Synthesis and reactions of 1-amino-1,5,6,10b-tetrahydroimidazo-[2,1-*a*]isoquinolin-2(3*H*)-ones

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Dedicated to Professor Henk Van der Plas on the occasion of his 80th anniversary

Abstract

1-Amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones, as previously unknown ring-annelated isoquinolines with a 3-aminoimidazolidin-4-one scaffold, were selectively prepared upon reacting 2-carbamoylmethyl- or 2-ethoxycarbonylmethyl-3,4-dihydroisoquinolinium salts with hydrazine hydrate. Acylation of the primary amino group with benzoyl chlorides, followed by reductive ring cleavage of the annelated 4-imidazolidinone ring and final cyclodehydration of the *N*,*N*'-diacylhydrazines resulted in the synthesis of 1-methyl-2-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolines which are of interest due to their potential use as bioisosteres of biologically active *N*-aryl-2-(1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)acetamides.

Keywords: Ring annelation, isoquinolines, 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones, hydrazides, 1,3,4-oxadiazoles

Introduction

Due to the natural occurrence and interesting chemical or biological properties of ring-annelated isoquinolines,[1] as exemplified by the tetrahydroisoquinoline antitumor antibiotics,[2] and lamellarin alkaloids,[3] a broad interest in the synthesis of this class of azaheterocyclic compounds

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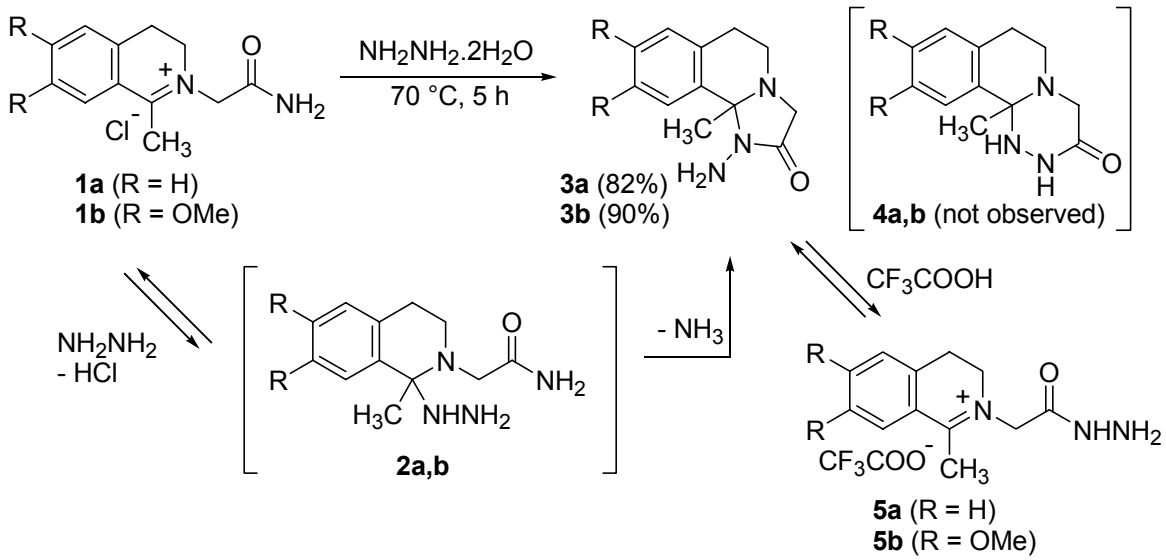
exists.[4] The tricyclic 1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones, which can be prepared via annelation of the imidazolidinone scaffold to 3,4-dihydroisoquinolines,[5] allows further access to heterocyclic compounds with biological interest such as antidepressant activity.[6] Recently, we demonstrated that the hydrazides derived from 1-carbamoylmethyl-3*H*-indolinium salts selectively cyclize to 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones and that the corresponding six-membered ring systems, that is, 1,2,10,10a-tetrahydro[1,2,4]triazino[4,3-*a*]indol-3(4*H*)-ones, by entering of the terminal NH_2 group into reaction, are not formed.[7] In an effort to broaden the scope of this regioselective ring-annelation reaction of hydrazides and to further expand the chemical space of ring-fused isoquinoline derivatives, the objective of this work is to investigate the synthesis of the unknown 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones and to study the transformation of the novel cyclic products to 1,3,4-oxadiazoles. Considerable interest in the synthesis of substituted 1,3,4-oxadiazoles exists due to their numerous pharmacological properties, including analgesic, antiinflammatory, anticonvulsive, diuretic, antiemetic, hypnotic and sedative activities.[8,9] More specific, 2-amino-1,3,4-oxadiazoles act as muscle relaxants[10] and possess antimitotic activity.[11]

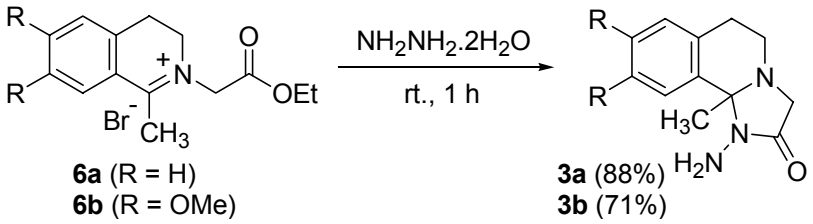
Results and Discussion

As previously reported, the annelation of the imidazolidine ring to the isoquinoline nucleus starts by reaction of 3,4-dihydroisoquinoline or the corresponding 6,7-dimethoxy derivative with chloroacetamide which affords 2-carbamoylmethyl-3,4-dihydroisoquinolinium chloride **1**.[5c] It was shown previously that the reaction of 2-carbamoylmethyl-3,4-dihydroisoquinolinium chloride **1** with aqueous potassium hydroxide afforded 10b-methyl-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-one.[5a] During the present investigations, it was found that heating 2-carbamoylmethyl-3,4-dihydroisoquinolinium chlorides **1** in the presence of hydrazine hydrate regioselectively lead to the formation of five-membered heterocycles, i.e. 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones **3** in good yields, with hydrazines **2** as potential intermediates and without any observation of the corresponding six-membered compounds **4** (Scheme 1). Similarly, 2-ethoxycarbonylmethyl-3,4-dihydroisoquinolinium bromide **6**, prepared by treatment of 1-methyl-3,4-dihydroisoquinoline with ethyl 2-bromoacetate,[12] efficiently reacted with hydrazine hydrate under mild reaction conditions to afford 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones **3** (Scheme 2). The main evidence for the assignment of structures **3a,b** containing the 1-amino-4-imidazolidinone ring, followed from the ^{15}N NMR data. The ^{15}N NMR spectrum showed three different N-atoms with chemical shifts at –341.7, –327.0 and –227.0 ppm (for compound **3a**) and –342.1, –327.2 and –226.6 (for compound **3b**). In ^{15}N DEPT experiments without ^{1}H-decoupling the central ^{15}N NMR resonance (~ –327 ppm) showed a triplet multiplicity (^{1}J = 68.9 Hz), thus unequivocally indicating the presence of an NH_2 moiety. This definitely ruled out the corresponding six-membered structure **4**, for which two NH substructures and a tertiary nitrogen

atom would be expected. Moreover, the $^{15}N,^{1}H$-HMBC spectrum of compound **3a** exhibited a clear correlation between the nitrogen atom with the largest chemical shift (N-1, $\delta = -227.0$ ppm) and the methyl protons of 10b-CH_3 ($\delta = 1.70$ ppm), what seems improbable with structure **4** where the involved nuclei would be separated by four bonds and thus no correlation is expected. In addition, the ^{1}H NMR spectra of compounds **3** contained only one sharp signal (at 3.97 ppm for **3a** and at 3.98 ppm for **3b**) with a relative intensity of two protons attributed to the NH_2-function. In contrast, for the corresponding six-membered structure **4**, two different NH-signals each with a relative intensity of one proton would be expected.



Scheme 1



Scheme 2

The assignments presented in Figures 1(a) and 2(a) were based on the combined application of standard NMR techniques such as NOE-difference (Figure 1(b) and 2(b)), NOESY, APT, DEPT, HSQC, HMBC and long-range INEPT spectra with selective excitation.[13]

As in the case of 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones,[7] no other ring-chain tautomeric forms of 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones (**3a,b**) were visible by ^{1}H and ^{13}C NMR in $CDCl_3$ or DMSO-d_6. Due to higher substitution and thereby higher conjugation, the tricyclic compound **3** is expected to be more favored than the

corresponding open-chain hydrazide. Nevertheless, by the action of protic acids on 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones **3**, a heterolytic cleavage of the N1-C10b bond in the imidazolidine ring took place with formation of isoquinolinium salts **5**. Formation of the latter was proven by NMR spectra of heterocycles **3** in deuterated trifluoroacetic acid. The appearance of a signal at 184.6 ppm (starting from compound **3a**) and 181.6 ppm (starting from compound **3b**) in ^{13}C NMR was indicative of a N^{+}=C carbon and cleavage of the imidazolidine ring.

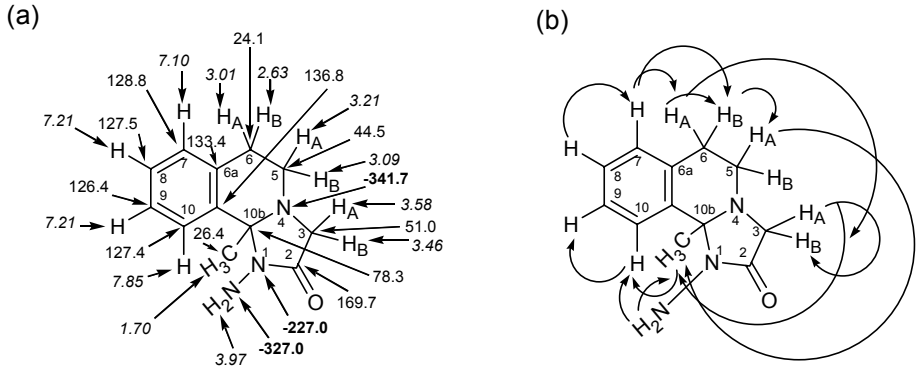


Figure 1. (a) ^{1}H (italics), ^{13}C and ^{15}N NMR (bold) chemical shifts [ppm; ref. TMS (^{1}H and ^{13}C) and CH_3NO_2 (^{15}N)] for **3a** in $CDCl_3$. (b) Relevant NOE correlations.

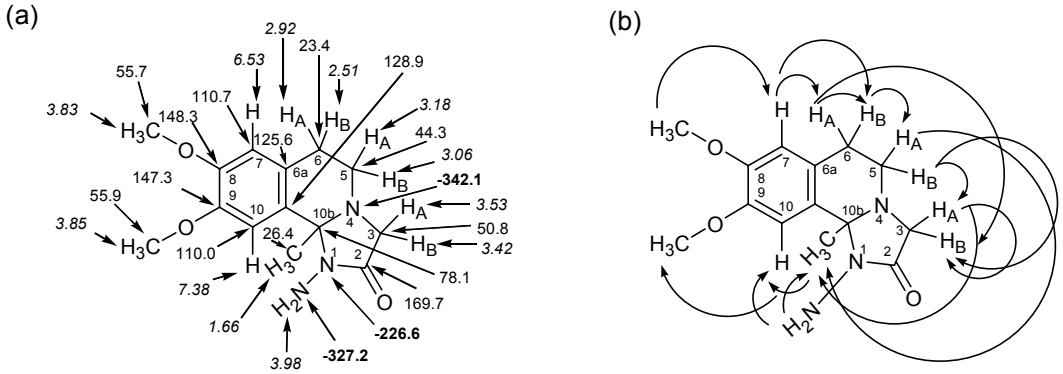
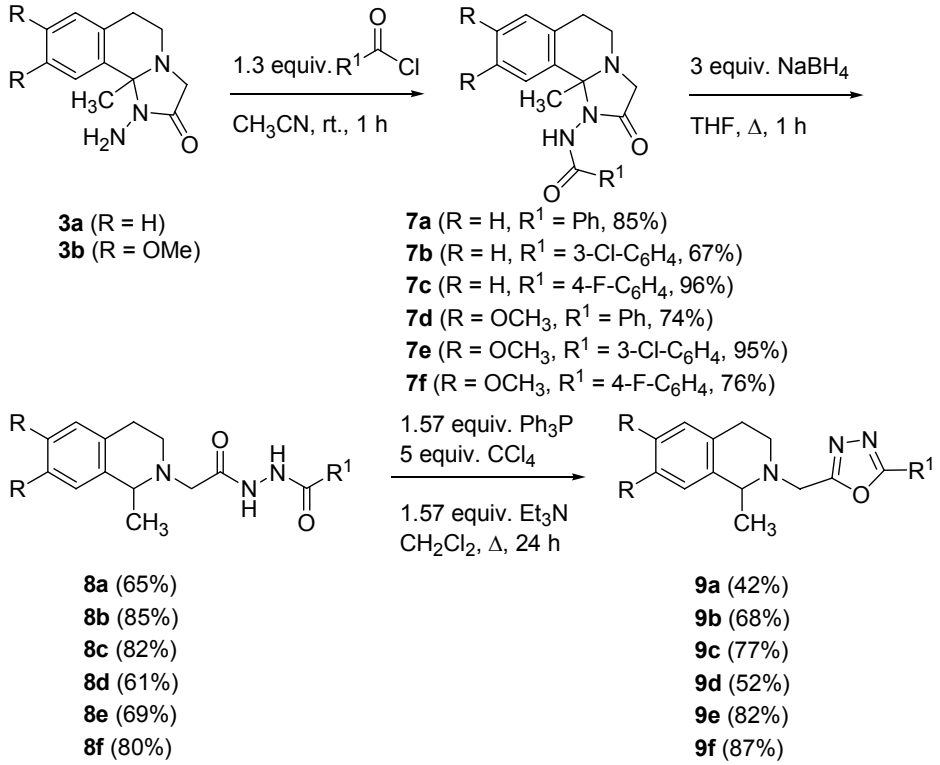


Figure 2. (a) ^{1}H (italics), ^{13}C and ^{15}N NMR (bold) chemical shifts [ppm; ref. TMS (^{1}H and ^{13}C) and CH_3NO_2 (^{15}N)] for **3b** in $CDCl_3$. (b) Relevant NOE correlations.

Further proof for the presence of the primary amino group in the cyclized compounds was obtained by reacting 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones **3** with benzoyl chlorides and benzaldehydes. Acylation of 3-amino-4-imidazolidinones **3** with benzoyl chlorides afforded *N*,*N*'-diacylhydrazines **7a-f** in 67-96% yield. Further reduction of the latter compounds with sodium borohydride upon heating in tetrahydrofuran resulted in ring cleavage of the annelated 4-imidazolidinone ring,[14] to give *N*,*N*'-diacylhydrazines **8a-f** (Scheme 3). The latter easily underwent cyclodehydration to 1-methyl-2-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-

1,2,3,4-tetrahydroisoquinolines **9a-f** under modified Appel conditions.[15] The 2-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline moiety was present as a structural feature in compounds acting as urotensin-II receptor antagonists.[16] 1,3,4-Oxadiazoles are used as bioisosteres of amide functionalities in bioactive compounds,[17] and, therefore, congeners **9** have potential for bioisosteric replacement of *N*-aryl-2-(1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)acetamides which act as antagonists of SNS sodium channels,[18] inhibitors of voltage-gated sodium channels,[19] and antiprotozoal agents.[20]

The exocyclic amino group in compounds **3** reacted with aromatic aldehydes by heating in ethanol in the presence of catalytic amounts of piperidine and afforded the corresponding hydrazones **10a-c**, albeit in low yields. Compounds **10** could also be forced to reductive ring opening by reaction with sodium borohydride in THF to give acylated hydrazones **11** (Scheme 4).[21]



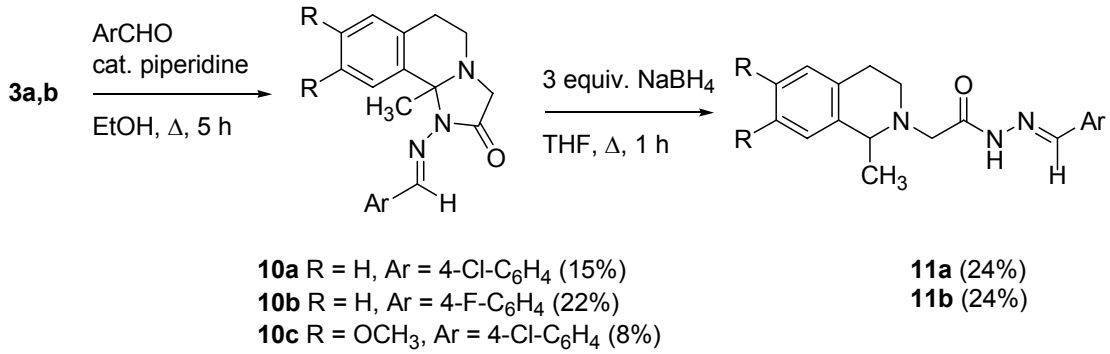
3a (R = H)
3b (R = OMe)

7a (R = H, R^1 = Ph, 85%)
7b (R = H, R^1 = 3-Cl-C_6H_4, 67%)
7c (R = H, R^1 = 4-F-C_6H_4, 96%)
7d (R = OCH_3, R^1 = Ph, 74%)
7e (R = OCH_3, R^1 = 3-Cl-C_6H_4, 95%)
7f (R = OCH_3, R^1 = 4-F-C_6H_4, 76%)

8a (65%)
8b (85%)
8c (82%)
8d (61%)
8e (69%)
8f (80%)

9a (42%)
9b (68%)
9c (77%)
9d (52%)
9e (82%)
9f (87%)

Scheme 3



10a R = H, Ar = 4-Cl-C_6H_4 (15%)
10b R = H, Ar = 4-F-C_6H_4 (22%)
10c R = OCH_3, Ar = 4-Cl-C_6H_4 (8%)

11a (24%)
11b (24%)

Scheme 4

Conclusions

2-Carbamoylmethyl- or 2-ethoxycarbonylmethyl-3,4-dihydroisoquinolinium salts regioselectively cyclised to 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones upon treatment with hydrazine hydrate. The latter heterocyclic compounds occurred as single tautomeric forms and were the first ring-annelated isoquinolines with a 3-aminoimidazolidin-4-one scaffold. The primary amino group was used as a handle via aroylation, reductive ring cleavage and cyclodehydration for further transformation to new 1,3,4-oxadiazoles which have potential as bioisosteres of biologically active *N*-aryl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)acetamides.

Experimental Section

General Procedures. Melting points were determined in open capillary tubes with a Büchi B-540 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum One spectrometer using potassium bromide pellets. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Unity Inova spectrometer and at 500 MHz on a Bruker Avance 500 spectrometer; ^{13}C NMR spectra were registered at 75 and 125 MHz, respectively. Chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). ^{15}N NMR spectra (50.69 MHz) were obtained on a Bruker Avance 500 spectrometer using a 'directly' detecting broadband observe probe and were referenced against neat, external nitromethane (coaxial capillary). Mass spectra were recorded on a Agilent 110 (series MS with VL) instrument. Elemental analyses were measured with a CE-440 elemental analyzer, Model 440 CHN/O/S. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used.

General procedures for the synthesis of 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones 3

Procedure 1. A mixture of 1-methyl-2-carbamoylmethyl-3,4-dihydroisoquinolinium chloride **1** (10 mmol) and hydrazine hydrate (55%, 10 mL) was heated at 70 °C for 5 h. The reaction mixture was cooled to room temperature, 10 ml of water was added and extraction was performed with dichloromethane (5 x 20 mL). The combined extracts were washed with water (25 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel with hexane/ethyl acetate/methanol 2:4:1 (for **3a**) or dichloromethane/methanol 100:5 (for **3b**) as eluent to yield **3**.

Procedure 2. A mixture of 2-carbamoylmethyl-3,4-dihydroisoquinolinium bromide **6** (10 mmol) and hydrazine hydrate (55%, 10 mL) was stirred at room temperature for 1 h. Water (10 mL) was added and extraction was performed with dichloromethane (5 x 20 mL). The combined extracts were washed with water (25 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel with hexane/ethyl acetate/methanol 2:4:1 (for **3a**) or dichloromethane/methanol 100:5 (for **3b**) as eluent to yield **3**.

1-Amino-10b-methyl-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-one (3a). Yield 82% (procedure 1), 88% (procedure 2). Mp 134-135 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.70 (3H, s, CH_3), 2.63 (1H, m, ^2J = 16.6 Hz, $^3J_{5A}$ = 4.3 Hz, $^3J_{5B}$ = 4.5 Hz, 6-CH_B), 3.01 (1H, m, ^2J = 16.6 Hz, $^3J_{5A}$ = 9.6 Hz, $^3J_{5B}$ = 4.6 Hz, 6-CH_A), 3.09 (1H, m, ^2J = 13.4 Hz, $^3J_{6A}$ = 4.6 Hz, $^3J_{6B}$ = 4.5 Hz, 5-CH_B), 3.21 (1H, m, ^2J = 13.4 Hz, $^3J_{6A}$ = 9.6 Hz, $^3J_{6B}$ = 4.3 Hz, 5-CH_A), 3.58 (1H, A-part of an AB-system, ^2J = 15.0 Hz, 3-CH_A), 3.46 (1H, B-part of an AB-system, ^2J = 15.0 Hz, 3-CH_B), 3.97 (2H, s, NH_2), 7.10 (1H, m, 7-CH), 7.21 (2H, m, 8-CH, 9-CH), 7.85 (1H, m, 10-CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.1 (6-CH_2), 26.4 (10b-CH_3), 44.5 (5-CH_2), 51.0 (3-CH_2), 78.3 (10*b*-C), 126.4 (9-C), 127.4 (10-C), 127.5 (8-C), 128.8 (7-C), 133.4 (6a-C), 136.8 (10a-C), 169.7 (2-C). ^{15}N NMR (50 MHz, $CDCl_3$): –341.7 (4-N), –327.0 (t, J = 68.9 Hz, NH_2), –227.0 (1-N). IR (KBr, cm^{-1}): ν_{N-H} = 3300; ν_{N-H} = 3173; $\nu_{C=O}$ = 1716. MS *m/z* (%): 218 ($M + H^+$, 100). Anal. Calcd for $C_{12}H_{15}N_3O$: C 66.34; H 6.96; N 19.34. Found: C 65.99; H 6.36; N 19.54.

1-Amino-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isquinolin-2(3*H*)-one (3b). Yield 90% (procedure 1), 71% (procedure 2). Mp 123-124 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.66 (3H, s, CH_3), 2.51 (1H, m, ^2J = 16.4 Hz, $^3J_{5A}$ = 4.3 Hz, $^3J_{5B}$ = 4.5 Hz, 6-CH_B), 2.92 (1H, m, ^2J = 16.4 Hz, $^3J_{5A}$ = 9.6 Hz, $^3J_{5B}$ = 4.6 Hz, 6-CH_A), 3.06 (1H, m, ^2J = 13.4 Hz, $^3J_{6A}$ = 4.6 Hz, $^3J_{6B}$ = 4.5 Hz, 5-CH_B), 3.18 (1H, m, ^2J = 13.4 Hz, $^3J_{6A}$ = 9.6 Hz, $^3J_{6B}$ = 4.3 Hz, 5-CH_A), 3.53 (1H, A-part of an AB-system, ^2J = 15.0 Hz, 3-CH_A), 3.42 (1H, B-part of an AB-system, ^2J = 15.0 Hz, 3-CH_B), 3.83 (3H, s, 8-OCH_3), 3.85 (3H, s, 9-OCH_3), 3.98 (2H, s, NH_2), 6.53 (1H, m, 7-CH), 7.38 (1H, m, 10-CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.4 (6-CH_2), 26.4 (10b-CH_3), 44.3 (5-CH_2), 50.8 (3-CH_2), 55.7 (8-OCH_3), 55.9 (9-OCH_3), 78.1 (10b-C), 110.0 (10-C), 110.7 (7-C), 125.6 (6a-C), 128.9 (10a-C), 147.3 (9-C), 148.3 (8-C), 169.7 (2-C). ^{15}N NMR (50 MHz, $CDCl_3$): –342.1 (4-N), –327.2 (t, J = 68.9 Hz, NH_2), –226.6 (1-N). IR (KBr, cm^{-1}): ν_{N-H} = 3317; ν_{N-H} = 3202; $\nu_{C=O}$ = 1712. MS *m/z* (%): 278 ($M + H^+$, 100). Anal. Calcd for $C_{14}H_{19}N_3O_3$: C 60.63; H 6.91; N 15.15. Found: C 60.86; H 6.76; N 14.80.

General procedure for the acylation of 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones 3 with benzoyl chlorides

To a stirred solution of **3** (10 mmol) in dry acetonitrile (7.5 mL), a solution of benzoyl chloride (11 mmol) in dry acetonitrile (10 mL) was added dropwise at room temperature and the mixture was stirred for 1 hour. The formed crystals were separated by filtration and dissolved in water (25 mL). Solid $NaHCO_3$ was added in portions to basify the mixture to pH 8-9. The mixture was extracted with dichloromethane (3 × 25 mL), the combined extracts were washed with water (25 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography with acetone/hexane 1:1 (for **7a-c**) or dichloromethane/methanol 9:1 (for **7d-f**) to give the corresponding *N*,*N*'-diacylhydrazines **7**.

***N*-(10b-Methyl-2-oxo-2,3,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-1(5*H*)-yl)benzamide (7a).** Yield 85%. Mp 82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (3H, s, 10b-CH_3), 2.63-3.08 (5H, m, 2×CH_2 and C*H*(H)), 3.59 (1H, d, *J* = 15.8 Hz, CH(*H*)), 7.09-7.77 (9H, m, aromatic protons), 9.21 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8 (CH_2), 26.2 (10b-CH_3), 45.4 (CH_2), 51.4 (CH_2), 80.3 (C), 126.5, 127.1, 127.5 (2×CH), 127.8, 128.4 (2×CH), 128.8, 131.1, 132.1, 133.6 (Ar-C), 166.1 (C=O), 170.3 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3250; $\nu_{C=O}$ = 1723; $\nu_{C=O}$ = 1686. MS *m/z* (%): 322 (M + H^+, 100). Anal. Calcd for $C_{19}H_{19}N_3O_2$: C 71.01; H 5.96; N 13.08. Found: C 71.18; H 5.98; N 12.71.

3-Chloro-*N*-(10b-methyl-2-oxo-2,3,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-1(5*H*)-yl)benzamide (7b). Yield 67%. Mp 162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (3H, s, 10b-CH_3), 2.64-3.09 (5H, m, 2×CH_2 and C*H*(H)), 3.60 (1H, d, *J* = 15.8 Hz, CH(*H*)), 7.10-7.69 (8H, m, aromatic protons), 9.47 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6 (CH_2), 26.1 (10b-CH_3), 45.3 (CH_2), 51.3 (CH_2), 80.4 (C), 125.1, 126.6, 127.1, 127.9, 128.1, 128.8, 129.7, 132.2, 132.4, 133.5, 134.6 (Ar-C), 164.4 (C=O), 170.3 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3193; $\nu_{C=O}$ = 1721; $\nu_{C=O}$ = 1691. MS *m/z* (%): 356/58 (M + H^+, 100). Anal. Calcd for $C_{19}H_{18}ClN_3O_2$: C 64.13; H 5.10; N 11.81. Found: C 64.50; H 5.07; N 11.43.

4-Fluoro-*N*-(10b-methyl-2-oxo-2,3,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-1(5*H*)-yl)benzamide (7c). Yield 96%. Mp 94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (3H, s, 10b-CH_3), 2.59-3.12 (5H, m, 2×CH_2 and C*H*(H)), 3.55 (1H, d, *J* = 15.8 Hz, CH(*H*)), 6.89 – 7.80 (8H, m, aromatic protons), 9.46 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5 (CH_2), 26.1 (10b-CH_3), 44.9 (CH_2), 51.1 (CH_2), 80.3 (C), 115.4 (d, *J* = 21.9 Hz, Ph 3,5-C), 126.6, 126.9 (d, *J* = 2.5 Hz, 1-C), 127.2, 127.9, 128.8, 129.9 (d, *J* = 9.1 Hz, Ph 2,6-C), 133.5, 164.9 (d, *J* = 252.9 Hz, Ph 4-C), 164.7 (C=O), 170.6 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3250; $\nu_{C=O}$ = 1722; $\nu_{C=O}$ = 1686. MS *m/z* (%): 340 (M + H^+, 100). Anal. Calcd for $C_{19}H_{18}FN_3O_2$: C 67.24; H 5.35; N 12.38. Found: C 67.63; H 5.57; N 12.15.

***N*-(8,9-Dimethoxy-10b-methyl-2-oxo-2,3,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-1(5*H*)-yl)benzamide (7d).** Yield 74%. Mp 93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (3H, s, 10b-CH_3), 2.49-3.09 (5H, m, 2×CH_2 and C*H*(H)), 3.53 (1H, d, *J* = 15.5 Hz, CH(*H*)), 3.77 (3H, s, CH_3), 3.86 (3H, s, CH_3), 6.54 (1H, s, C_7-H), 6.85 (1H, s, C_{10}-H), 7.18-7.24 (2H, m, $C_{3'}$-H and

$C_{5'}$-H), 7.32-7.37 (1H, m, $C_{4'}$-H), 7.74-7.76 (2H, m, $C_{2'}$-H and $C_{6'}$-H), 9.63 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.0 (CH_2), 26.3 (10b-CH_3), 45.2 (CH_2), 50.9 (CH_2), 55.9 (CH_3), 56.1 (CH_3), 80.4 (C), 109.9, 110.9, 125.7, 127.7 (2×CH), 128.7 (2×CH), 130.9, 132.4, 147.7, 148.7 (Ar-C), 166.3 (C=O), 170.9 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3245; $\nu_{C=O}$ = 1720; $\nu_{C=O}$ = 1684. MS *m/z* (%): 382 (M + H^+, 100). Anal. Calcd for $C_{21}H_{23}N_3O_4$: C 66.13; H 6.08; N 11.02. Found: C 66.49; H 6.46; N 11.04.

3-Chloro-*N*-(8,9-dimethoxy-10b-methyl-2-oxo-2,3,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-1(5*H*)-yl)benzamide (7e). Yield 95%. Mp 105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (3H, s, 10b-CH_3), 2.48-3.13 (5H, m, 2×CH_2 and C*H*(H)), 3.53 (1H, d, *J* = 15.6 Hz, CH(*H*)), 3.79 (3H, s, CH_3), 3.86 (3H, s, CH_3), 6.53 (1H, s, C_7-H), 6.81 (1H, s, C_{10}-H), 7.15-7.21 (1H, m, $C_{5'}$-H), 7.34-7.38 (1H, m, $C_{4'}$-H), 7.67-7.69 (2H, m, $C_{2'}$-H, $C_{6'}$-H), 9.87 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5 (CH_2), 25.9 (10b-CH_3), 44.7 (CH_2), 50.4 (CH_2), 55.6 (CH_3), 55.8 (CH_3), 80.2 (C), 109.6, 110.7, 124.8, 125.4, 128.2, 129.6, 132.1, 132.2, 134.7, 147.4, 148.5 (Ar-C), 164.4 (C=O), 170.8 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3194; $\nu_{C=O}$ = 1721; $\nu_{C=O}$ = 1686. MS *m/z* (%): 416/18 (M + H^+, 100). Anal. Calcd for $C_{21}H_{22}ClN_3O_4$: C 60.65; H 5.33; N 10.10. Found: C 60.32; H 5.88; N 9.86.

4-Fluoro-*N*-(8,9-dimethoxy-10b-methyl-2-oxo-2,3,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-1(5*H*)-yl)benzamide (7f). 76% yield. Mp 111 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (3H, s, 10b-CH_3), 2.47-3.14 (5H, m, 2×CH_2 and C*H*(H)), 3.51 (1H, d, *J* = 15.6 Hz, CH(*H*)), 3.79 (3H, s, CH_3), 3.86 (3H, s, CH_3), 6.53 (1H, s, C_7-H), 6.81 (1H, s, C_{10}-H), 6.86-6.91 (2H, m, $C_{3'}$-H and $C_{5'}$-H), 7.77-7.82 (2H, m, $C_{2'}$-H and $C_{6'}$-H), 9.81 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4 (CH_2), 25.8 (10b-CH_3), 44.5 (CH_2), 50.3 (CH_2), 55.6 (CH_3), 55.8 (CH_3), 80.1 (C), 109.6, 110.6, 115.4 (d, *J* = 21.9 Hz, 2×CH), 125.3, 126.7 (d, *J* = 2.4 Hz, Ph 1-C), 129.9 (br d, *J* = 8.9 Hz, Ph 2,6-C), 147.4, 148.4, 164.9 (d, *J* = 253.2 Hz, Ph 4-C) (Ar-C), 164.7 (C=O), 170.9 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3250; $\nu_{C=O}$ = 1718; $\nu_{C=O}$ = 1685. MS *m/z* (%): 400 (M + H^+, 100). Anal. Calcd for $C_{21}H_{22}FN_3O_4$: C 63.15; H 5.55; N 10.52. Found: C 63.41; H 5.83; N 10.75.

General procedure for the reduction of *N*-substituted 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones (7a-f, 10a,b) with sodium borohydride

To a solution of *N*-substituted 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-one **7** or **10** (1.35 mmol) in 7 mL of dry tetrahydrofuran, sodium borohydride (0.153 g, 4.05 mmol) was added. The mixture was heated at 70 °C for one hour, then cooled to room temperature, poured into water (30 mL) and extracted with dichloromethane (3 × 20 mL). The combined extracts were washed with water (20 mL) and dried over sodium sulfate. After filtration, the solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel with acetone/hexane 1:1 (for **8a-f**) or acetone/hexane 1:3 (for **11a,b**) to obtain the various hydrazines **8** and **11**.

***N*'-[2-(1-Methyl-3,4-dihydro-2(1*H*)-isoquinolinyl)acetyl]benzohydrazide (8a).** Yield 65%. Mp 115 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.33 (3H, d, *J* = 6.6 Hz, CH_3), 2.71-3.10 (4H, m, 2×CH_2), 3.27 (1H, d, *J* = 15.6 Hz, C*H*(H)), 3.37 (1H, d, *J* = 15.6 Hz, CH(*H*)), 3.95 (1H, q, *J* =

6.6 Hz, CH), 6.10-7.91 (9H, m, aromatic protons), 9.76 (1H, s, NH), 10.39 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.5 (CH_3), 27.3 (CH_2), 44.8 (CH_2), 56.3 (CH), 56.5 (CH_2), 125.6, 125.8, 127.2, 127.5 (2×CH), 128.5 (2×CH), 128.6, 131.8, 132.5, 133.9, 139.8 (Ar-C), 165.3 (C=O), 169.6 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3172; $\nu_{C=O}$ = 1698; $\nu_{C=O}$ = 1645. MS *m/z* (%): 324 (M + H$^+$, 100). Anal. Calcd for $C_{19}H_{21}N_3O_2$: C 70.57; H 6.55; N 12.99. Found: C 70.19; H 6.67; N 12.77.

3-Chloro-*N*'-[(1-methyl-3,4-dihydro-2(1*H*)-isoquinolinyl)acetyl]benzohydrazide (8b). Yield 85%. Mp 149 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.32 (3H, d, *J* = 6.6 Hz, CH_3), 2.69-3.09 (4H, m, 2×CH_2), 3.28 (1H, d, *J* = 15.6 Hz, C*H*(H)), 3.37 (1H, d, *J* = 15.6 Hz, CH(*H*)), 3.94 (1H, q, *J* = 6.6 Hz, CH), 7.08-7.93 (8H, m, aromatic protons), 9.82 (1H, s, NH), 10.54 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.5 (CH_3), 27.3 (CH_2), 44.8 (CH_2), 56.3 (CH), 56.6 (CH_2), 125.6, 125.8, 126.2, 127.1, 127.3, 128.6, 130.6, 131.7, 133.3, 133.9, 134.5, 139.8 (Ar-C), 163.9 (C=O), 169.6 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3213; $\nu_{C=O}$ = 1700; $\nu_{C=O}$ = 1646. MS *m/z* (%): 358/60 (M + H$^+$, 100). Anal. Calcd for $C_{19}H_{20}ClN_3O_2$: C 63.77; H 5.63; N 11.74. Found: C 64.02; H 5.65; N 11.62.

4-Fluoro-*N*'-[2-(1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)acetyl]benzohydrazide (8c). Yield 82%. Mp 106 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.32 (3H, d, *J* = 6.6 Hz, CH_3), 2.69-3.10 (4H, m, 2×CH_2), 3.27 (1H, d, *J* = 15.6 Hz, C*H*(H)), 3.37 (1H, d, *J* = 15.6 Hz, CH(*H*)), 3.94 (1H, q, *J* = 6.6 Hz, CH), 7.07-7.99 (8H, m, aromatic protons), 9.78 (1H, s, NH), 10.44 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.5 (CH_3), 27.3 (CH_2), 44.8 (CH_2), 56.3 (CH), 56.6 (CH_2), 115.5 (d, *J* = 21.9 Hz, Ph 3,5-C), 125.6, 125.8, 127.1, 128.6, 128.9 (d, *J* = 2.8 Hz, Ph 1-C), 130.2 (d, *J* = 9.4 Hz, Ph 2,6-C), 133.9, 139.8, 164.2 (d, *J* = 249.3 Hz, Ph 4-C), 164.3 (C=O), 169.6 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3252; $\nu_{C=O}$ = 1701; $\nu_{C=O}$ = 1650. MS *m/z* (%): 342 (M + H$^+$, 100). Anal. Calcd for $C_{19}H_{20}FN_3O_2$: C 66.85; H 5.91; N 12.31. Found: C 66.48; H 6.16; N 12.30.

***N*'-[2-(6,7-Dimethoxy-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)acetyl]benzohydrazide (8d)**. Yield 61%. Mp 69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (3H, d, *J* = 6.6 Hz, CH_3), 2.65-3.25 (4H, m, 2×CH_2), 3.37 (2H, s, CH_2), 3.83 (3H, s, CH_3), 3.84 (3H, s, CH_3), 3.81-3.88 (1H, m, CH), 6.53 (1H, s, C_5-H), 6.58 (1H, s, C_8-H), 7.35-7.40 (2H, m, $C_{3'}$-H and $C_{5'}$-H), 7.46-7.51 (1H, m, $C_{4'}$-H), 7.79-7.82 (2H, m, $C_{2'}$-H and $C_{6'}$-H), 9.55 (2H, br s, 2×NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5 (CH_3), 26.7 (CH_2), 45.2 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 57.0 (CH), 57.2 (CH_2), 109.9, 111.3, 125.2, 127.2 (2×CH), 128.5 (2×CH), 130.6, 131.3, 132.2, 147.3, 147.5 (Ar-C), 164.7 (C=O), 168.8 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3279; $\nu_{C=O}$ = 1703; $\nu_{C=O}$ = 1657. MS *m/z* (%): 384 (M + H$^+$, 100). Anal. Calcd for $C_{21}H_{25}N_3O_4$: C 65.78; H 6.57; N 10.96. Found: C 65.70; H 6.94; N 11.33.

3-Chloro-*N*'-[2-(6,7-dimethoxy-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)acetyl]benzohydrazide (8e). Yield 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (3H, d, *J* = 6.5 Hz, CH_3), 2.65-3.24 (4H, m, 2×CH_2), 3.38 (2H, s, CH_2), 3.840 (3H, s, CH_3), 3.843 (3H, s, CH_3), 3.81-3.89 (1H, m, CH), 6.53 (1H, s, C_5-H), 6.58 (1H, s, C_8-H), 7.27-7.78 (4H, m, aromatic protons), 10.09 (2H, br s, 2×NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5 (CH_3), 26.6 (CH_2), 45.1 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 56.9 (CH), 57.2 (CH_2), 109.9, 111.3, 125.1, 125.3, 127.7, 129.8, 130.5, 132.1, 132.9,

134.6, 147.3, 147.5 (Ar-C), 163.4 (C=O), 169.3 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3279; $\nu_{C=O}$ = 1701; $\nu_{C=O}$ = 1659. MS *m/z* (%): 418/20 ($M + H^+$, 100). Anal. Calcd for $C_{21}H_{24}ClN_3O_4$: C 60.36; H 5.79; N 10.06. Found: C 60.37; H 5.59; N 9.68.

4-Fluoro-*N*'-[2-(6,7-dimethoxy-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl)acetyl]benzohydrazide (8f). Yield 80%. Mp 161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (3H, d, *J* = 6.6 Hz, CH_3), 2.63-3.22 (4H, m, 2×CH_2), 3.32 (1H, d, *J* = 17.1 Hz, C*H*(H)), 3.38 (1H, d, *J* = 16.9 Hz, CH(*H*)), 3.82 (6H, s, 2×CH_3), 3.81-3.87 (1H, m, CH), 6.52 (1H, s, C_7-H), 6.56 (1H, s, C_{10}-H), 6.97-7.03 (2H, m, $C_{3'}$-H and $C_{5'}$-H), 7.77-7.82 (2H, m, $C_{2'}$-H and $C_{6'}$-H), 9.98 (2H, br s, 2×NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4 (CH_3), 26.6 (CH_2), 45.1 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 57.0 (CH), 57.2 (CH_2), 109.9, 111.3, 115.5 (d, *J* = 21.9 Hz, Ph 3,5-C), 125.1, 127.3 (d, *J* = 2.5 Hz, Ph 1-C), 129.7 (d, *J* = 8.8 Hz, Ph 2,6-C), 130.5, 147.3, 147.5, 164.9 (d, *J* = 253.3 Hz, Ph 4-C), 163.9 (C=O), 169.6 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3254; $\nu_{C=O}$ = 1694; $\nu_{C=O}$ = 1650. MS *m/z* (%): 402 ($M + H^+$, 100). Anal. Calcd for $C_{21}H_{24}FN_3O_4$: C 62.83; H 6.03; N 10.47. Found: C 62.52; H 6.41; N 10.18.

***N*'-[(1*E*)-(4-Chlorophenyl)methylene]-2-(1-methyl-3,4-dihydro-2(1*H*)-isoquinolinyl)acetohydrazide (11a).** Yield 24%. Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (3H, d, *J* = 6.7 Hz, CH_3), 2.28-3.19 (4H, m, 2×CH_2), 3.37 (1H, d, *J* = 17.1 Hz, C*H*(H)), 3.43 (1H, d, *J* = 17.1 Hz, CH(*H*)), 3.92 (1H, q, *J* = 6.7 Hz, CH), 7.06-7.69 (8H, m, aromatic protons), 8.12 (1H, s, NH), 10.34 (1H, s, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6 (CH_3), 27.9 (CH_2), 45.5 (CH_2), 57.5 (CH), 57.9 (CH_2), 126.1, 126.4, 127.1, 128.8 (2×CH), 128.9 (2×CH), 132.0, 133.0, 136.4, 138.9, 147.0 (Ar-C), 147.0 (C=N), 167.2 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3207; $\nu_{C=O}$ = 1679; $\nu_{C=N}$ = 1596. MS *m/z* (%): 342/44 ($M + H^+$, 100). Anal. Calcd for $C_{19}H_{20}ClN_3O$: C 66.76; H 5.90; N 12.29. Found: C 66.43; H 5.75; N 11.93.

***N*'-[(1*E*)-(4-Fluorophenyl)methylene]-2-(1-methyl-3,4-dihydro-2(1*H*)-isoquinolinyl)acetohydrazide (11b).** Yield 24%. Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (3H, d, *J* = 6.7 Hz, CH_3), 2.78-3.20 (4H, m, 2×CH_2), 3.40 (2H, s, CH_2), 3.93 (1H, q, *J* = 6.6 Hz, CH), 7.03-7.76 (8H, m, aromatic protons), 8.13 (1H, s, NH), 10.33 (1H, s, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7 (CH_3), 27.9 (CH_2), 45.5 (CH_2), 57.5 (CH), 57.8 (CH_2), 115.8 (d, *J* = 21.9 Hz, Ph 3,5-C), 126.1, 126.4, 127.2, 128.9, 129.5 (d, *J* = 8.6 Hz, Ph 2,6-C), 129.7 (d, *J* = 3.5 Hz, Ph 1-C), 133.0, 138.9, 147.2 (C=N), 164.1 (d, *J* = 251.0 Hz, Ph 4-C), 167.1 (C=O). IR (KBr, cm^{-1}): ν_{N-H} = 3212; $\nu_{C=O}$ = 1682; $\nu_{C=N}$ = 1603. MS *m/z* (%): 326 ($M + H^+$, 100). Anal. Calcd for $C_{19}H_{20}FN_3O$: C 70.13; H 6.20; N 12.91. Found: C 69.85; H 6.43; N 12.87.

General procedure for the synthesis of 1-methyl-2-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolines (9a-f)

To a stirred suspension of hydrazide **9** (1 mmol) in dichloromethane (12 mL) was added triphenylphosphine (1.57 mmol), carbon tetrachloride (5 mmol) and triethylamine (1.57 mmol), after which the mixture was heated to reflux for 24 h. The mixture was cooled to room temperature, poured into water (15 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane/acetone 2:1 to yield 1,3,4-oxadiazoles **9** as oils.

1-Methyl-2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (9a). Yield 42%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.34 (3H, d, J = 6.6 Hz, CH_3), 2.69 – 3.17 (4H, m, 2×CH_2), 3.92 (1H, q, J = 6.5 Hz, CH), 4.07 (1H, d, J = 15.1 Hz, C*H*(H)), 4.17 (1H, d, J = 15.1 Hz, CH(*H*)), 7.07 – 8.02 (9H, m, aromatic protons). ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.4 (CH_3), 27.3 (CH_2), 44.6 (CH_2), 47.6 (CH_2), 55.5 (CH), 123.3, 125.6, 125.7, 126.4 (2×CH), 127.0, 128.5, 129.4 (2×CH), 131.8, 135.5, 139.3 (Ar-C), 164.3, 164.4 (C-O-C). IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1609. MS *m/z* (%): 306 (M + H$^+$, 100). Anal. Calcd for $C_{19}H_{19}N_3O$: C 74.73; H 6.27; N 13.76. Found: C 74.76; H 6.32; N 13.70.

2-[5-(3-Chlorophenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline (9b). Yield 68%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.37 (3H, d, J = 6.6 Hz, CH_3), 2.71 – 3.20 (4H, m, 2×CH_2), 3.93 (1H, q, J = 6.6 Hz, CH), 4.10 (1H, d, J = 15.1 Hz, C*H*(H)), 4.20 (1H, d, J = 15.1 Hz, CH(*H*)), 7.08 – 7.98 (8H, m, aromatic protons). ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.5 (CH_3), 27.3 (CH_2), 44.7 (CH_2), 47.7 (CH_2), 55.6 (CH), 125.2, 125.3, 125.7, 125.8, 125.9, 127.1, 128.6, 131.5, 131.8, 133.6, 134.0, 139.4 (Ar-C), 163.3, 164.9 (C-O-C). IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1606. MS *m/z* (%): 340/42 (M + H$^+$, 100). Anal. Calcd for $C_{19}H_{18}ClN_3O$: C 67.15; H 5.34; N 12.37. Found: C 66.78; H 4.99; N 12.19.

2-[5-(4-Fluorophenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1-methyl-1,2,3,4-tetrahydroisoquinoline (9c). Yield 77%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.36 (3H, d, J = 6.6 Hz, CH_3), 2.68 – 3.17 (4H, m, 2×CH_2), 3.92 (1H, q, J = 6.6 Hz, CH), 4.09 (1H, d, J = 15.1 Hz, C*H*(H)), 4.19 (1H, d, J = 15.1 Hz, CH(*H*)), 7.08 – 8.08 (8H, m, aromatic protons). ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.5 (CH_3), 27.3 (CH_2), 44.7 (CH_2), 47.7 (CH_2), 55.5 (CH), 116.7 (d, J = 22.5 Hz, Ph 3,5-C), 120.1 (d, J = 3.6 Hz, Ph 1-C), 125.7, 125.8, 127.1, 128.6, 129.2 (d, J = 9.5 Hz, Ph 2,6-C), 133.6, 139.4, 164.1 (d, J = 250.2 Hz, Ph 4-C), 163.7, 164.5 (C-O-C). IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1610. MS *m/z* (%): 324 (M + H$^+$, 100). Anal. Calcd for $C_{19}H_{18}FN_3O$: C 70.57; H 5.61; N 12.99. Found: C 70.32; H 5.33; N 12.74.

6,7-Dimethoxy-1-methyl-2-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (9d). Yield 52%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (3H, d, J = 6.6 Hz, CH_3), 2.67 – 3.27 (4H, m, 2×CH_2), 3.83 (6H, s, 2×CH_3), 3.90 (1H, q, J = 6.6 Hz, CH), 4.08 (1H, d, J = 14.7 Hz, C*H*(H)), 4.16 (1H, d, J = 14.7 Hz, CH(*H*)), 6.55 (1H, s, C_5-H), 6.56 (1H, s, C_8-H), 7.46-7.55 (3H, m, $C_{3'}$-H, $C_{4'}$-H and $C_{5'}$-H), 8.05-8.08 (2H, m, $C_{2'}$-H and $C_{6'}$-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 (CH_3), 26.6 (CH_2), 45.2 (CH_2), 48.2 (CH_2), 55.8 (CH), 55.9 (CH_3), 56.0 (CH_3),

109.9, 111.2, 123.7, 125.4, 126.9 (2×CH), 128.9 (2×CH), 130.7, 131.7, 147.3, 147.4 (Ar-C), 164.2, 165.4 (C-O-C). IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1610. MS *m/z* (%): 366 ($M + H^+$, 100). Anal. Calcd for $C_{21}H_{23}N_3O_3$: C 69.02; H 6.34; N 11.50. Found: C 69.35; H 6.28; N 11.23.

2-[5-(3-Chlorophenyl)-[1,3,4]oxadiazol-2-ylmethyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (9e). Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (3H, d, *J* = 6.6 Hz, CH_3), 2.66 – 3.26 (4H, m, 2×CH_2), 3.82 (6H, s, 2×CH_3), 3.88 (1H, q, *J* = 6.6 Hz, CH), 4.06 (1H, d, *J* = 14.8 Hz, C*H*(H)), 4.15 (1H, d, *J* = 14.8 Hz, CH(*H*)), 6.55 (1H, s, C_5-H), 6.56 (1H, s, C_8-H), 7.40-7.51 (2H, m, $C_{4'}$-H and $C_{5'}$-H), 7.97-8.04 (2H, m, $C_{2'}$-H and $C_{6'}$-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 (CH_3), 26.6 (CH_2), 45.2 (CH_2), 48.2 (CH_2), 55.8 (CH), 55.9 (CH_3), 56.1 (CH_3), 110.1, 111.2, 125.0, 125.4, 126.9, 130.3, 130.7, 131.8, 135.1, 147.4, 147.5 (Ar-C), 164.2, 164.6 (C-O-C). IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1611. MS *m/z* (%): 400/02 ($M + H^+$, 100). Anal. Calcd for $C_{21}H_{22}ClN_3O_3$: C 63.08; H 5.55; N 10.51. Found: C 63.33; H 5.45; N 10.63.

2-[5-(4-Fluorophenyl)-[1,3,4]oxadiazol-2-ylmethyl]-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (9f). Yield 87%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (3H, d, *J* = 6.6 Hz, CH_3), 2.67 – 3.27 (4H, m, 2×CH_2), 3.83 (6H, s, 2×CH_3), 3.89 (1H, q, *J* = 6.6 Hz, CH), 4.06 (1H, d, *J* = 14.7 Hz, C*H*(H)), 4.14 (1H, d, *J* = 14.7 Hz, CH(*H*)), 6.55 (1H, s, C_5-H), 6.56 (1H, s, C_8-H), 7.15-7.22 (2H, m, $C_{3'}$-H and $C_{5'}$-H), 8.03-8.10 (2H, m, $C_{2'}$-H and $C_{6'}$-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 (CH_3), 26.5 (CH_2), 45.1 (CH_2), 48.1 (CH_2), 55.8 (CH), 55.9 (CH_3), 56.1 (CH_3), 109.9, 111.1, 116.3 (d, *J* = 22.1 Hz, Ph 3,5-C), 120.1 (d, *J* = 3.3 Hz, Ph 1-C), 125.3, 129.2 (d, *J* = 9.2 Hz, Ph 2,6-C), 130.6, 147.3, 147.4, 164.7 (d, *J* = 253.5 Hz, Ph 4-C), 164.2, 164.6 (C-O-C). IR (KBr, cm^{-1}): $\nu_{C=N}$ = 1607. MS *m/z* (%): 384 ($M + H^+$, 100). Anal. Calcd for $C_{21}H_{22}FN_3O_3$: C 65.78; H 5.78; N 10.96. Found: C 65.49; H 5.76; N 10.64.

General procedure for the condensation of 1-amino-1,5,6,10b-tetrahydroimidazo[2,1-*a*]isoquinolin-2(3*H*)-ones 3 with aromatic aldehydes

To a solution of amine **3** (4 mmol) and 4-substituted benzaldehyde (4.4 mmol) in absolute ethanol (20 mL), 3 drops of piperidine were added and the mixture was refluxed for 5 h. Evaporation of the solvent gave a residue, which was chromatographed on silica gel with hexane /acetone 3:1 (for **10a, b**) or dichloromethane/methanol 9:1 (for **10c**) to give the corresponding hydrazones **10.**

1-[(4-Chlorobenzylidene)amino]-10b-methyl-1,5,6,10b-tetrahydroimidazo[2,1-a]isoquinolin-2(3*H*)-one (10a). Yield 15%. Mp 150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89 (3H, s, CH_3), 2.64 – 3.38 (4H, m, 2×CH_2), 3.60 (1H, d, *J* = 15.2 Hz, C*H*(H)), 3.68 (1H, d, *J* = 15.2 Hz, CH(*H*)), 7.10 – 7.81 (8H, m, aromatic protons), 9.58 (1H, s, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6 (CH_2), 27.9 (CH_3), 43.9 (CH_2), 52.0 (CH_2), 80.3 (C), 126.5, 127.6, 127.8, 128.5 (2×CH), 128.8, 128.9 (2×CH), 133.2, 133.8, 136.2, 136.9 (Ar-C), 152.3 (C=N), 167.6 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ = 1703; $\nu_{C=N}$ = 1599. MS *m/z* (%): 340/42 ($M + H^+$, 100). Anal. Calcd for $C_{19}H_{18}ClN_3O$: C 67.15; H 5.34; N 12.37. Found: C 66.96; H 5.44; N 12.48.

1-[(4-Fluorobenzylidene)amino]-10b-methyl-1,5,6,10b-tetrahydroimidazo[2,1-a]isoquinolin-2(3*H*)-one (10b). Yield 22%. Mp 115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 (3H, s, CH_3),

2.73 – 3.47 (4H, m, 2×CH_2), 3.68 (1H, d, *J* = 15.2 Hz, C*H*(H)), 3.76 (1H, d, *J* = 15.2 Hz, CH(*H*)), 7.18 – 7.91 (8H, m, aromatic protons), 9.62 (1H, s, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6 (CH_2), 27.7 (CH_3), 43.8 (CH_2), 51.9 (CH_2), 80.2 (C), 115.7 (d, *J* = 21.9 Hz, Ph 3,5-C), 126.4, 127.5, 127.7, 128.6, 129.1 (d, *J* = 8.5 Hz, Ph 2,6-C), 131.3 (d, *J* = 2.7 Hz, Ph 1-C), 133.1, 136.8 (Ar-C), 152.6 (C=N), 163.9 (d, *J* = 251.1 Hz, Ph 4-C), 167.3 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ = 1703; $\nu_{C=N}$ = 1601. MS *m/z* (%): 324 ($M + H^+$, 100). Anal. Calcd for $C_{19}H_{18}FN_3O$: C 70.57; H 5.61; N 12.99. Found: C 70.96; H 5.30; N 12.88.

1-[(4-Chlorobenzylidene)amino]-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydroimidazo [2,1-a]isoquinolin-2(3*H*)-one (10c). Yield 8%. Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86 (3H, s, CH_3), 2.87 – 3.34 (4H, m, 2×CH_2), 3.56 (1H, d, *J* = 15.2 Hz, C*H*(H)), 3.64 (1H, d, *J* = 15.2 Hz, CH(*H*)), 3.74 (3H, s, CH_3), 3.82 (3H, s, CH_3), 6.53 – 7.71 (6H, m, aromatic protons), 9.68 (1H, s, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.0 (CH_3), 27.8 (CH_2), 43.8 (CH_2), 51.8 (CH_2), 55.6 (CH_3), 55.7 (CH_3), 80.1 (C), 110.2, 110.7, 125.5, 128.1 (2×CH), 128.8, 128.9 (2×CH), 133.7, 136.2, 147.4, 148.4 (Ar-C), 152.0 (C=N), 167.5 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ = 1703; $\nu_{C=N}$ = 1603. MS *m/z* (%): 400 ($M + H^+$, 100). Anal. Calcd for $C_{21}H_{22}ClN_3O_3$: C 63.08; H 5.55; N 10.51. Found: C 63.28; H 5.25; N 10.63.

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