Facile Synthesis of Non-nucleoside Compounds Starting from α-Chlorocarbenium Ions and Isocyanates as Potential HIV-1 Reverse Transcriptase Inhibitors

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Dedicated to Professor Volker Jaeger on the occasion of his 65th birthday

Chloro(phenyl)carbenium hexachloroantimonate salts react with isocyanates to afford either isoindolium (1) or benzoxazinium salts (2). Addition of one equivalent of alcohol to 2 led, after hydrolysis with aq. NaOH, to the formation of benzoxazin-2-ones 3. Treatment with a large excess of alcohol transformed the salts 1 and 2 to the corresponding isoindol-1-ones 11 and the isocyanates 5, respectively. Reaction of 5 with primary amines furnished the urea derivatives 6 in good yield. The biological activity of 6a – o against HIV-1 was determined.

Key words: α-Chlorocarbenium Salts, Isocyanates, Isoindoles, Urea Derivatives, Benzoxazinones, Reverse Transcriptase Inhibitors

Introduction

The life cycle of HIV-1 has been extensively studied, and a number of stages identified for possible intervention to prevent viral replication. Clinically relevant agents which have been successfully developed are: a) nucleoside reverse transcriptase inhibitors (NRTIs), for example zidovudine (AZT), didanosine (DDI), zalcitabine (DDC), stavudine (D4T), lamivudine (3TC), abacavir (ABC), emtricitabine, and tenofovir disoproxil; b) non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as atefivirdine, caprivirine, efavirenz, emivirine, lodenosine, nevirapine, etravirine, rilpivirine, delavirdine, and quinotadine; c) protease inhibitors (PIs) e.g., atazanavir, brecanavir, fosamprenavir, lopinavir, darunavir, nelfinavir, ritonavir, saquinavir, tipranavir, amprenavir, and indinavir; d) integrase inhibitors like raltegravir and elvitegravir; e) entry (fusion) inhibitors such as aplaviroce, enfuvirtide, maraviroc, vicriviroc, and ibalizumab; f) maturation inhibitors, for example bevirimat and vivecon. Several others are in preclinical or clinical development. From these compounds, thirty anti-HIV drugs have been approved and licensed for clinical use in the USA by the Food and Drug Administration (FDA). Four of them, namely, nevirapine [1, 2], delavirdine [3, 4], efavirenz [5] and – the first to be approved in 2008 – etravirine [6, 7] belong to the group of NNRTIs. These compounds have gained a definitive place in the treatment of HIV-1 infections. Starting from HEPT [8] and TIBO [9] derivatives, more than 40 structurally different classes of compounds have been identified as NNRTIs. However, as with all current HIV therapies, drug incompatibilities, adverse effects, the emergence of resistant viral strains or of cross-resistance continue to limit the clinical usefulness of the NNRTIs. Therefore, additional NNRTIs are needed that might have improved pharmacokinetics, limited toxicities, and more favorable resistance mutation profiles.

In continuation of our previous work on searching antiviral drugs [10, 11], we report in this communication on a facile access to a new series of urea, isoindole and benzoxazine derivatives, analogs of troviridine [PETT (LY300046)] [12], thiazoloisoindolinone (BM +51.0836) [13], and efavirenz (DMP 266) [5] compounds.

Results and Discussion

The starting materials, 1-oxoisoindolium salts (1), could be prepared as described in the literature [14] from the reaction of alkyl- or electron-rich arylisocyanates with α-chlorocarbenium salts, whereas the formation of benzoxazinium hexachloroantimon-
Scheme 1.

\begin{align*}
\text{R} & \text{Cl} \\
\text{SbCl}_3 & \text{R}_1^1 \\
\text{H} & \text{Ph} \\
\text{Me} & \text{Cl} \\
\text{N}^+ & \text{R}^2 \\
\text{Cl} & \text{SbCl}_6^- \\
\text{O} & \text{SbCl}_6^- \\
\text{Me} & \text{N}^+ \\
\text{Cl} & \text{SbCl}_6^- \\
1a, R^2 = \text{Et} & \\
1b, R^2 = \text{allyl} & \\
2 & \\
\end{align*}

Addition of a large excess of an alcohol to a cold (−10 °C) suspension of 2 in absolute CH$_2$Cl$_2$ led to the formation of the isocyanates 5a, b as yellow oils which could be used without further purification. Treatment of 5 with primary amines in warm diethyl ether gave the corresponding urea derivatives 6a–o in good yield, analogs of urea-PETT compounds [15, 16]. When 6 was exposed to a few drops of conc. H$_2$SO$_4$ or SbCl$_5$ in CH$_2$Cl$_2$, quinazolinone 8 was obtained instead of the expected 4-alkoxy derivative 7 (Scheme 2).

The structure assignment of the prepared compounds is based, beside elemental analyses, on their spectral (IR, $^1$H, $^{13}$C NMR) data. The IR spectra of 1b (Nujol) showed absorption bands at 1757 and 1811 cm$^{-1}$ for (C=O) and (C=N$^+$) groups, whereas compounds 3a, b exhibited bands in the ranges of 1720–1735 and 3350–3413 cm$^{-1}$ due to C=O and NH absorptions, respectively. The urea derivatives 6a–o showed in their IR spectra (KBr) absorption bands in the ranges 1664–1702 and 3348–3380 cm$^{-1}$ for C=O and (NH) groups. In the $^{13}$C NMR (CDCl$_3$) spectra, the ketal carbons of 6a–o resonated around 101.2 ppm.

Addition of a large excess of alcohol to a cold (−10 °C) suspension of 3-phenyl-2-substituted-1-oxoisindolium salts 1 in CH$_2$Cl$_2$ furnished 3-alkoxy derivatives 11a–f in moderate yield, whereas with traces of water or better aqueous base, 3-hydroxyisoindoles (9a, b) were obtained. Reduction of the latter compounds by H$_2$ / Pd / C in absolute methanol afforded isoindol-1-ones 10a, b (Scheme 3). The N-allyl group of 9b is converted to the n-propyl group during the reduction process. The constitutions of isoindoles 9, 10 and 11 were derived from spectroscopic data. IR spectra of 9a, b showed absorption bands in the ranges 1686–1690 and 3280–3290 cm$^{-1}$ for C=O and OH groups, whereas compounds 10a, b and 11a–f displayed bands in the range of 1674–1703 cm$^{-1}$ for the carbonyl groups. In the $^1$H NMR (CDCl$_3$) spectra of 9a, 10a and 11a–c diastereotopic CH$_2$ protons were observed. The OH groups of compounds 9a, b appeared in the range of 4.23–4.86 ppm, whereas the 3-H protons of 10a, b resonated as a singlet at 5.35–5.46 ppm. The $^{13}$C NMR spectra of 9, 10 and 11 displayed peaks for C-3 around 91.6, 64.2 and 94.6 ppm, respectively. The carbonyl carbons of the isoindole derivatives resonated between 167.0 and 168.3 ppm.
Antiviral activity

The urea compounds 6a–o were examined for possible antiviral activity against the HIV-1 strain HTLV-IIIB [17]. This strain of HIV-1 was propagated in H9 cells [18] at 37 °C, 5% CO₂, 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 were 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 compounds for 6 d in parallel with virus-infected control cultures without compound added. Expression of HIV in the culture medium was quantified by the HIV antigen detection assay ELISA [19].

Compounds 6a–o did not exhibit any significant activity at non-toxic concentrations.

It was reported in the literature that phenylethyl-thiazolylthiourea (PETT, LY73497) shows high potency against HIV-1. Optimization of this lead compound gave N-[2-(2-pyridyl)ethyl-N-[2-(5-bromopyridyl)] thiourea (LY300046:HCl) (troviridine) [12], which has been selected for clinical trials (Fig. 1). Ex-
Scheme 3. Reagents and conditions: i) aq. NaOH; ii) H₂, Pd/C, CH₃OH, 30 min; iii) R₁OH, −10 °C, aq. NaOH.

The phenyl group was replaced with 2-pyridyl, as in trovirdine, to give the most active compounds in a series with different heterocycles. In part 2, the ethyl linker was optimal for activity. In part 3, the N,N-unsubstituted thiourea was most active. Methyl substituents on nitrogen adjacent to the phenylethyl side chain completely eliminated the activity. In part 4, the most optimal compound was achieved by replacing the thiazole with a 5-bromopyrid-2-yl. Later on, it was found that the urea-PETT compounds may have better toxicological and pharmacokinetic properties than the PETT compounds. Comparing these results with those for compounds 6a–o leads us to believe that introducing the bulky group [dialkoxy(p-chlorophenyl)methyl] in position 2 of the tolyl substituent (part 4) is most likely the reason for elimination of the activity of compounds 6a–o.

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 a Perkin–Elmer Model 1720 FTIR spectrometer. ¹H and ¹³C NMR spectra were determined with Varian Gemini 2000 and Brucker AC-250 FT spectrometers. The chemical shifts in ppm are expressed on the δ scale using tetramethylsilane as internal standard. Coupling constants are given in Hz. Mass spectra were recorded on an AEIMS 30 spectrometer. TLC was performed on Merck silica gel 60-F254 precoated plastic plates. Microanalyses were performed in the unit of microanalysis at Cairo University (Egypt). The biological activity was determined in the Retrovirus Laboratory, State Serum Institute, Copenhagen (Denmark).

Synthesis of 2-allyl-1-oxo-3-phenyl-1H-isoindolium hexachloroantimonate (1b)

A solution of SbCl₅ (1.5 g, 5 mmol) in CH₂Cl₂ (5 mL) was added dropwise with stirring at −40 °C to a solution of dichlorodiphenylmethane (1.2 g, 5 mmol) and allylisocyanate (0.42 g, 6 mmol) in CH₂Cl₂ (15 mL). The reaction mixture was warmed to 23 °C, and stirring was continued for 6 h, upon which a yellowish orange precipitate was formed. Filtration, washing with CH₂Cl₂ (5 mL) and drying under vac-
General procedure for the preparation of 4,4-disubstituted 1,4-dihydro-benzo[d][1,3]oxazin-2-ones 3a, b

A solution of an alcohol (7 mmol) in absolute CH2Cl2 (10 mL) was added to a cold (−40 °C) suspension of 2 (5 mmol) in CH2Cl2 (50 mL). The orange suspension disappeared immediately, and the reaction mixture became a yellow solution. Subsequently, a solution of NaOH (2N, 50 mL) was added. Usual work-up, drying over Na2SO4, filtration and evaporation of the solvent afforded a yellow oil which was used without further purification.

4-(2-Chlorobenzylxylo)-4-(4-chlorophenyl)-6-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (3a)

Prepared from 2-chlorobenzyl alcohol and 2 as described before. Recrystallization from CHCl3/n-pentane afforded a colorless powder; m. p. 192 – 193 °C; yield: 1.83 g (63 %). – IR (KBr): ν = 1611 (C=C), 1719 (C=O), 3376 cm−1 (NH). – 1H NMR ([D6]DMSO): δ = 2.18 (s, 1H, CH3), 4.60 (s, 2H, OCH2), 6.80 – 7.53 (m, 11H, Ar-H), 10.67 (s, 1H, NH) ppm. – C22H17Cl2NO3 (414.3): calcd. C 63.78, H 4.14, N 3.0; found C 63.4, H 3.8, N 3.0.

4-(4-Chlorophenyl)-4-(4-ethoxyethyloxy)-6-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (3b)

From 2-ethoxyethanol and 2 as described for 3a. However, column chromatography on silica gel (EtOAc/n-hexane, 1:6) provided two fractions, which refer to compounds 3b (Rf = 0.75) and 4 (Rf = 0.55).

Compound 3b: pale-yellow powder, m. p. 175 – 177 °C; yield: 1.57 g (62 %). – IR (KBr): ν = 1631, 1590 (C=C), 1373 (C=O), 3215 cm−1 (NH). – 1H NMR ([D6]DMSO): δ = 1.10 (t, 3H, J = 7.2 Hz, CH3), 2.18 (s, 3H, CH3), 3.45 (q, 2H, J = 7.3 Hz, CH2), 3.54 (s, 4H, 2OCH2), 6.74 (s, 1H, Ar-H), 6.87 – 7.53 (m, 6H, Ar-H), 10.77 (s, 1H, NH) ppm. – C28H20Cl2N2O2 (455.1): calcd. C 73.83, H 4.40, N 6.15; found C 73.5, H 4.1, N 5.7.

6,12-Bis(4-chlorophenyl)-3,9-dimethylidibeno[b,f][1,5]diazocine (4)

Pale-yellow powder; m. p. 211 °C; yield: 0.16 g (5 %). – IR (KBr): ν = 1593 (C=C), 2291 cm−1 (NCO). – 1H NMR (CDCl3): δ = 2.36 (s, 3H, CH3), 3.77 (m, 4H, 2OCH2), 5.14 (dd, 2H, Jtrans = 10.3 Hz, 3'-H), 5.36 (dd, 2H, Jcis = 17.0 Hz, 3'-H), 5.90 (m, 2H, 2'-H), 7.16 – 7.59 (m, 7H, Ar-H). – C28H20Cl2N2O2 (455.7): calcd. C 73.82, H 4.40, N 6.15; found C 73.5, H 4.1, N 5.7.

General procedure for the preparation of the derivatives of 1-[2-[(4-chlorophenyl)-dialkoxyethyl]-4-methylphenyl]-urea, 6a – o

A mixture of 5 (5 mmol) and a primary amine (8 mmol) in diethyl ether (50 mL) was boiled under reflux for 10 min. The solid product that formed was filtered off and recrystallized from CH2Cl2/Et2O to give fine colorless crystals.
1-[4-Chlorophenyl][diethoxymethyl]-4-methylphenyl]-3-allylurea (6b)

From allylamine and 5a, m.p. 190–192 °C; yield: 1.45 g (72%). – IR (KBr): ν = 1594 (C=C), 1661 (C=O), 3371 cm⁻¹ (NH). – 1H NMR (CDCl₃): δ = 1.21 (t, 6H, J = 7.3 Hz, 2CH₃), 2.37 (s, 3H, CH₃), 3.44 (m, 4H, OCH₂), 3.60 (m, 2H, NCH₂), 4.11 (t, J = 5.7 Hz, 1H, NH), 4.95 (dd, 1H, J₁,₂ = 10.4 Hz, 3H₂), 5.02 (dd, 1H, Jtrans = 17.2 Hz, 3H₂), 5.59 (m, 1H, 2,4-H), 7.10–7.44 (m, 7H, Ar-H), 7.45 (s, 1H, NH). – 13C NMR: δ = 15.3 (2CH₃), 21.4 (CH₃), 42.9 (NCH₂), 57.5 (2OCH₂), 101.1 (OCO), 115.8, 133.7 (CH=CH), 124.1, 128.4, 128.6, 128.9, 130.2, 132.6, 133.4, 134.1, 135.3, 140.2 (Ar-C), 155.3 (C=O) ppm. – C₂₇H₂₃ClN₂O₅ (402.9); calcld. C 65.58, H 6.75, N 6.95; found C 65.9, H 7.1, N 7.2.

1-[4-Chlorophenyl][diethoxymethyl]-4-methylphenyl]-3-(1-phenylethyl)urea (6c)

From 1-phenylethylamine and 5a, m.p. 199–201 °C; yield: 1.66 g (71%). – IR (KBr): ν = 1593 (C=C), 1661 (C=O), 3370 cm⁻¹ (NH). – 1H NMR (CDCl₃): δ = 1.15–1.25 (m, 6H, 2CH₃), 1.29 (d, J = 6.8 Hz, 3H, CH₃), 2.36 (s, 3H, CH₃), 3.19–3.34 (m, 4H, OCH₂), 4.30 (m, 1H, CH), 4.77 (s, 1H, NH), 7.07–7.43 (m, 12H, Ar-H), 7.72 (s, 1H, NH). – 13C NMR: δ = 15.4 (2CH₃), 21.4 (CH₃), 22.5 (CH₂), 49.6 (NCH₃), 57.6 (2OCH₂), 101.1 (OCO), 123.8, 126.3, 127.4, 128.4, 128.6, 128.7, 128.9, 130.1, 132.2, 133.1, 133.8, 134.1, 140.3 (Ar-C), 154.5 (C=O) ppm. – C₂₇H₂₃ClN₂O₅ (466.9); calcld. C 69.45, H 6.66, N 6.00; found C 69.8, H 6.9, N 6.4.

Ethyl-2-[4-Chlorophenyl][diethoxymethyl]-4-methylphenylamino]-carboxylhydrazine carbamate (6d)

From ethyl carbamate and 5a, m.p. 203–205 °C; yield: 1.51 g (67%). – IR (KBr): ν = 1595 (C=C), 1702 (C=O), 3352 cm⁻¹ (NH). – 1H NMR (CDCl₃): δ = 1.18 (t, 6H, J = 7.3 Hz, 2CH₃), 1.30 (t, J = 7.2 Hz, 3H, CH₃), 2.37 (s, 3H, CH₃), 3.23–3.34 (m, 4H, OCH₂), 4.22 (q, J = 6.8 Hz, 2H, OCH₂), 6.40, 6.50 (2s, 2H, 2NH), 7.10–7.37 (m, 7H, Ar-H), 8.53 (s, 1H, NH). – 13C NMR: δ = 14.8 (CH₃), 15.2 (CH₂), 21.4 (CH₃), 57.6 (2OCH₂), 62.9 (OCH₂), 101.3 (OCO), 128.2, 128.3, 128.7, 128.8, 129.7, 130.0, 132.5, 133.1, 134.2, 139.7 (Ar-C), 155.6, 156.9 (2C=O) ppm. – C₂₂H₂₁ClN₂O₅ (449.9); calcld. C 58.73, H 6.27, N 9.34; found C 59.1, H 6.6, N 9.7.
From 4-methoxyaniline and 5a, m. p. 150 – 152 °C; yield: 1.86 g (83 %). – IR (KBr): ν = 1591 (C=C), 1669 (C=O), 3380 cm⁻¹ (NH). – 1H NMR (CDCl₃): δ = 2.37 (s, 3H, CH₃), 3.79 (m, 4H, 2OCH₂), 4.50 (s, 2H, NH₂), 5.17 (dd, 2H, Jtrans = 10.5 Hz, 3′-H₂), 5.32 (dd, 2H, Jtrans = 17.1 Hz, 3′-H₂), 5.92 (m, 2H, 2′-H), 7.12 – 7.51 (m, 7H, Ar-H). – 13C NMR: δ = 13.9 (CH₂), 56.3 (2OCH₂), 101.7 (OCHO), 117.0, 133.7, (2CH₂=CH), 117.1, 124.0, 128.5, 128.6, 128.9, 130.5, 131.0, 131.4, 133.4, 134.4, 139.5(Ar-C), 156.0 (C=O) ppm. – C₂H₅₂O₂ (386.9) calcd. C 65.20, H 6.29, N 5.97 found C 65.9, H 6.5, N 6.3.

1-[(4-Chlorophenyl)diallyloxyethyl]-4-methylphenyl]-3-(methoxycarbonyl)urea (6f)

From allylamine and 5b, m. p. 197 – 199 °C; yield: 1.64 g (77 %). – IR (KBr): ν = 1563 (C=C), 1642 (C=O), 3360 cm⁻¹ (NH). – 1H NMR (CDCl₃): δ = 2.38 (s, 3H, CH₃), 3.58 – 3.62 (m, 2H, NCH₂), 3.82 (m, 4H, 2OCH₂), 4.13 (bs, 1H, NH), 4.95 (dd, 2H, Jtrans = 9.5 Hz, 3′-H₂), 5.04 (dd, 2H, Jtrans = 16.7 Hz, 3′-H₂), 5.17 (dd, 1H, Jcis = 10.4 Hz, 3′-H₂), 5.50 (dd, 1H, Jtrans = 16.7 Hz, 3′-H₂), 5.62 (m, 2H, 2′-H), 5.89 (m, 1H, 2′-H), 7.07 – 7.49 (m, 7H, Ar-H). – 13C NMR: δ = 21.5 (CH₃), 42.9 (NCH₂), 63.3 (2OCH₂), 101.5 (OCHO), 115.8, 117.1, 133.7, 134.3 (CH₂=CH), 124.3, 128.5, 128.6, 130.4, 131.9, 133.5, 134.4, 135.3, 139.5 (Ar-C), 155.1 (C=O) ppm. – C₂H₅₂O₂ (426.9) calcd. C 67.52, H 6.37, N 6.56; found C 67.2, H 6.0, N 6.3.

From benzylamine and 5b, m. p. 193 – 194 °C; yield: 1.88 g (79 %). – IR (KBr): ν = 1592 (C=C), 1657 (C=O), 3369 cm⁻¹ (NH). – 1H NMR (CDCl₃): δ = 2.36 (s, 3H, CH₃), 3.78 (m, 4H, 2OCH₂), 4.20 (d, 2H, J = 5.7 Hz, NCH₂), 4.38 (s, 1H, NH), 5.15 (dd, 2H, Jcis = 10.9 Hz, 3′-H₂), 5.30 (dd, 2H, Jtrans = 17.6 Hz, 3′-H₂), 5.82 (m, 2H, 2′-H), 7.07 – 7.54 (m, 12H, Ar-H). – 13C NMR: δ = 21.2 (CH₃), 44.3 (NCH₂), 63.1 (2OCH₂), 101.3 (OCHO), 116.9, 134.1 (2CH₂=CH), 123.7, 127.4, 127.5, 128.3, 128.4, 128.6, 128.7, 130.3, 131.3, 133.1, 133.4, 134.2, 139.3 (Ar-C), 154.9 (C=O) ppm. – C₂H₅₂O₂ (477.0) calcd. C 70.5, H 6.13, N 5.87; found C 70.7, H 6.5, N 6.1.

1-[(4-Chlorophenyl)diallyloxyethyl]-4-methylphenyl]-3-(3-methoxypropionyl)urea (6m)

From 3-(dimethylaminopropyl)propylamine and 5b, m. p. 148 – 150 °C; yield: 1.77 g (75 %). – IR (KBr): ν = 1570 (C=C), 1640 (C=O), 3348 cm⁻¹ (NH). – 1H NMR (CDCl₃): δ = 1.41 – 1.50 (m, 2H, CH₂), 2.07 (s, 6H, N(CH₃)₂), 2.10 – 2.24 (m, 2H, NCH₂), 2.37 (s, 3H, CH₃), 3.02 – 3.08 (m, 2H, NCH₂), 3.79 – 3.85 (m, 4H, 2OCH₂), 5.16 (dd, 2H, Jcis = 9.6 Hz, 3′-H₂), 5.35 (dd, 2H, Jtrans = 17.1 Hz, 3′-H₂), 5.60 (1H, J = 4.2 Hz, NH), 5.84 – 5.97 (m, 2H, 2′-H), 7.10 – 7.45 (m, 7H, Ar-H), 7.77 (s, 1H, NH). – 13C NMR: δ = 21.4 (CH₃), 26.3 (CH₂), 40.7 (NCH₂), 45.7 (NCH₃), 59.1 (NCH₂), 63.2 (2OCH₂), 101.3 (OCHO), 116.9, 134.3 (2CH₂=CH), 124.2, 128.4, 128.6, 130.7, 130.3, 131.6, 133.0, 134.1, 134.2, 139.5 (Ar-C), 155.6 (C=O) ppm. – C₂H₅₂O₂ (472.0) calcd. C 66.16, H 7.26, N 8.90; found C 65.9, H 6.9, N 8.6.

From 2-furanylmethylamine and 5b, m. p. 166 – 168 °C; yield: 1.84 g (79 %). – IR (KBr): ν = 1594 (C=C), 1665
(C=O), 3361 cm⁻¹ (NH). – ¹H NMR (CDCl₃): δ = 2.37 (s, 3H, CH₃), 3.80 (m, 4H, 2OCH₂), 4.17 (m, 2H, NH₂), 4.40 (bs, 1H, NH), 5.18 (dd, 2H, Jcis = 10.0 Hz, 3′-H₆), 5.35 (dd, 2H, Jtrans = 17.0 Hz, 3″-H₆), 5.91 (m, 2H, 2′-H), 6.05 (d, J = 3.1 Hz, 1H, furanyl), 6.30 (d, J = 2.0 Hz, 1H, furanyl), 7.11 – 7.51 (m, 7H, Ar-H), 7.74 (s, 1H, NH). – ¹³C NMR: δ = 21.5 (CH₃), 37.6 (NCH₂), 63.3 (2OCH₂), 101.6 (OCO), 107.2, 107.3, 142.2, 152.3 (furanyl-C), 117.1, 134.3 (2CH₂=CH), 124.0, 128.6, 130.5, 133.5, 133.7, 134.4, 139.5 (Ar-C), 155.9 (C=O) ppm. – C₂₆H₂₇ClN₂O₄ (647.0): calcd. C 66.4, H 5.5, N 5.9; found C 66.2, H 5.5, N 5.8.

General procedure for the preparation of 9a, b

An aqueous solution of NaOH (2N, 50 mL) was added to a suspension of 1 (5 mmol) in CH₂Cl₂ (20 mL) at 0 ºC with stirring for 20 min. The organic layer was separated, and the aqueous layer was repeatedly extracted with CH₂Cl₂. The combined extract was dried over anhydrous Na₂SO₄. Evaporation of the solvent afforded a colorless powder, which can be recrystallized from CH₂Cl₂/n-pentane to give fine colorless crystals.

2-Ethyl-3-hydroxy-3-phenyl-2,3-dihydro-isoindol-1-one (9a)

From 1a as described before, m. p. 157 ºC; yield: 1.15 g (91 %). – IR (KBr): ν = 1620 (C=C), 1687 (C=O), 3325 cm⁻¹ (OH). – ¹H NMR (CDCl₃): δ = 0.94 (t, 3H, J = 7.3 Hz, CH₃), 2.97 – 3.09, 3.33 – 3.45 (2m, 2H, NCH₂), 4.23 (s, 1H, OH), 7.23 – 7.58 (m, 9H, Ar-H). – ¹³C NMR: δ = 14.4 (CH₃), 34.5 (NCH₂), 91.7 (C-3), 122.9, 123.4, 126.6, 128.6, 128.7, 129.7, 130.9, 132.8, 139.1, 149.4 (Ar-C), 168.0 (C=O) ppm. – C₁₆H₁₇NO₂ (253.3): calcd. C 75.8, H 5.97, N 5.53; found C 75.5, H 5.6, N 5.3.

General procedure for the preparation of 11a – f

Excess alcohol (2 mL) was added to a cold (–10 ºC) suspension of 1 (5 mmol) in CH₂Cl₂ (20 mL) with stirring for 20 min. Aqueous NaOH (2N, 50 mL) was added to the reaction mixture. Repeated extraction of the organic layer with CH₂Cl₂, filtration, drying over Na₂SO₄ and evaporation of the solvent afforded fine colorless crystals.

3-Allyloxy-2-ethyl-3-phenyl-2,3-dihydro-isoindol-1-one (11a)

From 1a and allyl alcohol as describe before, m. p. 132 ºC; yield: 1.36 g (93 %). – IR (KBr): ν = 1582 (C=C), 1697 cm⁻¹ (C=O). – ¹H NMR (CDCl₃): δ = 1.05 (t, 3H, J = 7.2 Hz, 2-H), 3.29 (m, 2H, CH₂), 4.17 (m, 2H, NCH₂), 5.35 (s, 1H, CH), 7.01 – 7.79 (m, 9H, Ar-H). – ¹³C NMR: δ = 11.2 (CH₂), 21.4 (CH₃), 41.7 (NCH₂), 64.3 (C-3), 122.9, 123.3, 127.4, 128.1, 128.5, 128.9, 131.5, 131.6, 137.0, 146.1 (Ar-C), 168.5 (C=O) ppm. – C₁₇H₁₇NO₂ (251.0): calcd. C 81.8, H 6.7, N 5.9; found C 81.6, H 7.1, N 5.8.
2-Allyl-3-ethoxy-3-phenyl-2,3-dihydro-isoindol-1-one (11b)

From 1a and methyl alcohol, m. p. 112 °C; yield: 1.26 g (94 %). – IR (KBr): ν = 1612 (C=C), 1703 cm⁻¹ (C=O). – ¹H NMR (CDCl₃): δ = 0.92 (t, 3H, J = 7.2 Hz, CH₃), 3.87 (s, 3H, OCH₃), 3.02 – 3.06 (2m, 2H, NCH₂), 5.70 – 5.73 (m, 2H, 3H), 7.00 – 7.07 (m, 9H, Ar-H). – ¹³C NMR: δ = 12.3 (CH₃), 33.2 (NCH₂), 49.3 (OCH₃), 94.5 (C-3), 112.1, 122.2, 125.3, 127.3, 128.5, 131.2, 131.3, 137.8, 144.2 (Ar-C), 167.5 ppm. – C₁₇H₁₇NO₂ (267.3): calcd. C 76.38, H 6.41, N 4.7; found C 77.5, H 6.6, N 4.9.

3-Ethoxy-2-ethyl-3-phenyl-2,3-dihydro-isoindol-1-one (11c)

From 1a and ethyl alcohol, m. p. 110 – 111 °C; yield: 1.26 g (94 %). – IR (KBr): ν = 1611 (C=C), 1702 cm⁻¹ (C=O). – ¹H NMR (CDCl₃): δ = 1.05 (t, 3H, J = 7.2 Hz, CH₃), 1.20 (t, 3H, J = 7.0 Hz, CH₃), 2.94 – 3.00, 3.39 – 3.67 (2m, 2H, NCH₂), 3.13 – 3.25 (2m, 2H, OCH₂), 7.11 – 7.88 (m, 9H, Ar-H). – ¹³C NMR: δ = 13.5, 14.9 (2CH₃), 34.2 (NCH₂), 58.1, 13 (OCH₃), 94.9 (C-3), 123.1, 126.3, 127.3, 128.3, 128.4, 129.4, 132.2, 139.1, 145.0 (Ar-C), 168.0 (C=O) ppm. – C₁₈H₁ₙNO₂ (281.4): calcd. C 76.8, H 6.81, N 4.98; found C 76.5, H 6.6, N 4.6.

2-Allyl-3-isopropoxyloxy-phenyl-2,3-dihydro-isoindol-1-one (11d)

From 1b and isopropyl alcohol, m. p. 150 °C; yield: 1.40 g (91 %). – IR (KBr): ν = 1610 (C=C), 1703 cm⁻¹ (C=O). – ¹H NMR (CDCl₃): δ = 0.91 (d, 3H, J = 6.1 Hz, CH₃), 1.41 (d, 3H, J = 6.1 Hz, CH₃), 3.37 – 3.48 (m, 1H, OCH), 3.51 – 3.60, 3.90 – 3.99 (2m, 2H, NCH₂), 4.88 – 4.93 (m, 2H, 3’-H, 5’-H), 5.53 – 5.69 (m, 1H, 2’-H), 7.18 – 7.81 (m, 9H, Ar-H). – ¹³C NMR: δ = 23.8, 23.9 (2CH₃), 41.9 (NCH₂), 66.1 (OCH), 91.3 (C-3), 117.4, 135.5 (CH₂=CH), 122.8, 123.2, 123.8, 126.7, 128.4, 129.4, 130.4, 132.2, 138.7, 146.4 (Ar-C), 168.1 (C=O) ppm. – C₂₀H₂₁NO₂ (307.4): calcd. C 78.15, H 6.89, N 4.5; found C 78.0, H 6.8, N 4.4.

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