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Synthesis and Antiulcer Activity of (Isochroman-1-yl)alkylamines. I

MASATOSHI YAMATO,* KUNIKO HASHIGAKI, SHIGETAKA ISHIKAWA, SUSUMU HITOMI, and TERUMI KOKEGUCHI

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okayama 700, Japan

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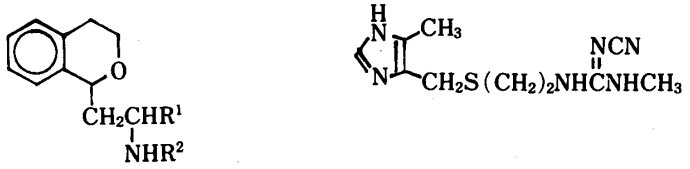
N-Benzyl-2-(isochroman-1-yl)-1-methylethylamine (**6f**), prepared by the reaction of 1-ethoxyisochroman (**4**) and acetone followed by reductive amination, was found to possess inhibitory activity against aspirin-induced ulcer but did not exhibit gastric antisecretory activity. Structural modification of **6f** was undertaken and the structure–activity relationships of the derivatives are discussed.

Keywords——isochroman; antiulcer activity; aspirin-induced ulcer; gastric antisecretory activity; structure–activity relationship

Various adrenergic agents contain a β-oxyphenethylamine moiety as an essential structure for their biological activity. *N*-Benzyl-2-(isochroman-1-yl)-1-methylethylamine (**6f**), considered to have a structural resemblance to β-oxyphenethylamines, was recently prepared, and in the biological screening of **6f**, it was found to inhibit the generation of experimental ulcers induced in rats by aspirin. However, it did not exhibit a significant gastric antisecretory activity in the pylorus-ligated rat model of Shay *et al.*

Known histamine H_2 receptor antagonists share structural features common to the prototype cimetidine molecule, *i.e.*, a thiobutyl (or oxabutyl) side chain connecting a basic or basic substituted heteroaromatic or aromatic ring to a neutral moiety incorporating a 1,3-amidino system of NH groups.[1] However, **6f** does not satisfy the above common structural requirement. Moreover, **6f** did not have gastric antisecretory activity. Structural modification of **6f** was undertaken with the aim of developing a new type of antiulcer drug. This paper describes the synthesis of *N*-substituted isochromanylalkylamines and the determination of their structure–activity relationships for gastric antisecretory activity and for inhibitory activity against aspirin-induced ulcer.



6f : $R^1=CH_3$, $R^2=CH_2C_6H_5$ cimetidine

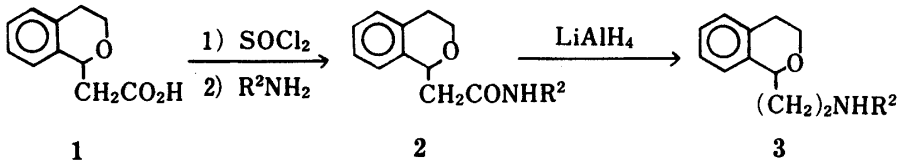
Chart 1

Chemistry

N-Substituted (R^2) (isochroman-1-yl)alkylamines (**3**, **6**—**8**, **11**, and **12**), which have an alkyl, aryl, or aralkyl group, or without a substituent at the α-position of the nitrogen atom (R^1), were prepared by three methods (A, B, and C).

Method A: *N*-Substituted 2-(isochroman-1-yl)ethylamines (**3**), without an α-substituent,

method A



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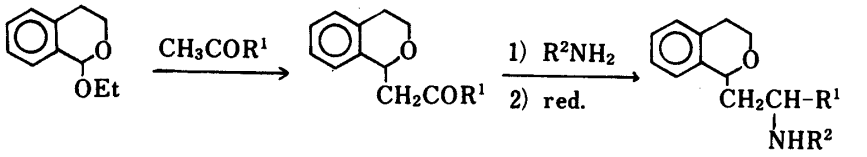
method B



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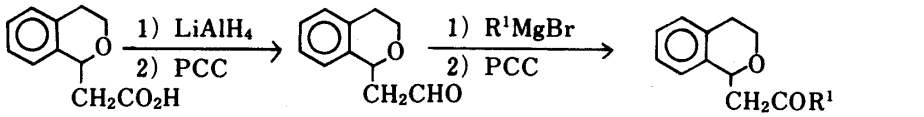
5a : $R^1=CH_3$
5b : $R^1=tert\text{-}C_4H_9$
5c : $R^1=C_6H_5$

6 : $R^1=CH_3$
7 : $R^1=tert\text{-}C_4H_9$
8 : $R^1=C_6H_5$

method C



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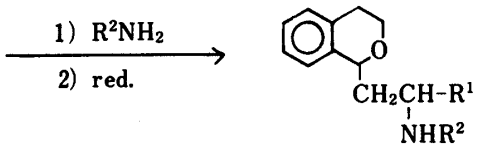
10a : $R^1=C_4H_9$
10b : $R^1=(CH_2)_2C_6H_5$



11 : $R^1=C_4H_9$
12 : $R^1=(CH_2)_2C_6H_5$

Chart 2

were prepared by the reduction of *N*-substituted (isochroman-1-yl)acetamides (**2**) with $LiAlH_4$.

Method B: Our previous study[2] on the reactivity of 1-ethoxyisochroman (**4**) showed that the reaction of **4** with active methylene compounds gives the corresponding isochroman derivatives. Ketones having one kind of active methylene group, such as acetone, acetophenone, or *tert*-butyl metyl ketone, were converted to the α-(isochroman-1-yl)methyl ketones (**5**) by heating with **4** in the presence of boron trifluoride etherate. Reduction of the Schiff's base, prepared by the reaction of **5** with the corresponding amine, was performed by the use of $NaBH_4$, $NaBH_3CN$, or $LiAlH_4$.

Method C: The reaction of **4** and ketones bearing two types of active methylene groups, such as methyl butyl ketone, and methyl phenethyl ketone, was predicted to give two kinds of nucleophilically substituted products. Therefore, the (isochroman-1-yl)methyl ketones (**10**) were prepared by the Grignard reaction of (isochroman-1-yl)acetaldehyde (**9**) followed by oxidation. The Schiff's bases, prepared by the reaction of **10** with the corresponding amines, were converted to the isochromanylalkylamines (**11** and **12**) by reduction with $NaBH_4$.

Biological Results and Discussion

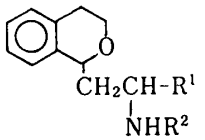
All compounds listed in Table I were tested for gastric antisercretory activity at a dose of 20 mg/kg in the pylorus-ligated rat according to Shay's method.[3] For comparison, cimetidine was tested. Compounds **6b** and **11g** showed substantial activity (>50% inhibition), but other analogues were inactive (<30% inhibition) or exhibited borderline activity. In the case of **8a**, acceleration of gastric secretion was observed, but the potency is weak.

Next, the listed compounds were tested for inhibitory activity on the generation of experimental ulcers in rats by aspirin.[4] These compounds showed remarkable variations in the activity as the substituents, R^1 and R^2, were changed.

In the compounds of type **6** with a methyl group at the α-position ($R^1 = CH_3$), variation of the *N*-substituent, R^2, remarkably influenced the activity. Compound **6e** with a phenyl group attached directly to the nitrogen atom was inactive, while **6f** and **6g**, in which a one- or two-carbon chain lies between the nitrogen atom and the benzene ring, were very much more potent than other analogues. However, elongation of the carbon chain to three carbons resulted in a loss of the activity.

Among the compounds of type **3** without an α-substituent ($R^1 = H$), *N*-methyl (**3a**) and *N*-butyl (**3c**) analogues were inactive, while *N*-benzyl (**3f**) and *N*-phenethyl (**3g**) analogues exhibited significant activity. The effect of the *N*-substituents on the potency of the activity

TABLE I. Biological Activity



Compd. No.	R^1	R^2	Antisecretory activity % inhibition of acid output in rats 20 mg/kg, i.d.	Aspirin-induced ulcer % inhibition of ulcer index in rats 20 mg/kg, *p.o.*
3a	H	CH_3	18.3[a]	10.0[a]
3c	H	C_4H_9	19.4	24.1
3f	H	$CH_2C_6H_5$	14.0	36.1
3g	H	$(CH_2)_2C_6H_5$	16.1	46.6
6a	CH_3	CH_3	23.7	38.5
6b	CH_3	iso-C_3H_7	61.0	14.6
6c	CH_3	C_4H_9	1.3	22.8
6d	CH_3	*tert*-C_4H_9	3.1	34.3
6e	CH_3	C_6H_5	23.5	−4.2
6f	CH_3	$CH_2C_6H_5$	30.1	67.3
6g	CH_3	$(CH_2)_2C_6H_5$	24.2	71.3
6h	CH_3	$(CH_2)_3C_6H_5$	24.8	26.6
7f	*tert*-C_4H_9	$CH_2C_6H_5$	23.8	18.9
7g	*tert*-C_4H_9	$(CH_2)_2C_6H_5$	−2.5	−66.4
8a	C_6H_5	CH_3	−45.9	−10.9
8c	C_6H_5	C_4H_9	38.5	22.1
8f	C_6H_5	$CH_2C_6H_5$	13.5	10.0
8g	C_6H_5	$(CH_2)_2C_6H_5$	11.8	72.7
8h	C_6H_5	$(CH_2)_3C_6H_5$	11.2	−7.9
11g	C_4H_9	$(CH_2)_2C_6H_5$	47.9	29.0
12g	$(CH_2)_2C_6H_5$	$(CH_2)_2C_6H_5$	18.4	22.0
Cimetidine			51.6[b]	84.0[c]

a) Treatments in which inhibition values were more than 30% were evaluated as significantly effective. *b*) Dose: 100 mg/kg. *c*) Dose: 30 mg/kg.

was similar to that in compounds of type **6**, but their potencies were remarkably reduced compared to those of **6**.

The results for **3** and **6** suggested that the presence or absence of the α-substituent, R^1, influenced the activity and that steric and/or physical properties of R^1 might modify the activity. In fact, change of R^1 had a drastic effect on the activity. In compounds of type **8** with a phenyl group ($R^1 = C_6H_5$), all analogues except the *N*-phenethyl analogue (**8g**) were inactive. In the case of compounds of type **7** ($R^1 = tert\text{-}C_4H_9$), **11** ($R^1 = C_4H_9$), or **12** ($R^1 = C_6H_5CH_2CH_2$), the respective *N*-phenethyl analogue was found to be inactive.

These results of variations of R^1 and R^2 suggested that the antiulcer activity of a series of isochromanylalkylamines is closely correlated to the basicity and/or steric environment of the nitrogen atom.

It has been proposed that aspirin induces gastric ulcers by disrupting the gastric mucosal barrier, resulting in the back-diffusion of acid.[5] Compounds **6f**, **6g**, and **8g** had a remarkable inhibitory activity on aspirin-induced ulcers in spite of having no gastric antisecretory activity. Moreover, an *in vitro* experiment revealed that **6f** and **6g** had no *anti*-cholinergic activity at 1×10^{-6} M. As described above, these isochromanylalkylamines do not satisfy the structural requirements for antagonistic activity on histamine H_2 receptor. In conclusion, the present results demonstrate that **6f** and **6g** are suitable as lead compounds for the development of a new type of antiulcer drug.

Experimental

Melting points (determined on Yanagimoto micromelting point apparatus) are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a Hitachi R-24 spectrometer at 60 MHz with Me_4Si. Mass spectra (MS) were measured with a Shimadzu LKB-9000 spectrometer. Infrared (IR) spectra were recorded on a Nihon Bunko A-102 spectrometer.

***N*-Methyl(isochroman-1-yl)acetamide (2a)**——A mixture of a solution of (isochroman-1-yl)acetic acid[6] (**1**; 10 g, 52 mmol) in dry benzene (95 ml) and $SOCl_2$ (17 g) was refluxed for 4 h, and the excess $SOCl_2$ and solvent were evaporated off *in vacuo* to give crude (isochroman-1-yl)acetyl chloride, which was used in the following reactions without further purification. IR ν (neat) cm^{-1}: 1800. NMR ($CDCl_3$) δ: 2.90 (2H, d, J=6 Hz, CH_2CO), 3.05—3.94 (2H, m, 4-H_2), 3.65—4.45 (2H, m, 3-H_2), 5.43 (1H, t, J=6 Hz, 1-H), 6.95—7.60 (4H, m, ArH).

The chloride (9.2 g, 44 mmol) was added to a 40% $MeNH_2$ in MeOH (100 g) containing Et_3N (4.4 g, 43 mmol) and the mixture was stirred for 4 h at room temperature, concentrated, and extracted with AcOEt. The extract was washed successively with 5% HCl, 5% $NaHCO_3$, and H_2O, dried over $MgSO_4$, and concentrated. Recrystallization of the residue from AcOEt gave **2a** (7 g, 78%), mp 116—118 °C. *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.11; H, 7.39; N, 6.72. Found: C, 70.27; H, 7.37; N, 6.82. IR ν (Nujol) cm^{-1}: 3270, 1635. NMR ($CDCl_3$) δ: 2.80 (3H, d, J=6 Hz, NHMe), 3.15—4.45 (4H, m, 3′-H_2 and 4′-H_2), 4.98—5.31 (1H, m, 1′-H), 6.36—6.79 (1H, br, NH), 7.20 (4H, s, ArH).

General Procedure for the Preparation of *N*-Alkyl(isochroman-1-yl)acetamide (2c, f, g)——A solution of (isochroman-1-yl)acetyl chloride (2.2 g, 10 mmol) in dry Et_2O (30 ml) was added to a solution of amine (12 mmol) and Et_3N (11 mmol) in dry Et_2O (40 ml). The mixture was stirred for 1 h at room temperature and then treated as described in the case of **2a**.

***N*-Butyl(isochroman-1-yl)acetamide (2c)**——Yield, 86%. mp 61—63 °C (AcOEt). *Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.01; H, 8.62; N, 5.72. IR ν (Nujol) cm^{-1}: 3280, 1630. NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6 Hz, Me), 1.02—1.58 (4H, m, $C\underline{H}_2C\underline{H}_2Me$), 2.65—3.40 (6H, m, $C\underline{H}_2CONHC\underline{H}_2$ and 4′-H_2), 5.13 (1H, t, J=6 Hz, 1′-H). MS m/z: 247 (M^+).

***N*-Benzyl(isochroman-1-yl)acetamide (2f)**——Yield, 74%. mp 121—122°C (Me_2CO). *Anal.* Calcd for $C_{18}H_{19}NO_2$: C, 76.91; H, 6.82; N, 4.94. Found: C, 76.84; H, 6.81; N, 4.98. IR ν (Nujol) cm^{-1}: 3290, 1630. NMR ($CDCl_3$) δ: 3.43—4.67 (4H, m, $C\underline{H}_2Ph$ and 3′-H_2), 6.93—7.50 (9H, m, ArH).

***N*-Phenethyl(isochroman-1-yl)acetamide (2g)**——Yield, 88%. mp 89—91 °C (Et_2O). *Anal.* Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.15; H, 7.21; N, 4.77. IR ν (Nujol) cm^{-1}: 3270, 1640. NMR ($CDCl_3$) δ: 2.56—3.01 (6H, m, $C\underline{H}_2CONHC\underline{H}_2C\underline{H}_2$), 7.19 (4H, s, ArH), 7.32 (5H, s, Ph). MS m/z: 295 (M^+).

General Procedure for the Preparation of *N*-Alkyl-2-(isochroman-1-yl)ethylamine (3)——A solution of **2** (14 mmol) in dry tetrahydrofuran (THF) (100 ml) was added to a suspension of $LiAlH_4$ (2.1 g, 55 mmol) in dry THF (200 ml). The mixture was refluxed until **2** disappeared on thin layer chromatography (TLC) and was then quenched with H_2O. The precipitate was filtered off and the filtrate was extracted with AcOEt. The extract was washed with

H_2O, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on alumina with petr. ether–AcOEt (3 : 1), followed by molecular distillation.

***N*-Methyl-2-(isochroman-1-yl)ethylamine (3a)**——Yield, 41%. Viscous oil. *Anal.* Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.21; H, 8.82; N, 7.34. IR ν (neat) cm^{-1}: 3320. NMR (CCl_4) δ: 1.79—2.12 (2H, m, CH_2CH_2NH), 2.30 (1H, s, NH), 2.35 (3H, d, J=4 Hz, NHMe), 2.49—2.89 (4H, m, CH_2CH_2NH and 4′-H_2), 3.39—4.29 (2H, m, 3′-H_2), 4.78 (1H, t, J=6 Hz, 1′-H), 7.10 (4H, s, ArH). MS *m/z*: 191 (M^+).

***N*-Butyl-2-(isochroman-1-yl)ethylamine (3c)**——Yield, 20%. Viscous oil. *Anal.* Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.28; H, 9.97; N, 5.97. IR ν (neat) cm^{-1}: 3320. NMR (CCl_4) δ: 0.92 (3H, t, J=6 Hz, Me), 1.24—1.71 (4H, m, CH_2CH_2Me), 1.36 (1H, s, NH), 1.81—2.21 (2H, m, CH_2CH_2NH), 4.80 (1H, t, J=6 Hz, 1′-H). MS *m/z*: 233 (M^+).

***N*-Benzyl-2-(isochroman-1-yl)ethylamine (3f)**——Yield, 30%. Viscous oil. *Anal.* Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.79; H, 7.97; N, 5.23. IR ν (neat) cm^{-1}: 3320. NMR (CCl_4) δ: 1.35 (1H, s, NH), 3.72 (2H, s, CH_2Ph), 4.74 (1H, t, J=6 Hz, 1′-H), 7.02 (4H, s, ArH), 7.21 (5H, s, Ph). MS *m/z*: 267 (M^+).

***N*-Phenethyl-2-(isochroman-1-yl)ethylamine (3g)**——Yield, 29%. Viscous oil. *Anal.* Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.49; H, 8.30; N, 5.01. IR ν (neat) cm^{-1}: 3290. NMR (CCl_4) δ: 1.17 (1H, s, NH), 2.30—2.95 (8H, m, $CH_2NHCH_2CH_2Ph$ and 4′-H_2), 4.76 (1H, t, J=6 Hz, 1′-H), 7.08 (4H, s, ArH), 7.21 (5H, s, Ph). MS *m/z*: 281 (M^+).

(Isochroman-1-yl)acetone (5a)——A mixture of 1-ethoxyisochroman (**4**; 40 g, 0.25 mol), dry Me_2CO (45 ml) and $BF_3 \cdot Et_2O$ (5 ml) was stirred for 20 min at 40°C and diluted with Et_2O. The Et_2O solution was washed with 5% $KHCO_3$ and H_2O, dried over $MgSO_4$, and concentrated. The residue was distilled under reduced pressure to give **5a** as a viscous oil (28.2 g, 66%), bp 118—120 °C (0.5 mmHg) [Lit.[7] bp 107—108 °C (0.5 mmHg)].

General Procedure for the Preparation of *N*-Alkyl-1-(isochroman-1-yl)-2-propylamine (6)——A solution of **5a** (4 g, 21 mmol) and an amine (63 mmol) in dry benzene (60 ml) was stirred at room temperature overnight. The mixture was diluted with absolute MeOH (50 ml), then $NaBH_4$ (1 g, 26 mmol) was added at 0 °C. The solution was stirred for 3 h at room temperature and the solvent was evaporated off. A solution of the residue in AcOEt was extracted with 10% HCl. The HCl layer was made basic with 10% NaOH and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was purified by alumina chromatography with hexane–AcOEt followed by molecular distillation to give **6**.

***N*-Isopropyl-2-(isochroman-1-yl)-1-methylethylamine (6b)**——Yield, 45%. Viscous oil. *Anal.* Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found: C, 77.39; H, 9.99; N, 6.04. IR ν (neat) cm^{-1}: 3330. NMR (CCl_4) δ: 0.90—1.31 (9H, m, $NCHMe_2$ and Me), 1.30—2.05 (4H, 1-H_2, $CHMe_2$ and NH), 2.69—3.18 (3H, m, 2-H and 4′-H_4), 3.69—4.26 (2H, m, 3′-H_2), 4.63—5.07 (1H, m, 1′-H), 7.09 (4H, s, ArH). MS *m/z*: 233 (M^+).

***N*-Butyl-2-(isochroman-1-yl)-1-methylethylamine (6c)**——Yield, 50%. Viscous oil. *Anal.* Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.59; H, 10.23; N, 5.70. IR ν (neat) cm^{-1}: 3350. NMR (CCl_4) δ: 0.85—1.20 (6H, m, 3-Me and CH_2Me), 1.62—2.02 (3H, m, 1-H_2 and NH), 2.41—3.04 (5H, m, 2-H, $NHCH_2$, and 4′-H_2). MS *m/z*: 247 (M^+).

***N*-Benzyl-2-(isochroman-1-yl)-2-propylamine (6f)**——Yield, 47%. Viscous oil. *Anal.* Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.20; N, 4.98. Found: C, 81.34; H, 8.29; N, 5.03. IR ν (neat) cm^{-1}: 3340. NMR (CCl_4) δ: 1.80, 1.13 (3H, each d, J=6 Hz, 3-Me), 1.53—2.18 (3H, m, NH and 1-H_2), 3.73 (2H, s, CH_2Ph), 4.59—5.09 (1H, m, 1′-H), 7.05 (4H, s, ArH), 7.25 (5H, s, Ph). MS *m/z*: 281 (M^+).

***N*-Methyl-2-(isochroman-1-yl)-1-methylethylamine (6a)**——A mixture of **5a** (5 g, 26 mmol) and 40% $MeNH_2$ in MeOH (4 g, 52 mmol) was stirred for 3 h at room temperature. Work-up and purification as described in the case of **6b** gave **6a** (1 g, 20%) as a viscous oil. *Anal.* Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.97; H, 9.25; N, 6.85. IR ν (neat) cm^{-1}: 3350. NMR (CCl_4) δ: 0.99, 1.05 (3H, each d, J=6 Hz, 3-Me), 1.55—2.00 (3H, m, NH and 1-H_2), 2.32, 2.34 (3H, each s, NHMe), 4.68, 4.84 (1H, each t, J=6 Hz, 1′-H), 7.04 (4H, s, ArH). MS *m/z*: 205 (M^+).

***N*-tert-Butyl-2-(isochroman-1-yl)-1-methylethylamine (6d)**——1-(Isochroman-1-yl)-2-propanol (**6d$_1$**): A solution of $NaBH_4$ (4 g, 107 mmol) in MeOH (100 ml) was added dropwise to a solution of **5a** (16.2 g, 85 mmol) in MeOH (140 ml) at 0 °C. The mixture was stirred for 2 h at room temperature and the solvent was evaporated off. The residue was extracted with AcOEt and the AcOEt layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was distilled under reduced pressure to give **6d$_1$** (15 g, 92%), bp 100—105 °C (0.03 mmHg) as a viscous oil. *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.03; H, 8.46. IR ν (neat) cm^{-1}: 3440. NMR (CCl_4) δ: 1.13, 1.17 (3H, each d, J=6.5 Hz, Me), 1.25—2.07 (2H, m, 1-H_2), 2.60—3.06 (2H, m, 4′-H_2), 3.33—3.59 (1H, br, OH), 3.62—3.89 (1H, m, 2-H), 3.92—4.31 (2H, m, 3′-H_2), 4.88, 5.00 (1H, each t, J=6 Hz, 1′-H), 7.10 (4H, s, ArH). MS *m/z*: 192 (M^+).

1-(Isochroman-1-yl)-2-propyl Bromide (**6d$_2$**): Bromine was added to a mixture of **6d$_1$** (2 g, 10 mmol), Ph_3P (3.3 g, 13 mmol) and anhydrous K_2CO_3 (2 g, 15 mmol) in dry dimethylformamide (DMF) (20 ml) at 0 °C until the orange-red color disappeared. The mixture was stirred for 1 h, poured into H_2O, and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel with petr. ether–AcOEt (10 : 1) and by distillation to give **6d$_2$** (1.84 g, 69%), bp 85—90 °C (0.03 mmHg). NMR (CCl_4) δ: 1.75, 1.81 (3H, each d, J=6 Hz, Me), 1.96—2.44 (2H, m, 1-H_2), 2.65—3.04 (2H, m, 4′-H_2), 3.49—

4.43 (3H, m, 2-H and 3′-H_2), 4.74—5.14 (1H, m, 1′-H), 7.14 (4H, s, ArH). MS *m/z*: 256 (M^++2), 254 (M^+).

6d: A mixture of **6d**$_2$ (5.1 g, 20 mmol), *tert*-butyl amine (8.8 g, 121 mmol), and anhydrous K_2CO_3 (4.1 g, 30 mmol) in dry DMF (50 ml) was stirred for 40 h at 60°C. Work-up and purification as described for **6b** gave **6d** (2 g, 41%) as a viscous oil. *Anal.* Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 6.47. Found: C, 77.81; H, 10.24; N, 6.52. IR ν (neat) cm^{-1}: 3350. NMR (CCl_4) δ: 1.01 (9H, s, CMe_3), 1.03, 1.07 (3H, each d, J=6 Hz, Me), 1.69—1.94 (2H, m, 1-H_2), 2.58—3.28 (3H, m, 2-H and 4′-H_2), 3.61—4.26 (2H, m, 3′-H_2), 4.52—4.84 (1H, m, 1′-H), 7.04 (4H, s, ArH). MS *m/z*: 247 (M^+).

***N*-Phenyl-2-(isochroman-1-yl)-1-methylethylamine (6e)**——A mixture of **5a** (3 g, 16 mmol) and aniline (2.2 g, 24 mmol) in dry benzene (50 ml) was refluxed for 4 h with removal of the water formed by azeotropic distillation, and then the solvent was removed. A solution of the residue in Et_2O (50 ml) was added to a suspension of $LiAlH_4$ (1.38 g, 36 mmol) in dry Et_2O (50 ml) at 0 °C. The mixture was stirred for 4 h at room temperature, quenched with H_2O, and made basic with 10% NaOH. The precipitate was filtered off and the filtrate was extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated. The excess aniline was distilled off and the residue was column-chromatographed on alumina with hexane–AcOEt to give **6e** (1.2 g, 29%), as a viscous oil. *Anal.* Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.91; N, 7.96; N, 5.32. IR ν (neat) cm^{-1}: 3400. NMR (CCl_4) δ: 1.34 (3H, d, J=7 Hz, Me), 1.82—2.29 (2H, m, 1-H_2), 2.72—2.82 (1H, m, 2-H), 4.49 (1H, s, NH), 6.52—6.92 (3H, m, ArH), 7.15 (4H, s, ArH), 7.02—7.52 (2H, m, ArH). MS *m/z*: 267 (M^+).

***N*-Phenethyl-2-(isochroman-1-yl)-1-methylethylamine (6g)**——A solution of **5a** (3 g, 16 mmol) and β-phenethylamine (2.8 g, 23 mmol) in dry benzene (40 ml) was stirred at room temperature overnight and the benzene was evaporated off. A solution of the residue in MeOH (40 ml) was treated with $NaBH_4$ (0.74 g, 20 mmol) and the mixture was stirred for 1 h at room temperature. Next, the solvent was evaporated off and the residue was extracted with AcOEt. The AcOEt layer was washed with H_2O and dried over $MgSO_4$. The solvent and excess β-phenethylamine were distilled off. Column chromatography on alumina with hexane–AcOEt followed by molecular distillation gave **6g** (3.7 g, 80%), as a viscous oil. *Anal.* Calcd for $C_{20}H_{25}NO$: C, 81.34; H, 8.53; N, 4.74. Found: C, 81.53; H, 8.49; N, 4.80. IR ν (neat) cm^{-1}: 3340. NMR (CCl_4) δ: 0.97, 1.07 (3H, each d, J=6 Hz, Me), 1.11 (1H, s, NH), 2.52—3.20 (7H, m, $NHC\underline{H}_2C\underline{H}_2$, 2-H, and 4′-$H_2$), 7.04 (4H, s, ArH), 7.20 (5H, s, Ph). MS *m/z*: 295 (M^+).

Similarly, *N*-(3-phenylpropyl)-2-(isochroman-1-yl)-1-methylethylamine (**6h**) was prepared in 58% yield, as a viscous oil. *Anal.* Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.80; N, 4.53. Found: C, 81.48; H, 8.82; N, 4.59. IR ν (neat) cm^{-1}: 3340. NMR (CCl_4) δ: 1.01, 1.18 (3H, each d, J=6 Hz, Me), 1.01 (1H, s, NH), 1.50—1.89 (4H, m, 2-H_2 and $C\underline{H}_2CH_2Ph$), 2.39—3.15 (7H, m, $C\underline{H}_2CH_2C\underline{H}_2Ph$, 2-H, and 3′-$H_2$), 7.08 (4H, s, ArH), 7.19 (5H, s, Ph). MS *m/z*: 309 (M^+).

***N*-Phenethyl-1-(isochroman-1-yl)-2,2-dimethylpropylamine (7g)**——A solution of $TiCl_4$[8] (0.49 g, 3 mmol) in dry benzene (6 ml) was added to a mixture of 1-(isochroman-1-yl)-3,3-dimethyl-2-butanone[2] (**5b**; 1 g, 4 mmol) and β-phenethylamine (2.1 g, 17 mmol) in dry benzene (10 ml) at 0 °C. After being stirred at room temperature overnight, the mixture was added to a solution of $NaBH_4$ (0.21 g, 6 mmol) in absolute MeOH (12 ml) at 0 °C. The mixture was stirred for 2 h at room temperature and made basic with 10% NaOH. The precipitated solid was filtered off and the filtrate was extracted with AcOEt. Subsequent procedures were the same as for **6b**, and **7g** was obtained as a viscous oil in 86% Yield. *Anal.* Calcd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 81.97; H, 9.34; N, 4.19. IR ν (neat) cm^{-1}: 3640. NMR (CCl_4) δ: 0.88, 0.93 (9H, each s, CMe_3), 1.15 (1H, s, NH), 7.12 (4H, m, ArH), 7.26 (5H, s, Ph). MS *m/z*: 337 (M^+).

Similarly, *N*-benzyl-1-(isochroman-1-yl)methyl-2,2-dimethylpropylamine (**7f**) was prepared in 50% yield, as a viscous oil. *Anal.* Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.86; H, 8.95; N, 4.34. IR ν (neat) cm^{-1}: 3360. NMR (CCl_4) δ: 0.84 (9H, s, CMe_3), 1.03 (1H, s, NH), 3.84 (2H, s, $C\underline{H}_2Ph$), 7.08 (4H, s, ArH), 7.14—7.44 (5H, m, Ph). MS *m/z*: 323 (M^+).

***N*-Methyl-2-(isochroman-1-yl)-1-phenethylamine (8a)**——A solution of α-(isochroman-1-yl)acetophenone[2b] (**5c**; 4 g, 16 mmol), $MeNH_2 \cdot HCl$ (5.36 g, 79 mmol), and $NaBH_3CN$ (1.05 g, 60 mmol) in absolute MeOH (60 ml) was stirred for 7 d at room temperature. The solvent was evaporated off, then the residue was made basic with 10% NaOH and extracted with Et_2O. The subsequent procedure was carried out as described for **6b**. Compound **8a** was obtained in 53% yield, as a viscous oil. *Anal.* Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.79; H, 7.96; N, 5.30. IR ν (neat) cm^{-1}: 3360. NMR (CCl_4) δ: 1.70 (1H, s, NH), 2.22 (3H, s, $NH\underline{Me}$), 7.04 (4H, s, ArH), 7.18 (5H, s, Ph). MS *m/z*: 267 (M^+).

***N*-Butyl-2-(isochroman-1-yl)-1-phenethylamine (8c)**——A solution of **5c** (3.5 g, 14 mmol) and butylamine (2 g, 28 mmol) in benzene was refluxed for 2 h with removal of the formed H_2O by azeotropic distillation, then the solvent was evaporated off. A solution of the residue in dry Et_2O (50 ml) was added to a suspension of $LiAlH_4$ (1.1 g, 30 mmol) in dry Et_2O and the mixture was refluxed for 5 h. Work-up and purification as described for **6b** gave **8c** (1 g, 24%) as a viscous oil. *Anal.* Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.80; N, 4.53. Found: C, 81.67; H, 8.91; N, 4.49. IR ν (neat) cm^{-1}: 3360. NMR (CCl_4) δ: 0.80—0.98 (3H, m, Me), 1.19—1.54 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 4.45 (0.69H, t, J= 6 Hz, 1′-H), 4.96 (0.31H, t, J=6 Hz, 1′-H), 6.94, 6.99 (4H, each s, ArH), 7.18—7.58 (5H, m, ArH). MS *m/z*: 309 (M^+).

Compounds **8f—h** were similarly prepared.

***N*-Benzyl-2-(isochroman-1-yl)-1-phenethylamine (8f)**——Yield, 24%. Viscous oil. *Anal.* Calcd for $C_{24}H_{25}NO$: C, 83.92; H, 7.34; N, 4.08. Found: C, 84.06; H, 7.45; N, 4.11. IR ν (neat) cm^{-1}: 3340. NMR (CCl_4) δ: 1.90 (1H, s, NH), 3.57 (2H, s, CH_2Ph), 4.49 (0.43H, t, $J=6$ Hz, 1′-H), 5.05 (0.57H, t, $J=6$ Hz, 1′-H), 7.05 (4H, s, ArH), 7.15—7.47 (10H, m, Ph×2). MS *m/z*: 343 (M^+).

***N*-Phenethyl-2-(isochroman-1-yl)-1-phenethylamine (8g)**——Yield, 20%. Viscous oil. *Anal.* Calcd for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; N, 3.92. IR ν (neat) cm^{-1}: 3350. NMR ($CDCl_3$) δ: 1.93 (1H, s, NH), 4.50 (0.5H, t, $J=6$ Hz, 1′-H), 4.97 (0.5H, t, $J\times6$ Hz, 1′-H), 7.18 (4H, s, ArH), 7.24—7.64 (10H, m, Ph×2). MS *m/z*: 357 (M^+).

***N*-(3-Phenylpropyl)-2-(isochroman-1-yl)-1-phenethylamine (8h)**——Yield, 8%. Viscous oil. *Anal.* Calcd for $C_{26}H_{29}NO$: C, 84.05; H, 7.87; N, 3.77. Found: C, 83.98; H, 7.80; N, 3.72. IR ν (neat) cm^{-1}: 3360. NMR (CCl_4) δ: 1.28 (1H, s, NH), 4.75—5.14 (1H, m, 1′-H), 6.76—7.41 (14H, m, ArH). MS *m/z*: 237 (M^+-134).

(Isochroman-1-yl)acetoaldehyde (9)——2-(Isochroman-1-yl)ethanol: A solution of **1** (33.5 g, 175 mmol) in dry THF (150 ml) was added to a suspension of $LiAlH_4$ (13.2 g, 348 mmol) in dry THF (350 ml) at 0 °C, and the mixture was refluxed for 3 h. Usual work-up gave a crude product, which was distilled under reduced pressure to give 2-(isochroman-1-yl)ethanol, bp 95 °C (0.02 mmHg), as an oil. *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 81.44; H, 8.70. Found: C, 81.69; H, 8.75. IR ν (neat) cm^{-1}: 3400. NMR (CCl_4) δ: 1.81—2.16 (2H, m, CH_2CH_2OH), 3.60—4.25 (5H, m, CH_2OH and 3′-H_2), 4.68—4.92 (1H, m, 1′-H), 7.09 (4H, s, ArH). MS *m/z*: 178 (M^+).

9: A solution of 2-(isochroman-1-yl)ethanol (8 g, 45 mmol) in dry CH_2Cl_2 (10 ml) was added to a solution of pyridine chlorochromate (PCC; 19.3 g, 90 mmol) in dry CH_2Cl_2 (110 ml). The mixture was stirred for 2 h at room temperature and usual work-up gave a crude product, which was column chromatographed on silica gel with hexane–AcOEt to give **9** (3.7 g, 47%) as an oil. *Anal.* Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 75.09; H, 6.93. IR ν (neat) cm^{-1}: 1722. NMR (CCl_4) δ: 2.75 (2H, dd, $J=2.5$, 6 Hz, CH_2CHO), 5.21 (1H, t, $J=6$ Hz, 1′-H), 7.06 (4H, s, ArH), 9.72 (1H, t, $J=2.5$ Hz, CHO). MS *m/z*: 176 (M^+).

1-(Isochroman-1-yl)-2-hexanone (10a)——1-(Isochroman-1-yl)-2-hexanol: A solution of **9** (5.3 g, 30 mmol) in dry THF (26 ml) was added to a solution of butylmagnesium bromide (36 mmol) in dry THF (49 ml). The mixture was stirred for 2 h at room temperature. Usual work-up followed by column chromatography on silica gel with hexane–AcOEt gave 1-(isochroman-1-yl)-2-hexaol (6 g, 86%) as a viscous oil. IR ν (neat) cm^{-1}: 3460. NMR (CCl_4) δ: 3.14—3.35 (1H, br, OH), 4.71—5.11 (1H, m, 1′-H), 7.10 (4H, s, ArH). MS *m/z*: 234 (M^+).

10a: Preparation and purification were carried out as described for **9**. Yield, 93%. Viscous oil. *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.89; H, 8.61. IR ν (neat) cm^{-1}: 1710. NMR (CCl_4) δ: 2.55 (2H, t, $J=6$ Hz, 3-H_2), 2.77 (2H, d, $J=6.5$ Hz, 1-H_2), 5.18 (1H, t, $J=6.5$ Hz, 1′-H), 7.10 (4H, s, ArH). MS *m/z*: 232 (M^+).

1-(Isochroman-1-yl)-4-phenyl-2-butanol and 1-(isochroman-1-yl)-4-phenyl-2-butanone (**10b**) were similarly prepared.

1-(Isochroman-1-yl)-4-phenyl-2-butanol: Yield, 84%. Viscous oil. *Anal.* Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 81.06; H, 7.92. IR ν (neat) cm^{-1}: 3450. NMR (CCl_4) δ: 3.09—3.38 (1H, br, OH), 4.71—5.05 (1H, m, 1′-H), 7.07 (4H, s, ArH), 7.21 (5H, s, Ph). MS *m/z*: 264 (M^+-18).

10b: Yield, 98%. mp 46—47 °C. *Anal.* Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.29; H, 7.25. IR ν (Nujol) cm^{-1}: 1705. NMR ($CDCl_3$) δ: 5.01—5.36 (1H, m, 1′-H), 7.08 (4H, s, ArH), 7.20 (5H, s, Ph). MS *m/z*: 280 (M^+).

***N*-Phenethyl-1-[(isochroman-1-yl)methyl]pentylamine (11g)**——Compound **11g** was prepared from **10a** and phenethylamine in the same manner as described for **8c** in 72% yield. Viscous oil. *Anal.* Calcd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 82.03; H, 9.19; N, 4.20. IR ν (neat) cm^{-1}: 3340. NMR (CCl_4) δ: 1.93 (1H, s, NH), 4.80 (1H, t, $J=6$ Hz, 1′-H), 7.10 (4H, s, ArH), 7.34 (5H, s, Ph). MS *m/z*: 337 (M^+).

N-Phenethyl-1-[(isochroman-1-yl)methyl]-3-phenylpropylamine (**12g**) was similarly prepared from **10b** and β-phenethylamine in 73% yield. *Anal.* Calcd for $C_{27}H_{31}NO$: C, 84.11; H, 8.11; N, 3.63. Found: C, 84.29; H, 8.05; N, 3.70. IR ν (neat) cm^{-1}: 3350. NMR (CCl_4) δ: 1.17 (1H, s, NH), 4.53—4.88 (1H, m, 1′-H), 7.07 (4H, s, ArH), 7.19 (10H, s, Ph×2). MS *m/z*: 385 (M^+).

Compounds **3**, **6**—**8**, **11**, and **12** were converted to their hydrochlorides, which were tested for biological activity.

Gastric Antisecretory Activity——Gastric antisecretory activity was evaluated using the technique of Shay.[3] Male SD rats, weighing 120—170 g, were fasted for 24 h prior to the test in cages with wire-mesh floors to prevent coprophagy, but they were allowed water *ad libitum*. After fasting, the rats were divided into groups of five animals each. One group served as the control. A small midline incision was performed, and the pylorus was ligated under ether anesthesia. A test compound, suspended in 0.5% carboxymethylcellulose solution, or the vehicle was administered intraduodenally to each group. Seven hours after closing the abdomen, the stomach was extirpated under ether anesthesia, and the volume of accumulated gastric juice therein was measured. The gastric juice was titrated against 0.1 N NaOH to determine the concentration of free acid (at pH 0.3), and hourly outputs of free acid were calculated for each rat. In the experiment, the test compounds were administered at a dose level of 20 mg/kg, and the results were represented as percentage inhibition with respect to the control.

Aspirin-Induced Ulcer——The technique used was essentially the same as that described elsewhere.[4] Male SD rats, weighing 150—200 g, were deprived of food for 24 h. Six animals per group were used. After fasting, the pylorus was ligated, and the test compounds were administered orally at a dose of 20 mg/kg. Thirty minutes later, aspirin,

suspended in 1% carboxymethylcellulose solution, was given orally at a dose of 100 mg/kg. Nine hours after aspirin administration, the stomach was extirpated, and the length of lesions in the glandular portion was measured. The ulcer index (mm) was obtained by summing the length of the lesions. The results were represented as percentage inhibition with respect to the control.

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