Convenient Route to Efavirenz Analogues as Potential non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors

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Dedicated to Prof. Dr. J. C. Jochims on the occasion of his 66th birthday

Treating 2-chloro-4-(4-chlorophenyl)-6-methylbenzo[d]-3,1-oxazinium hexachloroantimonate **(1)** with one equivalent of alcohol or mercaptane led, after hydrolysis with aq. NaOH, to the formation of 4,4-disubstituted-1,4-dihydro-2H-6-methyl-3,1-benzoxazin-2-ones **(3)**. Large excess addition of alcohol afforded either 4'-chloro-2-isocyanato-5-methylbenzophenone disubstitutedketal **(4)** or N-{2-[(4-chlorophenyl)dialkoxymethyl]-4-methylphenyl} alkylcarbamate **(5)**. Reaction of **4** with primary amines furnished 1-{2-[(4-chlorophenyl)dialkoxymethyl]-4-methylphenyl}-3-substituted urea **(6)**.

Key words: Efavirenz Analogues, 3,1-Benzoxazin-2-ones, Urea Derivatives, Ketals, Isocyanates, Human Immunodeficiency Virus

Introduction

The acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) is a serious health problem throughout the world. Effective therapies of this disease require combinations of antiviral drugs: a) nucleoside reverse transcriptase inhibitors (NRTI) such as AZT, DDC, DDI and D4T, b) protease inhibitors such as ritonavir, saquinavir, indinavir or nelfinavir, c) non-nucleoside reverse transcriptase inhibitors (NNRTI). The class of NNRTI's is rapidly developing and different type of compounds within this class have been described, for example, derivatives of dipyridodiazepinone (nevirapine) [1, 2], of bis (heteroaryl) piperazine (BHAP) (delavirdine,ateviridine) [3, 4], of benzoxazines (efavirenz) [5], of 1-[(2-hydroxyethoxy)-methyl)]-6-phenylthio) thymine (HEPT) and of its analogue MKC442 [6, 7], of dihydroalkoxy benzyloxopyrimidines and thio analogues (DABO's, S-DABO's) [8, 9], of phenethylthiazolyl thiourea (PETT) compounds (trovirdine) [10 – 12]. Other recent series belong to NNRTI's such as alkenyldiarylmethanes (ADAM's) [13, 16], anilinophenylacetamide (APA) (loviridine) [17], and thiocarboxanilide derivatives (UC84, UC38) [18]. From these compounds only nevirapine (Viramune®), delaviridine (Rescriptor®), and efavirenz (Sustiva™) have been approved as anti-HIV drugs by the Food and Drug Administration (FDA). Efavirenz (Fig. 1) showing high potency against HIV-1 is an essential component of an effective combination therapy when administered together with other HIV drugs. However, as with all current HIV therapies, the development of drug-resistant strains of the virus is of major concern. Therefore, it is necessary to develop improved efavirenz analogues to overcome or reduce this problem. Several approaches have been used to improve the potency of efavirenz against resistant mutants. Modifications were carried out by replacing the cyclopropyl ring with small heterocycle, alkyl or alkoxy group [19]. Other series was constructed by incorporating different atoms or groups on the aromatic ring [20, 21]. Recent studies were performed in which the heterocycle oxazine of efavirenz was transformed to quinazoline [22], quinoxaline [23], or thiadiazine [24]. Here we report on convenient and simple access to a new series of efavirenz analogues.

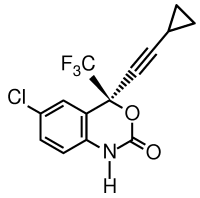

Fig. 1. Efavirenz (Sustiva).

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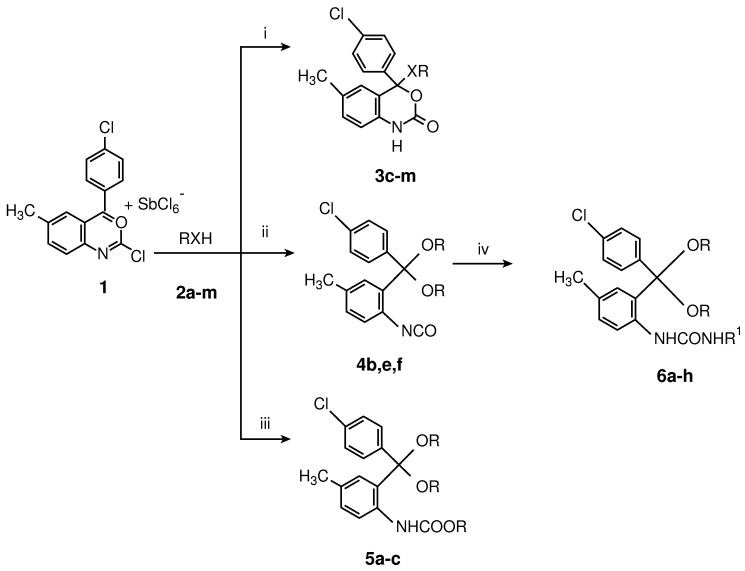

2-5	X	R
a	O	CH_3
b	O	CH_2CH_3
c	O	$(CH_2)_2CH_3$
d	O	$(CH_2)_2CN$
e	O	$(CH_2)_2OCH_3$
f	O	CH_2CHCH_2
g	O	CH_2CCH

2-5	X	R
h	O	$(CH_2)_2Cl$
i	O	$CH(CH_3)_2$
j	O	$(CH_2)_2C_6H_5$
k	S	$CH(CH_3)_2$
l	S	$(CH_2)CH_3$
m	S	CH_2CHCH_2

6	R	R^1
a	CH_2CH_3	$C_6H_5CH_2$
b	CH_2CH_3	4-CH_3-C_6H_4
c	CH_2CHCH_2	4-F-$C_6H_4CH_2$
d	CH_2CHCH_2	4-Cl-$C_6H_4CH_2$
e	CH_2CHCH_2	4-OCH_3-$C_6H_4CH_2$
f	$(CH_2)_2OCH_3$	4-F-$C_6H_4CH_2$
g	$(CH_2)_2OCH_3$	4-Cl-$C_6H_4CH_2$
h	$(CH_2)_2OCH_3$	4-OCH_3-$C_6H_4CH_2$

Scheme. 1. Reagents and Conditions: i: 1,2-Dichloroethane, −40 to 23 °C, aq. NaOH, 20 min. ii: large excess ROH, −10 to 23 °C, aq. NaOH, 20 min., iii: as described for ii except 3 – 4 h., iv: R^1NH_2, Et_2O, 35 °C, 10 min.

Results and Discussion

In this communication, the synthesis of efavirenz analogues is reported starting from the benzoxazinium salt **1**, which was prepared as described in literature [25] by adding a solution of $SbCl_5$ in CH_2Cl_2 to a cold (−30 °C) mixture of *p*-tolylisocyanate and *p*-chlorobenzotrichloride. This salt is extremely sensitive toward nucleophiles. For instance, on dropwise addition of one molar equivalent of an alcohol or thioalcohol **2** to a cold suspension of **1** in absolute dichloromethane or 1,2-dichloroethane, the orange suspension dissolved immediately. Subsequent hydrolysis with aqueous NaOH afforded the target compound **3** in 50 – 75% yield.

Considering the scope and limitation of the reaction, it should be mentioned that only electron rich arylisocyanates and electron deficient chlorocarbenium salts can be used to form benzoxazinium salts. Excess of alcohol or thioalcohol has to be avoided.

Addition of a large excess of alcohol to the cold (−10 °C) suspension of **1** in CH_2Cl_2 led to the formation of the isocyanate **4** in almost quantitative yield. Under these conditions the isocyanate group of **4** is not attacked by the alcohol. However, stirring the reaction mixture at room temperature for a few hours and subsequent hydrolysis with aqueous NaOH gave the corresponding carbamate **5** (Scheme 1).

The structural assignments of the prepared compounds are based on their spectral (IR, ^1H and ^{13}C NMR) and elemental analyses data. The IR spectrum of **3** showed an absorption bands in the range of 1715 – 1724 cm^{-1} (C=O), 3419 – 3423 cm^{-1} (NH). Besides, compounds **3d** and **3g** showed absorption bands at 2254 cm^{-1} (CN) and 2105 cm^{-1} (C≡C) respectively. In the ^1H NMR spectrum of **3**, diastereotopic CH_2 protons are observed. Singlet signals in the range of 2.10 – 2.27 and 9.34 – 10.20 ppm are attributed to CH_3 and NH groups respectively. Signals in the ranges of 95.9 – 107.8 and of 149.8 – 152.4 ppm in the ^{13}C NMR spectrum (CD_3Cl) are assigned to the saturated ketal carbon atoms and carbonyl carbons, respectively. Spectral data of the carbamates **5** were consistent with the assigned structure. The IR spectrum showed absorption bands at 1737 cm^{-1} characteristic for the ester group (COOR) and 3388 cm^{-1} for (NH).

The saturated ketal carbon atom of **5** showed a signal in ^{13}C NMR at 101.5 ppm. The constitution of the isocyanates **4** were derived from the spectral data. Its IR spectrum showed a strong NCO band at $\sim$ 2287 cm^{-1} (film) and the ^{13}C NMR spectrum exhibit a signal at $\sim$ 122 ppm (CD_3Cl) for NCO carbon. Further characterization of **4** was achieved by reaction with primary amines in warm diethylether affording the corresponding urea derivatives **6**. Spectral data and elemental analyses of **6** were consistent with the assigned structure (see Experimental Section). Recently, some urea derivatives such as urea - PETT compounds showed high potency against HIV strains [10 – 12, 26 – 28].

While several steps are required for synthesis of efavirenz [29] or its analogues [19 – 21], including reaction with phosgene, we have developed a simple one pot synthesis of a new series of efavirenz analogues.

Antiviral activity

Compounds **3b-m** were examined for possible antiviral activity against HIV-1 strain HTLV-IIIB [30]. This strain of HIV-1 was propagated in H9 cells [31] at 37 °C, 5% CO_2 using RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS) and antibiotics (growth medium). The culture supernatant was filtered (0.45 nm), aliquoted, and stored at −80 °C until use. The MT-4 cells, which used as target cells, were incubated with virus (0.005 MOI) for 2 h, washed, and added in a proportion of 1:10 to uninfected cells which had been preincubated in growth medium containing the test compound for six days in parallel with virus-infected control cultures without compound added. Expression of HIV in the culture medium was quantified by HIV antigen detection assay ELISA [32]. Compounds **3b-m** did not show any significant activity at non-toxic concentrations. The potent activity of the lead compound efavirenz against HIV-1 can be retained despite significant modification of its structure. For example, the cyclopropylacetylene group in position C-4 and the chlorine in position C-6 can be replaced by an alkoxy side chain [19] and methyl group [20] respectively. This leading us to believe that incorporating aryl group in position C-4 of compounds **3** instead of trifluoromethyl group in efavirenz may not be favorable for good activity.

Experimental Section

All solvents were dried by standard methods. All experiments were carried out with exclusion of moisture. Melting points were determined with a Kofler block apparatus and are uncorrected. IR spectra were recorded with Perkin-Elmer Model 1720 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were determined with Varian Gemini 2000 and Bruker AC-250 FT spectrometers.The chemical shifts in ppm are expressed on the δ scale using tetramethylsilane as internal standard. Coupling constants are giving in Hz. TLC was performed on Merck silica gel 60-F254 precoated plastic plates. Microanalyses were performed in the unit of microanalyses at the Universities of Cairo (Egypt) and Odense (Denmark).

The biological activity was determined in Retrovirus Laboratory, State Serum Institute, Copenhagen (Denmark).

*General procedure for the preparation of 4,4-disubstituted-1,4-dihydro-2H-3,1-benzoxazin-2-ones (***3b** – **m***)*

A solution of alcohol or thioalcohol **2** (7 mmol) in absolute dichloromethane or 1,2-dichloroethane (10 ml) is added to a cold (−40 °C) suspension of **1** (3.13 g, 5 mmol) in CH_2Cl_2 (50 ml). The orange suspension **1** is disappeared immediately and the reaction mixture become clear yellow solution. Subsequently, a solution of NaOH (2.00 g, 50 mmol) in H_2O is added. After warming to 23 °C, the reaction mixture is stirred for 20 minutes. The organic layer is separated and the aqueous layer is repeatedly extracted with CH_2Cl_2. The combined organic extracts is dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent afforded a solid product which recrystallized from appropriate solvents.

*4-(4-Chlorophenyl)-1,4-dihydro-6-methyl-4-propyloxy-2H-1,3-benzoxazin-2-one (***3c***)*

From *n*-propyl alcohol **2c** (0.42 g, 7 mmol) and **1** as described before. Recrystallization from $CHCl_3$ / *n*-pentane affords colourless powder; M.p. 198 – 200 °C; yield (73%). – IR (KBr): ν = 1610 (C=C), 1718 (C=O), 3432 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): δ = 0.93 (t, 3H, J = 7.2 Hz, CH_3), 1.67 (m, 2H, CH_2), 2.26 (s, 3H, CH_3), 3.54 (m, 2H, OCH_2), 6.79 – 7.47 (m, 7H, Ar-H), 9.55 (NH). – ^{13}C NMR ($CDCl_3$): δ = 10.9, 21.2 (CH_3), 23.2, 66.4 (CH_2), 107.1 (OCO), 115.0, 120.5, 127.1, 128.5, 128.9, 131.5, 132.9, 133.6, 135.4, 138.6 (Ar-C), 152.2 (C=O). -$C_{18}H_{18}ClNO_3$ (331.8): calcd. C 65.16, H 5.48, N 4.22; found C 64.8, H 5.1, N 3.8.

*4-(4-Chlorophenyl)-1,4-dihydro-4-(2-cyanoethoxy)-6-methyl-2H-1,3-benzoxazin-2-one (***3d***)*

From 2-cyanoethanol **2d** (0.50 g, 7 mmol) as described for **3c**. However, column chromatography on silica gel (25% EtOAc / *n*-hexane) provides a pure titled compound as pale yellow powder; M.p. 173 – 174 °C; yield (57%). – IR (KBr): ν = 1610 (C=C), 1723 (C=O), 2254 (CN),

3419 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): $\delta = 2.27$ (s, 3H, CH_3), 2.70 (m, 2H, CH_2), 3.83 (m, 2H,OCH_2), 6.88 – 7.51 (m,7H,Ar-H) 9.74(NH). – ^{13}C NMR ($CDCl_3$): $\delta = 21.1$ (CH_3), 19.2, 59.4(CH_2), 106.8 (OCO),117.6 (CN), 115.2, 119.4, 126.9, 128.3, 129.1, 132.0, 132.6, 134.1, 135.9, 137.2 (Ar-C), 151.4 (C=O). -$C_{18}H_{15}ClN_2O_3$ (342.8): calcd. C 63.06, H 4.42, N 8.17; found C 63.0, H 4.4, N 8.0.

*4-Chlorophenyl)-1,4-dihydro-4-(2-methoxyethoxy)-6-methyl-2H-1,3-benzoxazin-2-one (***3e***)*

From 2-methoxyethanol **2e** (0.53 g, 7 mmol) as described for **3c**. Recrystallization from EtOAc / *n*-hexane gives colourless powder. M.p. 187 – 189 °C; yield (75%). – IR (KBr): $\nu = 1610$ (C=C), 1718 (C=O), 3430 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): $\delta = 2.23$ (s, 3H, CH_3), 3.36 (s, 1H, OCH_3), 3.60 (t, 2H, $J = 4.1$ Hz, OCH_2), 3.77 (m, 2H, OCH_2), 6.81 – 7.51 (m, 7H, Ar-H) 9.44(NH). ^{13}C NMR ($CDCl_3$): $\delta = 21.1$ (CH_3), 59.3(CH_3), 46.1, 71.7(CH_2), 107.0 (OCO), 115.0, 120.0, 127.3, 128.7, 129.0, 131.6, 132.7, 133.7, 135.5, 137.8 (Ar-C), 151.9 (C=O). -$C_{18}H_{18}ClNO_4$ (347.8): calcd. C 62.16, H 5.23, N 4.03; found C 62.0, H 5.3, N 4.0.

*4-(4-Chlorophenyl)-1,4-dihydro-4-allyloxy-6-methyl-2H-1,3-benzoxazin-2-one (***3f***)*

From allyl alcohol **2f** (0.41 g, 7 mmol) as described for **3c**. Crystallization from EtOAc / *n*-hexane furnishes faint yellow powder. M.p. 192 – 194 °C; yield (75%). – IR (KBr): $\nu = 1610$ (C=C), 1718 (C=O), 3430 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): $\delta = 2.24$ (s, 3H, CH_3), 4.14 (m, 2H, OCH_2), 5.18 (dd, 1H, $J_{cis} = 10.4$ Hz, 3'-Ha), 5.30 (dd, 1H, $J_{trans} = 17.2$ Hz, 3'-Hb), 5.93 (m, 1H, 2'-H), 6.80 – 7.50 (m, 7H, Ar-H) 9.90 (NH). – ^{13}C NMR ($CDCl_3$): $\delta = 21.2$ (CH_3), 66.0 (CH_2), 107.2 (OCO), 117.7, 133.7 (CH=CH_2), 115.2, 120.3, 127.0, 128.5, 129.0, 131.6, 132.8, 133.7, 135.5, 138.1 (Ar-C), 152.2 (C=O). -$C_{18}H_{16}ClNO_3$ (329.8): calcd. C 65.55, H 4.90, N 4.25; found C 65.7, H 5.0, N 4.3.

*4-(4-Chlorophenyl)-1,4-dihydro-6-methyl-4-propargyloxy-2H-1,3-benzoxazin-2-one (***3g***)*

From propargyl alcohol **2g** (0.39 g, 7 mmol) as described for **3c**. Recrystallization from $CHCl_3$/*n*-pentane gives faint yellow powder. M.p. 196 – 198 °C; yield (67%). – IR(KBr): $\nu = 1609$ (C=C), 1722 (C=O), 2105 (C≡C), 3421 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): $\delta = 2.24$ (s, 3H, CH_3), 2.46 (s, 1H, 3'-H), 4.30 (m, 2H, OCH_2), 6.81 – 7.56 (m, 7H, Ar-H), 9.81(NH). – ^{13}C NMR ($CDCl_3$): $\delta = 21.2$ (CH_3), 53.4 (CH_2), 75.5, 79.0 (CCH), 107.1 (OCO), 115.3, 119.7, 127.1, 128.6,129.1, 131.9, 132.7, 133.9, 135.8, 137.0 (Ar-C), 151.7 (C=O). – $C_{18}H_{14}ClNO_3$ (327.8): calcd. C 65.95, H 4.31, N 4.27; found C 66.3, H 4.6, N 4.2.

*4-(4-Chlorophenyl)-1,4-dihydro-4-(2-chloroethoxy)-6-methyl-2H-1,3-benzoxazin-2-one (***3h***)*

From 2-chloroethanol **2h** (0.56 g, 7 mmol) as described for **3c**. However, column chromatography on silica gel (15% EtOAc / *n*-hexane) affords colourless powder. M.p. 184 – 186 °C; yield (58%). – IR(KBr): $\nu = 1610$ (C=C), 1718 (C=O), 3431 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): $\delta = 2.26$ (s, 3H, CH_3), 3.69 (m, 2H, OCH_2), 3.87 (t, 2H, $J = 5.5$ Hz, 2'-H), 6.86 – 7.50 (m, 7H, Ar-H), 9.68(NH). ^{13}C NMR ($CDCl_3$): $\delta = 21.2$ (CH_3), 42.9, 64.8 (CH_2), 106.9 (OCO), 115.2, 119.9, 127.1, 128.5, 129.1, 131.9, 132.7, 134.0, 135.8, 137.6 (Ar-C), 151.8 (C=O). -$C_{17}H_{15}Cl_2NO_3$ (352.2): calcd. C 57.97, H 4.30, N 3.98; found C 57.9, H 4.2, N 4.0.

*4-(4-Chlorophenyl)-1,4-dihydro-4-isopropyloxy-6-methyl-2H-1,3-benzoxazin-2-one (***3i***)*

From isopropyl alcohol **2i** (0.42 g,7 mmol) as described for **3c**. Recrystallization from $CHCl_3$/*n*-pentane gives colourless powder. M.p. 189 – 191 °C; yield (62%). – IR (KBr): $\nu = 1610$ (C=C), 1715 (C=O), 3431 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): $\delta = 1.06$ (d, 3H, $J = 5.9$ Hz, CH_3), 1.15 (d, 3H, $J = 6.2$ Hz, CH_3), 2.10 (s, 3H, CH_3), 3.92 (m, 1H, OCH), 6.73 – 7.34 (m, 7H, Ar-H), 10.04 (NH). ^{13}C NMR ($CDCl_3$): $\delta = 21.2$ (CH_3), 24.2, 24.3 (CH_3), 69.3 (CH),107.8 (OCO), 115.2, 120.5, 127.1,128.4, 128.6, 131.4, 132.7, 133.2, 135.1, 139.3 (Ar-C), 152.3 (C=O). -$C_{18}H_{18}ClNO_3$ (331.8): calcd. C 65.15, H 5.48, N 4.22; found C 64.8, H 5.2, N 3.9.

*4-(4-Chlorophenyl)-1,4-dihydro-6-methyl-4-(2-phenylethoxy)-2H-1,3-benzoxazin-2-one (***3j***)*

From 2-phenylethanol **2j** (0.85 g, 7 mmol) as described for **3c**. Recrystallization from EtOAc / *n*-hexane affords pale yellow powder. M.p. 205 – 207 °C; yield (58%). – IR (KBr): $\nu = 1611$ (C=C),1718 (C=O), 3422 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): 2.16 (s, 3H, CH_3), 2.93 (t, 2H, $J =$ 6.9 Hz, CH_2), 3.76 (m, 2H, OCH_2), 6.52 – 7.54 (m, 12H, Ar-H), 10.20 (NH). ^{13}C NMR ($CDCl_3$): $\delta = 20.5$ (CH_3), 35.7, 64.5 (CH_2), 105.6 (OCO), 114.3, 119.2, 126.1, 126.2, 127.6, 127.9, 128.0, 128.7, 130.6, 132.0, 133.1, 134.2, 138.1, 138.6 (Ar-C), 149.8 (C=O). $C_{23}H_{20}ClNO_3$ (393.9): calcd. C 70.14, H 5.13, N 3.56; found C 69.8, H 4.9, N 3.7.

*4-(4-Chlorophenyl)-1,4-dihydro-4-isopropylthio-6-methyl-2H-1,3-benzoxazin-2-one (***3k***)*

From isopropyl mercaptan **2k** (0.53 g, 7 mmol) as described for **3c**. Recrystallization from EtOAc / *n*-hexane provides pale yellow powder. M.p. 148 – 150 °C; yield (60%). – IR (KBr): $\nu = 1604$ (C=C), 1724 (C=O), 3430 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): $\delta = 1.21$ (d, 3H, $J = 6.8$ Hz, CH_3), 1.34 (d, 3H, $J = 7.1$ Hz, CH_3), 2.25 (s, 3H, CH_3), 3.02 (m, 1H, SCH), 6.82-7.68 (m, 7H, Ar-H), 9.46 (NH). – ^{13}C NMR ($CDCl_3$): $\delta = 21.3$ (CH_3), 24.4, 25.6 (CH_3), 37.4 (CH),

96.5 (OCS),115.4, 122.3, 126.7, 128.9, 129.4, 131.2, 132.4, 133.5, 135.1, 138.0 (Ar-C), 152.4 (C=O). -$C_{18}H_{18}ClNO_2S$ (347.9): calcd. C 62.14, H 5.23, N 4.03; found C 62.5, H 4.9, N 3.7.

*4-(4-Chlorophenyl)-1,4-dihydro-6-methyl-4-propylthio-2H-1,3-benzoxazin-2-one (**3l**)*

From *n*-propyl mercaptan **2l** (0.53 g, 7 mmol) as described for **3c**. Recrystallization from EtOAc / *n*-hexane affords pale yellow powder. M.p. 188 – 190 °C; yield (55%). – IR (KBr): $\nu = 1604$ (C=C), 1727 (C=O), 3431 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): $\delta = 0.92$ (t, 3H, $J = 7.3$ Hz, CH_3), 1.59 (m, 2H, CH_2), 2.26 (s, 3H, CH_3), 2.62 (m, 2H, SCH_2), 6.83 – 7.65 (m, 7H, Ar-H), 9.52 (NH). ^{13}C NMR ($CDCl_3$): $\delta = 10.9$, 21.3 (CH_3), 24.4, 35.6 (CH_2), 95.9 (OCS), 115.4, 122.2, 126.9, 129.0, 129.4, 131.2, 132.5, 133.6, 135.2, 137.9 (Ar-C), 152.5 (C=O). -$C_{18}H_{18}ClNO_2S$ (347.9): calcd. C 62.14, H 5.23, N 4.03; found C 61.9, H 5.2, N 3.9.

*4-(4-Chlorophenyl)-1,4-dihydro-6-methyl-4-allylthio-2H-1,3-benzoxazin-2-one (**3m**)*

From allyl mercaptan **2m** (0.52 g, 7 mmol) as described for **3c**. Recrystallization from EtOAc / *n*-hexane furnishes faint yellow powder. M. p. 175 – 176 °C; yield (56%). – IR (KBr): $\nu = 1619$ (C=C), 1723 (C=O), 3426 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): 2.27 (s, 3H, CH_3), 3.30 (m, 2H, SCH2), 5.05 (dd, 1H, $J_{cis} = 9.8$ Hz, 3'-Ha), 5.11 (dd, 1H, $J_{trans} = 16.9$ Hz, 3'-Hb), 5.82 (m, 1H, 2'-H), 6.83 – 7.76 (m, 7H, Ar-H), 9.34 (NH). – ^{13}C NMR ($CDCl_3$): $\delta = 21.3$ (CH_3), 34.7 (CH_2), 118.6, 131.3 (CH=CH_2), 95.9 (OCS), 115.4, 121.8, 127.0, 128.9, 129.0, 129.4, 133.2, 133.7, 135.3, 137.6 (Ar-C), 152.1 (C=O). -$C_{18}H_{16}ClNO_2S$ (345.9): calcd. C 62.50, H 4.67, N 4.05; found C 62.2, H 4.5, N 3.8.

*General procedure for the preparation of 4'-chloro-2-isocyanato-5-methylbenzophenonedisubstituted ketal (**4b**, **e**, **f**)*

A solution of large excess alcohol (3 ml) in CH_2Cl_2 (10 ml) is added in one portion to a cold (−10 °C) suspension of **1** (3.13 g, 5 mmol) in CH_2Cl_2 (40 ml). After warming to 23 °C in the course of 20 min., a solution of NaOH (2 g) in H_2O (50 ml) is added. Usual work-up, drying over Na_2SO_4, filtration and evaporation of the solvent give pure oily product.

*4'-Chloro-2-isocyanato-5-methylbenzophenone-diethylketal (**4b**)*

From ethanol (3ml) as described before [25].

*4'-Chloro-2-isocyanato-5-methylbenzophenone-di-(2-methoxyethyl)ketal (**4e**)*

From 2-methoxyethanol (3 ml) as described for **4b**; yellow oil (92%). – IR (film): $\nu = 1594$ (C=C), 2286 cm^{-1} (NCO). – ^{1}H NMR ($CDCl_3$): $\delta = 2.39$ (s, 3H, CH_3), 3.36 (s, 6H, 2OCH_3), 3.39, 3.58 (m, 8H, 4OCH_2), 6.83 - 7.86 (m, 7H, Ar-H). – ^{13}C NMR ($CDCl_3$): $\delta = 21.6$ (CH_3), 59.3 (2OCH_3), 61.4, 71.8 (4OCH_2), 100.9 (OCO), 121.7 (NCO), 126.5, 128.3, 128.8, 129.0, 129.6, 130.3, 134.2, 135.2, 135.5, 139.0 (Ar-C).- $C_{21}H_{24}ClNO_5$ (405.9): calcd. C 62.14, H 5.96, N 3.45; found C 62.5, H 5.7, N 3.2.

*4'-Chloro-2-isocyanato-5-methylbenzophenone-diallylketal (**4f**)*

From allyl alcohol (3 ml) as described for **4b**; yellow oil (90%). – IR (film): $\nu = 1594$ (C=C), 2287 cm^{-1} (NCO). – ^{1}H NMR ($CDCl_3$): $\delta = 2.40$ (s, 3H, CH_3), 3.78 (m, 4H, 2OCH_2), 5.15 (dd, 2H, $J_{cis} = 10.4$ Hz, 3'-Ha), 5.33 (dd, 2H, $J_{trans} = 17.1$ Hz, 3'-Hb), 5.93 (m, 2H, 2'-H), 6.84 – 7.90 (m, 7H, Ar-H). – ^{13}C NMR ($CDCl_3$): $\delta = 21.6$ (CH_3), 63.2 (2OCH_2), 100.8 (OCO), 123.4 (NCO), 116.6, 130.3 (2 CH=CH_2), 126.6, 128.3, 128.6, 129.0, 129.1, 129.5, 134.5, 135.3, 135.6, 139.1 (Ar-C). -$C_{21}H_{20}ClNO_3$ (369.9): calcd. C 68.19, H 5.45, N 3.79; found C 67.9, H 5.6, N 4.0.

*General procedure for the preparation of (**5a** – **c**)*

From excess alcohol (3 ml) as described for **4b**. However, the reaction mixture was stirred at room temperature for 4 h before the addition of aq. NaOH. Usual work-up, evaporation of the solvent affords oily residue. Recrystallization from *n*-hexane gives fine crystals.

*N-{2-[(4-Chlorophenyl)dimethoxymethyl]-4-methylphenyl}methylcarbamate (**5a**)*

From methanol (3 ml) as described before. Recrystallization from *n*-hexane affords pale yellow fine crystals (78%). – M.p. 80 – 81 °C. – IR (KBr): $\nu = 1595$ (C=C), 1734 (C=O), 3384 cm^{-1} (NH). – ^{1}H NMR ($CDCl_3$): $\delta = 2.35$ (s, 3H, CH_3), 3.10 (s, 6H, 2OCH_3), 3.60 (s, 3H, OCH_3), 7.11 – 8.00 (m, 7H, Ar-H), 8.28 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): $\delta = 21.3$ (CH_3), 49.5 (2OCH_3), 52.3 (OCH_3), 101.3 (OCO), 120.5, 128.4, 128.7, 128.8, 128.9, 130.2, 131.6, 133.5, 135.5, 139.0 (Ar-C), 154.2 (C=O). -$C_{18}H_{20}ClNO_4$ (349.8): calcd. C 61.81, H 5.76, N 4.00; found C 62.0, H 6.0, N 4.1.

*N-{2-[(4-Chlorophenyl)diethoxymethyl]-4-methylphenyl}ethylcarbamate (**5b**)*

From ethanol (3 ml) as described for **5a**. Recrystallization from *n*-hexane gives pale yellow fine crystals (73%). – M.p. 52 – 53 °C. – IR (KBr): $\nu = 1595$ (C=C), 1737 (C=O), 3386 cm^{-1} (NH). ^{1}H NMR ($CDCl_3$): $\delta = 2.34$ (s, 3H, CH_3),1.24 (m, 9H, 3CH_3), 3.32 (m, 4H, 2OCH_2), 4.04 (q, 2H, $J = 7.1$ Hz, OCH_2), 7.08 – 7.77 (m, 7H, Ar-H), 8.11 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): $\delta = 14.9$ (CH_3), 15.3 (2CH_3), 21.4 (CH_3), 57.6 (2OCH_2), 61.0 (OCH_2), 101.7 (OCO), 120.6, 128.3, 128.5, 128.6, 128.9, 130.0, 131.6,

133.5, 134.0, 140.0 (Ar-C), 153.9 (C=O). -$C_{21}H_{26}ClNO_4$ (391.9): calcd. C 64.36, H 6.69, N 3.57; found C 64.1, H 6.3, N 3.5.

*N-{2-[(4-Chlorophenyl)dipropyloxymethyl]-4-methylphenyl}propylcarbamate (***5c***)*

From *n*-propanol (3 ml) as described for **5a**. Recrystallization from *n*-hexane gives Pale yellow fine crystals (70%). – M. p. 47 – 48 °C. – IR (KBr): $\nu = 1595$ (C=C), 1737 (C=O), 3388 cm^{-1} (NH). ^1H NMR ($CDCl_3$): $\delta = 0.97$ (m, 9H, $3CH_3$), 1.61 (m, 6H, $3CH_2$), 2.34 (s, 3H, CH_3), 3.21 (m, 4H, $2OCH_2$), 3.96 (t, 2H, $J = 6.5$ Hz, OCH_2), 7.09 – 7.82 (m, 7H, Ar-H), 8.15 (NH). – ^{13}C NMR ($CDCl_3$): $\delta = 10.6$ (CH_3), 11.3 ($2CH_3$), 21.4 (CH_3) 22.7 (CH_2), 23.1($2CH_2$), 63.5 ($2OCH_2$), 66.6 (OCH_2), 101.5 (OCO), 120.8, 128.3, 128.6, 128.7, 128.9, 130.0, 132.2, 133.6, 134.0, 140.2 (Ar-C), 154.0 (C=O). – $C_{24}H_{32}ClNO_4$ (434.0): calcd. C 66.42, H 7.43, N 3.23: found C 66.7, H 7.7, N 2.9.

*General procedure for the preparation of (***6a** – **h***)*

A mixture of **4** (5 mmol) and primary amine (5 mmol) in diethylether (50 ml) is boiled under reflux for 10 min. The solid product is filtered off and recrystallized from CH_2Cl_2 / Et_2O to give colourless fine crystals.

*1-{2-[(4-Chlorophenyl)diethoxymethyl]-4-methylphenyl}-3-benzylurea (***6a***)*

From benzyl amine (0.46 g, 5 mmol) and **4b** (1.73 g, 5 mmol) as described before. M.p. 188 – 189 °C; yield (79%). – IR (KBr): $\nu = 1594$ (C=C), 1661 (C=O), 3370 cm^{-1}(NH). – ^1H NMR ($CDCl_3$): $\delta = 1.19$ (t, 6H, $J = 7.0$ Hz, $2CH_3$), 2.36 (s, 3H, CH_3), 3.28 (m, 4H, $2OCH_2$), 4.20 (d, 2H, $J = 5.6$ Hz, NCH_2), 4.43, 7.73 (2NH), 7.06 – 7.50 (m, 12H, Ar-H). – ^{13}C NMR ($CDCl_3$): $\delta = 15.4$ ($2CH_3$), 21.4 (CH_3), 44.5 (NCH_2), 57.6 ($2OCH_2$), 101.2 (OCO), 123.7, 127.6, 127.7, 128.4, 128.5, 128.6, 128.9, 130.2, 132.2, 133.1, 133.7, 134.0, 139.2, 140.1 (Ar-C), 155.3 (C=O). – $C_{26}H_{29}ClN_2O_3$ (453.0): calcd. C 68.94, H 6.45, N 6.19; found C 68.6, H 6.2, N 5.9.

*1-{2-[(4-Chlorophenyl)diethoxymethyl]-4-methylphenyl}-3-(4-methylphenyl)urea (***6b***)*

From *p*-toluidine (0.46 g, 5 mmol) and **4b** (1.73 g, 5 mmol), as described for **6a**. M.p. 194 – 195 °C; yield (72%). – IR (KBr): $\nu = 1594$ (C=C), 1667 (C=O), 3370 cm^{-1}(NH). ^1H NMR ($CDCl_3$): $\delta = 1.12$ (t, 6H, $J = 7.3$ Hz, $2CH_3$), 2.35, 2.37 ($2CH_3$), 3.22 (m, 4H, $2OCH_2$), 6.14, 7.71 (2NH), 7.00 – 7.65 (m, 11H, Ar-H). – ^{13}C NMR ($CDCl_3$): $\delta = 15.2$ ($2CH_3$), 21.2, 21.4 ($2CH_3$), 57.5 ($2OCH_2$), 101.1 (OCO), 123.4, 123.9, 128.6, 128.7, 130.0, 130.1, 131.8, 133.1, 133.5, 134.0, 134.8, 135.1, 139.7 (Ar-C), 153.7 (C=O). -$C_{26}H_{29}ClN_2O_3$ (453): calcd. C 68.94, H 6.45, N 6.19; found C 68.7, H 6.2, N 6.1.

*1-{2-[(4-Chlorophenyl)diallyloxymethyl]-4-methylphenyl}-3-(4-fluorobenzyl)urea (***6c***)*

From 4-fluorobenzyl amine (0.55 g, 5 mmol) and **4f** (1.85 g, 5 mmol), as described for **6a**. M.p. 205 – 206 °C; yield (69%). – IR (KBr): $\nu = 1594$ (C=C), 1654 (C=O), 3370 cm^{-1}(NH). – ^1H NMR ($CDCl_3$): $\delta = 2.37$ (s, 3H, CH_3), 3.82 (m, 4H, $2OCH_2$), 4.16 (d, 2H, $J = 5.8$ Hz, NCH_2), 4.36, 7.77 (2NH). 5.15 (dd, 2H, $J_{cis} = 10.5$ Hz, 3'-Ha), 5.30 (dd, 2H, $J_{trans} = 16.8$ Hz, 3'-Hb), 5.90 (m, 2H,2'-H), 6.96 – 7.50 (m, 11H, Ar-H). – ^{13}C NMR ($CDCl_3$): $\delta = 21.5$ (CH_3), 43.8 (NCH_2), 63.4 ($2OCH_2$), 101.5 (OCO), 117.2, 134.3 (2 $CH=CH_2$), 115.6, 115.9, 124.0, 128.6, 128.7, 128.9, 129.3, 129.4,130. 5, 133.6, 133.7, 134.4, 139.6, 164.0 (Ar-C), 155.1 (C=O). -$C_{28}H_{28}ClFN_2O_3$ (495): calcd. C 67.94, H 5.70, N 5.67; found C 68.2, H 5.8, N 5.4.

*1-{2-[(4-Chlorophenyl)diallyloxymethyl]-4-methylphenyl}-3-(4-chlorobenzyl)urea (***6d***)*

From 4-chlorobenzyl amine (0.63 g, 5 mmol) and **4f** (1.85 g, 5 mmol), as described for **6a**. M.p. 209 – 210 °C; yield (63%). – IR (KBr): $\nu = 1594$ (C=C), 1661 (C=O), 3391 cm^{-1}(NH). – ^1H NMR ($CDCl_3$): $\delta = 2.37$ (s, 3H, CH_3), 3.78 (m, 4H, $2OCH_2$), 4.16 (d, 2H, $J = 5.7$ Hz, NCH_2), 4.39, 7.77 (2NH). 5.16 (dd, 2H, $J_{cis} = 10.4$ Hz, 3'-Ha), 5.30 (dd, 2H, $J_{trans} = 17.0$ Hz, 3'-Hb), 5.88 (m, 2H, 2'-H), 6.98 – 7.50 (m, 11H, Ar-H). – ^{13}C NMR ($CDCl_3$): $\delta = 21.5$ (CH_3), 43.8 (NCH_2), 63.3 ($2OCH_2$), 101.5 (OCO), 117.2, 134.3 ($2CH=CH_2$), 124.1, 128.6, 128.7, 128.9, 129.0, 129.1, 130. 5, 131.7, 133.0, 133.6, 133.7, 134.4, 137.8, 139.6 (Ar-C), 155.1 (C=O). -$C_{28}H_{28}Cl_2N_2O_3$ (511.6): calcd. C 65.75, H 5.52, N 5.49; found C 66.0, H 5.7, N 5.1.

*1-{2-[(4-Chlorophenyl)diallyloxymethyl]-4-methylphenyl}-3-(4-methoxybenzyl)urea (***6e***)*

From 4-methoxybenzyl amine (0.61 g, 5 mmol) and **4f** (1.85 g, 5 mmol), as described for **6a**. M.p. 191 – 192 °C; yield (68%). – IR (KBr): $\nu = 1591$ (C=C), 1657 (C=O), 3368 cm^{-1}(NH). – ^1H NMR ($CDCl_3$): $\nu = 2.36$ (s, 3H, CH_3), 3.78 (m, 4H, $2OCH_2$), 3.80 (s, 3H, OCH_3), 4.13 (d, 2H, $J = 5.5$ Hz, NCH_2), 4.31, 7.75 (2NH). 5.15 (dd, 2H, $J_{cis} = 10.4$ Hz, 3'-Ha), 5.29 (dd, 2H, $J_{trans} = 17.0$ Hz, 3'-Hb), 5.90 (m, 2H, 2'-H), 6.83 – 7.52 (m, 11H, Ar-H). – ^{13}C NMR ($CDCl_3$): $\delta = 21.5$ (CH_3), 44.0 (NCH_2), 55.6 (OCH_3), 63.3 ($2OCH_2$), 101.5 (OCO), 117.1, 134.3 ($2CH=CH_2$), 114.3, 123.9, 128.5, 128.6, 128.8, 129.0, 130. 5, 131.1, 131.5, 133.3, 133.8, 134.4, 139.6, 159.2 (Ar-C), 155.1 (C=O). $C_{29}H_{31}ClN_2O_4$ (507.0): calcd. C 68.70, H 6.16, N 5.54; found C 69.1, H 5.8, N 5.2.

*1-{2-[(4-Chlorophenyl)dimethoxyethoxymethyl]-4-methylphenyl}-3-(4-fluorobenzyl) urea (**6f**)*

From 4-fluorobenzyl amine (0.55 g, 5 mmol) and **4e** (2.03 g, 5 mmol), as described for **6a**. M. p. 140 – 141 °C; yield (65%). – IR (KBr): ν = 1594 (C=C), 1666 (C=O), 3360 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): δ = 2.27 (s, 3H, CH_3), 3.29 (s, 6H, $2OCH_3$), 3.36 – 3.60 (m, 8H, $4OCH_2$), 4.28 (d, 2H, J = 5.7 Hz, NCH_2), 5.00, 8.60 (2NH), 6.96 – 7.7.87 (m, 11H, Ar-H). – ^{13}C NMR ($CDCl_3$): δ = 21.3 (CH_3), 43.7 (NCH_2), 59.0 ($2OCH_3$), 61.2, 71.8 ($4OCH_2$), 103.6 (OCO), 115.8, 122.7, 128.5, 128.6, 129.2, 129.4, 129.5, 130.3, 132.4, 134.2, 135.1, 139.9, 164.0 (Ar-C), 155.6 (C=O). $C_{28}H_{32}ClFN_2O_5$ (531.2): calcd. C 63.33, H 6.07, N 5.29; found C 62.9, H 5.8, N 4.9.

*1-{2-[(4-Chlorophenyl)dimethoxyethoxymethyl]-4-methylphenyl}-3-(4-chlorobenzyl) urea (**6g**)*

From 4-chlorobenzyl amine (0.63 g, 5 mol) and **4e** (2.03 g, 5 mmol), as described for **6a**. M. p. 93 – 94 °C; yield (69%). – IR (KBr): ν = 1594 (C=C), 1666 (C=O), 3370 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): δ = 2.27 (s, 3H, CH_3), 3.30 (s, 6H, $2OCH_3$), 3.33 – 3.63 (m, 8H, $4OCH_2$), 4.28 (d, 2H, J = 5.9 Hz, NCH_2), 5.03, 8.61 (2NH), 7.05 – 7.86 (m, 11H, Ar-H). – ^{13}C NMR ($CDCl_3$): δ = 21.3 (CH_3), 43.7 (NCH_2), 59.0 ($2OCH_3$), 61.2, 71.8 ($4OCH_2$), 103.6 (OCO), 122.7, 128.4, 128.5, 128.6, 128.9, 129.2, 129.4, 130.3, 132.4, 133.2, 134.2, 135.0, 138.5, 139.8 (Ar-C), 155.5 (C=O). – $C_{28}H_{32}Cl_2N_2O_5$ (547.6): calcd. C 61.42, H 5.89, N 5.13; found C 61.2, H 6.1, N 4.8.

*1-{2-[(4-Chlorophenyl)dimethoxyethoxymethyl]-4-methylphenyl}-3-(4-methoxybenzyl) urea (**6h**)*

From 4-methoxybenzyl amine (0.61 g, 5 mmol) and **4e** (2.03 g, 5 mmol), as described for **6a**. M.p. 83 – 84 °C; yield (73%). – IR (KBr): ν = 1593 (C=C), 1667 (C=O), 3368 cm^{-1}(NH). – ^{1}H NMR ($CDCl_3$): δ = 2.27 (s, 3H, CH_3), 3.28 (s, 6H, $2OCH_3$), 3.79 (s, 3H, OCH_3), 3.35 – 3.60 (m, 8H, $4OCH_2$), 4.26 (d, 2H, J = 5.5 Hz, NCH_2), 4.95, 8.52 (2NH), 6.83 – 7.87 (m, 11H, Ar-H). ^{13}C NMR ($CDCl_3$): δ = 21.3 (CH_3), 43.9 (NCH_2), 55.6 (OCH_3), 59.0 ($2OCH_3$), 61.2, 71.8 ($4OCH_2$), 103.5 (OCO), 114.2, 122.7, 128.5, 128.6, 128.8, 129.1, 129.2, 130.3, 131.9, 132.2, 134.1, 135.2, 139.8, 159.1 (Ar-C), 155.6 (C=O). -$C_{29}H_{35}ClN_2O_6$ (543.2): calcd. C 64.13, H 6.50, N 5.17; found C 63.8, H 6.2, N 4.9.

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