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MICROWAVE-ASSISTED SYNTHESIS OF 3,1-BENZOXAZIN-2-ONES FROM 3-HYDROXYOXINDOLES

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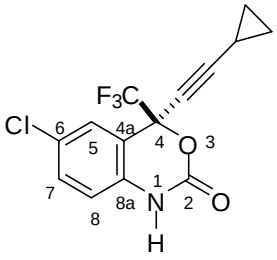
Abstract – A general protocol for the synthesis of 3,1-benzoxazin-2-ones **18** from 3-hydroxyoxindoles **16** in a two steps sequence through phenylsuccinates or phenylpropionates **17** is described. Best reaction conditions for ring opening of **16** to succinates or propionates **17** were achieved using alcohol/silica gel, while cyclization of **17** to benzoxazinones **18** was easily done with HCl/alcohol. It was also found that **17** and **18** can be transesterified using HCl/alcohol. Most transformations were carried out by traditional heating and by microwave (MW) irradiation to accelerate reaction rates.

INTRODUCTION

3,1-Benzoxazin-2-one derivatives have received considerable attention due to their strong biological activity.[1] For example, Sustive® (Efavirenz, **1**, Figure 1) is one of the most used non-nucleoside reverse transcriptase drugs for combating HIV-1 replication.[1a]



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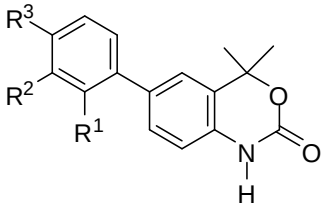
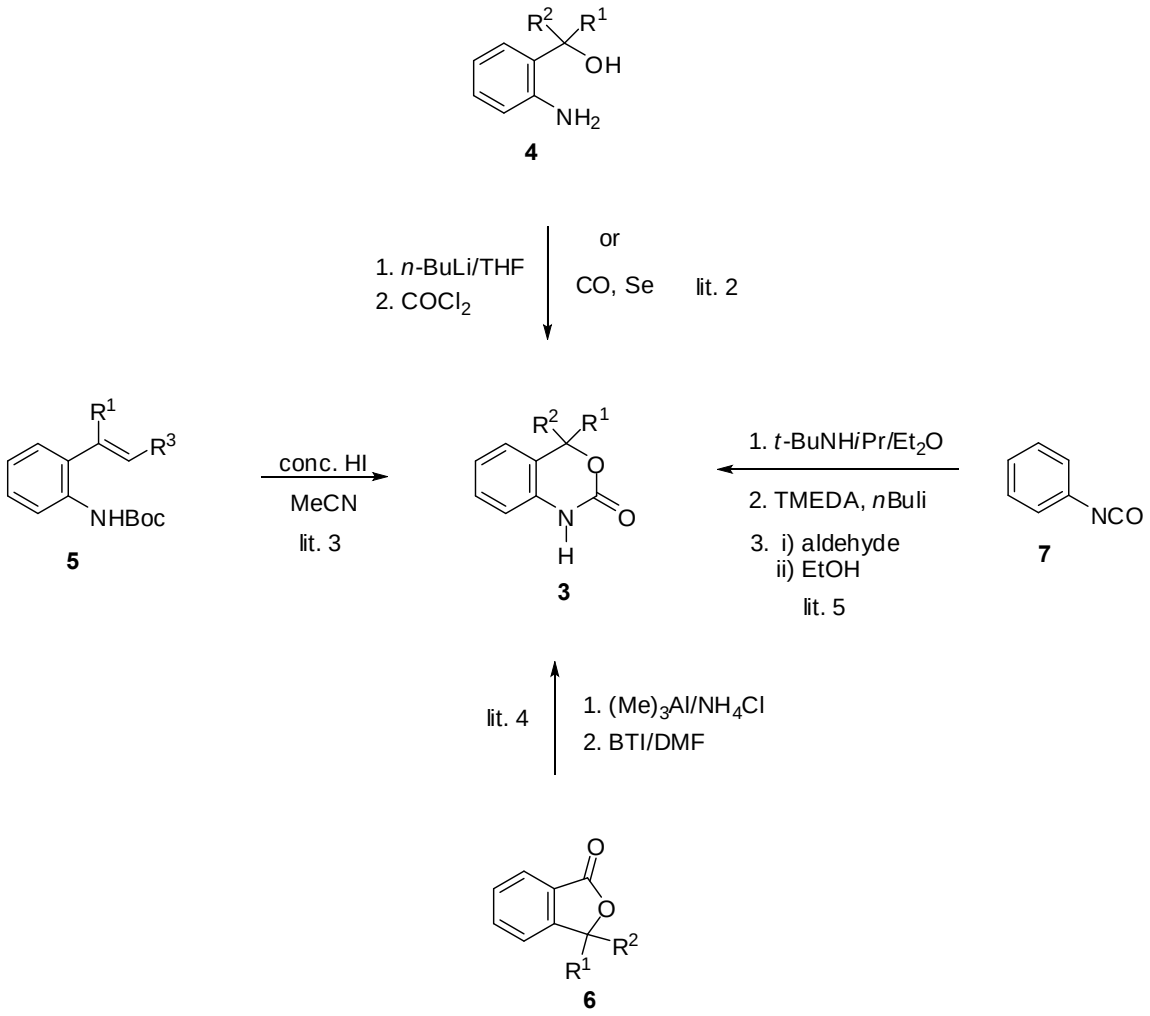


2a: $R^1 = R^3 = H$, $R^2 = F$
2b: $R^1 = Cl$, $R^2 = R^3 = H$
2c: $R^1 = H$, $R^2 = CN$, $R^3 = F$
2d: $R^1 = H$, $R^2 = Cl$, $R^3 = F$

Figure 1

Other 3,1-benzoxazin-2-one derivatives such as **2a-d** have shown to be non-steroidal potent and selective progesterone receptor antagonists.[1b,c] As clinically successful anti HIV and progesterone receptor antagonists, including 3,1-benzoxazin-2-one derivatives, are scarce and their therapeutic potential has not yet been fully realized, some reports on the synthesis of these heterocycles have appeared. At this respect, it is important to continue to develop efficient methods for the synthesis of this class of heterocycles, especially routes based upon readily available starting materials. A few general approaches for synthesizing the benzoxazinone skeleton **3** have been reported so far, for which representative examples are shown in Scheme 1. They include reaction of the corresponding *o*-aminobenzyl alcohol derivatives **4** with phosgene or its equivalents,[2] selenium-catalyzed cabonylation;[2] cyclization of *o*-vinyl-phenyl carbamates **5** reacting with I_2, Br_2, HI or H_2O_2;[3] and aminolysis of the lactone ring in 3-substituted phthalides **6** followed by Hofmann rearrangement and ring closure.[4] A recently developed methodology implies double-lithiation of a transient urea derived from phenylisocyanate **7** and subsequent reaction with aldehydes to give intermediate benzhydrols which cyclize to benzoxazinones.[3,5]

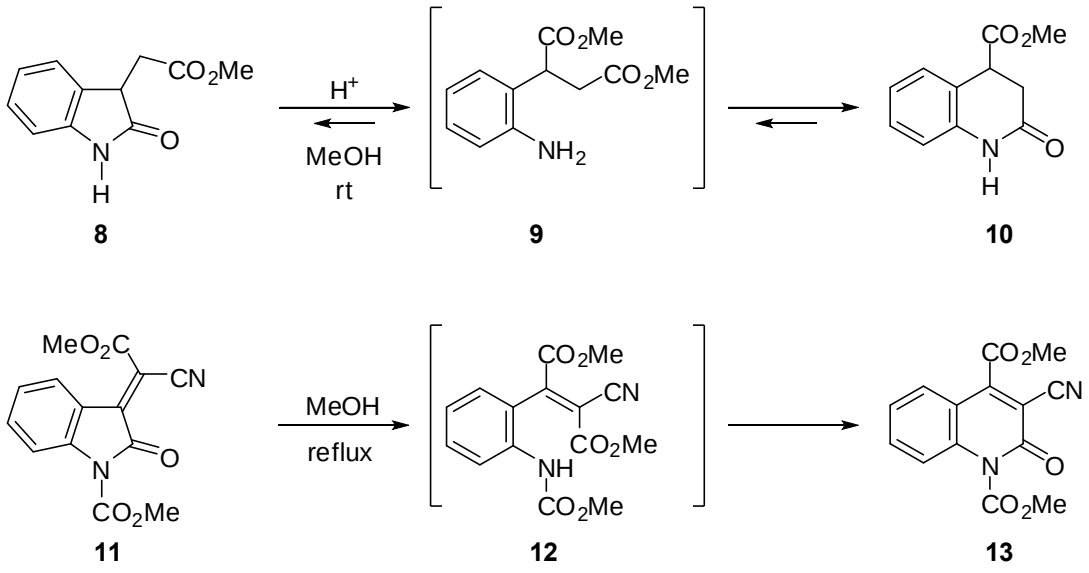


Scheme 1

In continuation with our studies aimed at developing new methods to synthesize heterocyclic compounds with potential biological activity, we describe herein an alternative procedure for the synthesis of the 3,1-benzoxazin-2-one core starting from 3-hydroxyoxindole derivatives. We also present the beneficial effect of microwaves on the transformations carried out in this work.

RESULTS AND DISCUSSION

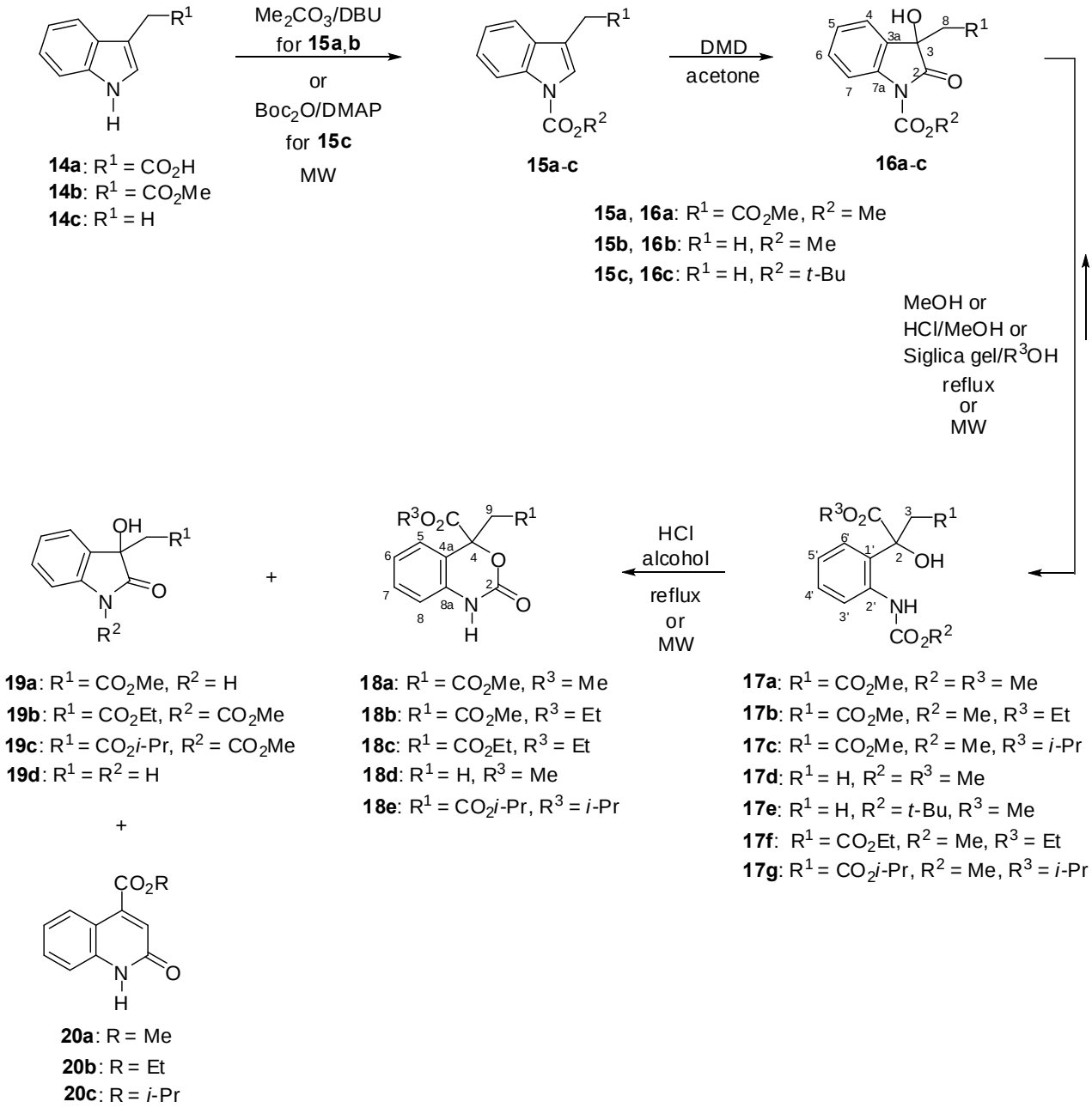
It is known that methyl 2-(2-oxo-3-indolyl)acetate (**8**, Scheme 2) is prone to undergo acid-catalyzed ring opening alkoxylation to give dimethylsuccinate **9**, which after recyclization leads to 2-quinolone **10**.[6] An equilibrium favoring **10** was identified[6] and succinate **9** could not be isolated. It is also known that *N*-carbomethoxy isatylidenes, like **11**, are smoothly opened to the corresponding benzylidene **12** on treatment with MeOH under reflux to give quinolinone **13** after ring reclosure.[7] In addition, we recently reported the preparation of 3-hydroxyoxindole derivatives like **16a** (Scheme 3) and their use for the total synthesis of natural products.[8] Thus, we envisioned that acid-catalyzed ring opening of these oxindoles could afford phenylsuccinates **17**, analogs of amino alcohols **4**, which in turn could be used to build the 3,1-benzoxazin-2-one scaffold **18**.



Scheme 2

The general synthesis of benzoxazinones is described in Scheme 3, showing 3-hydroxyoxindoles **16** as the key intermediates for the goal which were prepared from the corresponding indoles **14**. Compounds **14b** and **15a** have been synthesized under traditional heating,[8a] and in this work we explore for milder and practical reaction conditions to accelerate the rate of formation of compounds **14b**[8b] and **15a-c** by using microwave (MW) irradiation. The results are shown in Table 1, where comparisons of reaction times

clearly exemplifies the advantages of heating by MW irradiation to afford the products.[9] Thus, esterification of **14a** to **14b** and *N*-H protections of **14a-c** to **15a-c** always proceeded faster with MW-heating. In addition, oxidation of compounds **15a-c** to the corresponding 3-hydoxyoxindoles **16a-c** was achieved using dimethyl dioxirane (DMD).[10] The X-ray structure of **16b** is shown in Figure 2).



Scheme 3

With 3-hydroxyoxindoles **16a-c** in hand we focus our attention to the ring opening of compounds **16** with alcohols under reflux, giving rise to phenylsuccinates **17**. The reaction of **16a** with MeOH under reflux for 50 h afforded **17a** in 70% yield, together with unreacted starting material. When hydrogen chloride catalyzed methoxylation of **16a** was performed at rt, **17a** was obtained in 86% yield after a prolonged

reaction time (23 h). When the acid-catalyzed reaction was carried out under reflux for 5 h, the desired target 3,1-benzoxazin-2-one **18a** (Figure 4) and phenylsuccinate **17a** were obtained as major products in moderate 49% and 24% yields, respectively, together with minor amounts of quinolinone **20a** in 12% yield. In contrast, MW irradiation of **16a** for 1.5 h gave **17a** (41%), **18a** (20%) and **20a** (11%). Longer reaction times to increase selective formation of **18a** resulted in decomposition. These results clearly showed that 3-hydroxyoxindole **16a** could be a useful starting material to produce the 3,1-benzoxazin-2-one **18a** directly or in a two steps sequence through phenylsuccinate **17a**.

Table 1

Entry	Starting material	Product	Conditions[a]	Time	Yield (%)
1	**14a**	**14b**[b]	CH	4 h	94
2			MW	20 min	99
3	**14b**	**15a**[c]	CH	26 h	82
4			MW	6 h	80
5	**14c**	**15b**[c]	CH	26 h	92
6			MW	6 h	91
7	**14c**	**15c**[c]	rt	3 h	99
8			MW	10 min	97

[a]Conventional heating (CH), Microwave heating (MW).
[b]Product of esterification
[c]Product of indole protection

It is worth noting that most ^{1}H (Figure 5) and ^{13}C NMR signals of 3-hydroxyoxindole **16a** and 3,1-benzoxazin-2-one **18a** show quite similar signal patterns (see experimental) and could ambiguously be assigned to either compound, although the great differences in proton chemical shifts due to the OH (in **16a**), NH (in **18a**), H7 (in **16a**)[11] and H8 (in **18a**) signals as well as the specific AB pattern of the methylene protons for each isomer allow recognition of the spectrum for each isomer. The X-ray structures shown in Figures 2-4 evidence that H7, H3' and H5 in oxindoles **16**, succinates **17** and 3,1-benzoxazin-2-one **18**, respectively, could be affected by the anisotropic effect of the corresponding carbonyl groups in crystals, which is in exact coincidence with those results obtained in solution[11] (See experimental). Figure 3 shows succinate **17b** with a disordered ethyl group.

It is important to note that hydrogen chloride acid-catalyzed transformation of **16a** to **17a** or **18a** requires the use of freshly prepared concentrated HCl/MeOH (3.8 M) in order to avoid prolonged reaction times. Treatment of **16a** with silica gel[12] in refluxing MeOH, accomplished an efficient conversion (80%) in a

short time (1 h) to give phenylsuccinate **17a**. The MW irradiation was also efficiently achieved for this conversion since **17a** was obtained in only 8 min with a similar yield (81%) (Table 2, entries 1 and 2). On ring opening of 3-hydroxyoxindole **16a** to phenylsuccinate **17a** either with MeOH, HCl/MeOH or silica gel/MeOH, consumption of the starting material (**16a**) is close to completion and **16a** was always recovered. This suggested an equilibrium between **16a** and **17a**. In fact, when **17a** was treated with silica gel/MeOH under reflux for 1.5 h, TLC monitoring (by UV) of the reaction process always showed existence of two components corresponding to the starting material **17a** and 3-hydroxyoxindole **16a** in a constant ratio of 8:1 (by ^{1}H NMR).

In order to study the steric hindrance influence of the alcohol used in ring opening of **16a**, this compound was treated with EtOH, *i*-PrOH and *t*-BuOH using silica gel to catalyze the reaction under reflux and under MW irradiation. As is shown in Table 2 (Entries 3-6), ring opening of **16a** is greatly influenced by the steric bulkiness of the alcohol used. As the steric hindrance of the alcohol increases, conversion of **16a** to **17a-c** becomes considerably slower with starting material recovery and poor chemical yields. Even more, when **16a** was treated with *t*-BuOH, the desired product **18** was not detected, instead a trace amount of oxindole **19a** was obtained[8a] (Scheme 3) after a prolonged reaction time. Similarly, 3-hydroxyoxindoles **16b** and **16c** were converted to the corresponding phenylpropionates **17d** and **17e** in 87% and 76% yields, respectively, with MW irradiation (Table 2, entries 7-10). The synthesized phenylsuccinates **17a-d** were efficiently crystallized and their crystal structures are shown in Figure 3. With these results we can conclude that ring opening of 3-hydroxyoxindoles **16a-c** is steric hindrance dependent both on the alcohol and carbamate substituents. It is worth noting that the transformation of **16a-c** into **17a-e** is always accompanied by starting material recovery.

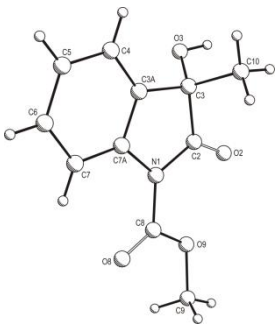
Once phenylsuccinates and propionates **17** were obtained, the next step was to find the best reaction conditions for benzoxazinone ring formation. Thus, when phenylsuccinate **17a** was treated with methanolic hydrogen chloride at rt, 3,1-benzoxazin-2-one **18a** was obtained in 70% yield but only after a prolonged reaction time (192 h) (Table 3, entry 1). The long reaction time for this transformation was drastically reduced by use of MW irradiation for 1 h, giving **18a** in 54% yield together with oxindole **16a** in 9% yield (Table 3, entry 2). In addition, when **17b** was treated with HCl/MeOH at rt for 288 h, the expected 3,1-benzoxazin-2-one **18b** was not obtained, but rather a mixture of transesterified phenylsuccinate **17a** and 3,1-benzoxazin-2-one **18a** was obtained in 33% and 64% yields, respectively (Table 3, entry 3). No traces of phenylsuccinate **17b** nor 3,1-benzoxazin-2-one **18b** were detected. This suggests that reactions from **17b** to **17a** or from **18b** to **18a** are faster than the ring closure of **17b** to 3,1-benzoxazin-2-one **18b**. To demonstrate this hypothesis, phenylsuccinate **17b** was treated with ethanolic hydrogen chloride at rt (for 288 h) to yield a mixture of phenylsuccinate **17f** (Figure 3) and 3,1-benzoxazin-2-one **18c** (Figure 4) in 32% and 60% yields (Table 3, entry 4), respectively, no traces of

3,1-benzoxazin-2-one **18b** or phenylsuccinate **17b** being detected. These results also demonstrated that steric hindrance for ring closure of **17a** or **17f** to the corresponding benzoxazinones does not influence significantly the reaction rate. When **17b** was reacted under the same reaction conditions using MW irradiation for 1 h, considerable enhancement was observed, giving rise to 3,1-benzoxazin-2-one **18c** in 43% yield, together with oxindole **19b** (19%), succinate **17f** (26%), and quinolinone **20b** (10%) (Table 3, entry 5).

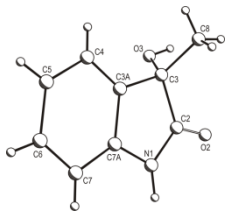
Table 2

Entry	Starting material	Alcohol used	Product	Conditions[a]	Time	Yield (%)
1	**16a**	MeOH	**17a**	CH	1 h	80
2				MW	8 min	81
3	**16a**	EtOH	**17b**	CH	14 h	70
4				MW	7 h	50
5	**16a**	*i*-PrOH	**17c**	CH	87 h	14
6				MW	21 h	10
7	**16b**	MeOH	**17d**	CH	1 h	85
8				MW	10 min	87
9	**16c**	MeOH	**17e**	CH	3 h	70
10				MW	45 min	76

[a]Conventional heating (CH) or Microwave heating (MW).



16b



19d

Figure 2. X-Ray crystal structures of 3-hydroxyoxindoles **16b** and **19d**

Less hindered phenylpropionate **17d** was also reacted with HCl/MeOH giving rise to 3,1-benzoxazin-2-one **18d** at rt in 76% after 192 h, a similar result than that obtained when **17a** was

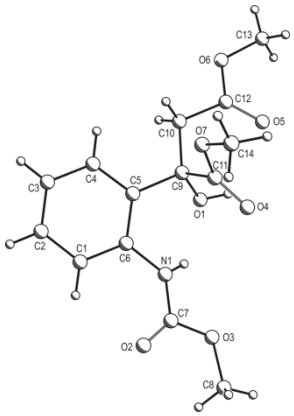
reacted under the same conditions. However, MW irradiation of **17d** during 1 h gave **18d** and oxindole **16b** in 81% and 8% yields, respectively (Table 3, entries 8 and 9).

Table 3

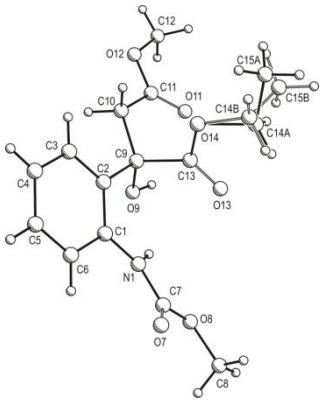
Entry	Starting material	Reaction conditions	Time (h)	Product (%)
1	**17a**	HCl/MeOH rt	192	**18a** (70)
2	**17a**	HCl/MeOH MW	1	**16a** (9), **18a** (54),
3	**17b**	HCl/MeOH rt	288	**17a** (33), **18a** (64)
4	**17b**	HCl/EtOH rt	288	**17f** (32), **18c** (60)
5	**17b**	HCl/EtOH MW	1	**17f** (26), **18c** (43), **19b** (19), **20b** (10)
6	**17c**	HCl/*i*-PrOH rt	432	**17g** (39), **18e** (16), **19c** (18)
7	**17c**	HCl/*i*-PrOH MW	1	**17g** (17), **18e** (42), **19c** (16), **20c** (12)
8	**17d**	HCl/MeOH rt	192	**18d** (76)
9	**17d**	HCl/MeOH MW	1	**16b** (8), **18d** (81)
10	**17e**	HCl/MeOH MW	1	**19d** (99)
11	**18a**	HCl/EtOH MW	1	**18c** (95)
12	**18a**	HCl/*i*-PrOH MW	1	**18e** (91)

The steric effect influence of ring closure from succinates to the benzoxazinone scaffold was evidenced when **17c** was treated with HCl/*i*-PrOH at rt since 3,1-benzoxazin-2-one **18e** (Figure 4) was obtained in only 16% yield after 432 h, together with succinate **17g** in 39% yield and oxindole **19c** in 18% yield (Table 3, entry 6), evidencing a steric effect dependence around C2 in the closure of phenylsuccinate **17a-c** and phenylpropionate **17d** to either 3,1-benzoxazin-2-one **18** or oxindole **19**. Attempting to reduce the long conversion time of **17c** to **18e** using MW afforded 3,1-benzoxazin-2-one **18e** in 42% yield,

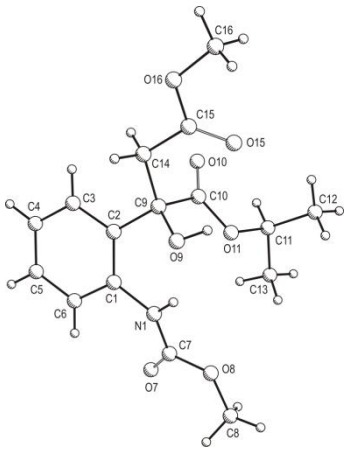
together with phenylsuccinate **17g** (17%), oxindole **19c** (16%) and quinolinone **20c** in 12% yield after 1 h (Table 3, entry 7). With less sterically hindered phenylsuccinates **17a-17b** and phenylpropionate **17d** nucleophilic attack of a OH group at C2 to form a carbonyl carbamate group is favored, giving rise to the corresponding 3,1-benzoxazin-2-ones **18a**, **18b** and **18d**, while with increased steric effect at this position nucleophilic attack of the NH group to the $-CO_2R^3$ group is favored affording oxindoles **19b** and **19c**. Reaction of *N*-Boc sterically hindered succinate **17e** with HCl/MeOH and MW irradiation conducted exclusively to oxindole **19d** (Figure 2, Table 5) in 99% after 1 h (Table 3, entry 10), probably due to acid labile hydrolysis of the NHBoc group.[13]



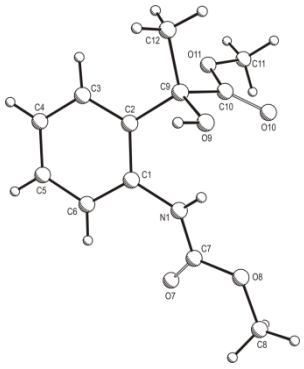
17a



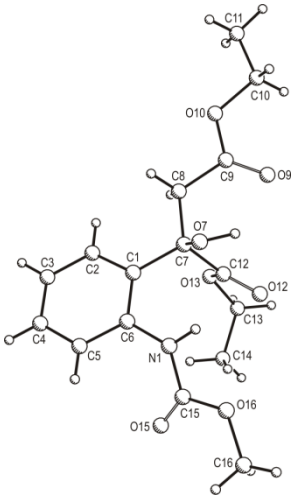
17b



17c



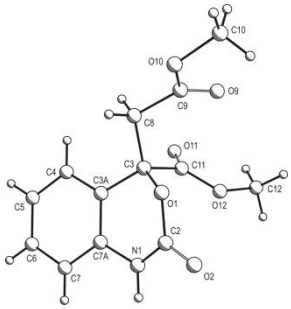
17d



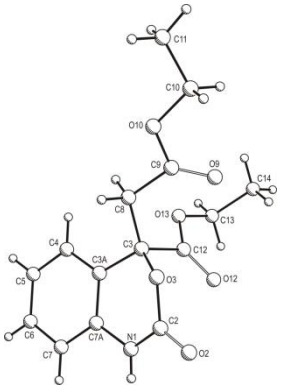
17f

Figure 3. X-Ray crystal structures of succinates **17a-17c** and **17f**, and phenylpropionate **17d**

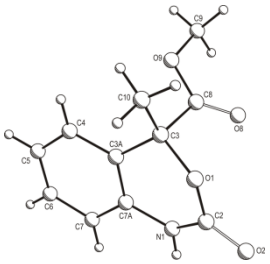
Although 3,1-benzoxazin-2-one **18c** and **18e** could easily be obtained from their corresponding succinates **17f** and **17g** using MW irradiation, the yields are low due to their transformation into unidentified products. Thus we decided to transesterify 3,1-benzoxazin-2-one **18a** with HCl/EtOH and HCl/*i*-PrOH using MW irradiation whereby 3,1-benzoxazin-2-ones **18c** and **18e** were obtained selectively in 95% and 91% yields, respectively (Table 3, entries 11 and 12).



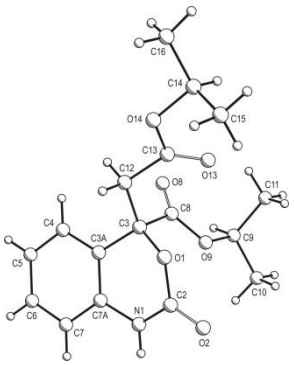
18a



18c



18d



18e

Figure 4. X-Ray crystal structures of 3,1-benzoxazin-2-ones **18a**, **18c-18e**

In conclusion, we have demonstrated that 3-hydroxyoxindoles **16** are suitable starting materials to synthesize 3,1-benzoxazin-2-ones **18** in a two steps sequence through phenylsuccinates or phenylpropionates **17**. A variety of 3,1-benzoxazin-2-ones could be obtained by transesterification of **17** or **18** with several alcohols. MW irradiation provides products in good yields and short reaction times as compared to conventional heating. In view of the ready availability of the starting materials, as well as the ease of operation, the present procedure offers a convenient synthetic methodology for this heterocycles.

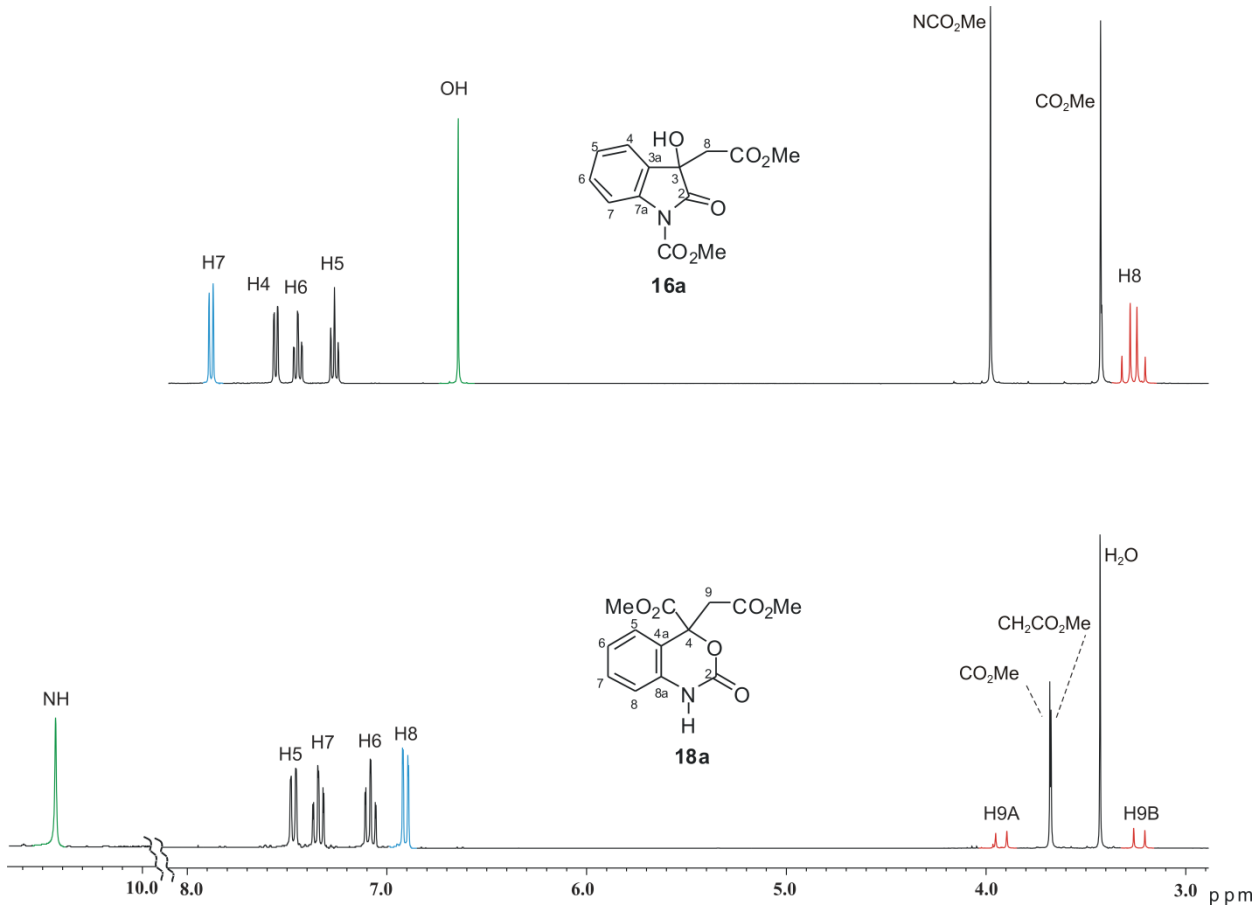


Figure 5. ^{1}H NMR spectra of 3-hydroxioxindole **16a** and 3,1-benzoxazin-2-one **18a** in DMSO-d_6, 400 MHz

EXPERIMENTAL

General experimental procedures

Melting points were determined on a Büchi B-540 apparatus. IR spectra were recorded on a Perkin-Elmer GX FT-IR spectrophotometer. The 400 and 100 MHz ^{1}H and ^{13}C NMR spectra were obtained on JEOL Eclipse + 400 and Varian VNMRS 400 spectrometers, while the 300 and 75 MHz ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury-300 spectrometer using $CDCl_3$ or DMSO-d_6, as solvents. The chemical shifts of $CHCl_3$ and DMSO present in the deuterated solvents were used as reference.[14] For complete assignments 2D NMR, gHSQC, and gHMBC spectra were used. Data are reported as follows: chemical shift in ppm, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sp = septet, m = multiplet, br = broad, AB = AB system), coupling constant (Hz), and assignment. GC/MS analyses were conducted on a Varian CP 3800 GC equipped with a Varian Saturn 2000 selective mass detector and a 30 m, 0.25 mm i.d., 0.25 mm CP-SIL capillary column, using helium as carrier gas (1 mL/min), programmed from 70 °C to 250 °C at a rate of 30 °C/min, with the injector temperature at 200 °C. MS analyses were obtained in the electron impact (EI) mode at an ionizing voltage of 70 eV on a Hewlett

Packard 5989-A spectrometer. High-resolution (HR) mass spectra were measured on a JEOL JMS-SX 102A mass spectrometer at Instituto de Química, UNAM-México. Microanalytical determinations were performed on a Perkin-Elmer 2400 series PCII apparatus. Analytical thin-layer chromatography (TLC) was done on silica gel F_{254} coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography was done using Silica Gel 60 (230-400 mesh) from Aldrich. Microwave irradiation reactions were carried out on a CEM *Mars 5*™ microwave reactor working at 300 watts ±15% and equipped with an ESP-1500 Plus Pressure Control System and a RTP-300 Plus Temperature Control System. The reaction mixtures were deposited in HP-500 vessels and the instrumental temperature settings were 60 °C for MeOH, 75 °C for EtOH, 85 °C for *i*-PrOH, 80 °C for CH_3CN, and 120 °C for Me_2CO_3.

Preparation of methyl 2-(1*H*-indol-3-yl)acetate 14b.

To a solution of indolylacetic acid (**14a**, 6.00 g, 34.25 mmol) in MeOH (50 mL) was added *p*-toluenesulfonic acid (100 mg) and the solution heated under microwave irradiation for 20 min. After cooling to rt, the MeOH was evaporated under reduced pressure and the residue was dissolved in EtOAc (100 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (2 x 30 mL) and brine (2 x 30 mL), dried over Na_2SO_4, filtered and evaporated to dryness in vacuum. The resultant crude product was purified by flash column chromatography on silica gel eluting with EtOAc/hexanes 1:4 to give **14b** as a yellow solid (6.450 g, 99%). Spectra were consistent with those reported.[8c]

General procedure for the preparation of indole carbamates 15b,c.[8]

A solution of 3-methylindole (**14c**, 1.0 g, 7.62 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) 0.1 equiv (114 μL) in Me_2CO_3 (30 mL) was stirred under reflux (*i*) for 26 h or (*ii*) during 6 h under microwave irradiation. Similarly, to a solution of **14c** (1.0 g, 7.62 mmol) in MeCN (25 mL) was added Boc_2O (2.0 g, 1.2 equiv) and DMAP (0.093 g, 0.1 equiv) and the mixture was stirred at rt (*iii*) for 3 h or (*iv*) during 10 min under microwave irradiation. After cooling to rt, the volatiles were evaporated and EtOAc (50 mL) was added to the reaction crudes. The organic solution was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 25 mL) and brine (2 × 25 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant crude products **15b**,**c** were purified by flash chromatography on silica gel using EtOAc/hexanes 1:7.

Methyl 3-methyl-1*H*-indolecarboxylate (15b). Prepared from **14c** as colorless oil:[8] (*i*) 1.330 g, 92%; (*ii*) 1.320 g, 91%. Although **15b** is known,[15] it is spectroscopically not yet fully characterized. Thus, NMR

data follow: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (1H, brs, H7), 7.52 (1H, dd, *J* = 7.1, 0.8 Hz, H4), 7.37 (1H, td, *J* = 7.1, 1.2 Hz, H6) and 7.37 (1H, brs, H2), 7.29 (1H, td, *J* = 7.4, 0.8 Hz, H5), 4.02 (3H, s, CO_2Me), 2.29 (3H, d, *J* = 1.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.7 (*C*O_2Me), 135.7 (C7a), 131.7 (C3a), 124.7 (C6), 122.9 (C5), 122.6 (C2), 119.2 (C4), 117.5 (C3), 115.3 (C7), 53.8 (CO_2*Me*), 9.9 (CH_3); IR (KBr) ν_{max} 3051, 2955, 1734, 1611 cm^{-1}; EIMS *m/z* 189 [M^+] (100), 144 (43), 130 (19), 103 (9), 77 (9); FABHRMS *m/z* 189.0790 (calcd for $C_{11}H_{11}NO_2$,189.0790).

***tert*-Butyl 3-methyl-1*H*-indole-1-carboxylate (15c).** Prepared from **14c** as colorless oil: (*iii*) 1.750 g, 99%; (*iv*) 1.700 g, 97%. Although **15c** is known,[16] it is spectroscopically not yet fully characterized. Thus, NMR data follow: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (1H, brs, H7), 7.48 (1H, d, *J* = 7.8 Hz, H4), 7.34 (1H, brs, H2), 7.30 (1H, td, *J* = 7.3, 1.3 Hz, H6), 7.23 (1H, td, *J* = 7.4, 1.3 Hz, H5), 2.25 (3H, s, CH_3), 1.65 (9H, s, CO_2*t*Bu); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.9 (*C*O_2*t*Bu), 134.7 (C7a), 130.8 (C3a), 123.6 (C6), 122.2 (C2), 121.8 (C5), 118.4 (C4), 115.9 (C3), 114.7 (C7), 83.3 (CO_2*t*Bu), 29.2 (CO_2*t*Bu), 10.9 (CH_3); IR (KBr) ν_{max} 2978, 2934, 1732, 1609, 1389 cm^{-1}; EIMS *m/z* 175 [M^+ − *t*Bu] (100), 130 (91), 77 (14), 57 (30); FABHRMS *m/z* 231.1252 (calcd for $C_{14}H_{17}NO_2$, 231.1259).

General procedure for the preparation of 3-hydroxyoxindoles 16b,c. To a solution of the appropriate indole **15b** (0.50 g, 2.64 mmol) or **15c** (0.50 g, 2.16 mmol) in acetone (15 mL) was added $NaHCO_3$ (3.5 equiv) dissolved in water (5-7 mL). The resulting thick mixture was treated dropwise, at rt over 10 min, with a solution of oxone monopersulfate complex (2.5 equiv of $KHSO_5$) and disodium EDTA (5 mg) in water (4-6 mL). After complete addition, the mixture was stirred at rt for additional 2 h for **15b**, and 4 h for **15c**. The solids were filtrated off and the acetone was evaporated under reduced pressure, and the residue was dissolved in EtOAc (30 mL). The organic solution was washed with brine (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant crude products were purified by flash column chromatography with EtOAc/hexanes 1:4.

Methyl 3-hydroxy-3-methyl-2-oxoindoline-1-carboxylate (16b). Prepared from **15b** as colorless crystals (0.350 g, 59%); mp 90−92 ºC (EtOAc/hexanes); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.85 (1H, d, *J* = 8.3 Hz, H7), 7.49 (1H, dd, *J* = 7.3, 1.0 Hz, H4), 7.42 (1H, td, *J* = 7.8, 1.4 Hz, H6), 7.28 (1H, td, *J* = 7.3, 1.0 Hz, H5), 6.32 (1H, s, OH), 3.95 (3H, s, CO_2Me), 1.49 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.8 (C2), 150.0 (*C*O_2Me), 137.1 (C7a), 131.6 (C3a), 128.6 (C6), 124.3 (C5), 123.1 (C4), 114.3 (C7), 72.7 (C3), 54.5 (CO_2*Me*), 26.2 (CH_3); IR (KBr) ν_{max} 3405, 3004, 2953, 1761, 1746, 1614 cm^{-1}; EIMS *m/z* 221 [M^+] (21), 204 (31), 193 (58), 178 (32), 146 (100); *Anal*. Calcd for $C_{11}H_{11}NO_4$: C 59.73; H 5.01; N

6.33. Found: C 59.73; H 4.92; N 5.98.

***tert*-Butyl 3-hydroxy-3-methyl-2-oxoindoline-1-carboxylate (16c).** Prepared from **15c** as colorless oil (0.350 g, 62%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.79 (1H, brd, J = 8.2 Hz, H7), 7.47 (1H, dd, J = 7.4, 1.2 Hz, H4), 7.40 (1H, td, J = 8.2, 1.2 Hz, H6), 7.25 (1H, td, J = 7.5, 1.1 Hz, H5), 6.25 (1H, s, OH), 1.61 (9H, s, CO_2tBu), 1.47 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.3 (C2), 149.7 (CO_2tBu), 139.1 (C7a), 133.2 (C3a), 130.1 (C6), 125.6 (C5), 124.5 (C4), 115.5 (C7), 84.6 (CO_2tBu), 73.1 (C3), 28.6 (CO_2tBu), 25.8 (CH_3); IR (film) ν_{max} 3452, 2980, 2934, 1781, 1732, 1611, 1288, 1146 cm^{-1}; EIMS *m*/*z* 163 [$M^+ - CO_2t$Bu] (32), 146 (26), 135 (91), 120 (100); FABHRMS *m/z* 263.1163 (calcd for $C_{14}H_{17}NO_4$, 263.1158).

Procedures for ring opening of 3-hydroxyoxindoles 16a-c.

Method A. A solution of dioxyindole **16a** (0.50 g, 1.791 mmol) in MeOH (25 mL) was heated under reflux for 50 h. After cooling to rt, the solvent was evaporated under reduced pressure and the resultant crude product was purified by flash column chromatography.

Method B. A solution of dioxyindole **16a** (0.10 g, 0.358 mmol) in HCl/MeOH (3.8 M, 2.5 mL) was stirred at rt for 23 h. The volatiles were evaporated under reduced pressure and the residue was diluted with EtOAc (25 mL), washed with an aqueous saturated aqueous solution of $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant crude product was purified by flash column chromatography.

Method C. A solution of dioxyindole **16a** (0.50 g, 1.791 mmol) in HCl/MeOH (3.8 M, 25 mL) was stirred under reflux (*i*) for 5 h or (*ii*) under microwave irradiation during 1.5 h. The volatiles were evaporated under reduced pressure and the residue was diluted with EtOAc (50 mL), washed with an aqueous saturated aqueous solution of $NaHCO_3$ (3 × 25 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant crude product was purified by flash column chromatography.

Method D. To a solution of the appropriate dioxyindole **16a** (0.50 g, 1.791 mmol), **16b** (0.50 g, 2.260 mmol) or **16c** (0.50 g, 1.899 mmol) in 25 mL of the appropriate alcohol (MeOH for **16a-c**, EtOH for **16a**, or *i*-PrOH for **16a**) was added silica gel (1.0 g) and the mixture heated (*i*) at reflux or (*ii*) under microwave irradiation for a specified period of time as follows: (*i*) **16a** and **16b** when reacting with MeOH for 1 h, **16c** for 3 h; **16a** when reacting with EtOH for 14 h; **16a** when reacting with *i*-PrOH for 87 h; (*ii*) **16a** when reacting with MeOH for 8 min, **16b** for 10 min and **16c** for 45 min; **16a** when reacting

with EtOH for 7 h; **16a** when reacting with *i*-PrOH for 21 h. After cooling to rt, the solids were filtrated, the alcohol was evaporated under reduced pressure and the residue was purified by column chromatography.

Dimethyl 2-hydroxy-2-(2-(methoxycarbonylamino)phenyl)succinate (17a). Prepared from **16a** and purified with EtOAc/hexanes 2:3 to afford colorless crystals. Method A: 0.389 g, 70% and 0.138 g of recovered **16a**; Method B: 0.096 g, 86% and 0.013 g of recovered **16a**; Method C: (*i*) 0.133 g, 24% and 0.045 g of recovered **16a**; (*ii*) 0.226 g, 41% and 0.044 g of recovered **16a**; Method D: (*i*) 0.446 g, 80% and 0.082 g of recovered **16a**; (*ii*) 0.449 g, 81% and 0.083 g of recovered **16a**; mp 145-147 ºC (EtOAc/hexanes); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.08 (1H, brs, NH), 7.90 (1H, brd, J = 8.0 Hz, H3'), 7.39 (1H, dd, J = 7.6, 1.1 Hz, H6'), 7.35 (1H, td, J = 7.6, 1.4 Hz, H4'), 7.11 (1H, td, J = 7.6, 1.1 Hz, H5'), 7.02 (1H, s, OH), 3.70 (3H, s, NCO_2Me), 3.65 (3H, s, CO_2Me), 3.64 (3H, s, $CH_2CO_2\mathit{Me}$), 3.56, 3.08 (2H, AB system, J = 15.0 Hz, H3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.9 ($\mathit{C}O_2Me$), 170.6 ($CH_2\mathit{C}O_2Me$), 154.6 ($N\mathit{C}O_2Me$), 137.9 (C2'), 130.8 (C1'), 129.7 (C4'), 127.4 (C6'), 124.1 (C5'), 122.5 (C3'), 77.4 (C2), 53.3 ($CO_2\mathit{Me}$), 52.9 ($CH_2CO_2\mathit{Me}$), 52.5 ($NCO_2\mathit{Me}$), 44.2 (C3); IR (KBr) ν_{max} 3451, 3352, 2957, 2850, 1731, 1590, 1455 cm^{-1}; EIMS *m*/*z* 311 $[M]^+$ (6), 279 (5), 252 (15), 220 (42), 178 (23), 146 (100), 120 (10), 90 (18), 59 (26). *Anal*. Calcd for $C_{14}H_{17}NO_7$: C 54.02; H 5.50; N 4.50. Found: C 54.31; H 5.57; N 4.10.

Methyl 4-(2-methoxy-2-oxoethyl)-2-oxo-2,4-dihydro-1*H*-benzo[*d*][1,3]oxazine-4-carboxylate (18a). Prepared from **16a** and purified with EtOAc/hexanes 2:3 to afford **18a** as colorless crystals. Method C: (*i*) 0.243 g, 49%; (*ii*) 0.102 g, 20%; mp 181-183 ºC (EtOAc/hexanes); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.43 (1H, s, NH), 7.47 (1H, dd, J = 7.7, 1.1 Hz, H5), 7.34 (1H, td, J = 7.7, 1.3 Hz, H7), 7.08 (1H, td, J = 7.7, 1.1 Hz, H6), 6.91 (1H, dd, J = 8.0, 1.1 Hz, H8), 3.92, 3.23 (2H, AB system, J = 16.8 Hz, H9), 3.68 (3H, s, CO_2Me), 3.67 (3H, s, CH_2CO_2Me); ^{13}C NMR (DMSO-d_6, 75.4 MHz) δ 170.2 ($\mathit{C}O_2Me$), 169.9 ($CH_2\mathit{C}O_2Me$), 149.8 (NCO_2), 136.5 (C8a), 131.3 (C7), 126.2 (C5), 123.9 (C6), 118.7 (C4a), 115.3 (C8), 83.1 (C4), 54.2 ($CH_2CO_2\mathit{Me}$), 52.9 ($CO_2\mathit{Me}$), 41.7 (C9); IR (KBr) ν_{max} 3431, 3131, 2960, 1723, 1599, 1490 cm^{-1}; EIMS *m*/*z* 279 $[M]^+$ (2), 220 (23), 188 (11), 146 (100); *Anal*. Calcd for $C_{13}H_{13}NO_6$: C 55.92; H 4.69; N 5.02. Found: C 55.96; H 4.64; N 4.74.

Methyl 2-oxo-1,2-dihydroquinoline-4-carboxylate (20a). The reaction of **16a** with method C also afforded quinolinone **20a** which was purified with EtOAc/hexanes 2:3 to afford **20a** as a white solid: (*i*) 0.042 g, 12%; (*ii*) 0.041 g, 11%; mp 246-248 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.20 (1H, brs, NH), 8.09 (1H, dd, J = 8.2, 1.2 Hz, H5), 7.61 (1H, td, J = 8.2, 1.2 Hz, H7), 7.42 (1H, dd, J = 8.2, 0.8 Hz, H8),

7.28 (1H, td, *J* = 7.5, 1.2 Hz, H6), 6.94 (1H, s, H3), 3.96 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.6 (CO_2Me), 161.9 (C2), 141.0 (C4), 140.4 (C8a), 132.2 (C7), 126.9 (C5), 125.0 (C3), 123.5 (C6), 116.9 (C8), 116.5 (C4a), 54.0 (CH_3); IR (KBr) ν_{max} 3453, 2919, 2850, 1727, 1671 cm^{-1}; EIMS *m*/*z* 203 $[M]^+$ (100), 173 (19), 144 (22), 117 (26).

1-Ethyl 4-methyl-2-hydroxy-2-(2-(methoxycarbonylamino)phenyl)succinate (17b). Prepared from **16a** and purified with EtOAc/hexanes 2:3 to afford colorless crystals. Method D: (*i*) 0.405 g, 70% and 0.135 g of recovered **16a**; (*ii*) 0.292 g, 50% and 0.222 g of recovered **16a**; mp 90-92 ºC (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.12 (1H, brs, NH), 7.92 (1H, brd, *J* = 8.0 Hz, H3'), 7.38 (1H, d, *J* = 7.7 Hz, H6'), 7.36 (1H, t, *J* = 7.3 Hz, H4'), 7.10 (1H, td, *J* = 7.3, 1.1 Hz, H5'), 6.99 (1H, s, OH), 4.13 (2H, dc, *J* = 15.0, 7.3 Hz, CO_2CH_2), 3.70 (3H, s, NCO_2Me), 3.64 (3H, s, CO_2Me), 3.57, 3.08 (2H, AB system, *J* = 15.0 Hz, H3), 1.15 (3H, t, *J* = 7.3 Hz, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.4 (CO_2CH_2), 170.6 (CO_2Me), 154.5 (NCO_2Me), 138.0 (C2'), 130.7 (C1'), 129.7 (C4'), 127.4 (C6'), 123.9 (C5'), 122.1 (C3'), 77.4 (C2), 62.2 (CO_2CH_2), 52.9 (NCO_2Me), 52.5 (CO_2Me), 44.2 (C3), 14.7 (Et); IR (KBr) ν_{max} 3460, 3366, 2957, 2849, 1732, 1589, 1452 cm^{-1}; EIMS *m*/*z* 325 $[M]^+$ (4), 279 (4), 252 (16), 220 (46), 178 (28), 146 (100), 90 (16), 59 (19). *Anal*. Calcd for $C_{15}H_{19}NO_7$: C 55.38; H 5.89; N 4.31. Found: C 55.51; H 5.88; N 3.91.

1-Isopropyl 4-methyl 2-hydroxy-2-(2-(methoxycarbonylamino)phenyl)succinate (17c). Prepared from **16a** and purified with EtOAc/hexanes 2:3 to afford colorless crystals. Method D: (*i*) 0.085 g, 14% and 0.390 g of recovered **16a**; (*ii*) 0.061 g, 10% and 0.414 g of recovered **16a**; mp 113-115 ºC (EtOAc/hexanes); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.17 (1H, brs, NH), 7.95 (1H, brd, *J* = 8.0 Hz, H3'), 7.36 (1H, d, *J* = 7.7 Hz, H6'), 7.35 (1H, t, *J* = 7.3 Hz, H4'), 7.09 (1H, td, *J* = 7.7, 1.1 Hz, H5'), 6.96 (1H, s, OH), 4.94 (1H, sp, *J* = 6.3 Hz, CH), 3.70 (3H, s, NCO_2Me), 3.64 (3H, s, CO_2Me), 3.57, 3.07 (2H, AB system, *J* = 15.0 Hz, H3), 1.18, 1.14 (6H, 2d, *J* = 6.3, 6.6 Hz, $2CH_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 171.8 (CO_2CH), 170.6 (CO_2Me), 154.4 (NCO_2Me), 138.1 (C2'), 130.4 (C1'), 129.7 (C4'), 127.4 (C6'), 123.7 (C5'), 121.7 (C3'), 77.5 (C2), 69.9 (CH), 52.8 (CO_2Me), 52.5 (NCO_2Me), 44.2 (C3), 22.1, 22.0 ($2CH_3$); IR (KBr) ν_{max} 3446, 3341, 2982, 2847, 1712, 1590 cm^{-1}; EIMS *m*/*z* 339 $[M]^+$ (4), 252 (21), 220 (44), 178 (31), 146 (100), 90 (22), 59 (20); *Anal*. Calcd for $C_{16}H_{21}NO_7$: C 56.63; H 6.24; N 4.13. Found: C 56.90; H 6.37; N 3.94.

Methyl 2-hydroxy-2-(2-(methoxycarbonylamino)phenyl)propionate (17d). Prepared from **16b** and purified with EtOAc/hexanes 1:7 to afford colorless crystals. Method D: (*i*) 0.484 g, 85% and 0.063 g of recovered **16b**; (*ii*) 0.499 g, 87% and 0.051 g of recovered **16b**; mp 108-110 ºC (EtOAc/hexanes); ^{1}H

NMR (DMSO-d_6, 400 MHz) δ 8.86 (1H, brs, NH), 7.77 (1H, brd, J = 7.8 Hz, H3'), 7.42 (1H, dd, J = 7.8, 1.4 Hz, H6'), 7.34 (1H, td, J = 7.3, 1.4 Hz, H4'), 7.13 (1H, td, J = 7.3, 1.1 Hz, H5'), 6.84 (1H, brs, OH), 3.68 (3H, s, NCO_2Me), 3.59 (3H, s, CO_2Me), 1.76 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.5 (CO_2Me), 153.0 (NCO_2Me), 136.2 (C2'), 131.9 (C1'), 128.1 (C4'), 125.8 (C6'), 123.1 (C5'), 121.4 (C3'), 75.7 (C2), 53.2 (CO_2Me), 52.8 (NCO_2Me), 26.9 (CH_3); IR (KBr) ν_{max} 3363, 3293, 3012, 2957, 1746, 1701, 1609 cm^{-1}; EIMS m/z [$M^+ - H_2O$] (0.1), 221 (37), 204 (100), 193 (51), 178 (27), 146 (83); *Anal*. Calcd for $C_{12}H_{15}NO_5$: C 56.91; H 5.97; N 5.53. Found: C 56.94; H 5.89; N 5.26.

Methyl 2-(2-(*tert*-butoxycarbonylamino)phenyl)-2-hydroxypropionate (17e). Prepared from **16c** and purified with CH_2Cl_2 to afford **17e** as colorless crystals. Method D: (*i*) 0.395 g, 70% and 0.120 g of recovered **16c**; (*ii*) 0.425 g, 76% and 0.079 g of recovered **16c**; mp 128-130 ºC (EtOAc/hexanes); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.58 (1H, brs, NH), 7.74 (1H, brd, J = 7.9 Hz, H3'), 7.40 (1H, dd, J = 7.6, 1.5 Hz, H6'), 7.32 (1H, td, J = 7.0, 1.5 Hz, H4'), 7.10 (1H, td, J = 7.6, 1.1 Hz, H5'), 6.80 (1H, brs, OH), 3.62 (3H, s, CO_2Me), 1.77 (3H, s, CH_3), 1.49 (9H, s, CO_2tBu); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.8 (CO_2Me), 153.4 (CO_2tBu), 138.0 (C2'), 133.1 (C1'), 129.2 (C4'), 127.0 (C6'), 123.9 (C5'), 122.8 (C3'), 80.2 (CO_2tBu), 76.1 (C2), 53.3 (CO_2Me), 29.0 (CO_2tBu), 26.5 (CH_3); IR (KBr) ν_{max} 3344, 3314, 2992, 2951, 1737, 1686, 1608 cm^{-1}; EIMS m/z 190 [M^+ − O-tBu + MeOH)] (0.1), 163 (30), 135 (93), 120 (100), 92 (19); FABHRMS m/z 295.1428 (calcd for $C_{15}H_{21}NO_5$, 295.1420).

Cyclization procedure for succinates and propionates 17a-e.

A solution of the appropriate succinate **17a** (0.250 g, 0.803 mmol), **17b** (0.250 g, 0.768 mmol), **17c** (0.250 g, 0.737 mmol) or propionate **17d** (0.250 g, 0.987 mmol), **17e** (0.250 g, 0.846 mmol) in the appropriate HCl/alcohol mixture (50 mL) was stirred at (*i*) rt or (*ii*) under microwave irradiation for a specified period of time as follows: (*i*) **17a** and **17d** when reacting with HCl/MeOH for 192 h, **17b** for 288 h, **17e** for 1 h; **17b** when reacting with HCl/EtOH for 288 h; **17c** when reacting with HCl/*i*-PrOH for 432 h; (*ii*) **17a** and **17d** when reacting with HCl/MeOH for 1 h, **17b** when reacting with HCl/EtOH for 1 h; **17c** when reacting with HCl/*i*-PrOH for 1 h. The volatiles were evaporated under reduce pressure and the residue was diluted with EtOAc (30-50 mL), washed with aqueous saturated aqueous solution of $NaHCO_3$ (3 × 25 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant crude product was purified by flash column chromatography. Cyclization of **17a** afforded **16a** and **18a**, cyclization of **17b** afforded **18c**, **17f**, **19b** and **20b**, cyclization of **17c** afforded **18e**, **17g**, **19c** and **20c**, cyclization of **17d** afforded **16b** and **18d**, while cyclization of **17e** afforded **19d**.

Methyl 3-hydroxy-3-(2-methoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate 16a. Prepared from **17a** and purified with EtOAc/hexanes 2:3 to afford colorless crystals (*ii*) 0.020 g, 9%; mp 132-133 ºC (EtOAc/hexanes), Lit.,[8] 132-133 °C.

Methyl 4-(2-methoxy-2-oxoethyl)-2-oxo-2,4-dihydro-1*H*-benzo[*d*][1,3]oxazine-4-carboxylate (18a). Prepared from **17a** and purified with EtOAc/hexanes 2:3 to afford colorless crystals (*i*) 0.156 g, 70% and 0.072 g of recovered **17a**; (*ii*) 0.120 g, 54% and 0.090 g of recovered **17a**.

Ethyl 4-(2-ethoxy-2-oxoethyl)-2-oxo-2,4-dihydro-1*H*-benzo[*d*][1,3]oxazine-4-carboxylate (18c). Prepared from **17b** and purified with EtOAc/hexanes 2:3 to afford colorless crystals (*i*) 0.141 g, 60%; (*ii*) 0.102 g, 43%; mp 132-134 ºC (EtOAc/hexanes); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.43 (1H, brs, NH), 7.45 (1H, d, *J* = 6.9 Hz, H5), 7.33 (1H, td, *J* = 7.8, 1.4 Hz, H7), 7.07 (1H, td, *J* = 7.8, 1.4 Hz, H6), 6.90 (1H, dd, *J* = 7.8, 0.9 Hz, H8), 4.20-4.04 (4H, m, 2OCH$_2$), 3.88, 3.17 (2H, AB system, *J* = 16.6 Hz, H9), 1.20, 1.13 (6H, 2t, *J* = 7.4, 7.3 Hz, 2CH$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.3, 167.0 (*C*O$_2$CH$_2$, CH$_2$*C*O$_2$CH$_2$), 148.0 (C2); 134.7 (C8a), 129.7 (C7), 124.6 (C5), 122.4 (C6), 117.4 (C4a), 113.9 (C8), 82.4 (C4), 62.6, 61.2 (2OCH$_2$), 42.0 (C9), 15.4, 15.2 (2CH$_3$); IR (KBr) ν_{max} 3235, 3104, 2982, 1749, 1560 cm^{-1}; EIMS *m*/*z* 307 [M]$^+$ (0.4), 234 (88), 146 (100). *Anal*. Calcd for C$_{15}$H$_{17}$NO$_6$: C 58.63; H 5.58; N 4.56. Found: C 58.63; H 5.54; N 4.27.

Diethyl 2-hydroxy-2-(2-(methoxycarbonylamino)phenyl)succinate (17f). Prepared from **17b** and purified with EtOAc/hexanes 2:3 to afford colorless crystals: (*i*) 0.084 g, 32%; (*ii*) 0.068 g, 26%; mp 73-75 ºC (EtOAc/hexanes); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.12 (1H, brs, NH), 7.92 (1H, brd, *J* = 7.8 Hz, H3'), 7.38 (1H, dd, *J* = 7.8, 1.5 Hz, H6'), 7.35 (1H, td, *J* = 8.3, 1.5 Hz, H4'), 7.10 (1H, td, *J* = 7.8, 1.5 Hz, H5'), 6.99 (1H, brs, OH), 4.19-4.04 (4H, m, 2OCH$_2$), 3.70 (3H, s, NCO$_2$Me), 3.56, 3.04 (2H, AB system, *J* = 14.9 Hz, H9), 1.21, 1.15 (6H, 2t, *J* = 7.3 Hz, 2CH$_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.4 (*C*O$_2$CH$_2$), 170.2 (CH$_2$*C*O$_2$CH$_2$), 154.6 (N*C*O$_2$Me), 138.1 (C2'), 130.7 (C1'), 129.8 (C4'), 127.5 (C6'), 124.0 (C5'), 122.1 (C3'), 77.5 (C2), 62.2, 61.3 (2OCH$_2$), 52.9 (NCO$_2$*Me*), 44.5 (C3), 14.9, 14.7 (2CH$_3$); IR (KBr) ν_{max} 3480, 3373, 3099, 2985, 1736, 1590, 1456 cm^{-1}; EIMS *m*/*z* 293 [M]$^+$ − EtOH] (15), 265 (16), 219 (70), 146 (100). *Anal*. Calcd for C$_{16}$H$_{21}$NO$_7$: C 56.63; H 6.24; N 4.13. Found: C 56.76; H 6.19; N 3.82.

Methyl 3-(2-ethoxy-2-oxoethyl)-3-hydroxy-2-oxoindoline-1-carboxylate (19b). Prepared from **17b** and purified with EtOAc/hexanes 2:3 to afford a white solid: (*ii*) 0.043 g, 19%; mp 66-68 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.85 (1H, brd, *J* = 7.9 Hz, H7), 7.53 (1H, dd, *J* = 7.5, 0.9 Hz, H4), 7.44 (1H, td, *J*

= 7.5, 1.4 Hz, H6), 7.26 (1H, td, *J* = 7.5, 0.9 Hz, H5), 6.68 (1H, s, OH), 3.96 (3H, s, NCO_2Me), 3.85, 3.80 (2H, 2dc, *J* = 10.6, 7.1 Hz, $CO_2CH_2CH_3$), 3.19 (2H, s, H8), 0.93 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.9 (C2), 169.7 ($CO_2CH_2CH_3$), 152.1 (NCO_2Me), 140.5 (C7a), 131.0 (C6), 130.7 (C3a), 125.9 (C5), 125.1 (C4), 115.6 (C7), 73.3 (C3), 61.4 ($CO_2CH_2CH_3$), 54.9 (NCO_2Me), 43.3 (C8), 14.6 ($CO_2CH_2CH_3$); IR (KBr) ν_{max} 3433, 2995, 2962, 1737, 1713, 1609 cm^{-1}; EIMS *m/z* 293 $[M]^+$ (15), 265 (16), 219 (75), 146 (100). FABHRMS *m/z* 293.0902 (calcd for $C_{14}H_{15}NO_6$, 293.0899).

Ethyl 2-oxo-1,2-dihydroquinoline-4-carboxylate (20b). Prepared from **17b** and purified with EtOAc/hexanes 2:3 to afford a white solid: (*ii*) 0.017 g, 10%; mp 208-210 ºC; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.18 (1H, brs, NH), 8.09 (1H, dd, *J* = 8.2, 1.2 Hz, H5), 7.61 (1H, td, *J* = 7.1, 1.2 Hz, H7), 7.42 (1H, dd, *J* = 7.4, 0.8 Hz, H8), 7.28 (1H, td, *J* = 7.0, 1.2 Hz, H6), 6.94 (1H, s, H3), 4.43 (2H, q, *J* = 7.0 Hz, CH_2), 1.39 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.0 (CO_2Et), 161.8 (C2), 141.2 (C4), 140.4 (C8a), 132.1 (C7), 126.8 (C5), 124.8 (C3), 123.4 (C6), 116.8 (C8), 116.4 (C4a), 62.9 (CH_2), 14.9 (CH_3); IR (KBr) ν_{max} 3454, 2923, 2851, 1724, 1655 cm^{-1}; EIMS *m/z* 217 $[M]^+$ (100), 189 (45), 172 (20), 161 (14), 144 (31), 116 (48); FABHRMS *m/z* 217.0737 (calcd for $C_{12}H_{11}NO_3$, 217.0739).

Isopropyl 4-(2-isopropoxy-2-oxoethyl)-2-oxo-2,4-dihydro-1*H*-benzo[*d*][1,3]oxazine-4-carboxylate (18e). Prepared from **17c** and purified with EtOAc/hexanes 2:3 to afford colorless crystals (*i*) 0.040 g, 16% and 0.060 g of recovered **17c**; (*ii*) 0.105 g, 42% and 0.020 g of recovered **17c**; mp 131-133 ºC (EtOAc/hexanes); ^1H NMR (DMSO-d_6, 400 MHz) δ 10.40 (1H, brs, NH), 7.43 (1H, brd, *J* = 6.7 Hz, H5), 7.33 (1H, td, *J* = 7.8, 1.2 Hz, H7), 7.07 (1H, td, *J* = 7.9, 1.2 Hz, H6), 6.89 (1H, dd, *J* = 7.8, 1.2 Hz, H8), 4.95, 4.88 (2H, 2 sp, *J* = 6.2, 6.3 Hz, 2CH), 3.81, 3.12 (2H, AB system, *J* = 16.5 Hz, H9), 1.21, 1.19, 1.18, 1.08 (12H, 4d, *J* = 6.3 Hz, $4CH_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.0 (CO_2CH), 168.7 (CH_2CO_2CH), 149.9 (C2), 136.4 (C8a), 131.1 (C7), 126.1 (C5), 123.7 (C6), 118.9 (C4a), 115.1 (C8), 83.2 (C4), 70.7, 69.0 (2CH), 42.2 (C9), 22.5, 22.4, 22.1, 22.0 ($4CH_3$); IR (KBr) ν_{max} 3168, 2986, 2941, 1741, 1603 cm^{-1}; EIMS *m/z* 292 $[M^+ - i\text{Pr}]$ (2), 248 (23), 234 (15), 206 (59), 146 (100).

Diisopropyl 2-hydroxy-2-(2-(methoxycarbonylamino)phenyl)succinate (17g). Prepared from **17c** and purified with EtOAc/hexanes 2:3 to afford a colorless oil: (*i*) 0.106 g, 39%; (*ii*) 0.045 g, 17%; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.15 (1H, brs, NH), 7.94 (1H, brd, *J* = 7.8 Hz, H3'), 7.35 (1H, d, *J* = 7.8 Hz, H6'), 7.34 (1H, t, *J* = 6.8 Hz, H4'), 7.08 (1H, td, *J* = 7.8, 1.0 Hz, H5'), 6.87 (1H, brs, OH), 4.94 (1H, sp, *J* = 6.3 Hz, CH_2CO_2CH), 4.92 (1H, sp, *J* = 6.3 Hz, CO_2CH), 3.70 (3H, s, NCO_2Me), 3.50, 3.00 (2H, AB system, *J* = 14.9 Hz, H3), 1.22 (6H, d, *J* = 6.3 Hz, $2CH_3$), 1.17, 1.11 (6H, 2d, *J* = 6.3 Hz, $2CH_3$); ^{13}C

NMR (DMSO-d_6, 100 MHz) δ 169.3 (CO_2CH), 167.2 (CH_2CO_2CH), 152.3 (NCO_2Me), 136.3 (C2'), 128.8 (C1'), 127.9 (C4'), 125.7 (C6'), 122.2 (C5'), 120.2 (C3'), 76.8 (C2), 69.2 (CO_2CH), 68.1 (CH_2CO_2CH), 52.5 (NCO_2Me), 44.4 (C3), 22.8, 22.7, 22.4, 22.3 ($4CH_3$); IR (KBr) ν_{max} 3363, 2982, 2939, 1736, 1591, 153, 1067 cm^{-1}; EIMS *m/z* (relative intensity) 307 $[M^+ - i\text{PrOH}]$ (13), 279 (23), 265 (27), 219 (81), 205 (66), 146 (100); FABHRMS *m/z* 367.1635 (calcd for $C_{18}H_{25}NO_7$, 367.1631).

Methyl 3-hydroxy-3-(2-isopropoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (19c). Prepared from **17c** and purified with EtOAc/hexanes 2:3 to afford a white solid: (*i*) 0.041 g, 18%; (*ii*) 0.036 g, 16%; mp 76-78 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.86 (1H, brd, *J* = 8.2 Hz, H7), 7.53 (1H, dd, *J* = 7.5, 0.8 Hz, H4), 7.44 (1H, td, *J* = 7.9, 1.2 Hz, H6), 7.26 (1H, td, *J* = 7.4, 1.2 Hz, H5), 6.66 (1H, s, OH), 4.60 (1H, sp, *J* = 6.3 Hz, CH), 3.97 (3H, s, NCO_2Me), 3.17, 3.11 (2H, AB system, *J* = 15.8, H8), 0.91, 0.85 (6H, 2d, *J* = 6.3 Hz, $2CH_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.8 (C2), 168.8 (CO_2CH), 152.1 (NCO_2Me), 140.5 (C7a), 130.9 (C6), 130.6 (C3a), 125.8 (C5), 125.0 (C4), 115.6 (C7), 73.3 (C3), 68.7 (CH), 54.8 (NCO_2Me), 43.7 (C8), 22.1, 21.8 ($2CH_3$); IR (KBr) ν_{max} 3464, 2971, 2928, 1794, 1727, 1611cm^{-1}; EIMS *m/z* 307 $[M]^+$ (17), 266 (31), 220 (66), 205 (85), 146 (100); FABHRMS *m/z* 307.1057 (calcd for $C_{15}H_{17}NO_6$, 307.1056).

Isopropyl 2-oxo-1,2-dihydroquinoline-4-carboxylate (20c). Prepared from **17c** and purified with EtOAc/hexanes 2:3 to afford a white solid: (*ii*) 0.021 g, 12%; mp 186-188 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.17 (1H, brs, NH), 8.06 (1H, dd, *J* = 8.2, 1.1 Hz, H5), 7.59 (1H, td, *J* = 7.1, 1.1 Hz, H7), 7.41 (1H, dd, *J* = 8.2, 1.2 Hz, H8), 7.27 (1H, td, *J* = 8.2, 1.2 Hz, H6), 6.90 (1H, s, H3), 5.25 (1H, sp, *J* = 6.3 Hz, CH), 1.39 (6H, d, *J* = 6.2 Hz, $2CH_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.5 (CO_2i-Pr), 161.8 (C2), 141.5 (C4), 140.4 (C8a), 132.0 (C7), 126.7 (C5), 124.6 (C3), 123.4 (C6), 116.9 (C8), 116.4 (C4a), 70.7 (CH), 22.4 ($2CH_3$); IR (KBr) ν_{max} 3418, 2923, 2850, 1712, 1662 cm^{-1}; EIMS *m/z* 231 $[M]^+$ (57), 189 (100), 172 (14), 161 (20), 144 (21), 117 (36); FABHRMS *m/z* 231.0887 (calcd for $C_{13}H_{13}NO_3$, 231.0895).

Methyl 3-hydroxy-3-methyl-2-oxoindoline-1-carboxylate (16b). Prepared from **17d** and purified with EtOAc/hexanes 1:4 to afford colorless crystals (*ii*) 0.017 g (8%).

Methyl 4-methyl-2-oxo-2,4-dihydro-1*H*-benzo[*d*][1,3]oxazine-4-carboxylate (18d). Prepared from **17d** and purified with EtOAc/hexanes 1:4 to afford colorless crystals: (*i*) 0.167 g, 76% and 0.046 g of recovered **17d**; (*ii*) 0.176 g, 81% and 0.018 g of recovered **17d**; mp 164-166 ºC (EtOAc/hexanes); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.38 (1H, s, NH), 7.42 (1H, dd, *J* = 7.8, 1.0 Hz, H5), 7.34 (1H, td, *J* = 7.8,

1.4 Hz, H7), 7.10 (1H, td, *J* = 7.8, 1.0 Hz, H6), 6.92 (1H, dd, *J* = 7.8, 1.0 Hz, H8), 3.68 (3H, s, CO_2Me), 1.93 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.1 (CO_2Me), 148.6 (C2), 134.7 (C8a), 129.3 (C7), 124.5 (C5), 122.4 (C6), 119.6 (C4a), 113.7 (C8), 82.1 (C4), 53.9 (CO_2Me), 24.1 (CH_3); IR (KBr) ν_{max} 3419, 3166, 2925, 1742, 1601, 1497 cm^{-1}; EIMS *m/z* 221 $[M]^+$ (3), 162 (100), 144 (23), 116 (27); *Anal*. Calcd for $C_{11}H_{11}NO_4$: C 59.73; H 5.01; N 6.33. Found: C 59.76; H 4.88; N 5.94.

3-Hydroxy-3-methylindolin-2-one (19d). Prepared from **17e** and purified with EtOAc/hexanes 2:3 to afford colorless crystals: (*i*) 0.137 g, 99%; mp 163-165 ºC (EtOAc/hexanes); ^1H NMR (DMSO-d_6, 400 MHz) δ 10.27 (1H, brs, NH), 7.32 (1H, dd, *J* = 6.7, 0.7 Hz, H4), 7.23 (1H, td, *J* = 7.4, 1.2 Hz, H6), 7.00 (1H, td, *J* = 7.5, 1.2 Hz, H5), 6.85 (1H, d, *J* = 7.4 Hz, H7), 5.91 (1H, s, OH), 1.40 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 180.7 (C2), 142.1 (C7a), 134.6 (C3a), 129.8 (C6), 124.4 (C4), 122.7 (C5), 110.6 (C7), 73.6 (C3), 25.5 (CH_3); IR (KBr) ν_{max} 3369, 3181, 2975, 1709, 1626 cm^{-1}; EMIE *m/z* 163 $[M]^+$ (18), 135 (73), 120 (100), 92 (21); FABHRMS *m/z* 163.0632 (calcd for $C_9H_9NO_2$, 163.0633).

General transesterification procedure for benzoxazinone 18a to 18c,e.

A solution of benzoxazinone **18a** (0.05 g, 0.179 mmol) in the appropriate mixture HCl/EtOH or HCl/*i*-PrOH (20 mL) was heated under microwave irradiation to afford **18c** for 1 h and to afford **18e** for 2.5 h. After cooling to rt, the volatiles were evaporated under reduced pressure and the residue was dissolved in EtOAc (20 mL). The organic solution was washed with a saturated aqueous solution of $NaHCO_3$ (3 x 20 mL) and brine (2 x 20 mL), dried over Na_2SO_4, filtrated and evaporated to dryness in vacuum. The resultant crude products were purified by flash column chromatography on silica gel eluting with EtOAc/hexanes, 2:3 to afford, respectively, **18c** and **18e** in 95% (0.052 g) and 92% (0.055 g) yield.

Single crystal X-ray diffraction analyses

Data collection for **17a** (Table 4) was carried out on a Bruker Smart 6000 CCD diffractometer using Mo/Kα radiation (λ = 0.7073 Å). A total of 1321 frames were collected at a scan width of 0.3° and an exposure time of 10 s/frame. These data were processed with the SAINT software package, provided by the diffractometer manufacturer, by using a narrow frame integration algorithm. An empirical absorption correction was applied. Data collections for **16b**, **17b-17f**, **18a**, **18c** and **18d** (Tables 4 and 5) were done on an Enraf-Nonius CAD4 diffractometer using Cu Kα radiation (λ = 1.54184 Å) while those for **18e** and **19d** were done on an Agilent Technologies Gemini A CCD diffractometer using Mo/Kα radiation (λ = 0.7073 Å). The structures were solved by direct methods using the SHELXS-97[17] program included in the WINGX v1.6 package.[18] Structural refinements were carried out by full-matrix least squares on F2. The

Table 4. Crystal data for **16b**, **17a-17d** and **17f**

	16b	**17a**	**17b**	**17c**	**17d**	**17f**
Empirical formula	$C_{11}H_{11}NO_4$	$C_{14}H_{17}NO_7$	$C_{15}H_{19}NO_7$	$C_{16}H_{21}NO_7$	$C_{12}H_{15}NO_5$	$C_{16}H_{21}NO_7$
Formula weight	221.21	311.29	325.31	339.34	253.25	339.34
Crystal size (mm)	0.30 x 0.28 x 0.16	0.49 x 0.42 x 0.32	0.34 x 0.30 x 0.30	0.34 x 0.28 x 0.28	0.38 x 0.22 x 0.16	0.32 x 0.32 x 0.30
Wavelength (Å)	1.54184	0.71073	1.54184	1.54184	1.54184	1.54184
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P2_1/a$	$P2_1/n$
Unit cell dimensions (Å) *a*	10.6352(6)	11.7106(8)	11.076(1)	8.116(4)	12.672(3)	7.953(2)
b	5.1542(9)	7.763(1)	8.562(1)	15.076(2)	8.2598(7)	13.088(2)
c	19.245(1)	16.584(2)	17.059(4)	14.482(4)	12.949(2)	16.637(4)
β (deg)	90.491(6)	90.975(3)	91.72(2)	102.05(4)	111.78(1)	100.10(2)
Volume (Å^3)	1054.9(2)	1507.3(3)	1616.9(5)	1733.0(10)	1258.7(4)	1705.0(6)
Z, Calculated density (mg/mm^3)	4, 1.39	4, 1.37	4, 1.34	4, 1.30	4, 1.34	4, 1.32
Absorption coefficient (mm^{-1})	0.904	0.111	0.906	0.866	0.884	0.881
F(000)	464	656	688	720	536	720
θ range for data collection (deg)	4.60 to 59.92	1.74 to 26.01	3.99 to 59.91	4.28 to 59.95	3.68 to 59.90	4.32 to 59.90
Limiting indices h, k, l	-11–11, 0–5, 0–20	-14–14, -9–9, -20–12	-12–12, 0–9, 0–18	-8–8, 0–15, 0–15	-13–13, 0–9, 0–14	-8–8, 0–4, 0–9
Collected reflections (Rint)	1871 (0.0001)]	9602 (0.0524)	2693 (0.0382]	2765 (0.0001)	2213 (0.0255)	1958 (0.0001)
Unique reflections	1511	2961	2317	2527	1836	1714
Completeness to θ (%)	96.7	99.8	96.3	98.2	98.1	67.9
Data / restraints / parameters	1439 / 0 / 149	1787 / 0 / 207	2087/ 0 / 226	2387/ 0 / 229	1548/ 0 / 175	1631 / 0 / 225
Goodness-of-fit on F^2	1.104	0.932	0.947	1.084	1.047	1.092
Final R indices [I>2sigma(I)] (%)	R1 = 4.7, wR2 = 13.5	R1 = 4.8, wR2 = 12.2	R1 = 4.7, wR2 = 14.0	R1 = 4.3, wR2 = 12.7	R1 = 3.8, wR2 = 10.4	R1 = 3.9, wR2 = 12.4
R indices (all data) (%)	R1 = 4.9, wR2 = 13.7	R1 = 8.1, wR2 = 14.6	R1 = 5.3, wR2 = 14.8	R1 = 4.5, wR2 = 12.8	R1 = 4.8, wR2 = 10.9	R1 = 4.1, wR2 = 12.5
Largest diff. peak and hole (e.Å^3)	0.209 and -0.175				209 and -0.136	0.126 and -0.145
CCDC No.	888703	888704	888705	888706	888707	888708

Table 5. Crystal data for **18a** and **18c-18e**, and **19d**.

	18a	**18c**	**18d**	**18e**	**19d**

Empirical formula	$C_{13}H_{13}NO_6$	$C_{15}H_{17}NO_6$	$C_{11}H_{11}NO_4$	$C_{17}H_{21}NO_6$	$C_9H_9NO_2$
Formula weight	279.24	307.30	221.21	335.35	163.17
Crystal size (mm)	0.38 x 0.34 x 0.26	0.40 x 0.32 x 0.28	0.28 x 0.22 x 0.20	0.45 x 0.22 x 0.20	0.43 x 0.16 x 0.14
Wavelength (Å)	1.54184	1.54184	1.54184	0.71073	0.71073
Crystal system	triclinic	monoclinic	triclinic	orthorhombic	monoclinic
Space group	P-1	$P2_1/c$	P-1	Pbca	$P2_1/c$
Unit cell dimensions (Å) *a*	6.8731(7)	11.753(2)	6.525(1)	14.1317(7)	7.2728(3)
b	8.3072(8)	11.054(1)	7.998(1)	15.319(1)	10.7090(4)
c	11.715(2)	12.439(3)	11.331(1)	16.2128(7)	10.9733(4)
α (deg)	87.67(1)	90	104.63(1)	90	90
β (deg)	81.24(1)	107.84	101.10(1)	90	101.851(4)
γ (deg)	72.70(1)	90	103.86(1)	90	90
Volume ($Å^3$)	631.2(1)	1538.2(4)	535.0(1)	3509.9	836.43(6)
Z, Calculated density (mg/mm^3)	2, 1.47	4, 1.33	2, 1.37	8, 1.27	4, 1.30
Absorption coefficient (mm^{-1})	1.006	0.873	0.892	0.096	0.093
F(000)	292	648	232	1424	344
θ range for data collection (deg)	6.75 to 59.95	3.95 to 59.88	6.00 to 59.94	3.17 to 29.36	3.44 to 29.48
Limiting indices h, k, l	-7–7, -9–9, 0–13	-12–12, 0–12, 0–13	-7–7, -8–8, 0–12	-18–19, -20–19, -22–20	-9–9, -14–14, -15–15
Collected reflections (Rint)	2037 (0.0001)	2545 (0.0001)	1736 (0.0001)	23143 (0.0275)	14540 (0.0001)
Unique reflections	1864	2234	1583	4466	2146
Completeness to θ (%)	99.6	98.1	99.8	92.4	92.5
Data / restraints / parameters	1809 / 0 / 186	2098/ 0 / 203	1476/ 0 / 152	3090/ 0/ 245	1573/ 0 / 119
Goodness-of-fit on F^2	1.095	1.076	1.118	1.019	1.030
Final R indices [I>2sigma(I)] (%)	R1 = 3.8, wR2 = 10.1	R1 = 4.2, wR2 = 12.1	R1 = 3.7, wR2 = 10.1	R1 = 4.3, wR2 = 9.3	R1 = 4.6, wR2 = 12.0
R indices (all data) (%)	R1 = 3.9, wR2 = 10.2	R1 = 4.4, wR2 = 12.2	R1 = 3.9, wR2 = 10.1	R1 = 7.1, wR2 = 10.4	R1 = 6.7, wR2 = 13.7
Largest diff. peak and hole ($e.Å^3$)	0.180 and -0.142	0.199 and -0.178	0.151 and -0.126	0.217 and -0.157	0.176 and -0.167
CCDC No.	888709	888710	888711	888712	888713

non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Atomic coordinates, bond lengths, bond angles and anisotropic thermal parameters are in deposit at the Cambridge Crystallographic Data Center. Tables 4 and 5 summarize the relevant data.

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