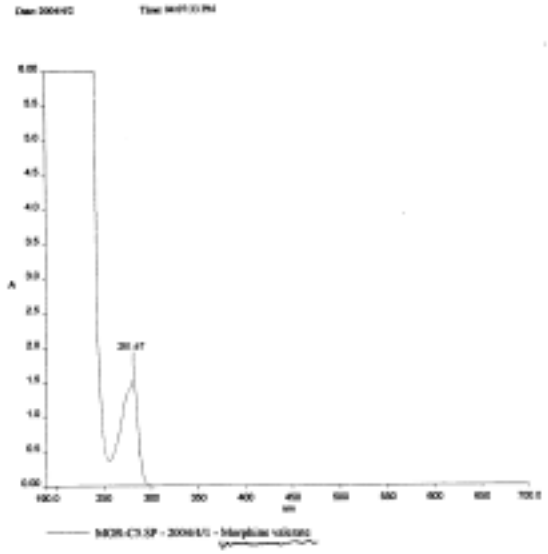

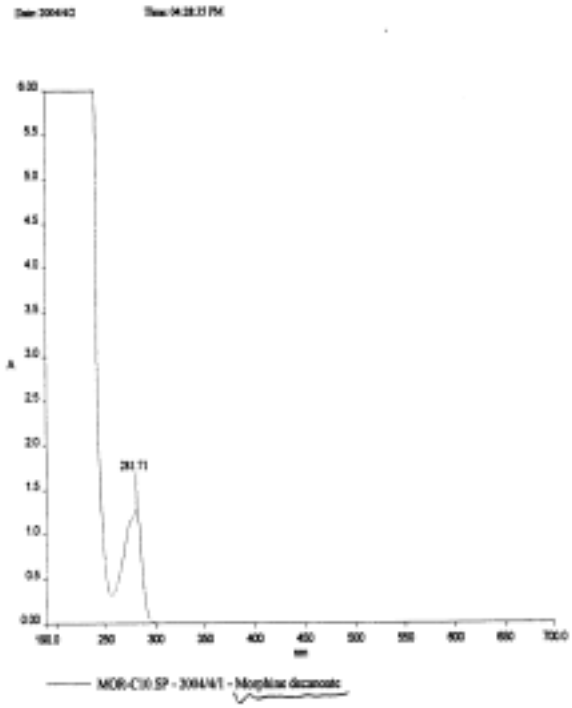

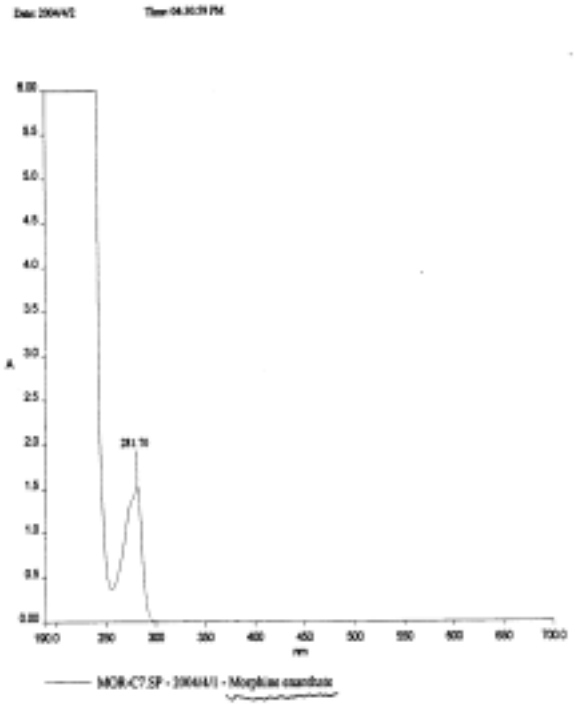

Morphine propionate

Morphine propionate 330 (8.050)

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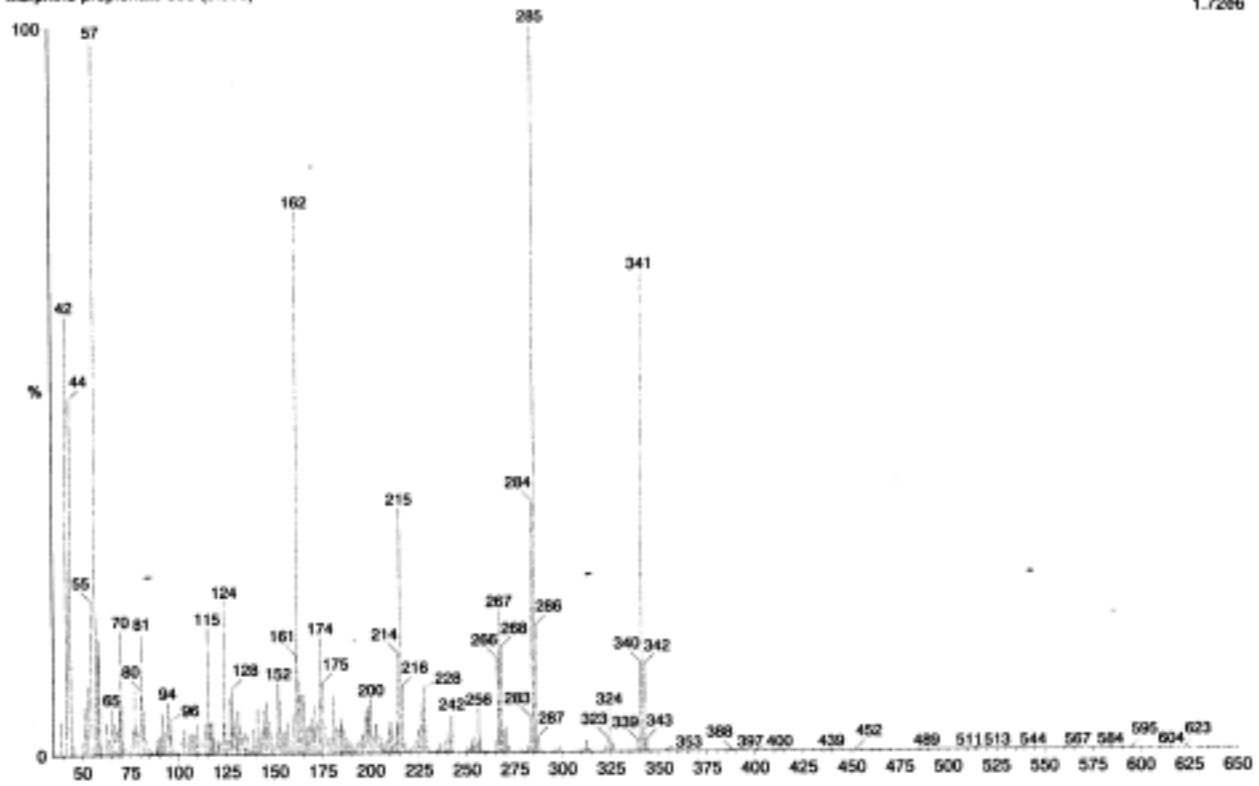

Morphine valerate

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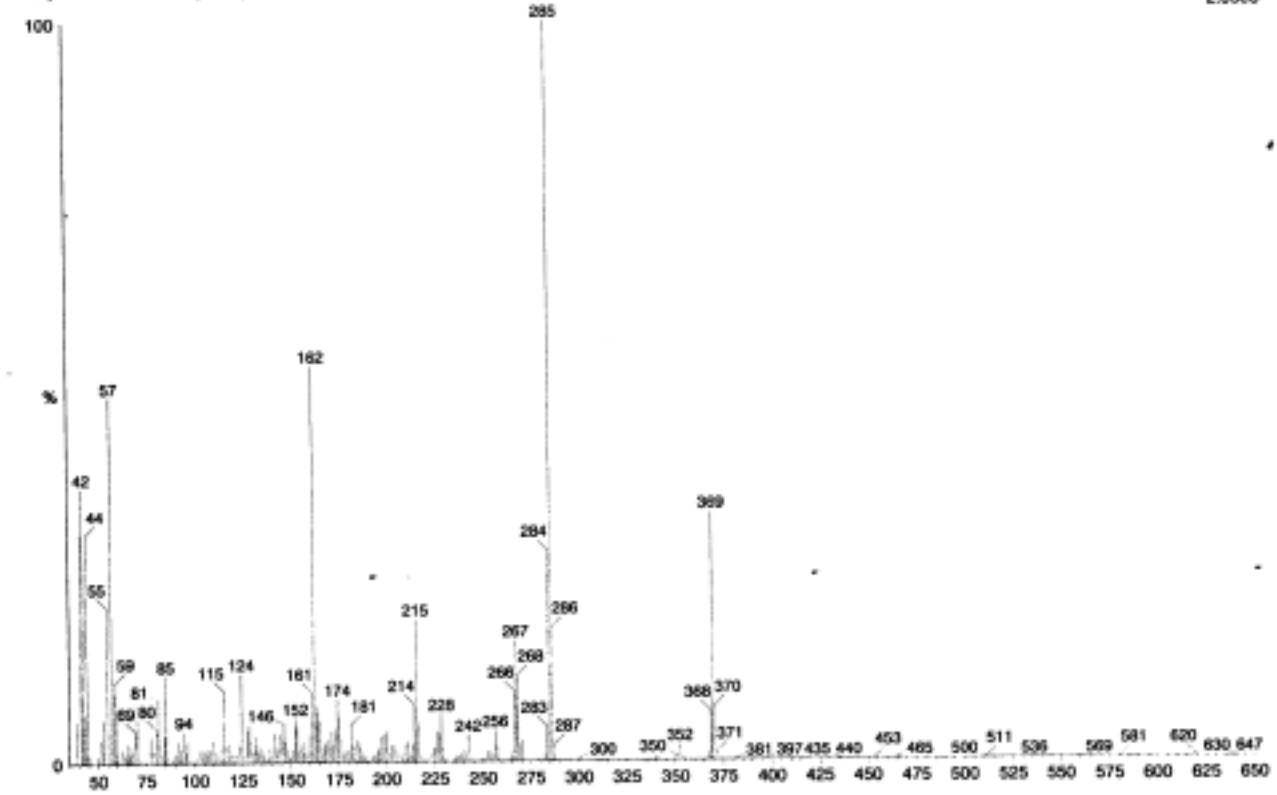

Morphine enanthate

Morphine enanthate 487 (10.929)

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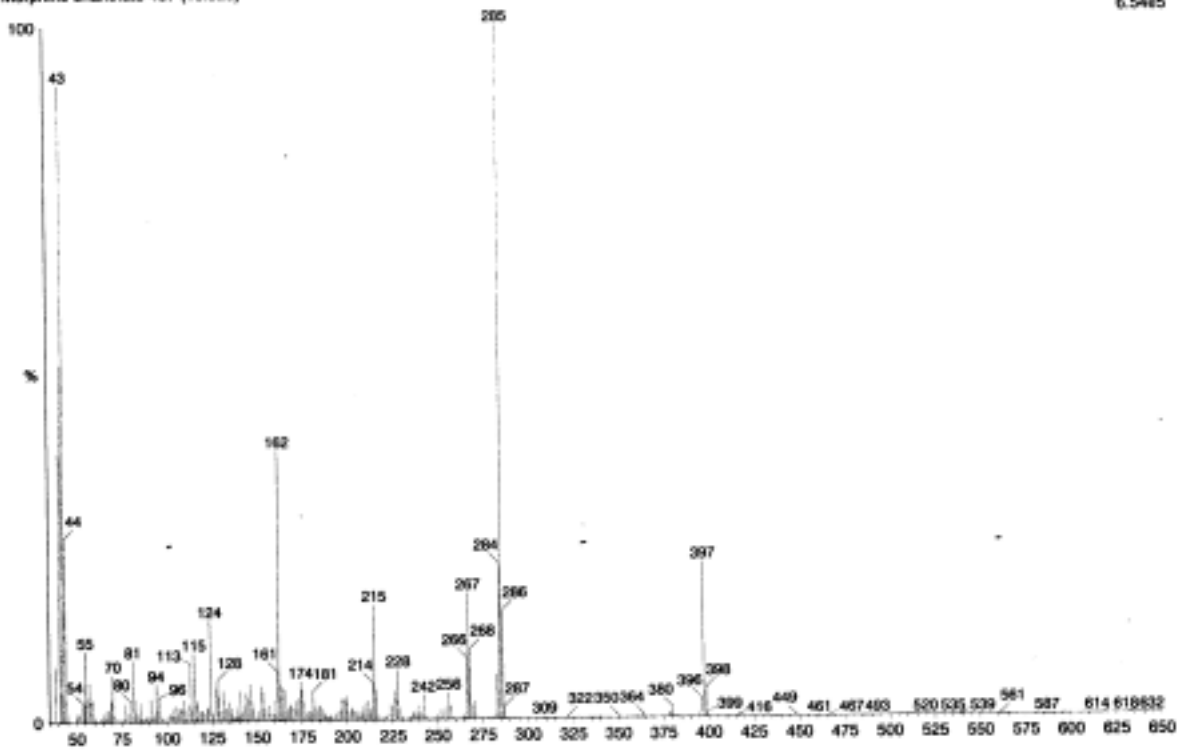
6.54e5



Morphine decanoate

Morphine decanoate 640 (13.734)

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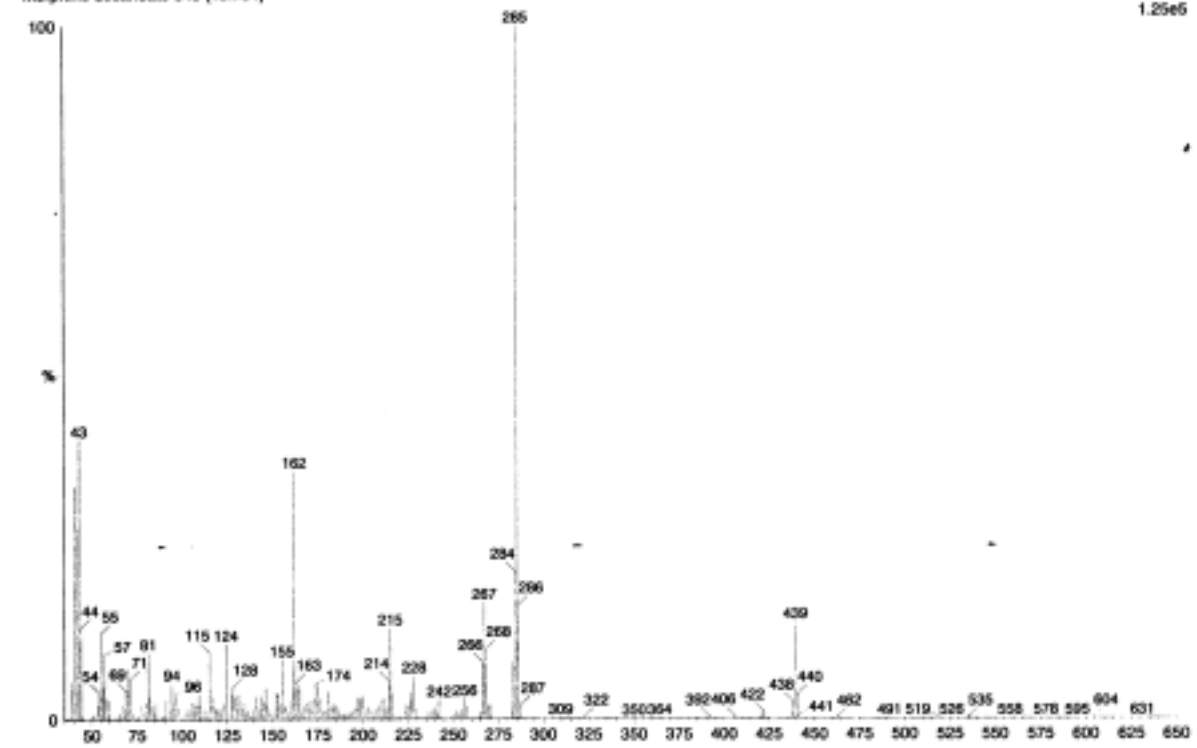


Morphine & Morphine prodrug HPLC

- Morphine

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)
=35 / 65

UV wavelength: 212nm

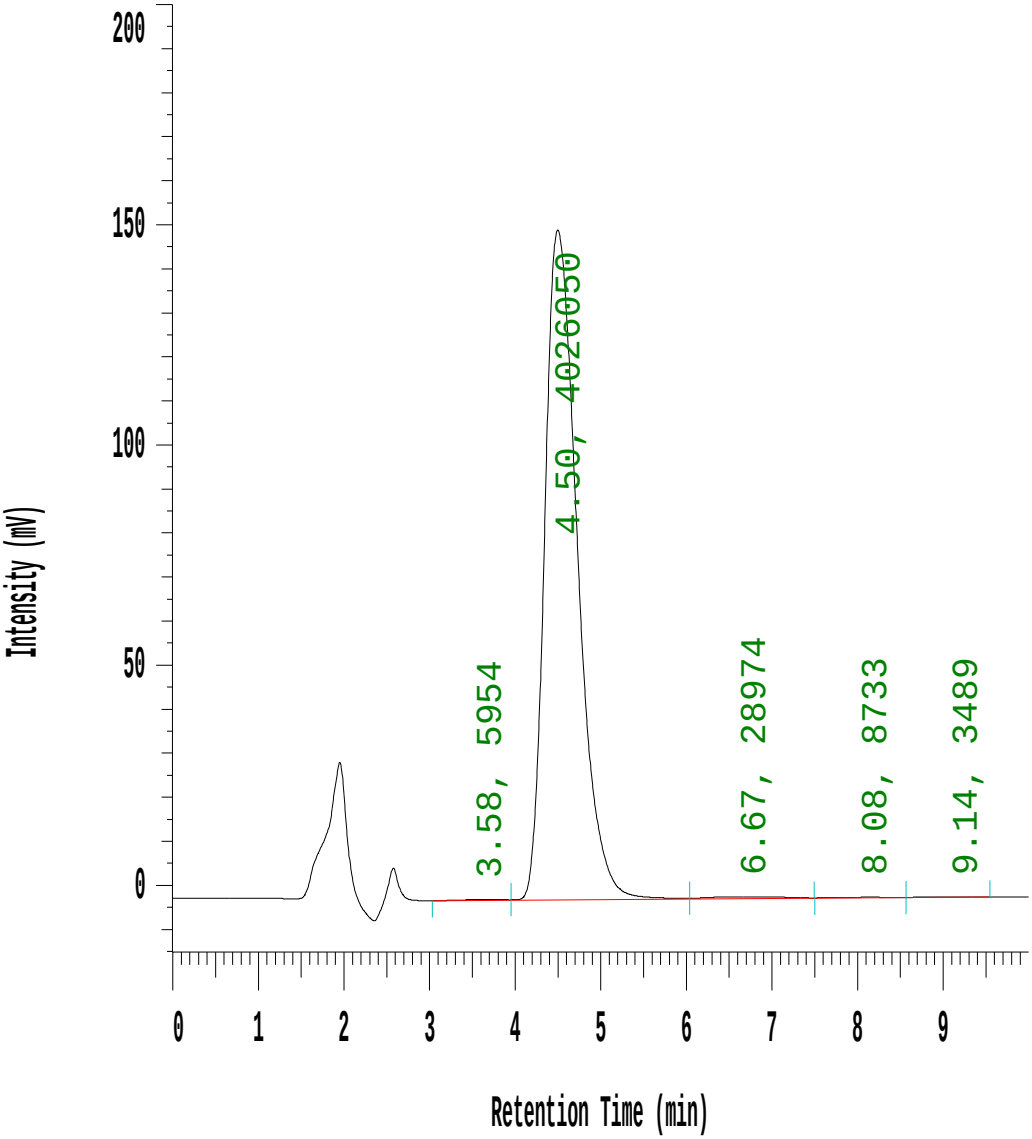
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time: 4.5min ; AUC: 4026050



- Morphine propinate

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS
=35 / 65

UV wavelength: 212nm

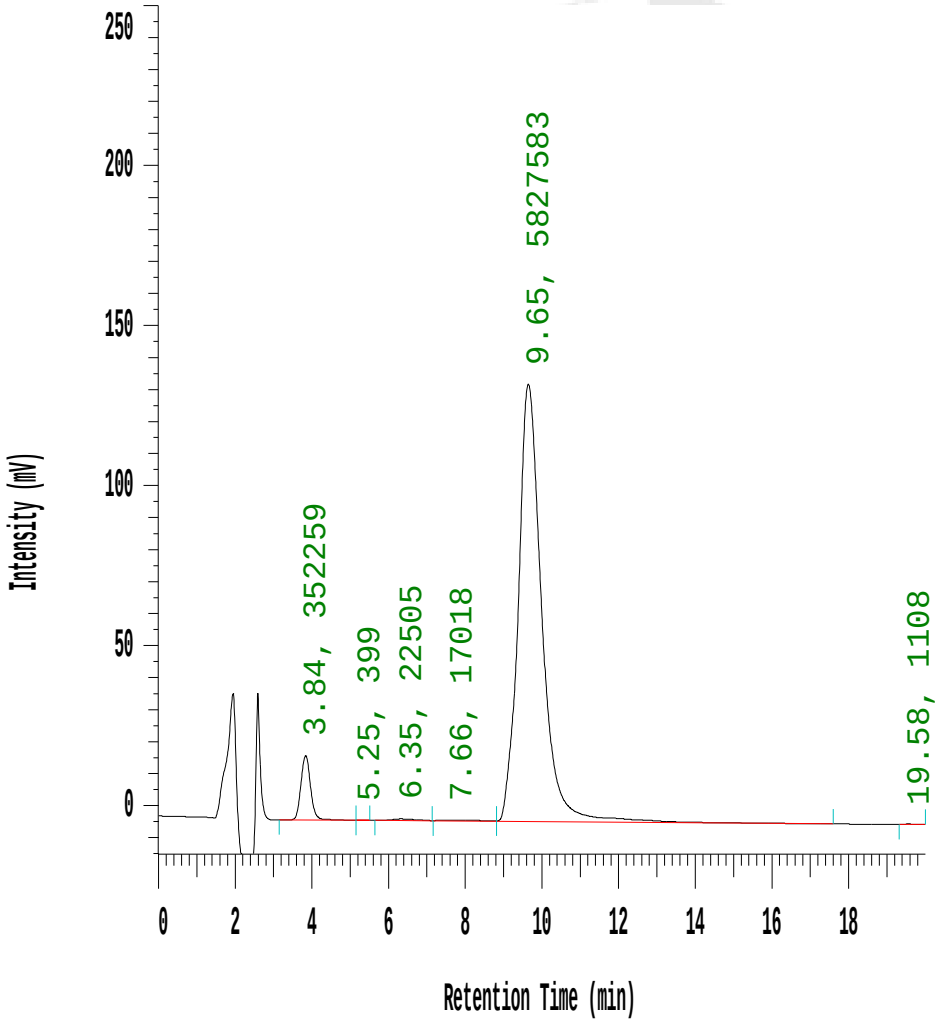
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time: 9.65min ; AUC: 5827583



- Morphine valerate

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)
=35 / 65

UV wavelength: 212nm

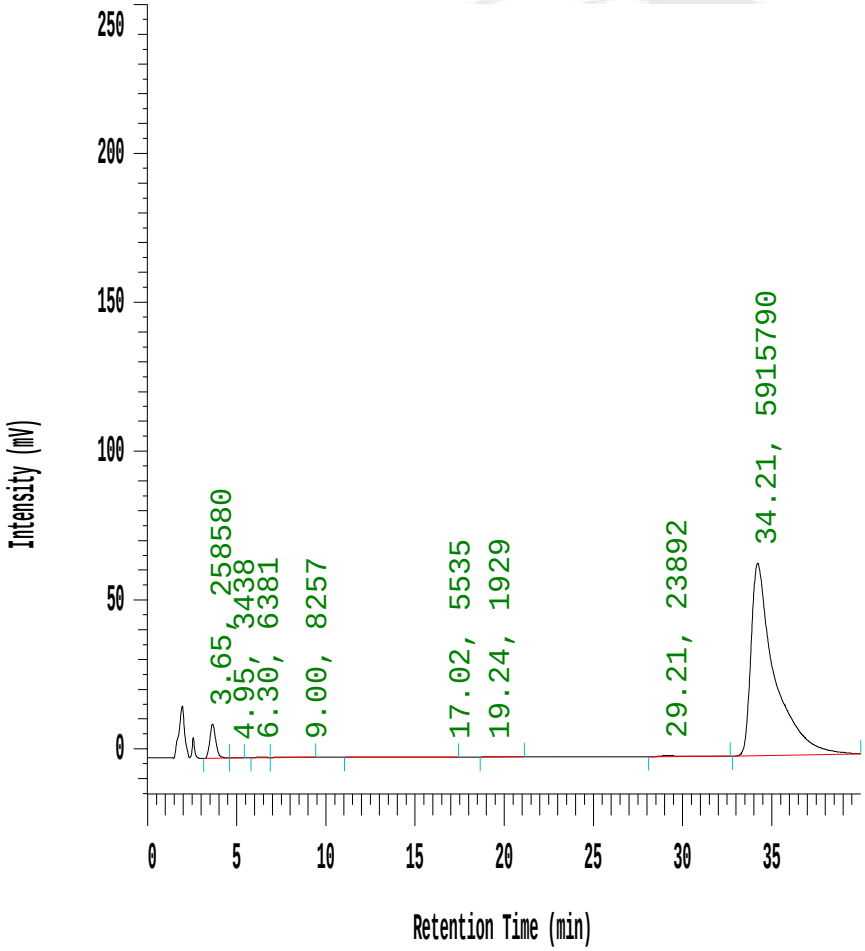
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time: 34.21 ; AUC: 5915790



- Morphine enanthate

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)
=55 / 45

UV wavelength: 212nm

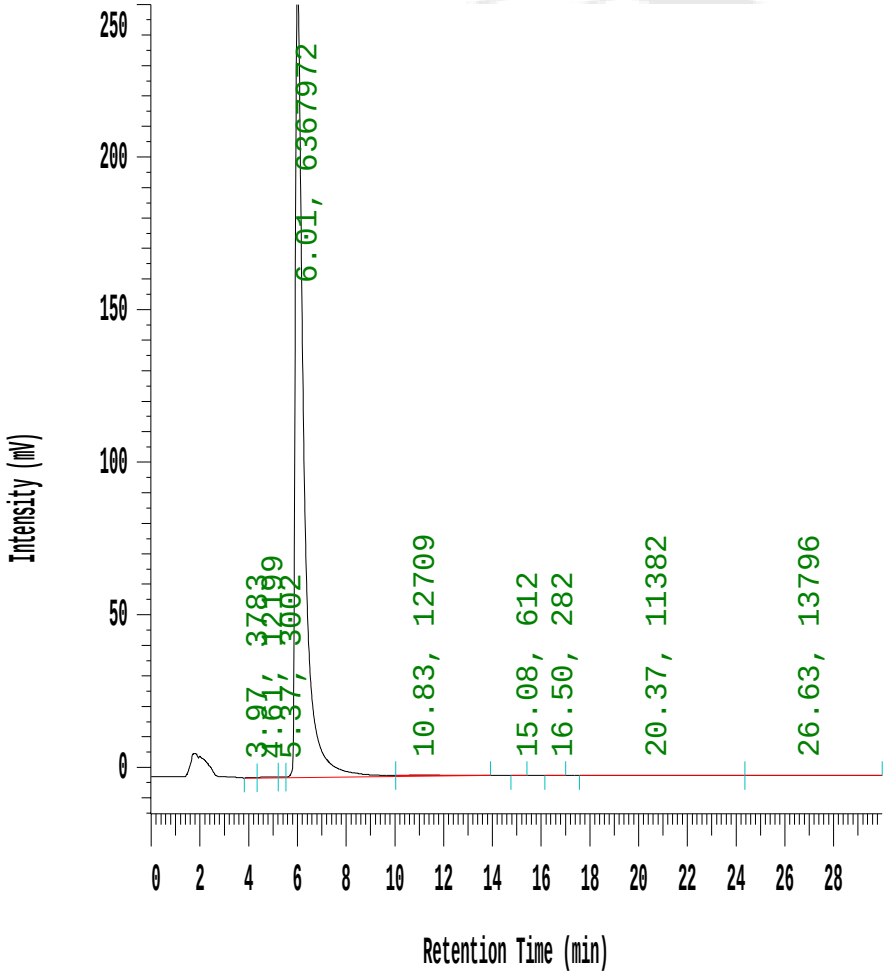
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time:6.01 ; AUC:6367972



- Morphine decanoate

column type: Merck ; Lichrospher RP-18 (25cm long)

mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)
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UV wavelength: 212nm

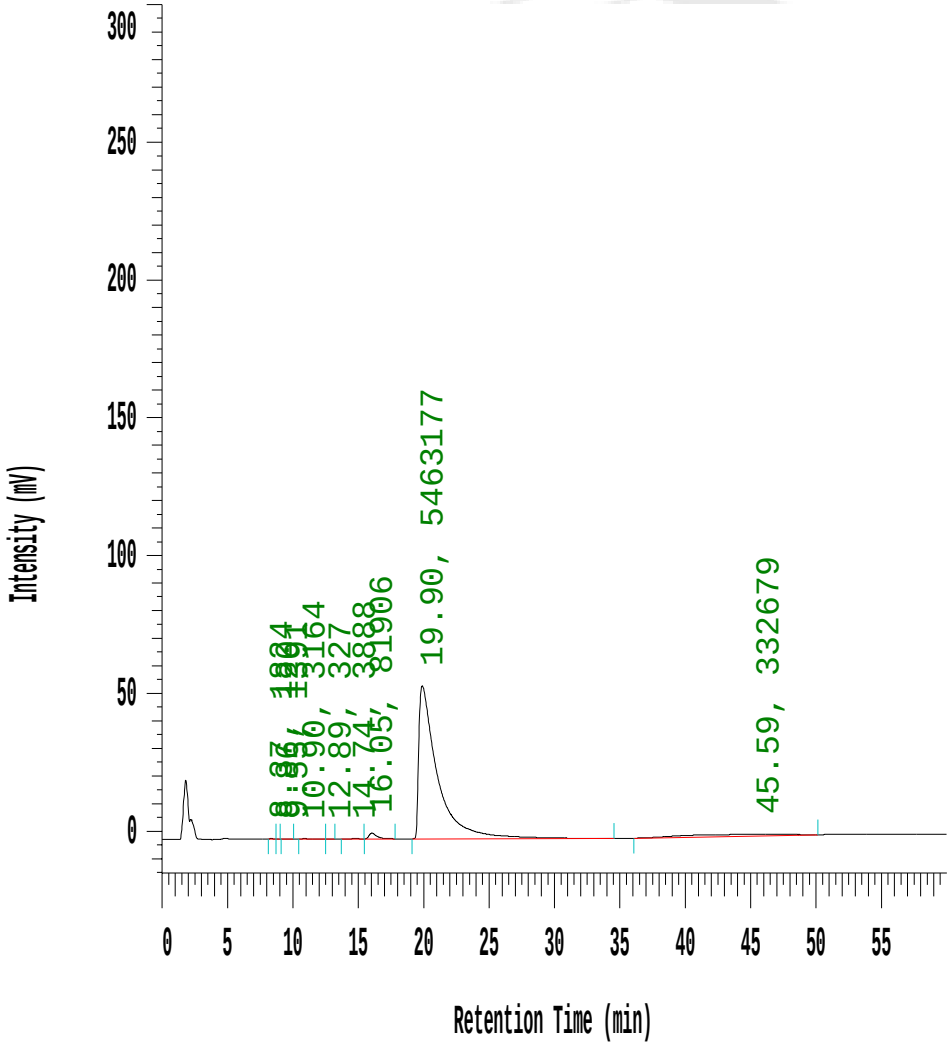
flow rate: 1ml/min

stock so'ln: 1mg/ml

soluble solvent: methanol

injection conc.: 100ug/ml

retention time:19.90 ; AUC:5463177



- Morphine+Morphine propionate+Morphine valerate

column type: Merck ; Lichrospher RP-18 (25cm long)
mobile phase: Acetonitrile / 20 mM phosphate buffer pH 2.2 (contain 1 mM SDS)
=35 / 65
UV wavelength: 212nm
flow rate: 1ml/min
stock so'ln: 1mg/ml
soluble solvent: methanol
injection conc.: 100ug/ml
morphine: 3.92, 1571148
morphine propionate: 9.70 , 1901370
morphine valerate :41.81,1783689