Synthesis, Hydrolysis, and Evaluation of 3-Acylamino-3,4-dihydro-2-oxo-2*H*-1,3-benzoxazinecarboxylic Acids and Linear Azadepsipeptides as Potential Substrates/Inhibitors of β-Lactam-Recognizing Enzymes

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The title compounds can be considered as stabilized aza analogs of previously studied dihydrobenzopyranones and linear depsipeptides, which behave as substrates or inhibitors of β-lactamases. Treatment of substituted hydrazides **9b** and **9b′** with a phosgene substitute resulted in a series of *N*-methylated 3-acylamino-3,4-dihydro-2-oxo-2*H*-1,3-benzoxazine-7- and -8-carboxylic acids **2b** and **2b′**. However, in the case of the corresponding free NH hydrazide **9a(m)**, a competitive cyclization gave instead a stable 4*H*-1,3,4-oxadiazol-5-one **10a**. To avoid this unwanted cyclization, an *N*-(*p*-methoxy)-benzylated hydrazide **9b′′** was prepared. After formation of the benzoxazinone ring with carbonyldiimidazole, the removal of this new N^1-hydrazide protecting group was achieved with methanesulfonic acid in trifluoroacetic acid to give the expected 3-phenacetamido-3,4-dihydro-2-oxo-2*H*-1,3-benzoxazine-7-carboxylic acid **2a(m)**. The corresponding linear azadepsipeptides **5** were generally obtained by reaction of a hydrazide with 3-*tert*-butoxycarbonylphenyl chlorocarbonate. Hydrolysis of the title compounds in buffer at neutral pH was more rapid than anticipated because of the presence of mechanisms more facile than the classical $B_{AC}2$. Hydrolysis of the cyclic azadepsipeptide **2a(m)**, for example, involved intramolecular nucleophilic participation by the amido side chain and a slowly hydrolyzing oxadiazolone intermediate (**10a**). These compounds, unlike their parent depsipeptides, were not substrates or inhibitors of β-lactamase or DD-peptidase. This result probably arises from a combination of the poor carbonyl electrophilicity and the close to planar geometry of the nitrogen atom of the oxazin-2-one ring.

Introduction

Non-β-lactam inhibitors of β-lactamases and DD-transpeptidases remain attractive targets for antibacterial drugs.[1] Recently, we observed that some δ-lactones, such as the dihydrobenzopyranones **1a** (*ortho*- and *meta*-CO_2H isomers; Figure 1), were new substrates of β-lactamases and inhibitors of D,D-peptidases.[2,3] However, their rates of spontaneous hydrolysis were high. To increase the stability of the molecules, we turned our attention towards their aza analogs: the 3-acylamino-3,4-dihydro-2-oxo-2*H*-1,3-benzoxazinecarboxylic acids **2a**. Incorporation of an electron-donating nitrogen atom α to the carbonyl function should stabilize the ground state of the molecule. Moreover, if a β-lactamase were to be acylated by a dihydrobenzoxazinone, the presence of this atom should also stabilize the acyl enzyme. A derivative of the parent heterocycle, 3,4-dihydro-3-methyl-6-nitro-2*H*-1,3-benzoxazin-2-one **3**, is known to react with chymotrypsin,[4] whereas several of its analogues or homologues result in the production, with cholinesterases, of stabilized carbamoyl-bound enzymes.[5,6]

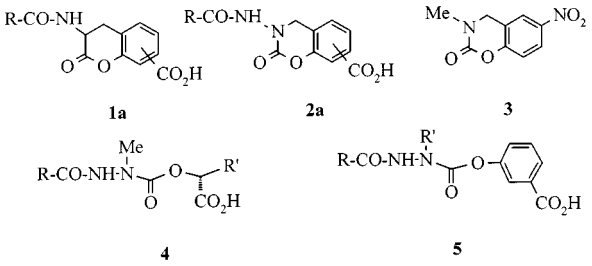

Figure 1. Structures of compounds **1a**, **2a**, **3**, **4**, and **5**

Such a stabilizing effect due to an adjacent nitrogen atom has previously also been observed in the case of linear azadepsipeptides, which behave as inhibitors or as active site titrants of several serine proteases, such as elastase, trypsin, or thrombin.[7] Azadepsipeptides derived from lactic acid **4** (R′ = Me) or from other hydroxy acids have been prepared for analogous purposes, but they were not inhibitors of class A and class C β-lactamases.[8] Since the replacement of the alcohol leaving group with an acidic phenol should give more reactive compounds,[7a] we also planned to synthesize azadepsipeptides derived from *meta*-hydroxybenzoic acids: compounds of type **5**. These molecules may be considered as linear analogs of the 3-acylamino-3,4-dihydro-2-oxo-2*H*-1,3-benzoxazinecarboxylic acids **2**.

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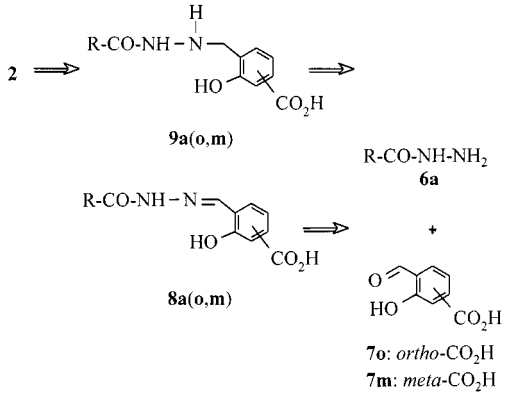
Results and Discussion

Syntheses

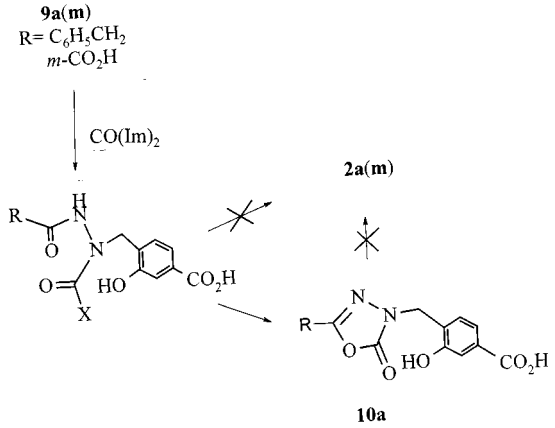
To the best of our knowledge, 3-amino- and 3-acylamino-3,4-dihydro-2*H*-1,3-benzoxazin-2-ones (3-acylamino-3,4-dihydro-2-oxobenz[*e*][1,3]oxazines) are unknown compounds. A retrosynthetic analysis (Scheme 1) showed a possible means to prepare them by treatment of substituted hydrazides **9a** (**o**: *ortho*-COOH; **m**: *meta*-COOH) with phosgene or a phosgene substitute, such as carbonyldiimidazole[9,5] or bis(trichloromethyl)carbonate.[10] The substituted hydrazides **9a(o,m)** could be obtained by reduction of the corresponding hydrazones **8a(o,m)**,[11] themselves prepared by condensation of hydrazides **6a** with a substituted hydroxybenzaldehyde **7o** or **7m**.



Scheme 1. Retrosynthetic analysis for the preparation of the 3-acylamino-3,4-dihydro-2-oxo-2*H*-1,3-benzoxazine-7- and -8-carboxylic acids **2**

The 5-carboxysalicylaldehyde **7m** was prepared by a Reimer−Tiemann or a modified Duff reaction.[12] Condensation of this aldehyde with phenylacetylhydrazide, followed by reduction of hydrazone **8a(m)** with sodium cyanoborohydride, led to the substituted hydrazide **9a(m)** (R = $CH_2C_6H_5$; *m*-CO_2H). However, treatment of this product with carbonyldiimidazole or triphosgene did not give the benzoxazinone, but led instead to the 1,3,4-oxadiazol-5(4*H*)-one **10a**: an aza analog[13] of the 5(4*H*)-oxazolones (compounds well known for their role in the epimerization of amino acid derivatives). However, these 1,3,4-oxadiazol-5(4*H*)-ones are not very reactive species,[8,13] and molecule **10a** did not rearrange to the benzoxazinone **2a(m)** on heating (Scheme 2).

To avoid participation of the neighboring amide group, leading to the oxadiazolone, we next used *N*-alkylated hydrazides as starting components (Scheme 3). Treatment of methylhydrazine with phenylacetic or benzoic anhydride gave the corresponding hydrazides **6b** and **6b′**.[14] Treatment of these hydrazides with substituted salicylaldehyde **7m** or **7o** and reduction of the intermediate hydrazones **8b** (R = $CH_2C_6H_5$) and **8b′** (R = C_6H_5) resulted in the substituted hydrazides **9b** and **9b′**. Subsequent cyclization with carbonyldiimidazole led to the *N*-methylated benzoxazinones **2b** and **2b′** in good yields.

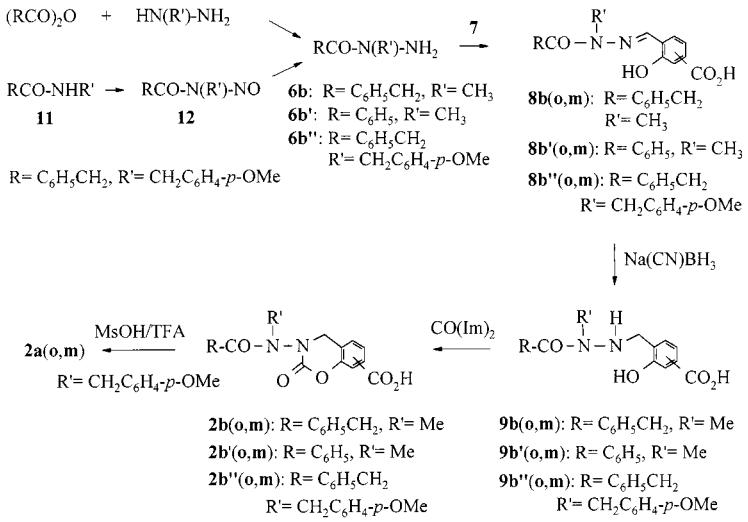


Scheme 2. Unwanted cyclization of the substituted hydrazide **9a(m)** to give 5(4*H*)-1,3,4-oxadiazolone **10a**, instead of the expected 3,4-dihydro-2-oxo-3-phenylacetamino-2*H*-1,3-benzoxazine-7-carboxylic lxacid **2a(m)**

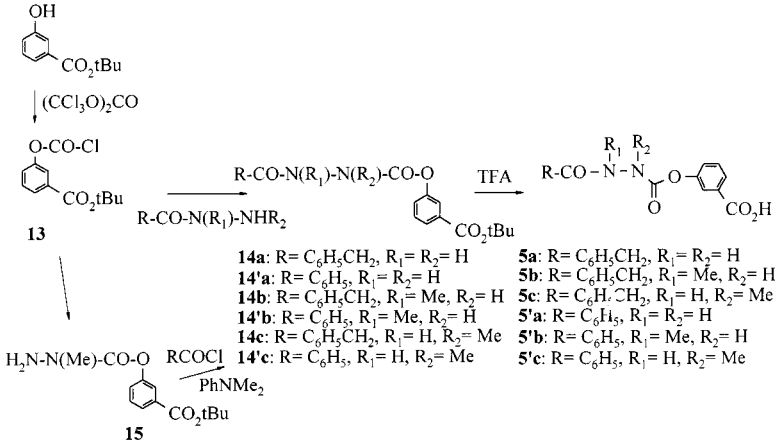
The above results made it clear that the synthesis of benzoxazinones possessing a free NH group would require the cleavage of a suitable *N*-protecting group after the formation of the oxazinone ring. While N^2-protected hydrazides are known,[15] N^1 hydrazide protecting groups have not yet been reported, to the best of our knowledge. Using the analogy with the protection of carboxamides,[16] we turned our attention towards the use of a *p*-methoxybenzyl substituent and its possible selective removal under acidic conditions. The starting methoxybenzylated hydrazide **6b′′** was prepared by nitrosation[17] of the corresponding *N*-substituted phenylacetamide **11**,[18] followed by reduction of the nitrosamide **12** by means of zinc metal in acetic acid.[19] A partial hydrogenolysis of the N−N bond was observed during this reduction step. Condensation of this hydrazide **6b′′** with substituted salicylaldehyde **7m**, as above, and reduction of the intermediate hydrazone **8b′′** (R = $CH_2C_6H_5$) yielded the substituted hydrazides **9b′′** (Scheme 3). Cyclization with carbonyldiimidazole then furnished the substituted benzoxazinone **2b′′** in good yield. Removal of the *p*-methoxybenzyl substituent in compound **2b′′**, to give the benzoxazinone **2a (m),** required treatment with methanesulfonic acid in trifluoroacetic acid; neat TFA was unable to effect the cleavage.[16b]

While the benzylic protons were nonequivalent in the NMR spectra of the series of *N*-substituted benzoxazinones **2b**, **2b′**, and **2b′′** (R′ = Me or *p*-MeO-bzl), those in the free NH benzoxazinone **2a** appeared as a singlet.

For the synthesis of the linear azadepsipeptides **5**, the 3-*tert*-butoxycarbonylphenyl chlorocarbonate **13** was prepared from the corresponding phenol[20] and triphosgene.[21] Treatment of this compound **13** with a series of free or *N*-methylated phenacetyl or benzoyl hydrazides **6b** and **6c** gave substituted hydrazides **14** (Scheme 4). However, substituted diacylhydrazine **14′c** was obtained in poor yield using this method. In this case, a better yield was obtained by first treating *N*-methylhydrazine with chlorocarbonate **13.** Acylation of carbamate **15** then smoothly afforded compounds **14′c**. Subsequent cleavage with trifluoroacetic acid



Scheme 3. Synthesis of the *N*-substituted 3-acylamino-3,4-dihydro-2-oxo-2*H*-1,3-benzoxazine-7- and -8-carboxylic acids **2b−b′′** and the free *N*H 3,4-dihydro-2-oxo-3-phenylacetamino-2*H*-1,3-benzoxazine-7-carboxylic acid **2a(m)**



Scheme 4. Synthesis of the linear azadepsipeptides **5**

of the *tert*-butyl protecting groups in the whole series of molecules **14** furnished the expected azadepsipeptides **5**.

Solution and Enzyme Studies

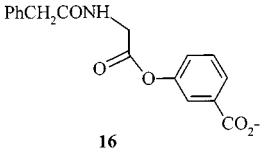
The hydrolysis of the azadepsipeptides (carbazates) in aqueous buffer was monitored spectrophotometrically (release of hydroxycarbonylphenol), and pseudo-first order rate constants were calculated from absorption vs. time data. These rate constants are reported in Table 1, along with those of the acyclic and cyclic depsipeptides **16** (Figure 2) and **1a(m)**. There are several points of interest here. Firstly, it is noticeable and surprising that **2a(m)** is more reactive than its deaza analogue **1a(m)**, conflicting with the original rationale for the preparation of the aza compounds. Similarly, **5a** is slightly more reactive than **16**. One would have expected carbazates to be several orders of magnitude less reactive to direct nucleophilic cleavage by solvent than the analogous esters. Another point, which emerges below as connected with the above, is the considerably lower reactivity of **2b(m)** relative to **2a(m)**. It is striking that the *N*-methyl group of **2b(m)**, so distant from the carbonyl group, could have such an effect on reactivity.[21]

Table 1. Rate constants for spontaneous reaction of azadepsipeptides in aqueous buffer; 0.1 M MOPS buffer, pH = 7.5, 25 °C

Compound	$k_{obs} \times 10^5$ [s^{-1}]
2a(m)	290
2b(m)	0.56
2b(o)	0.72
5a	1.68
5b	4.46
5c	3.97
5′a	6.02
5′c	6.74
1a(m)[a]	56
16[a]	1.0

[a] Ref.[2]

Both of the above phenomena can be rationalized in terms of intramolecular nucleophilic participation of the amido side chain of **2a(m)** in the hydrolysis of this compound. The alkaline hydrolysis of aryl esters of *N*-acyl am-



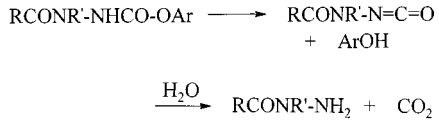
16

Figure 2. Structure of the depsipeptide **16**

ino acids is well known to involve such catalysis and thus a 5(4*H*)-oxazolone intermediate.[22,23] *N*-Methylation of the amido side chain significantly reduces the observed rates.[24] Furthermore, the alkaline hydrolysis of analogous azapeptide esters is also known to involve nucleophilic amide side chain participation and formation of 5(4*H*)-1,3,4-oxadiazolones.[7j,25,26] These latter heterocycles have been found to be quite refractory towards nucleophiles, particularly under alkaline conditions,[7e,13a,26,27] under which an inert anion is likely to form.[7e]

Accordingly, the hydrolysis of **2a(m)** was examined more closely by ^{1}H NMR spectroscopy. Approximately 1 mg of **2a(m)** was dissolved in 0.6 mL of 20 mM $NaHCO_3$ in D_2O. A ^{1}H NMR spectrum after ca. 10 min [**2a(m)** did not dissolve quickly] showed the presence of only one molecular species in solution [δ = 3.75 (s), 3.92 (s), 7.2−7.7 (m)]. No change was observed over a 4 h period. After 24 h, however, there was evidence of reaction, with the appearance of small additional peaks. This reaction was then accelerated by heating the sample at 40 °C for 4 days, at which point the reaction was almost complete. The ^{1}H NMR spectrum of the final product contained singlets at δ = 3.42 and 3.97, and an aromatic multiplet further downfield. A comparison with spectra of authentic samples under the same conditions showed that the initially observed product was the oxadiazolone **10a** and the slowly formed material was **9a**, the expected hydrolysis product. This experiment proved that the rapid reaction of **2a(m)** in neutral buffer occurs according to Scheme 5, yielding an oxadiazolone, which hydrolyses only very slowly.

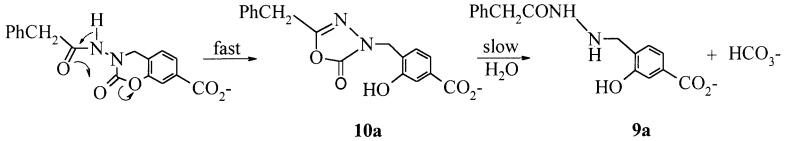
It seems possible from the hydrolysis rates that **5a** also hydrolyses by such a mechanism. The reactivity of **5b**, however, suggests that the alternative mechanism of Scheme 6 might also contribute in these acyclic compounds.[7f,7j,28] The greater rate of hydrolysis of **2a(m)** relative to that of **5c** presumably reflects the greater reactivity of the (*cis*) 6-membered ring carbamate over that of the acyclic (trans) species. The greater reactivity of **2(a)m** over **1a(m)** (and **5a** over **16**), despite the fact that the former is a carbazate, must reflect the more facile intramolecular participation of the side chain in the former case. This may be a consequence of the greater stability of the oxadiazolone generated from the former compound relative to that of the oxazolone from the latter.



Scheme 6. Dissociative mechanism for the hydrolysis of the linear azadepsipeptide **5b**

Within the constraints dictated by their lifetimes in aqueous buffer at pH 7.5 (Table 1), none of the carbamates appeared to be either a substrate or an inhibitor of the class C *Enterobacter cloacae* P99 β-lactamase or the class A TEM β-lactamase. Compound **2a(m)** also had no effect on the activity of the *Streptomyces* R61 DD-peptidase. The spontaneous reaction rate of **2a(m)** was smaller at lower pH; e.g., the pseudo-first order rate constant for disappearance of **2a(m)** at pH 6.5 (20 mM, MES) was 4.1×10^{-4}s^{-1}. Despite its reduced lability at this pH, **2a(m)** was neither a substrate nor an inhibitor of the P99 β-lactamase under these conditions.

Although the depsipeptides **1a(m)** and **16** have been shown to be substrates of class A and C β-lactamases,[2,3,29] their aza analogs **2a(m)** and **5** showed no sign of interaction with the active sites of these enzymes, nor with that of the *Streptomyces* R61 DD-peptidase. Thus, the better leaving group present in **5** did not appear to improve the reactivity of these compounds with the β-lactamases, relative to those compounds previously examined.[8] One reason for this negative result could still be the intrinsically much smaller carbonyl electrophilicity of these compounds (carbazates) relative to that of their deaza analogs (esters); this difference is perhaps indicated most directly by comparison of the hydrolysis rate of **2b(m)** with that of **1a(m)** (Table 1). A similar difference in the reactivities of azapeptide and peptide nitrophenyl esters towards the nucleophile hydroxylamine has been reported.[7i] Certainly, peptides are much poorer β-lactamase substrates than are the analogous esters.[30,31] This is not true of the R61 DD-peptidase, however, with which amides and esters are comparable as substrates.[30] In this case, subtle features of molecular shape must account for the low reactivity of **1a(m)**,[2] and now **2a** and **5**, with the enzyme. The lack of reactivity of **5a** and **5c** with the DD-peptidase, contrasting with the reactivity of **16** and its D-alanine analog,[30] must also reflect such differences. In particular, the probably close to planar arrangement of the α-nitrogen atom, in contrast with the tetrahedral carbon geometry of a substrate or inhibitor (β-lactam) at this position, is likely to be important. AMI calculations indicated that the sum of angles about the carbamate nitro-



10a **9a**

Scheme 5. Mechanism of hydrolysis of the 3,4-dihydro-2-oxo-3-phenylacetamino-2*H*-1,3-benzoxazine-7-carboxylic acid **2a(m)**: participation of the amide side chain, leading to a relatively stable 5(4*H*)-1,3,4-oxadiazolone **10a** intermediate

gen atom in the lowest energy conformation of **2a(m)** was 348°. A close to planar α-nitrogen atom has been observed in other carbazates, both free[32] and enzyme-bound.[7h]

Unlike serine proteases, serine β-lactamases and DD-peptidases seem unable to cope at all with aza(depsi)peptides. Acylation of the active site of the former enzymes does occur although deacylation is slow. In contrast, the latter enzymes are not acylated by these compounds. Beyond the factors mentioned above, this result may reflect stringent selection by β-lactamases and DD-peptidases, against and for − respectively − a D-methyl substituent at the position α to the carbonyl group.[30]

Experimental Section

The sources of the enzymes employed, and the analytical and kinetic methods used, were essentially as described earlier.[2] Azadepsipeptide concentrations of up to 1 mM were employed in the experiments designed to test for enzyme inhibition. − Melting points were determined with a Mettler FP61 and are uncorrected. − ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC300 instrument, at 300 MHz and 75.5 MHz, respectively. Chemical shifts are reported in ppm; internal standard was tetramethylsilane. − TLC was carried out on Merck 60F-254 precoated silica gel plates (0.25 mm) and column chromatography was performed with Merck silica gel (70−230 mesh), using various solvents as eluent. The solvents used are indicated in the procedures. Benzoylhydrazine was from Fluka, phenylacetylhydrazine and 3-formyl-2-hydroxybenzoic acid were from Acros.

Procedures

3-*tert*-Butoxycarbonylphenyl Chlorocarbonate 13: A solution of *tert*-butyl 3-hydroxybenzoate[20] (327 mg, 1.69 mmol) and dimethylaniline (225 mg, 1.69 mmol) in THF (3 mL) was added slowly with cooling to bis(trichloromethyl) carbonate (184 mg, 0.62 mmol) in THF (3 mL). The mixture was stirred at 0 °C for 10 min and then at room temperature for 3 h. The solution containing the crude 3-*tert*-butoxycarbonylphenyl chlorocarbonate **13** was used directly in the next step of the reaction sequence.

3-{[2-(Phenylacetyl)hydrazino]carbonyloxy}benzoic Acid 5a (typical procedure):[33] At 0 °C, a solution of phenylacetylhydrazine (150 mg, 1 mmol) and dimethylaniline (133 mg, 1.1 mmol) in THF (3 mL) was added with stirring to a solution of chlorocarbonate **13** obtained from 94 mg (0.5 mmol) of *tert*-butyl 3-hydroxybenzoate. The mixture was stirred for 3 h at room temperature. Then 10% HCl (10 mL) was added and the product was extracted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel (CH_2Cl_2/MeOH, 97.5:2.5) to give 151 mg (81%) of *tert*-butyl 3-{[2-(phenylacetyl)hydrazino]carbonyloxy}benzoate **14a**. − R_f = 0.28. − ^{1}H NMR ($CDCl_3$): δ = 1.56 (s, 9 H, *t*Bu), 3.58 (s, 2 H, CH_2), 7.26 (m, 5 H, Ar), 7.28 (d, J = 7.3 Hz, 1 H, H_6), 7.34 (t, J = 7.9 Hz, 1 H, H_5), 7.70 (d, J = 1.4 Hz, 1 H, H_2), 7.83 (dd, J = 6.3 and 1.4 Hz, 1 H, H_4), 7.85 (s, 1 H, NH), 8.23 (s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 28.1 (*t*Bu), 41.1 (CH_2), 81.6 (*t*Bu), 122.4 to 133.6 (Ar), 150.3 (Ar−O), 154.6, 164.8 and 171.2 (CO).

This diacylated hydrazine **14a** was next dissolved in dichloromethane (1 mL) and the solution cooled to 0 °C. Trifluoroacetic acid (0.5 mL) was added and the mixture was stirred for 3 h at room temperature. The solvents were removed by evaporation to give, quantitatively, the corresponding acid **5a**, which was recrystallized from methanol-dichloromethane, m.p. 199 °C. − R_f = 0.41 (CH_2Cl_2/MeOH, 8:2). − ^{1}H NMR ([D$_4$] methanol): δ = 3.58 (s, 2 H, CH_2), 7.24 to 7.49 (m, 7 H, Ar), 7.80 (s, 1 H, H_2), 7.89 (d, J = 7.6 Hz, 1 H, H_4). − ^{13}C NMR ([D$_4$]methanol): δ = 40.0 (CH_2), 122.4 to 134.4 (Ar), 150.7 (Ar−O), 155.0, 167.3 and 172.1 (CO). − $C_{16}H_{14}N_2O_5$ (314.3): calcd. C 61.14, H 4.49, N 8.91; found C 60.81, H 4.75, N 8.77.

3-{[2-Methyl-2-(phenylacetyl)hydrazino]carbonyloxy}benzoic Acid (5b): Treatment of 1-methyl-1-phenylacetylhydrazine[14b] (164 mg, 1 mmol) with 3-(*tert*-butoxycarbonyl)phenyl chlorocarbonate **13** as above gave a product which was chromatographed on silica gel (pentane/ethyl acetate, 1:1) to give *tert*-butyl 3-{[2-methyl-2-(phenylacetyl)hydrazino]carbonyloxy}benzoate **14b**: 157 mg (82%). − R_f = 0.55. − ^{1}H NMR ($CDCl_3$): δ = (2 isomers, *Z* and *E*) 1.58 and 1.60 (2s, 9 H, *t*Bu), 3.17 (s, 3 H, NCH_3), 3.57 and 3.76 (2s, 2 H, CH_2), 7.23 to 7.32 (m, 7 H, Ar), 7.74 to 7.89 (m, 2 H, H_2 and H_4), 8.36 and 8.43 (2s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 28.3 (*t*Bu), 35.8 and 36.5 (NCH_3), 40.1 and 40.5 (CH_2), 81.9 (*t*Bu), 122.4 to 134.6 (Ar), 150.3 and 151.1 (Ar−O), 153.2−153.7, 164.9 and 173.6−173.9 (CO).

The *tert*-butyl ester function of this diacylated hydrazine **14b** was quantitatively cleaved as above with trifluoroacetic acid. The product was purified by chromatography (CH_2Cl_2/MeOH, 85:15) to give the crystalline acid **5b**, m.p. 137 °C. − R_f = 0.58. − ^{1}H NMR ([D$_4$]methanol): δ = 3.37 (s, 3 H, NCH_3), 3.97 (s, 2 H, CH_2), 7.44 to 7.96 (m, 8 H, Ar). − ^{13}C NMR ([D$_4$]methanol): δ = 36.0 (NCH_3), 40.8 (CH_2), 123.9 to 136.0 (Ar), 152.1−152.6 (Ar−O), 155.5−156.2, 168.8 and 175.8−176.2 (CO). − $C_{17}H_{16}N_2O_5$ (328.3): calcd. C 62.18, H 4.91, N 8.53; found C 62.44, H 5.26, N 8.70.

3-{[1-Methyl-2-(phenylacetyl)hydrazino]carbonyloxy}benzoic Acid (5c): The same experimental procedure was used with 1-methyl-2-phenylacetylhydrazine[14b] (164 mg, 1 mmol). The product was chromatographed on silica gel (pentane/ethyl acetate, 1:1) to give *tert*-butyl 3-{[1-methyl-2-(phenylacetyl)hydrazino]carbonyloxy}-benzoate **14c**: 127 mg (66%). − R_f = 0.58. − ^{1}H NMR ($CDCl_3$): δ = (2 isomers, *Z* and *E*) 1.58 (s, 9 H, *t*Bu), 3.18 and 3.33 (2s, 3 H, NCH_3), 3.59 (s, 2 H, CH_2), 7.26 to 7.28 (m, 6 H, Ar), 7.36 (t, J = 7.9 Hz, 1 H, H_5), 7.64 and 7.72 (2s, 1 H, H_2), 7.84 (d, J = 7.4 Hz, 1 H, H_4), 7.93 and 8.07 (2s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 28.1 (*t*Bu), 37.7 and 38.6 (NCH_3), 41.4 (CH_2), 81.5 (*t*Bu), 121.5 to 133.7 (Ar), 150.7 and 150.9 (Ar−O), 154.5, 164.8−164.9 and 169.7−170.2 (CO).

The *tert*-butyl ester function of compound **14c** was then cleaved with trifluoroacetic acid to give the crystalline title acid **5c**, m.p. 162 °C. − R_f 0.63 (CH_2Cl_2/MeOH, 8:2). − ^{1}H NMR ([D$_4$] methanol): δ = 3.18 and 3.31 (2s, 3 H, NCH_3), 3.57 (s, 2 H, CH_2), 7.22 to 7.34 (m, 6 H, Ar), 7.43 (t, J = 8.0 Hz, 1 H, H_5), 7.65 and 7.81 (2s, 1 H, H_2), 7.87 (d, J = 7.7 Hz, 1 H, H_4). − ^{13}C NMR ([D$_4$] methanol): δ = δ 35.1 and 36.1 (NCH_3), 38.7 and 38.9 (CH_2), 121.2 to 133.1 (Ar), 149.8 (Ar−O), 153.3−153.4, 166.0 and 170.1−170.2 (CO). − $C_{17}H_{16}N_2O_5$ (328.3): calcd. C 62.18, H 4.91, N 8.53; found C 61.96, H 5.15, N 8.33.

3-{[2-(Benzoyl)hydrazino]carbonyloxy}benzoic Acid (5′a): Benzoylhydrazine (163 mg, 1.2 mmol) was treated with 3-*tert*-butoxycarbonylphenyl chlorocarbonate **13** (0.6 mmol). The product was chromatographed on silica gel (dichloromethane/methanol, 95:5) to give 169 mg (79%) of *tert*-butyl 3-{[2-(benzoyl)hydrazino]carbonyloxy}benzoate **14′a**. − R_f 0.68. − ^{1}H NMR ($CDCl_3$): δ = 1.56 (s, 9 H, *t*Bu), 7.20 to 7.50 (m, 5 H, Ar), 7.77 to 7.86 (m, 4 H, Ar), 8.32 (s, 1 H, NH), 9.24 (s, 1 H, NH). −

^{13}C NMR ($CDCl_3$): δ = 28.1 (*t*Bu), 81.6 (*t*Bu), 123.8 to 133.4 (Ar), 150.5 (Ar−O), 155.4, 164.9 and 167.6 (CO).

The *tert*-butyl ester function of compound **14′a** was cleaved with trifluoroacetic acid to give the title acid **5′a**, which was recrystallized from methanol, m.p. 193 °C. − R_f = 0.29 (CH_2Cl_2/MeOH/AcOH, 90:10:1). − ^{1}H NMR ([D$_4$]methanol): δ = 7.27 to 7.41 (m, 5 H, Ar), 7.48 to 7.51 (m, 4 H, Ar). − ^{13}C NMR ([D$_4$]methanol): δ = 123.8 to 133.4 (Ar), 152.1 (Ar−O), 156.5, 168.8 and 169.7 (CO). − $C_{15}H_{12}N_2O_5$ (300.3): calcd. C 59.99, H 4.03, N 9.33; found C 59.85, H 4.04, N 9.43.

3-[(2-Benzoyl-2-methylhydrazino)carbonyloxy]benzoic Acid (5′b): As above, 1-methyl-1-benzoylhydrazine[14a] (261 mg, 1.74 mmol) was treated with 3-(*tert*-butoxycarbonyl)phenyl chlorocarbonate **13** (0.87 mmol). The product was chromatographed on silica gel (pentane/ethyl acetate, 1:1) to give *tert*-butyl 3-[(2-benzoyl-2-methylhydrazino)carbonyloxy]benzoate **14′b**: 232 mg (72%), m.p. 51 °C. − R_f = 0.64 (dichloromethane/methanol, 1:1). − ^{1}H NMR ($CDCl_3$): δ = 1.56 (s, 9 H, *t*Bu), 3.26 (s, 3 H, CH_3), 7.27 to 7.81 (m, 9 H, Ar), 8.93 (s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 28.1 (*t*Bu), 81.6 (*t*Bu), 122.2 to 134.5 (Ar), 150.2 (Ar−O), 153.5, 164.9, and 171.5 (CO).

Then, the *tert*-butyl ester function of compound **14′b** was cleaved with trifluoroacetic acid as above to give the crystalline title acid **5′b**, m.p. 164 °C. − R_f = 0.49 (CH_2Cl_2/MeOH/AcOH, 90:10:1). − ^{1}H NMR ([D$_4$]methanol): δ = 3.32 (s, 3 H, CH_3), 7.42 to 7.55 (m, 8 H, Ar), 7.86 (d, *J* = 7.5 Hz, 1 H, H_4). − ^{13}C NMR ([D$_4$] methanol): δ = 36.8 (CH_3), 123.7 to 136.1 (Ar), 152.1 (Ar−O), 155.5, 168.7 and 175.8 (CO). − $C_{16}H_{14}N_2O_5$ (314.3): calcd. C 61.14, H 4.49, N 8.91; found C 61.24, H 4.27, N 8.57.

3-[(2-Benzoyl-1-methylhydrazino)carbonyloxy]benzoic Acid 5′c: Firstly, 1-[3-(*tert*-butoxycarbonyl)phenoxycarbonyl]-1-methylhydrazine **15** was prepared by a slow addition of a solution of methylhydrazine (190 mg, 4.12 mmol) in dichloromethane (2 mL) to 3-*tert*-butoxycarbonylphenyl chlorocarbonate **13** (1.03 mmol) in dichloromethane (4 mL). The reaction mixture was stirred for 3 h at room temperature, then washed with water and dried (Na_2SO_4). Evaporation of the solvent and chromatography on silica gel (pentane/ethyl acetate, 6:4) gave product **15**, 183 mg (67%). − R_f = 0.27. − ^{1}H NMR ($CDCl_3$): δ = 1.57 (s, 9 H, *t*Bu), 3.29 (s, 3 H, CH_3), 4.30 (s, 2 H, NH_2), 7.28 (dt, *J* = 7.9 and 1.8 Hz, 1 H, H_6), 7.41 (t, *J* = 7.9 Hz, 1 H, H_5), 7.70 (t, *J* = 1.8 Hz, 1 H, H_2), 7.85 (dt, *J* = 7.7 and 1.7 Hz, 1H, H_4).

Secondly, this hydrazide **15** (183 mg, 0.69 mmol) was dissolved in dichloromethane (3 mL). Then, dimethylaniline (92 mg, 0.76 mmol) and benzoyl chloride (107 mg, 0.76 mmol) in dichloromethane (3 mL) were added. The mixture was stirred for 18 h at room temperature. 10% HCl (10 mL) was added and the product extracted with dichloromethane (20 mL). The organic layer was washed with a $NaHCO_3$ solution, then dried (Na_2SO_4). Evaporation and chromatography on silica gel (pentane/ethyl acetate, 7:3) gave *tert*-butyl 3-[(2-benzoyl-1-methylhydrazino)carbonyloxy]benzoate **14′c**, 160 mg (74%), m.p. 54 °C. − R_f = 0.51. − ^{1}H NMR ($CDCl_3$): δ = (2 isomers, *Z* and *E*) 1.56 and 1.58 (2s, 9 H, *t*Bu), 3.31 and 3.47 (2s, 3 H, NCH_3), 7.24 to 7.87 (m, 9 H, Ar), 8.90 and 9.05 (2s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 28.1 (*t*Bu), 37.8 and 38.8 (NCH_3), 81.6 (*t*Bu), 122.5 to 133.5 (Ar), 150.8 and 151.0 (Ar−O), 155.1, 164.8−165.0, and 166.3−166.6 (CO).

Finally, the *tert*-butyl ester group of compound **14′c** was cleaved with trifluoroacetic acid to give the title acid **5′c**, which was recrystallized from dichloromethane, m.p. 172 °C. − R_f = 0.43 (CH_2Cl_2/MeOH, 9:1). − ^{1}H NMR ([D$_4$]methanol): δ = 3.28 and 3.43 (2s, 3 H, NCH_3), 7.27 to 7.86 (m, 9 H, Ar). − ^{13}C NMR ([D$_4$]methanol): δ = δ 37.7 and 38.7 (NCH_3), 123.3 to 132.7 (Ar), 155.0 and 155.3 (Ar−O), 150.7−150.9, 167.1−167.3 and 170.0 (CO). − $C_{16}H_{14}N_2O_5 \cdot 1/3\ H_2O$ (320.3): calcd. C 60.00, H 4.42, N 8.75; found C 60.04, H 4.37, N 8.76.

3-Hydroxy-4-{[2-(phenylacetyl)hydrazino]methyl}benzoic Acid 9a(m) (typical procedure): A solution of 4-formyl-3-hydroxybenzoic acid **7m**[12a,12b] (166 mg. 1 mmol) and phenylacetylhydrazine **6a** (164 mg, 1.2 mmol) in methanol (25 mL) was refluxed for 16 h. The reaction mixture was cooled and the crystalline product was collected. After drying, 3-hydroxy-4-{[2-(phenylacetyl)hydrazono]methyl}benzoic acid **8a(m)** was obtained: 232 mg (78%), m.p. > 300 °C. − R_f = 0.59 (CH_2Cl_2/MeOH/AcOH, 90:10:1). − ^{1}H NMR ([D$_4$]methanol): δ = (2 isomers, *Z* and *E*) 3.64 and 4.03 (2s, 2 H, CH_2), 7.25 to 7.57 (m, 8 H, Ar), 8.26 and 8.39 (2s, 1 H, HC=N). − ^{13}C NMR ([D$_6$]-DMSO): δ = 41.2 (CH_2), 116.9 to 144.8 (Ar and C=N), 156.1 and 156.9 (Ar−O), 166.7, 166.9, 167.1, and 172.4 (CO).

To a solution of this hydrazone **8a(m)** (95 mg, 0.32 mmol) in ethanol (10 mL) was added sodium cyanoborohydride (37.7 mg 0.6 mmol), and the reaction mixture was stirred for 18 h. The solution was acidified to pH ≈ 3 by addition of trifluoroacetic acid and stirred at room temperature for a further 18 h. The solvent was evaporated and excess hydride was destroyed by addition of 10% HCl (10 mL). A precipitate was removed by filtration and the filtrate was evaporated to dryness. The residue was purified by chromatography (CH_2Cl_2/MeOH/AcOH, 90:10:1) to give the title acid **9a(m)** as a white solid, 68 mg (68%), m.p. > 300 °C. − R_f = 0.49. − ^{1}H NMR ([D$_4$]methanol): δ = 3.40 (s, 2 H, CH_2), 3.99 (s, 2 H, CH_2N), 7.13 to 7.43 (m, 8 H, Ar). − ^{13}C NMR ([D$_6$]DMSO): δ = 40.4 (CH_2), 50.1 (CH_2N), 115.5 to 136.0 (Ar), 155.6 (Ar−O), 167.5 and 169.1 (CO). − $C_{16}H_{16}N_2O_4 \cdot 1/2\ H_2O$ (309.3): calcd. C 62.12, H 5.54, N 9.06; found C 61.96, H 5.41 N 8.96.

3-Hydroxy-4-(2-Oxo-5-benzyl-3*H*-1,3,4-oxadiazol-3-yl)benzoic Acid (10a): 3-Hydroxy-4-{[2-(phenylacetyl)hydrazino]methyl}benzoic acid **9a(m)** (81 mg, 0.27 mmol) was dissolved in anhydrous tetrahydrofuran (25 mL). The solution was cooled to 0 °C before the addition of triethylamine (0.11 mL, 0.7 mmol) and bis(trichloromethyl) carbonate (54 mg, 0. 18 mmol). The reaction mixture was stirred for 24 h at room temperature; then the solvent was evaporated. The residue was dissolved in ethyl acetate, washed with 10% HCl, and dried. Evaporation of the solvent gave the title oxadiazolone **10a**, 82 mg (94%), m.p. 190 °C. − R_f = 0.48 (CH_2Cl_2/MeOH/AcOH, 95:5:1). − ^{1}H NMR ([D$_6$]acetone): δ = 3.90 (s, 2 H, CH_2), 4.88 (s, 2 H, CH_2N), 7.25 to 7.59 (m, 8 H, Ar). − ^{13}C NMR ([D$_6$] acetone): δ = 33.1 (CH_2), 44.9 (CH_2N), 116.7 to 134.7 (Ar), 154.6 (Ar−O), 155.7, 155.9 and 167.2 (CO). − $C_{17}H_{14}N_2O_5 \cdot 1/2\ H_2O$ (335.3): calcd. C 61.07, H 4.52, N 8.38; found C 61.35, H 4.53, N 8.31.

3-Hydroxy-4-{[2-methyl-2-(phenylacetyl)hydrazino]methyl}benzoic Acid 9b(m): A solution of 4-formyl-3-hydroxybenzoic acid (83 mg, 0.5. mmol) and *N*-methyl-*N*-phenylacetylhydrazine (98 mg, 0.6 mmol) in methanol (25 mL) was refluxed for 18 h to give 98 mg (63%) of the 3-hydroxy-4-{[2-methyl-2-(phenylacetyl)hydrazono]methyl}benzoic acid **8b(m)**. − R_f = 0.61 (CH_2Cl_2/MeOH/AcOH, 90:10:1). − ^{1}H NMR ($CDCl_3$ + ε [D$_4$]methanol): δ = 3.39 (s, 3 H, CH_3), 4.06 (s, 2 H, CH_2Ph), 7.20−7.50 (m, 8 H, Ar), 7.89 (s, 1 H, HC=N). − ^{13}C NMR ($CDCl_3$+ ε [D$_4$]methanol): δ = 27.8 (CH_3), 40.1 (CH_2Ph), 117.6 to 134.1 (Ar), 140.9 (C=N), 156.4 (Ar−O), 168.0 and 172.4 (CO).

Then, this hydrazone **8b(m)** (65 mg, 0.2 mmol) was reduced with sodium cyanoborohydride (25 mg, 0.4 mmol) as above. Purification

by chromatography gave 45 mg (68%) of the title substituted hydrazine **9b(m)** as a white solid, m.p. 210 °C. – R_f = 0.47 (CH_2Cl_2/MeOH/AcOH, 90:10:1). – ^{1}H NMR ([D$_4$]methanol): δ = (2 isomers *Z* and *E*) 3.16–3.17 (2s, 3 H, CH_3), 3.69–3.76 (2s, 2 H, $ArCH_2$), 3.97–4.02 (2s, 2 H, CH_2Ph), 7.12–7.58 (m, 8 H, Ar). – ^{13}C NMR ([D$_4$]methanol): δ = 31.9 (CH_3), 38.3 (CH_2Ph), 46.4 (CH_2N), 115.6 to 136.9 (Ar), 155.7 (Ar–O), 167.4 and 172.6 (CO). – $C_{17}H_{18}N_2O_4 \cdot 1/2\ H_2O$ (323.3): calcd. C 63.14, H 5.93, N 8.66; found C 62.96, H 5.78, N 8.63.

3-[Methyl(phenylacetyl)amino]-3,4-dihydro-2-oxo-2*H*-1,3-benzoxazine-7-carboxylic Acid 2b(m): A solution of 3-hydroxy-4-{[2-methyl-2-(phenylacetyl)hydrazino]methyl}benzoic acid **9b(m)** (62 mg, 0.20 mmol), triethylamine (0.03 mL, 0.2 mmol), and carbonyldiimidazole (42 mg, 0.4 mmol) in anhydrous THF (15 mL) was refluxed for 4 h. The solvent was evaporated and the residue dissolved in dichloromethane. The organic solution was washed with 10% HCl, then with brine. Evaporation of the dried solvent gave a product which was chromatographed to give the title benzoxazinone **2b(m)**, 40 mg (59%), m.p. 264 °C. – R_f = 0.50 (CH_2Cl_2/MeOH/AcOH, 97:3:0.5). – ^{1}H NMR ($CDCl_3$ + ε [D$_4$]methanol): δ = (2 isomers) 3.06 (s, 3 H, CH_3), 3.47 and 3.68 (2d, *J* = 15.8 Hz, 2 H, CH_2Ph), 3.62–4.64 and 4.46–4.82 (2dd, *J* = 14.3 and 14.7 Hz, 2 H, CH_2Ar), 7.73 to 7.82 (m, 8 H, Ar). – ^{13}C NMR ($CDCl_3$ + ε [D$_4$]methanol): δ = 31.3 (CH_3), 40.6 (CH_2Ph), 48.7 (CH_2Ar), 117.6 to 135.6 (Ar), 148.2 and 149.3 (Ar–O and NC=O), 166.9 and 173.6 (CO). – $C_{18}H_{16}N_2O_5 \cdot H_2O$ (358.4): calcd. C 60.33, H 5.06, N 7.82; found C 60.46, H 4.92, N 7.68.

4-[(2-Benzoyl-2-methylhydrazino)methyl]-3-hydroxybenzoic Acid 9b′(m): A solution of 4-formyl-3-hydroxybenzoic acid (250 mg, 1.5. mmol) and *N*-methyl-*N*-benzoylhydrazine (225 mg, 1.5 mmol) in methanol (25 mL) was refluxed for 16 h to give 324 mg (74%) of 4-[(2-benzoyl-2-methylhydrazono)methyl]-3-hydroxybenzoic acid **8b′(m)**. – R_f = 0.54 (CH_2Cl_2/MeOH/AcOH, 95:5:1). – ^{1}H NMR ($CDCl_3$ + ε [D$_4$]methanol): δ = 3.43 (s, 3 H, CH_3), 7.18–7.39 (m, 8 H, Ar), 7.84 (s, 1 H, HC=N). – ^{13}C NMR ($CDCl_3$ + ε [D$_4$]methanol): δ = 28.1 (CH_3), 117.8 to 134.3 (Ar), 142.1 (C=N), 156.3 (Ar–O), 167.8 and 171.6 (CO).

Then, this hydrazone **8b′(m)** (284 mg, 1.05 mmol) was reduced with sodium cyanoborohydride (125 mg, 2 mmol) as above to give 157 mg (55%) of the title hydrazine **9b′(m)** as a white solid, m.p. 191 °C. – R_f 0.28 (CH_2Cl_2/MeOH/AcOH, 95:5/1). – ^{1}H NMR ([D$_4$]methanol): δ = 3.12 (s, 3 H, CH_3), 3.98 (s, 2 H, $ArCH_2$), 6.90 to 7.58 (m, 8 H, Ar). – ^{13}C NMR ([D$_4$]methanol): δ = 32.7 (CH_3), 37.3 (CH_2N), 115.5 to 130.1 (Ar), 153.3 (Ar–O), 168.2 and 169.9 (CO). – $C_{16}H_{16}N_2O_4$ (300.3): calcd. C 63.99, H 5.37, N 9.33; found C 64.11, H 5.39, N 9.01.

3-[Benzoyl(methyl)amino]-3,4-dihydro-2-oxo-2*H*-1,3-benzoxazine-7-carboxylic Acid 2b′(m): A solution of 4-[(2-benzoyl-2-methylhydrazino)methyl]-3-hydroxybenzoic acid **9b′(m)** (110 mg, 0.39 mmol), triethylamine (0.12 mL, 0.8 mmol), and carbonyldiimidazole (117 mg, 0.72 mmol) in anhydrous THF (20 mL) was refluxed for 4 h. The solvent was evaporated and the title benzoxazinone **2b′(m)** was obtained by chromatography (CH_2Cl_2/MeOH/AcOH, 97:3:0.5), 82 mg (68%), m.p. 252 °C. – R_f = 0.45. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.26 (s, 3 H, CH_3), 4.64 to 5.14 (m, 2 H, CH_2Ar), 7.30 to 7.71 (m, 8 H, Ar). – ^{13}C NMR ([D$_6$]DMSO): δ = 31.5 (CH_3), 48.8 (CH_2Ar), 116.0 to 132.0 (Ar), 147.9 and 148.6 (Ar–O and NC=O), 166.1 and 172.6 (CO). – $C_{17}H_{14}N_2O_5 \cdot 1/3\ H_2O$ (332.3): calcd. C 61.44, H 4.42, N 8.42; found C 61.48, H 4.48, N 8.23.

2-Hydroxy-3-{[2-methyl-2-(phenylacetyl)hydrazino]methyl}benzoic Acid 9b(o): A solution of 3-formyl-2-hydroxybenzoic acid (200 mg, 1.2 mmol), *N*-methyl-*N*-phenylacetylhydrazine (164 mg, 1.2 mmol), and triethylamine (0.17 mL, 1.22 mmol) in methanol (25 mL) was refluxed for 18 h to give 395 mg (79%) of the triethylammonium salt of the 2-hydroxy-3-{[2-methyl-2-(phenylacetyl)hydrazono]methyl}benzoic acid **8b(o)**, m.p. 152 °C. – R_f = 0.50 (CH_2Cl_2/MeOH/AcOH, 90:10:1). – ^{1}H NMR ([D$_4$]methanol): δ = 1.28 (s, 9 H, CH_3), 3.16 (s, 6 H, CH_2N^+), 3.37 (s, 3 H, CH_3), 4.21 (s, 2 H, CH_2Ph), 6.83 to 7.92 (m, 8 H, Ar), 8.26 (s, 1 H, HC=N). – ^{13}C NMR ([D$_4$]methanol): δ = 9.3 (CH_3), 28.4 (CH_3), 41.3 (CH_2Ph), 47.8 (CH_2N^+), 118.8 to 138.3 (Ar), 151.5 (Ar–O), 162.4 (C=N), 175.2 and 175.6 (CO).

Then, this hydrazone **8b(o)** (206 mg, 0.5 mmol) was reduced with sodium cyanoborohydride (38 mg, 0.6 mmol), as above. Chromatography on silica gel (CH_2Cl_2/MeOH/AcOH, 90:10:1) gave 120 mg (76%) of the title hydrazine **9b(o)** as a white solid, m.p. 153 °C. – R_f = 0.19. – ^{1}H NMR ([D$_4$]methanol): δ = 3.18 (s, 3 H, CH_3), 3.75 (s, 2 H, $ArCH_2$), 3.96 (s, 2 H, CH_2Ph), 6.87 to 7.84 (m, 8 H, Ar). – ^{13}C NMR ([D$_4$]methanol): δ = 33.4 (CH_3), 40.4 (CH_2Ph), 47.8 (CH_2N), 119.8 to 138.0 (Ar), 161.8 (Ar–O), 175.2 and 176.7 (CO). – $C_{17}H_{18}N_2O_4 \cdot 1/4\ H_2O$ (318.8): calcd. C 64.04, H 5.85, N 8.79; found C 63.92, H 5.81, N 8.87.

3,4-Dihydro-3-[methyl(phenylacetyl)amino]-2-oxo-2*H*-1,3-benzoxazine-8-carboxylic Acid 2b(o): A solution of 2-hydroxy-3-{[2-methyl-2-(phenylacetyl)hydrazino]methyl}benzoic acid **9b(o)** (121 mg, 0.39 mmol), triethylamine (0.06 mL, 0.39 mmol), and carbonyldiimidazole (132 mg, 0.81 mmol) in anhydrous THF (15 mL) was refluxed for 4 h. The title benzoxazinone **2b(o)** was purified by chromatography (CH_2Cl_2/MeOH/AcOH, 95:5:0.5), 70 mg (53%), m.p. 63 °C. – R_f = 0.44. – ^{1}H NMR ($CDCl_3$): δ = (2 isomers) 3.23 and 3.33 (2s, 3 H, CH_3), 3.64 to 3.78 (dd, *J* = 14.8 Hz, 2 H, CH_2Ph), 3.71–4.74 and 4.51–5.04 (2dd, *J* = 13.7 and 14.0 Hz, 2 H, CH_2Ar), 7.02 to 7.96 (m, 8 H, Ar). – ^{13}C NMR ($CDCl_3$): δ = 31.8 (CH_3), 40.8 and 40.9 (CH_2Ph), 48.7 and 49.1 (CH_2Ar), 118.6 to 134.3 (Ar), 148.0 and 149.0 (Ar–O and NC=O), 167.9 and 173.4 (CO). – $C_{18}H_{16}N_2O_5 \cdot 1/3\ H_2O$ (346.3): calcd. C 62.42, H 4.83, N 8.08; found C 62.41, H 4.79, N 7.78.

3-[(2-Benzoyl-2-methylhydrazino)methyl]-2-hydroxybenzoic Acid 9b′(o): A solution of 3-formyl-2-hydroxybenzoic acid (122 mg, 0.73 mmol) and *N*-methyl-*N*-benzoylhydrazine (110 mg, 0.73 mmol) was refluxed in methanol (15 mL) to give 174 mg (74%) of the 3-[(2-benzoyl-2-methylhydrazino)methyl]-2-hydroxybenzoic acid **8b′(o)**. – R_f = 0.42 (CH_2Cl_2/MeOH/AcOH, 90:10:1). – ^{1}H NMR ([D$_6$]DMSO): δ = 3.50 (s, 3 H, CH_3), 7.87–7.80 (m, 8 H, Ar), 8.13 (s, 1 H, HC=N). – ^{13}C NMR ([D$_4$] methanol): δ = 28.6 (CH_3), 114.0 to 135.5 (Ar), 147.1 (C=N), 159.7 (Ar–O), 170.0 and 171.9 (CO).

Then, this hydrazone **8b′(o)** (148 mg, 0.5 mmol) was reduced with sodium cyanoborohydride (63 mg, 1 mmol) to give 124 mg (83%) of the title hydrazine **9b′(o)** as a white solid, m.p. 168 °C. – R_f = 0.42 (CH_2Cl_2/MeOH/AcOH, 90:10:1). – ^{1}H NMR ([D$_6$]DMSO): δ = 3.19 (s, 3 H, CH_3), 3.89 (s, 2 H, $ArCH_2$), 6.73 to 7.67 (m, 8 H, Ar). – ^{13}C NMR ([D$_4$]methanol): δ = 32.9 (CH_3), 40.4 (CH_2N), 112.4 to 136.1 (Ar), 159.8 (Ar–O), 171.2 and 172.4 (CO). – $C_{16}H_{16}N_2O_4 \cdot 1/4\ H_2O$ (304.8): calcd. C 63.04, H 5.45, N 9.19; found C 63.16, H 5.29, N 9.01.

3-[(Benzoyl(methyl)amino]-3,4-dihydro-2-oxo-2*H*-1,3-benzoxazine-8-carboxylic Acid 2b′(o): A solution of 3-[(2-benzoyl-2-methylhydrazino)methyl]-2-hydroxybenzoic acid **9b′(o)** (83 mg, 0.29 mmol), triethylamine (0.07 mL, 0.29 mmol), and carbonyldiimidazole (94 mg, 0.58 mmol) in anhydrous THF (20 mL) was refluxed for 4 h. The title benzoxazinone **2b′(o)** was obtained as above, 55 mg

(66%), m.p. 179 °C. – R_f = 0.36 (CH_2Cl_2/MeOH/AcOH, 97:3:0.5). – ^{1}H NMR ([D$_4$]methanol): δ = 3.30 (s, 3 H, CH_3), 3.71 (s, 2 H, CH_2Ar), 7.12 to 7.76 (m, 8 H, Ar). – ^{13}C NMR ([D$_4$]methanol): δ = 32.3 (CH_3), 38.1 (CH_2Ar), 123.8 to 133.4 (Ar), 152.1 and 156.4 (Ar–O and NC=O), 168.8 and 169.7 (CO). – $C_{17}H_{14}N_2O_5$ (326.3): calcd. C 62.57, H 4.32, N 8.58; found C 62.32, H 4.46, N 8.44.

***N*-(4-Methoxybenzyl)phenylacetamide 11:** To a 1 N solution of sodium hydroxide (5 mL) were added, successively at 0 °C, 4-methoxybenzylamine (0.41 g, 3 mmol) and phenylacetyl chloride (0.46 g, 3 mmol). The mixture was then stirred at room temperature for 3 h. The product was extracted with dichloromethane and the organic layer dried over sodium sulfate. The solvent was evaporated and the residue purified by chromatography (pentane/AcOEt, 1:1), to give 0.56 g (73%) of the title amide **11**, m.p. 143 °C. – R_f = 0.49. – ^{1}H NMR ($CDCl_3$): δ = 3.61 (s, 2 H, CH_2), 3.79 (s, 3 H, CH_3), 4.34 (d, *J* = 5.7 Hz, 2 H, CH_2), 5.68 (s, 1 H, NH), 6.83 (d, *J* = 8.8 Hz, 2 H, Ar), 7.11 (d, *J* = 8.8 Hz, 2 H, Ar), 7.25 to 7.38 (m, 5 H, Ar). – ^{13}C NMR ($CDCl_3$): δ = 43.3 and 44.0 (CH_2Ar), 55.4 (CH_3), 114.2 to 135.0 (Ar), 159.1 (Ar–O), 171.0 (CO). – $C_{16}H_{17}NO_2$ (255.3): calcd. C 75.27, H 6.71, N 5.49; found C 75.48, H 6.74, N 5.41.

1-(4-Methoxybenzyl)-1-phenylacetylhydrazine 6b′′: In a first step, the nitroso derivative **12** was prepared in the following manner. *N*-(4-Methoxybenzyl)phenylacetamide **11** (0.7 g, 2.74 mmol) was dissolved in a mixture of acetic acid (3 mL) and acetic anhydride (18 mL). The solution was cooled to 0 °C, then sodium nitrite (1.86 g, 27 mmol) was added slowly, with stirring. The mixture was stirred for 1 h at room temperature, then poured onto ice. The product was extracted with ether and the organic layer washed with a saturated solution of sodium bicarbonate, dried over sodium sulfate and the solvent evaporated. The nitroso derivative **12** was not purified. – ^{1}H NMR ($CDCl_3$): δ = 3.75 (s, 3 H, CH_3), 4.46 (s, 2 H, CH_2), 4.83 (s, 2 H, CH_2), 6.65 to 7.42 (m, 9 H, Ar).The crude product was dissolved in ethyl acetate (5 mL); acetic acid (4 mL) and zinc dust (1.5 g) were then slowly added. After completion of the addition, the mixture was stirred for 3 h at room temperature. Excess zinc was removed by filtration and the filtrate was treated with a solution of sodium hydroxide; the alkaline solution was extracted with dichloromethane. The solvent was evaporated and the hydrazine purified by chromatography (pentane/AcOEt, 1:1), to give 0.48 g (65%) of the 1-(4-methoxybenzyl)-1-phenylacetylhydrazine **6b′′**, m.p. 122 °C. – R_f = 0.43. – ^{1}H NMR ([D$_4$]methanol): δ = 3.52 and 3.98 (2s, 2 H, CH_2), 3.76 and 3.78 (2s, 3 H, CH_3), 4.28 and 4.66 (2s, 2 H, CH_2), 6.82 to 7.30 (m, 9 H, Ar). – ^{13}C NMR ([D$_4$]methanol): δ = 40.7 (CH_2Ar), 43.9 and 44.0 (CH_2Ar′), 55.3 and 55.8 (CH_3), 115.0 to 132.0 (Ar), 160.5 and 161.0 (Ar–O), 173.9 and 176.2 (CO). – $C_{16}H_{18}N_2O_2$ (270.3): calcd. C 71.09, H 6.71, N 10.36; found C 71.25, H 6.64, N 10.48.

3-Hydroxy-4-{[2-(4-methoxybenzyl)-2-(phenylacetyl)hydrazino]-methyl}benzoic Acid 9b′′(m): A solution of 4-formyl-3-hydroxybenzoic acid **7m** (141 mg, 0.85 mmol), triethylamine 0.13 mL (0.93 mmol), and 1-(4-methoxybenzyl)-1-phenylacetylhydrazine **6b′′** (240 mg, 0.89 mmol) in methanol (15 mL) was refluxed for 16 h. The solvent was evaporated and the residue chromatographed (CH_2Cl_2/MeOH, 9:1) to give 248 mg (67%) of the 3-hydroxy-4-{[2-(4-methoxybenzyl)-2-(phenylacetyl)hydrazono]methyl}benzoic **8b′′(m)**, m.p. 234 °C. – R_f = 0.48. – ^{1}H NMR ($CDCl_3$ + ε [D$_4$]methanol]): δ = 3.77 (s, 3 H, CH_3), 4.31 (s, 2 H, CH_2), 5.26 (s, 2 H, CH_2), 6.88 to 7.78 (m, 12 H, Ar), 8.17 (s, 1 H, HC=N). – ^{13}C NMR ($CDCl_3$ + ε [D$_4$]methanol): δ = 41.48 (CH_2), 44.9 (CH_2), 55.9 (CH_3), 115.5 to 137.0 (Ar), 139.9 (C=N), 157.7 and 160.4 (Ar–O), 169.1 and 174.6 (CO).

Then, this hydrazone **8b′′(m)** (191 mg, 0.46 mmol) was reduced with sodium cyanoborohydride (50 mg, 0.8 mmol) in methanol (10 mL), at pH 3 (addition of trifluoroacetic acid). The reaction was stirred for 16 h at room temperature, the solvent evaporated, and the residue chromatographed (CH_2Cl_2/MeOH, 9:1) to give 131 mg (68%) of the title hydrazine **9b′′(m)** as a white solid, m.p. 187 °C. – R_f = 0.43. – ^{1}H NMR ([D$_4$]methanol): δ = 3.76 (s, 3 H, CH_3), 3.82 (s, 2 H, ArCH_2), 3.92 (s, 2 H, ArCH_2), 4.79 (s, 2 H, ArCH_2), 6.83 to 7.86 (m, 12 H, Ar). – ^{13}C NMR ([D$_4$]methanol): δ = 40.0 (CH_2Ar), 45.7 and 48.2 (CH_2Ar and CH_2N), 55.3 (CH_3), 114.2 to 136.1 (Ar), 155.7 and 159.2 (Ar–O), 169.0 and 174.9 (CO). – $C_{24}H_{24}N_2O_5 \cdot H_2O$ (438.5): calcd. C 65.74, H 5.97, N 6.39; found C 65.91, H 5.98, N 6.36.

3,4-Dihydro-3-[(phenylacetyl)amino]-2-oxo-2*H*-1,3-benzoxazine-7-carboxylic Acid 2a(m): A solution of 3-hydroxy-4-{[2-(4-methoxybenzyl)-2-(phenylacetyl)hydrazino]methyl}benzoic acid **9b′′(m)** (89 mg, 0.21 mmol), triethylamine (0.031 mL, 0.21 mmol), and carbonyldiimidazole (68 mg, 0.42 mmol) in anhydrous THF (5 mL) was refluxed for 4 h. Then, the solvent was evaporated and the residue dissolved in dichloromethane. The organic solution was washed with 10% HCl, then with brine. After drying, evaporation of the solvent gave a product which was chromatographed to give the 3,4-dihydro-3-[4-methoxybenzyl(phenylacetyl)amino]-2-oxobenz[*e*][1,3]oxazine-7-carboxylic acid **2b′′(m)**, 57 mg (60%), m.p. 55 °C. – R_f = 0.62 (AcOEt). – ^{1}H NMR ($CDCl_3$): δ = (2 isomers) 3.75 and 3.76 (2s, 3 H, OCH_3), 3.65 to 4.04 (m, 4 H, 2 CH_2Ar), 4.29 to 5.44 (2dd, *J* = 14.3 and 14.5 Hz, 2 H, NCH_2Ar), 6.75 to 7.51 (m, 12 H, Ar), 8.05 (s, 1 H, COOH). – ^{13}C NMR ($CDCl_3$): δ = 40.8 and 41.0 (CH_2Ph), 49.8 and 51.9 (CH_2Ar), 55.4 (CH_3), 114.4 to 133.9 (Ar), 148.5, 149.6 and 159.6 (Ar–O and NC=O), 170.1, 170.8 and 173.5 (CO).

Benzoxazinone **2b′′(m)** (30 mg, 0.67 mmol) was dissolved in TFA (0.5 mL), methanesulfonic acid (0.25 mL) was added, and the mixture was stirred for two days at room temperature. Water was added to the mixture, and the aqueous solution was saturated with NaCl and extracted with ethyl acetate. Drying over sodium sulfate and evaporation of the solvent gave a solid which was chromatographed to give the title compound **2a(m)**, 15.5 mg (71%), m.p. 180 °C. – R_f = 0.56 (AcOEt/AcOH, 99:1). – ^{1}H NMR ($CDCl_3$ + ε [D$_4$]methanol): δ = 3.67 (s, 2 H, CH_2Ar), 4.75 (s, 2 H, NCH_2Ar), 7.11 (d, *J* = 8.1, 1 H, H_5), 7.31 to 7.35 (m, 5 H, Ar), 7.64 (s, 1 H, H_2), 7.78 (d, *J* = 7.8 Hz, 1 H, H_6). – ^{13}C NMR ($CDCl_3$): δ = 40.9 (CH_2Ph), 50.7 (CH_2Ar), 117.7 to 133.7 (Ar), 148.8 and 150.3 (Ar–O and NC=O), 167.4 and 171.0 (CO). – $C_{17}H_{14}N_2O_5$ (326.3): calcd. C 62.57, H 4.32, N 8.58; found C 62.19, H 4.51, N 8.22.

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