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Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids into 2-(indol-2-carboxamido)benzoic acids and 2-indolyl-3,1-benzoxazin-4-ones and their NMR study†‡

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N-(α-ketoacyl)anthranilic acids reacted with phenylhydrazinium chloride in boiling acetic acid to afford 2-(indol-2-carboxamido)benzoic acids in good to excellent yields and 2-indolyl-3,1-benzoxazin-4-ones as by-products. The formation of the latter products could easily be suppressed by a hydrolytic workup. Alternatively, by increasing the reaction temperature and/or time, 2-indolyl-3,1-benzoxazin-4-ones can be obtained exclusively. Optimisations of the reaction conditions as well as the scope and the course of the transformations were investigated. The products were characterized by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy. The corresponding resonances were assigned on the basis of the standard 1D and gradient selected 2D NMR experiments (^{1}H–^{1}H *gs*-COSY, ^{1}H–^{13}C *gs*-HSQC, ^{1}H–^{13}C *gs*-HMBC) with ^{1}H–^{15}N *gs*-HMBC as a practical tool to determine ^{15}N NMR chemical shifts at the natural abundance level of ^{15}N isotope.

Introduction

Molecules containing indole[1] and anthranilic acid[2] scaffolds are ubiquitous in many natural products with diverse biological activities. Thus, it is not surprising that the compounds featuring both the indole and the anthranilic acid fragments are encountered in nature. Alkaloids cephalandole C and cephalinone B, isolated from the native orchid plant *Cephalanceropsis gracilis*,[3] and the alkaloids secofascaplysins, isolated from the sponge *Fascaplysinopsis reticulate*,[4] consist of the 2-(indol-2-carboxamido)benzoic acid **1** substructures, for example (Fig. 1). Derivatives of 2-(indol-2-carboxamido)benzoic acid **1** are receiving attention because of their antibacterial activities.[5] In materials sciences, the 2-(indol-2-carboxamido)benzoic acid derivatives are used as UV absorbers.[6] Compounds with indol-2-carboxamide scaffold are potent inhibitors of HIV-1 replication (Delavirdine, *Rescriptor*®)[7] and the androgen receptor binding function 3 (BF3),[8] and were identified as hydrogen-bonding organocatalysts for the ring-opening polymerization of cyclic esters.[9]

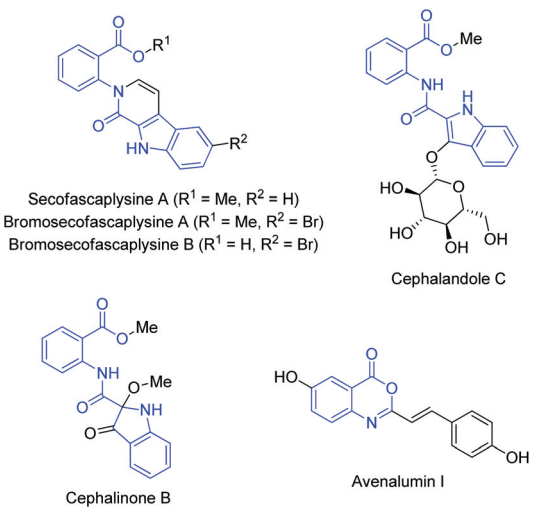

Fig. 1 Naturally occurring compounds containing 2-(indol-2-carboxamido)benzoic acid and 3,1-benzoxazin-4-one substructures (blue).

3,1-Benzoxazin-4-ones serve as valuable precursors for the preparation of fused heterocycles including an important pharmacophore, quinazolin-4-one.[10] It is also noteworthy that 3,1-benzoxazin-4-ones are potent inhibitors of the human leukocyte elastase,[11] human chymase,[12] chymotrypsin[13] and

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‡ Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c4ob01714e

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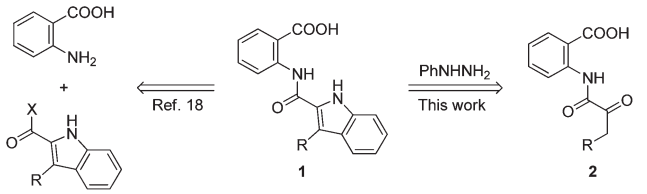


Scheme 1 Two retrosynthetic approaches to 2-(indol-2-carboxamido) benzoic acids **1**.

proteases of herpes simplex type 1,[14] human cathepsin G[15] and serine,[16] for example. Avenalumin I, phytoalexin of the 3,1-benzoxazin-4-one structure that is inhibitory to the growth of rust fungi, was isolated from oat leaves (Fig. 1).[17]

Surprisingly, despite the biological relevance and synthetic potential of 2-(indol-2-carboxamido)benzoic acids **1**, to our knowledge, the only published approach to access these compounds makes use of N-acylation of anthranilic acids with 1*H*-indol-2-carboxylic acid derivatives.[18] As an alternative to this, herein we report the protocol that is based on the Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids **2** (Scheme 1). Optimization of the reaction conditions and the scope as well as multinuclear NMR spectral analysis of the products is reported.

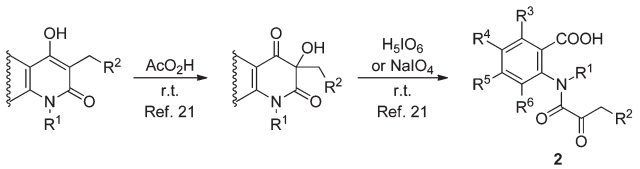
Results and discussion

Synthesis

Out of the available methods to access indoles, the Fischer indole synthesis remains one of the most important and versatile methods.[19] It is generally conducted by reacting an aryl hydrazine with a carbonyl compound.[19,20] Thus, for the construction of 2-(indol-2-carboxamido)benzoic acid **1** through this pathway *N*-(α-ketoacyl)anthranilic acid **2** appears to be the most suitable carbonyl substrate. Based on our recent report,[21] the latter is easily accessible through the consecutive oxidation protocol from 4-hydroxyquinolin-2-one as shown in Scheme 2.

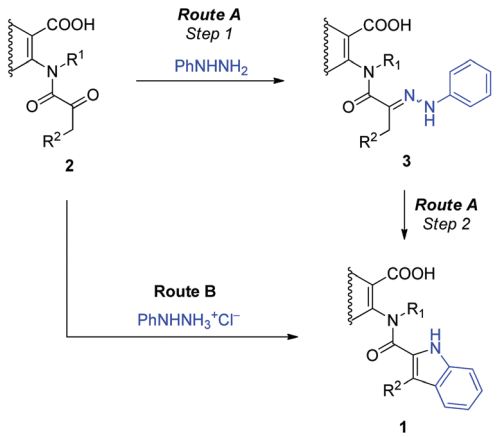
The Fischer indolisation is known to proceed through an intermediately formed hydrazone, which then undergoes several consecutive transformations. It isomerises to an enamine, which after protonation rearranges to an imine and then a cyclic aminal. Acid catalysed elimination of ammonia from the latter finally gives rise to the indole ring. The above mentioned hydrazone can in principle be pre-assembled by condensation of aryl hydrazine with an appropriate carbonyl compound. Herein, we decided to compare the stepwise protocol that proceeds through the isolated phenylhydrazone **3** (*Route A*, Scheme 3) with the direct-one in which *N*-(α-ketoacyl) anthranilic acids **2** are treated with phenylhydrazine directly into the 2-(indol-2-carboxamido)benzoic acid **1** (*Route B*).

To examine the stepwise protocol, *Route A*, phenylhydrazones **3a,c–e** were initially prepared by the condensation of *N*-(α-ketoacyl)anthranilic acids **2a,c–e** with phenylhydrazine. The isolated phenylhydrazones were in the subsequent step subjected to the thermally induced rearrangement into



2	R^1	R^2	R^3	R^4	R^5	R^6
a	H	Me	H	H	H	H
b	H	Me	H	OMe	H	H
c	H	Me	H	H	OMe	H
d	H	Me	H	H	H	OMe
e	Me	Me	H	H	H	H
f	H	*n*-Pr	H	H	H	H
g	H	Me	H	H	H	Me
h	H	Me	H	Me	H	H
i	H	Me	Me	H	H	Cl
j	H	*n*-Pr	H	Me	H	Me
k	H	*n*-Pr	H	OMe	H	OMe
l	H	Ph	H	H	H	H
m	H	*n*-Pr	H	H	–(CH)$_4$–	

Scheme 2 The preparation of the starting *N*-(α-ketoacyl)anthranilic acids **2** and the key of substituents R^1–R^6.



Scheme 3 The stepwise (*Route A*) and direct (*Route B*) routes to the 2-(indol-2-carboxamido)benzoic acids **1** by the Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids **2**.

Table 1 Results of the stepwise protocol to indoles 1 (Scheme 3, Route A)

Step 1		Step 2	
Reaction conditions	**3**, yield[a]	Reaction conditions	**1**, yield[a]
AcOH, 60 °C, 2 h	**3a**, 88	235 °C, 20 min	**1a**, 27
AcOH, 60 °C, 3 h	**3c**, 80	180 °C, 10 min	**1c**, 17
AcOH, 60 °C, 3 h	**3d**, 79	245 °C, 15 min	**1d**, 28
AcOH, 60 °C, 1.25 h	**3e**, 78	180 °C, 15 min	**1e**, 33

[a] Percent yields of isolated pure products are given.

2-(indol-2-carboxamido)benzoic acids **1a,c–e**. The results are collected in Table 1. Although the preparation of the phenylhydrazones **3a,c–e** proceeded in high 78–88% yields, the sub-

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Table 2 Solvent and catalyst screening for the Fischer indolisation of **2** into **1** following the Route B (Scheme 3)

Entry	2	Solvent[a]	Additive, reaction time in h	1	Yield[b]
1	**2a**	AcOH	None, 9	**1a**	78
2	**2a**	MeOH	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 8	**1a**	26
3	**2a**	MeCN	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 5	**1a**	65
4	**2a**	MeCN	10 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 12	**1a**	55
5	**2a**	MeCN	20 mol% $ZnCl_2$, 28	**1a**	49
6	**2a**	H_2O	130 mol% HCl, 3	**1a**	7[c]
7	**2a**	H_2O	120 mol% H_2SO_4, 2	**1a**	8[c]
8	**2a**	MeCN	2000 mol% AcOH, 22	**1a**	70
9	**2b**	MeCN	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 12	**1b**	53
10	**2b**	MeCN	10 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 19	**1b**	52
11	**2c**	MeCN	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 16	**1c**	71
12	**2d**	MeCN	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 11	**1d**	75
13	**2e**	MeCN	20 mol% $Bi(NO_3)_3{\cdot}5H_2O$, 11	**1e**	69

[a] All reactions were conducted under reflux. [b] Percent yields of isolated pure products are given. [c] Anthranilic acid was isolated as the main product in 35% (entry 6) and 26% (entry 7) yield (Experimental).

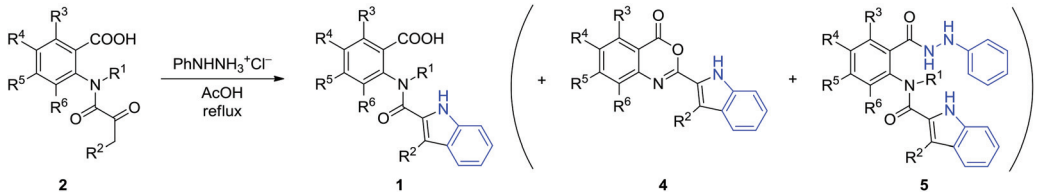
sequent indolisation step into the target 2-(indol-2-carboxamido)benzoic acids **1a,c–e** returned low 17–33% yields.

The disappointing overall results of the stepwise procedure prompted us to test the direct approach, outlined as *Route B* in Scheme 3. In screening for the optimal reaction conditions, a mixture of selected *N*-(α-ketoacyl)anthranilic acid **2** and phenylhydrazinium chloride was heated under reflux in different solvents including acetonitrile, acetic acid, methanol and water. Since Lewis[22] and Brønsted acids[23] are well known to promote the Fischer indolisation, we selected to test hydrochloric acid, sulphuric acid, acetic acid, zinc(II) chloride and bismuth(III) nitrate pentahydrate ($Bi(NO_3)_3{\cdot}5H_2O$)[24] as acid catalysts (Table 2). Good results in terms of the reaction time and the product yields were obtained for the reactions in boiling acetonitrile either in the presence of $Bi(NO_3)_3{\cdot}5H_2O$ (entries 3, 4, 9–13) or acetic acid (entry 8). However, the highest yields of the products **1** were seen by conducting the reaction in boiling acetic acid in the absence of the additives (entry 1). As expected, the heating of *N*-(α-ketoacyl)anthranilic acid **2a** in aqueous hydrochloric or sulphuric acid resulted in an amide bond hydrolysis to produce anthranilic acid (entries 6 and 7).

Having identified the optimal reaction conditions we turned to examine the scope of the reaction. Several *N*-(α-ketoacyl)anthranilic acids (**2a–l**) were allowed to react with phenylhydrazinium chloride in boiling acetic acid, which afforded the target 2-(indol-2-carboxamido)benzoic acids (**1a–l**) in good to excellent yields of the isolated products (Table 3). In few instances, the reactions were accompanied by the formation of small amounts of by-products, which were isolated and identified as 3,1-benzoxazin-4-ones **4** and phenylhydrazides **5**. The only exception to this was compound **2m**, which afforded naphthoxazinone **4m** as the sole product, with the anthranilic acid **1m** being undetected in the reaction mixture (entry 13).

In principle, the formation of 2-indolyl-3,1-benzoxazin-4-ones **4** could be realised by two different pathways as shown in Scheme 4. An initial formation of 2-acyl-3,1-benzoxazin-4-one **4′** through the *Path a* could be followed by the Fischer indolisation with phenylhydrazinium chloride. This pathway was, however, ruled out on the basis of the 3,1-benzoxazin-4-ones reactivity considerations. In the presence of nucleophiles these compounds are prone to undergo rapid ring opening into the anthranilic acid derivatives (*vide infra*) suggesting that somehow higher amounts of the phenylhydrazides **5** should

Table 3 The Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids 2 in boiling acetic acid



Entry	2	Substituents R[1]	R[2]	R[3]	R[4]	R[5]	R[6]	Reaction time (h)	Product, yield[a] 1	4	5
1	**a**	H	Me	H	H	H	H	9	78		
2	**b**	H	Me	H	OMe	H	H	14	83	5	2
3	**c**	H	Me	H	H	OMe	H	15	89		
4	**d**	H	Me	H	H	H	OMe	9	81	5	
5	**e**	Me	Me	H	H	H	H	8	91		
6	**f**	H	*n*-Pr	H	H	H	H	10	91	2	1
7	**g**	H	Me	H	H	H	Me	14	55	14	
8	**h**	H	Me	H	Me	H	H	14	76		
9	**i**	H	Me	Cl	H	H	Me	17	78	4	
10	**j**	H	*n*-Pr	H	Me	H	Me	12	51	12	
11	**k**	H	*n*-Pr	H	OMe	H	OMe	13	56	10	
12	**l**	H	Ph	H	H	H	H	19	62		
13	**m**	H	*n*-Pr	H	H	–(CH)$_4$–		9	0	87	

[a] Percent yields of isolated pure products are given.

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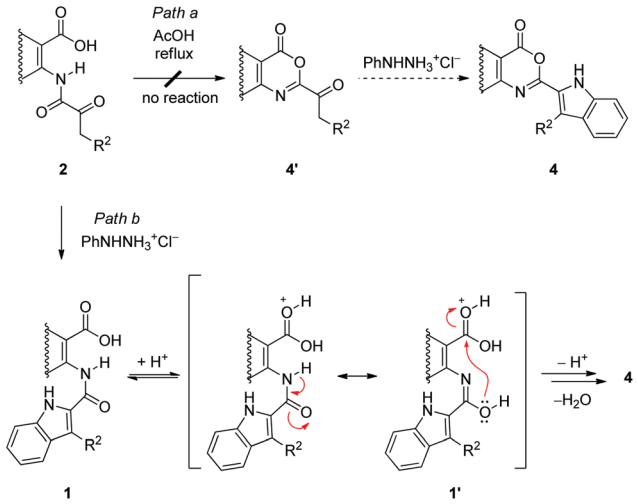


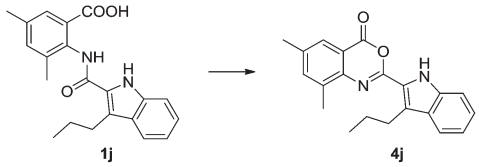
Scheme 4 The proposed formation of 3,1-benzoxazin-4-ones 4.

have been formed in the reactions shown in Table 3. The *Path a* was also ruled out experimentally by heating compound **2a** in neat acetic acid under the reflux conditions in the absence of phenylhydrazinium chloride, which resulted in no detectable formation of 2-acyl-3,1-benzoxazin-4-one **4′**. This left the *Path b*, *i.e.* the initial Fischer indolisation of the *N*-(α-ketoacyl)-anthranilic acid **2** with phenylhydrazinium chloride into 2-(indol-2-carboxamido)benzoic acid **1** and subsequent cyclodehydration into 2-indolyl-3,1-benzoxazin-4-one **4**, as the most plausible.

Generally, the 3,1-benzoxazin-4-one skeleton is formed by the reaction of anthranilic acids with an appropriate acid anhydride at the elevated temperatures.[25] Mechanistically, the amino group of the anthranilic acid is *N*-acylated and the carboxylic group is transformed into a mixed anhydride intermediate. This intermediate then undergoes an intramolecular nucleophilic displacement of the carboxylate ion from the anhydride moiety by the amide in its iminol form.[26] In turn, heating the 2-(indol-2-carboxamido)benzoic acid **1** in acetic acid is unlikely to produce mixed anhydride. Since an intramolecular nucleophilic attack of the carboxylic group to the amide is also unlikely because of the low electrophilicity of the amide, the formation of 3,1-benzoxazin-4-ones **4** could best be rationalized through the intramolecular nucleophilic attack of the iminol **1′** to the protonated carboxylic group as shown in Scheme 4. The formation of naphthoxazinone **4m** as the sole product from **2m** (Table 3, entry 13) could be accounted for by an enhanced resonance stabilisation of iminol **1m′**, the result of an extended conjugation through the naphthalene ring.

If the mechanism shown in Scheme 4 is operating, it can be expected that a prolonged reaction time and/or an elevated reaction temperature would work beneficially to the formation of 3,1-benzoxazin-4-one **4**. Indeed, by prolonging the heating of compound **1j** with phenylhydrazinium chloride in acetic acid (bp_{AcOH} = 118 °C) from 12 h to 40 h increased the yield of the expected product **4j** from 15% to 65% (compare entries 1 and 2 in Table 4). The use of the higher boiling propanoic acid

Table 4 The influence of the reaction time and temperature on transformation of 2-(indol-2-carboxamido)benzoic acid **1j** into 3,1-benzoxazin-4-one **4j**



Entry	Reaction conditions	Reaction time (h)	Yield of **4j**[a]
1	AcOH, reflux	12	12[b]
2	AcOH, reflux	40	65
3	CH_3CH_2COOH, reflux	17	72

[a] Percent yields of isolated pure products are given. [b] For comparison reasons the result is taken from Table 3, entry 10.

(bp = 141 °C) in place of acetic acid afforded the 3,1-benzoxazin-4-one **4j** in 72% yield already within 17 h (entry 3). It is noteworthy that these reaction conditions can potentially be utilized as a convenient one-pot protocol for the preparation of 3,1-benzoxazin-4-ones **4** from *N*-(α-ketoacyl)anthranilic acids **2** and aryl hydrazines. The synthetic methodologies toward 3,1-benzoxazin-4-ones, other than those utilizing anthranilic acids, have been reviewed.[27]

Minute amounts of the hydrazides **5** also accompanied the formation of 2-(indol-2-carboxamido)benzoic acids **1** (Table 3). As it is less likely that under the applied reaction conditions phenylhydrazinium chloride reacts with the carboxyl group of either the starting *N*-(α-ketoacyl)anthranilic acids **2** or the product 2-(indol-2-carboxamido)benzoic acids **1**, it is reasonable to assume that the formation of hydrazides **5** proceeds through the ring-opening at the 3,1-benzoxazin-4-ones **4**. Smooth reactivity of the 3,1-benzoxazin-4-ones towards different nucleophiles is well documented.[26,28] In our case the reactivity of compound **4f** towards phenylhydrazine to form **5f** was independently confirmed in boiling toluene as the reaction solvent (Table 5). Analogously, treatment with *n*-butylamine gave the appropriate amide **6f**.

Aqueous sodium hydroxide in DMSO mediated complete hydrolysis of 3,1-benzoxazin-4-ones **4f,j,m** to the corresponding 2-(indol-2-carboxamido)benzoic acids **1f,j,m** (Table 5). High tendency of related 3,1-benzoxazin-4-ones for hydrolysis into the corresponding anthranilic acids has been documented.[29,30] With these results in mind it can be assumed that higher quantities of the 3,1-benzoxazin-4-one products **4** are actually formed during the Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids **2** shown in Table 3 as they were actually isolated. During the isolation workup the latter most probably partly hydrolyse back into the 2-(indol-2-carboxamido)benzoic acids **1**.

The elemental composition of all the compounds under investigation was confirmed by combustion analysis and high-resolution mass spectrometry with electrospray ionization. In addition, low resolution mass spectra with electron impact

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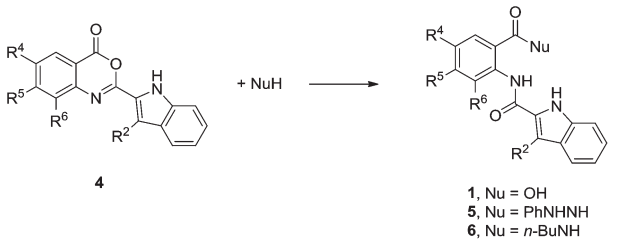
Table 5 Reaction of 3,1-benzoxazin-4-ones **4** with some nucleophiles



Entry	4	NuH	Reaction conditions, reaction time in h	Product, yield[a]
1	**4f**	$PhNHNH_2$	Toluene, reflux, 2	**5f**, 86
2	**4f**	n-$BuNH_2$	Toluene, reflux, 2	**6f**, 84%
3	**4f**	H_2O	DMSO, H_2O, NaOH, rt, 1	**1f**, 91%
4	**4f**	H_2O	dioxane, 0.1 M H_2SO_4, rt, 2	**1f**, 70%
5	**4j**	H_2O	DMSO, H_2O, NaOH, rt, 3	**1j**, 98%
6	**4m**	H_2O	DMSO, H_2O, NaOH, rt, 12	**1m**, 95%

[a] Percent yields of isolated pure products are given.

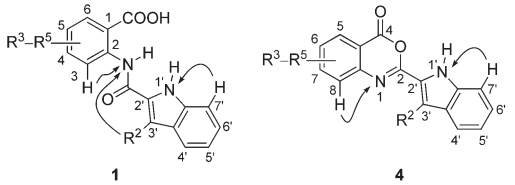


Fig. 2 Atom numbering scheme for compounds **1** and **4**. Curved arrows denote long-range ^1H–^{15}N *gs*-HMBC connectivities.

ionization and the infrared spectra were provided. In the latter, the characteristic absorption bands belonging to the indole N–H, C=O and C=N bonds were identified, where appropriate.

NMR study

The compounds **1**, **3–6** were fully characterized by ^1H, ^{13}C and ^{15}N NMR spectroscopy. The corresponding resonances were assigned on the basis of gradient-selected 2D NMR experiments including ^1H–^1H *gs*-COSY, ^1H–^{13}C *gs*-HSQC, ^1H–^{13}C *gs*-HMBC and ^1H–^{15}N *gs*-HMBC. The spectra of compounds **1**, **3**, **5** and **6** were recorded in DMSO-d_6. For 3,1-benzoxazin-4-ones **4**, which proved to rapidly hydrolyse in DMSO-d_6 into the 2-(indol-2-carboxamido)benzoic acids **1**, less polar $CDCl_3$ was identified as a suitable solvent. Acetone-d_6 was used as an alternative for dissolving compound **4k** due to its sparing solubility in $CDCl_3$. Some characteristic spectral features are discussed below. For the atom numbering scheme, see Fig. 2.

There is a wealth of ^1H and ^{13}C data[31] as well as ^{15}N NMR data[32] on indoles reported in the literature. The relatively unsubstituted indole ring in the compounds **1** and **4** enabled us to unequivocally assign all proton, carbon and nitrogen resonances *via* long-range ^1H–^{13}C and ^1H–^{15}N heteronuclear coupling pathways, which we found in agreement to those discussed in the literature.[33] For the indole ring in 2-(indol-2-carboxamido)benzoic acids **1** the order of shielding in the ^{13}C NMR spectra is C7′ > C3′ > C5′ > C4′ > C6′ > C2′ ≅ C3a′ > C7a′ (Table 6). By changing the indole C-2′ substituent from the carbamoyl group in compounds **1** into the 3,1-benzoxazin-4-one ring in **4**, the most dramatic changes in the chemical shift are seen for the carbon atoms of the fused 5-membered ring. In comparison with compounds **1**, the C2′ atoms of the indole ring in **4** are shielded by *ca.* 4 ppm, whereas the C3′ and C3a′ atoms are deshielded by *ca.* 6 ppm and *ca.* 1 ppm, respectively. By changing the R^2 = Me to the R^2 = *n*-Pr in either **1** or **4**, the carbon atom C3′ becomes more shielded for *ca.* 5–6 ppm (Tables 6 and 7).

The three-bond long-range couplings were observed in the ^1H–^{15}N *gs*-HMBC spectra from H7′ to the indole N1′ resonance in both **1** and **4** (Fig. 2). In addition, a one-bond direct NH doublet response corroborated the assignment of N1′ (Fig. 3). The chemical shifts of the N1′ atoms in indoles **1** appear at δ 130.2–136.9 ppm and are in good agreement with the literature values reported for Delavirdine.[34] In compounds **4**, the indole nitrogen atoms N1′ resonate in the narrow range of δ 120.3–121.4 ppm (Tables 6 and 7).

Systematic NMR investigations of 3,1-benzoxazin-4-ones are more scarce.[29,35] As pointed out by Osborne and Goolamali some early NMR data should be taken with care because these compounds often show high tendency for hydrolysis into the corresponding anthranilic acids, especially when measured in polar solvents such as DMSO-d_6.[29] High susceptibility towards hydrolysis has been illustrated by 2-methyl-3,1-benzoxazin-4-one that reacts with water into 2-acetylaminobenzoic acid already in the solid state.[30] Osborne and Goolamali reported an unequivocal differentiation between anthranilic acids and 3,1-benzoxazin-4-ones that was achieved through determination of characteristic J_{CH} coupling interactions in the carbonyl region of the proton coupled ^{13}C NMR spectra.[29]

Herein, the proton, carbon and nitrogen resonances belonging to the anthranilic moiety in **1** and the 3,1-benzoxazin-4-one group in **4** were rapidly assigned using the gradient-selected 2D NMR experiments. The results are collected in Tables 6 and 7. Characteristic for the downfield regions of the ^{13}C NMR spectra of the acylanthranilic acids **1** were two signals appearing at δ 160.2–161.6 ppm and δ 166.5–169.7 ppm for the amide carbonyl and for the carboxylic group, respectively. In 3,1-benzoxazin-4-one **4**, the downfield region of the spectra were occupied with three signals for C8a (δ 133.1–147.8 ppm), C2 (δ 151.0–154.3 ppm) and C4 (δ 156.2–159.7 ppm). Our results are in agreement with the literature data.[29]

Chemical shifts for the 3,1-benzoxazin-4-one nitrogen atoms in compounds **4** were in the range of δ 212.0–222.8 ppm (Table 7). Due to the lack of the ^{15}N NMR data no comparison with the literature could be done. In C8-unsubstituted 3,1-benzoxazin-4-ones **4b,c,f,h** (R^6 = H), three-bond long-range couplings were observed in the ^1H–^{15}N *gs*-HMBC spectra from H8 to the N1 resonance as illustrated in Fig. 2. The strongly electron donating C8-methoxy substituent in derivatives **4d,k**

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Table 6 ^{13}C and ^{15}N NMR chemical shifts for 2-(indol-2-carboxamido)benzoic acids **1** in ppm[a]

Atom[b]	1a	1b	1c	1d	1f	1g	1h	1i	1j	1k	1l[c]	1m[d]
C1	116.5	118.0	108.6	—[e]	116.4	126.8	116.4	—[e]	—[e]	—[e]	116.4	
C2	141.0	134.3	143.0	—[e]	140.8	136.3	138.6	—[e]	133.7	118.8	140.4	
C3	120.6	122.4	105.3	153.7	120.5	135.8	120.6	—[e]	—[e]	155.1	120.4	
C4	134.2	120.3	163.6	115.0	134.1	134.4	134.7	131.6	134.8	102.4	134.0	
C5	122.8	154.3	108.6	126.1	122.8	125.7	132.0	—[e]	—[e]	157.5	122.9	
C6	131.3	114.8	133.2	121.5	131.2	128.1	131.3	—[e]	128.3	105.1	131.1	
C3(CH_3)						18.7		17.5	18.4			
C5(CH_3)							20.2		20.2			
C3(OCH_3)				56.1						56.2		
C4(OCH_3)			55.5									
C5(OCH_3)		55.4								55.6		
C2′	128.2	128.2	128.1	127.2	127.7	127.3	128.1	126.8	126.8	—[e]	128.0	—[e]
C3′	113.3	112.9	113.4	115.2	119.3	114.6	113.1	114.6	120.2	120.6	118.5	121.2
C3a′	128.0	128.1	128.1	128.0	127.5	128.1	128.1	127.8	127.6	127.7	126.7	127.7
C4′	120.1	120.0	120.2	119.9	120.1	120.0	120.1	119.8	119.9	120.0	120.2	120.2
C5′	119.4	119.3	119.4	119.2	119.4	119.3	119.4	119.1	119.2	119.2	120.6	119.4
C6′	124.4	124.2	124.4	124.2	124.2	124.2	124.3	124.0	124.0	124.0	124.5	124.3
C7′	112.2	112.2	112.2	112.0	112.2	112.1	112.2	111.9	112.0	112.0	112.6	112.2
C7a′	136.0	135.9	136.1	135.6	136.0	135.7	136.0	135.4	135.5	135.5	136.0	135.7
C3′CH_2					25.7				26.0	26.1		
C3′CH_2CH_2					24.0				23.9	23.9		
C3′$(CH_2)_2CH_3$					13.9				14.0	14.1		
C3′CH_3	9.7	9.7	9.7	9.8		9.8	9.7	9.6				
*C*ONH	160.5	160.2	160.7	160.2	160.5	160.4	160.4	160.8	160.2	160.2	160.2	161.6
COOH	169.7	169.3	169.6	167.9	169.6	168.4	169.7	166.5	168.3	167.7	168.7	168.3
N1′	132.7	132.7	132.7	130.3	132.2	131.3	132.7	130.9	130.8	130.2	136.9	130.5
CO*N*H	126.9	125.1	127.7	116.1	126.6	122.8	126.3	120.7	121.4	113.9	129.5	—[f]

[a] In DMSO-d_6. [b] For atom numbering scheme, see Fig. 2. [c] Resonances for the C3′ phenyl ring: 132.9 ppm (C1″), 130.2 ppm (C2″, C6″), 128.7 ppm (C3″, C5″), 127.2 ppm (C4″). [d] For the complete set of resonances, see the Experimental section. [e] Could not be assigned unequivocally; for the complete list of resonances, see the Experimental section. [f] Not observed.

Table 7 ^{13}C and ^{15}N NMR chemical shifts for 3,1-benzoxazin-4-ones **4** in ppm[a]

Atom[b]	4b	4c	4d	4f	4g	4i	4j	4k[c]
C2	151.8	154.3	153.1	153.3	152.1	152.6	151.0	151.4
C4	159.3	158.7	158.9	159.0	159.6	156.2	159.7	159.6
C4a	117.1	—[d]	117.4	116.6	116.4	113.8	116.1	—[d]
C5	108.7	—[d]	120.0	128.7	126.3	133.1	125.9	100.6
C6	158.9	130.4	127.8	127.6	127.1	129.3	137.4	160.6
C7	126.1	166.3	117.1	136.6	137.4	136.8	138.7	108.0
C8	128.1	—[d]	153.8	126.6	135.5	134.5	135.3	156.7
C8a	141.4	—[d]	137.4	147.3	145.6	147.8	143.6	133.1
C6(CH_3)							17.2	
C8(CH_3)					17.3	17.7	21.2	
C6(OCH_3)	56.0							56.4
C7(OCH_3)		56.0						
C8(OCH_3)			56.4					57.0
C2′	123.4	123.3	123.5	123.0	123.4	122.9	123.2	—[d]
C3′	119.4	120.5	120.3	125.6	120.3	121.2	125.0	124.2
C3a′	129.3	129.2	129.2	128.9	129.2	129.2	128.9	129.6
C4′	120.5	120.6	120.6	120.8	120.5	120.6	120.6	121.0
C5′	120.1	120.2	120.1	120.1	120.2	120.3	120.1	120.6
C6′	125.6	125.9	125.9	125.8	125.8	126.1	125.5	125.7
C7′	111.3	111.4	111.5	111.5	111.5	111.6	111.5	113.0
C7a′	136.5	136.6	136.8	136.7	136.5	136.6	136.4	138.0
C3′CH_2				26.9			27.0	27.6
C3′CH_2CH_2				24.2			23.8	25.0
C3′$(CH_2)_2CH_3$				14.2			14.3	14.7
C3′CH_3	10.4	10.5	10.5		10.6	10.7		
N1	222.4	222.6	212.0	222.8		—[e]	—[e]	216.4
N1′	120.5	120.9	121.4	121.1	120.5	120.3	120.9	—[e]

[a] In $CDCl_3$, unless otherwise stated. [b] For atom numbering scheme, see Fig. 2. [c] In acetone-d_6. [d] Could not be unequivocally assigned. [e] Not observed.

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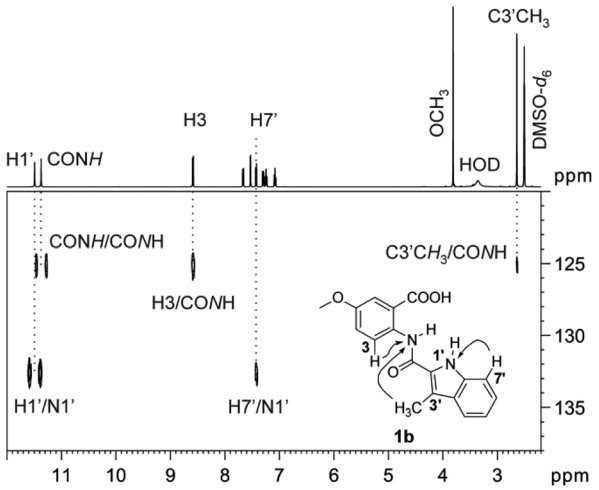

Fig. 3 $^{1}H–^{15}N$ *gs*-HMBC spectrum of 2-(indol-2-carboxamido)benzoic acid **1b** recorded in DMSO-d_6, optimized for 5 Hz long-range coupling. Direct responses for the N1′ and CO*N*H resonances were observed as doublets at 132.7 ppm and 125.1 ppm, respectively. The spectrum also features three-bond long-range response to N1′ and CO*N*H from H7′ and H3, respectively. Five-bond long-range correlation to CO*N*H from C3′CH_3 is also observed.

(R^6 = OMe) enabled a four-bond long-range couplings from H7 to the N1 whereas no such correlation could be observed in the C8-methyl substituent analogues **4g,i,j** (R^6 = Me).

The amide nitrogen atoms (CO*N*H) in acylanthranilic acids **1** resonate in the range of δ 113.9–129.5 ppm (Table 6). In analogy with the above, the cross-peaks between H3 and CO*N*H resonance were observed in $^{1}H–^{15}N$ *gs*-HMBC spectra of **1a–c,h,l**. In the 4-methoxy substituted acylanthranilic acid **1c** there was also a four-bond long-range coupling from H6 to the CO*N*H. With the exception of **1l** and **1m**, the $^{1}H–^{15}N$ *gs*-HMBC spectra also featured the one-bond direct NH doublet response. Interestingly, in 3-methylindoles **1a,b,g,h**, five-bond long-range couplings were observed in the $^{1}H–^{15}N$ *gs*-HMBC spectra from the C3′CH_3 to the amide nitrogen (CO*N*H) resonance. With the 2-(indol-2-carboxamido)benzoic acid **1b** as a representative example, the above mentioned $^{1}H–^{15}N$ *gs*-HMBC spectral features are illustrated in Fig. 3.

Conclusions

We have demonstrated that Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids can serve as a mild and highly efficient alternative for the preparation of 2-(indol-2-carboxamido) benzoic acids. By simple changes in the reaction conditions, this protocol offers a potential to access 2-indolyl-3,1-benzoxazin-4-ones. The anthranilic acid, indol-2-carboxamide and 3,1-benzoxazin-4-one structural motifs discussed herein were fully characterized by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy. The data presented will help in unequivocal identification of these classes of compounds.

Experimental section

General

The reagents and solvents were used as obtained from commercial sources. Compounds **2a–k,m** were prepared according to the literature procedure.[21] Column chromatography was carried out on Fluka Silica gel 60 (particle size 0.063–0.2 mm, activity acc. Brockmann and Schodder 2–3). Melting points were determined on the microscope hot stage, Kofler, PolyTherm, manufacturer Helmut Hund GmbH, Wetzlar and are uncorrected. TLC was carried out on pre-coated TLC sheets ALUGRAM® SIL G/UV_{254} for TLC, MACHEREY-NAGEL. NMR spectra were recorded with a Bruker Avance III 500 MHz NMR instrument operating at 500 MHz (^{1}H), 126 MHz (^{13}C) and 51 MHz (^{15}N). Proton spectra were referenced to TMS as an internal standard. Carbon chemical shifts were determined relative to the ^{13}C signal of DMSO-d_6 (39.5 ppm), $CDCl_3$ (77.0 ppm) or acetone-d_6 (high-field at 20.8 ppm). ^{15}N chemical shifts were extracted from $^{1}H–^{15}N$ *gs*-HMBC spectra (with 20 Hz digital resolution in the indirect dimension and the parameters adjusted for a long-range $^{1}H–^{15}N$ coupling constant of 5 Hz) determined with respect to external nitromethane and are corrected to external ammonia by addition of 380.5 ppm. Nitrogen chemical shifts are reported to one decimal place as measured from the spectrum; however, the data should not be considered to be more accurate than ±0.5 ppm because of the digital resolution limits of the experiment. Chemical shifts are given on the δ scale (ppm). Coupling constants (J) are given in Hz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broadened). Infrared spectra were recorded on a Mattson 3000 FTIR Spectrometer or a Thermo Scientific Nicolet iS10 FT-IR Spectrometer using samples in potassium bromide disks and only the strongest/structurally most important peaks are listed; absorption band intensities are indicated as follows: s (strong), m (medium), w (weak) or b (broad). Electron impact mass spectra (EI) were recorded on a Shimadzu QP–2010 instrument at 70 eV. HRMS spectra were recorded with the Agilent 6224 Accurate Mass TOF LC/MS system with electrospray ionization (ESI). Elemental analyses (C, H, N) were performed with the FlashEA1112 Automatic Elemental Analyzer (Thermo Fisher Scientific Inc.).

2-(2-Oxo-3-phenylpropanamido)benzoic acid (2l)

To a solution of 3-benzyl-3-hydroxyquinoline-2,4(1*H*,3*H*)-dione (669.4 mg, 2.50 mmol) in ethyl acetate (120 mL), a solution of sodium periodate (1.62 g, 7.55 mmol) in water (60 mL) was added. The two-phase reaction mixture was vigorously stirred for 7 hours at room temperature. The organic layer was separated, and extracted with 5% aqueous sodium thiosulphate (2 × 20 mL), 5% aqueous hydrochloric acid (2 × 20 mL) and finally with 5% aqueous potassium carbonate (7 × 10 mL). The potassium carbonate extract was washed with benzene (30 mL) and neutralised by addition of 10% aqueous hydrochloric acid. The resulting solution was extracted with ethyl acetate. The organic layer was separated, dried over sodium sulphate and

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concentrated *in vacuo*. The crude product was recrystallized from cyclohexane (85 mL) to give compound **2l** (424.3 mg, 60%) as colourless microcrystals, mp 179–181 °C, R_f = 0.49 (10% ethanol in chloroform), ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.32 (s, 2H), 7.23–7.37 (m, 6H), 7.67–7.72 (m, 1H), 8.07 (dd, 1H, J = 8.0, 1.6 Hz), 8.72 (d, 1H, J = 8.5 Hz), 12.39 (br s, 1H), 13.84 (br s, 1H); due to decomposition, no ^{13}C NMR spectrum could be recorded. IR (cm^{-1}): ν 3221 w, 3063 w, 3031 w, 1697 s, 1672 s, 1603 m, 1583 s, 1531 s, 1451 m, 1420 s, 1270 s, 1055 m, 755 m, 695 m; MS (EI) m/z (%): 284 (3), 283 (17, [M$^+$]), 164 (20), 146 (100), 137 (25), 118 (14), 92 (15), 91 (54), 90 (25), 65 (16); HRMS (ESI$^+$): m/z calcd for $C_{16}H_{14}NO_4^+$ [M + H]$^+$ 284.0917, found 284.0917; HRMS (ESI$^-$): m/z calcd for $C_{16}H_{12}NO_4^-$ [M − H]$^-$ 282.0772, found 282.0773. Found: C, 67.9; H, 4.6; N, 4.9. Calc. for $C_{16}H_{13}NO_4$: C, 67.8; H, 4.6; N, 4.9%.

The synthesis of phenylhydrazones (3a,c–e) (Table 1)

To a solution of an appropriate *N*-(α-ketoacyl)anthranilic acid **2** (3.0 mmol) in acetic acid (25 mL), phenylhydrazine (0.49 g, 4.5 mmol) was slowly added and the resulting solution was stirred at 60 °C until TLC analysis revealed complete consumption of the starting compound (Table 1). The reaction mixture was cooled and poured into crushed ice (200 g). For phenylhydrazones **3a,d,e**, the precipitated solid was collected by filtration and washed with water (3 × 20 mL) and cyclohexane (2 × 10 mL). For phenylhydrazone **3c** the filter cake was dried at 50 °C and recrystallized from ethyl acetate to yield **3c**·AcOH. The yields of compounds **3a,c–e** are collected in Table 1.

2-(2-(2-Phenylhydrazono)butanamido)benzoic acid (3a). Pale yellow solid, yield 822 mg (88%), mp 208–210 °C (benzene), R_f = 0.42 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.07 (t, 3H, J = 7.2 Hz, CH$_3$), 2.68–2.78 (m, 2H, CH$_2$), 6.91 (dd, 1H, J = 7.1, 7.1 Hz, H4 of phenyl), 7.14 (dd, 1H, J = 7.5, 7.5 Hz, H5), 7.30 (dd, 2H, J = 7.6, 7.6 Hz, H3 and H5 of phenyl), 7.55 (dd, 2H, J = 7.6, 7.6 Hz, H2 and H6 of phenyl), 7.59–7.64 (m, 1H, H4), 8.06 (dd, 1H, J = 1.5, 7.7 Hz, H6), 8.80 (d, 1H, J = 8.4 Hz, H3), 9.98 (s, 1H, NNH), 12.40 (s, 1H, CONH), 13.54 (br s, 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.2 (CH$_3$), 16.2 (CH$_2$), 113.7 (C2, C6 of phenyl), 115.9 (C1), 119.3 (C3), 120.7 (C4 of phenyl), 121.9 (C5), 129.0 (C3, C5 of phenyl), 131.4 (C6), 134.2 (C4), 139.5 (C=N), 141.2 (C2), 144.4 (C1 of phenyl), 163.2 (CONH), 169.4 (COOH); ^{15}N NMR (51 MHz, DMSO-d_6) δ 116.4 (CONH), 144.1 (NHPh), 327.6 (C=N); IR (cm^{-1}): ν 3287 m, 2970 w, 1665 s, 1650 s, 1604 m, 1586 m, 1577 m, 1518 s, 1496 s, 1449 m, 1241 s, 1225 s, 748 m, 694 m; MS (EI) m/z (%): 312 (8), 311 (40, [M$^+$]), 147 (11), 146 (91), 145 (16), 93 (19), 92 (55), 91 (100), 90 (18), 65 (46). Found: C, 65.6; H, 5.5; N, 13.25. Calc. for $C_{17}H_{17}N_3O_3$: C, 65.6; H, 5.5; N, 13.5%.

4-Methoxy-2-(2-(2-phenylhydrazono)butanamido)benzoic acid, acetic acid salt (3c·AcOH). Pale yellow microcrystals, yield 795 mg (66%), mp 223–226 °C (ethyl acetate), R_f = 0.66 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.06 (t, 3H, J = 7.5 Hz), 1.92 (s, 3H, CH_3CO$_2$H), 2.72 (q, 2H, J = 7.5 Hz), 3.84 (s, 3H), 6.70 (dd, 1H, J = 8.9, 2.6 Hz), 6.90 (dd, 1H, J = 7.3, 7.3 Hz), 7.28 (dd, 2H, J = 7.9, 7.9 Hz), 7.56 (d, 2H, J = 7.7 Hz), 7.99 (d, 1H, J = 8.9 Hz), 8.47 (d, 1H, J = 2.6 Hz), 9.99 (s, 1H), 12.54 (br s, 1H), 12.57 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.2, 16.2, 21.1 (*C*H$_3$CO$_2$H), 55.4, 103.9, 108.1, 108.4, 113.8, 120.7, 129.0, 133.2, 139.5, 143.2, 144.4, 163.4, 163.6, 169.3, 172.0 (CH$_3$*C*O$_2$H); IR (cm^{-1}): ν 2971 w, 2937 w, 1694 m, 1603 s, 1585 s, 1494 s, 1462 m, 1231 s, 1059 m, 751 m, 751 m, 692 w. Found: C, 59.6; H 5.7; N, 10.8. Calc. for $C_{20}H_{23}N_3O_6$: C, 59.8; H, 5.8; N, 10.5%.

3-Methoxy-2-(2-(2-phenylhydrazono)butanamido)benzoic acid (3d). Colourless crystals, yield 809 mg (79%), mp 210–212 °C (ethyl acetate), R_f = 0.52 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.02 (t, 3H, J = 7.5 Hz), 2.65 (q, 2H, J = 7.5 Hz), 3.85 (s, 3H), 6.86–6.91 (m, 1H), 7.22–7.40 (m, 7H), 9.69 (br s, 1H), 9.97 (br s, 1H), 12.82 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.2, 16.4, 56.2, 113.5, 114.8, 120.5, 121.3, 125.0, 126.1, 127.3, 129.1, 139.3, 144.5, 153.0, 162.0, 168.2; IR (cm^{-1}): ν 3334 w, 3303 m, 3249 m, 2967 m, 1695 s, 1650 s, 1603 s, 1583 s, 1493 s, 1461 s, 1277 s, 1261 s, 1232 s, 1056 s, 748 m, 691 m; MS (EI) m/z (%): 341 (1, [M]$^+$), 167 (78), 134 (54), 121 (73), 119 (59), 106 (59), 93 (76), 92 (64), 91 (100), 77 (73), 43 (74); HRMS (ESI$^+$): m/z calcd for $C_{18}H_{20}N_3O_4^+$ [M + H]$^+$ 342.1448, found 342.1450; HRMS (ESI$^-$): m/z calcd for $C_{18}H_{18}N_3O_4^-$ [M − H]$^-$ 340.1303, found 340.1303. Found: C, 63.15; H, 5.6; N, 12.15. Calc. for $C_{18}H_{19}N_3O_4$: C, 63.3; H, 5.6; N, 12.3%.

2-(*N*-Methyl-2-(2-phenylhydrazono)butanamido)benzoic acid (3e). Pale yellow microneedles, yield 761 mg (78%), mp 173–178 °C (ethyl acetate–benzene), R_f = 0.73 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.02 (t, 3H, J = 5 Hz), 2.37–2.52 (m, 2H, CH$_2$), 3.23 (s, 3H), 6.49 (d, 2H, J = 10 Hz), 6.67 (dd, 1H, J = 7.5, 7.5 Hz), 7.01 (dd, 2H, J = 7.5, 7.5 Hz), 7.28 (dd, 1H, J = 7.5, 7.5 Hz), 7.45 (d, 1H, J = 7.5 Hz), 7.63 (ddd, 1H, J = 7.7, 7.7, 1.6 Hz), 7.76 (d, 1H, J = 10 Hz), 9.15 (br s, 1H), 12.94 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.0, 18.8, 38.4, 112.9, 119.5, 126.3, 127.8, 128.4, 129.3, 131.0, 132.8, 139.9, 144.5, 146.0, 166.5, 166.8; IR (cm^{-1}): ν 3326 m, 1707 s, 1619 s, 1598 s, 1577 s, 1454 m, 1392 m, 1256 s, 1203 m, 760 m, 747 m, 694 m; MS (EI) m/z (%): 325 (1, [M]$^+$), 174 (100), 151 (24), 146 (24), 145 (34), 105 (28), 104 (26), 91 (34), 77 (37), 43 (25). Found: C, 66.2; H, 5.9; N, 12.7. Calc. for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.9; N, 12.9%.

General procedure for the Fischer indolisation of phenylhydrazones 3a,c–e into 2-(indol-2-carboxamido)benzoic acids 1a,c–e (Table 1)

Phenylhydrazones **3a,d,e** or **3c**· AcOH (2.0 mmol) were heated under a nitrogen atmosphere on a metal bath at the temperature and for the time given in Table 1. The course of reaction was monitored by a moistened pH test strip (alkaline reaction of released ammonia gas). After cooling the reaction mixture, the corresponding product was isolated as follows.

Compound **1a** was obtained from the solidified reaction mixture by two subsequent recrystallizations from ethanol and isopropyl alcohol.

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Compound **1c** was obtained from the oily reaction mixture by trituration with toluene (10 mL). The precipitate that formed was collected by filtration, recrystallized from isopropyl alcohol and additionally purified by column chromatography on silica gel using successive mixtures of ethyl acetate and ethanol as eluents.

Compound **1d** was obtained by triturating the solidified reaction mixture with toluene for 1 hour at ambient temperature followed by filtration. Pure **1d** was obtained after recrystallization of the filter cake from isopropyl alcohol.

Compound **1e** was obtained by washing the solidified reaction mixture with toluene (10 mL) and cyclohexane (10 mL). The solid was subjected to column chromatography on silica gel using successive mixtures of ethyl acetate and ethanol as eluents. Recrystallisation from the benzene–ethyl acetate mixture afforded pure **1e**.

Solvent and catalyst screening for the Fischer indolisation of 2 into 1 (Table 2)

A stirred mixture of *N*-(α-ketoacyl)anthranilic acid **2** (2.00 mmol), phenylhydrazinium chloride (310 mg, 2.15 mmol) and the catalyst in the solvent (entry 1: 7.5 mL; entries 2–13: 13 mL) was heated under reflux until TLC analysis indicated complete consumption of the starting material. The progress of the reaction was accompanied by the colour change of the reaction mixture from pale yellow to green and finally to dark red. The products were isolated as follows.

Entries 1 and 5: the cooled reaction mixture was poured into ice water (35–60 mL). The solid was collected by filtration, washed with water (20–60 mL) and recrystallized from ethanol affording pure compound **1a**.

Entries 2–4, 9–13: the cooled reaction mixture was poured into ice water (35 mL). If an oily organic phase was formed (entry 13), the resulting mixture was stirred overnight. The resulting solid was collected by filtration, washed with 10% HCl (16 mL) and water (25 mL), and recrystallized from ethanol affording the appropriate pure compound **1**.

Entries 6 and 7: the cooled reaction mixture was filtered. The filter cake was washed with water (10 mL) and recrystallized from ethanol affording a pure compound **1a**. The filtrate was evaporated to dryness and the residue was dissolved in a minimal amount of water (*ca.* 25 mL). The solution was made alkaline with 0.5 M NaOH, washed with benzene (3 × 5 mL) and carefully neutralised with 5% HCl. The precipitated anthranilic acid was filtered off as colourless crystals.

Entry 8: the reaction mixture was concentrated *in vacuo* and the oily residue was triturated with water (10 mL) to give white precipitate of pure **1a**, which was collected by filtration and washed with water (2 × 3 mL).

General procedure for the Fischer indolisation of *N*-(α-ketoacyl)anthranilic acids 2 into 2-(indol-2-carboxamido)-benzoic acids 1 (Table 3)

A mixture of *N*-(α-ketoacyl)anthranilic acid **2** (2.00 mmol) and phenylhydrazinium chloride (310 mg, 2.15 mmol) in acetic acid (7.5 mL) was heated under reflux until TLC indicated complete consumption of the starting material **2**. In the case of **2m** (entry 13), at the onset of the reaction the formation of solid prevented an efficient stirring of the reaction mixture. Thus an additional amount of acetic acid (5 mL) was added. The reaction mixture was cooled and diluted with ice water (60 mL). After stirring the resulting mixture for several hours, the *Precipitate A* was collected by filtration and washed with water (20 mL). The filtrates were combined into the *Filtrate A*. The *Precipitate A* and the *Filtrate A* were treated as follows.

Entries 1–6, 8, 10–12: recrystallization of the *Precipitate A* from ethanol gave pure products **1a–f,h,j–l**.

Entries 2, 4, 6, 11: the *Filtrate A* was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel using 30% ethyl acetate in chloroform as an eluent to isolate benzoxazinones **4d,f,k** and phenylhydrazides **5b,f** as indicated in Table 3.

Entry 7: recrystallisation of the *Precipitate A* from ethanol afforded the appropriate benzoxazinones **4g**. The mother liquor was concentrated *in vacuo*. From the residue the second crop of **1g** crystallized, which was collected by filtration and washed with a small amount of benzene and recrystallized from ethanol. The yield of the combined crops of **1g** is given in Table 3, entry 7.

Entry 13: recrystallisation of the *Precipitate A* from ethanol afforded benzoxazinone **4m**.

Entry 9: the *Precipitate A* was washed with boiling benzene (15 mL) and recrystallized from ethanol affording a pure compound **1i**. The benzene extract was concentrated to the oily residue and subjected to column chromatography on silica gel using 10% ethyl acetate in chloroform as an eluent, to give benzoxazinone **4i**.

Entry 10: the *Filtrate A* was evaporated to dryness and subjected to column chromatography on silica gel with chloroform as an eluent, affording benzoxazinone **4j**.

2-{[(3-Methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1a). Colourless solid, mp 276–284 °C (ethanol), R_f = 0.48 (20% methanol in ethyl acetate), R_f = 0.18 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.66 (s, 3H, CH_3), 7.09 (dd, 1H, J = 7.5, 7.4 Hz, H5′), 7.22 (dd, 1H, J = 7.6, 7.6 Hz, H5), 7.26 (dd, 1H, J = 7.6, 7.6 Hz, H6′), 7.44 (d, 1H, J = 8.2 Hz, H7′), 7.66–7.71 (m, 2H, H4 and H4′), 8.07 (dd, 1H, J = 7.9, 1.1 Hz, H6), 8.69 (d, 1H, J = 8.4 Hz, H3), 11.53 (s, 1H, H1′), 11.69 (s, 1H, CONH), 13.82 (br s, 1H, COOH); IR (cm^{-1}): ν 3328 s, 3061 w, 1682 s, 1664 s, 1581 w, 1524 s, 1450 m, 1412 m, 1338 m, 1261 s, 727 m, 662 w; MS (EI) m/z (%): 295 (12), 294 (63, [M]$^+$), 158 (95), 157 (100), 130 (56), 129 (48), 128 (26), 120 (78), 103 (36), 77 (36) m/z (%). Found: C, 69.1; H 4.8; N, 9.7. Calc. for $C_{17}H_{14}N_2O_3$: C, 69.4; H, 4.8; N, 9.5%.

5-Methoxy-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1b). Yellowish solid, mp 265–269 °C (ethanol), R_f = 0.41 (20% methanol in ethyl acetate), R_f = 0.16 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.64 (s, 3H, C3′ CH_3), 3.81 (s, 3H, OCH_3), 7.09 (dd, 1H, J = 7.3, 7.3 Hz, H5′), 7.25 (ddd, 1H, J = 7.6, 7.6, 0.8 Hz, H6′), 7.30 (dd, 1H, J = 9.2, 3.1 Hz, H4), 7.43 (d, 1H, J = 8.2 Hz, H7′), 7.53 (d, 1H, J = 3.2 Hz, H6), 7.67 (d, 1H, J = 8.0 Hz, H4′), 8.59 (d, 1H, J =

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9.2 Hz, H3), 11.37 (s, 1H, CONH), 11.49 (s, 1H, H1′), 13.88 (br s, 1H, COOH); IR (cm^{-1}): ν 3321 s, 1638 s, 1521 s, 1337 m, 1289 m, 1245 s, 1218 m, 1036 w, 744 s; MS (EI) *m/z* (%): 325 (19), 324 (90, $[M]^+$), 307 (16), 306 (71), 158 (97), 157 (40), 150 (57), 130 (65), 129 (41), 77 (41); HRMS (ESI^+): *m/z* calcd for $C_{18}H_{17}N_2O_4^+$ $[M + H]^+$ 325.1183, found 325.1184. Found: C, 66.5; H, 5.0; N, 8.6. Calc. for $C_{18}H_{16}N_2O_4$: C, 66.7; H, 5.0; N, 8.6%.

4-Methoxy-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1c). Colourless solid, mp 264–267 °C (iPrOH), R_f = 0.61 (20% methanol in ethyl acetate), R_f = 0.23 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 2.65 (s, 3H, C3′ CH_3), 3.87 (s, 3H, OCH_3), 6.79 (dd, 1H, *J* = 8.9, 2.6 Hz, H5), 7.09 (ddd, 1H, *J* = 7.2, 7.2, 0.6 Hz, H5′), 7.26 (ddd, 1H, *J* = 7.6, 7.6, 0.8 Hz, H6′), 7.43 (d, 1H, *J* = 8.3 Hz, H7′), 7.68 (d, 1H, *J* = 8.0 Hz, H4′), 8.02 (d, 1H, *J* = 8.9 Hz, H6), 8.38 (d, 1H, *J* = 2.6 Hz, H3), 11.53 (s, 1H, H1′), 11.91 (s, 1H, CONH), 13.47 (br s, 1H, COOH); IR (cm^{-1}): ν 3320 m, 3054 w, 2975 w, 1671 s, 1640 m, 1613 s, 1577 m, 1524 m, 1407 m, 1337 m, 1269 s, 1243 s, 1235 s, 1151 m, 740 m; MS (EI) *m/z* (%): 325 (2), 324 (8, $[M]^+$), 306 (42), 158 (35), 157 (26), 150 (28), 130 (33), 129 (23), 45 (30), 44 (100); HRMS (ESI^+): *m/z* calcd for $C_{18}H_{17}N_2O_4^+$ $[M + H]^+$ 325.1183, found 325.1187. Found: C, 66.6; H, 5.0; N, 8.45. Calc. for $C_{18}H_{16}N_2O_4$: C, 66.7; H, 5.0; N, 8.6%.

3-Methoxy-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1d). Colourless solid, mp 265–267 °C (ethyl acetate), R_f = 0.39 (20% methanol in ethyl acetate), R_f = 0.24 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 2.58 (s, 3H, C3′ CH_3), 3.85 (s, 3H, OCH_3), 7.08 (dd, 1H, *J* = 7.4, 7.4 Hz, H5′), 7.25 (ddd, 1H, *J* = 7.6, 7.6, 0.7 Hz, H6′), 7.30–7.34 (m, 2H, H4 and H5), 7.39–7.46 (m, 2H, H6 and H7′), 7.65 (d, 1H, *J* = 8.1 Hz, H4′), 9.31 (br s, 1H, CONH), 11.47 (br s, 1H, H1′), 12.91 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6): δ 9.8, 56.1, 112.0, 115.0, 115.2, 119.2, 119.9, 121.4, 124.2, 125.7, 126.1, 127.2, 128.0, 128.5, 135.6, 153.7, 160.2, 167.9; IR (cm^{-1}): ν 3387 w, 3292 s, 2837 m, 1690 s, 1619 s, 1538 m, 1506 s, 1478 s, 1459 m, 1280 s, 1257 s, 1056 m, 747 m, 510 w; MS (EI) *m/z* (%): 324 (3, $[M]^+$), 323 (26), 322 (100), 250 (13), 149 (48), 111 (6), 97 (8), 85 (8), 71 (10), 57 (24), 43 (8), 41 (13); HRMS (ESI^-): *m/z* calcd for $C_{18}H_{15}N_2O_4^-$ $[M - H]^-$ 323.1037, found 323.1039. Found: C, 66.5; H, 5.0; N, 8.5. Calc. for $C_{18}H_{16}N_2O_4$: C, 66.7; H, 5.0; N, 8.6%.

2-{Methyl[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1e). White solid, mp 216–219 °C (EtOAc–benzene), R_f = 0.54 (20% methanol in EtOAc), R_f = 0.36 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 1.95 (br s, 3H), 3.35 (s, 3H), 6.88–7.72 (m, 8H), 10.56 (br s, 1H), 13.07 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 9.0, 38.0, 111.3, 111.6, 118.6, 119.2, 122.7, 127.1, 127.3, 128.3, 129.7, 130.9, 132.7, 135.5, 143.5, 164.3, 166.5; IR (cm^{-1}): ν 3233 s, 2913 m, 1704 s, 1614 s, 1590 s, 1545 m, 1445 m, 1421 m, 1395 m, 1349 m, 1287 m, 1256 s, 759 m, 752 m, 741 m; MS (EI): *m/z* (%) 309 (14), 308 (67, $[M]^+$), 290 (100), 250 (89), 234 (37), 233 (80), 232 (63), 204 (52), 158 (48), 102 (37), 77 (42), 44 (53); HRMS (ESI^+): *m/z* calcd for $C_{18}H_{17}N_2O_3^+$ $[M + H]^+$ 309.1234, found 309.1237.

2-{[(3-Propyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1f). Colourless solid, mp 239–246 °C (ethanol), R_f = 0.23 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 0.94 (t, 3H, *J* = 7.3 Hz, C3′$(CH_2)_2CH_3$), 1.67–1.74 (m, 2H, C3′ CH_2CH_2), 3.08–3.14 (m, 2H, C3′CH_2), 7.08 (dd, 1H, *J* = 7.7, 7.7 Hz, H5′), 7.22 (dd, 1H, *J* = 8.0, 8.0 Hz, H5), 7.26 (dd, 1H, *J* = 7.8, 7.8 Hz, H6′), 7.44 (d, 1H, *J* = 8.2 Hz, H7′), 7.65–7.70 (m, 2H, H4, H4′), 8.07 (dd, 1H, *J* = 1.4, 8.0 Hz, H6′), 8.66 (d, 1H, *J* = 8.4 Hz, H3), 11.52 (br s, 1H, H1′), 11.64 (br s, 1H, CONH), 13.79 (br s, 1H, COOH); IR (cm^{-1}): ν 3311 s, 2956 m, 2870 w, 1673 s, 1655 s, 1580 m, 1540 m, 1521 m, 1511 m, br, 1449 m, 1407 m, 1262 s, 1166 m, 752 m, 730 m; MS (EI) *m/z* (%): 324 (4), 323 (11), 322 (56, $[M]^+$), 304 (11), 275 (39), 186 (40), 185 (100), 170 (21), 168 (15), 156 (48), 130 (21), 129 (22), 128 (47), 120 (50), 77 (13); HRMS (ESI^+): *m/z* calcd for $C_{19}H_{19}N_2O_3^+$ $[M + H]^+$ 323.1390, found 323.1390. Found: C, 70.8; H, 5.75; N, 8.6. Calc. for $C_{19}H_{18}N_2O_3$: C, 70.8; H, 5.6; N, 8.7%.

3-Methyl-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1g). Colourless solid, mp 234–241 °C (benzene), R_f = 0.26 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 2.29 (s, 3H, C3CH_3), 2.62 (s, 3H, C3′CH_3), 7.08 (dd, 1H, *J* = 7.4, 7.4 Hz, H5′), 7.25 (dd, 1H, *J* = 7.5, 7.5 Hz, H6), 7.30 (dd, 1H, *J* = 7.7, 7.7 Hz, H5), 7.44 (d, 1H, *J* = 8.2 Hz, H7′), 7.53 (d, 1H, *J* = 7.4 Hz, H4), 7.66 (d, 1H, *J* = 8.0 Hz, H4′), 7.77 (d, 1H, *J* = 7.1 Hz, H6), 9.83 (s, 1H, CONH), 11.45 (s, 1H, H1′), 13.14 (br s, 1H, COOH); IR (cm^{-1}): ν 3460 w, 3303 s, 3059 w, 2966 w, 1673 s, 1647 s, 1622 s, 1505 s, 1463 s, 1447 s, 1335 s, 1243 s, 744 s, 739 m; HRMS (ESI^+): *m/z* calcd for $C_{18}H_{17}N_2O_3^+$ $[M + H]^+$ 309.1234; found 309.1236.

5-Methyl-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1h). Pale yellow crystals, mp 268–274 °C (ethanol), R_f = 0.63 (20% methanol in ethyl acetate), R_f = 0.30 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 2.34 (s, 3H, C5CH_3), 2.65 (s, 3H, C3′CH_3), 7.09 (ddd, 1H, *J* = 7.5, 7.5, 0.7 Hz, H5′), 7.25 (ddd, 1H, *J* = 7.6, 7.6, 0.9 Hz, H6′), 7.44 (d, 1H, *J* = 8.2 Hz, H7′), 7.49 (dd, 1H, *J* = 8.6, 2.0 Hz, H4), 7.67 (d, 1H, *J* = 8.0 Hz, H4′), 7.88 (d, 1H, *J* = 1.8 Hz, H6), 8.58 (d, 1H, *J* = 8.5 Hz, H3), 11.51 (s, 1H, H1′), 11.58 (s, 1H, CONH), 13.76 (br s, 1H, COOH); IR (cm^{-1}): ν 3316 m, 2919 w, 2863 w, 1672 m, 1648 m, 1586 m, 1520 s, 1418 m, 1398 m, 1336 m, 1296 m, 1259 s, 1217 m, 736 m, 671 w; MS (EI) *m/z* (%): 310 (1), 309 (8), 308 (36, $[M]^+$), 290 (53), 158 (65), 157 (49), 134 (100), 130 (60), 129 (42), 103 (40), 77 (57); HRMS (ESI^+): *m/z* calcd for $C_{18}H_{17}N_2O_3^+$ $[M + H]^+$ 309.1234, found 309.1234. Found: C, 70.2; H, 5.4; N, 9.1. Calc. for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2; N, 9.1%.

6-Chloro-3-methyl-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]amino}-benzoic acid (1i). Colourless solid, mp 256–264 °C (ethanol), R_f = 0.38 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 2.23 (s, 3H, C3CH_3), 2.57 (s, 3H, C3′CH_3), 7.07 (ddd, 1H, *J* = 7.8, 7.2, 0.7 Hz, H5′), 7.24 (ddd, 1H, *J* = 8.1, 7.1, 0.9 Hz, H6′), 7.40–7.45 (m, 3H, H4, H5 and H7′), 7.64 (d, 1H, *J* = 8.0 Hz, H4′), 9.43 (br s, 1H, CONH), 11.35 (br s, 1H, H1′), 13.59 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 9.6, 17.5, 111.8, 114.6, 119.1, 119.8, 124.0, 126.3, 126.8, 127.75, 127.83, 131.6, 134.1, 134.2, 135.4, 136.3, 160.8, 166.5; IR

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(cm^{-1}): ν 3820 m, 3057 w, 2927 m, 1734 s, 1686 s, 1624 s, 1617 s, 1583 s, 1556 s, 1509 s, 1335 s, 1296 s, 743 s; MS (EI) *m/z* (%): 327 (7), 326 (35), 325 (22), 324 (100, $[M - H_2O]^+$), 295 (48), 130 (76), 129 (56), 128 (50), 103 (40), 102 (57), 77 (60), 44 (70); HRMS (ESI^+): *m/z* calcd for $C_{18}H_{16}ClN_2O_3^+$ $[M + H]^+$ 343.0844, found 343.0849. Found: C, 62.8; H, 4.5; N, 7.9. Calc. for $C_{18}H_{15}ClN_2O_3$: C, 63.1; H, 4.4; N, 8.2%.

3,5-Dimethyl-2-{[(3-propyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1j). Colourless solid, mp 240–244 °C (benzene), R_f = 0.51 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 0.92 (t, 3H, *J* = 7.4 Hz, C3′$(CH_2)_2CH_3$), 1.67 (tq, 2H, *J* = 7.4, 7.4 Hz, C3′CH_2CH_2), 2.23 (s, 3H, C3CH_3), 2.34 (s, 3H, C5CH_3), 3.07 (t, 1H, *J* = 7.6 Hz, C3′CH_2), 7.07 (ddd, 1H, *J* = 7.9, 7.2, 0.7 Hz, H5′), 7.24 (ddd, 1H, *J* = 8.1, 7.1, 0.9 Hz, H6′), 7.34, (d, 1H, *J* = 1.3 Hz, H4), 7.44 (d, 1H, *J* = 8.2 Hz, H7′), 7.58 (d, 1H, *J* = 1.7 Hz, H6), 7.66 (d, 1H, *J* = 8.1 Hz, H4′), 9.71 (br s, 1H, CONH), 11.41 (br s, 1H, H1′), 13.06 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6): δ 14.0, 18.4, 20.2, 23.9, 26.0, 112.0, 119.2, 119.9, 120.2, 124.0, 126.4, 126.8, 127.6, 128.3, 133.7, 134.8, 134.9, 135.5, 160.2, 168.3; IR (cm^{-1}): ν 3368 w, 3301 m, 3263 m, 3052 m, 2956 m, 1663 s, 1618 w, 1603 w, 1547 m, 1527 w, 1477 w, 1444 m, 1405 m, 1336 w, 1300 m, 1231 m, 742 w; MS (EI) *m/z* (%): 351 (11), 350 (46, $[M]^+$), 332 (5, $[M - H_2O]^+$), 186 (44), 185 (70), 156 (33), 148 (100), 130 (30), 129 (25), 128 (39); HRMS (ESI^+): *m/z* calcd for $C_{21}H_{23}N_2O_3^+$ $[M + H]^+$ 351.1703, found, 351.1702. Found: C, 71.7; H, 6.3; N, 7.9. Calc. for $C_{21}H_{22}N_2O_3$: C, 72.0; H, 6.3; N, 8.0%.

3,5-Dimethoxy-2-{[(3-propyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1k). Pale yellow solid, mp 227–230 °C (ethanol), R_f = 0.33 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 0.92 (t, 3H, *J* = 7.3 Hz, C3′$(CH_2)_2CH_3$), 1.64 (tq, 2H, *J* = 7.4 Hz, C3′CH_2CH_2), 3.05 (t, 3H, *J* = 7.6 Hz, C3′CH_2), 3.82 (s, 3H, C3OCH_3), 3.83 (s, 3H, C5OCH_3), 6.88 (d, 1H, *J* = 2.7 Hz, H4), 6.92 (d, 1H, *J* = 2.7 Hz, H6), 7.06 (dd, 1H, *J* = 7.4 Hz, H5′), 7.23 (ddd, 1H, *J* = 7.9, 7.2, 0.7 Hz, H6′), 7.43 (d, 1H, *J* = 8.2 Hz, H7′), 7.64 (d, 1H, *J* = 8.0 Hz, H4′), 9.06 (br s, 1H, CONH), 11.40 (br s, 1H, H1′), 12.92 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.1, 23.9, 26.1, 55.6, 56.2, 102.4, 105.1, 112.0, 118.8, 119.2, 120.0, 121.0, 124.0, 126.8, 127.7, 129.6, 135.5, 155.1, 157.5, 160.2, 167.7; IR (cm^{-1}): ν 3409 w, 3288 m, 2957 m, 1694 s, 1657 s, 1597 m, 1502 s, 1471 m, 1454 m, 1334 s, 1309 m, 1215 m, 1067 m, 1043 m, 752 m; MS (EI) *m/z* (%): 382 (6, $[M]^+$), 365 (25), 364 (100), 335 (82), 221 (35), 179 (50), 156 (32), 129 (38), 128 (56), 73 (51); HRMS (ESI^+): *m/z* calcd for $C_{21}H_{23}N_2O_5^+$ $[M + H]^+$ 383.1601, found 383.1601. Found: C, 65.9; H, 5.8; N, 7.1. Calc. for $C_{21}H_{22}N_2O_5$: C, 66.0; H, 5.8; N, 7.3%.

2-{[(3-Phenyl-1*H*-indol-2-yl)carbonyl]amino}benzoic acid (1l). Colourless crystals, mp 237–246 °C (ethanol), R_f = 0.36 (10% ethanol in chloroform). ^1H NMR (500 MHz, DMSO-d_6) δ 7.11–7.17 (m, 2H, H5, H5′), 7.29–7.36 (m, 2H, H6′, H4″), 7.44 (dd, 2H, *J* = 7.7, 7.7 Hz, H3″, H5″), 7.53–7.55 (m, 3H, H7′, H2″, H6″), 7.59 (d, 1H, *J* = 8.1 Hz, H4′), 7.64 (ddd, 1H, *J* = 8.6, 7.1, 1.6 Hz, H4), 7.91 (dd, 1H, *J* = 7.9, 1.5 Hz, H6), 8.60 (dd, 1H, *J* = 8.4, 0.6 Hz, H3), 11.28 (br s, 1H, CONH), 12.03 (br s, 1H, H1′), 13.36 (br s, 1H, COOH); IR (cm^{-1}): ν 3309 s, 3057 w, 1671 s, 1655 s, 1605 m, 1580 m, 1519 s, 1449 m, 1405 m, 1332 m, 1296 m, 1262 s, 1230 m, 754 m, 700 m; MS (EI) *m/z* (%): 357 (3), 356 (13, $[M]^+$), 339 (24), 338 (100), 337 (44), 293 (17), 220 (29), 219 (31), 207 (20), 191 (27), 190 (47), 165 (31), 164 (18), 90 (21), 44 (54); HRMS (ESI^+): *m/z* calcd for $C_{22}H_{17}N_2O_3^+$ $[M + H]^+$ 357.1234; found 357.1228. Found: C, 74.1; H, 4.6; N, 7.8. Calc. for $C_{22}H_{16}N_2O_3$: C, 74.2; H, 4.5; N, 7.9%.

6-Methoxy-2-(3-methyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4b). Pale-yellow microcrystals, mp 220–225 °C, R_f = 0.44 (20% ethyl acetate in petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 2.78 (s, 3H, C3′CH_3), 3.92 (s, 3H, OCH_3), 7.15 (ddd, 1H, *J* = 7.8, 7.0, 0.9 Hz, H5′), 7.32 (ddd, 1H, *J* = 7.5, 7.5, 0.9 Hz, H6′), 7.36–7.39 (m, 2H, H7 and H7′), 7.55 (d, 1H, *J* = 9.0 Hz, H8), 7.59 (d, 1H, *J* = 2.9 Hz, H5), 7.67 (d, 1H, *J* = 8.1 Hz, H4′), 8.94 (br s, 1H, H1′); IR (cm^{-1}): ν 3399 m, 3047 w, 2836 w, 1747 s, 1624 s, 1603 m, 1492 s, 1354 m, 1335 m, 1326 m, 1240 s, 1035 m, 838, 743 m; MS (EI) *m/z* (%): 307 (8), 306 (35, $[M]^+$), 181 (100), 158 (30), 157 (18), 130 (28), 129 (17), 103 (18), 77 (16); HRMS (ESI^+): *m/z* calcd for $C_{18}H_{15}N_2O_3^+$ $[M + H]^+$ 307.1077, found 307.1080.

7-Methoxy-2-(3-methyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4c). Pale-yellow crystals, mp 234–236 °C (benzene), R_f = 0.52 (20% ethyl acetate in petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 2.79 (s, 1H, C3′CH_3), 3.95 (s, 1H, OCH_3), 6.99–7.02 (m, 2H, H5 and H8), 7.16 (ddd, 1H, *J* = 7.8, 7.1, 0.8 Hz, H5′), 7.34 (ddd, 1H, *J* = 7.9, 7.2, 0.7 Hz, H6′), 7.39 (d, 1H, *J* = 8.2 Hz, H7′), 7.69 (d, 1H, *J* = 8.0 Hz, H4′), 8.11 (d, 1H, *J* = 9.0 Hz, H6), 8.98 (br s, 1H, H1′); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.5, 55.8, 108.4, 109.3, 111.4, 116.6, 120.2, 120.5, 120.6, 123.3, 125.9, 129.2, 130.4, 136.6, 149.7, 154.3, 158.7, 166.3; IR (cm^{-1}): ν 3376 m, 2946 w, 1736 s, 1622 s, 1599 s, 1565 s, 1548 s, 1493 m, 1444 m, 1439 m, 1287 m, 1203 m, 1043 m, 744 m; MS (EI) *m/z* (%): 308 (2), 307 (19), 306 (100, $[M]^+$), 277 (27), 249 (25), 157 (14), 150 (23), 130 (17), 129 (20), 128 (17), 120 (10), 103 (12), 102 (13), 77 (18); HRMS (ESI^+): *m/z* calcd for $C_{18}H_{15}N_2O_3^+$ $[M + H]^+$ 307.1077, found 307.1081; found: C, 70.2; H, 4.6; N, 9.0. Calc. for $C_{18}H_{14}N_2O_3$: C, 70.6; H, 4.6; N, 9.15%.

8-Methoxy-2-(3-methyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4d). Yellow microcrystals, mp 238–240 °C (benzene), R_f = 0.54 (20% ethyl acetate in petroleum ether). ^1H NMR (500 MHz, $CDCl_3$) δ 2.79 (s, 3H, C3′CH_3) 4.03 (s, 3H, OCH_3), 7.15 (ddd, 1H, *J* = 7.4, 7.0, 0.5 Hz, H5′), 7.27 (dd, 1H, *J* = 8.2, 0.7 Hz, H7), 7.32 (ddd, 1H, *J* = 7.5, 7.0, 0.6 Hz, H6′), 7.38 (d, 1H, *J* = 8.8 Hz, H7′), 7.40 (dd, 1H, *J* = 8.1, 8.1 Hz, H6), 7.68 (d, 1H, *J* = 8.1 Hz, H4′), 7.81 (dd, 1H, *J* = 7.9 Hz, 1.0 Hz, H5), 9.23 (br s, 1H, H1′); IR (cm^{-1}): ν 3379 m, 2838 w, 1755 s, 1612 s, 1597 s, 1574 s, 1488 m, 1445 m, 1335 s, 1274 s, 1046 m, 1023 m, 754 m, 738 m, 720 m; MS (EI) *m/z* (%): 308 (2), 307 (19), 306 (100, $[M]^+$), 305 (9, $[M - H]^+$], 260 (12), 130 (27), 129 (16), 128 (18), 103 (17), 102 (14), 77 (23); HRMS (ESI^+): *m/z* calcd for $C_{18}H_{15}N_2O_3^+$ $[M + H]^+$ 307.1077, found 307.1075. Found: C, 70.5; H, 4.6; N, 9.2. Calc. for $C_{18}H_{14}N_2O_3$: C, 70.6; H, 4.6; N, 9.15%.

2-(3-Propyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4f). Pale-yellow microcrystals, mp 160–165 °C (cyclohexane), R_f =

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0.60 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, 3H, J = 7.4 Hz, C3′$(CH_2)_2CH_3$), 1.81 (tq, 2H, J = 7.4, 7.4 Hz, C3′CH_2CH_2), 3.27 (t, 2H, J = 7.5 Hz, C3′ CH_2), 7.15 (ddd, 1H, J = 7.8, 7.1, 0.8 Hz, H5′), 7.31 (ddd, 1H, J = 8.0, 7.1, 0.9 Hz, H6′), 7.39 (d, 1H, J = 8.2 Hz, H7′), 7.46 (ddd, 1H, J = 8.0, 7.1, 1.0 Hz, H6), 7.60 (d, 1H, J = 7.9 Hz, H8), 7.70 (d, 1H, J = 8.0 Hz, H4′), 7.79 (ddd, 1H, J = 8.4, 7.0, 1.5 Hz, H7), 8.21 (dd, 1H, J = 7.9, 1.2 Hz, H5), 9.01 (br s, 1H, H1′); IR (cm^{-1}): ν 3372 s, 2957 w, 1754 s, 1621 s, 1603 s, 1571 m, 1472 m, 1261 m, 1240 w, 1055 m, 766 w, 741 m, 684 w; MS (EI) m/z (%): 305 (14), 304 (66, $[M]^+$), 289 (10, $[M - CH_3]^+$), 276 (24), 275 (100, $[M - CH_2CH_3]^+$), 257 (12), 247 (19), 146 (15), 128 (26), 90 (14); HRMS (ESI$^+$): m/z calcd for $C_{19}H_{17}N_2O_2^+$ $[M + H]^+$ 305.1285, found 305.1283. Found: C, 75.25; H, 5.45; N, 9.3. Calc. for $C_{19}H_{16}N_2O_2$: C, 75.0; H, 5.3; N, 9.2%.

8-Methyl-2-(3-methyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4g). Yellow microcrystals, mp 251–254 °C (benzene), R_f = 0.62 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64 (s, 3H, C8CH_3), 2.80 (s, 3H, C3′CH_3), 7.15 (ddd, 1H, J = 7.9, 7.1, 0.8 Hz, H5′), 7.34 (ddd, 1H, J = 8.1, 8.1, 1.0 Hz, H6′), 7.35 (dd, 1H, J = 7.5, 7.5 Hz, H6), 7.41 (d, 1H, J = 8.2 Hz, H7′), 7.66 (d, 1H, J = 7.4 Hz, H7), 7.69 (d, 1H, J = 8.0 Hz, H4′), 8.06 (dd, 1H, J = 7.6, 0.6 Hz, H5), 8.93 (br s, 1H, H1′); IR (cm^{-1}): ν 3365 s, 2918 w, 1746 s, 1623 s, 1597 m, 1548 m, 1446 m, 1322 m, 1322(m), 1234 m, 1062 m, 1029 m, 764 m, 740 m; MS (EI) m/z (%): 291 (23), 290 (100, $[M]^+$), 289 (17), 261 (21), 233 (20), 165 (22), 158 (99), 157 (86), 145 (18), 130 (68), 129 (55), 128 (27), 104 (17), 103 (37), 102 (24), 77 (46); HRMS (ESI$^+$): m/z calcd for $C_{18}H_{15}N_2O_2^+$ $[M + H]^+$ 291.1128, found 291.1127. Found: C, 74.4; H, 4.9; N, 9.4. Calc. for $C_{18}H_{14}N_2O_2$: C, 74.5; H, 4.9; N, 9.65%.

5-Chloro-8-Methyl-2-(3-methyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]-oxazin-4-one (4i). Pale-yellow microcrystals, mp 251–256 °C (cyclohexane), R_f = 0.82 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (s, 3H, C8CH_3), 2.79 (s, 3H, C3′CH_3), 7.17 (ddd, 1H, J = 7.9, 7.0, 0.9 Hz, H5′), 7.35 (ddd, 1H, J = 8.6, 7.7, 1.0 Hz, H6′), 7.36 (d, 1H, J = 8.1 Hz, H6), 7.42 (d, 1H, J = 8.3 Hz, H7′), 7.53 (dd, 1H, J = 8.1, 0.6 Hz, H7), 7.69 (dd, 1H, J = 7.5, 0.5 Hz, H4′), 8.92 (br s, 1H, H1′); IR (cm^{-1}): ν 3384 m, 3351 m, 3057 w, 2917 w, 1739 s, 1629 s, 1576 m, 1328 m, 1262 m, 1232 w, 1028 w, 914 m, 744 m, 730 m; MS (EI) m/z (%): 327 (7), 326 (34), 325 (22), 324 (100, $[M]^+$), 323 (4), 295 (49), 130 (53), 129 (46), 128 (44), 102 (50), 77 (51); HRMS (ESI$^+$): m/z calcd for $C_{18}H_{14}ClN_2O_2^+$ $[M + H]^+$ 325.0738, found 325.0740. Found: C, 66.4; H, 4.0; N, 8.8. Calc. for $C_{18}H_{13}ClN_2O_2$: C, 66.6; H, 4.0; N, 8.6%.

6,8-Dimethyl-2-(3-propyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4j). Pale-yellow microcrystals, mp 201–202 °C (benzene), R_f = 0.93 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, 3H, J = 7.4 Hz, C3′ $(CH_2)_2CH_3$), 1.81 (tq, 2H, J = 7.4, 7.4 Hz, C3′CH_2CH_2), 2.41 (s, 3H, C6CH_3), 2.59 (s, 3H, C8CH_3), 3.27 (t, 2H, J = 7.6 Hz, C3′ CH_2), 7.14 (ddd, 1H, J = 7.8, 7.2, 0.7 Hz, H5′), 7.32 (ddd, 1H, J = 8.0, 7.2, 0.8 Hz, H6′), 7.40 (d, 1H, J = 8.2 Hz, H7′), 7.46 (s, 1H, H7), 7.69 (d, 1H, J = 8.0 Hz, H4′), 7.84 (s, 1H, H5), 8.93 (br s, 1H, H1′); IR (cm^{-1}): ν 3363 s, 2953 w, 1740 s, 1623 s, 1603 s, 1477 m, 1249 m, 1054 m, 789 m, 729 m; MS (EI) m/z (%): 334 (3), 333 (18), 332 (77, $[M]^+$), 303 (100), 288 (33), 128 (37), 85 (31), 71 (36), 57 (65); HRMS (ESI$^+$): m/z calcd for $C_{21}H_{21}N_2O_2^+$ $[M + H]^+$ 333.1598, found 333.1597. Found: C, 75.9; H, 6.1; N, 8.35. Calc. for $C_{21}H_{20}N_2O_2$: C, 75.9; H, 6.1; N, 8.4%.

6,8-Dimethoxy-2-(3-propyl-1*H*-indol-2-yl)-4*H*-benzo[*d*][1,3]-oxazin-4-one (4k). Yellow crystals, mp 202–204 °C (cyclohexane), R_f = 0.69 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 0.97 (t, 1H, J = 7.4 Hz, C3′$(CH_2)_2CH_3$), 1.71 (tq, 2H, J = 7.7, 7.4 Hz, C3′CH_2CH_2), 3.19 (t, 2H, J = 7.7 Hz, C3′CH_2), 3.85 (s, 3H, C6OCH_3), 3.93 (s, 3H, C8OCH_3), 6.93 (d, 1H, J = 2.6 Hz, H7), 7.01 (ddd, 1H, J = 7.9, 7.2, 0.7 Hz, H5′), 7.05 (d, 1H, J = 2.6 Hz, H5), 7.18 (ddd, 1H, J = 8.1, 7.1, 0.9 Hz, H6′), 7.46 (d, 1H, J = 8.2 Hz, H7′), 7.62 (d, 1H, J = 8.0 Hz, H4′), 10.80 (br s, 1H, H1′); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ 14.6, 25.0, 27.6, 56.4, 57.0, 100.6, 108.0, 113.0, 118.9, 120.6, 121.0, 124.2, 125.7, 129.6, 133.1, 138.0, 151.4, 156.7, 159.6, 160.6; IR (cm^{-1}): ν 3368 m, 2963 w, 1736 s, 1619 s, 1491 m, 1437 m, 1373 s, 1325 m, 1300 m, 1219 m, 1036 m, 782 m, 739 m; MS (EI) m/z (%): 366 (4), 365 (24), 364 (100, $[M]^+$), 349 (18), 336 (22), 335 (82), 179 (48), 156 (24), 129 (29), 128 (44); HRMS (ESI$^+$): m/z calcd for $C_{21}H_{21}N_2O_2^+$ $[M + H]^+$ 365.1496, found 365.1494. Found: C, 69.1; H, 5.5; N, 7.6. Calc. for $C_{21}H_{20}N_2O_4$: C, 69.2; H, 5.5; N, 7.7%.

2-(3-Propyl-1*H*-indol-2-yl)-4*H*-naphtho[1,2-*d*][1,3]oxazin-4-one (4m). Bright yellow crystals, mp 273–274 °C (ethanol), R_f = 0.73 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, 3H, J = 7.4 Hz), 1.92 (tq, 2H, J = 7.6, 7.4 Hz), 3.42 (t, 2H, J = 7.6 Hz), 7.19 (dd, 1H, J = 7.4, 7.4 Hz), 7.38 (dd, 1H, J = 7.2, 7.2 Hz), 7.46 (d, 1H, J = 8.2 Hz), 7.72–7.80 (m, 3H), 7.86 (d, 1H, J = 8.6 Hz), 7.94 (dd, 1H, J = 8.1, 1.6 Hz), 8.13 (d, 1H, J = 8.6 Hz), 8.98 (dd, 1H, J = 8.2, 1.6 Hz), 9.10 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.4, 24.0, 27.2, 111.6, 112.3, 120.3, 120.9, 122.7, 123.2, 125.3, 126.1, 126.4, 127.4, 127.7, 128.1, 128.9, 129.0, 130.2, 136.7, 137.3, 146.6, 159.4 (one resonance could not be determined due to low solubility of the compound and thus the low signal/noise ratio); IR (cm^{-1}): ν 3360 m, 3057 w, 2951 w, 1744 s, 1602 s, 1564 s, 1542 w, 1509 w, 1444 w, 1394 w, 1272 m, 780 w, 765 m, 736 m, 626 w; MS (EI) m/z (%): 355 (22), 354 (86), 326 (27), 325 (100), 297 (23), 283 (18), 269 (18), 170 (23), 169 (18), 156 (17), 140 (46), 129 (15), 128 (49), 115 (18), 101 (17), 77 (12); HRMS (ESI$^+$): m/z calcd for $C_{23}H_{19}N_2O_2^+$ $[M + H]^+$ 355.1441; found 355.1438. Found: C, 78.1; H, 5.1; N, 8.0. Calc. for $C_{23}H_{18}N_2O_2$: C, 78.0; H, 5.1; N, 7.9%.

***N*′-Phenyl-5-methoxy-2-{[(3-methyl-1*H*-indol-2-yl)carbonyl]-amino}benzohydrazide (5b).** White solid *mp* 243–253 °C (benzene), R_f = 0.47 (20% benzene in ethyl acetate). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.52 (s, 3H, C3′CH_3), 3.87 (s, 3H, OCH_3), 6.72 (t, 1H, J = 7.3 Hz, H4″), 6.82 (d, 2H, J = 7.7 Hz, H2 and H6 of phenyl), 7.05 (ddd, 1H, J = 7.5, 7.5, 0.6 Hz, H5′), 7.14 (dd, 2H, J = 8.2, 7.6 Hz, H3 and H5 of phenyl), 7.20–7.25 (m, 2H, H4 and H6′), 7.40 (d, 1H, J = 8.2 Hz, H7′), 7.48 (d, 1H, J = 3.0 Hz, H6), 7.62 (d, 1H, J = 8.1 Hz, H4′), 8.00 (d, 1H, J = 1.0 Hz, N*H*Ph), 8.35 (d, 1H, J = 9.1 Hz, H3), 10.65 (d, 1H, J =

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1.0 Hz, N*H*NHPh), 11.00 (br s, 1H, C2NH), 11.45 (br s, 1H, H1′); ^{13}C NMR (126 MHz, DMSO-d_6): δ 9.7 (C3′CH$_3$), 55.6 (OCH$_3$), 112.1 (C7′), 112.4 (C2 and C6 of phenyl), 112.8 (C6), 113.0 (C3′), 117.9 (C4), 118.9 (C4 of phenyl), 119.3 (C5′), 120.0 (C4′), 121.9 (C1), 123.6 (C3), 124.1 (C6′), 127.9 (C3a′), 128.1 (C2′), 128.8 (C3 and C5 of phenyl), 131.6 (C2), 135.9 (C7a′), 149.1 (C1 of phenyl), 154.7 (C5), 160.1 (C2′CO), 168.0 (COOH); ^{15}N NMR (51 MHz, DMSO-d_6) δ 89.0 (NPh), 123.2 (C2N); 132.3 (N1′), 137.6 (C1CON); IR (cm^{-1}): ν 3374 m, 3302 m, 3053 w, 1655 s, 1609 m, 1541 s, 1524 s, 1494 m, 1419 m, 1335 m, 1283 m, 1234 m, 1223 m, 740 m; MS (EI) *m*/*z* (%): 338 (43), 181 (100), 158 (38), 130 (32), 129 (25), 77 (25), 60 (23), 45 (35), 44 (39), 43 (40); HRMS (ESI$^+$): *m*/*z* calcd for $C_{24}H_{23}N_4O_3^+$ [M + H]$^+$ 415.1765; found 415.1760; Found: C, 69.6; H, 5.3; N, 13.35. Calc. for $C_{24}H_{22}N_4O_3$: C, 69.6; H, 5.35; N, 13.5%.

***N*′-Phenyl-2-{[(3-propyl-1*H*-indol-2-yl)carbonyl]amino}benzohydrazide (5f).** Colourless needles, mp 214–216 °C (benzene), R_f = 0.61 (20% methanol in ethyl acetate), R_f = 0.28 (20% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.83 (t, 3H, J = 7.4, Hz, CH$_3$), 1.58 (tq, 2H, J = 7.4, 7.4 Hz, CH_2CH$_3$), 3.02 (t, 2H, J = 7.4 Hz, C3′CH$_2$), 6.72 (t, 1H, J = 7.3 Hz, H4 of phenyl), 6.82 (d, 2H, J = 7.8 Hz, H2 and H6 of phenyl), 7.05 (dd, 1H, J = 7.4, 7.4, Hz, H5′), 7.14 (dd, 2H, J = 7.8, 7.8 Hz, H3 and H5 of phenyl), 7.22 (dd, 1H, J = 7.5, 7.5 Hz, H6′), 7.27 (ddd, 1H, J = 7.6, 7.6, 0.7 Hz, H5), 7.41 (d, 1H, J = 8.2 Hz, H7′), 7.60–7.65 (m, 2H, H4 and H4′), 7.96 (dd, 1H, J = 7.9, 1.1 Hz, H6), 7.98 (br d, 1H, J = 2.3 Hz, CONHN*H*), 8.45 (d, 1H, J = 8.1 Hz, H3), 10.66 (br d, 1H, J = 2.3 Hz, CON*H*NH), 11.33 (br s, 1H, C2NH), 11.49 (br s, 1H, H1′); ^{13}C NMR (126 MHz, DMSO-d_6): δ 13.7 (CH$_3$), 24.0 (CH$_2$CH$_3$), 25.6 (C3′CH$_2$), 112.1 (C7′), 112.2 (C2 and C6 of phenyl), 118.8 (C4 of phenyl), 119.26 (C3′), 119.29 (C5′), 120.0 (C4′), 120.3 (C1), 121.8 (C3), 123.1 (C5), 124.1 (C6′), 127.3 (C2′), 127.7 (C3a′), 128.0 (C6), 128.7 (C3 and C5 of phenyl), 132.2 (C4), 135.9 (C7a′), 138.5 (C2), 149.0 (C1 of phenyl), 160.3 (C2′CO), 168.2 (COOH); ^{15}N NMR (51 MHz, DMSO-d_6) δ 88.9 (NPh), 124.6 (C2N), 131.9 (N1′), 137.6 (C1CON); IR (cm^{-1}): ν 3319 s, 2953 w, 2869 w, 1655 s, 1631 s, 1593 s, 1540 m, 1515 s, 1493 m, 1446 m, 1281 m, 1244 m, 740 s; MS (EI) *m*/*z* (%): 413 (3), 412 (12, [M]$^+$), 306 (21), 305 (100), 186 (67), 146 (28), 130 (22), 128 (22), 120 (68), 108 (37), 77 (21); HRMS (ESI$^+$): *m*/*z* calcd for $C_{25}H_{25}N_4O_2^+$ [M + H]$^+$ 413.1972, found 413.1971. Found: C, 72.7; H, 5.9; N, 13.6. Calc. for $C_{25}H_{24}N_4O_2$: C, 72.8; H, 5.9; N, 13.6%.

Reaction of 4f with phenylhydrazine into hydrazide 5f (Table 5, entry 1)

A mixture of benzoxazinone **4f** (332 mg, 1.09 mmol) and phenylhydrazine (143 mg, 1.32 mmol) in toluene (15 mL) was heated under reflux for 2 hours. After cooling, the precipitated solid was filtered off with suction and crystallized from benzene to give hydrazide **5f** (382 mg, 86%). The spectral and analytical data were in agreement with those for the authentic sample, as prepared above.

Reaction of 4f with *n*-butylamine into amide 6f (Table 5, entry 2). A mixture of benzoxazinone **4f** (305 mg, 1.00 mmol) and *n*-butylamine (90 mg, 1.23 mmol) in toluene (15 mL) was stirred at room temperature for 2 hours. The precipitated solid was filtered off with suction and crystallized from benzene to give amide **6f** (316 mg, 84%) as a white crystalline solid, mp 187–188 °C (benzene), R_f = 0.41 (20% methanol in ethyl acetate). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (t, 3H, J = 7.4 Hz, NH(CH$_2$)$_3$CH_3), 0.95 (t, 3H, J = 7.3 Hz, C3′(CH$_2$)$_2$CH_3), 1.29–1.38 (m, 2H, NH(CH$_2$)$_2$CH_2), 1.49–1.57 (m, 2H, NHCH$_2$CH_2), 1.62–1.72 (m, 2H, C3′CH$_2$CH_2), 3.08–3.14 (m, 2H, C3′CH_2), 3.26–3.32 (m, 2H, NHCH_2), 7.07 (ddd, 1H, J = 7.8, 7.2, 0.6 Hz, H5′), 7.21 (ddd, 1H, J = 8.4, 7.4, 1.0 Hz, H5), 7.24 (ddd, 1H, J = 7.9, 7.2, 0.8 Hz, H6′), 7.44 (d, 1H, J = 8.2 Hz, H7′), 7.56 (ddd, 1H, J = 7.4, 7.4, 1.3 Hz, H4), 7.67 (d, 1H, J = 8.0 Hz, H4′), 7.78 (dd, 1H, J = 7.8, 1.3 Hz, H6), 8.53 (dd, 1H, J = 8.3, 0.5 Hz, H3), 8.83 (br t, 1H, J = 5.4 Hz, C1′CONH), 11.48 (br s, 1H, H1′), 11.71 (br s, 1H, C2NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.6 (NH(CH$_2$)$_3$$CH_3$), 13.8 (C3′(CH$_2$)$_2$$CH_3$), 19.6 (NHCH$_2$$CH_2$), 24.1 (C3′CH$_2$$CH_2$), 25.7 (C3′$CH_2$), 30.9 (NHCH$_2$$CH_2$), 38.8 (NHCH$_2$), 112.2 (C7′), 118.6 (C3′), 119.2 (C5′), 120.0 (C4′), 121.2 (C3), 121.5 (C1), 122.7 (C5), 124.0 (C6′), 127.6 (C2′), 127.7 (C3a′), 128.0 (C6), 131.6 (C4), 135.9 (C7a′), 138.6 (C2), 160.3 (C2′CO), 168.1 (C1CO); ^{15}N NMR (51 MHz, DMSO-d_6) δ 120.33 (Cα-NH), 125.0 (C2-NH), 132.6 (N1′); IR (cm^{-1}): ν 3320 s, 2956 m, 2932 w, 2869 w, 1653 s, 1626 s, 1595 s, 1538 m, 1518 s, 1465 w, 1446 m, 1432 w, 1338 w, 1325 w, 1281 s, 1241 m, 762 w, 736 s, 677 m; MS (EI) *m*/*z* (%): 378 (19), 377 (70), 305 (20), 304 (76), 276 (22), 275 (88), 247 (15), 219 (20), 186 (29), 185 (100), 170 (62), 168 (39), 167 (20), 159 (20), 158 (33), 157 (31), 156 (56), 146 (23), 130 (46), 129 (36), 128 (58), 120 (66), 119 (30), 77 (15); HRMS (ESI$^+$): *m*/*z* calcd for $C_{23}H_{28}N_3O_2^+$ [M + H]$^+$ 378.2176, found 378.2168. Found: C, 73.0; H, 7.3; N, 11.1. Calc. for $C_{23}H_{27}N_3O_2$: C, 73.2; H, 7.2; N, 11.1%.

General procedure for the hydrolysis of benzoxazinones 4f,j,m into 2-(indol-2-carboxamido)benzoic acids 1f,j,m (Table 5, entries 3–6)

A mixture of benzoxazinone **4** (343 mg, 0.968 mmol), dimethyl sulfoxide (10 mL) and aqueous sodium hydroxide (0.5 M, 1 mL) was stirred at room temperature for the time indicated in Table 5 (for the reaction in entry 4, dioxane (3 mL) and aqueous sulphuric acid (0.1 M, 2 mL) were used). The reaction mixture was diluted with water (50 mL) and acidified with 10% hydrochloric acid to Congo red (for the reaction from entry 4, no additional acid was added). After stirring for 1 h, the precipitate was filtered off, washed with water and dried to afford 2-(indol-2-carboxamido)benzoic acid **1**. Yields of the products are indicated in Table 5. The spectral and analytical data for **1f,j** were in agreement with those for the authentic samples, prepared above.

1m: Colourless solid, mp 227–230 °C (ethanol), R_f = 0.39 (10% ethanol in chloroform). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.94 (t, 3H, J = 7.1 Hz, C3′(CH$_2$)$_2$CH_3), 1.69 (tq, 2H, J = 7.1, 7.1 Hz, C3′CH$_2$CH_2), 3.11 (t, 2H, J = 7.1 Hz, C3′CH$_2$), 7.10 (dd, 1H, J = 7.5, 7.5 Hz, H5′), 7.28 (dd, 1H, J = 7.5, 7.5 Hz, H6′), 7.50 (d, 1H, J = 8.2 Hz, H7′), 7.61 (dd, 1H, J = 7.5, 7.5 Hz, H7), 7.67 (dd, 1H, J = 7.5, 7.5 Hz, H6), 7.70 (d, 1H, J = 8.0 Hz, H4′), 7.95

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(d, 1H, J = 8.7 Hz, H4), 7.98 (d, 1H, J = 8.6 Hz, H3), 8.03 (d, 1H, J = 8.1 Hz, H5), 8.09 (d, 1H, J = 8.4 Hz, H8), 10.27 (br s, 1H, CONH), 11.54 (br s, 1H, H1′), 13.30 (br s, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 14.2 (C3′$(CH_2)_2CH_3$), 24.1 (C3′CH_2CH_2), 26.2 (C3′CH_2), 112.2 (C7′), 119.4 (C5′), 120.2 (C4′), 121.2 (C3′), 123.8 (C2), 124.3 (C6′), 125.5 (C8), 126.0 (C3), 126.2 (C4), 126.6 (C7), 126.7 (C2′), 127.7 (C3a′), 128.0 (C5), 128.1 (C6), 129.5 (C8a), 135.2 (C4a), 135.7 (C7a′), 135.8 (C1), 161.6 (CONH), 168.3 (COOH); IR (cm^{-1}): ν 3311 s, 3051 w, 2957 m, 2927 m, 2865 w, 1675 s, 1641 s, 1604 w, 1571 m, 1530 w, 1482 m, 1465 w, 1451 w, 1416 m, 1335 m, 1285 m, 1259 m, 1238 s, 1224 w, 1204 w, 1178 w, 767 m, 749 s; MS (EI) m/z (%): 373 (2), 372 (7), 355 (23), 354 (87), 326 (28), 325 (100), 297 (23), 283 (19), 269 (19), 170 (46), 169 (26), 156 (27), 140 (48), 129 (20), 128 (58), 115 (25), 77 (16); HRMS (ESI$^+$): m/z calcd for $C_{23}H_{21}N_2O_3^+$ $[M + H]^+$ 373.1547, found 373.1544. Found: C, 74.4; H, 5.5; N, 7.7. Calc. for $C_{23}H_{20}N_2O_3$: C, 74.2; H, 5.4; N, 7.5%.

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Notes and references

1 (*a*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893–930; (*b*) R. J. Sundberg, in *Indoles*, Academic Press, San Diego, 1996; (*c*) G. W. Gribble, *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Ress, E. F. V. Scriven and C. W. Bird, Pergamon Press, Oxford, 1996, vol. 2, p. 207.

2 P. Wiklund and J. Bergman, *Curr. Org. Synth.*, 2006, **3**, 379–402.

3 P.-L. Wu, Y.-L. Hsu and C.-W. Jao, *J. Nat. Prod.*, 2006, **69**, 1467–1470.

4 C. Jimènez, E. Quiñoa, M. Adamczeski, L. M. Hunter and P. Crews, *J. Org. Chem.*, 1991, **56**, 3403–3410.

5 (*a*) M. S. Shengelia, V. G. Avramenko, L. N. Kuleshova, N. N. Suvorov, V. A. Silin and E. N. Padeiskaya, *Khim.-Farm. Zh.*, 1985, **19**, 1075–1078; (*b*) A. Thorarensen, C. J. Ruble, J. F. Fisher, D. L. Romero, T. J. Beauchamp and J. M. Northuis, *PCT Int. Appl*, WO 2004018428 A1; *Chem. Abstr.*, 2004, **140**, 235498; (*c*) J. Li, B. D. Wakefield, J. C. Ruble, C. M. Stiff, D. L. Romero, K. R. Marotii, M. T. Sweeney, G. E. Zurenko, D. C. Rohrer and A. Thorarensen, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2347–2350; (*d*) C. Stiff, D. R. Graber, A. Thorarensen, B. D. Wakefield, K. R. Marotti, E. P. Melchior, M. T. Sweeney, F. Han, D. C. Rohrer, G. E. Zurenko and D. L. Romero, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6293–6297.

6 I. Amasaki and N. Hanaki, *U.S. Pat. Appl. Publ*, US 2009/0239982 A1; *Chem. Abstr.*, 2008, **149**, 567210.

7 (*a*) T. J. Dueweke, S. M. Poppe, D. L. Romero, S. M. Swaney, A. G. So, K. M. Downey, I. W. Althaus, F. Reusser, M. Busso, L. Resnick, D. L. Mayers, J. Lane, P. A. Aristoff, R. C. Thomas and W. G. Tarpley, *Antimicrob. Agents Chemother.*, 1993, **37**, 1127–1131; (*b*) M.-P. de Béthune, *Antiviral Res.*, 2010, **85**, 75–90.

8 F. Ban, E. Leblanc, H. Li, R. S. N. Munuganti, K. Frewin, P. S. Rennie and A. Cherkasov, *J. Med. Chem.*, 2014, **57**, 6867–6872.

9 S. Koeller, J. Kadota, F. Peruch, A. Deffieux, N. Pinaud, I. Pianet, S. Massip, J. M. Leger, J. P. Desvergne and B. Bibal, *Chem. – Eur. J.*, 2010, **16**, 4196–4205.

10 For recent examples, see: (*a*) A. M. Alanazi, A. A. M. Abdel-Aziz, I. A. Al-Suwaidan, S. G. Abdel-Hamide, T. Z. Shawer and A. S. El-Azab, *Eur. J. Med. Chem.*, 2014, **79**, 446–454; (*b*) M. A. El-Hashash and Y. A. El-Badry, *Helv. Chim. Acta*, 2011, **94**, 389–396.

11 (*a*) A. Krantz, R. W. Spencer, T. F. Tam, T. J. Liak, L. J. Copp, E. M. Thomas and S. P. Rafferty, *J. Med. Chem.*, 1990, **33**, 464–479; (*b*) A. Arcadi, C. Asti, L. Brandolini, G. Caselli, F. Marinelli and V. Ruggieri, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1291–1294.

12 U. Neumann, N. M. Schechter and M. Gütschow, *Bioorg. Med. Chem.*, 2001, **9**, 947–954.

13 L. Hedstrom, A. R. Moorman, J. Dobbs and R. H. Abeles, *Biochemistry*, 1984, **23**, 1753–1759.

14 R. L. Jarvest, M. J. Parratt, C. M. Debouck, J. G. Gorniak, J. L. Jennings, H. T. Serafinowska and J. E. Strickler, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2463–2466.

15 M. Gütschow and U. Neumann, *Bioorg. Med. Chem.*, 1997, **5**, 1935–1942.

16 (*a*) R. Krantz, E. W. Spencer, T. F. Tam, E. Thomas and L. J. Copp, *J. Med. Chem.*, 1987, **30**, 589–591; (*b*) J. L. Gilmore, S. J. Hays, B. W. Caprathe, C. Lee, M. R. Emmerling, W. Michael and J. C. Jaen, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 679–682; (*c*) S. J. Hays, B. W. Caprathe, J. L. Gilmore, N. Amin, M. R. Emmerling, W. Michael, R. Nadimpali, R. Nath, K. J. Raser, D. Stafford, D. Watson, K. Wang and J. C. Jaen, *J. Med. Chem.*, 1998, **41**, 1060–1067.

17 S. Mayama, T. Tani, T. Ueno, K. Hirabayashi, T. Nakashima, H. Fukami, Y. Mizuno and H. Irie, *Tetrahedron Lett.*, 1981, **22**, 2103–2106.

18 For example, see: (*a*) M. S. Shengelia, V. G. Avramenko, L. N. Kuleshova, N. N. Suvorov, V. A. Silin and E. N. Padeiskaya, *Khim.-Farm. Zh.*, 1985, **19**, 1075–1078; (*b*) S. P. Hiremath, A. C. Bajji and J. S. Biradar, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1988, **27**, 756–757; (*c*) S. A. Samsoniya, M. V. Trapaidze, N. A. Kuprashvili, D. S. Zurabishvili and N. N. Suvorov, *Chem. Heterocycl. Compd.*, 1998, **34**, 816–821; (*d*) E. S. Lee,

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This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

J. K. Son, Y. H. Na and Y. Jahng, *Heterocycl. Commun.*, 2004, **10**, 325–330.

19 For reviews of the Fischer indole synthesis, see: (*a*) B. Robinson, *Chem. Rev.*, 1963, **63**, 373–401; (*b*) B. Robinson, *Chem. Rev.*, 1969, **69**, 227–250; (*c*) G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045–1075.

20 For seminal studies of the Fischer indole synthesis, see: (*a*) E. Fischer and F. Jourdan, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 2241–2245; (*b*) E. Fischer and O. Hess, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 559–568.

21 S. Kafka, K. Proisl, V. Kašpárková, D. Urankar, R. Kimmel and J. Košmrlj, *Tetrahedron*, 2013, **69**, 10826–10835.

22 (*a*) M. Nakazaki and K. Yamamoto, *J. Org. Chem.*, 1976, **41**, 1877; (*b*) G. Baccolini and P. E. Todesco, *J. Chem. Soc., Chem. Commun.*, 1981, 563.

23 (*a*) K. G. Liu, A. J. Robichaud, J. R. Lo, J. F. Mattes and Y. Cai, *Org. Lett.*, 2006, **8**, 5769–5771; (*b*) S. Gore, S. Baskaran and B. König, *Org. Lett.*, 2012, **14**, 4568–4571.

24 A. Sudhakara, H. Jayadevappa, H. N. H. Kumar and K. M. Mahadevan, *Lett. Org. Chem.*, 2009, **6**, 159–164.

25 M. Shariat, M. W. Samsudin and Z. Zakaria, *Chem. Cent. J.*, 2013, **7**(58), 1–6.

26 G. M. Coppola, *J. Heterocycl.. Chem.*, 1999, **36**, 563–588.

27 (*a*) X. L. Lian, H. Lei, X. J. Quan, Z. H. Ren, Y. Y. Wang and Z. H. Guan, *Chem. Commun.*, 2013, **49**, 8196–8198; (*b*) Z. Y. Ge, Q. M. Xu, X. D. Fei, T. Tang, Y. M. Zhu and S. J. Ji, *J. Org. Chem.*, 2013, **78**, 4524–4529.

28 H. M. F. Madkour, *ARKIVOC*, 2004, **i**, 36–54.

29 A. G. Osborne and Z. Goolamali, *Spectrochim. Acta, Part A*, 2000, **56**, 1079–1100.

30 J. Vicens, M. C. Etter and L. A. Errede, *Tetrahedron Lett.*, 1983, **24**, 723–724.

31 (*a*) E. Wenkert, E. W. Hagaman, N. Kunesch, N. Y. Wang and B. Zsadon, *Helv. Chim. Acta*, 1976, **59**, 2711–2723; (*b*) M. S. Morales-Rios, J. Espiñeira and P. Joseph-Nathan, *Magn. Reson. Chem.*, 1987, **25**, 377–395; (*c*) M. S. Morales-Rios and P. Joseph-Nathan, *Magn. Reson. Chem.*, 1987, **25**, 911–918; (*d*) P. Joseph-Nathan, R. E. del Río and M. S. Morales-Ríos, *Heterocycles*, 1988, **27**, 377–383; (*e*) A. A. Panasenko, A. F. Caprosh, O. M. Radul and M. A. Rekhter, *Russ. Chem. Bull.*, 1994, **43**, 60–63.

32 (*a*) E. Rosenberg, K. L. Williamson and J. D. Roberts, *Org. Magn. Reson.*, 1976, **8**, 117–119; (*b*) R. M. Claramunt, D. Sanz, C. Lopez, J. Jimenez, M. L. Jimeno, J. Elguero and A. Fruchier, *Magn. Reson. Chem.*, 1997, **35**, 35–75; (*c*) M. d'Ischia, A. Napolitano and A. Pezzella, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, 2008, vol. 3.

33 D. C. G. A. Pinto, C. M. M. Santos and A. M. S. Silva, in *Recent Research Developments in Heterocyclic Chemistry 2007*, ed. T. M. V. D. Pinho e Melo, 2007, pp. 397–475.

34 K. A. Farley, G. S. Walker and G. E. Martin, *Magn. Reson. Chem.*, 1997, **35**, 671–679.

35 L. Lázár and F. Fülöp, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, 2008, vol. 8.

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