Scientific Research Publishing

Pharmacology & Pharmacy, 2022, 13, 429-446
https://www.scirp.org/journal/pp
ISSN Online: 2157-9431
ISSN Print: 2157-9423

Inhibitory Effect of 5-Adenylic Acid on Bitter Taste of Antipsychotic Drugs

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How to cite this paper: Kawahara, J., Uno, R., Kojima, H., Yoshida, M., Uchida, T., Ikezaki, H. and Habara, M. (2022) Inhibitory Effect of 5-Adenylic Acid on Bitter Taste of Antipsychotic Drugs. *Pharmacology & Pharmacy*, **13**, 429-446.
https://doi.org/10.4236/pp.2022.1310032

Received: September 16, 2022
Accepted: October 28, 2022
Published: October 31, 2022

Abstract

The purpose of the present study was to examine the effect of adenylic acid (adenosine 5-monophosphate; AMP), a known nutritional enhancer, on inhibiting the bitterness of antipsychotic medicines administered to patients with mental illnesses, including children. First, we chose four antipsychotic medicines, amitriptyline hydrochloride (AMT), chlorpromazine hydrochloride (CPZ), haloperidol (HPD) and risperidone (RIS) and evaluated the inhibition of their bitterness by AMP through taste sensor measurements. AMP showed a significant bitterness inhibition effect on all drugs. Second, MarvinSketch analysis revealed the potential formation of electrostatic interactions between ionic forms (IV) of AMP and ionic (cationic) forms of each drug, which resulted in bitterness suppression. Third, chemical shift perturbations in ^{1}H-NMR studies suggested an interaction between the phosphate group of AMP and amino group of AMT, CPZ, HPD and RIS. Last, conventional elution experiments of up to 1 min simulating oral cavity conditions were performed for 1 whole AMT tablet, half AMT tablet, crushed half AMT tablet, and crushed AMT tablet containing AMP powder/solution (1, 3 mM potency). The taste sensor output values of the crushed AMT tablet containing AMP powder/solution (1, 3 mM potency) were significantly lower than those of the crushed tablet.

Keywords

Adenylic Acid, Bitterness, Antipsychotic Medicine, Amitriptyline, Chlorpromazine, Haloperidol, Risperidone, Taste Sensor, Drug-Drug Interaction

1. Introduction

Antipsychotic drugs are administered to patients with mental disorders, such as

patients with schizophrenic, including children. Regarding the administration mode of such drugs, oral dosage formulations such as crushed tablets have been used, as patients with schizophrenia have either trouble swallowing or dysphagia [1] [2] [3]. However, there have been several reports suggesting a significant increase in the perception of bitterness intensity when such formulations are used, thereby leading to poor adherence to medication [4] [5] [6] [7]. Notably, patients with mental disorders, such as schizophrenic, are typically prescribed with several types of drugs and hence have to receive large amounts of medication daily. Combined with the repeated administration of crushed tablets, this might result in behavioral changes and complete rejection of medication, which is essential for these patients [8] [9] [10].

We have previously focused on the quantitative evaluation of the bitterness range of medicine formulations using an electrical tongue as a taste sensor [11] [12] [13] [14] [15]. In our previous studies [16] [17] [18], we confirmed the bitterness of some antipsychotic medicines, such as amitriptyline hydrochloride (AMT), chlorpromazine hydrochloride (CPZ) and haloperidol (HPD).

Identifying a safe agent that could be used for the suppression of bitterness of such antipsychotic medicines, would facilitate the adherence of patients, including children [19], to their prescribed medication. In a recent study [20], using taste sensor measurements, we identified the significant bitterness suppression effect of adenylic acid (adenosine monophosphate; AMP), which was used as a nucleotide-derived nutrient enhancer on the trimethoprim (TMP) and sulfamethoxazole (SMZ) combination formulation and also evaluated the underlying inhibitory mechanism.

In the present study, we chose four types of antipsychotic medicines that have been associated with bitterness, such as AMT, CPZ and HPD, which is first generation antipsychotic drugs, and risperidone (RIS) [15], a second generation antipsychotic drug.

AMT is used for the prevention of migraine in children [21]. CPZ is widely used in patients with schizophrenia and is only available in the form of tablets for adults; it is administered to children in its crushed form [22]. HPD is a drug typically used for the treatment of schizophrenia; its bitterness was confirmed in our previous study [16]. RIS is a second generation drug used for the treatment of schizophrenia and autism spectrum disorders [23], with very low solubility (44.74 mg/L at 25˚C) [24].

In the present study, we first examined the effect of AMP in inhibiting the bitterness perception of four types of antipsychotic medicines; AMT, CPZ, HPD and RIS, as evaluated using taste sensor measurements. Second, we performed MarvinSketch analysis to clarify the electrostatic interaction between AMP and each of the four antipsychotic drugs. Third, to clarify the drug-drug interaction between AMP and each of the four antipsychotic drugs, ^{1}H-NMR experiments were performed. Last, we performed conventional elution experiments for up to 1 min, using a whole AMT tablet, half AMT tablet, whole crushed half AMT

tablet, and whole crushed AMT tablet containing AMP powder/solution (1, 3 mM potency). We examined the bitterness taste sensor output of the whole AMT tablet, half AMT tablet, whole crushed AMT tablet, and whole crushed half AMT tablet containing AMP powder/solution and evaluated the effect of adding AMP to the crushed AMT tablet formulation.

2. Materials and Methods

2.1. Materials

Adenosine 5-monophosphate (AMP) and risperidone (RIS) were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Quinine hydrochloride was purchased from Sigma Aldrich (Missouri, USA). Amitriptyline hydrochloride (AMT), chlorpromazine hydrochloride (CPZ), haloperidol (HPD), sodium chloride, and potassium chloride were purchased from Fujifilm Wako Pure Chemical Co., Ltd. (Osaka, Japan). Polyoxyethylene sorbitan monooleate was purchased from Nacalai Tesque Inc. (Tokyo, Japan). Amitriptyline hydrochloride tablets (10 mg; Tryptanol tablets) were purchased from Nichiiko Co., Ltd. (Toyama, Japan). The structure of AMT, RIS, CPZ, and HPD were shown in Figures 1(a)-(d), respectively.

2.2. Evaluation of Bitterness Inhibition effect of AMP on AMT, CPZ, HPD, and RIS Using a Taste Sensor

Briefly, we prepared 0.1 mM AMT or CPZ or HPD or RIS mixed with 0.005,

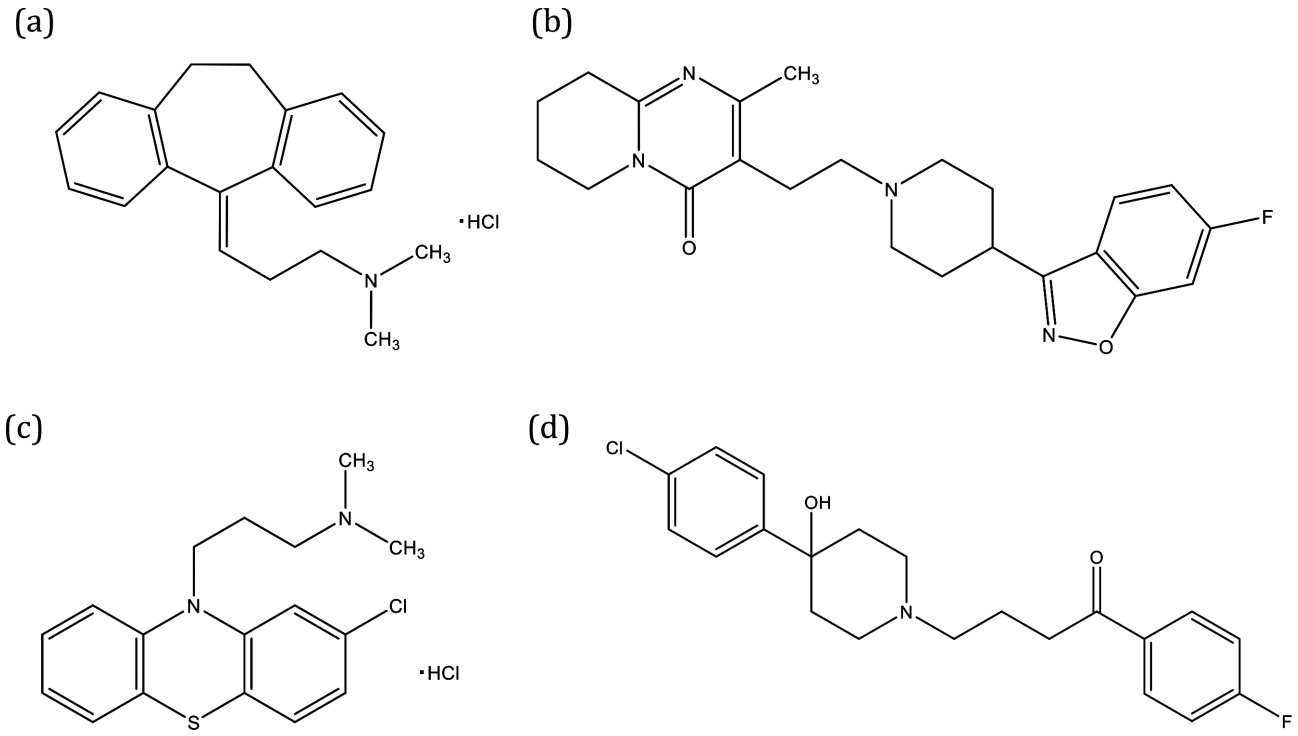


Figure 1. Chemical structures of (a) amitriptyline hydrochloride (AMT) (MW: 313.86), (b) risperidone (RIS) (MW: 410.49), (c) chlorpromazine hydrochloride (CPZ) (MW: 355.33), and (d) haloperidol (HPD) (MW: 375.86).

0.017, 0.05, or 0.15 mM AMP and measured their output values using a AC0 sensor according to previous studies [15]. Measurements using the taste sensor were performed as follows. The SA402B taste sensor (Intelligent Sensor Technology Inc., Atsugi, Japan) was used to determine the bitterness intensities of sample solutions using the AC0 sensor, developed specifically to detect the bitterness of basic substances.

Initially, a reference solution (corresponding to saliva) was measured and the electric potential obtained (mV) was defined as Vr_0. Then, a sample solution was measured and the electric potential obtained was defined as Vs. The relative sensor output (R), represented by the difference between the potentials of the sample and reference solution ($Vs - Vr_0$) corresponded to the "taste immediately after placing the sample in the mouth". The electrodes were subsequently rinsed with fresh reference solution for 6 s. When the electrode was dipped into the reference solution again, the new recorded potential was defined as Vr_1. The difference between the potentials of the reference solution before and after sample measurement ($Vr_1 - Vr_0$) was the "change in membrane potential caused by adsorption" (CPA) and corresponded to the so-called "aftertaste". The value obtained when CPA was scored by R was defined as the adsorption ratio. In this study, the CPA of AC0 (CPA AC0) was considered as the predicted bitterness intensity of the tested basic drug. The measurement of each sample was repeated 4 times and the average value of the last 3 measurements was used in data analysis [25].

2.3. Estimation of Drug Ionization

The pKa values of AMP, AMT, CPZ, HPD and RIS over the pH range of 0 - 14.0 at 298 K were calculated using MarvinSketch (Chem Axon).

2.4. ^{1}H-NMR Studies of the Interaction between AMP and AMT, CPZ, HPD or RIS

The ^{1}H-NMR spectra were measured on a JEOL 500 MHz spectrometer using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. AMP, AMT, CPZ, HPD and RIS and mixtures of AMP with AMT, CPZ, HPD or RIS were prepared as sample solutions. The mixing ratio of AMP to AMT, CPZ, HPD or RIS in the sample solution was 1, 3 and 10 by molar ratio.

2.5. Dissolution Tests of Different AMT Formulations for Up to 1 min and Determination of Bitterness through Taste Sensor Measurements

Samples, including 1 whole AMT tablet, half AMT tablet, crushed half AMT tablet and crushed half AMT tablet containing AMP powder (1, 3 mM potency) were used in the present study. The formula used as artificial saliva consisted of purified water, 1.47 g/L potassium chloride, 1.44 g/L sodium chloride, and 0.3% polyoxyethylene sorbitan monooleate [26]. The reason for testing samples of half tablets is that in Japan, 5 mg amitriptyline is often used to prevent migraines in

children [27].

In addition, the reason for testing 2 types of half tablet samples was because in clinical practice in Japan, half tablets are administered to patients to facilitate adherence to medication, with one tablet being crushed and administered as a powder equivalent to half tablet. As the AMT tablet used here does not have a score line for dividing the tablet, it was cut in half using a tablet dividing machine [28] [29]. The weight of each part of the tablet was precisely measured and confirmed to be half tablet. Tablets were pulverized according to the Japanese Pharmacopoeia and passed through a 500 μm sieve [30] [31].

The experimental procedure was as follows: In the case of 1 whole AMT tablet, half AMT tablet, crushed half AMT tablet, and crushed half AMT tablet containing AMP powder (1, 3 mM potency), each sample was gently dispersed on 20 mL [32] of artificial saliva inside a 50 mL beaker with a bottom stirrer rotating at 100 rpm/min. At 10, 30 and 60 s the whole sample suspension was filtered through a nylon mesh (N-No. 255HD, material: nylon 66, nylon fiber width 43 μm, mesh opening size 57 μm). Then, each sample was mixed with 20 mL of artificial saliva in another 50 mL beaker and measured using a taste sensor. Based on the results of past experiments in our laboratory, we adopted AC0 as the sensor.

In the case of experiments using the crushed half AMT tablet containing AMP solution (1, 3 mM potency), artificial saliva containing AMP solution (1, 3 mM potency) was used as an elution medium, with the rest of the procedure being essentially the same as mentioned above.

2.6. Statistical Analysis

BellCurve for Excel® (Social Survey Research Information Co., Ltd., Japan) was used for statistical analysis. Comparisons between groups were conducted using the Tukey's test.

3. Results and Discussion

3.1. Evaluation of Bitterness Inhibition Effect of AMP on AMT, CPZ, HPD and RIS Using the Taste Sensor

Figures 2(a)-(d) show the taste sensor output values (AC0 CPA (mV)) of AMT, CPZ, HPD and RIS (0.1 mM) containing increasing concentrations of AMP (0.005, 0.017, 0.05 and 0.15 mM). The addition of AMP significantly decreased the sensor output value of each drug compared with that of the drug without AMP. Interestingly, we observed that the bitterness inhibitory effect of AMP was greater in AMT and RIS; even though we detected a certain degree of bitterness inhibition in CPZ and HPD. We specifically found that the rate of bitterness suppression followed the order: RIS (76%) > AMT (63%) > CPZ (42%) > HPD (37%).

As shown in **Table 1**, the pH of 0.1 mM AMT, CPZ, HPD and RIS was proportionally decreased with the increasing concentration of AMP.

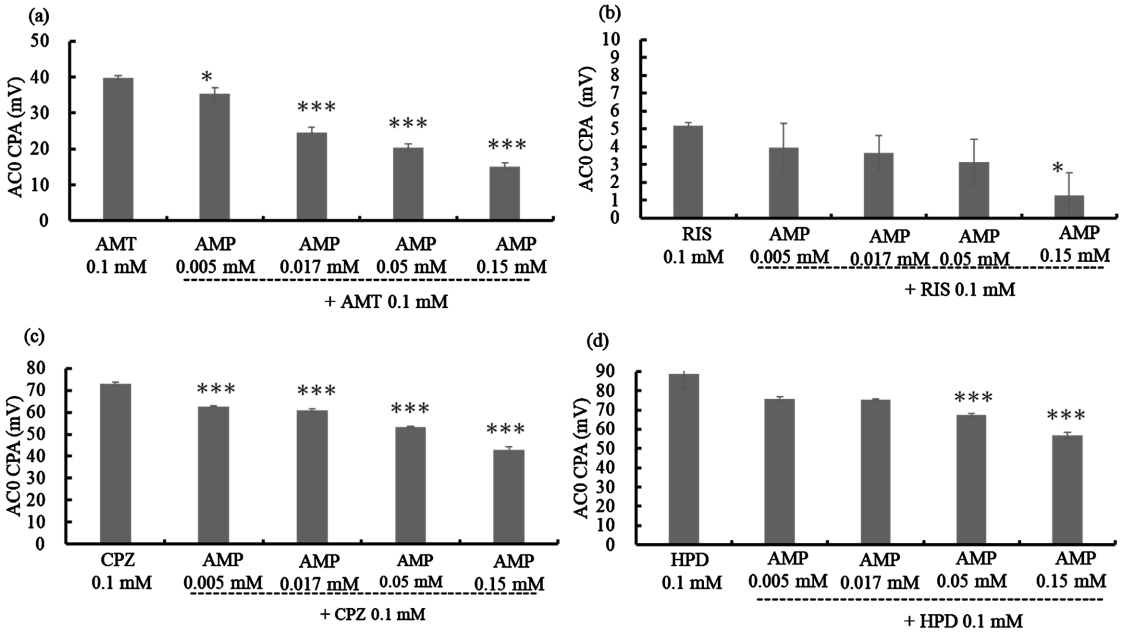


Figure 2. The influence of the nucleic acid-based umami component AMP on the taste sensor output value (AC0 CPA (mV)) of neuropsychiatric agents ((a) AMT, (b) RIS, (c) CPZ and (d) HPD. Values are given as the mean ± S.D., n = 3, *p < 0.05, ***p < 0.001 vs. each drug (0.1 mM) (Tukey's test).

Table 1. The pH values for four kinds of medicines (AMT, CPZ, HPD and RIS) containing various concentrations of AMP.

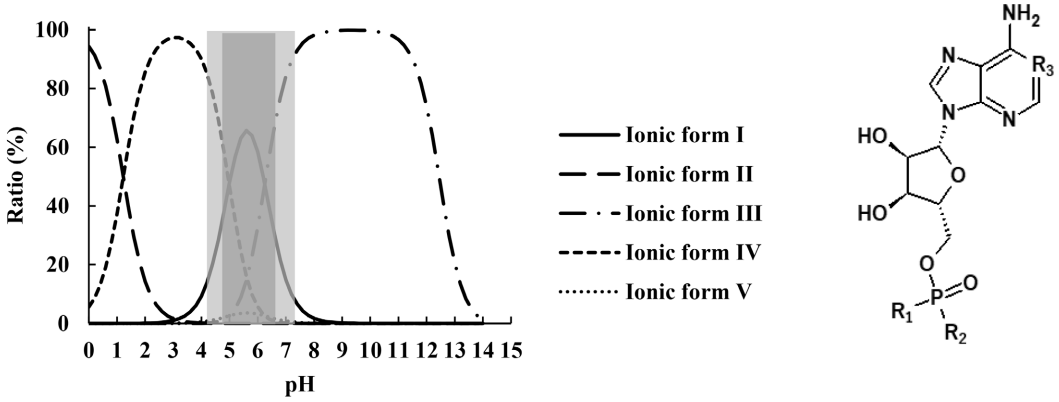
Sample	pH
AMT (0.1 mM)	6.89 ± 0.03
AMT (0.1 mM) + AMP (0.005 mM)	5.25 ± 0.03
AMT (0.1 mM) + AMP (0.017 mM)	4.98 ± 0.02
AMT (0.1 mM) + AMP (0.05 mM)	4.52 ± 0.00
AMT (0.1 mM) + AMP (0.15 mM)	4.11 ± 0.01
CPZ (0.1 mM)	6.21 ± 0.08
CPZ (0.1 mM) + AMP (0.005 mM)	5.41 ± 0.15
CPZ (0.1 mM) + AMP (0.017 mM)	5.09 ± 0.01
CPZ (0.1 mM) + AMP (0.05 mM)	4.54 ± 0.00
CPZ (0.1 mM) + AMP (0.15 mM)	4.21 ± 0.01
RIS (0.1 mM)	8.16 ± 0.01
RIS (0.1 mM) + AMP (0.005 mM)	7.64 ± 0.00
RIS (0.1 mM) + AMP (0.017 mM)	7.15 ± 0.03
RIS (0.1 mM) + AMP (0.05 mM)	6.23 ± 0.03
RIS (0.1 mM) + AMP (0.15 mM)	4.73 ± 0.04
HPD (0.1 mM)	8.01 ± 0.18
HPD (0.1 mM) + AMP (0.005 mM)	7.08 ± 0.05
HPD (0.1 mM) + AMP (0.017 mM)	6.65 ± 0.07
HPD (0.1 mM) + AMP (0.05 mM)	6.37 ± 0.04
HPD (0.1 mM) + AMP (0.15 mM)	4.63 ± 0.02

3.2. Estimation of Drug Ionization

The molecular and ionic form ratios based on pKa values over a pH range of 4.1 - 7.6, which covers all pH values at which various concentrations of AMP were added to AMT, RIS, CPZ and HPD based on MarvinSketch, and the corresponding molecular or ionic form species structures are shown in Figures 3(a)-(e), respectively.

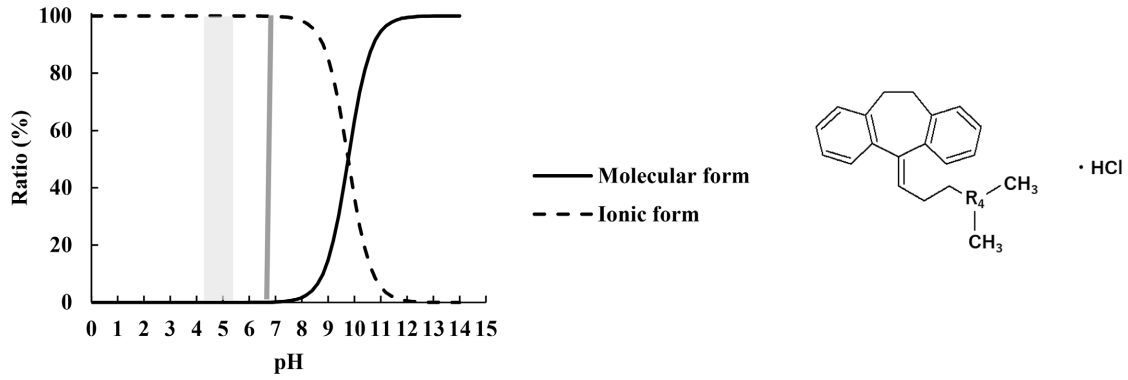
As shown in Figure 3(a), the ionized (amphipilic) form (IV) of AMP predominated at 64.0% - 87.6% at the pH range of 4.1 - 4.7, whereas the ionized (anonic) form (III) of AMP dominated at 84.1% - 95.5% at the pH range of 7.0 -

(a)

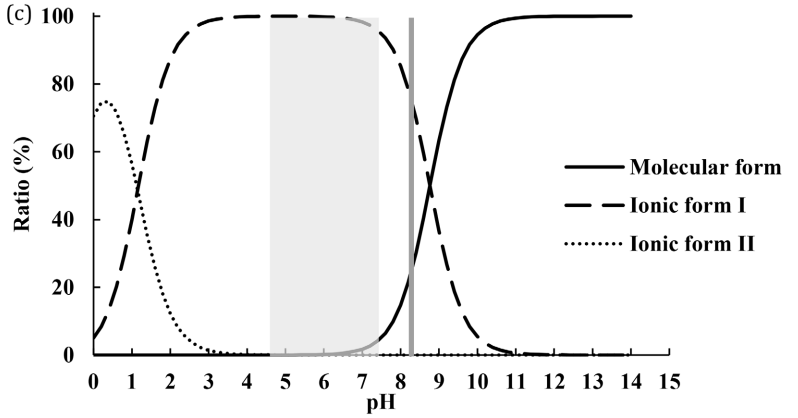


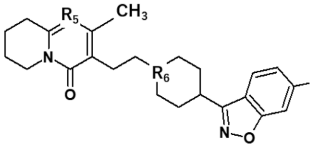
	R_1	R_2	R_3	pH 4.1	pH 4.2	pH 4.6	pH 4.7	pH 5.3	pH 5.4	pH 7.0	pH 7.6
Ionic form (I)	O^-	OH	N	11.56%	13.86%	28.38%	33.18%	60.02%	63.16%	14.97%	4.27%
Ionic form (II)	OH	OH	NH^+	0.12%	0.09%	0.03%	0.03%	0%	0%	0%	0%
Ionic form (III)	O^-	O^-	N	0.085%	0.12%	0.63%	0.99%	6.99%	8.91%	84.07%	95.48%
Ionic form (IV)	O^-	OH	NH^+	87.59%	85.15%	69.39%	63.99%	29.7%	24.47%	0.15%	0.01%
Ionic form (V)	O^-	O^-	NH^+	0.64%	0.76%	1.55%	1.82%	3.28%	3.45%	0.82%	0.23%

(b)

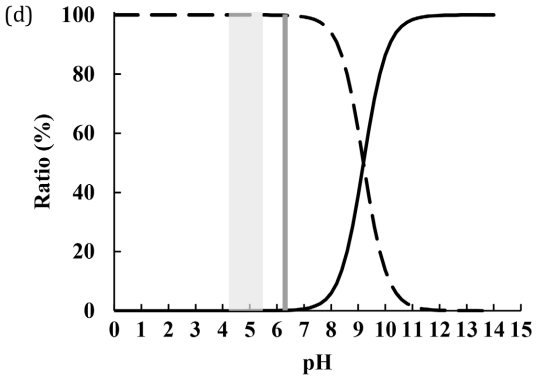


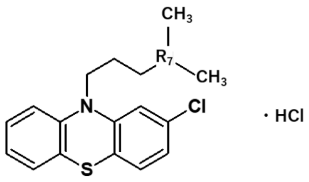
	R_4	pH 4.1	pH 5.3	pH 6.9
Molecular form	N	0%	0%	0.14%
Ionic form	NH^+	100%	100%	99.86%



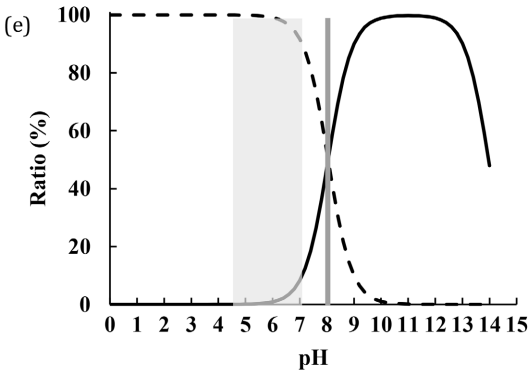


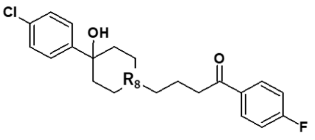
	R_5	R_6	pH 4.7	pH 7.6	pH 8.2
Molecular form	N	N	0.01%	6.43%	21.47%
Ionic form (I)	N	NH^+	99.96%	93.57%	78.53%
Ionic form (II)	NH^+	NH^+	0.03%	0%	0%





	R_7	pH 4.2	pH 5.4	pH 6.2
Molecular form	N	0%	0.02%	0.1%
Ionic form	NH^+	100%	99.98%	99.9%





	R_8	pH 4.6	pH 7.0	pH 8.0
Molecular form	N	0.04%	8.27%	47.4%
Ionic form	NH^+	99.96%	91.73%	52.6%

Figure 3. Marvin Sketch analysis of (a) AMP, (b) AMT, (c) RIS, (d) CPZ, and (e) HPD.

7.6. Figure 3(b) shows that approximately 100% of AMT existed only in its ionic (cationic) form of AMT at a pH range of 4.1 - 6.9. Additionally, the ionic (cationic) form (I) of RIS predominated at 78.5% - 100.0% at the pH range of 4.7 - 8.2 (Figure 3(c)). Likewise, the ionic (cationic) form of CPZ predominated at almost 100% at the pH range of 4.2 - 6.2, as shown in Figure 3(d). Figure 3(e) shows that the ionic (cationic) form of HPD predominated at 52.6% - 100.0% at the pH range of 4.6 - 8.0, whereas the ratio (%) of the molecular form of HPD was increased from 0.04% to 47.4% at the pH range of 4.6 - 8.0. Overall, based on our calculations using MarvinSketch, we expected that the most significant drug-drug interactions where the electrical interactions between the anionized AMP forms (IV) and cationized forms of each of the four tested drugs, that is, AMT, RIS, CPZ and HPD, respectively, and thereby give rise to bitterness inhibition in each drug.

3.3. ^{1}H-NMR Studies for Evaluation of the Interaction between AMP and AMT, RIS, CPZ or HPD

Figures 4-7 show the chemical shift of those and their corresponding assumed functions. In order to clarify the drug-drug interaction between AMP and each of AMT, RIS, CPZ and HPD, We examined the interaction of AMT with AMP and found that the 2.683 ppm dimethyl proton in AMT (Figure 4(d)) was slightly shifted downfield in an influenced the bitterness receptor binding capacity of AMT. We examined the interaction of RIS with AMP and detected that the 2.219 ppm methyl proton in RIS (Figure 5(d)) was slightly shift AMP dose-dependent manner (2.692 ppm; Figure 4(c) AMT:AMP = 1:1, 2.698 ppm; Figure 4(b) AMT:AMP = 1:3, 2.701 ppm; Figure 4(a) AMT:AMP = 1:10). We also found that 3.954 - 4.198 ppm of AMP was not shifted even if AMP was added in the sample solution. We could not confirm this interaction based on the ionization of proton movement, but we assumed that the hydrogen bond interaction between AMP and AMT ted downfield in an AMP dose-dependent manner (2.248 ppm; Figure 5(c) RIS:AMP = 1:1, 2.261 ppm; Figure 5(b) RIS:AMP = 1:3, 2.262 ppm; Figure 5(a) RIS:AMP = 1:10). Likewise, the 3.954 - 3.992 ppm methylene proton in AMP (Figure 5(e)) was slightly shifted upfield in an RIS dose-dependent manner (3.934 - 3.981 ppm; Figure 5(a) RIS:AMP = 1:10, 3.930 - 3.983 ppm; Figure 5(b) RIS:AMP = 1:3, 3.914 - 3.959 ppm; Figure 5(c) RIS:AMP = 1:1). We confirmed this interaction based on the ionization of proton movement, and assumed that the electrostatic interaction between AMP and RIS influenced the bitterness receptor binding capacity of RIS. We then examined the interaction of CPZ with AMP, as shown in Figure 6. We detected that the 2.708 ppm dimethyl proton in CPZ (Figure 6(d)) was slightly shifted downfield in an AMP dose-dependent manner (2.728 ppm; Figure 6(c) CPZ:AMP = 1:1, 2.732 ppm; Figure 6(b) CPZ:AMP = 1:3, 2.733 ppm; Figure 6(a) CPZ:AMP = 1:10). We noticed that the 3.954 - 4.198 ppm proton in AMP was not shifted even if AMP was added in the sample solution. The electron density was decreased at dimethyl proton of AMT or CPZ, and that a downfield shift occurred due to a deshielding

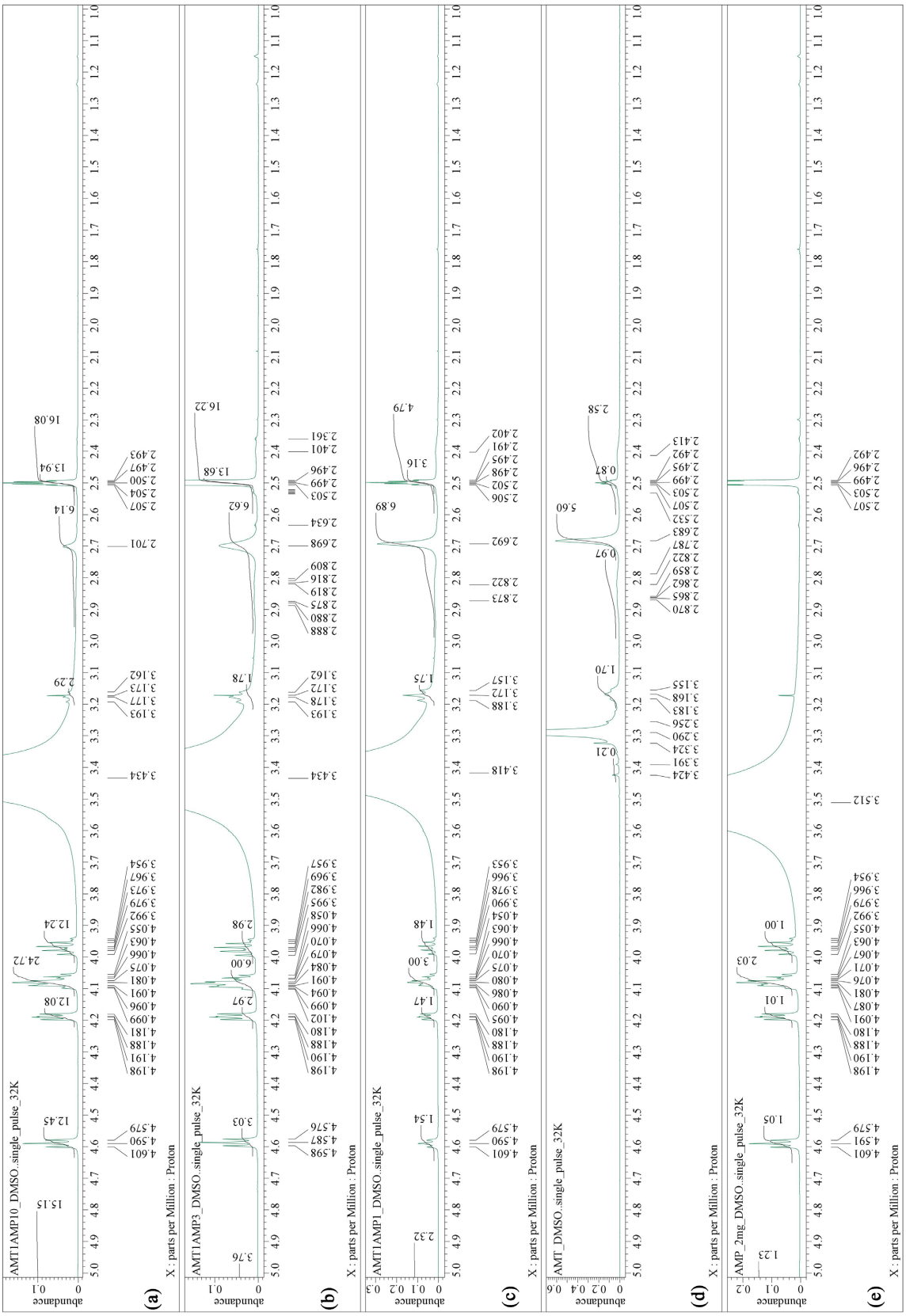


Figure 4. ^{1}H-NMR spectrum of AMP, AMT and mixture of AMT and AMP; (a) AMT: AMP = 1: 10; (b) AMT: AMP = 1: 3; (c) AMT: AMP = 1: 1; (d) AMT; (e) AMP.

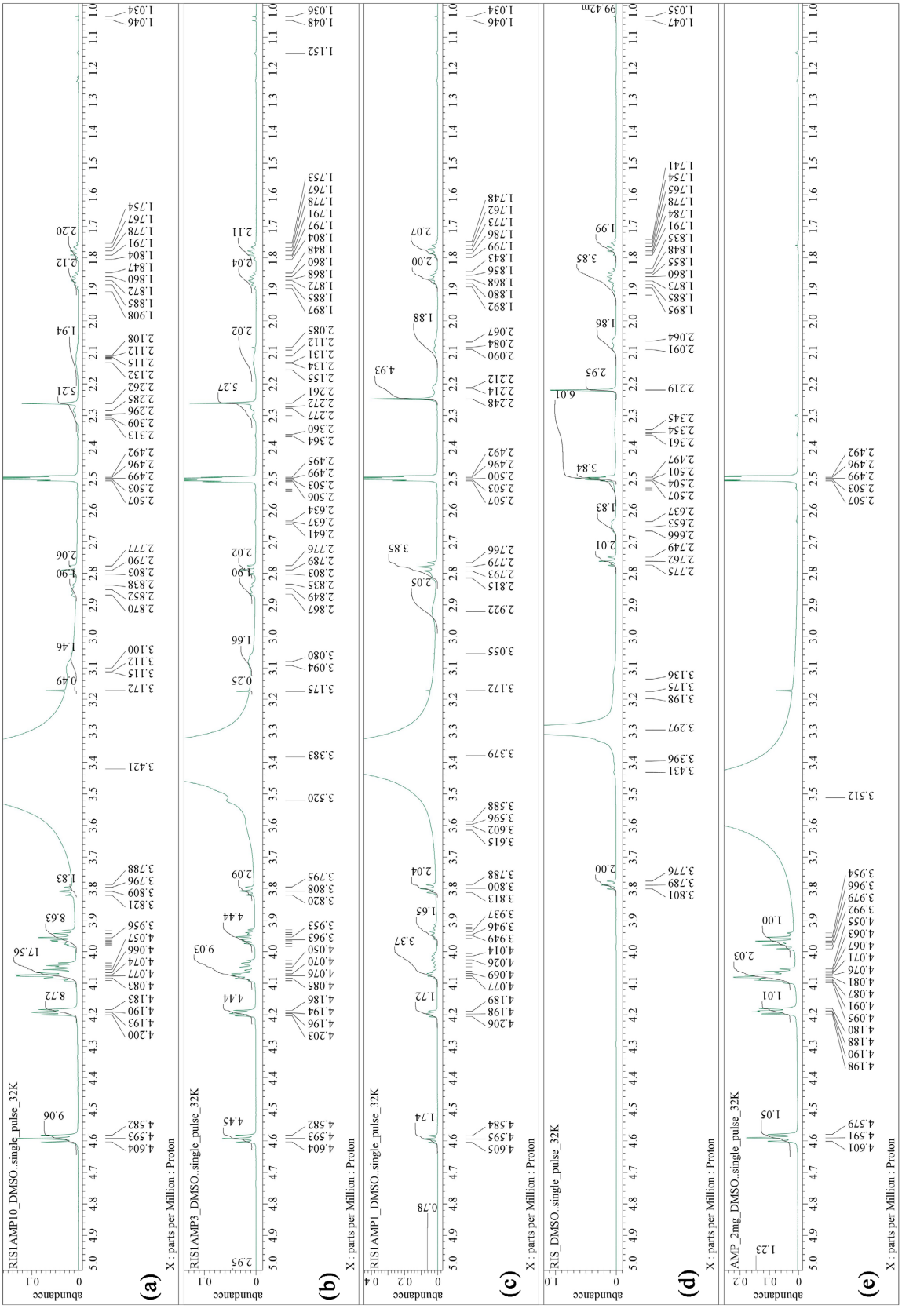


Figure 5. ^{1}H-NMR spectrum of AMP, RIS and mixture of RIS and AMP; (a) RIS: AMP = 1: 10; (b) RIS: AMP = 1: 3; (c) RIS: AMP = 1: 1; (d) RIS; (e) AMP.

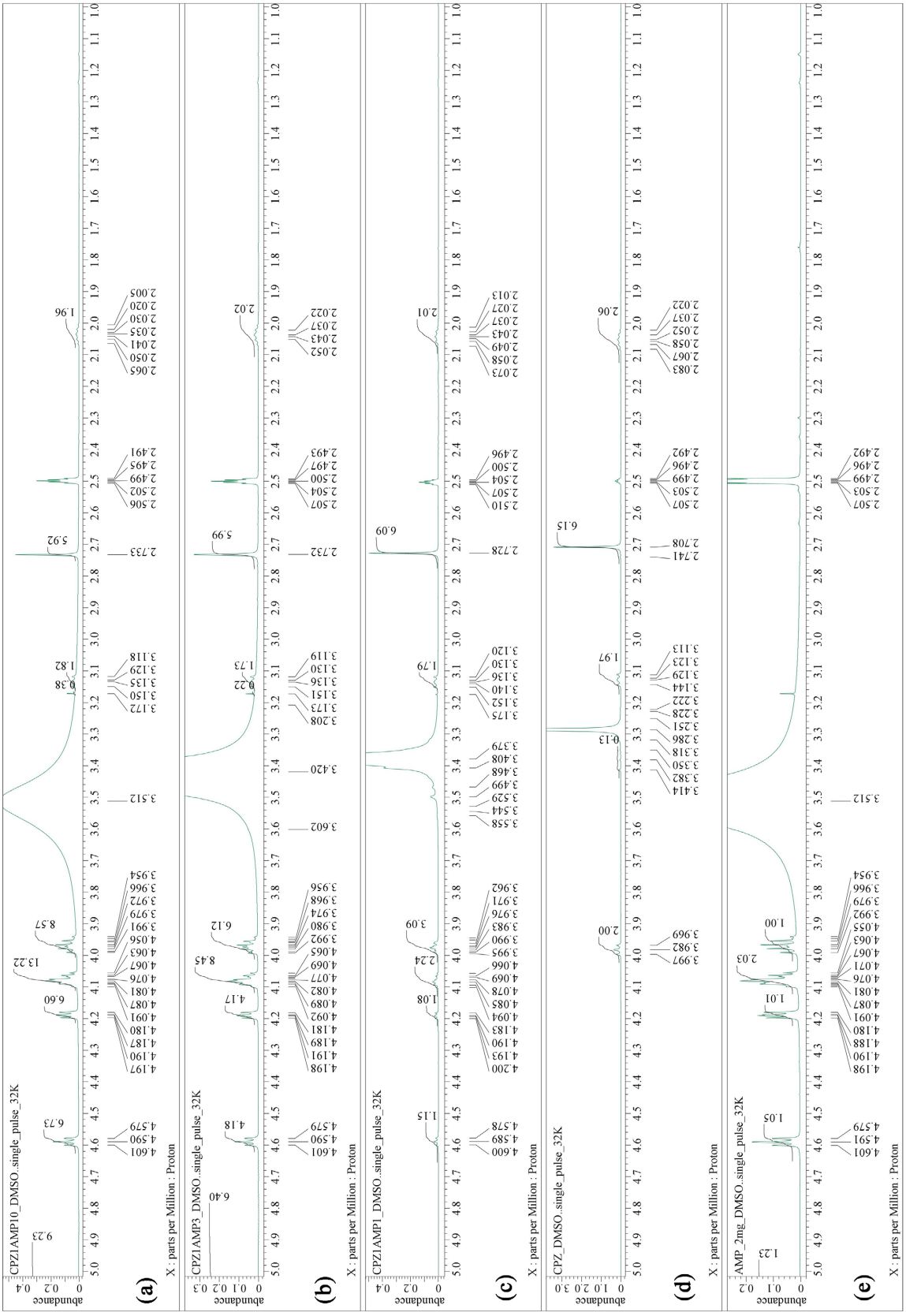


Figure 6. ^{1}H-NMR spectrum of AMP, CPZ and mixture of CPZ and AMP; (a) CPZ: AMP = 1: 10; (b) CPZ: AMP = 1: 3; (c) CPZ: AMP = 1: 1; (d) CPZ; (e) AMP.

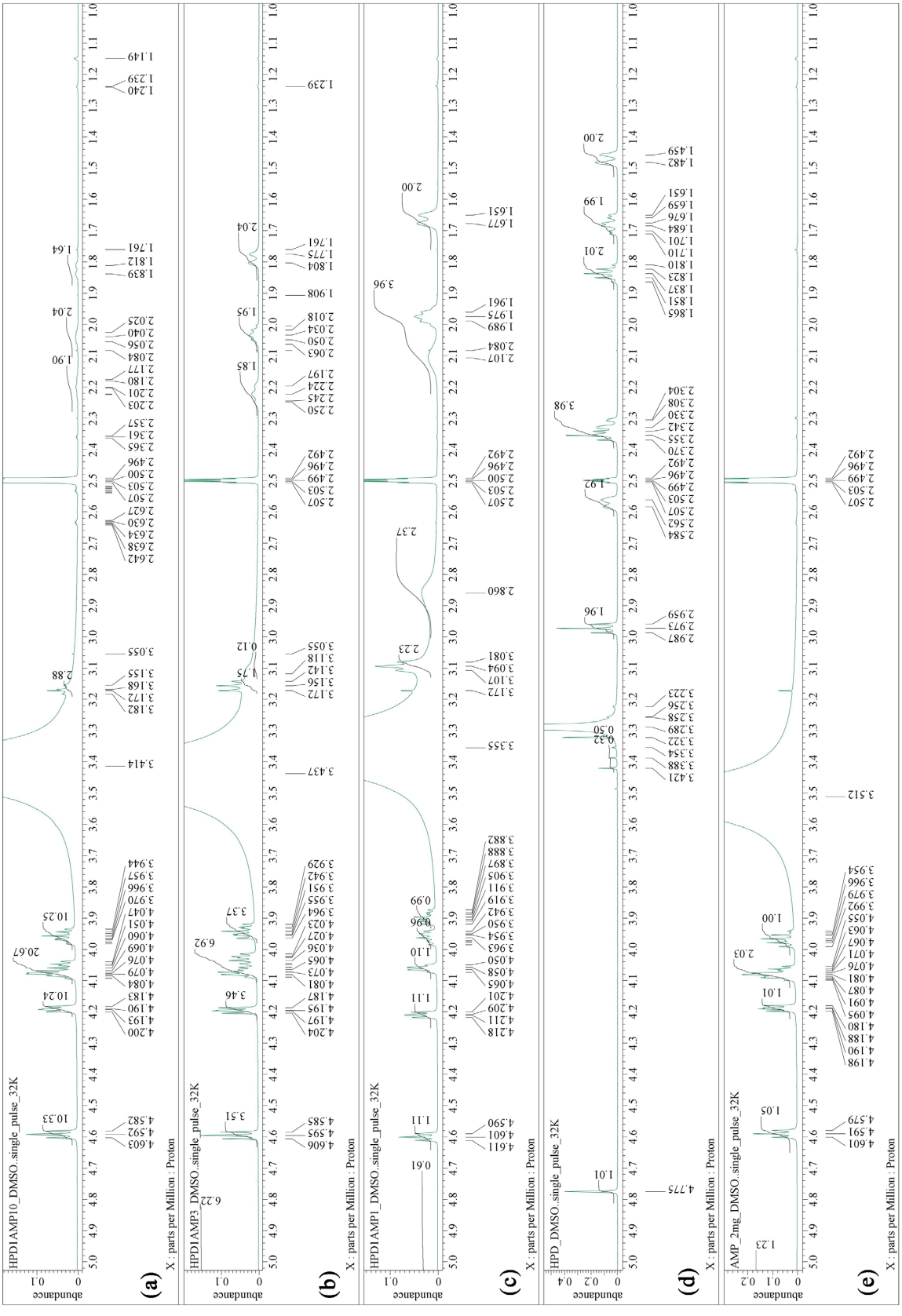


Figure 7. ^{1}H-NMR spectrum of AMP, HPD and mixture of HPD and AMP; (a) HPD: AMP = 1: 10; (b) HPD: AMP = 1: 3; (c) HPD: AMP = 1: 1; (d) HPD; (e) AMP.

effect. Both AMT and CPZ are salt compound accompanied by hydrochloric acid. Because hydrochloric acid is more potent acid than adenosine 5-monophosphate, AMT or CPZ interacts with hydrochloric acid in the vicinity of dimethyl proton in AMT or CPZ. And proton in AMP was not shifted even if AMP was added in the sample solution. We thus could not confirm the interaction based on the ionization of proton movement, but assumed that the hydrogen bond interaction between AMP and CPZ influenced the bitterness receptor binding capacity of CPZ. Finally, we examined the interaction of HPD with AMP, as shown in **Figure 7**. We observed that the 1.495 - 1.865 ppm methylene proton in HPD (**Figure 7(d)**) was slightly shifted downfield in an AMP dose-dependent manner (1.651 - 2.107 ppm; **Figure 7(c)** HPD:AMP = 1:1, 1.761 - 2.224 ppm; **Figure 7(b)** HPD:AMP = 1:3, 1.812 - 2.203 ppm; **Figure 7(a)** HPD:AMP = 1:10). In addition, we found that the 3.954 - 3.992 ppm methylene proton in AMP (**Figure 7(e)**) was slightly shifted upfield in an HPD dose-dependent manner (3.944 - 3.970 ppm; **Figure 7(a)** HPD:AMP = 1:10, 3.929 - 3.964 ppm; **Figure 7(b)** HPD:AMP = 1:3, 3.882 - 3.919 ppm; **Figure 7(c)** HPD:AMP = 1:1). We confirmed this interaction based on the ionization of proton movement, and assumed that the electrostatic interaction between AMP and HPD influenced the bitterness receptor binding capacity of HPD.

3.4. Conventional Elution Experiments of Different AMT Formulations for Up to 1 min and Determination of Bitterness through Taste Sensor Measurements

As shown in **Figure 8(a)**, the sensor output of the crushed half AMT tablet peaked at 10 s and was significantly higher than that of the whole and half AMT tablet.

Addition of AMP powder/solution (1, 3 mM potency) to crushed half AMT tablet significantly reduced the sensor output value compared with that of the crushed half AMT tablet at corresponding times, as shown in **Figure 8(b)**.

This fact suggested that adding AMP can successfully suppress the bitter taste of crushed half AMT tablet up to 1 min in the oral cavity. Accordingly, such a formulation is thereby expected to improve the adherence of many patients to such medications.

4. Conclusions

In the present study, we first chose four antipsychotic drugs, that is, AMT, CPZ, HPD and RIS, and evaluated the ability of AMP to inhibit the bitterness of each of these four through taste sensor measurements. In all drugs, AMP showed a significant bitterness inhibition effect.

MarvinSketch analysis suggested that the electrical interaction between the anionized AMP forms (IV) and cationized form of each of these four drugs, was the most significant drug-drug interaction, and thereby gave rise to bitterness inhibition.

Regarding other potential interactions of AMP with each of these four antipsychotic drugs based on the chemical shift perturbations revealed by our

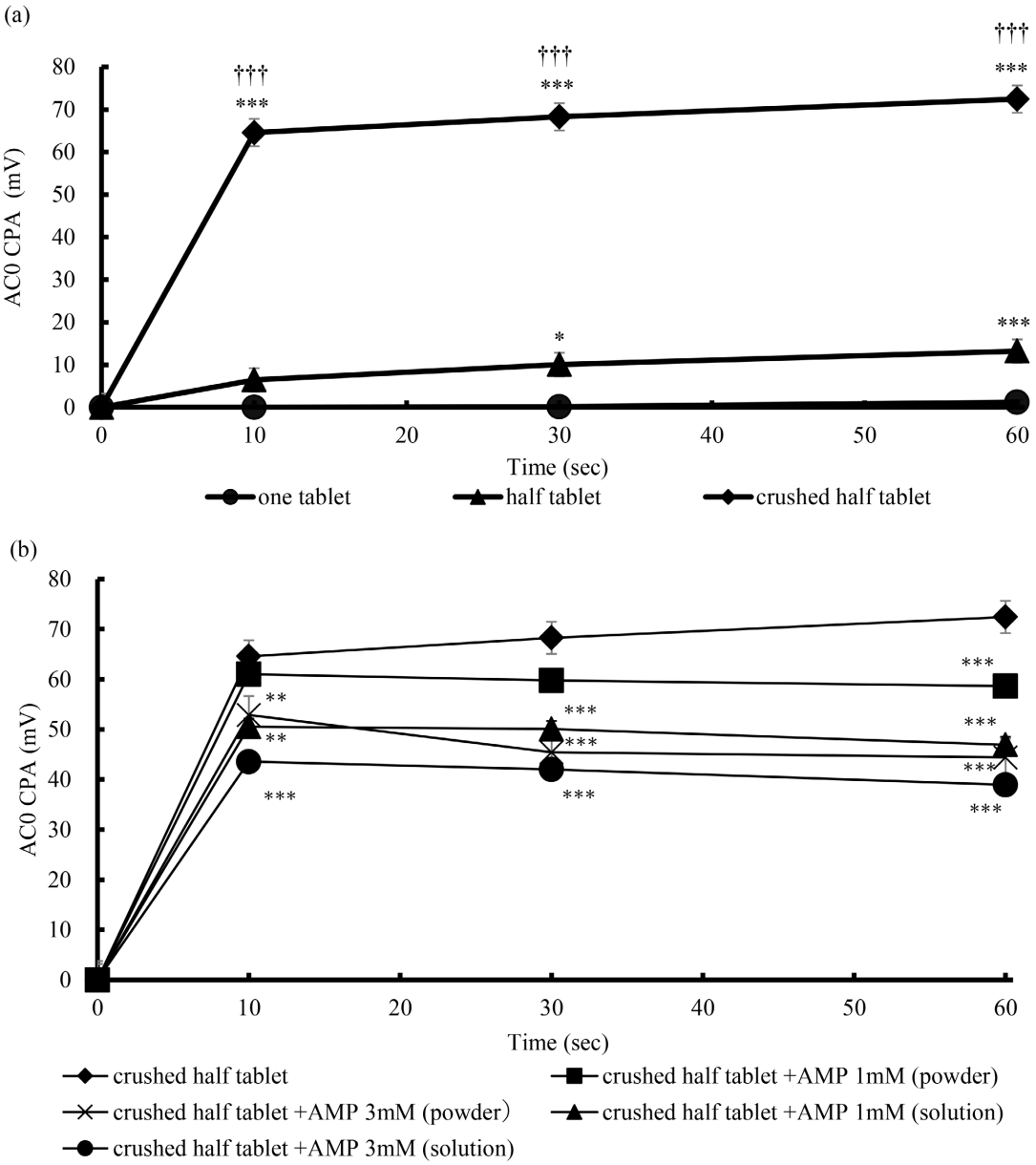


Figure 8. Taste sensor output (CPA value of AC0), time profile in dissolution test as assuming oral cavity using artificial saliva solution. (a) AMT tablet, half AMT tablet, Crushed half AMT tablet: mean ± S.D., n = 3, *p < 0.05, ***p < 0.001 vs. one tablet at the same time, †††p < 0.001 vs. half tablet at the same time (Tukey's Test), (b) Crushed half AMT tablet, Crushed half AMT tablet with AMP powder (corresponding to 1 mM/3 mM solution) or 1 mM/3 mM AMP solution: mean ± S.D., n = 3, **p < 0.01, ***p < 0.001 vs. crushed half tablet at the same time (Tukey's Test).

^{1}H-NMR study, suggested the occurrence of electrostatic interaction between AMP and RIS or HPD, and the formation of hydrogen bonds between AMP and AMT or CPZ.

Finally, in a simple dissolution test simulating oral conditions, addition of AMP powder/solution (1, 3 mM potency) into crushed half AMT tablet powder significantly reduced the sensor output value of the ground powder dissolution sample, suggesting a significant reduction in bitterness perception.

Acknowledgements

This work was supported by a JSPS KAKENHI Grant (Number 21H05006).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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