Hypoxic Radiosensitizers: Substituted Styryl Derivatives

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A number of novel styryl epoxides, *N*-substituted-styryl-ethanolamines, *N*-mono and *N,N'*-bis-(2-hydroxyethyl)-cinnamamides - analogues to the known radiosensitizers RSU- 1069, pimonidazole and etanidazole - display selective hypoxic radiosensitizing activity. The styryl group, especially when substituted by electron withdrawing groups, was found to be bioisosteric to the nitroimidazolyl functionality. The most active derivative 2-(2'-nitrophenyl)ethen-1-yl-oxirane **8a** displayed a sensitizer enhancement ratio (SER) of 5 relative to misonidazole.

Strahlensensibilisierende Verbindungen für hypoxische Zellen: Styrol-Derivate

Verschiedene chemische Strukturen besitzen strahlensensibilisierende Eigenschaften. Hauptsächlich handelt es sich um Nitro-Heterocyclen, insbesondere Nitroimidazole, z.B. Misonidazol (**1**)[1], Etanidazol (**2**)[2], Pimonidazol (**3**)[3], RSU-1069 (**4**)[4], das ein Nitroimidazol und ein alkylierendes Aziridin beinhaltet, und Propanolamino-Derivate **5**, die man durch Reaktion von Epoxiden mit Aminen erhält[5]. Die strahlensensibilisierenden Acridin-Derivate **6** haben eine 10^5-fach höhere selektive Toxizität gegenüber hypoxischen Zellen als **1**. Diese selektive Cytotoxizität könnte durch reduzierende Eigenschaften dieser Verbindung im biologischen Bereich bedingt sein. Noch stärkere Sensibilisatoren[8] und die Racemattrennung von **4** ($R^1 = R^2 = H$) wurden kürzlich beschrieben[9].

Various chemical structures have been associated with compounds possessing hypoxic cell radiosensitizing properties. The most frequently investigated derivatives are substituted nitro-heterocycles, primarily nitroimidazoles, such as misonidazole **1**[1], etanidazole **2**[2], pimonidazole **3**[3], compound **4** (RSU-1069)[4] which combines a nitroimidazole and an aziridinyl alkylating group, and propanolamino derivatives **5** obtained[5] upon reaction of epoxides with amines. The nitroacridine derivatives **6**, which also possess radiosensitizing qualities, exhibits 10^5 fold higher selective toxicity toward hypoxic cells than **1**[6]. This selective cytotoxicity[7] may be attributed to the radiosensitizers' bioreductive qualitites. More potent radiosensitizers[8] and the resolution of **4** ($R^1 = R^2 = H$) have been described recently[9].

This paper describes synthesis and biological properties of styryl derivatives **8-10**, substituted with electron withdrawing groups, primarily nitro. Some of these nitrostyryl derivatives disply *in vitro* radiosensitizing activity similar to that of the nitroimidazoles. In addition to the electron-withdrawing substituted styryl group, the prepared compounds possess a second functionality such as: a) an epoxide (**8**), isosteric to the aziridinyl alkylating group, b) an *N*-substituted ethanolamine (**9**), or c) an *N*-mono- (**15**) or an *N,N*-bis-(2-hydroxyethyl)amido (**16**) group. For further comparative purposes, several aryl-oxiranes **12** were prepared in order to evaluate the importance of the linking moiety, a single bond *vs.* a CH=CH group, between the aromatic ring and the oxirane ring.

Chemistry

Styryl oxiranes **8** were obtained by epoxidation[10] of the corresponding cinnamaldehydes **7**, which are commercial products, or were prepared by: a) aldol condensation of the respective arylaldehydes **11** and acetaldehyde[11]; or b) *Wittig-Horner*[12] or *Perkin*[13] type condensations of the arylaldehydes **11** to give the corresponding cinnamic acids **13** which in turn were converted to acyl chlorides **14** and were then reduced to the cinnamaldehydes **7** with $LiAl(O\text{-}tBu)_3H$[14]. Attempted synthesis of **8k** *via* initial epoxidation of 4-dimethylamino-cinnamaldehyde (**7k**) failed, because of the poor electrophilic character of the carbonyl group. However, the ammonium derivative **7l**, obtained by methylation of **7k**, was readily epoxidized. Epoxidation of 2-(5'-nitro-2'-furanyl)-2-propenal **7o** proceeded in poor yield due to extensive polymerization. Styryl epoxides **12** were prepared from the corresponding arylaldehydes **11**[10]. *N*-Substituted-ethanolamine derivatives **9** were obtained by treatment of the corresponding epoxides with prim. or sec. amines. In all cases small amounts of the isomeric aminoethanols **10** were also isolated. Alternatively, compounds **9** were prepared by the conversion of the acyl halides **14** to cyanides **17**[15], followed by reduction in acetone[16]. *N*-Mono- [**15**] and *N,N*-bis-(2-hydroxyethyl)amides **16** were derived from the corresponding acyl halides **14** and ethanolamine or *N,N*-bis-ethanolamine[14] (Scheme).

Biological Evaluation

For evaluation of the prepared compounds as radiosensitizers under both aerobic and hypoxic conditions, Chinese hamster ovary (CHO) HA1 cells were used. The solubility of the compounds was first determined in 1% DMSO in

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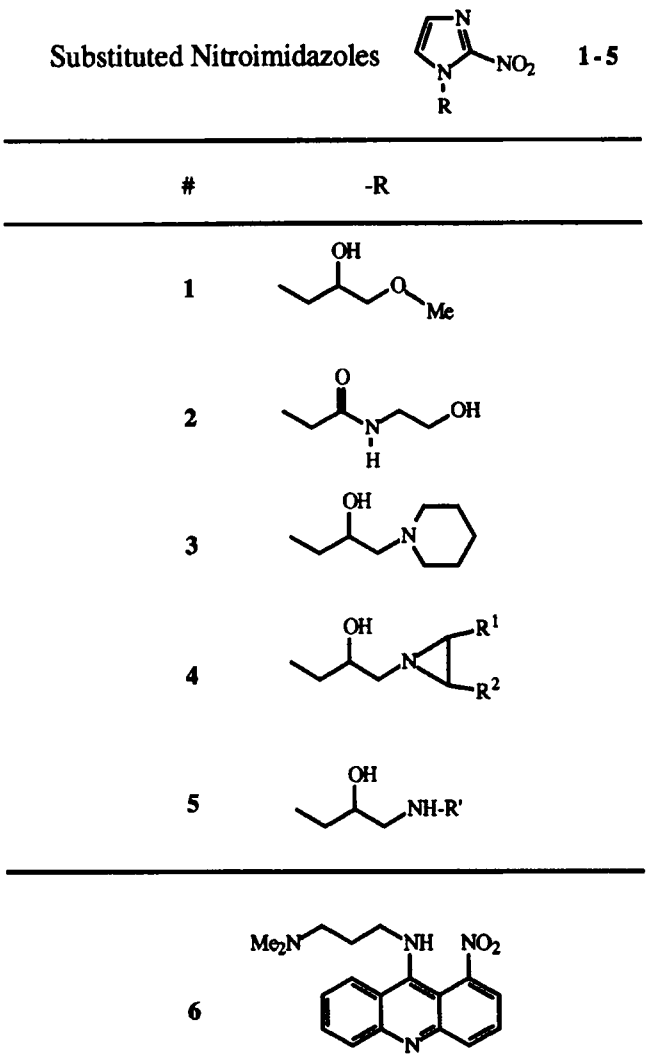


Scheme 1

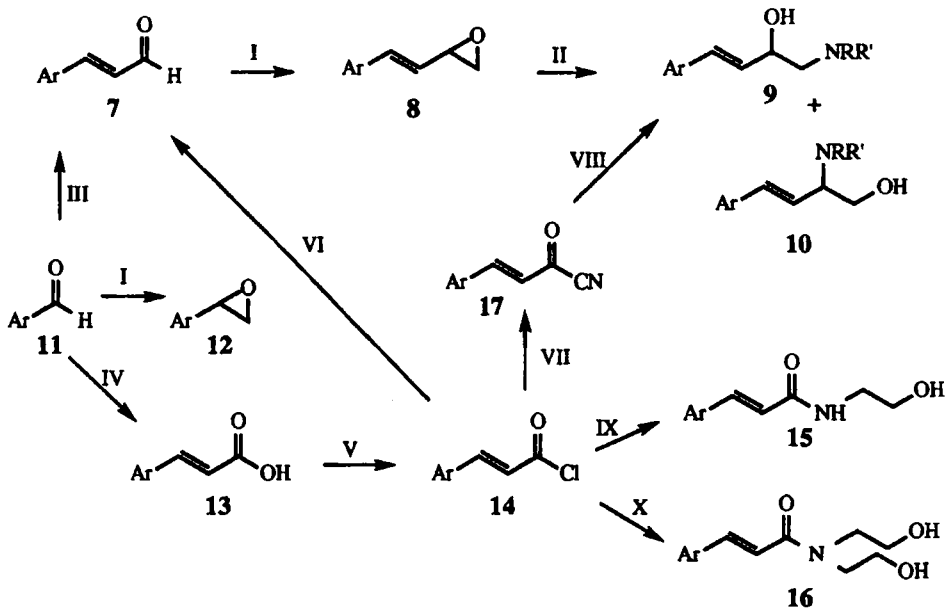
serum free *Eagle's* minimal essential medium (MEM). Radiosensitization was tested at a single drug concentration which was either 2 mM or the maximum soluble limit (in all cases ≥ 0.2 mM). 10^4 CHO cells were plated in 16 mm glass Petri dishes in Eagle's MEM, plus 10% fetal calf serum. Three days later, the medium was replaced by 2 ml of serum free MEM, plus 1% DMSO containing the appropriate concentration of the drug. The dishes were then placed into aluminum gassing chambers, and a vacuum was applied to reduce the air to 0.1 atm. The chambers were then gassed with ultra pure N_2 containing 5% CO_2, at a flow rate of 1.0 L/min. Evacuation and N_2 gassing were repeated five times, with 1 min intervals between gassing. To expedite gas exchange between the media and the air, the aluminum chambers were continuously shaken during the procedure. After the final gassing, the chambers were sealed, and at 0.5 h after the start of the gassing, were irradiated with ^{137}Cs γ rays at a dose rate of 0.9 Gy/min. For the hypoxic exposures, a single dose of 20 Gy, for the aerobic exposures, a single dose of 7.5 Gy was used. As an internal check of hypoxia and radiosensitization all chambers had a dish containing cells with 2 mM misonidazole (**1**).

Immediately following irradiation, the cells were trypsinized from the dish, counted and appropriate dilutions made in plastic Petri dishes. These were incubated for 13-15 days, at which point the medium was removed and the dishes fixed and stained with 1% crystal violet, and colonies containing > 50 cells were counted. The surviving fractions were fitted using the multi-target single hit model, assuming a common extrapolation number for the drug and control groups. The ratio of the slopes of the no drug/drug groups defined the sensitizer enhancement ratio (SER) from which the concentration to achieve an SER of 1.6 was determined assuming the same shape of the curve as misonidazole (**1**) and other 2-nitroimidazole radiosensitizers determined in our laboratory.

Table. *In Vitro* Radiosensitizing Activity of Ar-CH=CH-R Derivatives

Compound	C1.6 Drug	C1.6 Miso	SER	Cytotox. Air	Cytotox. N_2
8a	0.2	1	5	>1	>1
8b	NS (2.0)	0.8	NS	>0.2	>0.2
8c	NS (0.2)	2	NS	>0.2	>0.2
8d	NS (2.0)	0.8	NS	>0.2	>0.2
8f	NS (0.2)	2	NS		>1
9a	NS (0.2)	3	NS	>0.2	>0.2
9a"	1.7	4	2.4	>0.2	>0.2
12b	NS (0.2)	4	NS	>0.2	>0.2
12c	3	5	1.6		>1
12i	2.5	5	2		>1
15a	NS (2.0)	>2	NS	>2	>2
15b	NS (2.0)	>2	NS	>2	>2
15c	NS (0.4)	3	NS	>0.4	0.4
16a	NS (0.02)	1	NS	0.02-0.2	0.02-0.2

Aromatic substituent designation: **a)** 2-NO_2-C_6H_4-; **b)** 3-NHO_2-C_6H_4-; **c)** 4-NO_2-C_6H_4-; **d)** 2-CF_3-C_6H_4-; **f)** 2-furanyl-; **i)** 5-Cl-2-NO_2-C_6H_3-.
N-alkyl substituent designation: **9a)** NR^1R^2 = tBuNH; tBuNH; **9a")** NR^1R^2 = piperidinyl.



I) Me_3S^+ I⁻/NaOH/CH_2Cl_2; II) RR'NH/MeOH; III) MeCHO/KOH/MeOH; IV) $(EtO)_2POCH_2COOEt$/KOH or AcOK/Ac_2O; V) $SOCl_2$/pyridine; VI) LiAl(O-t-Bu)$_3$H; VII) Bu_3SnCN; VIII) [H]/acetone; IX) $HOCH_2CH_2NH_2$; X) $(HOCH_2CH_2)_2NH$

Aryl substituent designation: **a)** 2-NO_2-C_6H_4; **b)** 3-NO_2-C_6H_4; **c)** 4-NO_2-C_6H_4; **d)** 2-CF_3-C_6H_4; **e)** 3-CF_3-C_6H_4; **f)** 4-CF_3-C_6H_4; **g)** 4-Cl-3-NO_2-C_6H_3; **h)** 2-Cl-5-NO_2-C_6H_3; **i)** 5-Cl-2-NO_2-C_6H_3; **j)** 4-CN-C_6H_4; **k)** 4-Me_2N-C_6H_4 **l)** 4-Me_3N^+-C_6H_4; **m)** 1-naphthalenyl; **n)** 2-furanyl; **o)** 5-NO_2-2-furanyl
RNR': *t*BuNH; piperidinyl; *i*PrNH

Scheme 2

Compounds which did not contain aromatic rings substituted by nitro groups were inactive. In general the highest SER values were obtained in compounds where the nitro group was found *ortho* to the group which carried the epoxide function. This is evident in both the styryl and phenyl series. Thus, *o*-nitro derivatives **8a**, **9a** and **9a''** were the most active whereas the *m*-nitro **8b** and **p**-nitro **8c** were inactive. *o*-Nitro **12i** was more active than *p*-nitro **12c** and both were more active than *m*-nitro **12b** which was inactive altogether. However, it is surprising that the *p*-nitro **8c** was inactive, since **12c** did show activity.

Introduction of a *tert.* amino alcohol on the side chain afforded **9a''** (analogous to pimonidazole (**3**)) which was more active than the sec. amino alcohol **9a**. Here the greater lipophilicity and weaker hydrogen bonding ability of the tert. amine may be the controlling factor. Addition of a second electron withdrawing group to the aromatic ring may be of value since **12i** was more active than **12b** or **12c**, however, the *o*-nitro substituent may be the determining factor. *Mono*-ethanolamido derivatives **15**, even though they possessed aromatic nitro-substituents, did not display activity. The *bis*-ethanolamide **16a** did show some activity but was less active than the corresponding epoxide. Compound **8a** when tested *in vivo* at the highest concentration possible in water was inactive; the lack of activity may be related to its very poor water solubility.

Experimental Part

General remarks

^{1}H-NMR spectra 300 MHz: Brucker WH-300, $DCCl_3$, CD_3-CO-CD_3, or [D_6]DMSO/TMS.- Mass spectra: Varian Mat 731 (CI = chemical ionization, EI = electron ionization).- Progress of reactions was monitored by tlc on silica gel (Merck, Art. 5554) or alumina (Riedel-de Haen, Art. 37349).- Flash chromatography: silica gel (Merck, Art. 9385). The 3- and 4-nitro-, 5-chloro-2-nitro-benzaldehydes; 2- and 4-nitro-cinnamaldehydes; 2-, 3-, and 4-nitro-, 2-, 3-, and 4-trifluoromethyl-, 4-chloro-3-nitro-, and 2-chloro-5-nitro-cinnamic acids were purchased from Aldrich.

Synthesis of Aryl-2-propenals (**7**)

Acetaldehyde (20 mL) was added dropwise to a cold (-10°C) substituted-benzaldehyde **11** (33 mmol). To the solution so obtained, 20% KOH (0.5 mL) in MeOH was slowly added at 0-5°C, followed by the addition of Ac_2O (16 mL). The mixture was heated to 100°C for 30 min, poured into hot water (120 mL), acidified with conc. HCl (16 mL) and further heated

to 100°C for 20 min. Upon cooling overnight, the yellow precipitate obtained was filtered, washed with water and recrystallized from 30% AcOH (160 mL).

3-(3'-Nitrophenyl)-2-propenal (**7b**)

Yield 86%; mp. 109-110°C (lit.[11]: 109-110°C).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.83 (dd, J = 16; 8 Hz, 1H, CHCH=O), 7.53 (d, J = 16 Hz, 1H, ArCH), 7.65 (t, J = 8 Hz, 1H, 5'-H), 7.89 (m, 1H, 4'-H), 8.30 (ddd, J = 8; 2.5; 1.5 Hz, 1H, 6'-H), 8.42 (t, J = 1.5 Hz, 1H, 2'-H), 9.77 (d, J = 8 Hz, 1H, HC=O).

3-(2'-Trifluoromethyl)-2-propenal (**7d**)

Yield 86%, mp. 137-139°C (lit.[20]: 63-70°C/0.5 Torr).- MS (CH_4; CI^+): m/z = 201 (MH^+), 181 (MH^+ - HF), 153 (MH^+ - HF - CO).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.70 (dd, J = 16; 8 Hz, 1H, CHCH=O), 7.54 (bt, J = 7 Hz, 1H, 5'-H), 7.64 (bt, J = 7 Hz, 1H, 4'-H), 7.77 (m, 2H, 3'-H, 6'-H), 7.89 (dq, J = 16; 2 Hz, 1H, Ar-CH), 9.77 (d, J = 8 Hz, 1H, HC=O).

3-(4'-Trimethylammonium-phenyl)-2-propenal (**7l**)

A solution of **7k** (1 g, 5.7 mmol) and MeI (1.06 mL, 17.1 mmol) in DMF (15 mL) was heated at 50°C for 2 h, and was then poured into ether. The precipitated **7l** was filtered, washed with ether and dried (1.74 g, 96%), mp. 173-175°C.- MS (CH_4; CI^+): m/z = 176 (MH - MeI)$^+$.- ^{1}H-NMR (D_2O): δ (ppm) = 3.68 (s, 9H, 3 x CH_3), 6.88 (dd, J = 16; 8 Hz, 1H, CHCO), 7.82 (d, J = 16 Hz, 1H, ArCH), 7.94 (s, 4H aromat.), 9.62 (d, J = 8, 1H, CH=O). $C_{12}H_{16}INO$ (317.2) Calcd. C 45.5 H 5.08 N 4.4 Found C 45.4 H 4.67 N 4.3.

3-(1'-Naphthalenyl)-2-propenal (**7m**)

To **14m** (3 g, 13.7 mmol) in diglyme (15 mL), under N_2 at -78°C, was added $LiAl(O\text{-}tBuO)_3H$ (1.02 g, 4 mmol) in diglyme (20 mL). The mixture was stirred for 1 h allowing it to reach room temp. and was then poured into ice-water. The brown precipitate so obtained was filtered, washed with water and recrystallized from 95% EtOH, to give **7m** (0.8 g, 30%), mp. 48-50°C (lit.[11b]: 48-50°C).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.82 (dd, J = 16; 8 Hz, 1H, CHCH=O), 7.48-7.64 (m, 3H, 3'-H + 6'-H + 7'-H), 7.80 (d, J = 8 Hz, 1H, 5'-H), 7.90 (d, J = 8 Hz, 1H, 4'-H), 7.94 (d, J = 8 Hz, 1H, 2'-H), 8.17 (d, J = 8 Hz, 1H, 8'-H), 8.31 (d, J = 16 Hz, 1H, ArCH), 9.83 (d, J = 8 Hz, 1H, HC=O).

Oxiranes: Expoxidation of 3-(Substituted-aryl)-2-propenals **7** *and Arylaldehydes* **12**

To a 3-(substituted-aryl)-2-propenal **7** or an arylaldehyde **11** (11.3 mmol) in CH_2Cl_2 (50 mL) was added trimethylsulfonium iodide (14 mmol), tetrabutylammonium iodide (23 mg, 0.06 mmol) and 50% NaOH (11.5 mL). The mixture was heated to reflux for 24 h and was then poured into ice-water (50 mL). The org. phase was separated, dried and evaporated and the residue so obtained was distilled in a kugelrohr apparatus.

2-(2'-Nitrophenyl)ethen-1-yl-oxirane (**8a**)

Yield 82%; mp. 32-34°C.- MS (iBu; CI^+): m/z = 192 (MH^+), 174 (MH^+ - H_2O), 162 (MH^+ - CH_2O), 146 (MH^+ - NO_2).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.80 (dd, J = 5; 2.5 Hz, 1H, CHH'), 3.10 (dd, J = 5; 4 Hz, 1H, CHH'), 3.58 (dddd, J = 8; 4; 2.5; 1 Hz, 1H, CHCH$_2$), 5.86 (dd, J = 16, 8 Hz, 1H, ArCH=CH), 7.32 (dd, J = 16; 1 Hz, 1H, ArCH), 7.42 (m, 1H, 4'-H), 7.55-7.62 (m, 2H, 5'-H + 6'-H), 7.96 (d, J = 8 Hz, 1H, 3'-H).

2-(3'-Nitrophenyl)ethen-1-yl-oxirane (**8b**)

Yield 82%; mp. 115-116°C.- MS (iBu; CI^+): m/z = 192 (MH^+), 174 (MH^+ - H_2O), 162 (MH^+ - CH_2O).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.80 (dd, J = 5.3; 3 Hz, 1H, CHH'), 3.09 (dd, J = 5.3; 4 Hz, 1H, CHH'), 3.55 (dddd, J = 8; 4; 3; 1 Hz, 1H, CHCH$_2$), 6.04 (dd, J = 16; 8 Hz, 1H, ArCH=CH), 6.85 (d, J = 16 Hz, 1H, ArCH), 7.55 (t, J = 8 Hz, 1H, 5'-H), 7.66 (d, J = 8 Hz, 1H, 6'-H), 8.11 (ddd, J = 8; 3; 2 Hz, 1H, 4'-H); 8.23 (d, J = 2 Hz, 1H, 2'-H).- $C_{10}H_9NO_3$ (191.2) Calcd. C 62.8 H 4.74 Found C 62.5 H 4.81.

2-(4'-Nitrophenyl)ethen-1-yl-oxirane (**8c**)

Yield 82%; mp. 58-59°C.- MS (iBu; CI^+): m/z = 192 (MH^+), 174 (MH^+ - H_2O), 146 (MH^+ - NO_2).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.81 (dd, J = 2.5; 1 Hz, 1H, CHH'), 3.13 (dd, J = 4; 2.5 Hz, 1H, CHH'), 3.58 (dddd, J = 8; 4; 2.5; 1 Hz, 1H, CHCH$_2$), 6.10 (dd, J = 16; 8 Hz, 1H, ArCH=CH), 6.87 (d, J = 16 Hz, 1H, ArCH); 7.53 and 8.18 (AA'XX' system, J = 8 Hz, 4H aromat.).

2-(2'-Trifluoromethyl)ethen-1-yl-oxirane (**8d**)

Yield 78%; mp. 118-120°C.- MS (EI$^+$): m/z = 214 ($M^{+\cdot}$), 197 (M - OH)$^+$, 186 (M - CO)$^{+\cdot}$, 177 (M - OH - HF)$^+$, 115 ($C_9H_7^+$).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.79 (dd, J = 2.5; 1 Hz, 1H, CHH'), 3.09 (dd, J = 4; 2.5 Hz, 1H, CHH'), 3.56 (dddd, J = 8; 4; 2.5; 1 Hz, 1H, CHCH$_2$), 5.86 (dd, J = 16; 8 Hz, 1H, ArCH=CH), 7.19 (dq, J = 16; 2 Hz, 1H, ArCH), 7.35 (t, J = 10 Hz, 1H, 4'-H), 7.49 (t, J = 10 Hz, 1H, 5'-H), 7.62 (t, J = 10 Hz, 2H, 3'-H + 6'-H).

2-(4'-Trimethylammonium-phenyl)ethen-1-yl-oxirane iodide (**8l**)

Mp. 150-155°C.- ^{1}H-NMR (D_2O): δ (ppm) = 2.97-3.03 (m, 1H, CHH'), 3.22 (t, J = 5 Hz, 1H, CHH'), 3.66 (s, 9H, 3 x CH_3), 3.83-4.7 (m, 1H, CHCH$_2$), 6.10 (dd, J = 16; 8 Hz, 1H, CHCO), 7.01 (d, J = 16 Hz, 1H, ArCH), 7.70 and 7.81 (AA'XX' system, J = 9 Hz, 4H aromat.).

2-(1'-Naphthalenyl)ethen-1-yl-oxirane (**8m**)

Yield 82%; bp. 112-114°C (0.5 Torr).- MS (NH_3; CI^+): m/z = 197 (MH^+), 179 (MH^+ - H_2O), 155 (MH^+ - CH_2CO).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.72 (dd, J = 2.5; 1 Hz, 1H, CHH'), 3.20 (dd, J = 4; 2.5 Hz, 1H, CHH'), 3.55 (dddd, J = 8; 4; 2.5; 1 Hz, 1H, CHCH$_2$), 5.85 (dd, J = 16; 8 Hz, 1H, ArCH=CH), 7.4-7.5 (m, 5H aromat.), 7.65-7.8 (m, 2H aromat.), 8.13 (dd, J = 16; 1 Hz, 1H, ArCH).

2-(2'-Furanyl)ethen-1-yl-oxirane (**8n**)

Yield 82%; bp. 70-72°C (0.5 Torr).- MS (iBu, CI^+): m/z = 137 (MH^+), 119 ($M^{+\cdot}$ - H_2O), 107 (MH^+ - CH_2O).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.71 (dd, J = 5; 2.5 Hz, 1H, CHH'), 3.01 (dd, J = 5; 4 Hz, 1H, CHH'), 3.43 (dddd, J = 8; 4; 2.5; 1 Hz, 1H, CHCH$_2$), 5.81 (dd, J = 16; 8 Hz, 1H, ArCH=CH), 6.25 (d, J = 3 Hz, 1H, 3'-H), 6.34 (dd, J = 3; 2 Hz, 1H, 2'-H), 6.58 (dd, J = 16; 1 Hz, 1H, ArCH), 7.32 (d, J = 2 Hz, 1H, 1'-H).

2-(5'-Nitro-2'-furanyl)ethen-1-yl-oxirane (**8o**)

Obtained as an oil in < 10% yield. MS (NH_3; CI^+): m/z = 182 (MH^+), 152 (MH^+ - CH_2O).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.77 (dd, J = 5; 2.5 Hz, 1H, CHH'), 3.10 (dd, J = 5; 4 Hz, 1H, CHH'), 3.51 (ddd, J = 8; 4; 2.5 Hz, 1H, CHCH$_2$), 6.32 (dd, J = 16; 8 Hz, 1H, ArCH=CH), 6.47 (d, J = 3 Hz, 1H, 3'-H), 6.63 (d, J = 16 Hz, 1H, ArCH), 7.31 (d, J = 3 Hz, 1H, 4'-H).

3-Nitrophenyl-oxirane (**12b**)[21]

^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.81 (dd, J = 8; 4 Hz, 1H, CHH'), 3.22 (dd, J = 6; 4 Hz, 1H, CHH'), 3.97 (dd, J = 4; 3 Hz, 1H, CHCH$_2$), 7.53 (dt,

J = 8; 2 Hz, 1H, 5'-H), 7.62 (dt, J = 8; 2 Hz, 1H, 6'-H), 8.15 (d, J = 2 Hz, 1H, 2'-H), 8.18 (m, 1-H, 4'-H).

4-Nitrophenyl-oxirane (**12c**)[21]

MS (EI$^+$): m/z = 165 ($M^{+\cdot}$), 164 (M - H$^\cdot$)$^+$, 136 ($C_7H_6NO_2^+$)[22].- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.78 (dd, J = 8; 4 Hz, 1H, CHH'), 3.22 (dd, J = 6; 4 Hz, 1H, CHH'), 3.96 (dd, J = 4; 3 Hz, 1H, CHCH$_2$), 7.48 and 8.22 (AA'XX' system, J = 8 Hz, 4H aromat.).

5-Chloro-2-nitrophenyl-oxirane (**12i**)

Mp. 36-38°C.- MS (EI$^+$): m/z = 200* (MH^+), 183, 170 (MH^+ - CH_2O), 154 (MH^+ - NO_2), 125 (C_7H_6Cl)$^+$ (* although spectrum was obtained in EI mode, outoprotonation took place).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.68 (dd, J = 8; 4 Hz, 1H, CHH'), 3.31 (dd, J = 6; 4 Hz, 1H, CHH'), 4.48 (dd, J = 4; 3 Hz, 1H, CHCH$_2$), 7.44 (dd, J = 10; 2 Hz, 1H, 4'-H), 7.61 (d, J = 2 Hz, 1H, 6'-H), 8.11 (d, J = 10 Hz, 1H, 3'-H).

1-Alkylamino-4-(substituted-aryl)but-3-ene-2-ols (**9**) *and 2-Alkylamino-4-(substituted-aryl)but-3-ene-1-ols* (**10**)

To a solution of an oxirane **8** in MeOH an excess of the appropriate prim. or sec. amine was added and the mixture was stirred at room temp. for 48-72 h. The solvent and excess unreacted amine were evaporated, and the residue which consisted of the 2-ol and 1-ol isomers, was dried under high vacuum over H_2SO_4, and was flash chromatographed, eluted with $CHCl_3$:MeOH:NH_3 70:10:1.

1-(tert-Butylamino)-4-(2'-nitrophenyl)but-3-ene-2-ol (**9a**) *and 2-(tert-Butylamino)-4-(2'-nitrophenyl)but-3-ene-1-ol* (**10a**)

Amines **9a** and **10a** were obtained from **8a** and tert-butylamine, in 42% and 17% yield, respectively.

Amine **9a**, mp. 58-60°C.- MS (EI$^+$): m/z = 265 (MH^+), 86 (CH_2=NH^+-tBu).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.19 (s, 9H, tBu), 2.66 (dd, J = 12; 8 Hz, 1H, CHH'), 2.93 (dd, J = 12, 4 Hz, 1H, CHH'), 4.41 (m, 1H, CHOH), 6.18 (dd, J = 16, 6 Hz, 1H, ArCH=CH), 7.13 (dd, J = 16; 1 Hz, 1H, ArCH), 7.38-7.61 (m, 3H, 4'-H + 5'-H + 6'-H), 7.91 (d, J = 8 Hz, 1H, 3'-H).

Amine **10a**, mp. 93-95°C.- MS (EI$^+$): m/z = 265 (MH^+), 233 (M - CH_2OH)$^+$, 177 (233 - C_4H_8)$^{+\cdot}$.- ^{1}H-NMR ($CDCl_3$; δ (ppm) = 1.18 (s, 9H, tBu), 3.31 (dd, J = 12; 8 Hz, 1H, CH-NH), 3.56-3.63 (m, 2H, CH_2), 6.20 (dd, J = 16; 6 Hz, 1H, ArCH=CH), 7.10 (dd, J = 16; 1 Hz, ArCH), 7.34-7.65 (m, 3H, 4'-H + 5'-H + 6'-H), 7.93 (d, J = 8 Hz, 1H, 3'-H).

1-(tert-Butylamino)-4-(3'-nitrophenyl)but-3-ene-2-ol (**9b**) *and 2-(tert-Butylamino)-4-(3'-nitrophenyl)but-3-ene-1-ol* (**10b**)

Amines **9b** and **10b** were obtained from **8b** and tert-butylamine in 45% and 15% yield, respectively.

Amine **9b**, mp. 50-52°C.- MS (EI$^+$): m/z = 265 (MH^+), 86 (CH_2=NH^+-tBu).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.21 (s, 9H, tBu), 2.62 (dd, J = 12; 8 Hz, 1H, CHH'), 2.93 (dd, J = 12; 4 Hz, 1H, CHH'), 4.40 (m; 1H, CHOH), 6.35 (dd, J = 16; 5 Hz, 1H, ArCH=CH), 6.78 (dd, J = 16; 1 Hz, 1H, ArCH), 7.46 (t, J = 8 Hz, 1H, 5'-H), 7.65 (d, J = 8 Hz, 1H, 4'-H), 8.04 (ddd, J = 8; 3; 2 Hz, 1H, 6'-H), 8.22 (t, J = 2 Hz, 1H, 2'-H).- $C_{14}H_{20}N_2O_3$ (264.3) Calcd. C 63.6 H 7.63 N 10.6 Found C 63.4 H 7.44 N 10.4.

Amine **10b**, mp 83-84°C.- MS (EI$^+$): m/z = 265 (MH^+), 233 (M^+ - CH_2OH)$^+$, 177 (233 - C_4H_8)$^{+\cdot}$.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.20 (s, 9H, tBu), 3.41 (dd, J = 12; 9 Hz, 1H, CHNH), 3.6-3.7 (m, 2H, CH_2), 6.53 (dd, J = 16; 5 Hz, 1H, ArCH=CH), 6.82 (dd, J = 16; 1 Hz, 1H, ArCH), 7.66 (t, J = 8 Hz, 1H, 5'-H), 7.83 (dm, J = 8 Hz, 1H, 4'-H), 8.10 (ddd, J = 8; 3; 2 Hz, 1H, 6'-H), 8.25 (d, J = 2 Hz, 1H, 2'-H).

1-(tert-Butylamino)-4-(4'-nitrophenyl)but-3-ene-2-ol (**9c**) *and 2-(tert-Butylamino)-4-(4'-nitrophenyl)but-3-ene-1-ol* (**10c**)

Amines **9c** and **10c** were obtained from **8c** and tert-butylamine in 45% and 20% yield, respectively.

Amine **9c**, mp. 78-80°C.- MS (CH_4, CI$^+$): m/z = 265 (MH^+), 247 (MH^+ - H_2O), 179 (MH^+ - H_2C - NH - tBu)$^{+\cdot}$.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.23 (s, 9H, tBu), 2.69 (dd, J = 12; 8 Hz, 1H, CHH'), 3.05 (dd, J = 12; 4 Hz, 1H, CHH'), 4.45 (m, 1H, CHOH), 6.39 (dd, J = 16; 6 Hz, 1H, ArCH=CH), 6.81 (dd, J = 16; 1 Hz, 1H, ArCH), 7.61 and 8.19 (AA'XX' system, J = 8 Hz, 4H aromat.).

Amine **10c**, mp. 85-87°C.- MS (CH_4, CI$^+$): m/z = 265 (MH^+), 247 (MH^+ - H_2O), 233 (M - CH_2OH)$^+$, 192 (MH^+ - tBu-NH_2).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.20 (s, 9H, tBu), 2.89 (dd, J = 12; 10 Hz, 1H, CHNH), 3.4-3.6 (m, 2H, CH_2), 6.29 (dd, J = 16; 6 Hz, 1H, ArCH=CH), 6.81 (dd, J = 16; 1 Hz, 1H, ArCH), 7.61 and 8.19 (AA'XX' system, J = 8 Hz, 4H aromat.).

1-(tert-Butylamino)-4-[(2'-trifluoromethyl)phenyl]but-3-ene-2-ol (**9d**) *and 2-(tert-Butylamino)-4-[(2'-trifluoromethyl)-phenyl]but-3-ene-1-ol* (**10d**)

Amines **9d** and **10d** were obtained from **8d** and tert-butylamine in 38% and 12% yield, respectively.

Amine **9d**, mp. 100-103°C.- MS (EI$^+$): m/z = 288 (MH^+), 254, 86 (CH_2=NH^+-tBu).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.18 (s, 9H, tBu), 2.65 (dd, J = 12; 8 Hz, 1H, CHH'), 2.90 (dd, J = 12; 4 Hz, 1H, CHH'), 4.40 (m, 1H, CHOH), 6.16 (dd, J = 16; 6 Hz, 1H, ArCH=CH), 7.05 (dd, J = 16; 2 Hz, 1H, ArCH), 7.36 (tm, J = 10 Hz, 1H, 4'-H), 7.52 (tm, J = 10 Hz, 1H, 5'-H), 7.59-7.63 (tm, J = 10 Hz, 2H, 3'-H + 6'-H).

Amine **10d**, mp. 93-95°C.- MS (EI$^+$): m/z = 288 (MH^+), 256 (M - CH_2OH)$^+$, 200 (256 - C_4H_8).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.18 (s, 9H, tBu), 3.65 (dd, J = 12; 8 Hz, 1H, CHNH), 3.93-4.04 (m, 2H, CH_2), 6.26 (dd, J = 16; 6 Hz, 1H, ArCH=CH), 7.15 (dq, J = 16; 2 Hz, 1H, ArCH), 7.46 (tm, J = 10 Hz, 1H, 4'-H), 7.62-7.65 (tm, J = 10 Hz, 3H, 3'-H + 5'-H + 6'-H).

1-(1-Piperidinyl)-4-(2'-nitrophenyl)but-3-ene-2-ol (**9a''** *[RR'N=piperidinyl]) and 2-(1-Piperidinyl)-4-(2'-nitrophenyl)but-3-ene-1-ol* (**10a''** *[RR'N=piperidinyl]*)

Amines **9a''** and **10a''** were obtained from **8a** and piperidine in 42% and 12% yield, respectively.

Amine **9a''**, mp. 50-53°C.- MS (CH_4; CI): m/z = 305 ($MC_2H_5^+$), 277 (MH^+), 259 (MH^+ - H_2O), 98 (CH_2=N^+(CH_2)$_5$).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.4-1.7 (m, 6H, (CH_2)$_3$), 2.3-2.42 (m, 4H, N(CH_2)$_2$), 2.58-2.7 (m, 2H, HOCHCH_2), 4.3-4.42 (m, 1H, CHOH), 6.24 (dd, J = 16; 8 Hz, 1H, ArCH=CH), 7.20 (d, J = 16 Hz, 1H, ArCH), 7.36-7.44 (m, 1H, 4'-H), 7.58-7.7 (m, 2H, 5'-H + 6'-H), 7.92 (dd, J = 8; 1 Hz, 1H, 3'-H).- $C_{15}H_{20}N_2O_3$ (276.3) Calcd. C 65.2 H 7.30 N 10.1 Found C 65.0 H 7.29 N 10.0.

Amine **10a''**, mp. 39-42°C.- MS (CH_4; CI): m/z = 277 (MH^+), 259 (MH^+ - H_2O), 98 (CH_2=N^+(CH_2)$_5$).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.4-1.66 (m, 6H, (CH_2)$_3$), 2.3-2.42 (m, 4H, N(CH_2)$_2$), 2.58-2.7 (m, 1H, CH_2OH), 4.3-4.42 (m, 2H, CHCH_2OH), 6.24 (dd, J = 16; 8 Hz, 1H, ArCH=CH), 7.20 (d, J = 16 Hz, 1H, Ar-CH), 7.36-7.44 (m, 1H, 4'-H), 7.58-7.7 (m, 2H, 5'-H + 6'-H), 7.92 (dd, J = 8; 1 Hz, 1H, 3'-H).

3-(4'-Cyanophenyl)-2-propenoic acid (**13j**)

To a solution of **11i** (3 g, 22 mmol) in Ac_2O (9.24 mL, 98 mmol) was added AcOK (4 g, 40 mmol). This mixture was heated to reflux for 8 h, then poured into water (150 mL). The precipitate was filtered, dried, and recrystallized from AcOH to give **13j** (1.5 g, 50%), mp. 250-251°C (lit.[13]: 248-249°C).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.71 (d, J = 16 Hz, 1H, CHCO), 7.64 (d, J = 16 Hz, 1H, ArCH), 7.90 (d, J = 2 Hz, 4H, Ar).

3-(1'-Naphthalenyl)-2-propenoic acid (**13m**)

To a mixture of triethyl phosphonoacetate (9 g, 0.04 mol) and KOH (13.4 g, 0.24 mol) was added a solution of 1-naphthaldehyde (**11m**) (6.2 g, 0.04 mol) in acetonitrile (80 mL/H_2O (0.2 mL). The mixture was heated for 3 h at 60°C. A white solid which precipitated was filtered off and the filtrate was diluted with water and acidified with conc. HCl. The solid **13m** which precipitated was filtered and dried (5 g, 63%), mp. 172-174°C (lit.[18]: 172-174°C).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.57 (d, J = 16 Hz, 1H, CHCO), 7.48-7.64 (m, 3H, 3'-H + 6'-H + 7'-H), 7.81 (d, J = 8 Hz, 1H, 5'-H), 7.87-7.96 (m, 2H, 2'-H + 4'-H), 8.21 (d, J = 8 Hz, 1H, 8'-H), 8.66 (d, J = 16 Hz, 1H, ArCH).

3-(1'-Naphthalenyl)-2-propenoyl chloride (**14m**)

The solution of **13m** (4 g, 0.02 mol), pyridine (2 mL, 0.026 mol), CH_2Cl_2 (20 mL) and $SOCl_2$ (3 mL, 0.026 mol) was stirred for 5 min until a clear solution was obtained, which was washed initially with H_2O (pH 4) and finally with 5% $NaHCO_3$ (pH 10). The org. phase was separated, dried and evaporated to give **14m** (3.3 g, 76%), mp. 191-193°C (lit.[19]: 191-193°C).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.76 (d, J = 16 Hz, 1H, CHCO), 7.49-7.68 (m, 3H, 3'-H + 6'-H + 7'-H), 7.83 (dm, J = 8 Hz, 1H, 5'-H), 7.91 (dd, J = 8; 2 Hz, 1H, 4'-H), 7.98 (d, J = 8 Hz, 1H, 2'-H), 8.17 (d, J = 8 Hz, 1H, 8'-H), 8.70 (d, J = 16 Hz, 1H, ArCH).

3-(1'-Naphthalenyl)-2-propenoyl cyanide (**17m**)

To tributyltin cyanide (1.43 g, 4.6 mmol) was added **14m** (1.2 g, 5.5 mmol). The mixture was stirred at 75°C until a homogeneous solution was obtained (ca. 20 min), and was then distilled in a kugelrohr apparatus at 80°C (1 Torr). The distillate which partially solidified, was recrystallized from $CHCl_3$-pentane 1:3, to give **17m** (1 g, 88%), mp. 180-182°C (lit.[16]: 180-182°C).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.63 (d, J = 16 Hz, 1H, CHCO), 7.49-7.68 (m, 3H, 3'-H + 6'-H + 7'-H), 7.83 (dm, J = 8 Hz, 1H, 5'-H), 7.91 (dd, J = 8, 2 Hz, 1H, 4'-H), 7.96 (d, J = 8 Hz, 1H, 2'-H), 8.17 (d, J = 8 Hz, 1H, 8'-H), 8.63 (d, J = 16 Hz, 1H, ArCH).

1-(Isopropylamino)-4-(1'-naphthalenyl)but-3-en-2-ol (**9m'**-*[RR'N=iPrHN]*)

To a solution of $LiAlH_4$ (1.52 g, 0.04 mol) in ether (500 mL) at -5°C was added a solution of **17m** (2.07 g, 0.01 mol) in acetone (5.8 g, 0.1 mol). The mixture was stirred at 0°C for 3 h and at room temp. overnight. The reaction was worked up[20] with 10% NaOH to give **9m'** (0.9 g, 35%), mp. 95-97°C.- MS (CH_4; CI^+): m/z = 256 (MH^+), 238 (MH^+ - H_2O), 197 (MH^+ - C_3H_9N).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.13 (d, J = 6 Hz, 3H, Me), 1.13 (d, J = 6 Hz, 3H, Me'), 2.85 (dd, J = 12; 8 Hz, 1H, CHH'), 2.96 (sept, J = 6 Hz, 1H, CHMe$_2$), 3.22 (dd, J = 12; 4 Hz, CHH'), 4.55 (m, 1H, CHOH), 6.50 (dd, J = 16; 8 Hz, 1H, ArCH=CH), 7.4-7.6 (m, 3H, 3'-H + 6'-H + 7'-H), 7.80 (d, J = 8 Hz, 1H, 5'-H), 7.90 (d, J = 8 Hz, 2H, 2'-H + 4'-H), 8.13 (d, J = 8 Hz, 1H, 8'-H), 8.21 (d, J = 16 Hz, 1H, ArCH).

N-(2-Hydroxyethyl)-3-(substituted-phenyl)-2-propen-amides (**15**) *and N,N-Bis-(2-hydroxyethyl)-3-(substituted-phenyl)-2-propenamides* (**16**)

A substituted cinnamic acid **13** (15 mmol) was added to $SOCl_2$ (10-15 mL) and the mixture was refluxed for 1 h. Excess $SOCl_2$ was removed under vacuum and the residual acyl chloride **14** was dissolved in dioxane (2-3 mL). This solution was added dropwise to ethanolamine or *N,N*-bis-ethanolamine (30 mmol) in dioxane (2-3 mL) at 20°C and the mixture so obtained was stirred at room temp. for 30-60 min. For the ethanolamides **15**, the mixture was dissolved in $CHCl_3$, washed with 5% HCl, 5% $NaHCO_3$ and finally with H_2O till neutral pH. The org. phase was dried and evaporated to give **15**. The *N,N*-bis-ethanolamides **16** which crystallized from the respective reaction mixtures, were filtered, washed with dioxane and dried.

N-(2-Hydroxyethyl)-3-(2'-nitrophenyl)-2-propenamide (**15a**)

Mp. 92-93°C.- MS (CH_4; CI^+): m/z = 237 (MH^+), 219 (MH^+ - H_2O).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.75 (bs, 1H, OH), 3.54 (s, 1H, NH), 3.58 (t, J = 5 Hz, 2H, NHC$\underline{H}_2$), 3.82 (t, J = 5 Hz, 2H, C$\underline{H}_2$OH), 6.36 (d, J = 16 Hz, 1H, CHC=O), 7.51 (ddd, J = 8; 6; 2 Hz, 1H, 5'-H), 7.60 (dd, J = 8; 6 Hz, 1H, 4'-H), 7.62 (d, J = 6 Hz, 1H, 6'-H), 7.98 (d, J = 8 Hz, 1H, 3'-H), 8.00 (d, J = 16 Hz, 1H, ArCH).- $C_{11}H_{12}N_2O_4$ (236.2) Calcd. C 55.9 H 5.12 N 11.8 Found C 55.7 H 4.96 N 11.4.

N-(2-Hydroxyethyl)-3-(3'-nitrophenyl)-2-propenamide (**15b**)[23]

^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.44 (t, J = 5 Hz, 1H, OH), 3.60 (dd, J = 10; 5 Hz, 2H, NHC$\underline{H}_2$), 3.82 (dd, J = 10; 5 Hz, 2H, C$\underline{H}_2$OH), 6.56 (d, J = 15 Hz, 1H, CHC=O), 7.57 (t, J = 8 Hz, 1H, 5'-H), 7.70 (d, J = 15 Hz, 1H, ArCH), 7.78 (d, J = 8 Hz, 1H, 6'-H), 8.20 (d, J = 8 Hz, 1H, 4'-H), 8.38 (t, J = 1 Hz, 1H, 2'-H).

N-(2-Hydroxyethyl)-3-(4'-nitrophenyl)-2-propenamide (**15c**)[23]

^{1}H-NMR (CD_3-CO-CD_3): δ (ppm) = 2.91 (bs, 1H, OH), 3.40 (s, 1H, NH), 3.45 (t, J = 5 Hz, 2H, NHC$\underline{H}_2$), 3.66 (t, J = 5 Hz, 2H, C$\underline{H}_2$OH), 6.96 (d, J = 16 Hz, 1H, CHC=O), 7.63 (d, J = 16 Hz, 1H, ArCH), 7.86 and 8.26 (AA'XX' system, J = 8 Hz, 4H, Ar).

N-(2-Hydroxyethyl)-3-(4'-cyanophenyl)-2-propenamide (**15j**)[23]

^{1}H-NMR (CD_3-CO-CD_3): δ (ppm) = 2.82 (bs, 1H, OH), 3.43 (t, J = 5 Hz, 2H, NHC$\underline{H}_2$), 3.64 (t, J = 5 Hz, 2H, C$\underline{H}_2$OH), 3.99 (t, J = 5 Hz, 1H, NH), 6.90 (d, J = 16 Hz, 1H, CHC=O), 7.57 (d, J = 16 Hz, 1H, ArCH), 7.79 (d, J = 2 Hz, 4H, Ar).

N,N-Bis-(2-hydroxyethyl)-3-(2'-nitrophenyl)-2-propenamide (**16a**)

Mp. 128-129°C.- MS (EI^+): m/z = 280 ($M^{+\cdot}$), 262 ($M^{+\cdot}$ - H_2O), 249 (M - CH_2OH)$^+$, 234 (M - NO_2)$^+$, 262 (M - H_2O)$^{+\cdot}$, 249 (M - CH_2OH)$^+$, 234 (M - NO_2)$^+$, 176 (M - N(CH_2CH_2OH)$_2$)$^+$.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 3.4-3.6 (m, 8H, CH_2's), 4.75 (t, J = 5 Hz, 1H, OH), 4.87 (t, J = 4 Hz, 1H, OH'), 7.38 (d, J = 11 Hz, 1H, CHC=O), 7.58 (d, J = 11 Hz, 1H, ArCH), 7.70 (t, J = 6 Hz, 1H, 5'-H), 8.14 (d, J = 6 Hz, 1H, 4'-H), 8.21 (dd, J = 6; 2 Hz, 1H, 6'-H), 8.54 (t, J = 2 Hz, 1H, 2'-H).- $C_{13}H_{16}N_2O_5$ (280.3) Calcd. C 55.7 H 5.75 N 10.0 Found C 55.3 H 5.55 N 9.8.

N,N-Bis-(2-hydroxyethyl)-3-(3'-nitrophenyl)-2-propenamide (**16b**)

Mp. 129-130°C.- MS (EI^+): m/z = 280 ($M^{+\cdot}$), 262 (M - H_2O)$^{+\cdot}$, 249 (M - CH_2OH)$^+$, 234 (M - NO_2)$^{+\cdot}$, 176 (M - N(CH_2CH_2OH)$_2$)$^+$.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 3.4-3.7 (m, 8H, CH_2's), 4.76 (t, J = 4 Hz, 1H, OH), 4.88 (t, J = 5 Hz, 1H, OH'), 7.20 (d, J = 15 Hz, 1H, CHC=O), 7.63 (dt, J = 8; 1 Hz, 1H, 5'-H), 7.71 (d, J = 15 Hz, 1H, ArCH), 7.78 (dt, J = 8; 1 Hz, 1H, 4'-H), 7.96 (dd, J = 8; 1 Hz, 1H, 6'-H), 8.04 (dd, J = 8; 1 Hz, 1H, 3'-H).- $C_{13}H_{16}N_2O_5$ (280.3) Calcd. C 55.7 H 5.75 N 10.0 Found C 55.7 H 6.00 N 10.0.

N,N-Bis-(2-hydroxyethyl)-3-(4'-nitrophenyl)-2-propenamide (**16c**)

Mp. 127-128°C.- MS (EI^+): m/z = 280 ($M^{+\cdot}$), 262 (M - H_2O)$^{+\cdot}$, 249 (M - CH_2OH)$^+$, 234 (M - NO_2)$^+$, 176 (M - N(CH_2CH_2OH)$_2$)$^+$.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 3.4-3.6 (m, 8H, CH_2's), 4.72 (t, J = 5 Hz, 1H,

OH), 4.84 (t, J = 5 Hz, 1H, OH'), 7.41 (d, J = 15 Hz, 1H, CHC=O), 7.55 (d, J = 1 Hz, 1H, ArCH), 7.95 and 8.23 (AA'XX' system, J = 8 Hz, 4H aromat.).- $C_{13}H_{16}N_2O_5$ (280.3) Calcd. C 55.7 H 5.75 N 10.0 Found C 54.4 H 5.55 N 9.9.

N,N-Bis-(2-hydroxyethyl)-3-[(2'-trifluoromethyl)phenyl]-2-propenamide (**16d**)

Mp. 82-83°C.- MS (EI^+): m/z = 303 ($M^{+\cdot}$), 285 (M - H_2O)$^{+\cdot}$, 272 (M - CH_2OH)$^+$, 199 (M - $N(CH_2CH_2OH)_2$)$^+$.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 3.45-3.65 (m, 8H, CH_2's), 4.75 (t, J = 5 Hz, 1H, OH), 4.87 (t, J = 5 Hz, 1H, OH'), 7.26 (d, J = 15 Hz, 1H, CHC=O), 7.83 (t, J = 8 Hz, 1H, 5'-H), 7.74 (t, J = 8 Hz, 1H, 4'-H), 7.75 (d, J = 8 Hz, 1H, 6'-H), 7.77 (d, J = 15 Hz, 1H, ArCH), 8.04 (d, J = 8 Hz, 1H, 3'-H).- $C_{14}H_{16}F_3NO_3$ (303.3) Calcd. C 55.4 H 5.32 N 4.6 Found C 55.5 H 5.30 N 4.7.

N,N-Bis-(2-hydroxyethyl)-3-[(3'-trifluoromethyl)phenyl)]-2-propenamide (**16e**)

Mp. 114-115°C.- MS (EI^+): m/z = 303 ($M^{+\cdot}$), 285 (M - H_2O)$^{+\cdot}$, 272 (M - CH_2OH)$^+$, 199 (M - $N(CH_2CH_2OH)_2$)$^+$.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 3.46-3.63 (m, 8H, CH_2's), 4.72 (t, J = 5 Hz, 1H, OH), 4.83 (t, J = 5 Hz, 1H, OH'), 7.31 (d, J = 15 Hz, 1H, CHC=O), 7.54 (d, J = 15 Hz, 1H, ArCH), 7.63 (t, J = 8 Hz, 1H, 5'-H), 7.72 (d, J = 8 Hz, 1H, 4'-H), 7.98 (d, J = 8 Hz, 1H, 6'-H), 8.06 (bs, 1H, 2'-H).- $C_{14}H_{16}F_3NO_3$ (303.3) Calcd. C 55.4 H 5.32 N 4.6 Found C 54.2 H 4.98 N 4.3.

N,N-Bis-(2-hydroxyethyl)-3-[(4'-trifluoromethyl)phenyl]-2-propenamide (**16f**)

Mp. 103-104°C.- MS (EI^+): m/z = 303 ($M^{+\cdot}$), 285 (M - H_2O)$^{+\cdot}$, 272 (M - CH_2OH)$^+$, 199 (M - $N(CH_2CH_2OH)_2$)$^+$.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 3.4-3.7 (m, 8H, CH_2's), 7.32 (d, J = 15 Hz, 1H, CHC=O), 7.53 (d, J = 1 Hz, 1H, ArH), 7.75 and 7.89 (AA'XX' system, J = 8 Hz, 4H aromat.).- $C_{14}H_{16}F_3NO_3$ (303.3) Calcd. C 55.4 H 5.32 N 4.6 Found C 55.2 H 5.42 N 4.7.

N,N-Bis-(2-hydroxyethyl)-3-(4'-chloro-3'-nitrophenyl)-2-propenamide (**16g**)

Mp. 138-139°C.- MS (EI^+): m/z = 314:316 ($M^{+\cdot}$), 296:298 (M - H_2O)$^{+\cdot}$, 283:285 (M - CH_2OH)$^+$, 210:212 (M - $N(CH_2CH_2OH)_2$)$^+$.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 3.4-3.7 (m, 8H, CH_2's), 4.73 (t, J = 5 Hz, 1H, OH), 4.83 (t, J = 5 Hz, 1H, OH'), 7.36 (d, J = 15 Hz, 1H, CHC=O), 7.51 (d, J = 15 Hz, 1H, ArCH), 7.80 (d, J = 8 Hz, 1H, 5'-H), 8.01 (dd, J = 8; 1 Hz, 1H, 6'-H), 8.44 (s, 1H, 2'-H).- $C_{13}H_{15}ClN_2O_5$ (314.7) Calcd. C 49.6 H 4.80 N 8.9 Found C 49.4 H 4.76 N 8.7.

N,N-Bis-(2-hydroxyethyl)-3-(2'-chloro-5'-nitrophenyl)-2-propen-amide (**16h**)

Mp. 158-159°C.- MS (EI^+): m/z = 314:316 ($M^{+\cdot}$), 296:298 (M - H_2O)$^{+\cdot}$, 283:285 (M - CH_2OH)$^+$, 210:212 (M - $N(CH_2CH_2OH)_2$)$^+$.- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 3.4-3.75 (m, 8H, CH_2's), 4.76 (t, J = 5 Hz, 1H, OH), 4.88 (t, J = 5 Hz, 1H, OH'), 7.47 (d, J = 15 Hz, 1H, CHC=O), 7.77 (d, J = 15 Hz, 1H, ArCH), 7.83 (d, J = 8 Hz, 1H, 5'-H), 8.21 (dd, J = 8; 3 Hz, 1H, 4'-H), 8.73 (d, J = 3 Hz, 1H, 2'-H).- $C_{13}H_{15}ClN_2O_5$ (314.7) Calcd. C 49.6 H 4.80 N 8.9 Found C 49.5 H 4.51 N 8.6.

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