Synthesis and Anti-inflammatory Activity of Resveratrol Analogs

Guoliang CHEN,*[,a] Wei SHAN,[a] Yingliang WU,[b] Lixiang REN,[b] Jinhua DONG,[a] and Zhizhong JI[a]

[a] *Pharmaceutical Engineering Department, Shenyang Pharmaceutical University; and* [b] *School of Pharmacy, Shenyang Pharmaceutical University; No103, Wenhua Road, Shenyang, 110016, P.R. China.*

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Seventeen novel resveratrol derivatives were synthesized. Their anti-inflammatory activities were tested on xylene-induced mouse ear edema. The pharmacological results showed that some compounds have potent anti-inflammatory activities.

Key words resveratrol; analogue; synthesis; anti-inflammatory activity

Resveratrol (3,4′,5-trihydroxystilbene) is a phytoalexin found in grapes and certain other plants. In recent years, there have been a large of reports about resveratrol and it exhibits a variety of useful bioactivities including anti-inflammatory, cancer chempreventive, antiplatelet aggregation, antioxidative and antibacterial activities.[1—4)]

In past years, resveratrol and some its analogs were synthesized.[5—8)] This intrigued us to prepare its analoges and their derivatives and investigate their bioactivities. In order to increase its stability and water-solubility, we designed and synthesized some analogues of resveratrol by substituting one of two benzenes with pyridyl and their Mannich base and phenoxy acetic acid derivatives of phenol, and tested their anti-inflammatory activity in mice in order to find new potent anti-inflammatory agents.

Results and Discussion

Resveratrol and its analogues were synthesized according to Chart 1. Starting from 3,5-dihydroxybenzoic acid or 4-hydroxybenzoic acid, the compounds **2a**, **b** were prepared in good yield, followed by reduction with $LiAlH_4$. Subsequent treatment of **3a**, **b** with $SOCl_2$ afforded **4a**, **b** in about 94%. Using Wittig-Horner reaction, the compounds **5a**, **b** were obtained by refluxing **4a**, **b** with $P(OEt)_3$, which were condensed with ArCHO in NaOEt/DMF to give **6a**—**f**, only the *trans* isomer was obtained. BBr_3 was used for deprotection of methyl groups in CH_2Cl_2 to afforded **7a**—**f**.

The derivatives were prepared according to Scheme I or II. The ethyl aryloxyacetates **8a**—**f** were synthesized by the reaction of compounds **7a**—**f** with ethyl chloroacetate in the presence of KOH in ethanol–DMF and hydrolyzed to afford aryloxyacetic acids **9a**—**e**. Some Mannich base derivatives were prepared by the Mannich reaction of compounds **7** with morpholine and 36% HCHO in boiling ethanol or 1,4-dioxane (Scheme II).

The structures and physical data of these new compounds were listed in Table 1.

Ten target compounds, three intermediates and resveratrol with ibuprofen were tested for anti-inflammatory activity at doses of 200 mg/kg body weight by xylene-induced ear-edemaic mice according to the method described by Xu Shuyun.[9)] The results were summarized in Table 2.

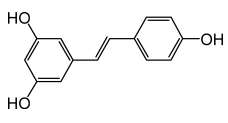


Fig. 1. The Chemical Structure of Resveratrol

At the tested doses, resveratrol was the most active compounds inhibiting the edematous response by 38.9%. Target compound **9c** showed almost the same inhibition rate as resveratrol by 37.0%. The other compounds (**9d**, **11b**, **12c**) showed an edema reduction ranging from 30 to 35%. As expected, the reference NSAID Ibuprofen provoked 42.2% edema reduction. The pharmacological tests showed that resveratrol pyridyl-substituted analogs and the Mannich base have potent anti-inflammatory activity.

Experimental

General Except where indicated, materials and reagents were used as supplied by the manufacturer. Melting points were determined with Yanaco micro melting point apparatus and were not corrected. NMR spectra were recorded at 300 MHz using Bruker ARX-300 instrument with TMS as internal reference. Mass spectra (ESI-MS) were measured on Agilent 1100 Series MSD Trap (SL). Element analysis was performed using a Vario EL apparatus.

Methyl 3,5-Dimethoxybenzoate (2a) To a well-stirred suspension of 3,5-dihydroxybenzoic acid (7.70 g, 0.05 mol) and freshly powered anhydrous K_2CO_3 (20 g, 0.15 mol) in 100 ml of acetone was added dimethyl sulfate (15 ml, 0.15 mol) at room temperature. After the mixture was refluxed for 3 h, the acetone was removed under reduced pressure and water (100 ml) was added to the residue. The resulted mixture was extracted with dichloromethane (50 ml×3) and the organic layer was dried over $MgSO_4$ and concentrated in vacuum to afford 9.53 g of white solid (93.6%), mp 42—43 °C.

Methyl 4-Methoxybenzoate (2b) Compound **2b** was prepared in the same way as white solid (yield 95.3%), mp 47—49 °C.

3,5-Dimethoxybenzyl Alcohol (3a) To a well-stirred suspension of $LiAlH_4$ (4.0 g, 0.04 mol) in anhydrous ether (30 ml) was added a solution of methyl 3,5-dimethoxybenzoate (4.0 g, 0.02 mol) in anhydrous ether (30 ml). After the addition was finished, the mixture was refluxed for 4 h, then moisture ether (10 ml) and water (60 ml) were added to the mixture respectively. The water layer was extracted with ether (30 ml×3). The organic layer was dried over $MgSO_4$ and concentrated to provide 3.15 g of white solid (92.3%), mp 47—49 °C.

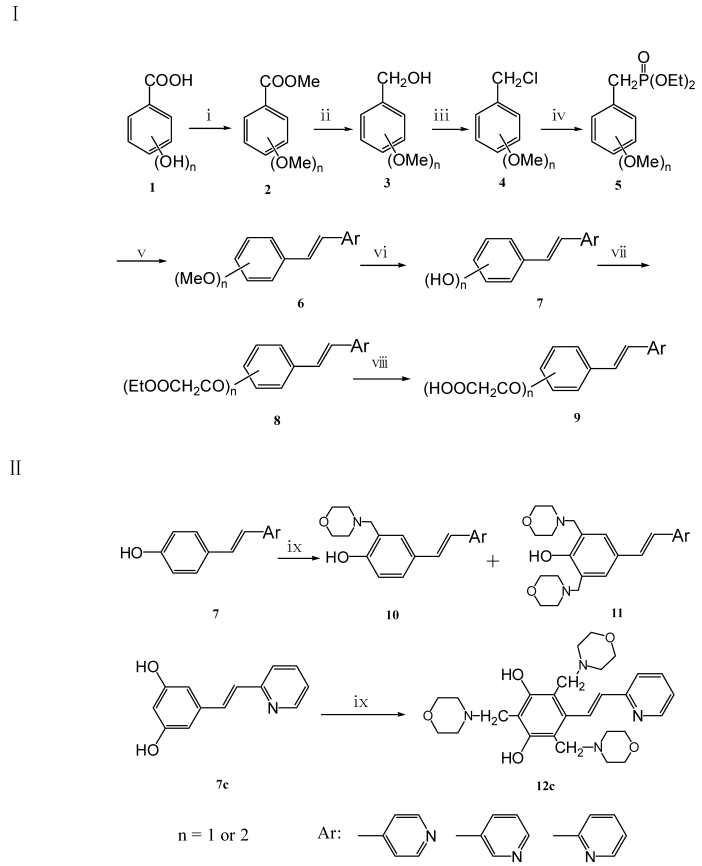
4-Methoxybenzyl Alcohol (3b) Compound **3b** was prepared in the above method as colorless oil (94.4%).

3,5-Dimethoxybenzyl Chloride (4a) To a well-stirred solution of 3,5-dimethoxy benzyl alcohol (16.8 g, 0.1 mol) in anhydrous ether (150 ml) was added $SOCl_2$ (15 ml, 0.2 mol) and the mixture was stirred for 3 h at room temperature, then poured into water, and extracted with ether (50 ml×3) and the organic layer was dried over $MgSO_4$ and concentrated to afford 18.9 g of white solid (94.4%), mp 46—47 °C (lit. [10)] 46 °C).

4-Methoxybenzyl Chloride (4b) Compound **4b** was prepared in the same way as a yellowish oil (93.8%).

General Procedure for Wittig-Horner Reaction. A. Diethyl (3,5-Dimethoxybenzyl) Phosphonate (5a) A mixture of 3,5-dimethoxybenzyl chloride (3.7 g, 0.02 mol) and triethyl phosphate (7 ml, 0.04 mol) was refluxed for 4 h, then the excess triethyl phosphate was removed *in vacuo* and

* To whom correspondence should be addressed. e-mail: guoliang222@yahoo.com.cn



Reagents and conditions: ⅰ. Me_2SO_4, K_2CO_3, CH_3COCH_3, reflux 3 h, 93.6～95.3%; ⅱ. $LiAlH_4$, Et_2O, reflux 4 h, 92.3～94.4%; ⅲ. $SOCl_2$, Et_2O, rt 3 h, 93.8～94.4%; ⅳ. $P(OEt)_3$, reflux 3 h; ⅴ. NaOEt, RCHO, DMF, rt 3 h, 65～70% (for ⅳ, ⅴ steps), ⅵ. BBr_3, CH_2Cl_2,-10℃ 2 h, 60～88%; ⅶ. $ClCH_2COOEt$, KOH, DMF, rt 4 h,75～80%; ⅷ. NaOH, rt 1 h, HCl, 68.5～81.5%; ⅸ. 36% HCHO, morpholine, EtOH, reflux 2h.

Chart 1. The Synthetic Route of Target Compounds

Table 1. The Structures and Physical Data of Target Compounds

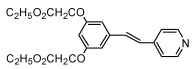
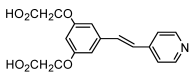
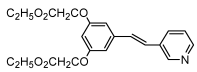
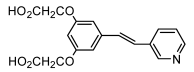
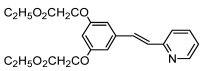
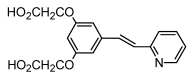
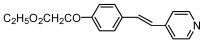
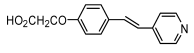
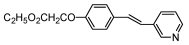
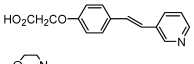
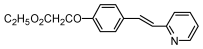
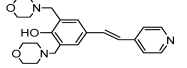
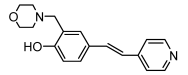
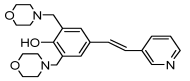
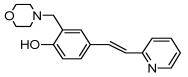
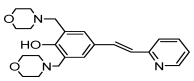
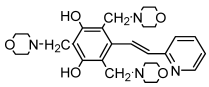
Compd.	Structure	mp (°C)	Compd.	Structure	mp (°C)
8a		89—91	**9a**		135—137
8b		92—94	**9b**		150—153
8c		65—67	**9c**		235—238
8d		91—93	**9d**		258—260
8e		82—83	**9e**		225—228
8f		106—108	**11a**		150—151
10a		154—156	**11b**		136—137
10c		93—95	**11c**		90—93
12c		75—78			

Table 2. Inhibitory Effects of Some Target Compounds and Intermediates on Xylene-Induced Mouse Ear Edema

Compoud	Dose (mg/kg)	Number of mice	Edema mean±S.D. (mg)	Inhb. rate (%)
CMC-Na	—	10	15.8±5.0	—
Ibupr.	200	10	9.1±3.2**	42.2
Resveratrol	200	10	9.7±4.0**	38.9
8c	200	10	13.2±2.8	16.4
8d	200	10	12.0±4.2*	24.0
9b	200	10	13.2±4.6	16.4
9c	200	10	10.0±2.5**	37.0
9d	200	10	11.0±2.7**	30.4
9e	200	10	12.7±3.7	19.6
10c	200	10	13.5±4.2	14.6
11a	200	10	12.2±2.2*	22.8
11b	200	10	10.4±4.6**	34.2
12c	200	10	10.4±4.0**	34.2
6a	200	10	11.5±3.7*	27.2
7a	200	10	11.8±3.3*	25.3
7b	200	10	12.4±4.1*	21.5

* $p<0.05$, ** $p<0.01$ compared with CMC-Na group.

the orange oil was dissolved in DMF (15 ml) and used without further purification.

B. Diethyl (4-Methoxybenzyl) Phosphonate (5b) Compound **5b** was prepared in the same way.

The Preparation of (*E*)-Stilbenes (6) To a well-stirred above solution of phosphonate (**5a**, **b**) was added sodium ethoxide (made of 0.54 g sodium and 10 ml absolute alcohol), 5 min later, was added appropriate aldehyde at room temperature. The mixture was stirred for 3 h at the same temperature and poured to water to provide the desired *E*-stilbenes **6**.

(*E*)-4-[2-(3,5-Dimethoxyphenyl)vinyl]pyridine (**6a**): Yield 68.5%, white needle solid, mp 139—141 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.84 (6H, s), 6.45 (1H, s), 6.69 (2H, d), 7.01 (1H, d, J=18.6 Hz), 7.23 (1H, d, J=18.6 Hz), 7.36 (2H, d, J=6.2 Hz), 8.58 (2H, d, J=5.9 Hz).

General Procedure for Demethylation. The Preparation of Compounds 7 To a well-stirred solution of compounds **6** in CH_2Cl_2 was added BBr_3 (1.3 mol for 1 mol methoxy) in CH_2Cl_2 at −10 °C. After the mixture was stirred for 4 h at −5—0 °C, the reaction mixture was poured into ice-water. The precipitate was collected and recrystallized in alcohol or methanol.

(*E*)-5-[2-(Pyridin-4-yl)vinyl]benzene-1,3-diol (**7a**): Yield 78.5%, yellow powder, mp 260—263 °C (dec). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.24 (1H, s), 6.51 (2H, br s), 7.12 (1H, d, J=16.4 Hz), 7.49 (1H, d, J=16.4 Hz), 7.74 (2H, d, J=5.6 Hz), 8.60 (2H, d, J=5.6 Hz), 9.41 (2H, s).

(*E*)-5-[2-(Pyridin-3-yl)vinyl]benzene-1,3-diol (**7b**): Yield 74.8%, yellow powder, mp 230—233 °C (dec). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.18 (1H, s), 6.46 (2H, d), 7.07 (1H, d, J=16.5 Hz), 7.23 (1H, d, J=16.5 Hz), 7.38 (1H, m), 8.03 (1H, d, J=7.7 Hz), 8.43 (1H, br s), 8.75 (1H, s), 9.32 (2H, s).

General Procedure for Preparation of Compounds 8 A solution of KOH (1 mol for 1 mol hydroxyl) in methanol was added to a well-stirred solution of compounds **7** in methanol at room temperature. The resulting mixture was stirred for 30 min and removal of the solvent *in vacuo* to afford a solid. DMF was added to dissolve the residue and ethyl chloroacetate (1.3 mol for 1 mol hydroxyl) was added to the resulting solution at 40 °C. The reaction mixture was stirred for 1 h at the same temperature and poured into water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$. Removal of ethyl acetate in reduced pressure provide the crude product. The crude product was separated by silica gel column chromatography (hexane/ethyl acetate 20 : 1) to afford the compounds **8**.

Ethyl [3-Ethoxycarbonylmethoxy-5-[(*E*)-2-pyridin-4-ylvinyl]phenoxy]acetate (**8a**): Yield 63.5%, white solid, mp 89—91 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (6H, t, J=7.1 Hz, CH_3), 4.30 (4H, q, J=7.1 Hz, –OCH_2–), 4.65 (4H, s), 6.48 (1H, s), 6.72 (2H, d, J=2.1 Hz), 6.95 (1H, d, J=16.2 Hz, –CH=CH–), 7.18 (1H, d, J=16.2 Hz, –CH=CH–), 7.34 (2H, d, J=5.9 Hz), 8.58 (2H, d, J=5.9 Hz). ESI-MS m/z: 386.1 $[M+H]^+$. *Anal.* Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.14; H, 5.98; N, 3.40.

Ethyl [3-Ethoxycarbonylmethoxy-5-[(*E*)-2-pyridin-3-ylvinyl]phenoxy]acetate (**8b**): Yield 62.3%, light-yellow powder, mp 92—94 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.30 (6H, t, J=7.1 Hz, CH_3), 4.28 (4H, m, –OCH_2–), 4.64 (4H, s, –OCH_2Ph), 6.46 (1H, s), 6.72 (2H, s), 6.98 (1H, d, J=16.7 Hz, –CH=CH–), 7.15 (1H, d, J=16.7 Hz, –CH=CH–), 7.35 (1H, s), 7.87 (1H, d, J=7.1 Hz), 8.51 (1H, s), 8.73 (1H, s). ESI-MS m/z: 386.2 $[M+H]^+$. *Anal.* Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.10; H, 5.86; N, 3.49.

Ethyl [3-Ethoxycarbonylmethoxy-5-[(*E*)-2-pyridin-2-ylvinyl]phenoxy]acetate (**8c**): Yield 61.5%, white solid, mp 65—67 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (6H, t, J=7.1 Hz, CH_3), 4.27 (4H, q, J=7.1 Hz, –OCH_2–), 4.63 (4H, s, –OCH_2Ph), 6.47 (1H, s), 6.79 (2H, d, J=2.0 Hz), 7.15 (1H, d, J=16.0 Hz, –CH=CH–), 7.21 (1H, m), 7.42 (1H, d, J=7.7 Hz), 7.58 (1H, d, J=16.0 Hz, –CH=CH–), 7.73 (1H, t, J=7.2 Hz), 8.61 (1H, d, J=4.1 Hz). ESI-MS m/z: 386.2 $[M+H]^+$. *Anal.* Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.63; H, 5.78; N, 3.78.

Ethyl [4-[(*E*)-2-Pyridin-4-ylvinyl]phenoxy]acetate (**8d**): Yield 75.2%, yellow solid, mp 91—93 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (3H, t, J=7.1 Hz, CH_3), 4.30 (2H, q, J=7.1 Hz, –OCH_2–), 4.67 (2H, s, –OCH_2Ph), 6.92 (1H, d, J=16.2 Hz, –CH=CH–), 6.95 (2H, d, J=8.7 Hz), 7.27 (1H, d, J=16.2 Hz, –CH=CH–), 7.37 (2H, d, J=5.2 Hz), 7.51 (2H, d, J=8.6 Hz), 8.57 (2H, br s). ESI-MS m/z: 284.1 $[M+H]^+$, 567.3 $[2M+H]^+$. *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.13; H, 6.01; N, 4.83.

Ethyl [4-[(*E*)-2-Pyridin-3-ylvinyl]phenoxy]acetate (**8e**): Yield 77.3%, white solid, mp 82—83 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (3H, t, J=7.1 Hz, CH_3), 4.29 (2H, q, J=7.1 Hz, –OCH_2–), 4.65 (2H, s, –OCH_2Ph), 6.92 (2H, d, J=8.8 Hz), 6.94 (1H, d, J=16.8 Hz, –CH=CH–), 7.11 (1H, d, J=16.4 Hz, –CH=CH–), 7.29 (1H, m), 7.46 (2H, d, J=8.7 Hz), 7.82 (1H, d, J=8.0 Hz), 8.47 (1H, d), 8.70 (1H, s). ESI-MS m/z: 284.1 $[M+H]^+$. *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.95; H, 5.90; N, 4.75.

Ethyl [4-[(*E*)-2-Pyridin-2-ylvinyl]phenoxy]acetate (**8f**): Yield 74.5%, white solid, mp 106—108 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (3H, t, J=7.1 Hz, CH_3), 4.29 (2H, q, J=7.1 Hz, –OCH_2–), 4.64 (2H, s, –OCH_2Ph), 6.92 (2H, d, J=8.7 Hz), 7.06 (1H, d, J=16.1 Hz, –CH=CH–), 7.13 (1H, dd, J=4.9, 7.4 Hz), 7.37 (1H, d, J=7.8 Hz), 7.53 (1H, d, J=16.1 Hz, –CH=CH–), 7.54 (1H, d), 7.60 (1H, m), 7.66 (1H, m), 8.59 (1H, d, J=4.7 Hz). ESI-MS m/z: 284.2 $[M+H]^+$. *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.83; H, 5.88; N, 4.68.

General Procedure for Preparation of Compounds 9 Compounds **8** (1 mmol) were added to 4 M NaOH solution (10 ml). The resulting mixture was stirred for 1 h to afford a solution at room temperature. The solution was acidified and the precipitate was filtered off to provide compounds **9**.

[3-Carboxymethoxy-5-[(*E*)-2-pyridin-4-ylvinyl]phenoxy]acetic Acid (**9a**): Yield 68.5%, light-yellow powder, mp 135—137 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.73 (4H, s, –OCH_2Ph), 6.48 (1H, s), 6.86 (2H, d, J=2.0 Hz), 7.32 (1H, d, J=16.4 Hz, –CH=CH–), 7.53 (1H, d, J=16.3 Hz, –CH=CH–), 7.62 (2H, d, J=5.6 Hz), 8.58 (2H, d, J=4.9 Hz), 13.20 (2H, s, COOH). ESI-MS m/z: 328.0 $[M-H]^-$. *Anal.* Calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.95; H, 4.43; N, 4.09.

[3-Carboxymethoxy-5-[(*E*)-2-pyridin-3-ylvinyl]phenoxy]acetic Acid (**9b**): Yield 70.6%, light-yellow powder, mp 150—153 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.72 (4H, s, –OCH_2Ph), 6.48 (1H, s), 6.83 (2H, d, J=2.1 Hz), 7.40 (1H, d, J=16.6 Hz, –CH=CH–), 7.50 (1H, d, J=16.6 Hz, –CH=CH–), 7.77 (1H, dd, J=7.9, 5.4 Hz), 8.45 (1H, d, J=8.2 Hz), 8.65 (1H, d, J=5.1 Hz), 8.94 (1H, s), 13.10 (2H, s, COOH). ESI-MS m/z: 327.9 $[M-H]^-$, 657.0 $[2M-H]^-$. *Anal.* Calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.90; H, 4.31; N, 4.15.

[3-Carboxymethoxy-5-[(*E*)-2-pyridin-2-ylvinyl]phenoxy]acetic Acid (**9c**): Yield 69.2%, light-yellow powder, mp 235—238 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.72 (4H, s, –OCH_2Ph), 6.47 (1H, s), 6.85 (2H, d, J=2.1 Hz), 7.36 (1H, d, J=15.9 Hz, –CH=CH–), 7.37 (1H, m), 7.65 (1H, d, J=15.9 Hz, –CH=CH–), 7.66 (1H, m), 7.92 (1H, m), 8.61 (1H, d, J=4.2 Hz), 13.05 (2H, br s, COOH). ESI-MS m/z: 327.9 $[M-H]^-$, 657.0 $[2M-H]^-$. *Anal.* Calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.85; H, 4.35; N, 4.11.

[4-[(*E*)-2-Pyridin-4-ylvinyl]phenoxy]acetic Acid (**9d**): Yield 80.0%, yellow solid, mp 225—228 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.74 (2H, s, –OCH_2Ph), 7.00 (2H, d, J=8.8 Hz), 7.26 (1H, d, J=16.3 Hz, –CH=CH–), 7.57 (2H, d, J=8.8 Hz), 7.58 (1H, d, J=16.3 Hz, –CH=CH–), 7.90 (1H, m), 8.60 (1H, m), 8.68 (1H, d, J=5.2 Hz), 9.00 (1H, s), 13.00 (1H, br s, COOH). ESI-MS m/z: 256.0 $[M+H]^+$, 253.9 $[M-H]^-$. *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.29; H, 5.11; N, 5.30.

[4-[(*E*)-2-Pyridin-3-ylvinyl]phenoxy]acetic Acid (**9e**): Yield 81.5%, yellow solid, mp 258—260 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.77 (2H, s,

–OCH_2Ph), 7.02 (2H, d, J=8.8 Hz), 7.37 (1H, d, J=16.3 Hz, –CH=CH–), 7.70 (2H, d, J=8.7 Hz), 7.94 (1H, d, J=16.3 Hz, –CH=CH–), 8.11 (2H, d, J=6.4 Hz), 8.78 (2H, d, J=6.3 Hz), 13.10 (1H, br s, COOH). ESI-MS m/z: 256.0 $[M+H]^+$, 253.8 $[M-H]^-$, 508.9 $[2M-H]^-$. *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.35; H, 5.07; N, 5.15.

General Procedure for the Mannich Reaction To a well-stirred solution of **7** (4—20 mmol) in 1,4-dioxane (10—50 ml) was added amine (morpholine 5—50 mmol) and 37% formaldehyde (6—60 mmol). The resulting mixture was refluxed for 24 h and then concentrated to give a viscous solid *in vacuo*. The viscous solid was dissolved in 5% HCl (20—100 ml) and extracted with dichloromethane (10—30 ml, two times). The water phase was basified to pH 11 and extracted with dichloromethane (30—50 ml, 4 times). The combined organic phase was washed with water and dried over anhydrous $MgSO_4$ and removal of dichloromethane provided the crude products. The crude product was recrystallized from alcohol or separated by silica gel column chromatography (CH_2Cl_2/ethyl acetate 10 : 1).

2-Morpholin-4-ylmethyl-4-[(*E*)-2-pyridin-4-ylvinyl]phenol (**10a**): Yield 28.7%, white needle solid, mp 154—156 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.60 (4H, m), 3.75 (2H, s, $PhCH_2$-N), 3.77 (4H, m), 6.84 (1H, d, J=16.1 Hz, –CH=CH–), 6.83 (1H, s), 7.20 (1H, d), 7.21 (1H, d, J=16.2 Hz, –CH=CH–), 7.31 (2H, d, J=5.9 Hz), 7.38 (1H, dd, J=8.4, 2.0 Hz), 8.54 (2H, d, J=5.7 Hz). ESI-MS m/z: 297.2 $[M+H]^+$, 294.9 $[M-H]^-$. *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.04; H, 6.70; N, 9.31.

2-Morpholin-4-ylmethyl-4-[(*E*)-2-pyridin-2-ylvinyl]phenol (**10c**): Yield 25.8%, white solid, mp 93—95 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.61 (4H, s), 3.74 (2H, s, $PhCH_2$-N), 3.76 (4H, s), 6.84 (1H, d, J=8.4 Hz), 7.02 (1H, d, J=16.1 Hz, –CH=CH–), 7.14 (2H, m), 7.37 (1H, d, J=7.9 Hz), 7.44 (1H, m), 7.56 (1H, d, J=16.1 Hz, –CH=CH–), 7.67 (1H, m), 8.58 (1H, d, J=3.9 Hz). ESI-MS m/z: 297.1 $[M+H]^+$, 294.9 $[M-H]^-$. *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.10; H, 6.47; N, 9.20.

2,6-Bis(morpholin-4-ylmethyl)-4-[(*E*)-2-pyridin-4-ylvinyl]phenol (**11a**): Yield 42.3%, light-green solid, mp 150—151 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.58 (8H, m), 3.68 (4H, s, $PhCH_2$-N), 3.76 (8H, m), 6.86 (1H, d, J=16.3 Hz, –CH=CH–), 7.20 (1H, d, J=16.3 Hz, –CH=CH–), 7.29 (2H, s), 7.32 (2H, d, J=6.1 Hz), 8.54 (2H, d, J=6.0 Hz). ESI-MS m/z: 396.2 $[M+H]^+$, 394.0 $[M-H]^-$. *Anal.* Calcd for $C_{23}H_{29}N_3O_3$: C, 69.85; H, 7.39; N, 10.62. Found: C, 70.10; H, 7.34; N, 10.90.

2,6-Bis(morpholin-4-ylmethyl)-4-[(*E*)-2-pyridin-3-ylvinyl]phenol (**11b**): Yield 38.5%,white solid, mp 136—137 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.58 (m, 8H), 3.55 (4H, s, $PhCH_2$-N), 3.79 (8H, m), 6.93 (1H, d, J=16.4 Hz, –CH=CH–), 7.08 (1H, d, J=16.4 Hz, –CH=CH–), 7.25 (1H, m), 7.30 (2H, d, J=3.4 Hz), 7.80 (1H, m), 8.46 (1H, m), 8.71 (1H, d, J=2.0 Hz). ESI-MS m/z: 396.2 $[M+H]^+$, 394.0 $[M-H]^-$. *Anal.* Calcd for $C_{23}H_{29}N_3O_3$: C, 69.85; H, 7.39; N, 10.62. Found: C, 70.15; H, 7.56; N, 10.85.

2,6-Bis(morpholin-4-ylmethyl)-4-[(*E*)-2-pyridin-2-ylvinyl]phenol (**11c**): Yield 40.5%, light-yellow solid, mp 90—93 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.59 (8H, m), 3.68 (4H, s, $PhCH_2$-N), 3.77 (8H, m), 7.03 (1H, d, J=16.1 Hz, –CH=CH–), 7.11 (1H, m), 7.36 (3H, m), 7.53 (1H, d, J=16.1 Hz, –CH=CH–), 7.65 (1H, m), 8.58 (1H, d, J=4.3 Hz). ESI-MS m/z: 396.2 $[M+H]^+$, 394.0 $[M-H]^-$. *Anal.* Calcd for $C_{23}H_{29}N_3O_3$: C, 69.85; H, 7.39; N, 10.62. Found: C, 69.95; H, 7.49; N, 10.88.

2,4,6-Tri(morpholin-4-ylmethyl)-5-[(*E*)-2-pyridin-2-ylvinyl]benzene-1,3-diol (**12c**): Yield 50.2%, light-yellow solid, mp 75—78 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.53 (8H, m), 2.60 (4H, m), 3.68 (6H, s, $PhCH_2$-N), 3.76 (12H, m), 6.59 (1H, d, J=16.3 Hz, –CH=CH–), 7.20 (1H, m), 7.32 (1H, d, J=7.9 Hz), 7.69 (1H, d, J=16.4 Hz, –CH=CH–), 7.62 (1H, m), 8.63 (1H, d, J=4.0 Hz). ESI-MS m/z: 511.3 $[M+H]^+$, 509.1 $[M-H]^-$. *Anal.* Calcd for $C_{28}H_{38}N_4O_5$: C, 65.86; H, 7.50; N, 10.97. Found: C, 65.68; H, 7.22; N, 10.68.

Evaluation of Anti-inflammatory Effect *in Vivo* All tested compounds were homogenized with 0.5% sodium carboxymethylcellulose and administered orally to Swiss male mice (22—26 g body weight, 10 animals per group) at a dose of 200 mg/kg. Control mice received the vehicle only (0.5% sodium carboxymethylcellulose, 0.2 ml/10 g). One hour later, the mice were anaesthetized and 30 μl xylene was applied to the surface of the right ear by a micropipette. After 20 min, mice were sacrificed and a plug (7 mm diameter) was excised from both the treated and untreated ears: edema was quantified by the difference in weight between the two plugs. The anti-inflammatory activity was expressed as percent reduction of the control mice using as reference, the NSAID Ibuprofen. Edema values, expressed as mean±standard deviation, were evaluated statistically using Student's t-test. A level of $p<0.05$ was adopted as the test of significance.

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