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Optimized *N*-phenyl-*N*′-(2-chloroethyl)ureas as potential antineoplastic agents: Synthesis and growth inhibition activity

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Abstract—In our ongoing research program aimed at the optimization of microtubule-self-assembly disrupting agents, we have prepared three series of phenylurea analogues (CEU), derived from *N*-(3-ω-hydroxyalkyl or 4-ω-hydroxyalkyl or 3-ω-hydroxyalkynyl)-phenyl-*N*′-(2-chloroethyl)ureas. Most compounds exhibit potent growth inhibitory activity on human colon carcinoma HT-29, human skin melanoma M21, and human breast carcinoma MCF-7 tumor cell lines, with a GI_{50} ranging from 250 nM to 8 μM. Among these new molecules, three CEUs exhibit GI_{50} in the nanomolar range. They are more potent by approximately an order of magnitude than previously described CEU analogues. As such, they are attractive hit compounds for the development of potent new alkylating antitubulin drugs.

1. Introduction

Cancers are a group of malignant diseases responsible for tremendous health costs associated with high level of mortality and morbidity. As a result, numerous chemotherapeutic agents have been developed to impede the progression of malignant tumors or prevent their recurrence. Chemotherapeutic treatments are largely palliative and are useful for limited periods of time.[1] Chemotherapeutic agents often fail when drug resistant tumor cells become predominant, when the dose-related toxicity is too high to obtain optimal anticancer activity or when side effects are simply unbearable. Amongst the anticancer agents developed in the past decades, molecules acting on the cellular microtubule dynamics form one of the largest group of effective chemotherapeutics.

Microtubules are heterodimers composed of α- and β-tubulin isoforms. Microtubules' assembly forms cytoskeleton components, present in all eukaryotic cells.[2] During mitosis, microtubules are highly dynamic and are constantly reshaping in fast polymerization–depolymerization processes. When natural or synthetic ligands interact with microtubule dynamics, they disrupt the cytoskeleton and block mitosis into the G_2/M phase. Cells then initiate an apoptotic program. Tubulin cellular importance still makes it an attractive target for the development of potent anticancer drugs.[3]

Antitubulin agents[4] bind to tubulin according to four different modes.[5] In the first mode, drugs bind preferentially to polymerized tubulin. It includes the well-known paclitaxel and other members, such as epothilone B, discodermolide, and dyctyostatin.[4,5] For the three other modes, agents either form a covalent link to tubulin cysteine residues, bind to the colchicine site, or bind in the vinca domain. Vinblastine, vincristine, and peptides,

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such as dolastatins and hemiasterlins, are agents acting on the vinca domain.[4,5] Colchicine,[6] combretastatin,[7] and podophyllotoxins[8] interact with the colchicine-binding site. The site is located on β-tubulin at the interface between α- and β-tubulins, close to the T7 loop and the H8 helix.[9] Ligand interactions with the colchicine-binding site are mainly electrostatic in nature (docking) and thus reversible for most compounds. *N*-Phenyl-*N*′-(2-chloroethyl)ureas (CEUs)[10] form a covalent link with cysteine residue within the colchicine-binding site. Originally developed by our laboratory, CEUs react specifically with a few proteins, including β-tubulin.[10] We demonstrated that CEUs substituted at the 4-position of the phenyl ring by hydrophobic moieties are potent tumor cell growth inhibitors. They act as angiogenesis inhibitors both in vitro and in vivo.[11] They also inhibit tumor cell growth in vivo on the murine colon carcinoma CT-26 model.[12] Interestingly, some CEU derivatives have been shown to be orally bioavailable.[13] The antimicrotubule activity of many CEUs is based on the alkylation of an amino acid within the colchicine-binding site. We showed that CEU-022, that is, *N*-[4-(1,1-dimethylethyl)-phenyl]-*N*′-(2-chloroethyl) urea, alkylates specifically the cysteine 239 residue of β-tubulin.[10] β-Tubulin alkylation by CEUs can be detected in an electrophoretic shift assay.[14]

In the context of pharmacomodulating the properties of *N*-phenyl-*N*′-(2-chloroethyl)ureas, we prepared molecules with phenyl ring substituents bearing terminal functional group that are more hydrophilic to alter the molecule's biodistribution and toxicity in animal pharmacokinetics and metabolism studies. We describe here the synthesis and growth inhibition activity of three different series of derivatives designed as *N*-(3-ω-hydroxyalkyl or 4-ω-hydroxyalkyl or 3-ω-hydroxyalkynyl)phenyl-*N*′-(2-chloroethyl)ureas.

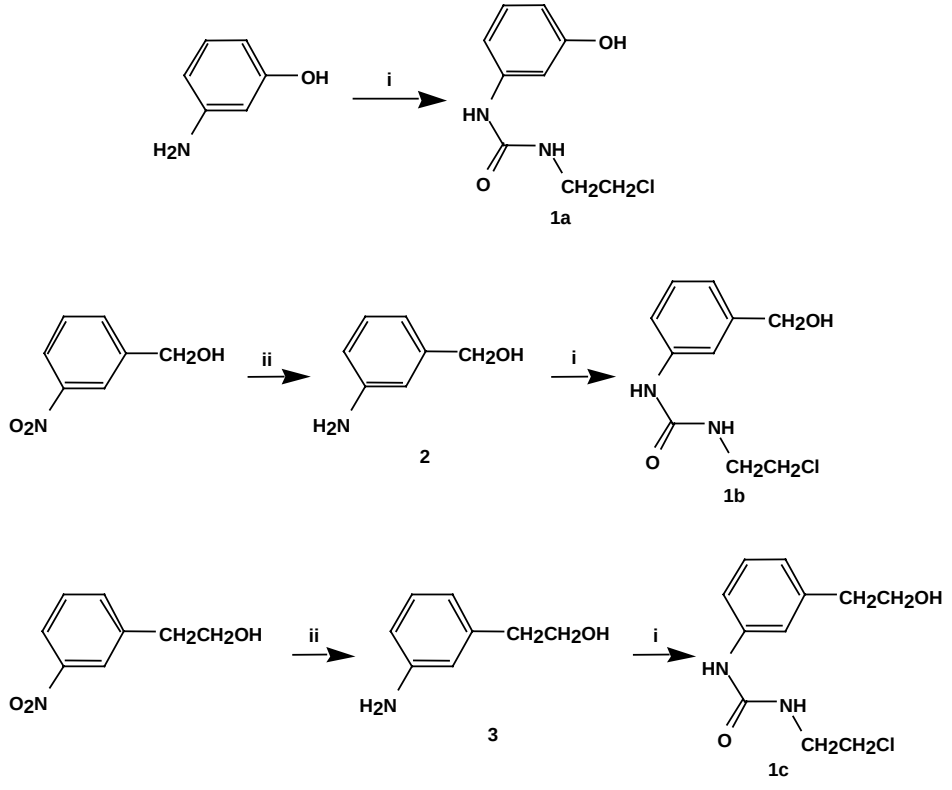
2. Results and discussion

2.1. Synthesis of *N*-phenyl-*N*′-(2-chloroethyl)ureas (CEUs)

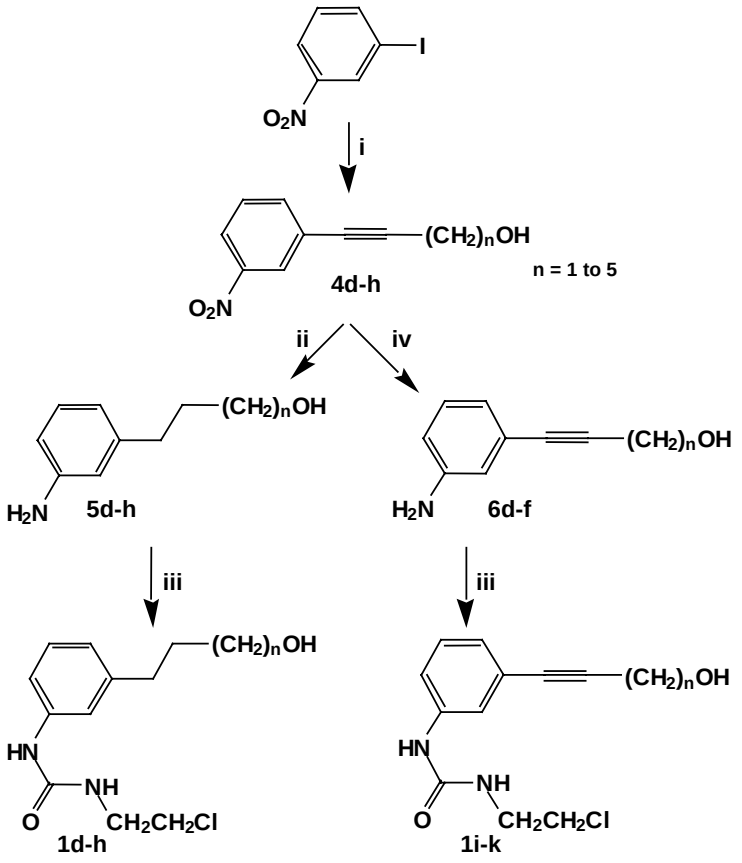
2.1.1. Synthesis of 3-substituted derivatives. Schemes 1 and 2 depict the synthetic procedure used for the preparation of *N*-(3-ω-hydroxyalkylphenyl)-*N*′-(2-chloroethyl)ureas. The preparation of CEUs **1a** to **n** was straightforward, which involved the nucleophilic addition of 3-hydroxyaniline and aniline derivatives **2**[15] and **3**[16] to 2-chloroethylisocyanate.

Therefore, commercially available 3-hydroxyaniline was converted into the corresponding *N*-(hydroxyphenyl)-*N*′-(2-chloroethyl)urea (**1a**). Compounds **1b** and **c** were also obtained by direct addition of the respective anilines **2** and **3** to 2-chloroethylisocyanate in dry dichloromethane. Anilines **2** and **3** were obtained through the reduction of the nitro group of commercially available 3-nitrobenzylalcohol and 2-(3-nitrophenyl)-1-ethanol using metallic reduction with $SnCl_2{\cdot}2H_2O$ in ethanol.

Scheme 2 describes the approach used to introduce longer hydroxyalkyl chains in compounds **1d**–**k**. We under-



Scheme 1. Reagents: (i) 2-chloroethylisocyanate, CH_2Cl_2; (ii) $SnCl_2{\cdot}2H_2O$, EtOH.



Scheme 2. Reagents: (i) alkyne, CuI, K_2CO_3, PPh_3, Pd/C, DME/H_2O; (ii) H_2, Pd/C, EtOH; (iii) 2-chloroethylisocyanate, CH_2Cl_2; (iv) Fe/HCl, EtOH/H_2O.

took a Sonogashira-like[17,18] addition with propargyl alcohol, 3-butyn-1-ol, 4-pentyn-1-ol, 5-hexyn-1-ol[19] or 6-heptyn-1-ol, mixed with 1-iodo-3-nitrobenzene (**8**), using Pd(0)/PPh_3 as catalyst. The reactions proceeded smoothly to afford the corresponding ω-hydroxyalkynyl derivatives **4d**–**h**[20] in yields ranging from 43% to 88%. Compounds **4d**–**h**[20] were then converted into the corresponding anilino-ω-hydroxyalkyl derivatives **5d**–**h**[21] by hydrogenation in ethanol using palladium on carbon as catalyst. Compounds **5d**–**h**[21] were obtained in yields ranging from 80% to 100%. Afterwards, the latter products were converted into their corresponding 2-chloroethylureas **1d**–**h** by addition of 2-chloroethylisocyanate to anilines **5d**–**h**[21] in dry dichloromethane with 28% to 51% urea yields.

Compounds **6d**–**f** were prepared by chemoselective reduction of the aromatic nitro group of compounds **4d**–**f** by catalytic reduction using iron in a mixture of concentrated hydrochloric acid and ethanol to obtain **6d**–**f** in fair to good yields. Finally, compounds **6d**–**f** were converted into **1i** to **1k** by addition of 2-chloroethylisocyanate with 51% to 63% yields.

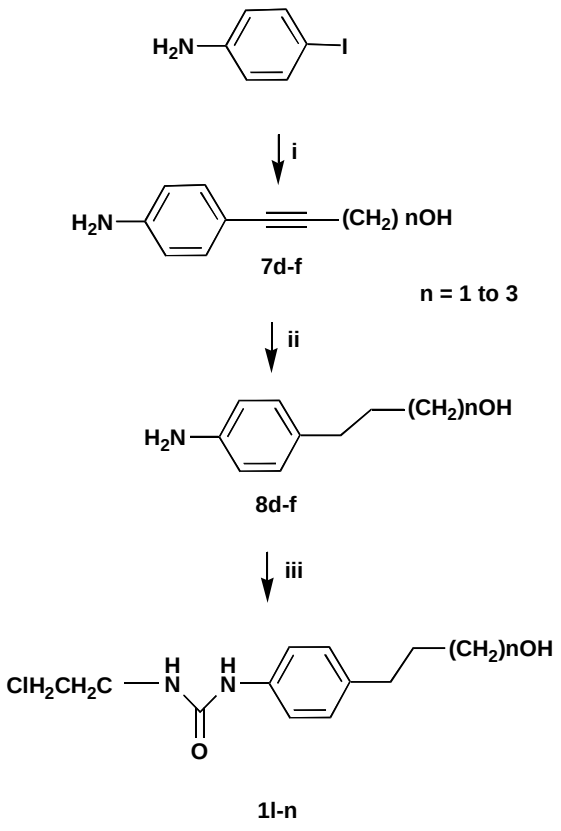
2.1.2. Synthesis of 4-substituted CEUs. Scheme 3 shows the preparation of 4-substituted CEUs **1l**–**n**. The last series of compounds was prepared using conditions similar to those described previously for compounds **1d**–**f**. Starting from 4-iodoaniline, introduction of the alkyne produced **7d**–**f** with 32%–73% yields. Catalytic hydrogenation of **7d**–**f** using palladium on carbon, followed by condensation of the aniline **8d**–**f** with 2-chloroethylisocyanate, gave **1l**–**n** in good yields (36–96%).

2.2. Growth inhibition activity

The growth inhibition assays[22] were conducted twice in triplicate on three human tumor cell lines of different tissue origin. The tumor cell lines used were HT-29 (human colon carcinoma), M21 (human skin melanoma), and MCF-7 (human breast carcinoma), respectively. Growth inhibition activity is expressed in terms of GI_{50} value (μM), which is the drug concentration required to inhibit tumor cell growth by 50%.

Table 1 summarizes the ability of **1a**–**h** to inhibit tumor cell growth. After two days of treatment, the GI_{50} value was determined using the NIH sulforhodamine assay. Compounds **1a**–**c** bearing short saturated ω-hydroxyalkyl side chains ($n < 3$) were inactive at the concentrations tested. Interestingly, compounds **1d**–**h** bearing longer ω-hydroxyalkyl side chains had a significant impact on growth inhibition activity in all tumor cells tested as the side chain increased, reaching the best GI_{50} value at five carbon atoms.

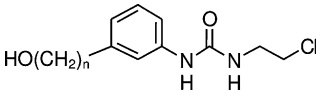
The growth inhibition potency of compounds **1d**–**f** inspired us to prepare compounds **1l**–**n**, substituted in



Scheme 3. Reagents: (i) alkyne, CuI, K_2CO_3, PPh_3, Pd/C, DME/H_2O; (ii) H_2, Pd/C, EtOH; (iii) 2-chloroethylisocyanate, CH_2Cl_2.

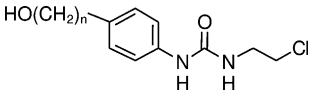
position 4 of the aromatic ring, instead of position 3 with identical hydroxyalkyl chains (see Table 2). There was no impact on growth inhibition activity by compounds **1l**–**n** at the concentration tested, as opposed to compounds **1d**–**f**. However, CEUs substituted by alkyl moieties in 4-position or an iodine atom (see Table 3)[23] demonstrated a much better growth inhibition activity. The switch from 4- to 3-position with hydroxyalkyl chains generated CEU compounds **1d**–**f** with a growth inhibition activity improved by an order of magnitude compared to the previous CEUs with the best growth inhibition activity (see Table 3).

Table 1. Growth inhibition activity of compounds (**1a**–**h**) on three different human cancer cell lines



Compound	*n*	GI_{50} (μM)		
		HT-29	M21	MCF-7
1a	0	>10	>10	>10
1b	1	>10	>10	>10
1c	2	>10	>10	>10
1d	3	5.2	6.0	7.9
1e	4	1.1	1.7	2.5
1f	5	0.25	0.39	0.49
1g	6	0.47	0.52	0.55
1h	7	0.53	0.54	0.58

Table 2. Growth inhibition activity of compounds (**1l**–**m**) on three different human cancer cell lines



Compound	*n*	GI_{50} (μM)		
		HT-29	M21	MCF-7
1l	3	>10	>10	>10
1m	4	>10	>10	>10
1n	5	>10	>10	>10

The impact of substituents in position 3 was evaluated further by increasing the rigidity of the ω-hydroxyalkyl side chain with the introduction of a triple bond. It seems to abrogate the growth inhibition activity (see Table 4).

We are contemplating two hypotheses to explain the increase in cell growth inhibition activity due to: (i) the three isomeric form, (ii) less rigid forms of potent CEU, and (iii) the effect of ω-hydroxyalkyl side chains in position 3 as opposed to position 4. The first hypothesis is based on a model of colchicine interactions—that we are developing—to its own β-tubulin binding site where a hydrogen or π-bond interaction could take place between an oxygen atom on the colchicine C ring and a key amino acid in tubulin.[24] In that context and based on previous alkylation results of β-tubulin by a CEU moiety,[10] CEUs substituted in position 3 with 4- to 7-carbon atom ω-hydroxyalkyl groups might be able to interact similarly to colchicine by generating either a hydrogen bond or a π-bond with amino acids located into the colchicine-binding site. The oxygen atom on the ω-hydroxyalkyl chain would stabilize, the molecules in a proper spatial configuration favoring the alkylation of cysteine 239 residue by the chloroethylurea moiety of the molecule. Such a configuration seems to be unfavorable for the 4-isomers composed of hydroxyalkenyl homologues and 3-isomers hydroxyalkyl chains shorter than four carbon atoms. A second hypothesis points toward an intrinsic role of the five-carbon chain in position 3 and nature of the end-chain substituent. To explore this possibility, several CEU compounds are being synthesized to evaluate the relative impact of chain length and end-chain functional groups. Structure–activity relationships will determine if the five-carbon chain with a terminal hydroxyl group is the cause of an increase in potency and optimal combination.

3. Conclusion

In summary, compounds **1f**–**h** appear to be essentially equivalent with GI_{50} in the nanomolar range if we consider structure–activity relationships. These three CEUs are approximately 1 order of magnitude more potent than all hydrophobic CEUs tested so far (see Table 3). These findings demonstrate that the growth inhibition activities of *N*-(3-ω-hydroxyalkyl, 4-ω-hydroxyalkyl, and 3-ω-hydroxyalkynyl)phenyl-*N*′-(2-chloroethyl)urea

Table 3. Previously synthesized compounds with the best growth inhibition activity [23]

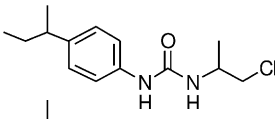
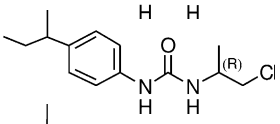
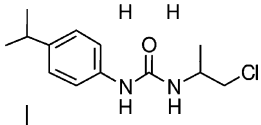
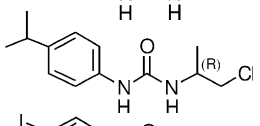
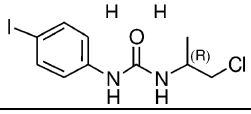
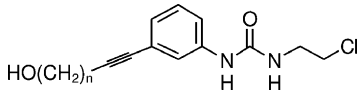
Compound	Names		GI_{50} (μM)	
			HT-29	MCF-7
	CEU-071	*N*-4-(1-Methylpropyl)phenyl-*N*′-(2-chloroethyl)urea	1.8	5.2
	CEU-087(R)	*N*-4-(1-Methylpropyl)phenyl-*N*′-[(1*R*)-2-chloro-1-methylethyl]urea	1.9	4.8
	CEU-070	*N*-4-(1-Methylethyl)phenyl-*N*′-(2-chloroethyl)urea	2.3	4.7
	CEU-085(R)	*N*-4-(1-Methylethyl)phenyl-*N*′-[(1*R*)-2-chloro-1-methylethyl]urea	1.0	2.9
	CEU-107(R)	*N*-(4-Iodophenyl)-*N*′-[(1*R*)-2-chloro-1-methylethyl]urea	1.3	3.2

Table 4. Growth inhibition activity of compounds (**1i**–**k**) on three different human cancer cell lines



Compound	*n*	GI_{50} (μM)		
		HT-29	M21	MCF-7
1i	1	>10	>10	>10
1j	2	>10	>10	>10
1k	3	>10	>10	>10

series are not equivalent. Growth inhibition by CEUs tested here requires substitution in position 3, a chain length clearly defined between 4 and 7 carbon atoms, without the rigidity induced by a triple bond, and a terminal hydroxyl group. The ability of these compounds to alkylate β-tubulin is currently under way. It will then be possible to determine if the degree of β-tubulin alkylation and growth inhibition values are related. CEUs' computer modelization within the recently available cocrystallized colchicine-α- and β-tubulin coordinates[27] will be used to test the stabilizing effect of 3-ω-hydroxyalkyl substituents.

4. Experimental

4.1. Cell growth inhibition assay

The growth inhibition potency of CEUs was assessed using the procedure described by the National Cancer Institute for its drug screening program.[22] Ninety-six well tissue culture plates were seeded with 100 μL tumor cell lines suspended in high glucose DMEM supplemented with 5% (v/v) defined bovine calf serum iron (Hyclone). Plates were incubated at 37 °C, 5% CO_2 for 24 h. Freshly solubilized drugs in DMSO were diluted in fresh medium and aliquots of 100 μL containing sequential dilution of drugs were added. Final drug concentrations ranged from 100 to 0.3 μM. DMSO concentration was maintained lower than 0.5% so to avoid solvent's cytotoxicity. Plates were incubated for 48 h. Assays were stopped by addition of cold trichloroacetic acid to the wells (final concentration being 10%), followed by incubation for 60 min at 4 °C. Plates were washed five times with tap water. Sulforhodamine B solution (50 μL) at 0.1 % (w/v) in 1% acetic acid was added to each well, and plates were incubated for 15 min at room temperature. After staining, unbound dye was removed by washing five times with 1% acetic acid. Bound stain was solubilized with 10 mM Tris base, and the absorbance was read using a μQuant Universal Microplate Spectrophotometer (Biotek, Winooski, VT) at 585 nm. The results were compared with those of a control reference plate fixed on the treatment day and the growth inhibition percentage was calculated for each drug contact period. The experiments were performed at least twice in triplicate. The GI_{50} assay was considered valid when the variability among data for a given set of conditions, within the same experiment, was less than 10% with respect to the mean value. For that reason, data are reported with two significant figures.

4.2. Experimental procedures

4.2.1. Chemistry and chemical methods. Proton NMR spectra were recorded on a Bruker AM-300 spectrometer (Bruker, Germany). Chemical shifts (δ) are reported in parts per million, relative to the internal tetramethylsilane standard. IR spectra were recorded on a Unicam spectrometer. Uncorrected melting points were determined on an electrothermal melting point apparatus. All reactions were conducted under a dried nitrogen atmosphere. Chemicals were supplied by Aldrich Chemical (Milwaukee, WI). Liquid flash chromatography was performed on silica gel 60 A (American Chemicals Ltd., Montreal, Canada), using the indicated solvent mixture

expressed as volume/volume ratios. Solvents and reagents were used without purification unless specified otherwise. The progress of all reactions was monitored using TLC on precoated silica gel plates (Merck Silica Gel 60 F_{254}). The chromatograms were viewed under UV light at 254 nm. For column chromatography, Merck Silica Gel (70–230 mesh) was used.

4.3. General preparation of compounds 2, 3, 5d–h, 6d–f, and 8d–f

Method A: The 3-nitro group of 3-nitrobenzylalcohol or 2-(3-nitrophenyl)-1-ethanol (1.00 mmol) was reduced by catalytic reduction using $SnCl_2{\cdot}2H_2O$ (6 mmol) in ethyl alcohol (10 mL) and refluxed for 6 h. After cooling and evaporation of the solvent, the residue was taken up in 1 N NaOH (20 mL) and extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by flash chromatography on silica gel provided anilines **2** or **3**.

Method B: The appropriate nitro compound **4d–f** (1.00 mmol) was dissolved in a mixture (10:1) of ethanol and water (22 mL). Powdered iron (7.28 mmol) and five drops of concentrated hydrochloric acid were added. The mixture was refluxed for 4 h. After cooling, the mixture was evaporated to dryness. A saturated solution of Na_2CO_3 (20 mL) was added, and the mixture was extracted with dichloromethane (3 × 15 mL). The organic portions were pooled, dried over Na_2SO_4, and concentrated under reduced pressure. The solid residue was then purified by flash chromatography on silica gel to afford **6d–f**.

Method C: A mixture of the appropriate alkenyl derivatives **4d–h** or **7d–f** (0.43 mmol), Pd/C 10% in ethanol (30 mL) was reduced under hydrogen atmosphere (38 psi) overnight. The catalyst was removed by filtration on Celite and the filtrate was evaporated to dryness. The residue was purified by flash chromatography on silica gel to afford **5d–h** or **8d–f**.

4.3.1. 3-Aminobenzyl alcohol (2).[15] Compound **2** was synthesized from 3-nitrobenzylalcohol using general method A. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 98:2). Yield 100%; mp 89–92 °C; IR (KBr) *v*: 3364 (OH), 2913 (NH), 1030 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.15 (m, Ar, 1H), 6.74 (m, Ar, 2H), 6.62 (m, Ar, 1H), 4.60 (s, CH_2, 2H), 2.90 (br s, OH, NH_2, 3H); ^{13}C NMR ($CDCl_3$) δ: 146.7, 139.9, 129.5, 117.1, 114.4, 113.6, 65.4.

4.3.2. 2-(3-Aminophenyl)-1-ethanol (3).[16] Compound **3** was synthesized from 2-(3-nitrophenyl)-1-ethanol using general method A. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 98:2). Yield 49%; mp 51–53 °C; IR (KBr) *v*: 3303 (OH), 2917 (NH), 1057 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.10 (m, Ar, 1H), 6.62 (d, Ar, 1H, J = 7.5 Hz), 6.55 (m, Ar, 2H), 3.81 (t, 2H, J = 7.3 Hz, CH_2), 3.04 (s, OH, NH_2, 3H), 2.76 (t, 2H, J = 7.3 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ: 146.6, 139.8, 129.5, 119.3, 115.9, 113.4, 63.5, 39.2.

4.3.3. 3-(3-Aminophenyl)-2-propyn-1-ol (6d). Compound **6d** was synthesized from **4d** using general method B. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 4:6). Yield 75%; IR (NaCl) *v*: 3375 (OH, NH), 2229 (C≡C), 1287 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.08 (t, 1H, J = 7.9 Hz, Ar), 6.83 (d, 1H, J = 7.7 Hz, Ar), 6.75 (s, 1H, Ar), 6.64 (d, 1H, J = 8.0 Hz, Ar), 4.46 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): 146.2, 19.3, 122.1, 118.0, 115.6, 86.7, 85.9, 51.6.

4.3.4. 4-(3-Aminophenyl)-3-butyn-1-ol (6e). Compound **6e** was synthesized from **4e** using general method B. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate 6:4). Yield 49%; IR (NaCl) *v*: 3348 (OH, NH), 2228 (C≡C), 1285 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.03 (t, 1H, J = 7.9 Hz, Ar), 6.80 (d, 1H, J = 7.5 Hz, Ar), 6.70 (s, 1H, Ar), 6.57 (d, 1H, J = 8.0 Hz, Ar), 3.73 (t, 2H, J = 6.4 Hz, CH_2), 3.45 (br s, 2H, NH_2), 2.60 (t, 2H, J = 6.4 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ: 146.3, 129.3, 124.1, 122.1, 118.2, 115.2, 86.2, 82.4, 61.1, 23.7.

4.3.5. 5-(3-Aminophenyl)-4-pentyn-1-ol (6f). Compound **6f** was synthesized from **4f** using general method B. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate 6:4). Yield 75%; IR (NaCl) *v*: 3354 (OH, NH), 2232 (C≡C), 1289 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.03 (t, 1H, J = 7.7 Hz, Ar), 6.77 (d, 1H, J = 7.7 Hz, Ar), 6.69 (s, 1H, Ar), 6.57 (d, 1H, J = 7.7 Hz, Ar), 3.76 (t, 2H, J = 6.0 Hz, CH_2), 3.25 (br s, 2H, NH_2), 2.47 (t, 2H, J = 6.0 Hz, CH_2), 1.81 (t, 2H, J = 6.0 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ: 146.3, 129.2, 124.4, 122.0, 118.0, 114.9, 88.9, 81.3, 61.6, 31.4, 16.0.

4.3.6. 3-(3-Aminophenyl)-1-propanol (5d).[21c] Compound **5d** was synthesized from **4d** using general method C. The crude product was purified by flash chromatography (silica gel, ether/hexanes 90:10). Yield 85%; IR (NaCl) *v*: 3351 (OH), 2927 (NH), 1057 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.08 (t, 1H, J = 7.5 Hz, Ar), 6.61 (d, 1H, J = 7.0 Hz, Ar), 6.52 (s, 2H, Ar), 3.62 (t, 2H, J = 7.0 Hz, CH_2), 3.29 (br s, 2H, NH_2), 2.59 (t, 2H, J = 7.0 Hz, CH_2), 1.84 (t, 2H, J = 7.0 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ: 147.8, 131.3, 129.3, 118.8, 115.3, 112.8, 62.4, 34.1, 32.1.

4.3.7. 4-(3-Aminophenyl)-1-butanol (5e).[21a] Compound **5e** was synthesized from **4e** using general method C. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 95:5). Yield 100%; IR (NaCl) *v*: 3363 (OH), 2934 (NH), 1167 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.06 (m, 1H, Ar), 6.59 (d, 1H, J = 7.5 Hz, Ar), 6.50 (m, 2H, Ar), 3.59 (t, 2H, J = 6.0 Hz, CH_2), 3.17 (s, 2H, NH_2), 2.53 (t, 2H, J = 7.5 Hz, CH_2), 1.62 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$); δ: 146.4, 143.7, 129.2, 118.9, 115.4, 112.8, 62.6, 35.6, 32.3, 27.4.

4.3.8. 5-(3-Aminophenyl)-1-pentanol (5f). Compound **5f** was synthesized from **4f** using general method C. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 70:30). Yield 85%; IR (NaCl) *v*: 3357 (OH), 2934 (NH), 1167 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.07 (m, 1H, Ar), 6.60 (d, 1H, $J = 7.5$ Hz, Ar), 6.52 (m, 2H, Ar), 3.59 (t, 2H, $J = 7.0$ Hz, CH_2), 3.23 (s, 3H, NH_2OH), 2.53 (t, 2H, $J = 7.0$ Hz, CH_2), 1.57 (m, 4H, $2 \times CH_2$), 1.38 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 146.3, 143.9, 129.2, 118.9, 115.5, 112.8, 62.7, 35.9, 32.6, 31.1, 25.5.

4.3.9. 6-(3-Aminophenyl)-1-hexanol (5g). Compound **5g** was synthesized from **4g** using general method C. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 97:3). Yield 91%; IR (NaCl) *v*: 3384 (OH), 2917 (NH), 1059 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.09 (t, 1H, $J = 6.0$ Hz, Ar), 6.55 (m, 3H, Ar), 3.59 (t, 2H, $J = 6.6$ Hz, CH_2), 3.14 (s, 2H, NH_2), 2.52 (t, 2H, $J = 7.0$ Hz, CH_2), 1.67 (m, 4H, CH_2), 1.34 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 147.0, 144.0, 129.1, 119.0, 115.5, 112.8, 62.8, 35.9, 32.7, 31.3, 29.1, 25.7.

4.3.10. 7-(3-Aminophenyl)-1-heptanol (5h).[21a] Compound **5h** was synthesized from **4h** using general method C. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 70:30). Yield 65%; IR (NaCl) *v*: 3359 (OH), 2928 (NH), 1056 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.09 (m, Ar, 1H), 6.69 (m, Ar, 3H), 3.62 (t, 2H, $J = 6.6$ Hz, CH_2), 2.53 (t, 2H, $J = 6.6$ Hz, CH_2), 1.57 (m, 4H, $2\times$ CH_2), 1.33 (m, 6H, $3\times$ CH_2) NMR ^{13}C ($CDCl_3$) δ: 142.2, 129.3, 124.3, 121.4, 117.3, 114.5, 63.0, 35.7, 32.7, 31.0, 29.1, 29.0, 25.6.

4.3.11. 3-(4-Aminophenyl)-1-propanol (8d).[25] Compound **8d** was synthesized from **7d** using general method C. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 95:5). Yield 63%; IR (NaCl) *v*: 3366 (OH), 2916 (NH) cm^{-1}; ^1H NMR (acetone-d_6) δ: 7.01 (d, 2H, $J = 7.6$ Hz, Ar), 6.71 (d, 2H, $J = 7.6$ Hz, Ar), 3.73 (t, 2H, $J = 6.0$ Hz, CH_2), 2.83 (t, 2H, $J = 6.0$ Hz, CH_2), 2.71 (br s, 2H, NH_2), 1.71 (t, 2H, $J = 6.0$ Hz, CH_2); ^{13}C NMR (acetone-d_6) δ: 146.8, 131.2, 120.2, 115.2, 61.6, 35.8, 31.9.

4.3.12. 4-(4-Aminophenyl)-1-butanol (8e).[21a] Compound **8e** was synthesized from **7e** using general method C. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 95:5). Yield 50%; IR (NaCl) *v*: 3349 (OH), 2926 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.04 (d, 2H, $J = 7.7$ Hz, Ar), 6.68 (d, 2H, $J = 7.7$ Hz, Ar), 3.61 (t, 2H, $J = 6.0$ Hz, CH_2), 2.78 (br s, 2H, NH_2), 1.69 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 143.8, 132.3, 128.4, 114.9, 62.6, 35.3, 31.9, 25.9.

4.3.13. 5-(4-Aminophenyl)-1-pentanol (8f). Compound **8f** was synthesized from **7f** using general method C. The crude product was purified by flash chromatography (silica gel, dichloromethane/ethanol 95:5). Yield 63%; IR (NaCl) *v*: 3349 (OH), 2930 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.96 (d, 2H, $J = 7.7$ Hz, Ar), 6.61 (d, 2H, $J = 7.7$ Hz, Ar), 3.61 (t, 2H, $J = 6.5$ Hz, CH_2), 2.82 (br s, 2H, NH_2), 2.51 (t, 2H, $J = 6.5$ Hz, CH_2), 1.58 (m, 4H, CH_2), 1.38 (t, 2H, $J = 6.5$ Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ: 143.9, 132.9, 128.9, 115.3, 62.9, 35.0, 32.7, 31.6, 25.4.

4.4. Typical synthesis procedure for the preparation of compounds 4d–h and 7d–f

To a mixture of the appropriate iodinated compound (3-iodonitrobenzene or 4-iodoaniline) (4.56 mmol), K_2CO_3 (1.57 g, 11.4 mmol) in a mixture of 1,2-DME/water (1:1; 30 mL) were successively added CuI (34 mg, 0.18 mmol), PPh_3 (95.80 mg, 0.36 mmol), and Pd/C 10% (97.05 mg, 0.09 mmol). The mixture was stirred at room temperature for 1 h. Afterwards, the ω-hydroxyalkenyl derivative (14.40 mmol) was added, and the mixture was refluxed overnight. After cooling, the mixture was filtered on Celite and the solvent was evaporated under reduced pressure. An aqueous solution of 1 N HCl (20 mL) was then added to the residue and extracted with ethyl acetate (3×15 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel.

4.4.1. 3-(3-Nitrophenyl)-2-propyn-1-ol (4d). Compound **4d** was synthesized from 3-iodonitrobenzene and propargyl alcohol. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 75:25). Yield 43%; mp 46–48 °C; IR (KBr) *v*: 3263 (OH), 1529 (NO_2), 1023 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.29 (s, 1H, Ar), 8.17 (m, 1H, Ar), 7.74 (d, 1H, $J = 7.8$ Hz, Ar), 7.51 (t, 1H, $J = 8.0$ Hz, Ar), 4.53 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 148.1, 137.4, 129.4, 126.5, 124.4, 123.2, 90.0, 83.2, 51.4.

4.4.2. 4-(3-Nitrophenyl)-3-butyn-1-ol (4e). Compound **4e** was synthesized from 3-iodonitrobenzene and 3-butyn-1-ol. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 65:35). Yield 65%; mp 72–74 °C; IR (KBr) *v*: 3323 (OH), 1524 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.26 (m, 1H, Ar), 8.14 (m, 1H, Ar), 7.71 (m, 1H, Ar), 7.48 (t, 1H, $J = 8.0$ Hz, Ar), 3.87 (m, 2H, CH_2), 2.73 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 148.1, 137.4, 129.3, 126.5, 125.2, 122.7, 89.7, 80.1, 61.0, 23.7.

4.4.3. 5-(3-Nitrophenyl)-4-pentyn-1-ol (4f). Compound **4f** was synthesized from 3-iodonitrobenzene and 4-pentyn-1-ol. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 70:30). Yield 77%; IR (NaCl) *v*: 3357 (OH), 1530 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.24 (s, 1H, Ar), 8.13 (d, 1H, $J = 8.0$ Hz, Ar), 7.68 (d, 1H, $J = 7.0$ Hz, Ar), 7.46 (t, 1H, $J = 8.0$ Hz, Ar), 3.83 (t, 2H, $J = 6.0$ Hz, CH_2), 2.58 (t, 2H, $J = 6.0$ Hz, CH_2), 1.89 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 148.0, 137.3, 129.2, 126.3, 125.6, 122.3, 92.6, 78.8, 61.4, 31.1, 15.9.

4.4.4. 6-(3-Nitrophenyl)-5-hexyn-1-ol (4g). Compound **4g** was synthesized from 3-iodonitrobenzene and 5-hexyn-1-ol. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 75:25). Yield

88%; IR (NaCl) *v*: 3354 (OH), 1530 (NO_2), 1063 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.05 (s, 1H, Ar), 7.98 (d, 1H, J = 8.0 Hz, Ar), 7.55 (d, 1H, J = 7.7 Hz, Ar), 7.34 (t, 1H, J = 8.0 Hz, Ar), 3.61 (t, 2H, J = 6.0 Hz, CH_2), 3.07 (br s, 2H, NH_2), 2.37 (t, 2H, J = 6.0 Hz, CH_2), 1.63 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 147.9, 137.3, 129.2, 126.1, 125.7, 122.2, 93.1, 78.7, 61.9, 31.7, 24.8, 19.1.

4.4.5. 7-(3-Nitrophenyl)-6-heptyn-1-ol (4h). Compound **4h** was synthesized from 3-iodonitrobenzene and 6-heptyn-1-ol. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 75:25). Yield 77%; IR (NaCl) *v*: 3378 (OH), 1529 (NO_2), 1049 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.17 (s, 1H, Ar), 8.07 (m, 1H, Ar), 7.65 (m, 1H, Ar), 7.43 (m, 1H, Ar), 3.64 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 2.12 (m, 1H, OH), 1.53 (m, 6H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 148.0, 137.3, 129.2, 126.3, 125.8, 122.2, 93.3, 78.7, 62.6, 32.2, 28.2, 25.1, 19.3.

4.4.6. 3-(4-Aminophenyl)-2-propyn-1-ol (7d).[25] Compound **7d** was synthesized from 4-iodoaniline and propargyl alcohol. The crude product was purified by flash chromatography (silica gel, dichloromethane/ethanol 95:5). Yield 76%; mp 84–86 °C; IR (KBr) *v*: 3374 (OH, NH_2), 2233 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.24 (d, 2H, J = 7.0 Hz, Ar), 6.60 (d, 2H, J = 7.0 Hz, Ar), 4.57 (s, 2H, CH_2), 3.69 (br s, NH_2); ^{13}C NMR ($CDCl_3$) δ: 146.9, 133.1, 114.7, 113.1, 86.4, 85.1, 51.8.

4.4.7. 4-(4-Aminophenyl)-2-butyn-1-ol (7e). Compound **7e** was synthesized from 4-iodoaniline and 3-butyn-1-ol. The crude product was purified by flash chromatography (silica gel, dichloromethane/ethanol 95:5). Yield 32%; IR (KBr) *v*: 3347 (OH, NH_2), 2213 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.19 (d, 2H, J = 7.0 Hz, Ar), 6.54 (d, 2H; J = 7.0 Hz, Ar), 3.72 (t, 2H, J = 6.5 Hz, CH_2), 2.62 (t, 2H, J = 6.5 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ: 146.4, 132.7, 114.8, 113.4, 83.9, 82.8, 61.3, 23.9.

4.4.8. 5-(4-Aminophenyl)-2-pentyn-1-ol (7f).[26] Compound **7f** was synthesized from 4-iodoaniline and 4-pentyn-1-ol. The crude product was purified by flash chromatography (silica gel, dichloromethane/ethanol 95:5). Yield 73%; mp 99–100 °C; IR (KBr) *v*: 3443 (OH, NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.17 (d, 2H, J = 7.0 Hz, Ar), 6.54 (d, 2H, J = 7.0 Hz, Ar), 3.73 (t, 2H, J = 7.0 Hz, CH_2), 3.18 (br s, 2H, NH_2), 2.30 (t, 2H, J = 7.0 Hz, CH_2), 1.81 (t, 2H, J = 7.0 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ: 146.2, 132.8, 114.9, 113.2, 86.9, 81.5, 61.8, 31.2, 16.0.

4.5. Typical synthesis of 2-chloroethylureas 1a–n

2-Chloroethylisocyanate (1.640 mmol) was added dropwise to a cold solution (ice bath) of the appropriate aniline (1.370 mmol) in dry dichloromethane (15 mL/g of aniline). The ice bath was then removed and the reaction mixture was stirred at room temperature for 20 h. After completion of the reaction, the solvent was evaporated under reduced pressure to give an off-white solid, which was purified by flash chromatography on silica gel.

4.5.1. *N*-(3-Hydroxyphenyl)-*N′*-(2-chloroethyl)urea (1a). Compound **1a** was synthesized from 3-hydroxyaniline and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 99:1). Yield 96%; mp 117–119 °C; IR (KBr) *v*: 3310 (NH, OH), 1633 (C=O), 1250 (C–O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.57 (s, Ph, 1H), 8.23 (s, 1H, NH), 7.25 (s, 1H, OH), 7.06 (m, 1H, Ar), 6.80 (m, 1H, Ar), 6.50 (m, 1H, Ar), 6.35 (m, NH, 1H), 3.64 (m, 2H, CH_2), 3.55 (m, 2H, CH_2); ^{13}C NMR (acetone-d_6) δ: 158.7, 156.8, 141.7, 130.4, 110.9, 110.3, 107.0, 44.8, 42.6.

4.5.2. *N*-(3-Hydroxybenzyl)-*N′*-(2-chloroethyl)urea (1b). Compound **1b** was synthesized from **2** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 95:5). Yield 56%; mp 106–109 °C; IR (KBr) *v*: 3326 (NH, OH), 1636 (C=O), 1242 (C–O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.09 (s, NH, 1H), 7.46 (s, 1H, Ar), 7.37 (m, 1H, Ar), 7.18 (t, 1H, J = 8.0 Hz, Ar), 6.95 (d, 1H, J = 7.4 Hz, Ar), 6.15 (s, 1H, NH), 4.57 (s, 2H, CH_2), 4.23 (br s, 1H, OH), 3.67 (m, 2H, CH_2), 3.53 (m, 2H, CH_2); ^{13}C NMR (acetone-d_6) δ: 156.0, 143.9, 141.0, 129.2, 120.7, 117.6, 117.3, 64.6, 44.8, 42.4.

4.5.3. *N*-[3-(2-Hydroxyethyl)phenyl]-*N′*-(2-chloroethyl) urea (1c). Compound **1c** was synthesized from **3** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 95:5). Yield 41%; mp 109–111 °C; IR (KBr) *v*: 3330 (NH, OH), 1636 (C=O) 1246 (C–O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.08 (s, 1H, NH), 7.33 (m, 2H, Ar), 7.13 (m, 1H, Ar), 6.82 (d, 1H, J = 7.5 Hz, Ar), 6.15 (s, 1H, NH), 3.69 (m, 4H, CH_2), 3.53 (m, 2H, CH_2), 2.93 (br s, 1H, OH), 2.74 (t, 2H, J = 7.0 Hz, CH_2); ^{13}C NMR (acetone-d_6) δ: 177.3, 155.9, 140.9, 129.2, 123.1, 119.5, 116.7, 63.7, 44.8, 42.4, 40.3.

4.5.4. *N*-[3-(3-Hydroxypropyl)phenyl]-*N′*-(2-chloroethyl) urea (1d). Compound **1d** was synthesized from **5d** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, dichloromethane/ethyl acetate 80:20). Yield 51%; mp 96–98 °C; IR (KBr) *v*: 3320 (NH, OH), 1636 (C=O), 1249 (C–O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.00 (s, 1H, NH), 7.36 (s, 1H, Ar), 7.29 (m, 1H, Ar), 7.13 (t, 1H, J = 8.0 Hz, Ar), 6.80 (d, 1H, J = 7.4 Hz, Ar), 6.09 (br s, NH, 1H), 3.68 (m, 2H, CH_2), 3.55 (m, 4H, CH_2), 2.63 (m, 2H, CH_2), 1.79 (m, 2H, CH_2); ^{13}C NMR (acetone-d_6) δ: 155.9, 143.8, 141.2, 129.2, 122.6, 119.1, 116.5, 61.7, 44.8, 42.5, 35.3, 32.8.

4.5.5. *N*-[3-(4-Hydroxybutyl)phenyl]-*N′*-(2-chloroethyl) urea (1e). Compound **1e** was synthesized from **5e** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 97:3). Yield 41%; mp 72–74 °C; IR (KBr): *v*: 3323 (NH, OH), 1635 (C=O), 1249 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$ et CD_3OD) δ: 7.83 (br s, 1H, NH), 7.15 (m, 3H, Ar), 6.75 (d, 1H, J = 6.8 Hz, Ar), 6.06 (br s, 1H, NH), 3.43 (m, 8H, CH_2), 2.50 (t, 2H, J = 7.5 Hz, CH_2), 1.51 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$ and

CD_3OD) δ: 156.3, 143.3, 138.9, 128.8, 123.1, 119.6, 116.9, 62.1, 44.4, 41.7, 35.5, 31.9, 27.2.

4.5.6. *N*-[3-(5-Hydroxypentyl)phenyl]-*N*′-(2-chloroethyl) urea (1f). Compound **1f** was synthesized from **5f** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 97:3). Yield 31%; mp 92–95 °C; IR (KBr): *v*: 3318 (NH, OH), 1641 (C=O), 1055 (C–O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.05 (s, 1H, NH), 7.31 (m, 2H, Ar), 7.12 (t, 1H, $J = 8.9$ Hz, Ar), 6.78 (d, 1H, $J = 7.4$ Hz, Ar), 6.13 (s, 1H, NH), 3.67 (t, 2H, $J = 7.0$ Hz, CH_2), 3.51 (m, 4H, CH_2), 2.90 (s, 1H, OH), 2.57 (t, 2H, $J = 7.7$ Hz, CH_2) 1.56 (m, 4H, CH_2), 1.40 (m, 2H, CH_2); ^{13}C NMR (acetone-d_6) δ: 155.8, 143.9, 141.1, 129.2, 122.5, 119.0, 116.4, 62.3, 44.8, 42.5, 36.5, 33.5, 32.0, 26.2.

4.5.7. *N*-[3-(6-Hydroxyhexyl)phenyl]-*N*′-(2-chloroethyl) urea (1g). Compound **1g** was synthesized from **5g** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 97:3). Yield 52%; mp 83–84 °C; IR (KBr) *v*: 3323 (NH, OH), 1636 (C=O), 1245 (C–O) cm^{-1}; ^1H (NMR $CDCl_3$ and CD_3OD) δ: 8.16 (br s, 1H, NH), 7.32 (m, 3H, Ar), 6.70 (t, 1H, $J = 6.5$ Hz, Ar), 6.25 (br s, 1H, NH), 3.66 (m, 6H, CH_2), 2.55 (t, 2H, $J = 7.5$ Hz, CH_2), 1.45 (m, 4H, CH_2), 1.23 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$ and CD_3OD) δ: 156.2, 144.1, 141.0, 129.2, 122.7, 119.2, 116.6, 62.4, 44.8, 42.5, 36.5, 33.6, 32.1, 29.7, 26.4.

4.5.8. *N*-[3-(7-Hydroxyheptyl)phenyl]-*N*′-(2-chloroethyl) urea (1h). Compound **1h** was synthesized from **5h** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol 98:2). Yield 36%; mp 86–88 °C; IR (KBr) *v*: 3336 (NH, OH), 1656 (C=O), 1243 (C–O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.01 (s, 1H, NH), 7.29 (m, 3H, Ar), 6.78 (m, 1H, Ar), 6.09 (s, 1H, NH), 3.67 (m, 2H, CH_2), 3.52 (m, 4H, CH_2), 2.87 (m, 4H, CH_2), 2.54 (m, 2H, CH_2), 1.35 (m, 6H, CH_2); ^{13}C NMR (acetone-d_6) δ: 156.9, 144.3, 138.2, 129.1, 124.3, 121.2, 118.5, 63, 44.7, 42.0, 35.8, 32.6, 31.1, 29.1, 29.0, 25.6.

4.5.9. *N*-[3-(3-Hydroxy-1-propynyl)phenyl]-*N*′-(2-chloroethyl) urea (1i). Compound **1i** was synthesized from **6d** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 60/40). Yield 63%; IR (KBr) *v*: 3315 (NH, OH), 2229 (C≡C), 1686 (C=O), 1243 (C–O) cm^{-1}; ^1H (NMR acetone-d_6) δ: 8.06 (br s, 1H, NH), 7.08 (m, 1H, Ar), 6.83 (d, 1H, $J = 7.5$ Hz, Ar), 6.75 (s, 1H, Ar), 6.63 (d, 1H, $J = 7.9$ Hz, Ar), 3.57 (m, 4H, CH_2), 2.04 (s, 2H, CH_2); ^{13}C NMR (acetone-d_6) δ: 155.2, 129.8, 123.3, 123.1, 118.0, 115.6, 86.7, 85.9, 51.6, 44.8, 42.3.

4.5.10. *N*-[3-(4-Hydroxy-1-butynyl)phenyl]-*N*′-(2-chloroethyl)urea (1j). Compound **1j** was synthesized from **6e** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 60/40). Yield 51%; IR (NaCl) *v*: 3351 (NH, OH), 1701 (C=O), 1248 (C–O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.21 (br s, 1H, NH), 7.03 (m, 1H, Ar), 6.79 (d, 1H, $J = 7.0$ Hz, Ar), 6.71 (s, 1H, Ar), 6.57 (d, 1H, $J = 7.9$ Hz, Ar), 6.23 (br s, 1H, NH), 3.71 (m, 4H, CH_2), 3.45 (m, 2H, CH_2) 2.60 (t, 2H, $J = 7.0$ Hz, CH_2); ^{13}C NMR (acetone-d_6) δ: 155.8, 146.3, 129.3, 124.1, 122.1, 118.2, 115.2, 86.2, 82.5, 61.1, 44.7, 42.3, 23.7.

4.5.11. *N*-[3-(5-Hydroxy-1-pentynyl)phenyl]-*N*′-(2-chloroethyl) urea (1k). Compound **1k** was synthesized from **6f** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, ethanol/ethyl acetate 2/98). Yield 63%; mp: 86–88 °C; IR (KBr) *v*: 3302 (NH, OH), 1684 (C=O), 1272 (C–O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.12 (br s, 1H, NH), 7.03 (m, 1H, Ar), 6.79 (d, 1H, $J = 7.0$ Hz, Ar), 6.69 (s, 1H, Ar), 6.57 (d, 1H, $J = 8.0$ Hz, Ar), 3.74 (t, 2H, $J = 7.0$ Hz, CH_2), 3.49 (m, 4H, CH_2), 2.47 (t, 2H, $J = 7.0$ Hz, CH_2), 1.23 (t, 2H, $J = 7.0$ Hz, CH_2); ^{13}C NMR (acetone-d_6) δ: 156.1, 146.3, 129.2, 125.3, 124.4, 122.0, 118.0, 88.9, 81.3, 61.6, 45.1, 42.8, 37.3, 31.4, 16.0.

4.5.12. *N*-[4-(3-Hydroxypropyl)phenyl]-*N*′-(2-chloroethyl) urea (1l). Compound **1l** was synthesized from **8d** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 60/40). Yield 51%; mp 113–115 °C; IR (KBr) *v*: 3323 (NH, OH), 1630 (C=O), 1268 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.23 (br s, 1H, NH), 7.30 (d, 1H, $J = 7.9$ Hz, Ar), 7.06 (d, 1H, $J = 8.0$ Hz, Ar), 6.36 (br s, 1H, NH), 3.58 (m, 4H, CH_2), 3.42 (m, 2H, CH_2), 2.47 (m, 2H, CH_2), 1.81 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 155.2, 138.2, 134.0, 128.5, 118.0, 63.3, 44.5, 43.1, 35.7, 30.4.

4.5.13. *N*-[4-(4-Hydroxybutyl)phenyl]-*N*′-(2-chloroethyl) urea (1m). Compound **1m** was synthesized from **8e** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, hexanes/ethyl acetate 60/40). Yield 87%; mp 143–146 °C; IR (KBr) *v*: 3312 (NH), 1639 (C=O), 1244 (C–O) cm^{-1}; ^1H NMR (acetone-d_6) δ: 8.00 (br s, 1H, NH), 7.39 (d, 2H, $J = 8.0$ Hz, Ar), 7.07 (d, 2H, $J = 8.0$ Hz, Ar), 6.50 (br s, 1H, NH), 3.51 (m, 8H, CH_2), 2.57 (t, 2H, $J = 7.5$ Hz, CH_2), 1.58 (m, 2H, CH_2); ^{13}C NMR (acetone-d_6) δ: 155.9, 139.0, 136.3, 130.0, 119.2, 64.8, 42.8, 42.5, 42.4, 35.2, 19.7.

4.5.14. *N*-[4-(5-Hydroxypentyl)phenyl]-*N*′-(2-chloroethyl) urea (1n). Compound **1n** was synthesized from **8f** and 2-chloroethylisocyanate. The crude product was purified by flash chromatography (silica gel, ethanol/ethyl acetate 2:98). Yield 67%; mp 124–126 °C; IR (KBr) *v*: 3320 (NH), 1627 (C=O), 1268 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.63 (br s, 1H, NH), 7.36 (d, 2H, $J = 7.9$ Hz, Ar), 7.13 (d, 2H, $J = 7.9$ Hz, Ar), 6.43 (br s, 1H, NH), 3.96 (t, 2H, $J = 6.5$ Hz, CH_2), 3.57 (m, 6H, CH_2), 2.57 (t, 2H, $J = 7.5$ Hz, CH_2), 1.54 (m, 2H, CH_2), 1.42 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 155.2, 129.5, 128.4, 123.2, 117.9, 60.6, 43.4, 40.9, 34.4, 32.7, 25.0, 19.2.

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