NEW AMIDINO-SUBSTITUTED BENZIMIDAZOLYL FURYL-THIENYL-ACRYLATES AND BENZO-THIENOFURANS; SYNTHESIS AND PHOTOCHEMICAL SYNTHESIS

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Abstract

New amidino-substituted benzimidazolyl 3-(2-furyl)-2-(2-thienyl)acrylates **4-6**, benzo[1,2-b]thieno-benzo[4,3-b']furans **8-10** were prepared by the condensation of amidino-substituted o-phenylenediamines with corresponding aldehydes **3** and **7**. All prepared amidino-substituted compounds could serve as intercalators or groove binders of DNA in HIV infection.

Introduction

The benzimidazole nucleus play very important role in the variety of naturally occurring compounds such as *vitamin* B_{12} and its derivatives (1) and is also a key feature in cardiotonic agents such as *pimobenden* (2), *adibenden* (3), potential antitumor agents (4) and antiulcer drugs (5). Amidino compounds are widely investigated on their biological activity too. Many authors synthesized a lot of bis-amidino substituted heterocyclic compounds for screening against the rat model of *Pneumocystis carinii pneumonia* (PCP) (6-11). The amidine groups at the termini of the molecules seemed to contribute significantly to the dications and the DNA complex stability (12,13). A number of aromatic diamidines have been shown to bind in minor groove on DNA at AT-rich sites and to be affective against many opportunistic organisms (14,15). Several hypotheses have been proposed to explain the mode of action of these compounds. The factors important in minor groove binding are hydrogen-bonding, electrostatic interactions, Van der Waals interactions, and the radius of curvature of the observed molecule (16, 17). Wang found that a series of an aromatic dication with an amidine-phenyl-furan-benzimidazole-amidine structure could recognize specific sequences of DNA by binding in the minor groove of DNA as a dimer (18). Recently synthesized bis-cationic bis-amidino benzimidazolyl substituted diphenylfurans inhibited HIV-1 infection (19)

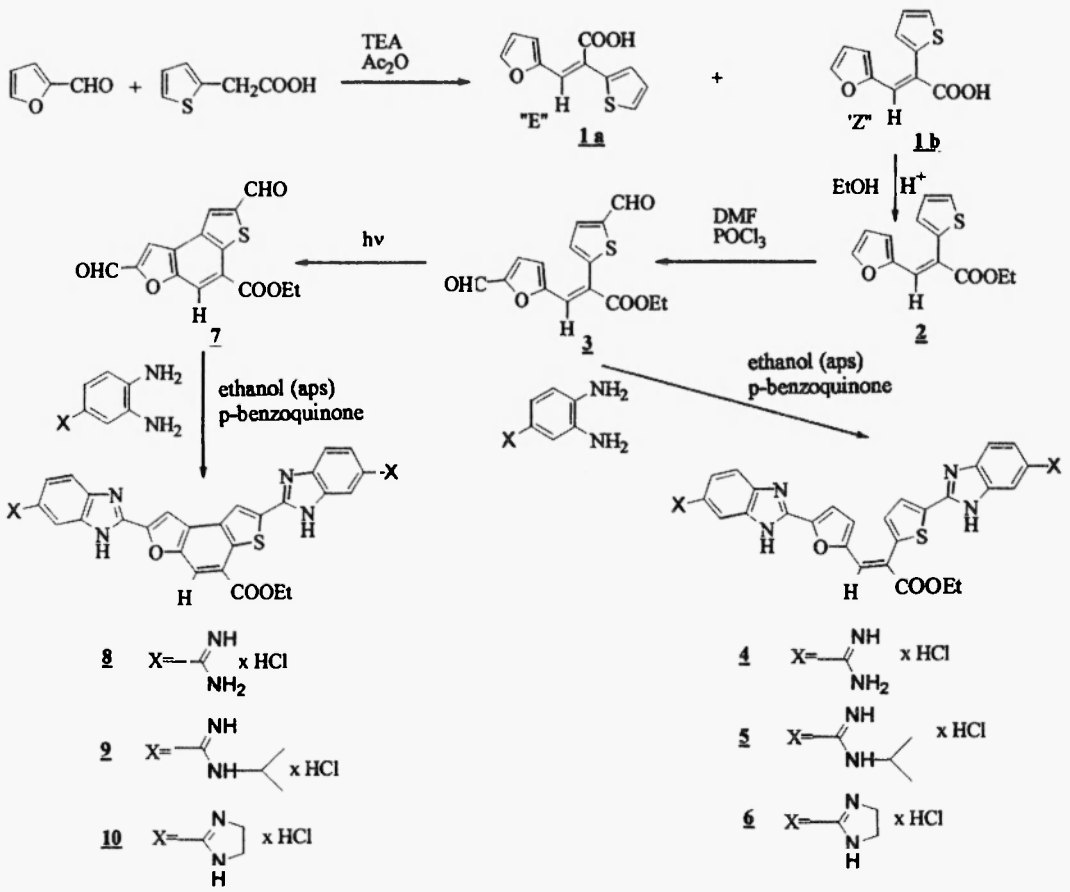
Results and Discussion

The influence of the amidino and substituted amidino groups in heterocyclic compounds, on the biological activity, as well as, well known different biological activities of a number of amidino substituted benzimidazoles, prompted us to synthesize new amidino substituted heterocyclic systems (20, 21).

In this work we prepared in the multistep synthesis new amidino-substituted benzimidazolyl 3-(2-furyl)-2-(2-thienyl)acrylates **4-6** and benzo[1,2-b]thieno-benzo[4,3-b']furans **8-10**. First were prepared 3,4-diaminobenzamidine, 3,4-diamino-N-isopropylbenzamidine and 4-[N-(2-imidazolinyl)]-1,2-phenylenediamine in the Pinner reaction starting from acetamidobenzonitrile (22).

Amidino substituted 1, 2-phenylene diamines are used later in the condensation with earlier prepared dialdehydes **3** and **7** (11). Dialdehyde **3** was prepared in two step reaction. Starting from 2-furaldehyde and 2-thienylacetic acid by the condensation reaction in Ac_2O and in the presence of TEA, were prepared "E" and "Z" 3-(2-furyl)-2-(2-thienyl)acrylic acids. **1a** and **1b**. **1b** was esterificated and formylated by the Vilsmeyer method into the "Z" ethyl 3-(5-formyl-2-thienyl) acrylate **3** (23). Dialdehyde **3** was also transformed into the "Z"-ethyl-2,7-di-formyl-benzo[1,2-b] thieno-benzo[4,3-b']furan **7** by the reaction of photochemical dehydrogenation described earlier (24). Both dialdehydes **3** and **7** reacted later with earlier prepared amidino substituted phenylenediamines in the presence of p-benzoquinone (11). On this way were prepared " Z"-ethyl-3-[5-(5-amidino-2-benzimidazolyl)-2-furyl]-2-[5-(5-amidino-2-benzimidazolyl)-2-thienyl]acrylate dihydrochloride **4**, "*Z*"ethyl-3-[5-(5-*N*-isopropylamidino-2-benzimidazolyl)-2-furyl]-2-[5-(5-isopropylamidino-2-benzimidazolyl-2-thienyl]acrylate dihydrochloride **5**, "*Z*"-ethyl-3-[5-(5-imidazolyl-2-benzimidazolyl)-2-furyl]-2-[5-(5-imidazolyl-2-benzimidazolyl)-2-thienyl]acrylate dihydrochloride **6**, 4-ethyl-2,7-bis-[(5-amidino)-2-benzimidazolyl]-benzo[1,2-b]tieno-benzo[4,3-b']furan dihydrochloride **8**, 4-ethyl-2,7-bis-[(5-*N*-isopropylamidino)-2-benzimidazolyl]benzo[1,2-b]thieno-benzo[4,3-b']furan dihydrochloride **9** and 4-ethyl-2,7-bis- [(5-imidazolyl)-2- benzimidazolyl]benzo[1,2-b]thieno-benzo[4,3-b']furan dihydrochloride **10** according to the Scheme.

All new bis-amidino-benzimidazolyl compounds were prepared in good yields.



Scheme

Experimental

Melting points were determined on a Kofler block apparatus and are uncorrected. IR spectra were determined with a Nicolet Magna 760 infrared spectrophotometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectral data were determined using Brucker Avance DPX 300 MHz NMR or Varian- Gemini 300 MHz spectrometers with tetramethylsilane as an internal standard. Elemental analyses were carried out in the Microanalytical laboratory at the "Rugjer Boskovic" Institute.

***"E"*and*"Z"*3-(2-furyl)- 2-(2-thienyl)acrylic acids 1a, 1b**

Compounds **1a** and **1b** were prepared by 45 min. heating of 2-furylcarboxaldehyde (6.5 ml, 78 mmol) and thiopheneacetic acid (10g,, 70mmol) in triethylamine (10 ml), and acetic anhydride (10 ml). After the reaction was completed, the mixture was cooled, acidified with diluted hydrochloric acid (1:1) and extracted with ether (350 ml). The organic layer was washed with water and the acids **1a** and **1b** were extracted into 10% sodium carbonate solution (1000 ml). The alkaline solution of sodium salts of compounds **1a** and **1b** was boiled with charcoal, filtered off, cooled and acidified to pH 5 with acetic acid. The precipitated *"Z"* isomer **1b** was filtered off and recrystallized from methanol. The yield was 7.63g (58.7%), mp 197-200 °C. Concentrated hydrochloric acid was added to the filtrate and additional crystalline crops consisting of the *"E"* isomer were filtered off. The yield on the *"E"* isomer of **1a** was 3.26g (27,2 %) mp 178-184 °C. Ir (cm^{-1}) (KBr) for **1b**: 1615 (C=C), 1670 (COOH). ^{1}H NMR (DMSO-d_6) (δ ppm): 6.22 (1H, d, J=3.36 Hz, H_c), 6.53 (1H, $AB_{syst.}$, J=3.67 Hz, J=4.88 Hz, H_b), 7.03 (1H, d, J=3.60 Hz, H_e), 7.12 (1H, $AB_{syst.}$, J=3.66 Hz, J=4.89 Hz, H_f), 7.65 (1H, d, J=4.58 Hz, H_g), 7.67 (1H, s, H_d), 7.75 (1H, d, H_a), 12.6 (1H, s, COOH). Anal. Calcd for: $C_{11}H_8O_3S$: C, 59.99; H, 3.66; S, 14.56. Found: C, 59.87; H, 3.61; S, 14.62.

Ethyl*"Z "*3-(2-furyl)-2-(2-thienyl)acrylate 2

Ethyl ester **2** was prepared by 17 h refluxing of **1b** (8.3 g, 38 mmol) dissolved in absolute ethanol (150 ml) to which conc. sulfuric acid (1.5 ml) was added. After that time, the volume of the reaction mixture was reduced to 50 ml and the content was poured into crushed ice (300 g). Crystalline crops were recrystallized from ethanol. White crystals, in the yield of 9.1 g (97.2 %), mp 56-58 °C were obtained. ·Ir (cm^{-1}) (KBr): 1615 (C=C), 1700 (COOEt). ^{1}H NMR (DMSO-d6) (δ ppm): 1.20 (3 H, t, J=7.32 Hz, J=7.02 Hz, CH_3), 4.20 (2H, q, J= 7.02 Hz, CH_2), 6.25 (1H, d, J=3.67 Hz, H_c), 6.54 (1H, $AB_{syst.}$, J=3.67 Hz, J=4.88 Hz, H_b), 7.05 (1H, d, J=3.60 H_e). 7.14 (1H, $AB_{syst.}$, J=3.67 Hz, J=4.88 Hz, H_f), 7.67 (1H, d, J=4.57 Hz, H_g), 7.69 (1H, s, H_d), 7.78 (1H, d, H_a). Anal. Calcd for: $C_{13}H_{12}O_3S$: C 62.89; H.4.87, S,12.91. Found: C, 62.93; H, 4.83; S, 13.02.

Ethyl*"Z "*3-(5-formyl-2-furyl)-3-(5-formyl-2-thienyl)acrylate 3

Ethyl ester 2 was formylated by Vilsmeier reaction. Phosphorus oxychloride (11.1 ml, 0.11 mmol) was added dropwise and with cooling to the solution of ethyl ester **2** (5g, 24mmol) in DMF (10.6 ml, 12.6 mmol) with such a rate that the temperature of the reaction mixture not exceed 10 °C. After the addition was completed, the mixture was stirred for 30 min. at room temperature, then heated at 90-95 °C for 45 min, cooled and poured into crushed ice (300 g), made weakly alkaline with 10% sodium hydroxide solution and left overnight on ice. The gummy product was decanted, washed with water and recrystallized from methanol. Yellow crystalline product was obtained in the yield of 2.76 g (38 %), mp 120-123 °C. Ir (cm^{-1}) (KBr): 1665 (CHO), 1675 (CHO), 1710 (COOEt). ^{1}H NMR ($CDCl_3$) (δ ppm): 1.27 (3H, t, J=7.1 Hz, CH_3), 4.31 (2H, q, J=7.05 Hz, CH_2), 6.30 (1H, d, J=3.65 Hz, H_b), 7.14 (1H, d, J=3.93 Hz, H_d), 7.20 (1H, d, J=3.65, H_a), 7.80 (1H, d,

J=3.94 Hz, H_e), 7.84 (1H, s, H_c), 9.59 (1H, s, CHO), 9.97 (1H, s, CHO).^{13}C NMR ($CDCl_3$) δ : 14.0, 62.1, 127.0, 144.1, 145.4, 152.7, 153.7, 1684.8, 177.7, 182.7. Anal. Calcd for $C_{15}H_{12}O_5$: C, 59.21; H, 3.95; S, 10.53. Found: C, 59.43; H, 3.95; S, 10.20.

"Z" Ethyl-3-[5-(5-amidino-2-benzimidazolyl)-2-furyl]-2-[5-(5-amidino-2-benzimidazolyl)-2-thienyl]-acrylate dihydrochloride 4

Compound **4** was prepared using the method described earlier (11). A mixture of compound **3** (0.61 g, 2 mmol), and 3,4-diamino-benzamidine (0.6 g, 4 mmol), p-benzoquinone (0.43 g, 4 mmol) in abs. EtOH (80 ml) was stirred at reflux for 4 h (under nitrogen). The reaction mixture was cooled to room temperature and the resulting precipitated dark crystals were filtered off. The crude product was suspended in conc HCl, heated to boiling and stirred over night at room temperature. Acetone was added into the solution, the resulting dark green crystals were filtered off and washed with dry ether. The crystals of **3** were dissolved in water and precipitated with acetone again, filtered off and dried. It was repeated few times until the crystals were analytically pure. It was obtained 0.47 g, (36%) dark green crystals mp>300oC. IR (cm^{-1}; KBr) 3370 3105 1687 1615. ^{1}H NMR (δ ppm) (DMSO-d_6): 9.37 (s, 1H, NH) 9.03 (s, 1H, NH), 8.15 (d, 1H, J=3.28Hz, H-fur.), 8.14 (d, 1H, J=4.05Hz, H-tio.), 7.87 (s, 1H, H-vinyl), 7.83 (d, 1H, J=3.26Hz, H-fur.), 7.78 (d, 2H, J=8.37Hz, H-arom.), 7.71 (d, 2H, J=8.67Hz, H-arom.), 7.45 (d, 1H, J=3.88Hz, H-tio.), 7.41 (d, 2H, J=7.92Hz, J=1.5Hz, H-arom.), 4.34-4.28 (m, 2H, OCH_2), 1.32 (t, 3H, J=6.94Hz, CH_3) Anal.Calc. for $C_{29}H_{26}N_8O_3SCl_2$: C 54.59 H 4.08 N 17.57 Found: C 54.81 H 4.39 N 17.18

"Z" Ethyl-3-[5-(5-N-isopropylamidino-2-benzimidazolyl)-2-furyl]-2-[5-(5-N-isopropylamidino-2-benzimidazolyl)-2-thienyl]-acrylate dihydrochloride 5

Compound **5** was prepared using the method described earlier (11). A mixture of **3** (0.69 g, 23mmol), 3,4-diamino-N-isopropylbenzamidine (0.87 g, 5 mmol) and p-benzoquinone (0.49 g, 4 mmol) in abs. EtOH (50 ml) was stirred at reflux for 4 h (under nitrogen). The reaction mixture was cooled to room temperature, and ethyl-ether was added and the resulting yellow-green solid was filtered off. The crude product was suspended in abs. ethanol and cooled to 0-5°C. Into the suspension was introduced HCl gas until the suspension was saturated and the content was stirred over night on the room temp. Dry ether was added and the precipitated yellow-green crystals were filtered off and washed with dry ether. It was repeated few times until the crystals were analytically pure. It was obtained 0.61 g (36%) yellow-green crystals mp >300oC. IR (cm^{-1}; KBr) 3371 3092 2979 1667 1615. ^{1}H NMR (δ ppm) (DMSO-d_6): 9.61 (s, 1H, NH) 9.47 (s, 1H, NH), 9.07 (s, 1H, NH), 8.04 (s, 2H, H-arom.), 7.82 (d, 2H, J=8.49Hz, H-arom.) 7.65-7.60 (m, 3H, H-ar., H-vinyl) 7.25 (d, 1H, J=3.5Hz, H-fur.) 7.14 (d, 1H, J=3.8Hz, H-tio.) 6.95 (d, 1H, J=3.5Hz, H-fur.) 4.13-4.07 (m, 2H, CH) 3.48-3.40 (m, 2H, OCH_2) 1.31 (d, 12H, J=6.3Hz) 1.06 (t, 3H, CH_3, J=7.0Hz). Anal. Calc. for $C_{35}H_{38}N_8O_3SCl_2$: C 58.19 H 5.27 N 15.52 Found: C 58.25 H 5.62 N 15.01.

"Z" Ethyl-3-[5-(5-imidazolyl-2-benzimidazolyl)-2-furyl]-2-[5-(5-imidazolyl-2-benzimidazolyl)-2-thienyl]-acrylate dihydrochloride 6

Compound **6** was prepared using the method described for preparation **of 5** from **3** (0.14 g, 0.47mmol), 4-[N-(2-imidazolinyl)]-1,2-phenylenediamine (0.27 g, 0.94 mmol) and p-benzoquinone (0.10 g, 0.94 mmol) in abs. ethanol (50 ml). It was obtained 0.1 g, (32%) dark green crystals mp > 300°C. IR (cm^{-1}; KBr) 3390 3093 2974 1699 1632 1606. ^{1}H NMR (δ ppm) (DMSO-d_6): 10.54 (s, 2H, NH) 8.28 (s, 2H, H-arom.), 7.87 (s, 1H, H-eth.), 7.82-7.80 (m, 5H, Hfu_r., H-tio., 3H-arom), 7.41-7.38 (m, 2H, H-tio., H-arom..), 6.45 (d, 1H, J=3.87Hz, H-fur), 4.28 (q, 2H, J=7.14Hz, $-CH_2$), 1.29 (t, 3H,J=7.14Hz, OCH_3) Anal. Calc. for $C_{33}H_{30}N_8O_3SCl_2$: C 57.43 H 4.35 N 16.24 Found: C 57.14 H 4.47 N 15.79.

4-Ethyl-2,7-bis-formyl-benzo[1,2-b]thieno-benzo[4,3-b']furan 7

Compound 7 was prepared from **3** (0.3 g, 0.9 mmol) which was dissolved in toluene (300 ml) and irradiated with high pressure mercury arch lamp during 2.5 h. I_2 (0.1 g) was added into the solution and the air was bubbled through. The solvent was evaporated and the residue recrystallized from methanol. It was obtained 0.14 g (51.5%) orange crystals, mp 190-193oC.

IR (cm^{-1}; KBr) 1694, 1666, 1569. ^1H NMR (δ ppm) (DMSO-d_6): 10.21 (s, 1H, -CHO thio.), 9.99 (s, 1H, -CHO fur.), 8.82 (s, 1H, H-arom.), 8.49 (s, 1H, H-thio.), 8.45 (s, 1H, H-fur.), 4.47 (q, 2H, J=7.16Hz, OCH_2), 1.43 (t, 3H, J=7.14Hz, CH_3). ^{13}C NMR (δ ppm) (DMSO-d_6) 186.3, 181.1, 164.7, 155.1, 153.2, 146.7, 137.7, 133.9, 131.8, 127.5, 124.4, 116.1, 115.4, 62.3, 14.4 Anal. Calc. for $C_{15}H_{10}O_5S$: C 59.60 H 3.31 Found: C 59.81 H 3.27

4-Ethyl-2,7-bis-[(5-amidino)-2-benzimidazolyl]-benzo[1,2-b]thieno-benzo[4,3-b']furan dihydrochloride 8

Compound 8 was prepared on the way described for preparation of **4**, from 7 (0.60g, 2 mmol), 3,4-benzamidine (0.6 g, 4mmol) and p-benzoquinone (0.43 g) in aps. EtOH (50). It was obtained 0.54 g (42.8%) dark green crystals, mp>300°C. IR (cm^{-1}; KBr) 3365 3080 1673 1624. ^{1}HNMR (DMSO-d_6): 9.40 (s, 1H, NH) 9.00 (s, 1H, NH), 8.85 (s, 1H, H-tiof.), 8.48 (s, 1H, H-fur), 8.36 (s, 1H, H-vinyl), 8.26 (s, 1H, H-arom.), 7.88 (d, 2H, J=8.45Hz, H-arom.), 7.75 (d, 2H, J=8.5Hz, H-arom.), 4.55-4.52 (m, 2H, OCH_2), 1.48 (t, 3H, J=7.02Hz, CH_3). Anal. Calc. for $C_{29}H_{24}N_8O_3SCl_2$: C 54.8 H 3.8 N 17.6 Found: C 54.99 H 4.01 N 17.44.

4-Ethyl-2,7-bis-[(5-N-isopropylamidino)-2-benzimidazolyl]-benzo[1,2-b]thieno-benzo[4,3-b']furan dihydrochloride 9

Compound 9 was prepared on the way described for preparation of **5**, from **3** (0.60g,, 2 mmol), 3,4-diamino-N-isopropylbenzamidine (0.76 g, 4.5 mmol) and p-benzoquinone (0.43 g, 4 mmol) in aps. EtOH(50 ml). It was obtained 0.57 g, (58.7%) dark green crystals, mp > 300oC. IR (cm^{-1}; KBr) 3389 3105 2981 1667 1614. ^1H NMR (δ ppm) (DMSO-d_6): 9.67 (s, 1H, NH) 9.51 (s, 1H, NH), 9.08 (s, 1H, NH), 8.96 (s, 1H, H-thioph.), 8.56 (s, 1H, H-fur.), 8.46 (s, 1H, H-vinil..), 8.19 (d, 2H, J=8.85Hz, H-arom.), 7.98-7.90 (m, 2H, H-arom.), 7.74-7.68 (m, 2H, H-arom.), 4.60 (q, 2H, OCH_2), 4.17-4.13 (m, 1H, CH), 1.56 (t, 3H, J=7.14Hz, J=1.55Hz -CH_3), 1.40 (d, 12H, J=6.3 CH_3). ^{13}C NMR (δ ppm) (DMSO-d_6): 165.19, 162.43, 152.48, 149.86, 149.49,145.22, 137.01, 135.90, 133.55, 127.61, 123.81, 123.35, 122.87, 122.12, 121.27, 112.33, 107.03, 61.94, 45.17, 21.42, 14.35 Anal. Calc. for $C_{35}H_{36}N_8O_3SCl_2$ C 58.36 H 5.0 N 15.56 Found: C 58.58 H 5.37 N 15.15

4-Ethyl-2,7-bis-[(5-imidazolyl)-2-benzimidazolyl]-benzo[1,2-b]thieno-benzo[4,3-b']furan dihydrochloride 10

Compound **10** was prepared on the way described for preparation of **5**, from **3** (0.38 g,, 1.3 mmol),), 4-[N-(2-imidazolinyl)]-1,2-phenylenediamine (0.72 g, 2.6 mmol) and p-benzoquinone (0.27 g, 2.6 mmol) in abs. EtOH (80 ml). It was obtained 0.5 g (58.7%) dark crystals, mp > 300°C. IR (cm^{-1}; KBr) 3390 3094 2982 1698 1633 1606. ^1H NMR (δ ppm) (DMSO-d_6): 10.61 (s, 2H,NH) 10.58 (s, 2H, NH) 8.84 (s, 1H, H-tio.) 8.46 (s, 1H, H-fur) 8.43 (s, 1H, H-vinyl) 8.37 (d, 2H, J=7.64 , H-arom.) 7.91-7.88 (m, 4H, H arom.t) 4.56-4.49 (q, 2H, OCH_2) 4.05 (s, 8H, CH_2) 1.47 (t, 3H, , J=7.16 Hz, CH_3). Anal. Calc. for $C_{33}H_{26}O_3N_8Sx6\ H_2O$ C 49.78 H 4.77 N 14.08 Found: C49.65 H 4.74 N 14.01.

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