Chapter 7

Synthesis and Characterization of Several New (2-Chloroethyl) Nitroso-Carbamates Derivatives
7.1 Chemistry

The (2-Chloroethyl)nitrosocarbamates conjugates were prepared via reaction of Anthranilamide $\text{131}$ and substituted benzaldehyde ($\text{132a-d}$) in the presence of FeCl$_3$.6H$_2$O to produce substituted 4-hydroxyquinazoline($\text{133a-e}$)$^{62}$, followed by treatment of $\text{133a-e}$ with POCl$_3$ to give substituted 4-chloroquinazoline($\text{134a-e}$)$^{63}$. Reaction of $\text{134a}$ with resorsinol in xylene containing DMAP to give 3-(2-phenylquinazolin-4-yloxy) phenol($\text{135a}$). The other compounds $\text{135b-f}$ was obtained by the treatment of Substituted aniline in isopropanol (IPA) in the presence of concentrated HCl as previously described$^{64}$. Condensation of $\text{135a-f}$ with the commercially available 2-chloroethylisocynate in anhydrous chloroform in the presence of triethylamine (TEA) at room temperature to furnish the carbamate derivatives ($\text{136a-f}$)$^{5}$, which were subsequently nitrosated with NOBF$_4$ in acetonitrile to give nitrosocarbamates $\text{137a-f}$.$^{5}$ The latter compounds were purified by column chromatography on silica gel with a mixture of ethylacetate/hexane as eluent.
7.2 Reaction Scheme

Scheme 1: Synthetic route of N-nitrosocarbamate derivatives

![Reaction Scheme Diagram]

**Scheme 1**: (a) FeCl3.6H2O/water/reflux; (b) POCl3/reflux; (c) DMAP/xylene/140°C; (d) HCl/IPA/reflux; (e) Triethylamine/Chloroform, room temperature; (f) Nitrosonium tetrafluoroborate/acetonitrile/room temperature.
7.3 Physical data

Table 1. Analytical data and yields of compounds (5a-f).

![Chemical structure](image)

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<th>Yield %</th>
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<td>135b</td>
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<td>135f</td>
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Table 2. Analytical data and yields of Carbamate derivatives (6a-f).

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Table 3. Analytical data and yields of Nitrosocarbamate derivatives (7a-f).

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7.4 Experimental

Chemistry: general methods

All commercial chemicals and solvents were reagent grade and were used without further purification unless otherwise specified. Melting points were determined on a Fargo melting point apparatus and are uncorrected. Column chromatography was carried out on Silica Gel G60 (70–230 mesh, ASTM; Merck and 230–400 mesh, Silicycle Inc.). Thin-layer chromatography was performed on Silica Gel G60 F254 (Merck) with short-wavelength UV light for visualization. All reported yields are isolated yields after chromatography or crystallization. Elemental analyses were done on a Heraeus CHN–O Rapid instrument. 1H NMR spectra were recorded on a Brucker AVANCE 600 DRX and 400 MHz, Brucker Top-Spin spectrometers in the indicated solvent. The chemical shifts were reported in ppm (d) relative to TMS.

Procedure:

2-Phenylquinazolin-4(3H)-one (133a). A mixture of an anthranilamide 131 (10.0 g, 73.5 mmole), benzaldehyde (132a, 7.8 g, 73.5 mmole) and FeCl₃·6H₂O (39.1 g, 147.0 mmole) in refluxing water (700 mL) was stirred for 1 h. After completion of the reaction, the reaction mixture was cooled to room temperature and filtered to give the crude product. The crude product was purified by recrystallization from DMF and water, to give 133a, 14 g (86 %); mp 235–237 °C; ¹H NMR (DMSO-d₆) δ 7.48–7.59 (4H, m, 4 × ArH), 7.71–7.73 (1H, m, ArH), 7.79–8.13 (1H, m, ArH), 8.16–8.18 (3H, m, 3 × ArH), 12.51 (1H, s, exchangeable, NH).

2-(Furan-2-yl)-quinazolin-4(3H)-one (133b). Compound 133b was synthesized from anthranilamide 1 (10.0 g, 73.5 mmole), furan-2-carbaldehyde (132b, 7.0 g, 73.5 mmole) and FeCl₃·6H₂O (39.1 g, 147.0 mmole) in water (700 mL): Yield 11.0 g (73 %); mp 217–219 °C; ¹H NMR (DMSO-d₆) δ 6.75–6.76 (1H, m, ArH), 7.50 (1H, t, J = 7.0 Hz, ArH), 7.63–8.64 (1H, m, ArH), 7.69 (1H, d, J = 8.0 Hz, ArH), 7.80–7.84 (1H, m, ArH), 8.00 (1H, d, J = 1.2 Hz, ArH), 8.12 (1H, d, J = 8.0 Hz, ArH), 12.50 (1H, s, exchangeable, NH).

2-(Thiophen-2-yl)-quinazolin-4(3H)-one (133c). Compound 133c was synthesized from anthranilamide 131 (10.0 g, 73.5 mmole), thiophen-2-carbaldehyde (132c, 8.2 g, 73.5 mmole) and FeCl₃·6H₂O (39.1 g, 147.0 mmole) in water (700 mL): Yield 17.0 g
(80 %); mp 280–281 °C; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 7.23–7.24 (1H, m, ArH), 7.25–7.51 (2H, m, 2 × ArH), 7.79–7.88 (2H, m, 2 × ArH), 8.11–8.13 (1H, m, ArH), 8.23–8.24 (1H, m, ArH), 12.66 (1H, s, exchangeable, NH).

**2-(3-Methoxyphenyl)-quinazolin-4(3H)-one (133d).** Compound 133c was synthesized from anthranilamide 131 (10.0 g, 73.5 mmole), 3-methoxybenzaldehyde (132c, 10.0 g, 73.5 mmole) and FeCl\(_3\).6H\(_2\)O (39.1 g, 147.0 mmole) in water (700 mL): Yield 16.0 g (88 %); mp 208–209 °C; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 3.88 (3H, s, Me), 7.10–7.13 (1H, m, ArH), 7.20–7.22 (1H, m, ArH), 7.53–7.58 (2H, m, 2 × ArH), 7.72–7.75 (2H, m, 2 × ArH), 7.83–7.87 (1H, m, ArH), 8.16–8.18 (1H, m, ArH), 12.12 (1H, s, exchangeable, NH).

**4-Chloro-2-phenylquinazoline (134a).** To a magnetically stirred solution of POCl\(_3\) (25 mL) at 0°C was added portion wise 2-phenylquinazolin-4(3H)-one 133a (5.0 g, 22.4 mmole). The reaction mixture was refluxed for 2 hrs. After completion of the reaction, the excess POCl\(_3\) was removed by vacuo. The residue was poured into a mixture of chloroform (50 mL) + ice cold water (80 mL) + ammonia solution (20 mL). The chloroform layer was separated and the aqueous layer was extracted with an additional 20 ml of chloroform. The united chloroform extracts were dried over Na\(_2\)SO\(_4\) and filtered, and the solvent was removed by distillation to give 134a, 4.5 g (87 %); mp 125–127 °C (lit.\(^{21}\) 124–125 °C); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 7.58–7.69 (4H, m, 4 × ArH), 7.91–7.92 (2H, m, 2 × ArH), 8.16–8.21 (3H, m, 3 × ArH). Anal. (C\(_{14}\)H\(_9\)ClN\(_2\)): C, H, N.

**4-Chloro-2-(furan-2-yl)-quinazoline (134b).** Compound 134b was synthesized from 2-(furan-2-yl)-quinazolin-4(3H)-one 133b (5.0 g, 23.5 mmole) in POCl\(_3\) (25 mL): Yield 5.0 g (92 %); mp 115–116 °C; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 6.74–6.76 (1H, m, ArH), 7.44–7.53 (1H, m, ArH), 7.76–7.80 (2H, m, 2 × ArH), 7.81–7.85 (1H, m, ArH), 8.00–8.13 (2H, m, 2 × ArH).

**4-Chloro-2-(thiophen-2-yl)-quinazoline (134c).** Compound 134c was synthesized from 2-(thiophen-2-yl)-quinazolin-4(3H)-one 133c (5.0 g, 21.9 mmole) in POCl\(_3\) (25 mL): Yield 4.5 g (83 %); mp 121–123 °C; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 6.72–6.76 (1H, m, ArH), 7.43–7.53 (1H, m, ArH), 7.76–7.80 (2H, m, 2 × ArH), 7.81–7.88 (2H, m, 2 × ArH), 8.12–8.13 (1H, m, ArH).
4-Chloro-2-(3-methoxyphenyl)-quinazoline (134d). Compound 134d was synthesized from 2-(3-methoxyphenyl)-quinazolin-4(3H)-one 133d (5.0 g, 19.8 mmole) in POCl₃ (25 mL): Yield 5.0 g (94 %); mp 110–111 °C; ¹H NMR (DMSO-d₆) δ 3.84 (3H, s, Me), 7.02–7.05 (1H, m, ArH), 7.36–7.38 (2H, m, 2 × ArH), 7.50–7.52 (1H, m, ArH), 7.83–7.87 (3H, m, 3 × ArH), 8.16–8.18 (1H, m, ArH).

4-Chloroquinazoline (134e). Compound 134e was synthesized from quinazolin-4(3H)-one 133e (5.0 g, 34.2 mmole) in POCl₃ (25 mL): Yield 5.2 g (89 %); mp 98–99 °C; ¹H NMR (DMSO-d₆) δ 7.61–7.69 (1H, m, ArH), 7.79–7.83 (1H, m, ArH), 7.90–7.99 (1H, m, ArH), 8.16–8.18 (1H, m, ArH), 8.79 (1H, s, ArH).

3-(2-Phenylquinazolin-4-yloxy)phenol (135a). To a solution of 4-chloro-2-phenylquinazoline 134a (3 g, 12.5 mmole), resorcinol (2.1 g, 18.7 mmole) and xylene (30 mL), was added DMAP at room temperature. The reaction mixture was stirred at 140°C for 24 hours. After completion of the reaction, the reaction mixture was cooled up to 0-5 °C. The product was collected by filtration and washed with 10% NaOH and finally with water, to give 135a, 1.3 g (34 %); mp 194–195 °C; ¹H NMR (DMSO-d₆) δ 6.78–6.80 (1H, m, ArH), 6.83–6.88 (2H, m, 2 × ArH), 7.32–7.36 (1H, m, ArH), 7.46–7.50 (3H, m, 3 × ArH), 7.72–7.76 (1H, m, ArH), 8.01–8.05 (2H, m, 2 × ArH), 8.06–8.26 (2H, m, 2 × ArH), 8.35–8.37 (1H, m, ArH), 9.79 (1H, s, exchangeable, OH). Anal. (C₂₀H₁₄N₂O₂): C, H, N.

3-((2-Phenylquinazolin-4-yl)amino)phenol (135b). To a solution of 4-chloro-2-phenylquinazoline 134a (3.0 g, 12.5 mmole) and m-aminophenol (1.36 g, 12.5 mmole) in 40 mL of isopropanol (IPA) was added HCl two drops at room temperature. The reaction mixture was heated up to reflux temperature for 3 h and then was cooled to room temperature. The solid was collected by filtration and washed with IPA, and dried to give 135b, 2.5 g (64 %); mp 239–241 °C; ¹H NMR (DMSO-d₆) δ 6.77–6.82 (1H, m, ArH), 6.83–6.90 (2H, m, 2 × ArH), 7.23–7.36 (1H, m, ArH), 7.34–7.40 (3H, m, 3 × ArH), 7.79–8.05 (3H, m, 3 × ArH), 8.08–8.26 (2H, m, 2 × ArH), 8.28–8.32 (1H, m, ArH), 9.70 (1H, brs, exchangeable, OH), 11.30 (1H, brs, exchangeable, NH). Anal. (C₂₀H₁₅N₃O): C, H, N.

3-((2-(Furan-2-yl)quinazolin-4-yl)amino)phenol (135c). Compound 135c was synthesized from 4-chloro-2-(furan-2-yl)-quinazoline 134b (2.0 g, 8.6 mmole), m-
aminophenol (1.0 g, 8.7 mmole) and IPA (30 mL) containing HCl 1-2 drops: yield 2.1 g (80 %); mp 297–298 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 6.75–6.77 (1H, m, ArH), 6.91–6.93 (1H, m, ArH), 7.27–7.36 (2H, m, 2 × ArH), 7.40–7.41 (1H, m, ArH), 7.75–7.81 (2H, m, 2 × ArH), 8.03–8.07 (1H, m, ArH), 8.19–8.26 (2H, m, 2 × ArH), 8.91–8.93 (1H, m, ArH), 9.75 (1H, brs, exchangeable, OH), 11.35 (1H, brs, exchangeable, NH). Anal. (C$_{18}$H$_{13}$N$_3$O$_2$): C, H, N.

3-((2-(Thiophen-2-yl)quinazolin-4-yl)amino)phenol (135d). Compound 135d was synthesized from 4-chloro-2-(thiophen-2-yl)-quinazoline 134b (2.0 g, 8.1 mmole), m-aminophenol (0.88 g, 8.1 mmole) and IPA (30 mL) containing HCl 1-2 drops: yield 2.0 g (77 %); mp 280–281 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 6.76–6.77 (1H, m, ArH), 7.28–7.39 (4H, m, 4 × ArH), 7.74–7.78 (1H, m, ArH), 8.03–8.33 (2H, m, 2 × ArH), 8.34–8.35 (1H, m, ArH), 8.82–8.84 (2H, m, 2 × ArH), 9.25 (1H, brs, exchangeable, OH), 11.26 (1H, brs, exchangeable, NH). Anal. (C$_{18}$H$_{13}$N$_3$O$_2$): C, H, N.

3-((2-(3-Methoxyphenyl)quinazolin-4-yl)amino)phenol (135e). Compound 135e was synthesized from 4-chloro-2-(3-methoxyphenyl)-quinazoline 134d (1.0 g, 3.7 mmole), m-aminophenol (0.40 g, 3.7 mmole) and IPA (30 mL) containing HCl 1-2 drops: yield 1.0 g (79 %); mp 270–272 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 3.57 (3H, s, Me), 6.77–6.79 (1H, m, ArH), 7.25–7.34 (4H, m, 4 × ArH), 7.54–7.57 (1H, m, ArH), 7.81–7.85 (1H, m, ArH), 7.90–7.96 (2H, m, 2 × ArH), 8.07–8.11 (1H, m, ArH), 8.23–8.26 (1H, m, ArH), 8.79–8.81 (1H, m, ArH), 8.90 (1H, brs, exchangeable, OH), 11.46 (1H, brs, exchangeable, NH). Anal. (C$_{21}$H$_{17}$N$_3$O$_2$): C, H, N.

3-(Quinazolin-4-ylamino)phenol (135f). Compound 135f was synthesized from 4-chloroquinazoline 134e (2.0 g, 12.1 mmole), m-aminophenol (1.3 g, 12.1 mmole) and IPA (30 mL) containing HCl 1-2 drops: yield 2.5 g (87 %); mp 231–232 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 6.76–6.78 (1H, m, ArH), 7.13–7.18 (2H, m, 2 × ArH), 7.25–7.29 (1H, m, ArH), 7.84–7.88 (1H, m, ArH), 7.97–7.99 (1H, m, ArH), 8.09–8.13 (1H, m, ArH), 8.87–8.93 (2H, m, 2 × ArH), 9.80 (1H, brs, exchangeable, OH), 11.56 (1H, brs, exchangeable, NH). Anal. (C$_{14}$H$_{11}$N$_3$O): C, H, N.

3-((2-Phenylquinazolin-4-yl)oxy)phenyl (2-chloroethyl)carbamate (136a). To a solution of 3-(2-phenylquinazolin-4-yloxy)phenol 135a (1.2 g, 3.8 mmole) and chloroform (15 mL) containing triethylamine (0.6 mL) was added 2-
chloroethylisocynate (0.45 g, 4.0 mmole) at 0 °C over 20 min. The reaction mixture was stirred at room temperature for 1 hour. After that, the reaction mixture was poured into ice cold water and separated organic layer. The aqueous layer was extracted two times by chloroform and combined all organic layers. The organic layer was washed with 10% K₂CO₃ solution and water, which was dried over Na₂SO₄ and evaporated by vacuo. The solid was collected and purified by Column chromatography using dichloromethane as an eluent, to give 136a, 0.9 g (64 %); mp 140–142 °C; ¹H NMR (DMSO-d₆) δ 3.40 (2H, q, J = 6.0 Hz, CH₂), 3.68 (2H, t, J = 6.0 Hz, CH₂), 7.14–7.16 (1H, m, ArH), 7.16–7.35 (2H, m, 2 × ArH), 7.44–7.48 (3H, m, 3 × ArH), 7.54–7.58 (1H, m, ArH), 7.74–7.78 (1H, m, ArH), 8.04–8.11 (2H, m, 2 × ArH), 8.12 (1H, t, J = 5.6 Hz, exchangeable, NH), 8.27–8.29 (2H, m, 2 × ArH), 8.37–8.39 (1H, m, ArH). Anal. (C₂₃H₁₈ClN₃O₃): C, H, N.

3-((2-Phenylquinazolin-4-yl)amino)phenyl (2-chloroethyl)carbamate (136b).
Compound 136b was synthesized from 3-((2-Phenylquinazolin-4-yl)amino)phenol 135b (2.0 g, 6.3 mmole) and 2-chloroethylisocynate (0.72 g, 6.9 mmole) in chloroform (30 mL) containing triethylamine (1.1 mL): Yield 2.0 (75 %); mp 230–231 °C; ¹H NMR (DMSO-d₆) δ 3.44 (2H, q, J = 6.0 Hz, CH₂), 3.72 (2H, t, J = 6.0 Hz, CH₂), 6.81–6.83 (1H, m, ArH), 6.91–7.02 (1H, m, ArH), 7.40–7.48 (3H, m, 3 × ArH), 7.52–7.55 (1H, m, ArH), 7.75–7.82 (2H, m, 2 × ArH), 8.04–8.09 (2H, m, 2 × ArH), 8.06–8.07 (1H, m, ArH), 8.08–8.09 (1H, m, ArH), 8.11 (1H, t, J = 5.6 Hz, exchangeable, NH), 8.49–8.50 (1H, m, ArH), 9.75 (1H, s, exchangeable, NH). Anal. (C₂₃H₁₉ClN₄O₂): C, H, N.

3-((2-(Furan-2-yl)quinazolin-4-yl)amino)phenyl (2-chloroethyl)carbamate (136c).
Compound 136c was synthesized from 3-((2-(Furan-2-yl)quinazolin-4-yl)amino)phenol 135c (1.0 g, 3.3 mmole) and 2-chloroethylisocynate (0.52 g, 4.9 mmole) in chloroform (20 mL) containing triethylamine (0.5 mL): Yield 1.0 (74 %); mp 247–249 °C; ¹H NMR (DMSO-d₆) δ 3.45 (2H, q, J = 6.0 Hz, CH₂), 3.71 (2H, t, J = 6.0 Hz, CH₂), 6.67–6.69 (1H, m, ArH), 6.87–6.90 (1H, m, ArH), 7.02–7.28 (1H, m, ArH), 7.41–7.45 (1H, m, ArH), 7.57–7.62 (1H, m, ArH), 7.82–7.89 (4H, m, 4 × ArH), 8.04–8.06 (1H, m, ArH), 8.12 (1H, t, J = 5.6 Hz, exchangeable, NH), 8.56–8.58 (1H, m, ArH), 9.88 (1H, s, exchangeable, NH). Anal. (C₂₁H₁₇ClN₄O₃·H₂O): C, H, N.
3-((2-(Thiophen-2-yl)quinazolin-4-yl)amino)phenyl (2-chloroethyl)carbamate (136d). Compound 136d was synthesized from 3-((2-(thiophen-2-yl)quinazolin-4-yl)amino)phenol 135d (1.5 g, 4.7 mmole) and 2-chloroethylisocynate (0.74 g, 7.0 mmole) in chloroform (25 mL) containing triethylamine (0.8 mL): Yield 1.4 (70 %); mp 236–237 °C; 1H NMR (DMSO-d6) δ 3.44 (2H, q, J = 6.0 Hz, CH2), 3.72 (2H, t, J = 6.0 Hz, CH2), 6.90–6.92 (1H, m, ArH), 7.20–7.22 (1H, m, ArH), 7.43–7.47 (1H, m, ArH), 7.58–7.62 (1H, m, ArH), 7.72–7.73 (1H, m, ArH), 7.80–7.88 (3H, m, 3 × ArH), 7.96–7.97 (1H, m, ArH), 8.04–8.05 (1H, m, ArH), 8.13 (1H, t, J = 5.6 Hz, exchangeable, NH), 8.57–8.59 (1H, m, ArH), 9.99 (1H, s, exchangeable, NH). Anal. (C21H17ClN4O2S): C, H, N.

3-((2-(3-Methoxyphenyl)quinazolin-4-yl)amino)phenyl (2-chloroethyl)carbamate (136e). Compound 136e was synthesized from 3-((2-(3-methoxyphenyl)quinazolin-4-yl)amino)phenol 135e (0.7 g, 2.0 mmole) and 2-chloroethylisocynate (0.32 g, 3.1 mmole) in chloroform (10 mL) containing triethylamine (0.4 mL): Yield 0.75 (82 %); mp 170–171 °C; 1H NMR (DMSO-d6) δ 3.45 (2H, q, J = 6.0 Hz, CH2), 3.70 (2H, t, J = 6.0 Hz, CH2), 3.85 (3H, s, Me), 6.91–6.93 (1H, m, ArH), 7.07–7.09 (1H, m, ArH), 7.41–7.48 (2H, m, 2 × ArH), 7.62–7.66 (1H, m, ArH), 7.85–7.93 (3H, m, 3 × ArH), 8.03–8.04 (1H, m, ArH), 8.05–8.06 (1H, m, ArH), 8.07–8.09 (2H, m, 2 × ArH), 8.59–8.61 (1H, m, ArH), 9.94 (1H, s, exchangeable, NH). Anal. (C24H21ClN4O3): C, H, N.

3-(Quinazolin-4-ylamino)phenyl (2-chloroethyl)carbamate (136f). Compound 136f was synthesized from 3-(quinazolin-4-ylamino)phenol 135f (0.5 g, 2.1 mmole) and 2-chloroethylisocynate (0.33 g, 3.2 mmole) in chloroform (10 mL) containing triethylamine (0.3 mL): Yield 0.51 (69 %); mp 165–167 °C; 1H NMR (DMSO-d6) δ 3.41 (2H, q, J = 6.0 Hz, CH2), 3.70 (2H, t, J = 6.0 Hz, CH2), 6.88–6.91 (1H, m, ArH), 7.37–7.41 (1H, m, ArH), 7.76–7.68 (1H, m, ArH), 7.77–7.82 (3H, m, 3 × ArH), 7.86–7.88 (1H, m, ArH), 8.09 (1H, t, J = 5.6 Hz, exchangeable, NH), 8.58–8.59 (1H, m, ArH), 8.65 (1H, s, ArH), 9.85 (1H, s, exchangeable, NH). Anal. (C17H15ClN4O2): C, H, N.

3-((2-Phenylquinazolin-4-yl)oxy)phenyl (2-chloroethyl)(nitroso)carbamate (137a). 3-((2-phenylquinazolin-4-yl)oxy)phenyl (2-chloroethyl)carbamate 136a (0.5 g, 1.1 mmole) were suspended in anhydrous acetonitrile (15 mL) containing acetic
acid (0.2 mL). Nitrosoniumtetrafluoroborate (0.21 g, 1.7 mmole) was added, and the reaction mixture was stirred at room temperature until disappearance of starting material as monitored by TLC. The reaction mixture was poured into 100 mL of ice-cooled water/ethyl acetate (50 % v/v) solution, and the pH was adjusted to 5-6 by careful addition of 5 % sodium bicarbonate solution. The water phase was extracted twice with ethyl acetate, and the organic extracts were washed with brine, dried over sodium sulphate, and concentrated under reduced pressure. The crud product was purified by using Column Chromatography on silica gel eluting with a mixture of ethyl acetate/hexane, to give 137a, 0.2 g (37 %); mp 98–99 °C; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 4.01 (2H, t, \(J = 6.0\) Hz, CH\(_2\)), 4.60 (2H, t, \(J = 6.0\) Hz, CH\(_2\)), 7.36–7.38 (1H, m, ArH), 7.39–7.40 (3H, m, 3 × ArH), 7.61–7.62 (1H, m, ArH), 7.66–7.70 (1H, m, ArH), 7.75–7.79 (1H, m, ArH), 8.04–8.07 (2H, m, 2 × ArH), 8.27–8.31 (3H, m, 3 × ArH), 8.39–8.40 (1H, m, ArH). Anal. (C\(_{23}\)H\(_{17}\)ClN\(_4\)O\(_4\)): C, H, N.

3-((2-Phenylquinazolin-4-yl)amino)phenyl (2-chloroethyl)(nitroso)carbamate (137b). Compound 7b was synthesized from 3-((2-phenylquinazolin-4-yl)amino)phenyl (2-chloroethyl)carbamate 136b (0.5 g, 1.2 mmole), Nitrosoniumtetrafluoroborate (0.21 g, 1.7 mmole) in acetonitrile (10 mL) containing acetic acid (0.5 mL): Yield 0.21 (38 %); mp 133–135 °C; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 3.74 (2H, t, \(J = 6.0\) Hz, CH\(_2\)), 4.27 (2H, t, \(J = 6.0\) Hz, CH\(_2\)), 7.21–7.24 (1H, m, ArH), 7.46–7.49 (3H, m, 3 × ArH), 7.58–7.67 (2H, m, 2 × ArH), 7.89–7.92 (3H, m, 3 × ArH), 8.27–8.28 (1H, m, ArH), 8.47–8.49 (2H, m, 2 × ArH), 8.59–8.61 (1H, m, ArH), 10.00 (1H, s, exchangeable, NH). Anal. (C\(_{23}\)H\(_{18}\)ClN\(_5\)O\(_3\)·0.5H\(_2\)O): C, H, N.

3-((2-(Furan-2-yl)quinazolin-4-yl)amino)phenyl(2-chloroethyl)(nitroso)carbamate (137c). Compound 137c was synthesized from 3-((2-(furan-2-yl)quinazolin-4-yl)amino)phenyl (2-chloroethyl)carbamate 136c (0.5 g, 1.2 mmole), Nitrosoniumtetrafluoroborate (0.21 g, 1.7 mmole) in acetonitrile (10 mL) containing acetic acid (0.5 mL): Yield 0.18 (34 %); mp 109–110 °C; \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 3.75 (2H, t, \(J = 6.0\) Hz, CH\(_2\)), 4.21 (2H, t, \(J = 6.0\) Hz, CH\(_2\)), 6.64–6.65 (1H, m, ArH), 7.19–7.21 (2H, m, 2 × ArH), 7.56–7.64 (2H, m, 2 × ArH), 7.82–7.99 (4H, m, 4 × ArH), 8.28–8.29 (1H, m, ArH), 8.57–8.59 (1H, m, ArH), 10.02 (1H, s, exchangeable, NH). Anal. (C\(_{21}\)H\(_{16}\)ClN\(_5\)O\(_4\)): C, H, N.
3-((2-(Thiophen-2-yl)quinazolin-4-yl)amino)phenyl(2-chloroethyl)(nitroso)carbamate (137d). Compound 137c was synthesized from 3-((2-(thiophen-2-yl)quinazolin-4-yl)amino)phenyl (2-chloroethyl)carbamate 136d (1.0 g, 2.4 mmole), nitrosoniumtetrafluoroborate (0.39 g, 3.4 mmole) in acetonitrile (20 mL) containing acetic acid (0.5 mL): Yield 0.5 (47%); mp 107–108 °C; $^1$H NMR (DMSO-$d_6$) δ 3.72 (2H, t, $J = 6.0$ Hz, CH$_2$), 4.31 (2H, t, $J = 6.0$ Hz, CH$_2$), 6.66–6.67 (1H, m, ArH), 7.20–7.31 (3H, m, 3 × ArH), 7.56–7.64 (1H, m, ArH), 7.81–7.99 (4H, m, 4 × ArH), 8.30–8.32 (1H, m, ArH), 8.58–8.59 (1H, m, ArH), 10.12 (1H, s, exchangeable, NH). Anal. (C$_{21}$H$_{16}$ClN$_5$O$_3$S): C, H, N.

3-((2-(3-Methoxyphenyl)quinazolin-4-yl)amino)phenyl (2-chloroethyl)(nitroso)carbamate (137e). Compound 137e was synthesized from 3-((2-(3-methoxyphenyl)quinazolin-4-yl)amino)phenyl (2-chloroethyl)carbamate 136e (0.5 g, 1.1 mmole), nitrosoniumtetrafluoroborate (0.21 g, 1.7 mmole) in acetonitrile (10 mL) containing acetic acid (0.5 mL): Yield 0.30 (56%); mp 140–141 °C; $^1$H NMR (DMSO-$d_6$) δ 3.58 (3H, s, Me), 3.72 (2H, t, $J = 6.0$ Hz, CH$_2$), 4.30 (2H, t, $J = 6.0$ Hz, CH$_2$), 7.22–7.26 (1H, m, ArH), 7.44–7.46 (2H, m, 2 × ArH), 7.59–7.67 (2H, m, 2 × ArH), 7.90–7.91 (3H, m, 3 × ArH), 8.27–8.28 (1H, m, ArH), 8.49–8.51 (2H, m, 2 × ArH), 8.60–8.61 (1H, m, ArH), 10.12 (1H, s, exchangeable, NH). Anal. (C$_{24}$H$_{20}$ClN$_5$O$_4$): C, H, N.

3-(Quinazolin-4-ylamino)phenyl (2-chloroethyl)(nitroso)carbamate (137f). Compound 137f was synthesized from 3-(quinazolin-4-ylamino)phenyl (2-chloroethyl)carbamate 136f (0.5 g, 1.5 mmole), nitrosoniumtetrafluoroborate (0.25 g, 2.1 mmole) in acetonitrile (15 mL) containing acetic acid (0.5 mL): Yield 0.25 (45%); mp 101–102 °C; $^1$H NMR (DMSO-$d_6$) δ 3.72 (2H, t, $J = 6.0$ Hz, CH$_2$), 4.25 (2H, t, $J = 6.0$ Hz, CH$_2$), 7.46–7.49 (2H, m, 2 × ArH), 7.58–7.60 (1H, m, ArH), 7.89–7.92 (2H, m, 2 × ArH), 8.27–8.28 (1H, m, ArH), 8.44–8.49 (2H, m, 2 × ArH), 8.66 (1H, s, ArH), 10.05 (1H, s, exchangeable, NH). Anal. (C$_{17}$H$_{14}$ClN$_5$O$_3$): C, H, N.

7.5 Conclusion

In this study, we have designed and synthesized a series DNA-alkylating agents, in which the $N$-(2-chloroethyl)-$N$-nitrosocarbamate residue is linked to DNA-binding 4-anilinoquinazoline via a carbamate spacer. All the compounds were characterized by
$^1$H NMR and elemental analysis. The antitumor activity of all newly synthesized derivatives is under investigation.
7.6 $^1$HNMR spectra

7.6.1 $^1$H NMR Spectrum for compound 135a.

7.6.2 $^1$H NMR Spectrum for compound 135a (D2O).
7.6.3 $^1$H NMR Spectrum for compound 135a (ARO).

7.6.4 $^1$H NMR Spectrum for compound 136a.
7.6.5 $^1$H NMR Spectrum for compound 136a (D2O).

7.6.6 $^1$H NMR Spectrum for compound 136a (ARO).
7.6.7 $^1$H NMR Spectrum for compound 137a.

7.6.8 $^1$H NMR Spectrum for compound 137a (ARO).
7.6.9 $^1$H NMR Spectrum for compound 133b.

7.6.10 $^1$H NMR Spectrum for compound 133b (ARO).
7.6.11 $^1$H NMR Spectrum for compound 134b.

7.6.12 $^1$H NMR Spectrum for compound 134b (ARO).
7.6.13 $^1$H NMR Spectrum for compound 135c.

7.6.14 $^1$H NMR Spectrum for compound 135c (D2O).
7.6.15 $^1$H NMR Spectrum for compound 135c (ARO).

7.6.16 $^1$H NMR Spectrum for compound 136c.
7.6.17 $^1$H NMR Spectrum for compound 136c (ARO).

7.6.18 $^1$H NMR Spectrum for compound 137c.
7.6.19 $^1$H NMR Spectrum for compound 136c (ARO).
7.7 Elemental analysis

**Table 2.3** Elemental analysis of compounds 135a-f.

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<td>76.66</td>
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**Table 2.3** Elemental analysis of compounds 136a-f.

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### Table 2.3 Elemental analysis of compounds 137a-f.

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<td>54.78</td>
<td>3.52</td>
<td>15.03</td>
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Section - B

References
References


21. Schabel, F. M., Jr.; Johnston, T. P.; McCaleb, G. S.; Montgomery, J. A.; Laster, 
W.; Skipper, H. E. Cancer Res. 1963, 23, 725
Chem. 1966, 9, 892.
1977, 13, 937.
33. Bigler, A. J.; Buus, L.; Bregnedal, P.; Atassi, G.; Muntzing, J.; Jensen, G. In 
Nitrosoureas in Cancer Treatment; Serrou, B., Schein, P. S., Imbach, J. L., Eds.; 
INSERM Symp. No. 19; Elsevier/North Holland Biomedical Press: Amsterdam, 
1981; p 113.
41. Berger, M.; Zeller, W. J.; Eisenbrand, G.; Lin, P. Z.; Nakra, M.; Schmahl, D. 
   Arzneim.-Forsch./Drug Res. 1982, 32, 481.
42. Filippatos, E.; Papadaki-Valiraki, A.; Roussakis, C.; Verbist, J. F. Arch. Pharm. 
   (Weinheim) 1993, 326, 451.
43. Reynolds, R. C.; Tiwari, A.; Harwell, J. E.; Gordon, D. G.; Garrett, B. D.; Gilbert, 
   397.
   Mathe, G. Biomedicine 1975, 23, 410.
   references therein.
52. Foster, D. O.; Pardee, A. B. J. Biol. Chem. 1969, 244, 2675.
   335.
57. Characterization and Treatment of Human Tumors; Davies, W., Harrap, K. R., 
   Eds.; Exerpta Medica: Amsterdam, 1978; p 303.
58. Bouveng, R.; Ellman, M.; Gunnarsson, P. O.; Jensen, G.; Liljekvist, J.; Muntzing, 
   1972, 15, 1158.
   130.


CONFERENCES/SEMINARS/WORKSHOPS ATTENDED

» “International conference on bridging gaps in discovery and development: chemical & biological science for affordable health, wellness & sustainability” jointly organized by ISCBC and Saurashtra University, Rajkot. February, 04-07, 2011

» “The 7th International Symposium for Chinese Medicinal Chemists” (ISCMC) Kaohsiung, Taiwan, February, 01-05, 2010.

» “2009 PST Medicinal Chemistry Symposium” Si-Tao, Taiwan, June 28-30, 2009.

» “International Conference On The Interface of Chemistry-Biology In Biomedical Research” jointly organized by ISCBC and Birla Institute of Technology & Science, Pilani. February, 22-24, 2008

» “National Workshop On Management And Use Of Chemistry Database And Patent Literature” organized by GUJCOST & Dept. of Chemistry of Saurashtra University, Rajkot, (Gujarat), February, 27-29, 2008.


» “National Conference On Selected Topics In Spectroscopy And Stereochemistry” organized by the Department of Chemistry, Saurashtra University, Rajkot, March, 18-20, 2009.
Paper/Poster presented at the International Conference:


