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Original paper

Synthesis and analgesic activity of 4-amino-1,2-dihydro-5-(2-hydroxyphenyl)-3*H*-pyrazol-3-ones and 5-amino-6-(2-hydroxyphenyl)pyrimidin-4(3*H*)-ones

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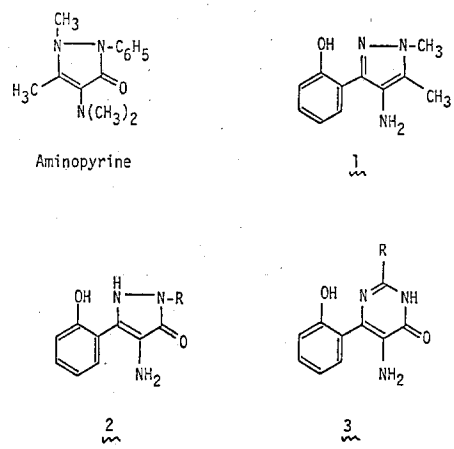
Summary — 4-Amino-1,2-dihydro-5-(2-hydroxyphenyl)-3*H*-pyrazol-3-ones **2a**—**c** and 5-amino-6-(2-hydroxyphenyl)pyrimidin-4(3*H*)-ones **3a**—**f** were synthesized from 4-methoxy- and 4-hydroxy-3-nitrocoumarins, and tested for analgesic activity upon oral administration to mice. Most of the compounds prepared exhibited analgesic activity which was superior to that of aminopyrine. In particular, **2a**—**c** and **3a**, **d** showed prominent activity which was 3—4.5 times as potent as that of aminopyrine.

Résumé — **Synthèse et activité analgésique d'amino-4 dihydro-1,2 (hydroxy-2 phényl)-5 pyrazol (3*H*)-ones-3 et d'amino-5 (hydroxy-2 phényl)-6 pyrimidin (3*H*)-ones-4.** *Les amino-4 dihydro-1,2 (hydroxy-2 phényl)-5 pyrazol(3H)-ones-3* ***2a—c*** *et les amino-5 (hydroxy-2 phényl)-6 pyrimidin(3H)-ones-4* ***3a—f*** *ont été synthétisés à partir des méthoxy-4 et hydroxy-4 nitro-3 coumarines, et leur activité analgésique a été étudiée par voie orale chez la souris. La plupart des composés ont manifesté une activité analgésique supérieure à celle de l'aminopyrine. En particulier,* ***2a—c*** *et* ***3a, d*** *ont montré une activité 3—4,5 fois plus forte que celle de l'aminopyrine.*

4-amino-1,2-dihydro-5-(2-hydroxyphenyl)-3*H*-pyrazol-3-ones / 5-amino-6-(2-hydroxyphenyl)pyrimidin-4(3*H*)-ones / analgesic activity

Introduction

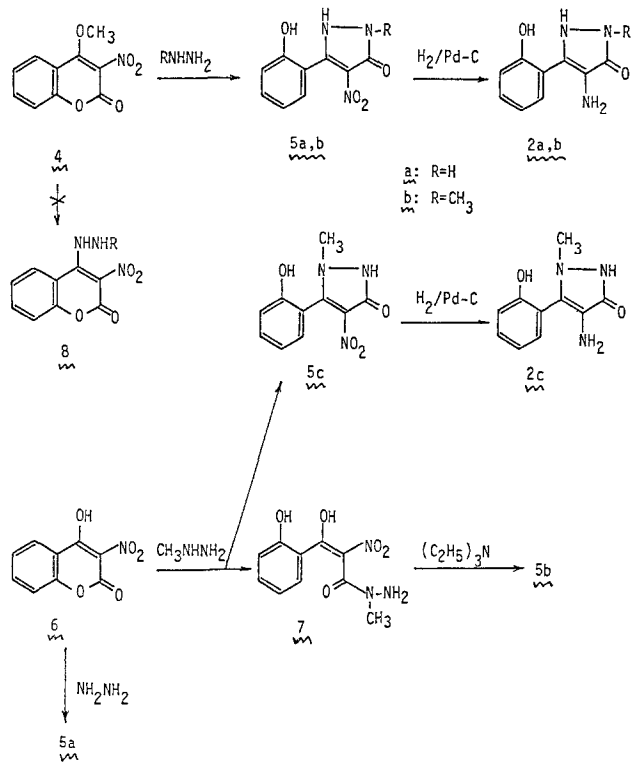
Previously, we reported [1] the synthesis and biological activities of 4-amino-3(5)-(2-hydroxyphenyl)pyrazoles, one of which, 4-amino-3-(2-hydroxyphenyl)-1,5-dimethylpyrazole **1**, exhibited potent analgesic activity in terms of the inhibition of the writhing syndrome induced by acetic acid. In continuation of our study on the structure—analgesic activity relationships in this series of compounds, we were particularly interested in the modification of type **1** pyrazoles into pyrazolone derivatives **2**, closely related to the structure of aminopyrine, and in the ring expansion of **2** to pyrimidinone structure **3** (Scheme 1). Some of the new pyrazolones and pyrimidinones synthesized in the present work were found to have more potent analgesic activity than that of the pyrazole **1** which was 2 times as active as aminopyrine upon oral administration. This paper describes the synthesis and the analgesic activity of 4-amino-1,2-dihydro-5-(2-hydroxyphenyl)-3*H*-pyrazol-3-ones **2** and 5-amino-6-(2-hydroxyphenyl)pyrimidin-4(3*H*)-ones **3**.



Scheme 1

Chemistry

It is known that certain coumarins are transformed into 5-(2-hydroxyphenyl)-3*H*-pyrazol-3-ones by reaction with hydrazines [2]. Upon application of this method, the expected pyrazolones **2** were synthesized starting from 3-nitrocoumarins as shown in Scheme 2. Treatment of 4-methoxy-3-nitrocoumarin **4** [3] with hydrazine hydrate and methylhydrazine in ethanol at room temperature for 3 h



Scheme 2

gave 1,2-dihydro-5-(2-hydroxyphenyl)-4-nitro-3*H*-pyrazol-3-one **5a** and 1,2-dihydro-5-(2-hydroxyphenyl)-2-methyl-4-nitro-3*H*-pyrazol-3-one **5b** in 70 and 51% yields, respectively. Compound **5a** was also obtained in 17% yield by heating of 4-hydroxy-3-nitrocoumarin **6** [4] with hydrazine hydrate in ethanol. Similar reaction of **6** with methylhydrazine in boiling ethanol did not afford **5b** because of the decomposition of the starting coumarin. However, when **6** was treated with methylhydrazine at room temperature for 24 h without solvent, the ring-opened methylhydrazine adduct **7** (36% yield) and 1,2-dihydro-5-(2-hydroxyphenyl)-1-methyl-4-nitro-3*H*-pyrazol-3-one **5c** (11% yield) were obtained. Compound **7** was cyclized to **5b** when heated in benzene in the presence of triethylamine. The formation of **5b** by the reaction of **4** with methylhydrazine resulted from selective attack of the secondary amino group of methylhydrazine at the 2-position of **4**. This selectivity may be due to the methoxyvinylcarbonyl moiety in **4**. (The reaction of asymmetrical 1,3-dicarbonyl compounds with methylhydrazine as a rule gives two isomeric pyrazoles, as observed in the reaction of **6** with methylhydrazine [5]. Further experiments are necessary to clarify the reaction pathway of the exclusive formation of **5b** from **4** and methylhydrazine.) It is worth noting that the reaction of **4** with hydrazines did not give 4-hydrazino-3-nitrocoumarins **8** [3] which could arise by simple condensation of the hydrazines at the 4-position of **4**. This also suggests initial attack of the hydrazines at the 2-position of **4** in the pyrazolone formation.

Compounds **5a**—**c** were reduced to the corresponding aminopyrazolones **2a**—**c** by catalytic hydrogenation over 5% Pd-C in methanol. These aminopyrazolones were isolated as hydrochlorides because the free bases were decomposed in air with red coloring. The structural assignments of **5a**—**c** and **2a**—**c** were based on elemental analysis and spectral data.

The position of the methyl group of **2b**, **c** was deduced from high resolution mass analysis as shown in Figs. 1 and 2. The mass fragmentation pattern of **2b** was quite different from that of **2c**, thus assuring the different position of the methyl group of these two isomers.

The pyrimidinones **3** were also synthesized from **4** as shown in Scheme 3. Pène *et al.* reported [6] that the coumarin **6** reacted with guanidine to give 2-amino-6-(2-hydroxyphenyl)-5-nitropyrimidin-4(3*H*)-one **9f**. However, this method

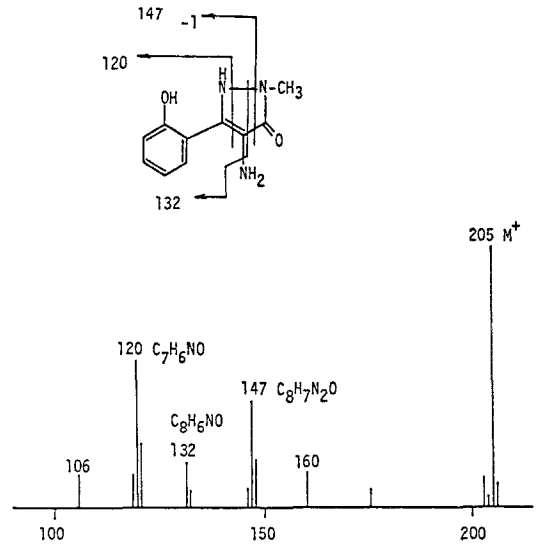


Fig. 1. MS of **2b**.

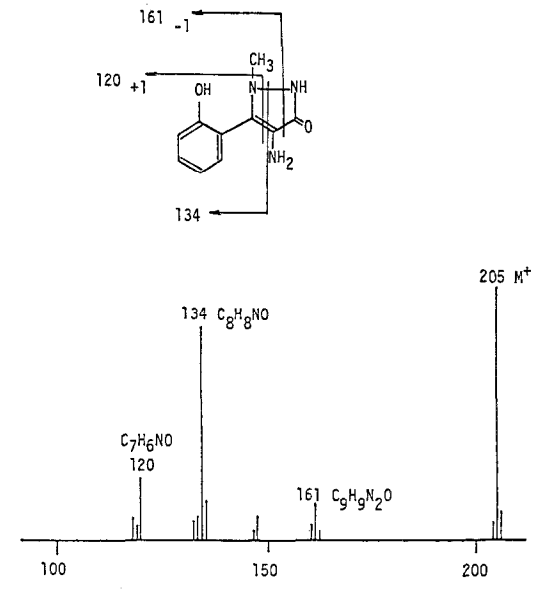
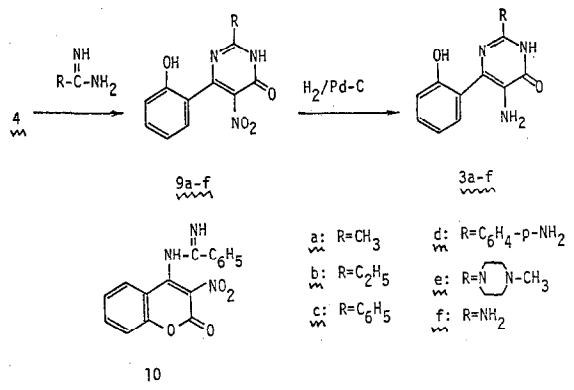


Fig. 2. MS of **2c**.



Scheme 3

was not suitable for the pyrimidinone formation when amidines were employed in place of guanidine. We therefore used **4** as a starting material, which readily gave the expected pyrimidinones by treatment with amidines. Heating of **4** with the appropriate amidine and guanidine (Scheme 3) in anhydrous ethanol for 1 h gave 2-substituted-6-(2-hydroxyphenyl)-5-nitropyrimidin-4(3H)-ones **9a—f** (Table I). Catalytic hydrogenation of these nitropyrimidines over 5% Pd-C in ethanol provided the corresponding aminopyrimidinones **3a—f** (Table II). The structures of **9a—f** and **3a—f** were determined on the basis of elemental analysis and spectral data.

Table I. 6-(2-Hydroxyphenyl)-5-nitropyrimidin-4(3H)-ones **9a—f.**

Compound	Yield (%)	mp (°C)	Formula	MS (m/z) (M^+)	(M^+-NO_2)	IR (KBr) cm^{-1}
9a	70	239-241	$C_{11}H_9N_3O_4$	247	201	1660, 1530, 1380
9b	72	196-199	$C_{12}H_{11}N_3O_4$	261	215	1660, 1535, 1360
9c	75	248-249	$C_{16}H_{11}N_3O_4$	309	263	1675, 1535, 1370
9d	33	285-288	$C_{16}H_{12}N_4O_4$	324	278	3380, 1650, 1510, 1310
9e	83	260-261	$C_{15}H_{17}N_5O_4$	331	284 **	1670, 1530, 1380
9f	81	268-270 *	$C_{10}H_8N_4O_4$	248	202	3370, 1690, 1340

* Lit. [5], mp 297°C.
** M^+—NO_2H.

Table II. 5-Amino-6-(2-hydroxyphenyl)pyrimidin-4(3H)-ones **3a—f.**

Compound	Yield (%)	mp (°C)	Formula	MS (m/e) (M^+)	IR (KBr) cm^{-1}
3a	49	252-253	$C_{11}H_{11}N_3O_2$	217	3420, 3350, 1640
3b	54	222-224	$C_{12}H_{13}N_3O_2$	231	3450, 3360, 1645
3c	38	237-238	$C_{16}H_{13}N_3O_2$	279	3370, 3250, 1640
3d	56	273-275	$C_{16}H_{14}N_4O_2$	294	3350, 3450, 1640
3e	90	232-235	$C_{15}H_{19}N_5O_2$	301	3350, 1630
3f	26	243-245	$C_{10}H_{10}N_4O_2$	218	3350, 3200, 1650.

It should be noted that in the reaction of **4** with benzamidine, 4-phenylcarbonimidoylamino-3-nitrocoumarin **10** was obtained together with the pyrimidinone **9c**. Analogous results in the reaction of 3-halo-4-methoxycoumarin with amidines were reported in our previous paper [7] and the reaction mechanisms for the formation of type **10** 4-carbonimidoylamino-coumarins and type **9** pyrimidinones were discussed therein.

Pharmacology and Discussion

The compounds **2a—c** and **3a—f** were tested for analgesic activity by oral administration *(p.o.)* in mice in terms of the inhibition of the writhing syndrome induced by acetic acid [8]. The ED_{50} which represents the dose producing 50% inhibition of writhing induced by acetic acid was determined. The ED_{50} values of the compounds tested are summarized in Table III. The pyrazolones **2a—c** showed more potent analgesic activity than **1** and aminopyrine. In particular, when compared with aminopyrine the activity of **2b** was more than 4 times greater. Replacement of the pyrazole ring in **1** by the pyrazolone nucleus resulted in an increase of the activity. The pyrimidinones **3a—f** also exhibited analgesic activity which was comparable or superior to that of aminopyrine. Among these, **3a, d** showed prominent activity which was superior to that of **1** and about 3 times as potent as that of aminopyrine. From the data shown in Table III, it is difficult to estimate the contribution of the substituent R in the compounds **2** and **3** to the activity. However, 4-amino-1,2-dihydro-5-(2-hydroxyphenyl)-3*H*-pyrazol-3-one and 5-amino-6-(2-hydroxyphenyl)pyrimidin-4(3*H*)-one appear to be interesting structures for developing new analgesic agents.

Table III. Analgesic activity.

Compound	ED_{50}, mg/kg, p.o. (95% CL)	Compound	ED_{50}, mg/kg, p.o. (95% CL)
2a *	15.8 (11.0-23.7)	3d	14.4 (11.2-18.4)
2b *	9.8 (7.5-12.1)	3e	31.6 (29.1-34.4)
2c *	12.0 (8.8-16.1)	3f	35.0 (29.7-41.1)
3a	16.5 (13.4-20.8)	1 *	20.2 (18.4-22.2)
3b	34.5 (28.7-41.8)	Aminopyrine	44.8 (38.7-51.8)
3c	39.5 (33.5-46.7)		

* Administered in the form of hydrochloride.

Experimental protocols

Chemistry

Melting points were determined using Yamato Scientific stirred liquid apparatus and are uncorrected. Analyses of all new compounds in this text were within ± 0.4% of the theoretical values for C, H and N. Nuclear magnetic resonance (^1H NMR) spectra were measured with

a Jeol-C-60H spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a Jeol-JMS-DX300 spectrometer. Infrared (IR) spectra were recorded on a JASCO A-102 spectrophotometer.

1,2-Dihydro-5-(2-hydroxyphenyl)-4-nitro-3H-pyrazole-3-ones **5a, b**
A mixture of **4** (1.1 g, 5 mmol) and hydrazine hydrate (0.75 g, 15 mmol) in ethanol (10 ml) was stirred at room temperature for 3 h. The reaction mixture was poured into water (50 ml) and the resulting solution was acidified with 10% HCl. The precipitates were collected by filtration, washed with water and recrystallized from benzene—ethanol to yield 0.84 g (70%) of **5a** as monohydrate, mp 191—192°C. IR (KBr) cm^{-1}: 3400, 1585, 1365. ^1H NMR (DMSO-d_6) δ: 7.70—7.52 (4H, m, Ph). The signals of NH and OH were not observed clearly. MS *m/z*: 221 (M^+), 175 (M^+—NO_2). Anal. $C_9H_7N_3O_4 \cdot H_2O$ = 239.2.

In the reaction of **4** with methylhydrazine under the same conditions, the reaction mixture provided a crystalline solid which was filtered and dissolved in a small quantity of water (7 ml). The resulting solution was acidified by conc. HCl and the precipitates were collected, washed with water and recrystallized from isopropanol—*n*-hexane to give 0.60 g (51%) of **5b**, mp 176—178°C. IR (KBr) cm^{-1}: 1605, 1530, 1360. ^1H NMR (DMSO-d_6) δ: 3.63 (3H, s, HCH_3); 6.70—7.50 (4H, m, Ph); 8.7—9.6 (2H, br. NH and OH). MS *m/z*: 235 (M^+), 189 (M^+—NO_2). Anal. $C_{10}H_9N_3O_4$ = 235.2.

Heating of **6** (1.0 g, 5 mmol) with hydrazine hydrate (0.75 g, 15 mmol) in ethanol (10 ml) for 5 h also gave 0.20 g (17%) of **5a**·H_2O, mp 191—192°C.

Reaction of **6** *with methylhydrazine*
A mixture of **6** (4.2 g, 20 mmol) and methylhydrazine (9.2 g, 200 mmol) was stirred at room temperature for 24 h. The reaction mixture was poured into ice water (150 ml) and the solution was acidified with 10% HCl. The precipitates were collected, washed with water and recrystallized from ethanol—water to yield 1.8 g (36%) of **7**, mp 167—167.5°C. IR (KBr) cm^{-1}: 3310, 1675, 1560. ^1H NMR (DMSO-d_6) δ: 3.17 (3H, s, NCH_3); 5.53 (2H, s, NH_2); 6.72—7.96 (4H, m, Ph); 9.6—11.8 (2H, br, 20H). MS *m/z*: 253 (M^+). Anal. $C_{10}H_{11}N_3O_5$ = 253.2.

The aqueous filtrate was concentrated under reduced pressure to give **5c**. Recrystallization from ethanol—water gave 0.5 g (11%) of pure sample, mp 187—188°C. IR (KBr) cm^{-1}: 3100, 1610, 1510, 1355. ^1H NMR (DMSO-d_6) δ: 3.38 (3H, s, NCH_3); 6.65—7.38 (4H, m. Ph); 8.7—11.9 (2H, br. NH and OH). MS *m/z*: 235 (M^+), 189 (M^+—NO_2). Anal. $C_{10}H_9N_3O_4$ = 235.2.

Cyclization of **7** *to* **5b**
A mixture of **7** (1.3 g, 5 mmol) and triethylamine (0.5 g, 10 mmol) in benzene (50 ml) was refluxed for 42 h. The reaction mixture was concentrated to give a residue which was treated with 10% HCl (50 ml). The whole was extracted with ethyl acetate and the organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to yield **5b**. Recrystallization from isopropanol—*n*-hexane gave 0.4 g (34%) of pure sample, mp 176—178°C.

2-Substituted-6-(2-hydroxyphenyl)-5-nitropyrimidin-4(3H)-ones **9a—f**
A mixture of acetamidine·HCl (1.13 g, 12 mmol) and **4** (1.11 g, 5 mmol) in an ethanolic sodium ethoxide solution (0.23 g of Na in 50 ml of anhydrous ethanol) was refluxed for 1 h. The solvent was evaporated under reduced pressure to give a residue which was treated with 5% NaOH solution (30 ml). The resulting solution was filtered to eliminate a small quantity of insoluble product. The filtrate was acidified with 10% HCl and the precipitates were collected, washed with water and recrystallized from ethanol—water to give **9a** (Table I). In a similar manner, **9b—f** were obtained by using propionamidine·HCl, benzamidine·HCl, *p*-aminobenzamidine·HCl, *N*-methylpiperazine carboxamidine·1/2 H_2SO_4 [9] and guanidine·HCl, respectively, in place of acetamidine·HCl (Table I).

In the reaction of **4** with benzamidine·HCl, the reaction mixture was concentrated under reduced pressure to give a residue which was treated with 5% NaOH solution. Precipitates were collected by filtration, washed with water and recrystallized from isopropanol—*n*-hexane to yield 0.08 g (5%) of **10**. The alkaline filtrate afforded **9c** by acidification with 10% HCl. **10**: mp 220—222°C. IR (KBr) cm^{-1}: 1700, 1523, 1370. ^1H NMR (DMSO-d_6) δ: 7.27—8.13 (11H, m, Ph and 2NH): MS *m/z*: 309 (M^+), 263 (M^+—NO_2). Anal. $C_{16}H_{11}N_3O_4$ = 309.3.

4-Amino-1,2-dihydro-5-(2-hydroxyphenyl)-3H-pyrazol-3-ones **2a—c**
A solution of **5a—c** (3 mmol) in methanol (50 ml) containing 2 ml of conc. HCl was stirred under a hydrogen atmosphere over 5% Pd-C (0.3 g) at room temperature. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give a residue which was recrystallized from ethanol—ether to yield **2a—c** as monohydrochloride.

2a·HCl·H_2O: yield 0.51 g (69%), mp 258°C (decomp.). IR (KBr) cm^{-1}: 3400, 1637. ^1H NMR (DMSO-d_6) δ: 6.71—7.59 (4H, m, Ph). The signals of NH and OH were not observed clearly. MS *m/z*: 191 (M^+). Anal. $C_9H_9N_3O_2 \cdot HCl \cdot H_2O$ = 245.7. **2b**·HCl·H_2O: yield 0.41 g (53%), mp 233°C (decomp.). IR (KBr) cm^{-1}: 3380, 3170, 1630. ^1H NMR (DMSO-d_6) δ: 3.58 (3H, s, NCH_3); 6.67—7.61 (4H, m, Ph). The signals of NH and OH were not observed clearly. MS *m/z*: 205 (M^+). Anal. $C_{10}H_{11}N_3O_2 \cdot HCl \cdot H_2O$ = 259.7. **2c**·HCl: yield 0.36 g (49%), mp 238—239°C (decomp.). IR (KBr) cm^{-1}: 3230, 1620. ^1H NMR (DMSO-d_6) δ: 3.45 (3H, s, NCH_3); 6.73—7.53 (4H, m, Ph), 7.5—11.3 (5H, br, N^+H_3, NH and OH). MS *m/z*: 205 (M^+). Anal. $C_{10}H_{11}N_3O_2 \cdot HCl$ = 241.7.

2-Substituted-5-amino-6-(2-hydroxyphenyl)pyrimidin-4(3H)-ones **3a—f**
A solution of a nitropyrimidinone (**9a—f**) in ethanol (50 ml) was stirred under a hydrogen atmosphere over 5% Pd-C (0.3 g). The reaction mixture was treated as described above. Recrystallization from ethanol (**3a, c, e**) or ethanol—water (**3b, d, f**) gave pure samples (Table II).

^1H NMR (DMSO-d_6) δ: **3a**: 2.25 (3H, s, CH_3); 4.2—4.9 (2H, br, NH_2); 6.76—7.56 (4H, m, Ph); 10.4—11.4 (1H, br, NH); 12.3—13.1 (1H, br, OH). **3b**: 1.17 (3H, t, J = 7 Hz, CH_3); 2.52 (2H, q, J = 7 Hz, CH_2); 4.1—5.3 (2H, br, NH_2); 6.60—7.63 (4H, m, Ph); 10.0—10.8 (1H, br, NH); 11.7—12.7 (1H, br, OH). **3c**: 4.1—5.8 (2H, br, NH_2); 6.82—8.33 (9H, m, Ph); 9.7—10.9 (1H, br, NH); 12.3—13.2 (1H, br, OH). **3d**: 4.2—6.3 (4H, br, $2NH_2$); 6.58—8.20 (8H, m, Ph); 10.3—13.5 (2H, br, NH and OH). **3e**: 2.17 (3H, s, CH_3); 2.17—2.53 (4H, m, protons of piperazine ring); 3.23—3.60 (4H, m, protons of piperazine ring); 5.4—10.0 (3H, br, NH and NH_2); 6.60—7.70 (4H, m, Ph); the signal of OH was not observed clearly. **3f**: 5.4—10.1 (3H, br, NH and NH_2); 6.37 (2H, br, s, NH_2); 6.74—7.82 (4H, m, Ph); 11.0—12.6 (1H, br, OH).

Biology

Acetic acid writhing assay
Groups of 6 male ICR mice weighing 20—25 g were used. The test compound, suspended in a 3% gum arabic solution, was administered orally 60 min before the intraperitoneal injection (10 mg/kg) of 0.7% acetic acid solution. The number of writhes by each mouse was counted during a period of 10—20 min after the challenge with acetic acid. The inhibition percent was calculated by comparing the number of writhes in the test group with that in the untreated control group. The ED_{50} values were estimated by the method of Litchfield and Wilcoxon [10].

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