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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Anti-inflammatory effects of two new methyl and morpholine derivatives of diphenhydramine on rats

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Abstract Diphenhydramines are one of the first-generation histamine H_1-receptor antagonists of the ethanolamine class that demonstrate many pharmacological properties including anti-inflammatory effects. In this research, bromo (**II**) and two new tolyl derivatives of **I**, (Di [*p*-tolyl] [dimethylaminoethoxy] methane, **III**) and (Di [*p*-tolyl] [2-morpholinoethoxy] methane, **IV**) were synthesized. Their acute and chronic anti-inflammatory activities were evaluated with the formalin and histamine-induced rat paw edema. The vascular permeability in formalin and histamine-induced paw edema, in xylene-induced ear edema, and in peritonitis after acetic acid application into peritoneal cavity were also measured and compared to **II**. Cotton pellet-induced granuloma model was selected for inducing chronic inflammations in rats. The newly synthesized analogs of diphenhydramine seemed effective to decrease acute inflammations. It was concluded that the prominent anti-phlogistic effects of the new drugs could be related to its reduction vascular permeability mechanism(s) or to its antagonistic effects on H_1 histamine receptors.

Keywords Diphenhydramine · Anti-inflammatory activities · Histamine H_1-receptor antagonist

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Introduction

Diphenhydramine (2-(diphenylmethoxy)-*N*,*N*-dimethylethanamine), DPH, [CAS 58-73-1, **I**] is one of the first-generation histamine H_1-receptor antagonist of the ethanolamine class. It is a competitive inhibitor to interaction between histamine and H_1-receptor antagonist (Santiago-Palma *et al*., 2001). In addition to their antihistamine effects, H_1-receptor antagonists possess such pharmacological properties as anti-inflammatory, anti-allergic, anti-platelet effects, and suppressive impact to the respiratory burst of professional phagocytes which are not uniformly distributed in this class of drugs (Králová *et al*., 2008; Leurs *et al*., 2002). Histamine is an intercellular chemical messenger which plays a critical role in several diverse physiological processes. Four human G-proteins coupled with histamine receptor subtypes (H_{1-4}) are currently recognized to mediate various actions by monoamine histamine, including smooth muscle contraction, inflammatory responses, gastric acid secretion, and mediation of neurotransmitter release in the central nervous system (Saxena *et al*., 2006; Triggiani *et al*., 2001). Recently, our knowledge about the histamine roles in specific activation or blockade of the receptor subtypes, both in physiology and pathology, has dramatically increased. Among the four subtypes, histamine H_1-receptor has been an attractive target to drug discovery for several

years. H_1-receptor antagonists have been proved to be effective therapeutic agents in many diseases; hence they incorporated into an important class of available drugs (Saxena *et al*., 2006). Histamine is also a potent mediator in inflammation and tissue remodeling and a modulator in various autoimmune diseases such as rheumatoid arthritis osteoarthritis and allergic diseases, respectively (Králová *et al*., 2009; Estelle and Simons, 2003). In this study, bromo (**II**, a well-known drug in this family) and two new (**III** and **IV**) derivatives of **I** and intermediates (**1**–**4**) were synthesized and their acute and chronic anti-inflammatory activities were evaluated by the published procedures (Matos Gomes *et al*., 2010; Gupta *et al*., 2006; Winter *et al*., 1962; D'Arcy *et al*., 1960; Miles and Miles, 1952).

Materials and methods

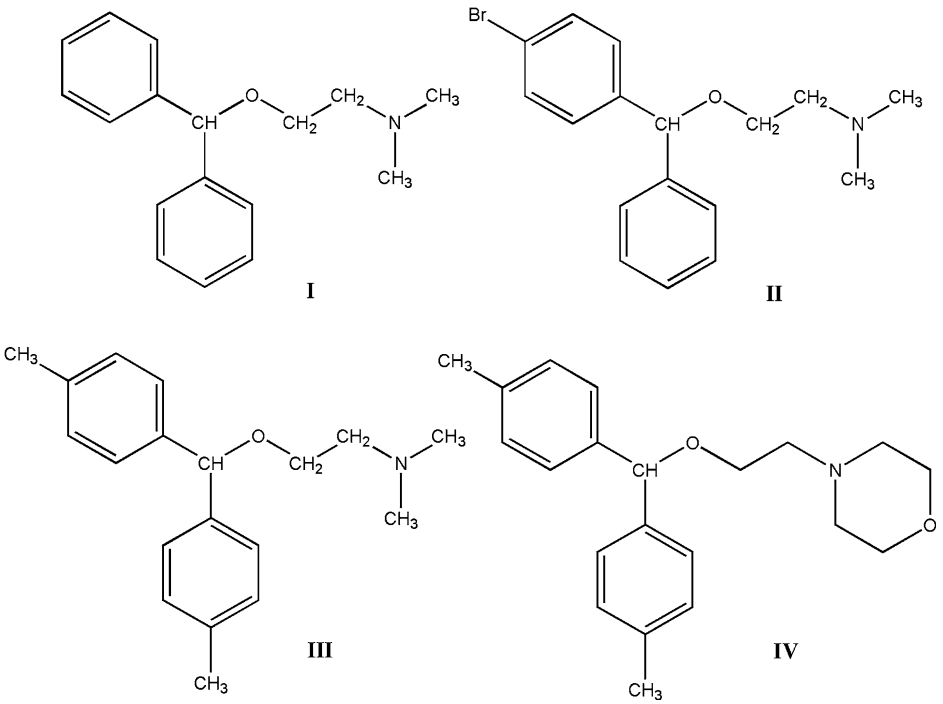
General

4-Bromobenzaldehyde, 4-methylbenzaldehyde, acetyl bromide, dimethylaminoethanol, 2-morpholino ethanol, magnesium turning, diethyl ether, xylene, benzene, and all used chemicals in this study were purchased from Merck Chemical Co. (Darmstadt, Germany). Melting points (uncorrected) were determined after with a digital Electrothermal melting point apparatus (9100, Electrothermal Engineering Ltd., Essex, UK). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 300 MHz (model AMX, Karlsruhe, Germany) spectrometer (internal reference: TMS). IR spectra were recorded with a Thermo Nicolet FT-IR (Nexus-870, Nicolet Instrument Corp, and Madison, WI, USA) spectrometer. Mass spectra were also recorded with an Agilent Technologies 5973, Mass Selective Detector (MSD) spectrometer (Wilmigton, USA). Column chromatographic separations were performed over Acros silica gel (No. 7631-86-9 particle size 35–70 μm, Geel, Belgium). Adult female wistar rats (Pasteur Institute, Tehran, Iran), weighing 250–300 g, were selected as the subjects in pharmacological testing.

Preparations (Schemes 1, 2, 3, 4)

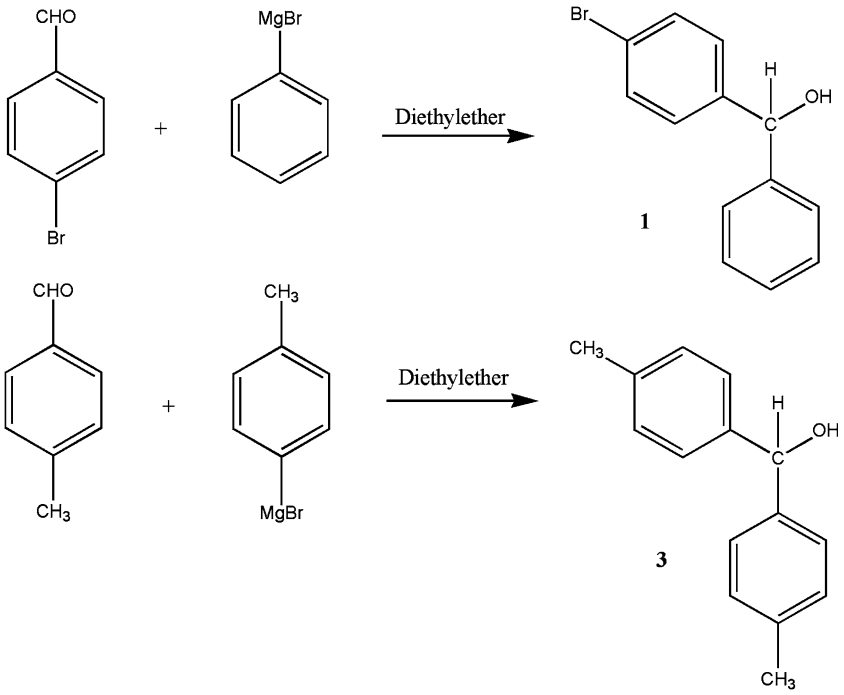
*Phenyl (p-bromophenyl) methanol (p-bromobenzhydrol) (**1**)*

This compound was prepared following a published method (Rieveschi and Woods, 1950) with some imparting modification. To the solution of *p*-bromobenzaldehyde (1.4 g, 0.1 mol) in diethyl ether (50 ml), phenyl magnesium bromide (prepared from 15.7 g bromobenzene and 2.43 g of Mg in 50 ml of dry ether) was added dropwise and refluxed for 5 h. Poured into ice-NH_4Cl, the organic layer was separated, water-washed, re-extracted with diethyl ether, dried over $MgSO_4$, and evaporated under vacuum. Eventually, the solid compound (m.p.: 60–62°C) was obtained (Scheme 2).

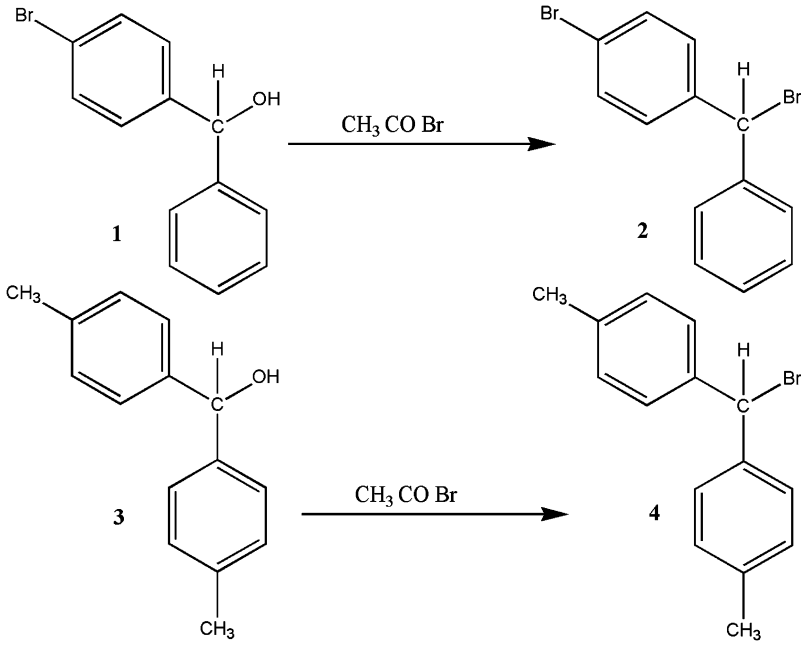


Scheme 1 Structure formulas of Diphenhydramine (2-(diphenylmethoxy)-*N*, *N*-dimethylethanamine, **I**), Bromodiphenhydramine (Phenyl [*p*-bromophenyl] [dimethylaminoethoxy] methane, Bromodiphen, **II**), and two new analogs of **I** (Di [*p*-tolyl] [dimethylaminoethoxy] methane, Bromodiphen-1, **III**) and (Di [*p*-tolyl] [2-morpholinoethoxy] methane, Bromodiphen-2, **IV**)

Scheme 2 Synthesis of intermediates **1** and **3**



Scheme 3 Synthesis of intermediates **2** and **4**



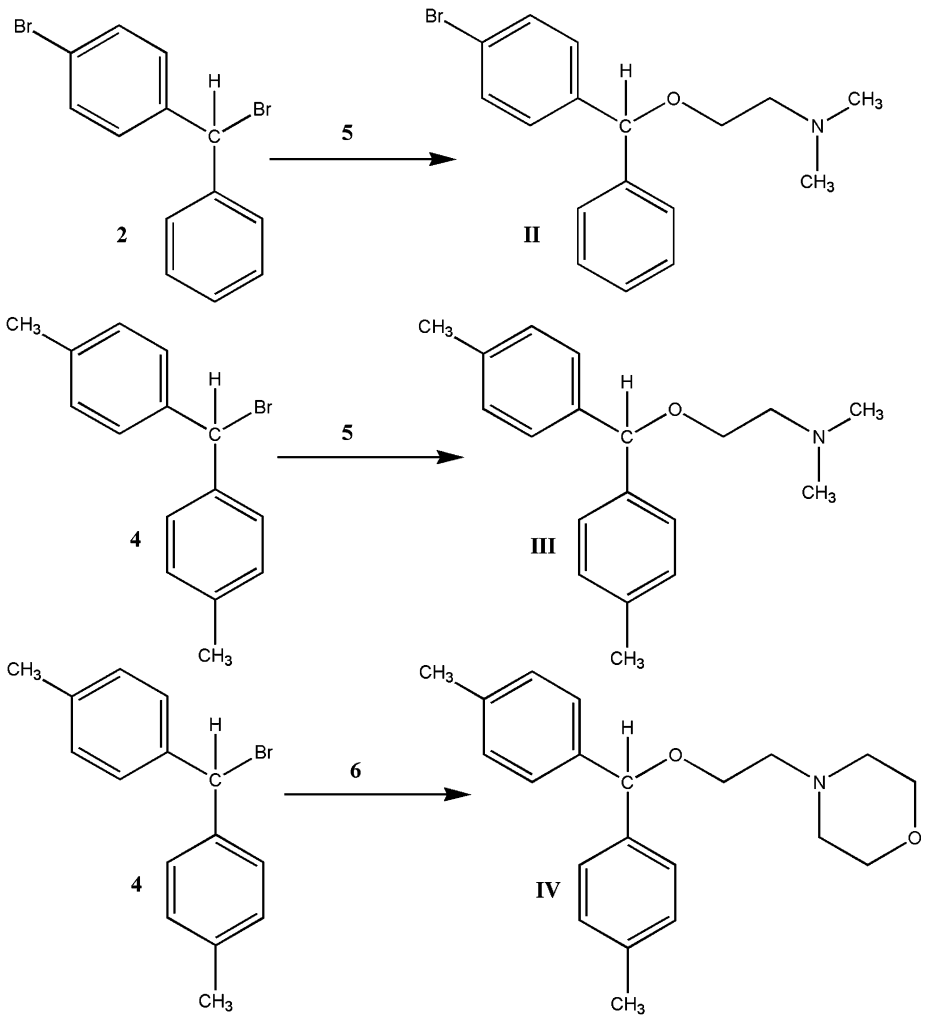
*Phenyl (p-bromophenyl) methyl bromide (p-bromobenzhydryl bromide) (**2**)*

This compound was prepared following a published method (Rieveschi and Woods, 1950) with some imparting modification. A benzene (20 ml) solution of alcohol (1,16 g, 0.06 mol) was added into acetyl bromide (11.4 g, 0.09 mol) and refluxed for 11 h. The reaction mixture was concentrated to yield the desired compound as brown oil. This compound was used in the next step without further purification (Scheme 3).

*Phenyl (p-bromophenyl) (dimethylaminoethoxy) methane (Bromodiphenhydramine, Bromodiphen) **II***

This compound was prepared following a published method (Rieveschi and Woods, 1950) with some imparting modification. A xylene (20 ml) solution of bromobenzhydryl

Scheme 4 Synthesis of target compounds (**II–IV**)



bromide (**2**, 13 g, 0.4 mol) was slowly added into a xylene (10 ml) solution of dimethylaminoethanol (**5**, 7.1 g, 0.08 mol) and refluxed for 24 h. The reaction mixture was cooled, treated with water before the aqueous layer was extracted with ether, re-extracted with 10% HCl, neutralized with 10% NaOH, dried over $MgSO_4$, and evaporated under vacuum to obtain the desired oily compound. The hydrochloride salt of **II** (m.p.: 143–145°C) was prepared using diethyl ether and HCl and was recrystallized from 2-propanol (Scheme 4).

*Di (p-tolyl) methanol (Di [p-methylbenzhydrol]) (**3**)*

Phenyl magnesium bromide (prepared from 1.7 g *p*-bromo toluene and 2.43 g of Mg in 25 ml of dry ether) was added dropwise to a THF (50 ml) solution of *p*-methyl benzaldehyde (12 g, 0.1 mol) and refluxed for 6 days. It was poured into ice-NH_4Cl, washed with brine, re-extracted with diethyl ether, dried over $MgSO_4$, and evaporated under vacuum. An oily compound (8.2 g, 38.67% yield) was obtained that was directly used in the next step without further purification (Scheme 2).

IR (KBr): 3459, 2923, 2734, 1606, 1517, 1455, 1385, 1272, 1169, 1019, 809, 757 cm^{-1}.
^{1}H-NMR. ($CDCl_3$) (ppm): 2.19 (6H, s), 2.02 (OH, m), 5.78 (1H, s), 7.15 (4H, d. J_{HH} = 16 Hz), 7.24 (4H, d. J_{HH} = 16 Hz).
$^{13}C\{^1H\}$-NMR. ($CDCl_3$) (ppm): 25.9, 77.8, 128.5, 129.8, 134.2, 140.7.
MS: m/z (regulatory intensity): 212 (22).

*Di (p-tolyl) methyl bromide (Di [p-methylbenzhydryl] bromide) (**4**)*

A benzene (20 ml) solution of alcohol (**3**, 8 g, 0.038 mol) was added into acetyl bromide (11.4 g, 0.09 mol) and refluxed for 9 days. The reaction mixture was concentrated to yield the desired compound as brown oil (5.4 g, 51% yield). This compound was used in the next step without further purification (Scheme 3).

IR (KBr): 2923, 1610, 1514, 1448, 1253, 1176, 1116, 973, 872, 751 cm^{-1}.
^{1}H-NMR. ($CDCl_3$) (ppm): 2.19 (6H, s), 6.2 (1H, s), 7.15(4H, d. $J_{HH} = 17$ Hz), 7.24(4H, d. $J_{HH} = 17$ Hz).
$^{13}C\{^{1}H\}$-NMR. ($CDCl_3$) (ppm): 25.7, 63.5, 128.2, 129.7, 134.4, 139.7.
MS: m/z (regulatory intensity): 275 (23).

Di (p-tolyl) (dimethylaminoethoxy) methane (Bromodiphen-1) ***III***

A xylene (20 ml) solution of Di [*p*-methylbenzhydryl] bromide (**4**, 5 g, 0.018 mol) was added slowly to a xylene (10 ml) solution of dimethylaminoethanol (**5**, 7.1 g, 0.08 mol) and refluxed for 90 h. The reaction mixture was cooled, treated with water before the aqueous layer was extracted with ether, re-extracted with 10% HCl, neutralized with 10% NaOH, dried over $MgSO_4$, and evaporated under vacuum to obtain the desired oily compound (3.3 g, 57% yield). The hydrochloride salt of **III** was prepared using diethyl ether and HCl and was recrystallized from 2-propanol (Scheme 4).

IR (KBr): 2919, 2645, 1615, 1510, 1469, 1357, 1177, 1020, 804, 763 cm^{-1}.
^{1}H-NMR. ($CDCl_3$) (ppm): 2.19 (6H, s. $2CH_3Ph$–), 2.33 (6H, s. –$N(CH_3)$), 2.86 (2H, t. –CH_2–N), 3.65 (2H, t. –CH_2–O), 5.78 (1H, s), 7.19(4H, d. $J_{HH} = 17$ Hz), 7.59(4H, d. $J_{HH} = 17$ Hz).
$^{13}C\{^{1}H\}$-NMR. ($CDCl_3$) (ppm): 26, 53.2, 60.8, 66.2, 77.8, 128.5, 129.8, 134.2, 140.7.
MS: m/z (regulatory intensity): 284 (16).

Di (p-tolyl) (2-morpholinoethoxy) methane (Bromodiphen-2) ***IV***

A xylene (20 ml) solution of Di [*p*-methylbenzhydryl] bromide (**4**, 5 g, 0.018 mol) was added slowly to a xylene (10 ml) solution of 2-morpholinoethanol (**6**, 10.48 g, 0.08 mol) and refluxed for 96 h. The reaction mixture was cooled, treated with water before the aqueous layer was extracted with ether, re-extracted with 10%, neutralized with 10% NaOH, dried over $MgSO_4$, and evaporated under vacuum to obtain the desired oily compound (3.8 g, 58% yield). The hydrochloride salt of **IV** was prepared using Diethyl ether and HCl was recrystallized from 2-propanol (Scheme 4).

IR (KBr): 2921, 2850, 1608, 1514, 1461, 1377, 1276, 1113, 1015, 795 cm^{-1}.
^{1}H-NMR. ($CDCl_3$) (ppm): 2.17 (6H, s. $2CH_3Ph$–), 2.29–2.37 (6H, m), 3.2–3.9 (6H, m), 5.78 (1H, s), 7.16(4H, d. $J_{HH} = 16$ Hz), 7.53(4H, d. $J_{HH} = 16$ Hz).
$^{13}C\{^{1}H\}$-NMR. ($CDCl_3$) (ppm): 26, 52.2, 56.7, 64, 73.1, 78.1, 128.5, 129.8, 134.3, 140.8.
MS: m/z (regulatory intensity): 325 (11).

Pharmacological methods

Animals

Some adult female Wistar rats (Pasteur Institute, Tehran, Iran), weighing 250–300 g, at the beginning of the experiment, were randomly housed with three to four per cage, in a temperature-controlled colony room under 12 h light/dark cycle. Rats were given free access to water and standard laboratory rat chow (Pars Company, Tehran, Iran). All the experiments were conducted between 11 a.m. and 4 p.m., under a normal room light and at 25°C. This study was carried out in line with policies mentioned in the Guidelines for the Care and Use of Laboratory Animals (NIH) and the Research Council of Shahed University of Medical Sciences (Tehran, Iran).

Anti-inflammatory activities

Acute inflammation Formalin-induced rat paw edema. Thirty-two rats were divided into four groups ($n = 8$). Control (normal saline) and treatment groups received **II**–**IV** (17 mg/kg, i.p.), respectively. The administration of drugs was 30 min before the injection of 50 µl of 3% formalin into the right hind-paw subplantar in individual rats. The paw volume was initially measured (zero time), followed by formalin injection at 0.5, 1, 2, and 3 h using caliper (Gupta *et al*., 2006). The observed differences in paw diameters between control and treatment groups were statistically analyzed.

Histamine-induced rat paw edema. In this study, rats were treated similarly to formalin-induced paw edema models. Only histamine (300 µg, 100 µl) was applied in hind-paw subplantar surface (Matos Gomes *et al*., 2010).

Vascular permeability in formalin and histamine-induced paw edema. All treatments and induction of edema in this experiment were identical to formalin or histamine models, following the procedure in Miles and Miles (1952). Thirty minutes after formalin or histamine injection, the animals received intravenous injection of Evans Blue dye (30 mg/kg). At the next 30 min, the rats were anesthetized with CO_2 inhalation and sacrificed. The inflamed formalin or histamine paws were cut from their wrist region and sectioned to pieces. The paw pieces were stored in a mixture of acetone and sodium sulfate (1%) at ratio 3/1 at room temperature applying 24 h shaking (IKA-Vibrax, Germany). The mixed solution plus paw sections were centrifuged before their supernatants were collected and

absorbance at 590 nm were measured as the scores of inflammation (Spectronic 20, Germany).

Vascular permeability in acetic acid-induced to peritoneal cavity. Test drugs or vehicles in this study were administered to only rats. Thirty minutes after every rat was given an intravenous injection of Evans Blue solution (30 mg/kg), they received an intra peritoneal injection of 0.7% acetic acid at 10 ml/kg (Winter *et al*., 1962). Rats were sacrificed by cervical dislocation in the next 30 min following the acetic acid injection, whereas their peritoneal cavity was washed three times with 10 ml of total normal saline. Saline washes were combined and centrifuged for 10 min at 581 rpm in a table top centrifuge (Sigma-4-10, Germany). Supernatants were collected and their absorbance at 590 nm was measured with a spectrophotometer (Spectron 20 Genesys, USA). The amount of Evans Blue extruded into the peritoneal cavity was estimated based on the standard curve.

Vascular permeability in xylene-induced ear edema. This experiment followed the previously described procedure (Winter *et al*., 1962), except for inducing ear edema as xylene (0.03 ml) was applied topically on both surfaces of the right ear. Ear disks of 8.0 mm in diameter were punched out, sectioned to pieces and, subjected to Evans blue extraction and measurement methods as previously mentioned in acetic acid peritonitis.

Chronic inflammation: cotton pellet-induced granuloma formation The control and treatment rats were anaesthetized (ketamine 100 mg/kg) before sterile cotton pellets, weighing 30 ± 1 mg, were subcutaneously implanted into both sides of the groin region of individual rats (D'Arcy *et al*., 1960). The animals in both groups received the vehicle (saline) or drugs for 7 consecutive days after cotton pellet implantation. On the 8th day, the animals were anaesthetized and the pellets together with the granuloma tissues were carefully removed and cleaned from extraneous tissues. The wet pellets were weighed, dried in an oven at 60°C for 24 h to a constant weight before the dried pellets were re-weighed. Increment in the dry weight of the pellets was taken as a measure of granuloma formation.

Results

Chemistry

Bromodiphenhydramine (Phenyl [*p*-bromophenyl] [dimethylaminoethoxy] methan, Bromodiphen, **II**, as a well-known drug in this family) and two new analogs of **I** (Di [*p*-tolyl] [dimethylaminoethoxy] methane, Bromodiphen-1, **III**) and (Di [*p*-tolyl] [2-morpholinoethoxy] methane, Bromodiphen-2, **IV**) were synthesized by the reaction of substituted benzhydryl bromide (**2** and **4**) re-agents and substituted for aminoethanol compounds (**5**, **6**). Methyl group on the aromatic rings bears a high electron donating character that produces an electron density and dipole moments on the molecules (Ahmadi *et al*., 2009, 2010, 2011; Johnson *et al*., 1981). Replacing dimethylamine group with a morpholine with several pharmacological properties (Chen *et al*., 2003; Kaneyoshi *et al*., 1994; Regnie *et al*., 1991; Rekka *et al*., 1990) induced more anti-inflammatory activities on our newly synthesized drugs (**III** and **IV**, Table 1). The known procedures were applied in synthesizing the compounds **II**, **1**, and **2** after appropriate modifications (Rieveschi and Woods, 1950). Spectroscopic data (IR, ^{1}H and ^{13}C-NMR, Mass) confirmed the structure of the compounds **3**, **4**, **III**, and **IV**. The melting points of the known compounds also confirmed their identity. The purity of individual compounds was checked by TLC using ethyl acetate–hexane as the eluent.

Pharmacology

General consideration

In this study, mortality (number of death), morbidity (defined as any abnormal condition or behavior due to a disorder), irritability (a condition of aggressiveness or increased response on handling), and other related abnormal states were observed in experimental animals. However, the motor coordination index (measured by Rota-rod apparatus, Harvard, UK) did not indicate any significant differences between treated rats.

Table 1 Effects of **II–IV** on formalin and histamine paw inflammations, xylene-induced ear edema, and acetic acid-induced peritonitis

	Pontamine sky blue dye extracted solution light absorbance (inflammation score)			
Inflammation-induced methods	Histamine injection to hind paw	Formalin injection to hind paw	Xylene injection to ear	Acetic acid injection to peritoneal
Animal groups tested				
Control	0.35 ± 0.08	0.30 ± 0.06	0.21 ± 0.02	0.49 ± 0.07
Brom (**II**)	0.31 ± 0.08	0.28 ± 0.05	0.19 ± 0.04	0.37 ± 0.06
Brom1 (**III**)	0.15 ± 0.02 *$	0.10 ± 0.08 **$$	0.19 ± 0.02	0.17 ± 0.04 **$
Brom2 (**IV**)	0.14 ± 0.03 *$	0.12 ± 0.04 **$$	0.18 ± 0.01	0.18 ± 0.05 **$

* $P < 0.05$, ** $P < 0.01$ (Versus control group); $ $P < 0.05$, $$ $P < 0.01$ (Versus Brom (**II**) treatment animals)

Acute inflammation

Formalin-induced rat paw edema The anti-inflammatory activity of **II–IV** measured at the dose of 25 mg/kg b.w. against acute paw edema induced by formalin is summarized in Fig. 1. As illustrated, 1 h after formalin injection, **II** and **III** could produce significant ($P < 0.05$) anti-inflammatory activities as 14.28 and 34.69%, respectively. However, comparing the effects of **II** and **III** showed a marked potent anti-inflammatory effect more for **III** than **II**.

Histamine-induced rat paw edema The anti-inflammatory effects of **II–IV** against acute paw edema induced by phlogistic agent histamine are shown in Fig. 2. An hour after histamine injection, compounds **II** and **III** generated more significant anti-inflammatory effects as 22.44 and 40.81%, respectively ($P < 0.05$) than the control groups.

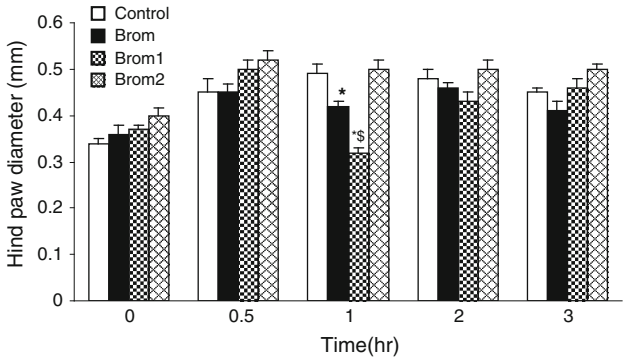


Fig. 1 Anti-inflammatory effects of **II–IV** in formalin-induced rat paw edema. Edema was measured in 0, 0.5, 1, 2, and 3 h after formalin injection. *Bars* show mean ± SEM of paw diameter. * and $ show $P < 0.05$ compared with control and compound **II**, respectively ($n = 12$)

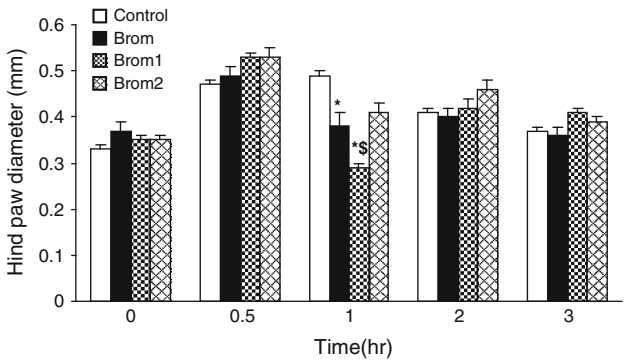


Fig. 2 Anti-inflammatory effects of **II–IV** in histamine-induced rat paw edema. Edema was measured in 0, 0.5, 1, 2, and 3 h after histamine injection. *Bars* show mean ± SEM of paw diameter. * and $ show $P < 0.05$ compared with control and compound **II**, respectively ($n = 12$)

Vascular permeability in formalin and histamine-induced paw edema As indicated in Table 1, compounds **III** and **IV** could reduce dye extrusion (edema) from plantar surface of paws at 57.14 and 60.00%, respectively in the histamine-induced inflammation model ($P < 0.05$). Also, **III** and **IV** revealed more anti-inflammatory effects than **II** ($P < 0.05$) (Table 1). In the formalin-induced edema method, a prominent anti-phlogistic effect for **III** and **IV** were obtained at about 66.66 and 60.00%, respectively ($P < 0.001$).

Vascular permeability in xylene-induced ear edema Neither original nor new drugs showed any significant inhibitory effects on the xylene-induced ear edema compared to control groups (Table 1).

Vascular permeability in acetic acid-induced to peritoneal cavity Compounds **III** and **IV** were able to inhibit acetic acid-induced dye extrusion into the peritoneal cavity by 65.30 and 63.26%, respectively (Table 1). Statistical analysis showed the significant effects for new drugs compared to control group ($P < 0.01$) as well as compound **II** to experimental groups ($P < 0.05$).

Chronic inflammation: cotton pellet-induced granuloma formation in rats

The effects of compounds **II–IV** on cotton pellet-induced granuloma formation are shown in Fig. 3. Any significant increment in the weight of cotton pellet from 67.10 ± 11.58 g in control group rats to 76.20 ± 18.24 g for compound **I**, 73.17 ± 14.47 g for compound **III** and 70.95 ± 9.26 g for compound **IV** was not observed.

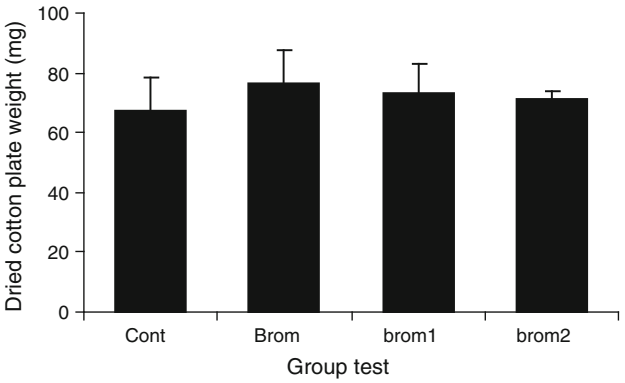


Fig. 3 Chronic anti-inflammatory effects of **II–IV** in cotton plate implantation model. Significant effects between control and treatment animals are not observed. *Bars* show mean ± SEM cotton dry weight ($n = 12$)

Discussion

Compounds with the potential of H_1-antihistaminic activities might be considered for more useful therapeutic qualities in the treatment of various allergic and inflammatory conditions due to histamine release. Although, antihistamines belong to different chemical classes, they mostly render remarkable chemical similarities (Settimo *et al*., 1992). Since, their discovery and early developments in the 1940s, histamine H_1-receptor antagonists (antihistamines) have been known as one of the most widely used classes of medications for allergic disorders. Earlier "first-generation" antihistamines exhibited a high binding affinity for H_1-receptors, although they mostly exhibited binding affinities for other classes of cellular receptors, such as muscarinic cholinergic subtypes (M_1–M_5) (Orzechowski *et al*., 2005). It has been reported that the first-generation of the H_1-receptor antagonists is among the most widely used medications around the world. These compounds induce the inhibition effects of histamine mediated by H_1–receptors (Simons and Simons, 1994), as they are the receptor-independent G-protein activators in HL-60 cells, basophils, and mast cells (Burde *et al*., 1996). Diphenhydramine (**I**) has a relatively low molecular weight with high lipid solubility which allows easy blood–brain barrier and placental passages (Moraes *et al*., 2004). So in this study, some of its new derivatives (**III** and **IV**) were synthesized and their anti-inflammatory effects were tested by the known procedures. The results indicate that inclusion of the methyl group with high electron distribution and dipole moments (Ahmadi *et al*., 2009, 2010, 2011; Johnson *et al*., 1981) on phenyl rings beside the morpholine group with many pharmacological properties (Chen *et al*. 2003; Kaneyoshi *et al*. 1994; Regnie *et al*., 1991; Rekka *et al*., 1990) cause more anti-inflammatory activities on the newly synthesized drugs (**III** and **IV**) than **II** in control groups (Table 1). However, these effects were remarkable only when methyl groups were replaced for bromine in phenyl rings (**III**), so the new drug could diminish inflammatory effects in all acute inflammation tests (Figs. 1, 2; Table 1). Also, it seems replacing dimethylamine by morpholine is not effective by itself; only with methyl group in phenyl rings (**IV**), it could effectively diminish the inflammatory effects. This finding could be explained with methyl high electron distribution and dipole moments which makes it also effective in dimethylamine for activating basicity potent of nitrogen atom (in amine group) in this moiety.

From pharmacokinetic point of view, more antagonizing actions done by these new drugs (especially **III**) on H_1 histamine receptors and their inhibitory effects of histamine release from must cells might cause their more anti-inflammatory activities. Meanwhile, because of anti-inflammatory actions (Schiene *et al*., 2011) by some analgesic drugs (especially opiate component) which act through μ receptors (Zhang *et al*., 2005), and because of agonistic actions of those drugs via these receptors (Seo *et al*., 2011), some remarkable effects occur. However, the non-efficiency effects of these drugs on alleviating chronic inflammation bring us the probability of their short half-lives or complexity of chronic inflammation mechanism(s) which are unaffected by (only) histamine release. Nevertheless, it must be reminded that anti-inflammatory actions by these new drugs in both formalin and histamine injection tests show that they must act through other unknown mechanism(s) than preventing histamine release. Regarding to higher vessel permeability, as a main factor for developing inflammation (McDougall *et al*., 2004), it seems the antagonizing action by these new drugs against high vessel permeability may cause their more anti-inflammatory effects.

Conclusions

Compound **I** new derivatives, including **III** and **IV** could markedly diminish acute anti-inflammatory effects. However, the prominent anti-phlogistic effects of these newly synthesized drugs might be related to their reducing potential for vascular permeability mechanism(s) or to their more potent antagonistic effects on H_1 histamine receptors.

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Conflict of interest This research is not a part of the researchers' normal lectures, employment, consultation, and involvement; no institution would require any rights from this work, either. In addition, no patent has been applied, nor any commercial rights have been given to any company and/or institution, as it will not be done later either.

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