Synthesis of N^3-Substituted Uridine and Related Pyrimidine Nucleosides and Their Antinociceptive Effects in Mice

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Seventy eight N^3-substituted derivatives of uridine (1), thymidine (2), 2′-deoxyuridine (3), 6-azauridine (4), 2′,3′-*O*-isopropylideneuridine (5), and arabinofuranosyluracil (6) were synthesized and their antinociceptive effects were evaluated. N^3-(2′,4′-Dimethoxyphenacyl)uridine (1l), N^3-(2′,4′-dimethoxyphenacyl)2′-deoxyuridine (3l), and N^3-(2′,5′-dimethoxyphenacyl)arabinofuranosyluracil (6m) possessed 93, 86, and 82% of the antinociceptive effects tested by hot plate, respectively. The antinociceptive effects of three derivatives were 5.8, 5.4, and 5.1-folds of the effect of N^3-phenacyluridine (1h) (16%), respectively. The structure–activity relationship of N^3-substituted pyrimidine nucleosides was also discussed.

Key words antinociceptive effect; pyrimidine nucleoside; N^3-substituted arabinofuranosyluracil; structure–activity relationship

We were the first to report that N^3-phenacyluridine (**1h**) (0.5 μmol/mouse) injected by i.c.v. exhibited antinociceptive effect by the tail pinch, hot plate and acetic-acid induced abdominal constriction method.[1)] In connection with this finding, uridine is known to possess central nervous system (CNS) depressant effects such as anticonvulsant activity and decreasing spontaneous activities in mice.[2,3)] CNS depressant effects of uridine were partly explained through the action on the GABA receptor.[4)] In addition, uridine was reported to have the natural sleep-promoting effect by intracerebral infusion to rats,[5)] and the potent sedative-hypnotic activity of N^3-substituted uridine was also revealed in mice.[6)] Further studies have been conducted using thymidine, 2′-deoxyuridine, 6-azauridine, 2′,3′-*O*-isopropylideneuridine as lead compounds. The results indicated that **1h** was the most potent hypnotic compound among derivatives tested.[7—16)] Those N^3-substituted pyrimidine nucleosides also possess certain pharmacological effects *i.e.*, barbiturate- and/or benzodiazepine-induced sleep prolonging effects, motor incoordination, decreasing spontaneous activity, and so on. However, the antinociceptive effects of pyrimidine nucleosides and their derivatives have not been well investigated. Since **1h** has the antinociceptive property, we, therefore, synthesized series of the derivatives of N^3-phenacyl pyrimidine nucleosides in order to find more potent antinociceptive compounds than **1h**.

The present study evaluated the antinociceptive effects of N^3-substituted derivatives synthesized from 6 kinds of pyrimidine nucleosides in mice.

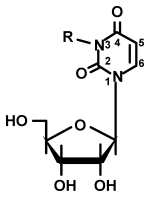
Chemistry

The structural modification was mainly carried out at the N^3-position of the pyrimidine ring. Seventy eight of N^3-substituted pyrimidine nucleosides, methyl (**1—6 a**), ethyl (**1—6 b**), allyl (**1—6 c**), benzyl (**1—6 d**), xylyl (methylbenzyl) (**1—6 e**, **f**, **g**), phenacyl (**1—6 h**), methoxyphenacyl (**1—6 i**, **j**, **k**) and dimethoxyphenacyl derivatives (**1—6 l**, **m**), were synthesized from uridine (**1**), thymidine (**2**), 2′-deoxyuridine (**3**), 6-azauridine (**4**), 2′,3′-*O*-isopropylideneuridine (**5**), and arabinofuranosyluracil (**6**) as lead compounds according to the method of reported previously.[6—17)]

Results and Discussion

The antinociceptive effects of uridine (**1**) and its derivatives at the dose of 0.5 μmol/mouse by i.c.v. injection are summarized in Table 1. Uridine (**1**), the alkyl and allyl compounds **1a**—**c** were inactive or only slightly active by the hot plate test, whereas benzyl and phenacyl substituted uridines (**1d**, **h**) possessed 22 and 16% of the activities, respectively. The results supported that **1h** possessed the antinociception in mice reported previously.[1)] The other analogues, N^3-*o*-, *m*-, and *p*-xylyl- (**1e**—**g**), and N^3-*o*, *m*, and *p*-methoxyphenacyl

Table 1. Effect Profile of N^3-Substituted Uridine



R	No.	Antinociceptive effect[a)] (%)
H	Uridine (**1**)	12±2[b)]
CH_3	**1a**	5±1[c)]
CH_3CH_2	**1b**	4±1[c)]
$CH_2{=}CHCH_2$	**1c**	2±1[b)]
$C_6H_5CH_2$	**1d**	22±1[b)]
o-$CH_3C_6H_4CH_2$	**1e**	28±6[c)]
m-$CH_3C_6H_4CH_2$	**1f**	27±6[c)]
p-$CH_3C_6H_4CH_2$	**1g**	13±2[c)]
$C_6H_5COCH_2$	**1h**	16±2[e)]
o-$CH_3OC_6H_4COCH_2$	**1i**	56±7[c)]
m-$CH_3OC_6H_4COCH_2$	**1j**	26±6[b)]
p-$CH_3OC_6H_4COCH_2$	**1k**	46±9[b)]
2′,4′-$(CH_3O)_2C_6H_3COCH_2$	**1l**	93±3[e)]
2′,5′-$(CH_3O)_2C_6H_3COCH_2$	**1m**	74±8[d)]

Compounds tested were administered by i.c.v. injection at a dose of 0.5 μmol/mouse. *a*) Antinociceptive effect (%) is expressed as the maximal antinociceptive effect. The maximal antinociceptive effects were observed at *b*) 5 min, *c*) 15 min, *d*) 30 min, or *e*) 60 min after i.c.v. administration.

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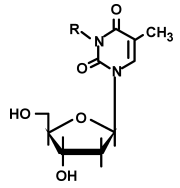
(**1i**—**k**) exhibited 13—56% of the activities at the same dose. The order of their activities of xylyl derivatives was **1e**=**1f**>**1g**, while that of the methoxyphenacyls was **1i**>**1k**>**1j**. The effects of methoxyphenacyl derivatives of **1** were much more potent as compared to those of xylyl derivatives. This finding prompted us to prepare dimethoxyphenacyl derivatives of **1**. The effects of 2′,4′-dimethoxyphenacyl- and 2′,5′-dimethoxyphenacyl-substituted **1** (**1l**, **m**) were particularly strong in view of the fact that their potency were 93 and 74%, respectively. The potent effect of 2′,4′(*o* and *p* position)-dimethoxyphenacyluridine (**1l**) might be due to the introduction of methoxy groups to the phenacyl moiety, because **1i** (*o*-substitution) and **1k** (*p*-substitution) possessed the activities to some extents (56, 46%). However, the most potent compound **1l** among all N^3-substituted pyrimidine nucleosides tested in the present study also caused seizures in mice (data not shown).

The antinociceptive effects of thymidine (**2**) and its derivatives are shown in Table 2. Thymidine itself showed 26% of the activity, and **2a**—**c** exhibited relatively high potency (16—34%) as compared to the corresponding N^3-substituted uridine derivatives. Although *o*- and *p*-xylyl derivatives of **2** (**2e**, **g**) retained the same potency as **1e** and **1g**, respectively, *m*-xylyl substitution of **2** (**2f**) resulted in the decrease of effects than that of **1f**. In the N^3-methoxyphenacylthymidines, *m*-methoxyphenacyl substituted **2** (**2j**) exhibited 58% of the activities, whereas, *o*- (**2i**) and *p*- (**2k**) substituents were less effective as compared to the corresponding **1i** and **1k**. As for N^3-dimethoxyphenacyl substituted derivatives, though **2l** exhibited higher potency of 75%, **2m** had only 13% of the activity. The results indicated that the additional substitution of methoxy group increased the antinociceptive effect of **2i** and **2k**. The structure of thymidine differs from that of uridine on the 5-methyl and 2′-hydroxy groups, and it appears that these differences give rise to change in their effects.

Table 3 shows the antinociceptive effects of 2′-deoxyuridine (**3**) and its N^3-substituted derivatives. 2′-Deoxyuridine (**3**), the alkyl and allyl derivatives, **3a**—**c,** were slightly active like in the case of uridine derivatives. In benzyl and the xylyl derivatives, **3d**—**f** possessed 31—38% of the antinociceptive effects, while the activity of **3g** was 14%. Their potencies were similar to those of corresponding **1d**—**g**. The effect of N^3-phenacyl substituted **3** (**3h**; 56%) was comparable to that of **2h**, and N^3-methoxyphenacyl derivatives of **3** (**3i**—**k**) produced 62—78% of the effects. In the 2′-deoxyuridine derivatives, there is no regioselectivity of methoxy group on the aromatic ring of phenacyl moiety for the antinociceptive effects of **3i**—**k**. Compounds **3l** and **3m** (N^3-dimethoxyphenacyl derivatives) exhibited relatively potent effects with their activities of 86 and 55 %, respectively.

The antinociceptive effects of 6-azauridine (**4**) and its N^3-substituted derivatives are summarized in Table 4. The activity of **4** was 25%, and the alkyl, allyl, benzyl, xylyl, and phenacyl substitutions at the N^3-position of **4** resulted in decrease of the effect as compared with **4**. On the other hand, an introduction of methoxy group to phenacyl moiety of **4h** produced potentiation of the effects. N^3-*o*-Methoxyphenacyl- (**4i**), 2′,4′-dimethoxyphenacyl- (**4l**), and 2′,5′-dimethoxyphenacyl- (**4m**) showed 45—47% of the effect. However, none of the derivatives of **4** produced more than 50% of the effects. The results suggest that **4** is not a good functional structure for exhibiting the antinociceptive effect in the pyrimidine nucleoside derivatives.

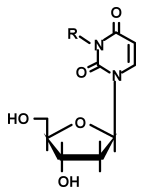
Table 2. Effect Profile of N^3-Substituted Thymidine



R	No.	Antinociceptive effect[a] (%)
H	Thymidine (**2**)	26±5[d]
CH_3	**2a**	16±3[b]
CH_3CH_2	**2b**	34±2[c]
CH_2=$CHCH_2$	**2c**	18±2[c]
$C_6H_5CH_2$	**2d**	20±2[c]
o-$CH_3C_6H_4CH_2$	**2e**	27±2[c]
m-$CH_3C_6H_4CH_2$	**2f**	7±2[c]
p-$CH_3C_6H_4CH_2$	**2g**	9±2[e]
$C_6H_5COCH_2$	**2h**	51±6[c]
o-$CH_3OC_6H_4COCH_2$	**2i**	22±5[e]
m-$CH_3OC_6H_4COCH_2$	**2j**	58±8[c]
p-$CH_3OC_6H_4COCH_2$	**2k**	12±2[e]
2′,4′-$(CH_3O)_2C_6H_3COCH_2$	**2l**	75±7[b]
2′,5′-$(CH_3O)_2C_6H_3COCH_2$	**2m**	13±3[c]

Compounds tested were administered by i.c.v. injection at a dose of 0.5 μmol/mouse. *a*) Antinociceptive effect (%) is expressed as the maximal antinociceptive effect. The maximal antinociceptive effects were observed at *b*) 5 min, *c*) 15 min, *d*) 30 min, or *e*) 60 min after i.c.v. administration.

Table 3. Effect Profile of N^3-Substituted 2′-Deoxyuridine

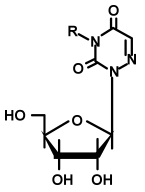


R	No.	Antinociceptive effect[a] (%)
H	2′-Deoxyuridine (**3**)	13±1[d]
CH_3	**3a**	18±3[b]
CH_3CH_2	**3b**	18±2[d]
CH_2=$CHCH_2$	**3c**	16±3[b]
$C_6H_5CH_2$	**3d**	31±5[c]
o-$CH_3C_6H_4CH_2$	**3e**	38±7[b]
m-$CH_3C_6H_4CH_2$	**3f**	32±6[b]
p-$CH_3C_6H_4CH_2$	**3g**	14±2[b]
$C_6H_5COCH_2$	**3h**	56±6[b]
o-$CH_3OC_6H_4COCH_2$	**3i**	78±8[c]
m-$CH_3OC_6H_4COCH_2$	**3j**	73±7[d]
p-$CH_3OC_6H_4COCH_2$	**3k**	62±5[c]
2′,4′-$(CH_3O)_2C_6H_3COCH_2$	**3l**	86±7[b]
2′,5′-$(CH_3O)_2C_6H_3COCH_2$	**3m**	55±8[c]

Compounds tested were administered by i.c.v. injection at a dose of 0.5 μmol/mouse. *a*) Antinociceptive effect (%) is expressed as the maximal antinociceptive effect. The maximal antinociceptive effects were observed at *b*) 5 min, *c*) 15 min, or *d*) 30 min after i.c.v. administration.

The antinociceptive effects of 2′,3′-*O*-isopropylideneuridine (**5**) and N^3-substituted derivatives are summarized in Table 5. The effects of all **5** derivatives tested including methoxyphenacyl and dimethxyphenacyl substituted were less than 35%. N^3-Dimethoxyphenacyl substituted derivatives of **1**—**4** except for **2m** had 45—93% of the effects, while **5l** and **5m** only exhibited 14 and 12% of the effects, re-

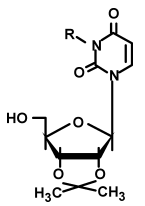
Table 4. Effect Profile of N^3-Substituted 6-Azauridine



R	No.	Antinociceptive effect[a] (%)
H	6-Azauridine (**4**)	25±5[d]
CH_3	**4a**	13±2[b]
CH_3CH_2	**4b**	13±2[c]
$CH_2=CHCH_2$	**4c**	19±5[b]
$C_6H_5CH_2$	**4d**	17±2[c]
o-$CH_3C_6H_4CH_2$	**4e**	18±5[c]
m-$CH_3C_6H_4CH_2$	**4f**	8±3[d]
p-$CH_3C_6H_4CH_2$	**4g**	11±2[c]
$C_6H_5COCH_2$	**4h**	13±1[c]
o-$CH_3OC_6H_4COCH_2$	**4i**	45±5[b]
m-$CH_3OC_6H_4COCH_2$	**4j**	31±3[c]
p-$CH_3OC_6H_4COCH_2$	**4k**	28±4[d]
2′,4′-$(CH_3O)_2C_6H_3COCH_2$	**4l**	47±8[c]
2′,5′-$(CH_3O)_2C_6H_3COCH_2$	**4m**	45±7[c]

Compounds tested were administered by i.c.v. injection at a dose of 0.5 μmol/mouse. *a*) Antinociceptive effect (%) is expressed as the maximal antinociceptive effect. The maximal antinociceptive effects were observed at *b*) 5 min, *c*) 15 min, or *d*) 30 min after i.c.v. administration.

Table 5. Effect Profile of N^3-Substituted 2′,3′-*O*-Isopropylideneuridine



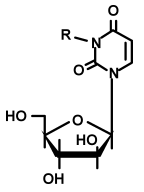
R	No.	Antinociceptive effect[a] (%)
H	2′,3′-*O*-Isopropylideneuridine (**5**)	7±2[c]
CH_3	**5a**	6±1[e]
CH_3CH_2	**5b**	12±1[e]
$CH_2=CHCH_2$	**5c**	15±2[e]
$C_6H_5CH_2$	**5d**	35±5[c]
o-$CH_3C_6H_4CH_2$	**5e**	11±1[e]
m-$CH_3C_6H_4CH_2$	**5f**	8±2[c]
p-$CH_3C_6H_4CH_2$	**5g**	11±1[c]
$C_6H_5COCH_2$	**5h**	11±2[c]
o-$CH_3OC_6H_4COCH_2$	**5i**	15±1[c]
m-$CH_3OC_6H_4COCH_2$	**5j**	24±5[d]
p-$CH_3OC_6H_4COCH_2$	**5k**	31±6[c]
2′,4′-$(CH_3O)_2C_6H_3COCH_2$	**5l**	14±4[f]
2′,5′-$(CH_3O)_2C_6H_3COCH_2$	**5m**	12±4[b]

Compounds tested were administered by i.c.v. injection at a dose of 0.5 μmol/mouse. *a*) Antinociceptive effect (%) is expressed as the maximal antinociceptive effect. The maximal antinociceptive effects were observed at *b*) 5 min, *c*) 15 min, *d*) 30 min, *e*) 60 min, or *f*) 90 min after i.c.v. administration.

spectively. The results confirm that 2′ and/or 3′-hydroxy group have an important role to produce the antinociceptive effects of N^3-substituted pyrimidine nucleosides.

The antinociceptive effects of arabinofuranosyluracil (**6**) and its derivatives are shown in Table 6. The structure of **6** is different from that of uridine only on the configuration of 2′-hydroxy group. The compound **6** and **6a**—**c** did not show any significant effect at 0.5 μmol/mouse. However, benzyl (**6d**), phenacyl (**6h**) and the other derivatives (**6e**, **i**—**m**) possessed

Table 6. Effect Profile of N^3-Substituted Arabinofuranosyluracil



R	No.	Antinociceptive effect[a] (%)
H	Arabinofuranosyluracil (**6**)	9±2[b]
CH_3	**6a**	3±1[e]
CH_3CH_2	**6b**	8±2[b]
$CH_2=CHCH_2$	**6c**	2±0[b]
$C_6H_5CH_2$	**6d**	73±2[c]
o-$CH_3C_6H_4CH_2$	**6e**	73±7[c]
m-$CH_3C_6H_4CH_2$	**6f**	41±7[c]
p-$CH_3C_6H_4CH_2$	**6g**	21±3[c]
$C_6H_5COCH_2$	**6h**	60±3[f]
o-$CH_3OC_6H_4COCH_2$	**6i**	50±2[d]
m-$CH_3OC_6H_4COCH_2$	**6j**	71±3[c]
p-$CH_3OC_6H_4COCH_2$	**6k**	76±4[b]
2′,4′-$(CH_3O)_2C_6H_3COCH_2$	**6l**	68±9[c]
2′,5′-$(CH_3O)_2C_6H_3COCH_2$	**6m**	82±3[c]

Compounds tested were administered by i.c.v. injection at a dose of 0.5 μmol/mouse. *a*) Antinociceptive effect (%) is expressed as the maximal antinociceptive effect. The maximal antinociceptive effects were observed at *b*) 5 min, *c*) 15 min, *d*) 30 min, *e*) 60 min, or *f*) 90 min after i.c.v. administration.

relatively potent effect as compared with those of N^3-benzyl and N^3-phenacyl derivatives of the other nucleosides. In the N^3-xylyl derivatives, the order of the potency was *o*-(**6e**)>*m*- (**6f**)>*p*-xylyl (**6g**) derivatives, suggesting same tendency to those order of corresponding **1**, **2**, and **3** derivatives. It was also noted that **6d** and **6e** possessed the most potent effects (73%) among all the N^3-benzyl and xylyl substitutents of the pyrimidine nucleosides prepared in the present study. N^3-Methoxyphenacyl and N^3-dimethoxyphenacyl derivatives (**6i**—**m**) exhibited relatively higher activities of 50—82% as compared to the other pyrimidine nucleoside derivatives. In summary, many kinds of derivatives of **6** exhibited potent effects. Since the antinociceptive effects of N^3-substituted arabinofuranosyl (**6i**—**m**) were predominant than the hypnotic effects (data not shown), they may be a good tool for the investigation of pyrimidine nucleosides exhibited antinociception.

The present study demonstrated the three important points on the antinociceptive effect of pyrimidine nucleosides and their derivatives. First, it was suggested that the substitution at the N^3-position by aromatic ring was better than that by alkyl groups for exhibiting the antinociceptive effect. Second, the existence and/or configuration of a hydroxy group on the 2′- and 3′-position in the pyrimidine nucleosides affected their antinociceptive effects. It is noted that N^3-phenacyl derivatives are less active as compared with those of N^3-benzyl derivatives in N^3-substituted uridine (**1**), 6-azauridine (**4**), and arabinofuranosyluracil (**6**), but not in thymidine (**2**) and 2′-deoxyuridine (**3**) derivatives, which do not have a hydroxy group at the 2′-position in the structure. Moreover, derivatives of 2′,3′-*O*-isopropylideneuridine (**5**) had little or weak effects. These findings suggested that a hydroxy group at the 3′-position as well as the 2′-position might also be critical for the antinociceptive effect of N^3-substituted pyrimidine nucleosides. Third, the change of the base moiety in pyrimi-

dine nucleosides induced different potency of the effects. The change in oxopyrimidine ring of the nucleoside to oxo-1,2,4-triazine ring (6-azauracil) resulted in decrease in the effects, while introduction of methyl group(s) to 5 position of the pyrimidine ring produced modulation of the effects in methoxyphenacyl analogues of thymidine as compared to those of 2′-deoxyuridine. Namely, the 5-substitutional group also modifies the effects.

In addition to these three points, the position of methyl and methoxy groups onto benzyl or phenacyl groups is also an important factor for the antinociceptive effect of N^3-substituted pyrimidine nucleosides. Some of *p*- and 2′,4′- (*o*, *p*-) substituted derivatives caused seizures (data not shown), and the effects of *o*-substituted derivatives tended to be more potent than those of *m*- and *p*-substituted derivatives.

Since three N^3-dimethoxyphenacyl substituted pyrimidine nucleosides, **1l**, **3l**, and **6m**, produced more than 80% of the efffect, their potency was compared for a period of 300 min after their administrations (Fig. 1). The highest potency (93%) was noticed at 60 min after the administration of **1l**, whereas its potency was rapidly decreased thereafter. On the other hand, **6m** continued to having high potency (maximum 82%, 15 min) for 240 min after the administration, while the effect of **3l** (maximum 86%, 5 min) showed a short time duration of action as shown in Fig. 1. These results indicates that the antinociceptive effect of **6m** is the most potent of all the compounds tested.

It has become apparent that most of the N^3-substituted derivatives of arabinofuranosyluracil possessed more potent and sustained antinociceptive effect as compared with **1h**. In particular, the antinociceptive effects of N^3-methoxyphenacyl- and N^3-dimethoxyphenacyl-substituted arabinofuranosyluracil were significantly potent among the pyrimidine nucleosides derivatives tested in the present study. Thus, the effects of **6m** (0.325, 0.4, 0.5 μmol/mouse) were compared with those of morphine (1.5, 2.5, 5.0 nmol/mouse) by i.c.v. administration (Fig. 2). The compound **6m** dose-dependently showed antinociceptive effect, and the effect of **6m** at the dose of 0.5 mmol/mouse was comaprable to that of morphine at a dose of 5.0 nmol/mouse. Although the potency of **6m** was 100-folds less than that of morphine, it is of interest to find that the pyrimidne nucleoside derivative possessed the antinociceptive effect.

Further studies are now in progress to explore the mechanism of the antinociceptive effect of these pyrimidine nucleoside derivatives as well as the studies to obtain more potent compounds.

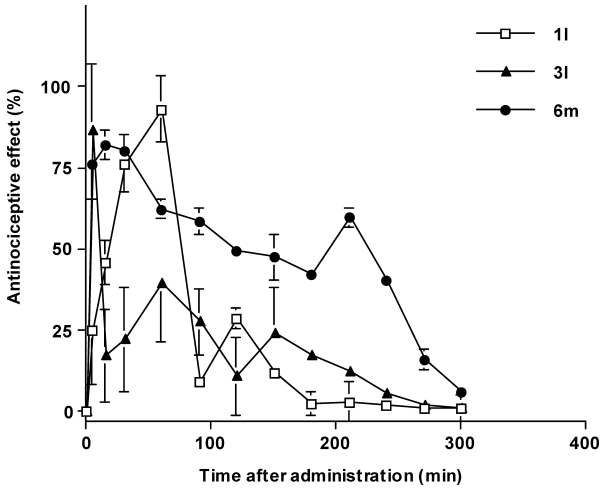


Fig. 1. Time Courses of the Antinociceptive Effects of **1l**, **3l**, and **6m** by i..c.v. Injection to Mice

The compounds, **1l** (open square), **3l** (closed triangle), and **6m** (closed circle) were administered i.c.v. by 0.5 μmol/mouse at time 0. The values are presented as the mean±S.E.M. (n=8).

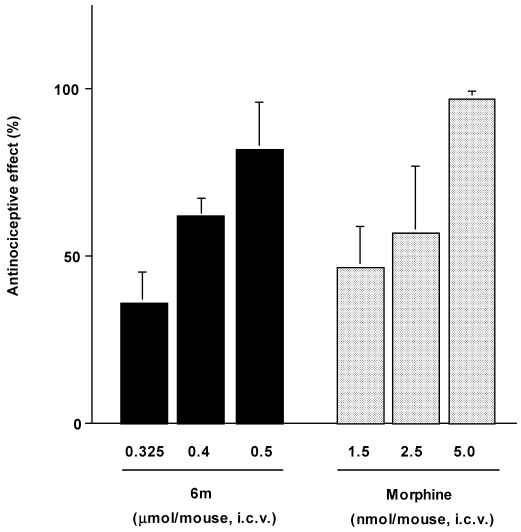


Fig. 2. Comparison of Antinociceptive Effects of **6m** and Morphine by i.c.v. Injection

The antinociceptive effects of **6m** (closed bar) and morphine (gray bar) were examined in mice by the hot plate test 15 min after the administration. The values are presented as the mean±S.E.M. (n=8).

Experimental

General Procedure Uridine (1-β-D-ribofuranosyluracil) and 2′,3′-*O*-isopropylideneuridine were purchased from Yamasa Co., Ltd. (Tokyo, Japan). Thymidine (1-(2-deoxy-β-D-ribofuranosyl)thymine) was obtained from Wako Co., Ltd. (Tokyo, Japan), and 6-azauridine (2-β-D-ribofuranosyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione), arabinofuranosyluracil (1-β-D-arabinofuranosyluracil), *o*-, *m*-, and *p*-methoxyphenacyl bromide, 2′,4′- and 2′,5′-dimethoxyphenacyl bromide were purchased from Sigma-Aldrich Co., Ltd. (St. Louis, MO, U.S.A.). 2′-Deoxyuridine (1-(2-deoxy-β-D-ribofuranosyl)uracil) and halogenated alkyls except for the reagents described above were obtained from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). Morphine hydrochloride was obtained from Takeda Pharmaceutical Co. Ltd. (Japan). N^3-Substituted derivatives of uridine, thymidine, 2′-deoxyuridine, 6-azauridine, 2′,3′-*O*-isopropylideneuridine, and arabinofuranosyluracil were synthesized according to the method of Sasaki *et al.*[17] Briefly, uridine (2 mmol) was dissolved in dimethylsulfoxide (DMSO) (3 ml) and acetone (3 ml) and was reacted with halogenated alkyls (3 mmol) in the presence of a base (K_2CO_3 3 mmol). The product was purified by silica gel column chromatography with a solvent system of chloroform–ethyl acetate–methanol (5 : 4 : 1). N^3-Methyl (**1**—**6 a**), ethyl (**1**—**6 b**), allyl (**1**—**6 c**), benzyl (**1**—**6 d**), *o*-, *m*- and *p*-xylyl (**1**—**6 e**—**g**), and phenacyl (**1**—**4 h**) substituted pyrimidine nucleosides were prepared according to the method of previously reported.[6—17] Other N^3-substituted compounds also synthesized by the method of above mentioned. The analytical data of the novel derivatives in the present study prepared were as follows:

N^3-(*o*-Methoxyphenacyl)uridine (N^3-(*o*-Methoxyphenacyl)-1-β-D-ribofuranosyluracil) (**1i**): Recrystallization solvents, acetone and *n*-hexane (3 : 1); mp 130—133 °C; yield 58%; ^{1}H-NMR (DMSO-d_6) δ: 3.71—3.84 (2H, m, 5′-H_2), 3.95—4.17 (1H, m, 2′-H), 4.28 (3H, s, OCH_3), 4.36—4.53 (1H, m, 3′-H), 5.39—5.60 (1H, m, 4′-H), 5.72 (2H, s, NCH_2), 6.20—6.33 (2H, m, 5-H, 1′-H), 7.77—8.60 (5-H, m, C_6H_4, 6-H). MS: m/z=392 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_8$: C, 55.08; H, 5.14; N, 7.14. Found: C, 54.93; H, 5.28; N, 7.09.

N^3-(*m*-Methoxyphenacyl)uridine (N^3-(*m*-Methoxyphenacyl)-1-β-D-ribofuranosyluracil) (**1j**): Recrystallization solvents, acetone and *n*-hexane

(3 : 1); mp 152—154 °C; yield 77%; ^{1}H-NMR (DMSO-d_6) δ: 3.58—4.00 (3H, m, 5′-H_2, 2′-H), 4.06 (3H, s, OCH_3), 4.23—4.38 (1H, m, 3′-H), 5.22—5.45 (1H, m, 4′-H), 5.59 (2H, s, NCH_2), 5.93—6.21 (2H, m, 5-H, 1′-H), 7.46—8.43 (5H, m, C_6H_4, 6-H). MS: m/z=392 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_8$: C, 55.08; H, 5.14; N, 7.14. Found: C, 54.96; H, 5.31; N, 6.89.

N^3-(*p*-Methoxyphenacyl)uridine (N^3-(*p*-Methoxyphenacyl)-1-β-D-ribofuranosyluracil) (**1k**): Recrystallization solvents, chloroform and *n*-hexane (5 : 1); mp 164—166 °C; yield 55%; ^{1}H-NMR (DMSO-d_6) δ: 3.63—4.16 (3H, m, 5′-H_2, 2′-H), 4.30 (3H, s, OCH_3), 4.30—4.57 (1H, m, 3′-H), 5.43—5.91 (3H, m, NCH_2, 4′-H), 6.19—6.40 (2H, m, 5-H, 1′-H), 7.41—8.65 (5H, m, C_6H_4, 6-H). MS: m/z=392 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_8$: C, 55.08; H, 5.14; N, 7.14. Found: C, 54.90; H, 5.11; N, 7.10.

N^3-(2′,4′-Dimethoxyphenacyl)uridine (N^3-(2′,4′-Dimethoxyphenacyl)-1-β-D-ribofuranosyluracil) (**1l**): Oil; yield 42%, ^{1}H-NMR (DMSO-d_6) δ: 3.40—3.47 (2H, m, 5′-H_2), 3.84 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 5.23—5.35 (4H, m, NCH_2, 2′-H, 3′-H), 5.40—5.55 (1H, m, 4′-H), 5.84—6.03 (2H, m, 1′-H, 5-H), 7.30—7.46 (3H, m, C_6H_3), 8.22 (1H, d, J=8 Hz, 6-H). MS: m/z=422 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_9$: C, 54.00; H, 5.25; N, 6.63. Found: C, 53.94; H, 5.10; N, 6.89.

N^3-(2′,5′-Dimethoxyphenacyl)uridine (N^3-(2′,5′-Dimethoxyphenacyl)-1-β-D-ribofuranosyluracil) (**1m**): Recrystallization solvents, ethanol and *n*-hexane (3 : 1); mp 163—165 °C; yield 69%; ^{1}H-NMR (DMSO-d_6) δ: 3.29—3.47 (2H, m, 5′-H_2), 3.80 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 5.08—5.51 (5H, m, NCH_2, 2′-H, 3′-H, 4′-H), 5.87—6.04 (2H, m, 1′-H, 5-H), 7.18—7.24 (3H, m, C_6H_3), 8.09 (1H, d, J=8 Hz, 6-H). MS: m/z=422 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_9$: C, 54.00; H, 5.25; N, 6.63. Found: C, 53.74; H, 4.98; N, 6.88.

N^3-Phenacylthymidine (N^3-Phenacyl-1-(2-deoxy-β-D-ribofuranosyl)thymine) (**2h**): Recrystallization solvents, ethyl acetate and *n*-hexane (1 : 5), mp 121—122 °C, yield 71%, ^{1}H-NMR (DMSO-d_6) δ: 1.88 (3H, s, CH_3), 2.03—2.37 (2H, m, 2′-H_2), 2.47—3.62 (2H, m, 5′-H_2), 3.51—3.93 (1H, m, 3′-H), 4.20—4.38 (1H, m, 4′-H), 5.18 (2H, s, NCH_2), 6.12—6.32 (1H, m, 1′-H), 7.52—8.18 (6H, m, C_6H_5, 6-H). MS: m/z=360 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_6$: C, 60.00; H, 5.56; N, 7.78. Found: C, 59.99; H, 5.59; N, 7.77.

N^3-(*o*-Methoxyphenacyl)thymidine (N^3-(*o*-Methoxyphenacyl)-1-(2-deoxy-β-D-ribofuranosyl)thymine) (**2i**): Recrystallization solvents, chloroform and *n*-hexane (1 : 4), mp 187—189 °C, yield 45%, ^{1}H-NMR (DMSO-d_6) δ: 2.24 (3H, s, 5-CH_3), 2.36—2.71 (2H, m, 2′-H_2), 3.70—3.83 (2H, m, 5′-H_2), 4.27 (3H, s, OCH_3), 4.56—4.80 (1H, m, 3′-H), 5.38—5.80 (3H, m, NCH_2, 4′-H), 6.47—6.83 (1H, m, 1′-H), 7.56—8.44 (5H, m, C_6H_4, 6-H). MS: m/z=390 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_7$: C, 58.46; H, 5.64; N, 7.18. Found: C, 58.29; H, 5.64; N, 7.10.

N^3-(*m*-Methoxyphenacyl)thymidine (N^3-(*m*-Methoxyphenacyl)-1-(2-deoxy-β-D-ribofuranosyl)thymine) (**2j**): Recrystallization solvents, chloroform and *n*-hexane (1 : 4), mp 138—140 °C, yield 50%, ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s, 5-CH_3), 2.34—2.65 (2H, m, 2′-H_2), 3.68—3.79 (2H, m, 5′-H_2), 4.23 (3H, s, OCH_3), 4.46—4.83 (1H, m, 3′-H), 5.27—5.75 (3H, m, NCH_2, 4′-H), 6.51—6.75 (1H, m, 1′-H), 7.66—8.38 (5H, m, C_6H_4, 6-H). MS: m/z=390 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_7$: C, 58.46; H, 5.64; N, 7.18. Found: C, 58.48; H, 5.72; N, 7.11.

N^3-(*p*-Methoxyphenacyl)thymidine (N^3-(*p*-Methoxyphenacyl)-1-(2-deoxy-β-D-ribofuranosyl)thymine) (**2k**): Recrystallization solvents, ethyl acetate and *n*-hexane (1 : 5), mp 164—166 °C, yield 71%, ^{1}H-NMR (DMSO-d_6) δ: 2.21 (3H, s, 5-CH_3), 2.24—2.55 (2H, m, 2′-H_2), 3.59—3.72 (2H, m, 5′-H_2), 4.20 (3H, s, OCH_3), 4.40—4.73 (1H, m, 3′-H), 5.21—5.65 (3H, m, NCH_2, 4′-H), 6.41—6.61 (1H, m, 1′-H), 7.23—7.50 (4H, m, C_6H_4), 7.86 (1H, s, 6-H). MS: m/z=390 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_7$: C, 58.46; H, 5.64; N, 7.18. Found: C, 58.80; H, 5.76; N, 7.15.

N^3-(2′,4′-Dimethoxyphenacyl)thymidine (N^3-(2′,4′-Dimethoxyphenacyl)-1-(2-deoxy-β-D-ribofuranosyl)thymine) (**2l**): Recrystallization solvents, chloroform and *n*-hexane (1 : 4), mp 167—169 °C, yield 47%, ^{1}H-NMR (DMSO-d_6) δ: 1.94 (3H, s, 5-CH_3), 2.05—2.40 (2H, m, 2′-H_2), 3.29—3.43 (2H, m, 5′-H_2), 3.94 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 5.00—5.39 (4H, m, NCH_2, 3′-H, 4′-H), 6.13—6.42 (1H, m, 1′-H), 6.62—6.87 (3H, m, C_6H_3), 7.86 (1H, d, J=6 Hz, 6-H). MS: m/z=420 (M^+). *Anal.* Calcd for $C_{20}H_{24}N_2O_8$: C, 57.14; H, 5.71; N, 6.66. Found: C, 56.77; H, 5.89; N, 6.54.

N^3-(2′,5′-Dimethoxyphenacyl)thymidine (N^3-(2′,5′-Dimethoxyphenacyl)-1-(2-deoxy-β-D-ribofuranosyl)thymine) (**2m**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 204—206 °C, yield 70%, ^{1}H-NMR (DMSO-d_6) δ: 1.83 (3H, s, CH_3), 2.26—2.37 (2H, m, 2′-H_2), 3.37—3.81 (2H, m, 5′-H_2), 3.92 (3H, m, OCH_3), 4.06 (3H, s, OCH_3), 5.03—5.42 (4H, m, NCH_2, 3′-H, 4′-H), 6.15—6.47 (1H, m, 1′-H), 6.65—6.91 (3H, m, C_6H_3), 7.96 (1H, d, J=6 Hz, 6-H). MS: m/z=420 (M^+). *Anal.* Calcd for $C_{20}H_{24}N_2O_8$: C, 57.14; H, 5.71; N, 6.66. Found: C, 56.51; H, 5.74; N, 6.56.

N^3-(*o*-Methoxyphenacyl)-2′-deoxyuridine (N^3-(*o*-Methoxyphenacyl)-1-(2-deoxy-β-D-ribofuranosyl)uracil) (**3i**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 128—131 °C, yield 58%, ^{1}H-NMR (DMSO-d_6) δ: 2.05—2.38 (2H, m, 2′-H_2), 3.24—3.41 (2H, m, 5′-H_2), 3.51—3.96 (2H, m, 3′-H, 4′-H), 4.02 (3H, s, OCH_3), 5.19 (2H, s, NCH_2), 5.84—6.00 (1H, m, 1′-H), 6.26 (1H, d, J=6 Hz, 5-H), 7.36—7.60 (4H, m, C_6H_4), 8.09 (1H, d, J=6 Hz, 6-H). MS: m/z=376 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.32; N, 7.44. Found: C, 57.54; H, 5.31; N, 7.14.

N^3-(*m*-Methoxyphenacyl)-2′-deoxyuridine (N^3-(*m*-Methoxyphenacyl)-1-(2-deoxy-β-D-ribofuranosyl)uracil) (**3j**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 136—138 °C, yield 62%, ^{1}H-NMR (DMSO-d_6) δ: 2.15—2.44 (2H, m, 2′-H_2), 2.87—2.96 (2H, m, 5′-H_2), 3.87 (3H, s, OCH_3), 4.30—4.63 (2H, m, 3′-H, 4′-H), 5.39 (2H, s, NCH_2), 5.77—5.93 (1H, m, 1′-H), 6.28 (1H, d, J=8 Hz, 5-H), 7.07—7.78 (4H, m, C_6H_4), 8.02 (1H, d, J=8 Hz, 6-H). MS: m/z=376 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.32; N, 7.44. Found: C, 57.33; H, 5.37; N, 7.32.

N^3-(*p*-Methoxyphenacyl)-2′-deoxyuridine (N^3-(*p*-Methoxyphenacyl)-1-(2-deoxy-β-D-ribofuranosyl)uracil) (**3k**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 146—148 °C, yield 42%, ^{1}H-NMR (DMSO-d_6) δ: 2.45—2.72 (2H, m, 2′-H_2), 3.59—3.83 (2H, m, 5′-H_2), 3.90—4.21 (1H, m, 3′-H), 4.31 (3H, s, OCH_3), 4.64—4.80 (1H, m, 4′-H), 5.70 (2H, s, NCH_2), 6.28—6.48 (1H, m, 1′-H), 6.62 (1H, d, J=6 Hz, 5-H), 7.41—7.65 (4H, m, C_6H_4), 8.52 (1H, d, J=8 Hz, 6-H). MS: m/z=376 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.32; N, 7.44. Found: C, 57.48; H, 5.38; N, 7.38.

N^3-(2′,4′-Dimethoxyphenacyl)-2′-deoxyuridine (N^3-(2′,4′-Dimethoxyphenacyl)-1-(2-deoxy-β-D-ribofuranosyl)uracil) (**3l**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 183—185 °C, yield 67%, ^{1}H-NMR (DMSO-d_6) δ: 2.20—2.49 (2H, m, 2′-H_2), 2.84—3.04 (2H, m, 5′-H_2), 3.60—4.09 (8H, m, $(OCH_3)_2$, 3′-H, 4′-H), 5.22 (2H, s, NCH_2), 5.71—5.93 (1H, m, 1′-H), 6.47 (1H, s, 5-H), 7.60—8.12 (5H, m, C_6H_4, 6-H). MS: m/z=406 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_8$: C, 56.15; H, 5.42; N, 6.89. Found: C, 56.21; H, 5.40; N, 6.77.

N^3-(2′,5′-Dimethoxyphenacyl)-2′-deoxyuridine (N^3-(2′,5′-Dimethoxyphenacyl)-1-(2-deoxy-β-D-ribofuranosyl)uracil) (**3m**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 168—170 °C, yield 57%, ^{1}H-NMR (DMSO-d_6) δ: 2.39—2.67 (2H, m, 2′-H_2), 3.68—3.85 (2H, m, 5′-H_2), 4.13 (3H, s, OCH_3), 4.32 (3H, s, OCH_3), 4.57—4.82 (1H, m, 3′-H), 5.30—5.71 (3H, m, NCH_2, 4′-H), 6.15—6.35 (1H, m, 1′-H), 6.59 (1H, d, J=6 Hz, 5-H), 7.54—7.72 (3H, m, C_6H_5). MS: m/z=406 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_8$: C, 56.15; H, 5.42; N, 6.89. Found: C, 56.15; H, 5.53; N, 6.88.

N^3-(*o*-Methoxyphenacyl)-6-azauridine (N^3-(*o*-Methoxyphenacyl)-2-β-D-ribofuranosyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione) (**4i**): Oil, yield 49%, ^{1}H-NMR (DMSO-d_6) δ: 3.00 (3H, s, OCH_3), 3.76—4.07 (3H, m, 2′-H, 5′-H_2), 4.28—4.70 (2H, m, 3′-H, 4′-H), 5.31 (2H, s, NCH_2), 6.16—6.25 (1H, m, 1′-H), 6.96—8.18 (5H, m, C_6H_4, 5-H). MS: m/z=393 (M^+). *Anal.* Calcd for $C_{17}H_{19}N^3O_8$: C, 51.91; H, 4.87; N, 10.68. Found: C, 51.89; H, 4.82; N, 10.64.

N^3-(*m*-Methoxyphenacyl)-6-azauridine (N^3-(*m*-Methoxyphenacyl)-2-β-D-ribofuranosyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione) (**4j**): Oil, yield 58%, ^{1}H-NMR (DMSO-d_6) δ: 2.91 (3H, s, OCH_3), 3.62—3.98 (3H, m, 2′-H, 5′-H_2), 4.25—4.80 (2H, m, 3′-H, 4′-H), 5.32 (2H, s, NCH_2), 6.07—6.24 (1H, m, 1′-H), 7.02—7.73 (4H, m, C_6H_4), 8.05 (1H, m, 5-H). MS: m/z=393(M^+). *Anal.* Calcd for $C_{17}H_{19}N_3O_8$: C, 51.91; H, 4.87; N, 10.68. Found: C, 51.85; H, 4.88; N, 10.65.

N^3-(*p*-Methoxyphenacyl)-6-azauridine (N^3-(*p*-Methoxyphenacyl)-2-β-D-ribofuranosyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione) (**4k**): Recrystallization solvents, chloroform and *n*-hexane (1 : 4), mp 128—130 °C, yield 65%, ^{1}H-NMR (DMSO-d_6) δ: 3.48 (3H, s, OCH_3), 3.85—4.03 (3H, m, 2′-H, 5′-H_2), 4.70—4.96 (1H, m, 3′-H), 5.10—5.33 (3H, m, 4′-H, NCH_2), 6.55—6.67 (1H, m, 1′-H), 7.13—8.33 (5H, m, C_6H_4, 5-H). MS: m/z=393 (M^+). *Anal.* Calcd for $C_{17}H_{19}N_3O_8$: C, 51.91; H, 4.87; N, 10.68. Found: C, 51.77; H, 4.72; N, 10.45.

N^3-(2′,4′-Dimethoxyphenacyl)-6-azauridine (N^3-(2′,4′-Dimethoxyphenacyl)-2-β-D-ribofuranosyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione) (**4l**): Oil, yield 52%, ^{1}H-NMR (DMSO-d_6) δ: 3.41 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 3.90—4.12 (3H, m, 2′-H, 5′-H_2), 4.62—4.87 (1H, m, 3′-H), 5.19 (2H, s, NCH_2) , 5.96—6.06 (1H, m, 1′-H), 5.96—6.06 (3H, m, C_6H_3), 7.97 (1H, s, 5-H). MS: m/z=423 (M^+). *Anal.* Calcd for $C_{18}H_{21}N_3O_9$: C, 51.06; H, 5.00; N, 9.92. Found: C, 50.94; H, 5.10; N, 9.89.

N^3-(2′,5′-Dimethoxyphenacyl)-6-azauridine (N^3-(2′,5′-Dimethoxyphenacyl)-2-β-D-ribofuranosyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione) (**4m**): Recrystallization solvents, methanol and *n*-hexane (1 : 3), mp 133—135 °C, yield 52%, ^{1}H-NMR (DMSO-d_6) δ: 3.38 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.87—4.16 (3H, m, 5′-H_2, 2′-H), 4.55—4.89 (1H, m, 3′-H), 5.06—5.45

(3H, m, NCH_2, 4′-H), 5.98—6.02 (1H, m, 1′-H), 7.28—7.38 (3H, m, C_6H_3), 7.91 (1H, s, 5-H). MS: m/z=423 (M^+). *Anal.* Calcd for $C_{18}H_{21}N_3O_9$: C, 51.06; H, 5.00; N, 9.92. Found: C, 50.74; H, 4.98; N, 9.88.

N^3-Phenacyl-2′,3′-*O*-isopropylideneuridine (**5h**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 163—166 °C, yield 62%, ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, s, CH_3), 1.55 (3H, s, CH_3), 3.72—3.88 (2H, m, 5′-H_2), 4.17—4.31 (1H, m, 4′-H), 4.86—4.99 (2H, m, 2′-H, 3′-H,), 5.38 (2H, s, NCH_2), 5.60—5.87 (2H, m, 1′-H, 5-H), 734—8.07 (6H, m, C_6H_5, 6-H). MS: m/z=402 (M^+). *Anal.* Calcd for $C_{20}H_{22}N_2O_7$: C, 59.70; H, 5.47; N, 6.97. Found: C, 59.64; H, 5.59; N, 6.83.

N^3-(*o*-Methoxyphenacyl)-2′,3′-*O*-isopropylideneuridine (**5i**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 181—184 °C, yield 62%, ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, s, CH_3), 1.58 (3H, s, CH_3), 3.47—3.93 (5H, m, 5′-H_2, OCH_3), 4.24—4.43 (1H, m, 4′-H), 4.81—5.00 (2H, m, 2′-H, 3′-H), 5.40 (2H, s, NCH_2), 5.81—5.95 (2H, m, 1′-H, 5-H), 7.16—7.82 (5H, m, C_6H_4, 6-H). MS: m/z=432 (M^+). *Anal.* Calcd for $C_{21}H_{24}N_2O_8$: C, 58.33; H, 5.56; N, 6.48. Found: C, 58.37; H, 5.57; N, 6.26.

N^3-(*m*-Methoxyphenacyl)-2′,3′-*O*-isopropylideneuridine (**5j**): Oil, yield 70%, ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, s, CH_3), 1.54 (3H, s, CH_3), 3.27—3.96 (5H, m, 5′-H_2, OCH_3), 4.16—4.40 (1H, m, 4′-H), 4.81—4.97 (2H, m, 2′-H, 3′-H), 5.33 (2H, s, NCH_2), 5.73—5.90 (2H, m, 1′-H, 5-H), 7.03—7.78 (5H, m, C_6H_4, 6-H). MS: m/z=432 (M^+). *Anal.* Calcd for $C_{21}H_{24}N_2O_8$: C, 58.33; H, 5.56; N, 6.48. Found: C, 58.32; H, 5.70; N, 6.44.

N^3-(*p*-Methoxyphenacyl)-2′,3′-*O*-isopropylideneuridine (**5k**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 181—184 °C, yield 63%, ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, s, CH_3), 1.54 (3H, s, CH_3), 2.16—2.20 (2H, m, 5′-H_2), 3.89—2.20 (3H, s, OCH_3), 4.17—4.34 (1H, m, 4′-H), 4.85—4.99 (2H, m, 2′-H, 3′-H), 5.31 (2H, s, NCH_2), 5.62—5.96 (2H, m, 1′-H, 5-H), 6.85—8.07 (5H, m, C_6H_4, 6-H). MS: m/z=432 (M^+). *Anal.* Calcd for $C_{21}H_{24}N_2O_8$: C, 58.33; H, 5.56; N, 6.48. Found: C, 58.23; H, 5.59; N, 6.73.

N^3-(2′,4′-Dimethoxyphenacyl)-2′,3′-*O*-isopropylideneuridine (**5l**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 144—147 °C, yield 50%, ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, s, CH_3), 1.56 (3H, s, CH_3), 2.14—2.20 (2H, m, 5′-H_2), 3.85 (6H, s, OCH_3×2), 4.16—4.37 (1H, m, 4′-H), 4.83—5.08 (2H, m, 2′-H, 3′-H), 5.32 (2H, s, NCH_2), 5.60—5.87 (2H, m, 1′-H, 5-H), 7.82—8.10 (5H, m, C_6H_4, 6-H). MS: m/z=462 (M^+). *Anal.* Calcd for $C_{22}H_{26}N_2O_9$: C, 57.13; H, 5.51; N, 6.28. Found: C, 57.14; H, 5.63; N, 6.06.

N^3-(2′,5′-Dimethoxyphenacyl)-2′,3′-*O*-isopropylideneuridine (**5m**): Recrystallization solvents, acetone and *n*-hexane (1 : 5), mp 115—118 °C, yield 48%, ^{1}H-NMR ($CDCl_3$) δ: 1.67 (3H, s, CH_3), 1.99 (3H, s, CH_3), 2.02—2.17 (2H, m, 5′-H_2), 4.13 (3H, s, OCH_3), 4.28 (3H, s, OCH_3), 4.53—4.67 (1H, m, 4′-H), 5.24—5.39 (2H, m, 2′-H, 3′-H), 5.32 (2H, s, NCH_2), 5.61—5.92 (2H, m, 1′-H, 5-H), 7.28—8.03 (6H, m, C_6H_5, 6-H). MS: m/z=462 (M^+). *Anal.* Calcd for $C_{22}H_{26}N_2O_9$: C, 57.13; H, 5.51; N, 628. Found: C, 57.14; H, 5.63; N, 6.06.

N^3-Phenacylarabinofuranosyluracil (N^3-Phenacyl-1-β-D-ribofuranosyluracil) (**6h**): Oil; yield 33%; ^{1}H-NMR (DMSO-d_6) δ: 3.22—3.66 (2H, m, 5′-H_2), 3.99—4.39 (1H, m, 4′-H), 4.56—5.15 (2H, m, 2′-H, 3′-H), 5.40 (2H, m, NCH_2), 6.11—6.22 (2H, m, 1′-H, 5-H), 7.72—7.96 (5H, m, C_6H_5), 8.10 (1H, d, J=8 Hz, 6-H). MS: m/z=362 (M^+). *Anal.* Calcd for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 5.01; N, 7.73. Found: C, 55.94; H, 5.37; N, 7.89.

N^3-(*o*-Methoxyphenacyl)arabinofuranosyluracil (N^3-(*o*-Methoxyphenacyl)-1-β-D-arabinofuranosyluracil) (**6i**): Recrystallization solvents, acetone, chloroform and *n*-hexane (1 : 3 : 2), mp 80—84 °C, yield 65%, ^{1}H-NMR (DMSO-d_6) δ: 3.43—4.23 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H_2), 3.94 (3H, s, OCH_3), 5.14 (2H, s, NCH_2), 5.47—5.75 (2H, m, 5-H, 1′-H), 6.90—7.92 (5H, m, C_6H_4, 1′-H). MS: m/z=392 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_8$: C, 55.08; H, 5.14; N, 7.14. Found: C, 54.68; H, 5.26; N, 7.09.

N^3-(*m*-Methoxyphenacyl)arabinofuranosyluracil (N^3-(*m*-Methoxyphenacyl)-1-β-D-arabinofuranosyluracil) (**6j**): Recrystallization solvents, ethanol and *cyc.*-hexane (2 : 1), mp 80—84 °C, yield 60%, ^{1}H-NMR (DMSO-d_6) δ: 3.17—4.39 (5H, m, 2′-H, 3′-H, 4′-H , 5′-H_2), 3.90 (3H, s, OCH_3), 5.38 (2H, s, NCH_2), 5.75—6.27 (2H, m, 5-H, 1′-H), 6.90—8.05 (5H, m, C_6H_4, 6-H), MS: m/z=392 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_8$: C, 55.08; H, 5.14; N, 7.14. Found: C, 54.76; H, 5.41; N, 6.75.

N^3-(*p*-Methoxyphenacyl)arabinofuranosyluracil (N^3-(*p*-Methoxyphenacyl)-1-β-D-arabinofuranosyluracil) (**6k**): Recrystallization solvents, acetone, chloroform and *n*-hexane (2 : 2 : 1), mp 168—171 °C, yield 64%, ^{1}H-NMR (DMSO-d_6) δ: 3.13—4.16 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H_2), 3.26 (3H, s, OCH_3), 4.83—6.13 (2H, m, 5-H, 1′-H), 5.21 (2H, s, NCH_2), 6.80—8.16 (5H, m, C_6H_4, 6-H). MS: m/z=392 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_8$: C, 55.08; H, 5.14; N, 7.14. Found: C, 54.91; H, 5.12; N, 7.12.

N^3-(2′,4′-Dimethoxyphenacyl)arabinofuranosyluracil (N^3-(2′,4′-Dimethoxyphenacyl)-1-β-D-arabinofuranosyluracil) (**6l**): Recrystallization solvents, ethyl acetate, chloroform and *n*-hexane (2 : 1 : 1), mp 96—100 °C, yield 42%, ^{1}H-NMR (DMSO-d_6) δ: 3.86 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 5.06 (2H, s, NCH_2) , 6.03 (1H, d, J=6 Hz, 5-H), 6.50—6.87 (3H, m, C_6H_3), 7.76 (1H, d, J=12 Hz, 6-H). MS: m/z=422 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_9$: C, 54.00; H, 5.25; N, 6.63. Found: C, 53.71; H, 5.43; N, 6.64.

N^3-(2′,5′-Dimethoxyphenacyl)arabinofuranosyluracil (N^3-(2′,5′-Dimethoxyphenacyl)-1-β-D-arabinofuranosyluracil) (**6m**): Recrystallization solvents, ethyl acetate, chloroform and *n*-hexane (2 : 1 : 1), mp 94—98 °C, yield 52%, ^{1}H-NMR (DMSO-d_6) δ: 3.37 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.30 (2H, s, NCH_2), 7.70—7.43 (3H, m, C_6H_3), 7.77 (1H, d, J=12 Hz, 6-H). MS: m/z=422 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_9$: C, 54.00; H, 5.25; N, 6.63. Found: C, 53.77; H, 5.25; N, 6.49.

Evaluation of Antinociceptive Effect Male std-ddY mice weighing 22 to 25 g were obtained from Sankyo Laboratories (Shizuoka, Japan). The mice were kept in an air-conditioned room (24±2 °C) with controlled lighting (7:00 to 19:00 light period). They were given food and water *ad libitum*. Experiments on antinociceptive effect were carried out from 8:00 and each animal was used only once. N^3-Substituted pyrimidine nucleosides were dissolved in saline containing 1% Tween 80 and administered to mice by i.c.v. injection (25 μl/mouse) according to the method of Haley and McCormick.[18] Control mice were injected by i.c.v. with 1% Tween 80-saline as a vehicle. Antinociceptive effect was assessed by placing mice on a stainless steal plate maintained at 55±2 °C.[19] The latent time for the rodent to lick its hindpaws or jump was determined before drug administration and the mean was taken as control latency. We only used the mice which had control latency of 20 s or less. The antinociceptive effect (%) was expressed as: 100×(test latency (s)−control latency (s))/(60 s−control latency (s)). The cut-off time was 60 s to avoid tissue damage.

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