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THREE NEW DERIVATIVES OF 3–AMINO–1,2–PROPANEDIOL; THEIR SPECTRAL PROPERTIES AND BIOLOGICAL EVALUATION

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Abstract: Three new derivatives of 3–amino–1,2–propanediol have been synthesized. Full assignments of signals in their ^{1}H– and ^{13}C–NMR spectra are given. The influence of these compounds on the cardiovascular system in the anaesthetized rat was examined. In contrast to CGP 12177 which induced a strong increase in heart rate and a slight increase in blood pressure, compounds **1**, **2** and **3** × HCl at doses up to 1 μmol/kg and compound **3** at doses of 0.01 and 0.1 μmol/kg did not change the cardiovascular parameters. The highest dose of compound **3** – 1 μmol/kg caused a very short–lasting decrease in heart rate (by 14%) and in blood pressure (by 25%).

Keywords: β–blockers; 3–amino–1,2–propanediol derivatives; conformational analysis; NMR spectra.

Several derivatives of 3–amino–1,2–propanediol were described as β–adrenoceptor antagonists and/or cardioactive compounds (eg. CGP 12177, pindolol or cyanopindolol) (1). One of the most potent hydrophilic antagonists at β–adrenergic receptors is CGP 12177 (2–4). We have previously shown (5) that CGP 12177 and cyanopindolol elicit a strong positive chronotropic effect in pithed and vagotomized rats, which is mediated *via* atypical (β_4)–adrenoceptors. While extensive systematic structure–activity relationship studies have not been performed yet, data obtained from the examination of rat hearts show that the 3–amino–1,2–propanediol moiety is essential for biological activity. The most active derivatives have a terminal amino group alkylated, preferentially with the *t*–butyl group.

An aryl substituent at O–1 is always present. From structures of the best ligands for β–adrenergic receptors, a conclusion could be drawn that the presence of an amino group at *meta* position assures greater efficacy. The most potent compounds (such as CGP 12177 or cyanopindolol) have a weak acidic N(ar)–H bond which may be important for their interaction with a receptor. We have therefore designed the synthesis of two simple 3–amino–1,2–propanediol derivatives with different N(ar)–H acidity – benzamide **1** and sulfonamide **2**. The third compound chosen for this study was the lipophilic estrone derivative **3**. The central carbon atom in 3–amino–1,2–propanediol and in all its derivatives is chiral. The interaction of a chiral molecule with a receptor protein is a diastereomeric one, and corollary to this is that two enantiomers can exhibit quite different properties. For example, (R)–propranolol acts as a contraceptive, whereas the (S)–isomer is a β–blocker. Clearly, if a chiral molecule is directed towad a biological target, the two enantiomers should be viewed as distinct compounds that are capable of acting in different ways. It is well known that the enantiomers may exhibit differential metabolism, protein binding, biodistribution, toxicity, pharmacokinetics and pharmacological effect. The designed structures **1** and **2** are chemically similar to CGP 12177. It has low non–specific binding to membranes and low cellular uptake and so only binds to cell–surface receptors rather than to internalized receptors (6, 7). Studies *in vitro* have shown that the S–enantiomer of CGP 12177 has about eighty–fold greater affinity for β–adrenergic receptors than the R–enantiomer. However, for our preliminary study racemic forms of benzamide **1** and sulfonamide **2** were sufficient. In the case of the estrone derivative **3**, a diastereomeric mixture was studied, since the estrone molecule itself is chiral.

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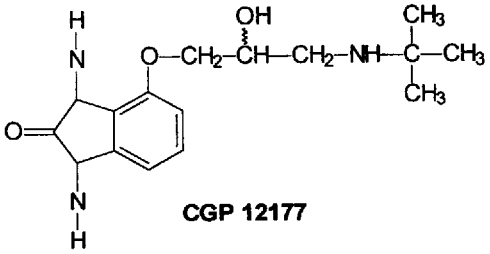
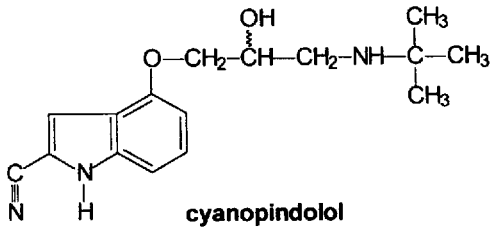


CGP 12177



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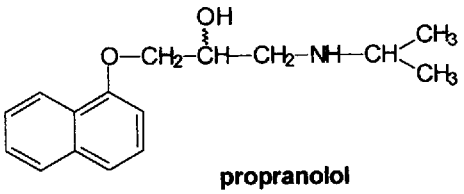

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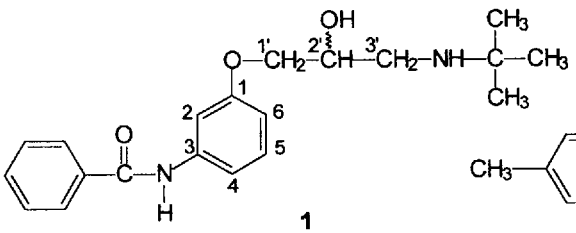
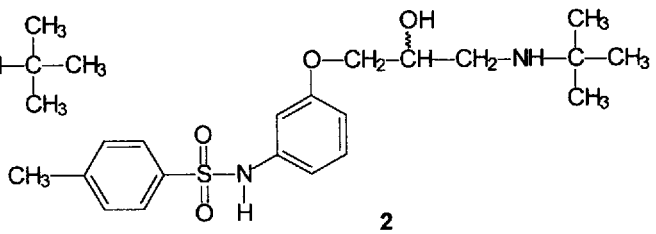


1



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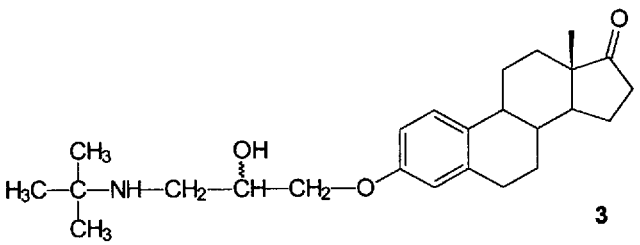

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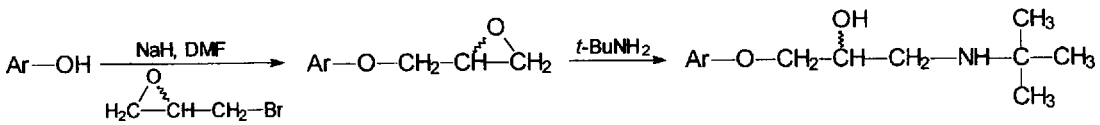

Scheme 1.

EXPERIMENTAL

Materials and methods

Melting points were determined on a Kofler apparatus of the Boetius type and are uncorrected. NMR spectra were recorded with a Bruker AC 200F spectrometer using $CDCl_3$ solutions with *TMS* as the internal standard. Infrared spectra were recorded on a Specord 75 IR as chloroform solutions. The reaction products were isolated by column chromatography performed on silica gel 70–230 mesh (J.T. Baker). Thin–layer chromatograms were developed on aluminium TLC sheets precoated with silica gel F_{254} and visualized with 50% sulfuric acid after heating. All solvents were dried and freshly distilled prior to use. CGP 12177 ((±)–4(3–*t*–butylamino–2–hydroxypropoxy)–benzimidazol–2–one) was purchased from Ciba–Geigy (Basel, Switzerland), urethane from Sigma (Deisenhofen, Germany). The newly synthesized drugs were dissolved in a mixture of ethanol and 0.9% NaCl: compound **1** (1:14); compound **2** (1:12), compound **3** and its hydrochloride (1:1.5). CGP 12177 and urethane were dissolved in saline. None of the solvents affected cardiovascular parameters. All pharmacological experiments were performed on male Wistar rats weighing 170–265 g. Rats were anaesthetized with urethane 14 mmol/kg. The trachea was cannulated. Diastolic blood pressure was measured from the right carotid artery *via* a pressor transducer (DTX, Spectramed, Bromma, Sweden); the pressure wave triggered a rate–meter. Body temperature was kept constant at approximately 36°C using a tungsten lamp and monitored by a rectal probe thermometer. The transducers were connected to the monitor Trendscope 8031 (AxMediTec, Białystok, Poland). The left femoral vein was cannulated for i.v. administration of drugs in a volume of 0.5 ml/kg. In rats with a low level of basal diastolic blood pressure, vasopressin (0.04–0.4 IU/kg/min) was infused to raise diastolic blood pressure to about 85 mmHg, since vasopressor/vasodepressor effects are more marked at a higher level of blood pressure (see e.g. ref. 17). Body temperature was kept constant at approximately 36°C using a tungsten lamp and monitored by a rectal probe transducer. After 15–20 min of equilibration, during which the cardiovascular parameters were allowed to stabilize, experiments were performed.

The effects of each of the compounds were studied in separate animals (only one dose/response curve per animal or only one dose in the case of CGP 12177). Animals received increasing doses of the drug with sufficient time for full recovery to the preinjection value. The lowest or only (CGP 12177) dose was administered 5 min after injection of saline solution.

Results of measurements are given as means ±SEM throughout the paper (n is the number of rats). For comparison of the mean values the t–test for unpaired data was used. Differences were considered as significant when $P<0.05$.

Synthesis of N–(3{3'–[t–butylamino]–2'–hydroxypropoxy}phenyl)benzamide (1)

N–(3–hydroxyphenyl)benzamide

3–Aminophenol (0.8 g; 6.7 mmol) was dissolved in *N,N*–dimethylacetamide (100 ml) and benzoyl chloride (1 g; 6.7 mmol) was added. The mixture was stirred at room temperature for 18 hours and then poured onto ice. The aqueous mixture was extracted with chloroform (3×30 ml), dried over anhydrous magnesium sulfate and evaporated to leave an oily residue. The residue was crystallized from chloroform/methanol to give the pure product (1.3 g; 86%).

^{1}H–NMR, δ (ppm): 6.52 (m, 1H, 6–H), 7.14 (m, 2H, 4–H and 5–H), 7.38 (s, 1H, 2–H), 7.53 (m, 3H, *meta*–H and *para*–H), 7.94 (m, 2H, *orto*–H), 9.42 (s, 1H, NH), 10.13 (s, 1H, OH).

N–[3–(2',3'–epoxy)propoxyphenyl]benzamide

A solution of epibromohydrin (0.81 g; 5.9 mmol) and *N*–(3–hydroxyphenyl)benzamide (1.3 g; 5.9 mmol) in acetone (80 ml) was stirred with anhydrous potassium carbonate (1 g; 7.2 mmol) at 50–55°C for 16 hours. The solvent was removed under reduced pressure. The residue was extracted with chloroform (3×30 ml), washed with water (3×30 ml) and dried over anhydrous magnesium sulfate. Removal of the solvent gave the crystalline residue, which was recrystallized from hexane/dichloromethane to afford the pure product (1.2 g; 75%).

^{1}H–NMR, δ (ppm): 2.73 (dd, J=4.9 and 2.7 Hz, 1H, 3'–H), 2.88 (m, 1H, 3'–H), 3.33 (m, 1H, 2'–H), 3.89 (dd, J=5.8 and 11 Hz, 1H, 1'–H), 4.22 (dd, J=3.0 and 11.0 Hz, 1H, 1'–H), 6.73 (m, 1H, 6–H), 7.18 (m, 2H, 4–H and 5–H), 7.45 (m, 4H, 2–H, *meta*–H and *para*–H), 7.84 (m, 2H, *orto*–H), 8.23 (s, 1H, NH).

N–(3{3'–[t–butylamino]–2'–hydroxypropoxy}phenyl)benzamide

A solution of *N*–[3–(2',3'–epoxy)propoxyphenyl]benzamide (1.2 g; 4.4 mmol) and *t*–butylamine (3.21 g; 44 mmol) in ethanol (60 ml) was stirred for 20 hours at ambient temperature. The solvent was removed under reduced pressure to leave an oily residue, which was redissolved in hydrochloric acid

(1M; 60 ml). Then potassium hydroxide solution (1M, 100 ml) was added. The mixture was extracted with chloroform (3×30 ml). The chloroform extract was dried with anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to give a yellow solid. Recrystallization from hexane/chloroform gave 1 g (66%) of **1** as colorless crystals, m.p. 40–41°C.
The ^{1}H– and ^{13}C–NMR data are listed in Tables 1 and 2, respectively.

Synthesis of (3{3'–[(tert–butyl)amino]–2'–hydroxypropoxy}phenyl)–p–toluenesu lfonamide (2)

N–(3–hydroxyphenyl)–p–toluenesulfonylamide

A mixture of 3–aminophenol (1 g; 9.2 mmol), *p*–toluenesulfonylchloride (1.75 g; 9.2 mmol) and ethanol (70 ml) was stirred at room temperature for 10 hours. The solvent was removed under reduced pressure. Chromatography of the crude product on silica gel column and elution with dichloromethane/methanol (97:3) gave the pure product (2 g; 83%).
^{1}H–NMR, δ (ppm): 2.32 (s, 3H, *p*–CH_3), 6.39 (m, 1H, 6–H), 6.50 (m, 2H, 2–H and 4–H), 6.98 (t, 1H, J=8.0 Hz, 5–H), 7.33 (d, J=8.0 Hz, 2H, *meta*–H), 7.65 (d, J=8.0 Hz, 2H, *orto*–H), 9.46 (s, 1H, NH), 10.11 (s, 1H, OH).

N–(3–[2',3'–epoxypropoxy]phenyl)–p–toluenesulfonamide

A solution of epibromohydrin (1.04 g; 7.6 mmol) and *N*–(3–hydroxyphenyl)–*p*–toluenesulfonamide (2 g; 7.6 mmol) in acetone (60 ml) was stirred overnight with anhydrous potassium carbonate (1.13 g; 8.2 mmol) at 50–55°C. Removal of the solvent gave a brown oily residue, which was subjected to silica gel column chromatography. Elution with hexane/ethyl acetate (92:8) gave the oily product (1.5 g; 62%).
^{1}H–NMR, δ (ppm): 2.38 (s, 3H, *p*–CH3), 3.47 (1H, dd, J=4.5 and 2.6 Hz, 3'–H), 2.70 (t, 1H, J=4.5 Hz, 3'–H), 3.15 (m, 1H, 2'–H), 3.67 (m, 2H, 1'–H), 6.52 (dd, 1H, J=2.6 and 4.0 Hz; 6–H), 6.70 (t, J=2.1 Hz, 1H, 2–H), 6.72 (m, 1H, 4–H), 7.09 (t, J=8.0 Hz, 1H, 5–H), 7.23 (d, J=8.2 Hz, 2H, *meta*–H), 7.52 (d, J=8.2 Hz, 2H, *orto*–H).

(3{3'[(tert–butyl)amino]–2'–hydroxypropoxy}phenyl)–p–toluenesulfonamide

The procedure for preparation of compound **2** from *N*–(3–[2',3'–epoxypropoxy]phenyl)–*p*–toluenesulfonamide was identical to that described above for preparation of **1**. Product **2** (m.p. 89–91°C) was obtained in 73% yield.
The NMR data for **2** are given in Tables 1 and 2.

Synthesis of 3–[(3'–tert–butylamino)–2'–hydroxypropoxy]–1,3,5(10)–estratrien– 17–one (3) and its hydrochloride (3 × HCl)

3–[(2',3'–epoxy)propoxy]–1,3,5(10)–estratrien–17–one

Epibromohydrin (0.15 g; 1.1 mmol) was added to the solution of (0.04 g; 1.7 mmol) sodium hydride (60% dispersion in mineral oil) and 1,3,5(10)–estratrien–3–ol–17–one (0.3 g; 1.1 mmol) in *N,N*–dimethylformamide (40 ml) cooled in ice bath. After the addition was completed, the ice bath was removed and the solution was stirred at room temperature for 3 hours, and then poured into ice. The mixture was extracted with chloroform (3×30 ml). The organic extracts were washed with water (3×20 ml), dried over anhydrous magnesium sulfate and evaporated to leave on oily residue. It was purified by a silica gel column chromatography. Dichloromethane/hexane (80:20) eluted the product (0.32 g; 89%).
^{1}H–NMR, δ (ppm): 0.90 (s, 3H, 18–H), 2.76 (dd, J=4.9 and 2.6 Hz, 1H, 3'–H), 2.90 (m, 3H, 3'H and 16–H), 3.35 (m, 1H, 2'–H), 3.95 (dd, J=11.1 and 5.5 Hz, 1H, 1'–H), 4.20 (dd, 1H, J=11.1 and 3.3 Hz, 1'–H), 6.72 (m, 2H, 1–H and 2–H), 7.21 (d, J=8.5 Hz, 1H, 4–H).

3–[(3'–tert–butylamino)–2'–hydroxypropoxy]–1, 3,5(10)–estratrien–17–one

The procedure used in order to obtain compound **3** was identical to that described above for compounds **1** and **2**. Yield: 79%, m.p. 104–106°C.
IR, ν (cm^{-1}): 3607, 3464, 3344, 1743, 1500.
^{1}H–NMR and ^{13}C–NMR data are listed in Tables 1 and 2.

3–[(3'–t–butylamino]–2'–hydroxypropoxy–1,3,5 (10)–estratrien–17–one hydrochloride

Compound **3** (0.31 g; 0.8 mmol) was dissolved in ethanol saturated wit HCl and stirred for 15 minutes. Then the solvent was removed under reduced pressure to give hydrochloride in almost quantitative yield, m.p. 198–199°C.
IR, ν (cm^{-1}): 3344, 2931, 2858, 2768, 1743, 1500.
^{1}H–NMR and ^{13}C–NMR data are listed in Tables 1 and 2.

RESULTS AND DISCUSSION

Chemical part

For the synthesis of compounds **1–3** routine procedures were used (8, 9). The starting phenol (Scheme 1) was treated with sodium hydride in DMF or K_2CO_3 in acetone. A reaction of the

resulting phenoxide with epibromohydrin furnished the corresponding 1–aryloxy–2,3–epoxypropane in high yield. There are two possible pathways of the reaction: direct displacement of bromine by phenoxide, or an attack of the latter on epoxide followed by ring reclosure with simultaneous withdrawal of bromine. The reaction mechanism is important in the case of a stereocontrolled synthesis (10–12) but when racemic epibromohydrin is used, both pathways lead to the same racemic or (if the phenol is chiral) diastereomeric 1–aryloxy–2,3–epoxypropane. The reaction of the latter with *t*–butylamine proceeded smoothly at room temperature yielding the final product **1**, **2** or **3**. There was no manifestation of a diastereomeric character of compound **3** in its spectra. The mixture could not be separated by any of the chromatographic techniques. The reason for that is the long distance between differentiating steroid chiral atoms from the side chain chiral center. In order to establish a privileged conformation of propane side chain in compounds **1–3** their spectral properties were briefly examined and a molecular modelling study was performed. Analysis of IR spectra shows a significant contribution from free O–H stretching vibrations at 3607 cm^{-1}. A broad absorption band around 3464 cm^{-1} indicates presence of some intermolecular hydrogen bonds. A carbonyl group absorption in estrone derivative **3** at 1743 cm^{-1} is not affected by intermolecular interactions (an identical band as in estrone methyl ether was observed). In the NMR spectra, an averaged two–proton signal (a broad singlet at about δ 3.2–3.5 ppm) comes from protons at heteroatoms. This signal is slightly shifted upfield on dilution. In the case of compound **3** hydrochloride, the three–proton signal appeared at δ 6.23 ppm (it is also sensitive to concentration changes). There is fast exchange of the sulfonamide proton in **2** with the side chain protons at heteroatoms. That is not the case for the benzamide proton in **1**. Full assignments of proton and carbon signals for compounds **1**, **2** and **3** (free amine and its hydrochloride) in their NMR spectra (200 MHz, $CDCl_3$) are given in the Tables **1** and **2**. The most important from the point of view of their potential biological activity are differences between the compounds in the side chain region. In the sulfonamide, the oxygen atom is conjugated to the aromatic ring less efficiently than in other compounds, and its electron density is much higher.

Table 1. ^{1}H–NMR data (δ, ppm) for 1, 2, 3 and 3 × HCl

Proton No.	Compound			
	1[a]	2[a]	3[a] (steroid numbering)	3 × HCl[a] (steroid numbering)
2–H	7.39 s	6.55 s	6.67 d,J=2.6 Hz (4–H)	6.66 d, J=2.5 Hz (4–H)
4–H	7.1–7.3 m	6.59 d, J=9.9 Hz		
5–H	7.1–7.3 m	7.03 t, J=8.0 Hz	7.20 d, J=8.5 Hz (1–H)	7.17 d, J=8.6 Hz (1–H)
6–H	6.66 def d, J=7.2 Hz	6.33 d, J=10.8 Hz	6.73 dd, J=8.5, 2.6 Hz (2–H)	6.70 dd, J=8.5, 2.5 Hz (2–H)
1'–H	3.93 m, 2H, J=9.0, 5.5, 4.5 Hz	3.48 m, 3.52 m, J=10.7, 5.8, 4.8 Hz[b]	3.97 m, 2H	3.96 dd, J=9.5, 6.0 Hz; 4.08 dd, J=9.5, 4.0 Hz
2'–H	3.98 m	3.56 m	4.01 m	4.60 m
3'–H	2.67 dd, J=12.0, 7.7 Hz; 2.82 dd, J=12.0, 3.5 Hz	2.67 dd, J=11.6, 7.4 Hz; 2.76 dd, J=11.6, 1.4 Hz	2.90 m, 3H (overlapped with one steroid–H)	3.07 dd, J=12.1, 10.0 Hz; 3.28 dd, J=12.1, 1.8 Hz
protons at heteroatoms	3.26 bs, 2H; 8.37 bs	3.37 bs, 3H	3.18 bs, 2H	6.23 bs, 3H
t–butyl protons	1.13 s, 9H	1.14 s, 9H	1.17 s, 9H	1.47 s, 9H

[a]Other signals:
1: 7.3–7.5 m, 3H, *meta*–H and *para*–H; 7.85 def d, J=8.2 Hz, 2H, *orto*–H
2: 2.40 s, 3H; 7.23 d, J=8.2 Hz, 2H and 7.47 d, J=8.2 Hz, 2H (AA'XX' system of *orto*–H and *meta*–H)
3: 0.91 s, 3H, 18–H; 1.2–2.9 – methylene and methine steroid–H
3 × HCl: 0.90 s, 3H, 18–H; 1.2–2.6 – methylene and methine steroid–H; 2.85 m, 2H
[b]Coupling constants were obtained by analysis of signal with a WIN–DAISY program (Bruker)

Table 2. ^{13}C–NMR data (δ, ppm) for 1, 2, 3 and 3 × HCl

Carbon No.	Compound			
	1[a]	2[a]	3[a] (steroid numbering)	3 × HCl[a] (steroid numbering)
1	159.1	157.8	156.6 (C–3)	156.2 (C–3)
2	106.7	116.1	114.5 (C–4)	114.5 (C–4)
3	139.2	134.7	137.7 (C–5)	137.7 (C–5)
4	112.9	118.4	132.3 (C–10)	132.5 (C–10)
5	129.6	129.9	126.3 (C–1)	126.3 (C–1)
6	110.9	116.2	112.1 (C–2)	112.1 (C–2)
1'	70.5	54.6	70.3	69.5
2'	68.3	67.0	68.2	65.7
3'	44.7	45.3	44.8	45.5
C (*t*–but)	51.0	51.6	51.3	57.3
CH_3 (*t*–but)	28.6	28.0	28.6	25.9

[a] Other signals:
1: 166.0 (c), 134.8 (*ipso*), 131.7 (*para*), 129.6 (*meta*), 127.1 (*orto*)
2: 143.6 (*para*), 139.3 (*ipso*), 129.4 (*meta*), 127.7 (*orto*), 21.5 (*p*–CH_3)
3: 220.9 (C–17), 50.3 (C–14), 47.9 (C–13), 43.9 (C–9), 38.3 (C–8), 35.8 (C–16), 31.5 (C–12), 29.6 (C–6), 26.5 (C–7), 25.9 (C–11), 21.5 (C–15), 13.8 (C–18)
3 × HCl: 220.8 (C–17), 50.3 (C–14), 47.9 (C–13), 43.8 (C–9), 38.2 (C–8), 35.8 (C–16), 31.5 (C–12), 29.5 (C–6), 26.4 (C–7), 25.8 (C–11), 21.5 (C–15), 13.7 (C–18)

Table 3. Effects of CGP 12177 and new 3-amino-1,2-propanediol derivatives (compounds **1, 2, 3, 3** × HCl) on diastolic blood pressure (DBP) in urethane anaesthetized rats

Compound	n	BDBP (mmHg)	Changes in DBP (mmHg) after administration of the drug at a dose (μmol/kg)		
			0.01	0.1	1
CGP 12177	5	84.5 ± 4.7	-	+7.5 ± 1.5*	-
1	5	78.2 ± 1.2	-6.2 ± 1.3	-6.6 ± 3.5	-4.4 ± 1.8
2	4	85.7 ± 5.4	-5.7 ± 2.3	-9.7 ± 1.7	-11.0 ± 1.6
3	6	81.0 ± 6.7	-8.1 ± 2.2	-6.8 ± 2.7	-20.3 ± 3.5**
3 × HCl	4	87.7 ± 6.7	-5.0 ± 2.3	-4.5 ± 1.2	-10.2 ± 1.5
0.9% NaCl	23	-80.6 ± 1.4		-4.9 ± 1.4	

BDBP – basal diastolic blood pressure immediately before administration of the first dose of agonist. *P < 0.05; **P < 0.01 compared to changes induced by 0.9% NaCl. Results are given as means ± SEM.

Table 4. Effects of CGP 12177 and new 3-amino-1,2-propanediol derivatives (compounds **1, 2, 3, 3** × HCl) on heart rate (HR) in urethane anaesthetized rats

Compound	n	BHR (beats/min)	Changes in HR (beats/min) after administration of the drug at a dose (μmol/kg)		
			0.01	0.1	1
CGP 12177	5	364.2 ± 10.6	-	+69.0 ± 14.1**	-
1	5	433.4 ± 10.0	-15.8 ± 4.3	-16.8 ± 3.5	-34.4 ± 15.7
2	4	407.7 ± 29.7	-16.2 ± 3.0	-21.0 ± 4.6	-15.5 ± 3.5
3	6	375.0 ± 22.1	-14.0 ± 3.6	-12.2 ± 2.3	-50.5 ± 7.9**
3 × HCl	4	318.0 ± 23.7	-7.7 ± 2.7	-13.0 ± 4.1	-20.7 ± 7.2
0.9% NaCl	23	382.3 ± 19.3		-14.2 ± 3.3	

BHR – basal heart rate immediately before administration of the first dose of agonist. *P < 0.01; **P < 0.001 compared to changes induced by 0.9% NaCl. Results are given as means ± SEM.

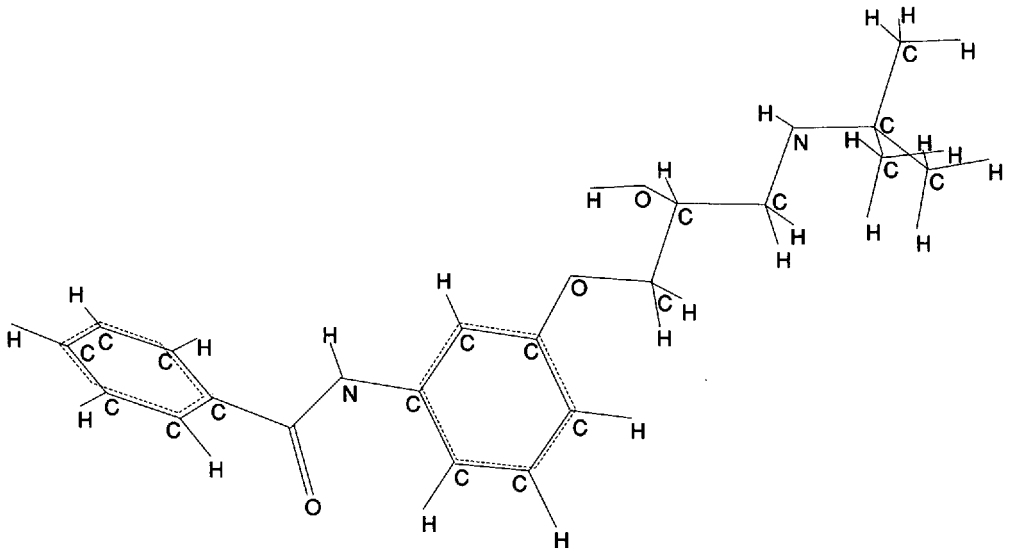

Figure 1. Optimized structure of benzamide **1**

This explains the significant upfield shift of the carbon atom C–1' signal in the ^{13}C–NMR spectrum of **1**. Also, protons attached to this carbon atom are deshielded, if compared with the corresponding protons in other compounds. Protonation at the nitrogen atom affects the side chain carbons and protons at the β position in higher extent than those in the α position. Conformational analysis of the side chain was performed using HyperChem™, Release 5.01 for Windows, from Hypercube, Inc. Geometry optimization applying a semi–empirical AM1 method preceded by molecular modelling with MM+force field and Polak–Ribiere routine, proved preference for a fully extended (all–*trans*) conformation in all cases (Figure 1 shows an optimized structure of benzamide **1**). However, the *gauche* rotamer around the C1'–C2' bond appeared to be only 0.9 kcal/mol less stable than the *trans* one (C3' and O(ar) on the opposite sides). Similarly, the *trans* rotamer (*trans* C1' and N) around the C2'–C3' bond proved more stable by 1.6 kcal/mol than the lower energy *gauche* rotamer.

The side chain region in compounds **1–3** is so flexible that numerous conformers are formed. Some of them are stabilized by an intramolecular hydrogen bond. The small energy differences between the conformers allow for the simultaneous coexistence of a few similar forms at room temperature. Most likely, the results obtained for molecules *in vacuo* are also valid for chloroform solutions. From the vicinal coupling constants of protons at C1' a conclusion can be drawn that the prevailing all–*trans* conformation is accompanied by significant population of the *gauche* conformations. A contribution from the latter is slightly varying between the compounds studied but is always considerable. The *trans* conformation around the C2'–C3' bond predominates in all compounds (one big and one small coupling constant was found in their ^{1}H–NMR spectra) (13). The findings are in agreement with the results obtained for the other 3–amino–1,2–propanediol derivatives (14–16).

Pharmacological part

In the various experimental groups of urethane anaesthetized rats, basal diastolic blood pressure and heart rate ranged from 78.2±1.2 mmHg (n=5) to 85.7±5.4 mmHg (n=4; Table 3) and from 318.0±23.7 beats/min (n=4) to 433.4±10.0 beats/min (n=5; Table 4).

Intravenous injection of saline solution (solvent for CGP 12177) caused a short–lasting fall in both parameters (Tables 3 and 4). Similar changes were also observed for other solvents used (data not shown). The non–conventional β–adrenoceptor agonist CGP 12177 at a dose of 0.1 μmol/kg increased blood pressure by about 9% and heart rate by about 19%. The maximum changes in blood pressure were reached within 1 min and they lasted for about 5 min. The maximum positive chronotropic effect of this substance was reached within 5 min and it lasted for more than 30 min. In contrast to the reference drug CGP 12177, compounds **1**, **2** and **3** × HCl (at doses of 0.01–1 μmol/kg each) and compound **3** (at doses of 0.01

and 0:1 μmol/kg) modified blood pressure and heart rate in the way similar to saline solution (Table 3, 4). The highest dose of compound **3** – 1 μmol/kg induced a short–lasting (about 15–30 sec) decrease in blood pressure (by about 25%; Table 3) and heart rate (by about 14%; Table 4). We conclude that the new derivatives of 3–amino–1,2–propanediol do not possess β–adrenergic activity.

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