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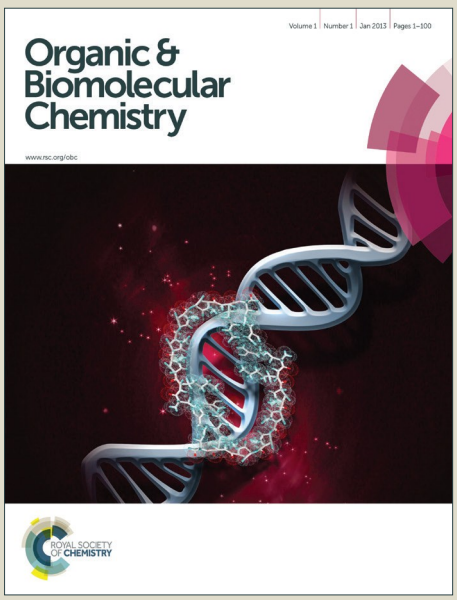

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ARTICLE

A Facile hybrid 'flow and batch' access to substituted 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinones

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We describe a simple flow chemistry approach to libraries of ethyl 3-oxo-2-(substituted-phenylamino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylates (**12a**-**l**) and *N*-ethyl-3-oxo-2-(substituted-phenylamino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamides (**13a**-**l**) in 38-87% yields. This scaffold is poorly described in the chemical literature. Screening against a panel of 11 cancer and one normal cell line showed that the amide linked library **13a**-**l** was devoid of toxicity. Whereas the ester linked analogues **12b**, **12c**, **12g**, **12j** and **12l** were highly cytotoxic with growth inhibition (GI_{50}) values from 0.34 to > 50 μM across all cell lines, with the 2-OH-Ph substituted **12l** analogue presenting with sub-micromolar potency against the A2780 (ovarian; 0.34 ± 0.04 μM), BEC-2 (glioblastoma; 0.35 ± 0.06 μM), MIA (pancreas; 0.91 ± 0.054 μM) and SMA (murine glioblastoma; 0.77 ± 0.029 μM) carcinoma cell lines. Interestingly, the U87 glioblastoma cell line showed inherent resistance to growth inhibition by all analogues (GI_{50} 32 to > 50 μM) while the A2780 cells were highly sensitive (GI_{50} 3.8 – 0.34 μM), suggesting that the analogues developed herein may be valuable lead compounds for the development of ovarian carcinoma specific cytotoxic agents. The differences in amide versus ester cytotoxicity was consitent with esterase cleaveage to release the cytotoxic warhead.

Introduction

The medicinal chemistry toolbox is replete with a wide array of robust synthetic approaches typically geared towards the rapid development of structure activity relationship (SAR) data. Such approaches generally use a common central scaffold with pendant arms that best position key pharmacophore moieties to engage with binding site residues. The medicinal chemistry toolkit has been reviewed by Roughly and Walters, [1,2] as has bioisosteric approaches to potency enhancements.[3,4] Independent of the target, access to a core scaffold is imperative and often requires significant synthetic effort to access in a quantity appropriate for SAR development. We recently commenced a program that sought access to a 2-(amino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (e.g. **1-3**, Figure 1) and were surprised to discover that robust chemistry permitting rapid access was poorly described in the literature.[5,6]

Prior to this investigation, the synthesis of 2-aniliobenzoxazinone derivatives and their biological activity has only ever been the subject of limited investigations. Similarly, the only report of 2-*N*-substituted benzoxazinones, by Ilaš and Kikelji, presented only one derivative (**3**, Figure 1).[7]

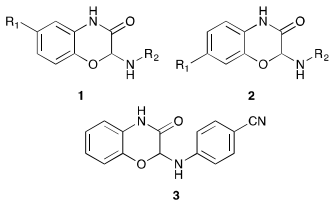

Figure 1. Target scaffold, 6- and 7- substituted 2-(amino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamides (**1** and **2**) and 4-((3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)amino)benzonitrile (**3**).

Recently there has been considerable progress in the use of flow chemistry approaches in multi-step synthesis,[8-17] the synthesis of drug like molecules,[18-22] selective hydrogenations[23] and in the use of unstable and /or dangerous reagents.[14-16,24,25] Herein, we envisaged a simple flow chemistry approach allowing a scalable access to two key intermediates for use in either flow chemistry library development or using robust batch approaches.[1,2]

Herein we report on our efforts in this area and highlight the scope of this approach in the development of targeted libraries of **1** and **2**.

Results and discussion

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Electronic Supplementary Information (ESI) available: PDF copies of ^{1}H and ^{13}C NMR spectra, MS and cytotoxicity data for the compounds synthesised herein. See DOI: 10.1039/x0xx00000x

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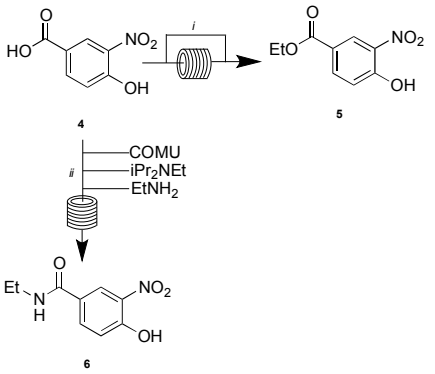
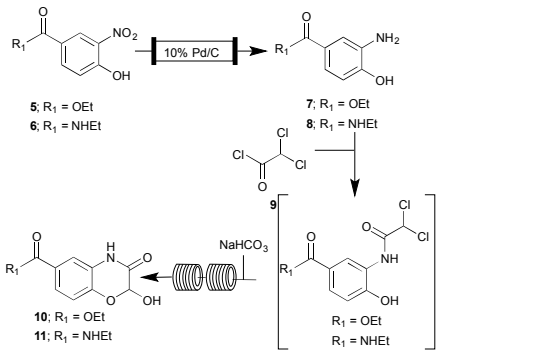
Our investigations commenced with the esterification of 4-hydroxy-3-nitrobenzoic acid (**4**). Batch esterification resulted in incomplete conversion of **4** to the ethyl ester **5** (ESI†). Under flow conditions (0.05M ethanolic **4**, H_2SO_4, 140 °C, 1 mL.min^{-1}) **5** was afforded in 69% yield (2 g.h^{-1}). Alternatively simple amines were readily installed *via* flow amide coupling conditions, e.g. **6**, in an improved isolated yield (0.38 g.h^{-1}), when compared to batch synthesis *ca*. 77% *vs* 50% (Scheme 1).



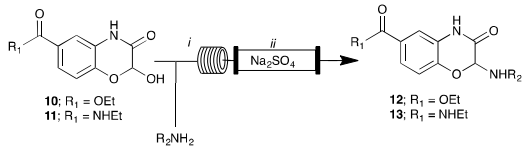
Scheme 1. Reagents and conditions. (i) EtOH, H_2SO_4, 140 °C, 1 mL.min^{-1}; (ii), COMU, iPr_2NEt, $EtNH_2$, DMF 18 °C, 1 mL.min^{-1}.

Optimised H-Cube Pro™ reduction of **5/6** (0.01 M **5/6** in EtOAc, 10% Pd/C, 50 °C, 50 bar H_2, 3 mL.min^{-1}) afforded the corresponding anilines **7** and **8,** in a single pass (1.9 g.h^{-1}; 98% yield; ESI†). The H-Cube Pro™ eluent stream containing **7** and **8** was introduced into twin streams of dichloroacetyl chloride **9** in 1,1-dichloroethane (0.1 M, 0.75 mL.min^{-1}, 18 °C) and $NaHCO_3$ (0.5 M, 0.75 mL.min^{-1}, 18 °C) and passed through two 4 mL PFA coils (18 °C) to selectively *N*-acylate the aniline NH_2 moiety. Again without isolating the product stream, the biphasic solution was flowed into two 10 mL PFE coils, maintained at 100 °C and 5 bar backpressure, to afford the desired hemiacetals **10** and **11** in 44 and 52% yield, 0.5 and 0.36 g.h^{-1}, respectively. Although the dichloroacetamide adduct could be isolated in high yield (94%), it was determined that the direct conversion of anilines **7** and **8** to hemiacetals **10** and **11** by flow synthesis allowed continuous supply of scaffold for further derivatisation and increased the overall synthetic efficiency (Scheme 2).

With a scalable flow synthesis of the advanced scaffolds **10** and **11** in hand, these materials were subjected to a flow condensation reaction with a library of selected anilines through an Omnifit cartridge packed with anhydrous sodium sulphate to afford hemiaminal ethers **12a-l** and **13a-l** (Scheme 3; Table 1). In most instances the flow condensation reaction afforded product in high yield and without extensive work up, when compared to the batch synthesis which required column chromatography. Generally, the installation of a wide range of substituted anilines proceeded smoothly with isolated yields ranging from modest (**13a**; 38%) to excellent (**12e**; 87%).



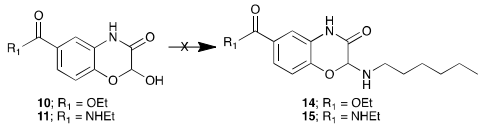
Scheme 2. Reagents and conditions. (i) ThalesNano H-Cube Pro™, 10% Pd/C (70 mm cartridge), CH_3CN, 50 °C, 50 bar H_2 pressure, 3 ml.min^{-1}; (ii) VapourTec easy-MedChem, **9**, 2 x 10 mL reactor, 0.75 mL.min^{-1}, 18 °C; (iii) 2 x 10 mL reactor, 100 °C, 0.75 mL.min^{-1}, 5 bar.



Scheme 3. Reagents and conditions. (i) R^2NH_2, Na_2SO_4; (ii) anhydrous Na_2SO_4

There were however limitations to this flow transformation (Scheme 3), in some instances where aniline coupling partners possessed an additional nucleophiles, *i.e.* aminophenol, the flow dehydration reaction failed to proceed to completion in the same time as batch conditions. Moreover we noted that the presence of the electron withdrawing 2-bromophenyl, or 2-carboxyphenyl moiety failed to produce any evidence of the desired 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazines, supporting the importance of the amine nucleophilicity.

In a similar manner, we were not able to exploit the hemiacetal moiety to access 2-*N*-alkylated benzoxazinone derivatives with the reaction failing to go to completion, by both flow and batch approaches, the product was found to be unstable and decomposed during attempted chromatography (SiO_2) (Scheme 4).



Scheme 4. Reagents and conditions. (i) $CH_3(CH_2)_5NH_2$, 1:4 v/*v* EtOAc/Et_2O, anhydrous Na_2SO_4, 30 °C, 19 h.

With two 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine libraries (**12a-l** and **13a-l**), and the parent analogues **10** and **11**, in hand we examined these compounds for their ability to inhibit the growth of eleven cancer and one normal cell line (see Table 2 for cell line details). Compounds were initially screened at a single 25 μM concentration (ESI†), and those analogues that displayed growth inhibition >90% for any specific cell line were subject to a full dose evaluation to determine GI_{50} values.[26] From the initial cytotoxicity screening, neither the parent hemiaminals **10** and **11**, nor the amide based library **13a-1** displayed any noteworthy cytotoxicity (ESI†). Of the remaining analogues only **12b**, **12c**, **12g**, **12j** and **12l** proceeded to full

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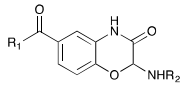
dose response evaluation and these data are presented in Table 2.

Table 1. Isolated yields and diversity of substituted anilines used in the preparation of 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazines **12a**-**l** and **13a**-**l**.



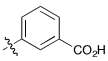
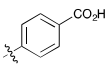
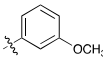
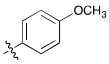
Compound	R_1	R_2	Yield (%)	Compound	R_1	Yield (%)
5	EtO	OH	44	**6**	EtNH	94
12a	EtO		82	**13a**	EtNH	38
12b	EtO		73	**13b**	EtNH	81
12c	EtO		72	**13c**	EtNH	80
12d	EtO		80	**13d**	EtNH	55
12e	EtO		87	**13e**	EtNH	64
12f	EtO		65	**13f**	EtNH	85
12g	EtO		51	**13g**	EtNH	73
12h	EtO		60	**13h**	EtNH	69
12i	EtO		72	**13i**	EtNH	41
12j	EtO		70	**13j**	EtNH	73
12k	EtO		67	**13k**	EtNH	47
12l	EtO		64	**13l**	EtNH	80

Table 2. Dose response growth inhibition of a panel of cancer cell lines by analogues 12b, 12c, 12g, 12j and 12l. Values given represent the compound dose required to elicit 50% of cell growth inhibition relative to an untreated control (GI_{50} values; μM).

Compound Cell Line	12b	12c	12g	12j	12l
HT29 [a]	10±0.23	>50	20±0.67	7.8±0.85	6.1±3.0
U87 [b]	32±3.00	>50	>50	>50	48 ± 3
SJ-G2 [b]	6.4±0.24	4.8±1.0	13±0.88	4.9±0.72	2.3±0.70
MCF-7 [c]	7.6±0.82	>50	18 ± 1.8	5.5 ± 1.3	ND [l]
A2780 [d]	2.3±0.39	3.8±0.51	3.8±0.12	1.7±0.07	0.34±0.04
H460 [e]	4.6±0.74	>50	9.1±0.33	3.7±0.20	1.3±0.26
A431 [f]	5.4±0.60	>50	11±1.3	4.2±0.17	1.7±0.16
Du145 [g]	13±1.8	>50	33±8.3	9.1±0.55	6.7±0.88
BE2-C [h]	2.5±0.74	>50	4.3±0.40	1.8±0.13	0.35±0.05
MIA [i]	4.1±0.06	>50	8.4±0.37	3.2±0.03	0.91±0.05
SMA [j]	5.0±0.40	13±5.9	9.1±0.76	3.4±0.27	0.77±0.03
MCF10A [k]	6.8±0.56	>50	15±1.9	4.8±0.80	2.2±0.74

[a] colon; [b] glioblastoma; [c] breast; [d] lung; [e] skin; [f] prostate; [g] neuroblastoma; [h] glioblastoma; [i] pancreas; [j] murine glioblastoma; [k] normal breast; [l] ND = not determined

Of the five analogues that proceeded to full dose response evaluation, analysis of the data presented in Table 2 highlights effectively very low levels of activity against the U87 cell line with GI_{50} values form 32 (**12b**) to ≥ 50 μM (**12c, g, j, l**), suggesting that this scaffold, regardless of the substituents has very limited effect on the growth of this glioblastoma cell line. Examining each analogue in turn it was apparent that **12b** displays good levels of broad spectrum growth inhibition with the 3-bromo moiety, with GI_{50} values ≤10 μM against all cell lines examined with the exception of U87 and Du145. Repositioning of the bromine moiety from 3- (**12b**) to 4- (**12c**) resulted in a significant drop in observed cytotoxicity with all cell lines returning GI_{50} values > 50 μM, except SJ-G2 (4.8 ± 1.0 μM), A2780 (3.8 ± 0.51 μM) and SMA (13 ± 5.9 μM) cells, suggesting a key role for this moiety. Introduction of a $–OCH_3$ moiety (Br replacement) resulted in moderate levels of broad spectrum activity with GI_{50} values ranging from 3.8 ± 0.12 μM (A2780) to 20 ± 0.67 μM (HT29). Both **12j** and **12l** were significantly more potent than the other analogues noted thus far, but with the same lack of activity against the U87 cell line. Analogue **12j** displayed growth inhibition from 1.7 ± 0.07 μM (A2780) to 9.1 ± 0.55 μM (Du145). The activity of **12l** was most notable with GI_{50} values ranging from 0.34 ± 0.04 μM (A2780) to 6.7 ± 0.88 μM (Du145). Indeed **12l** displayed sub-micromolar potency across the A2780, BEC-2 (0.35 ± 0.05 μM), MIA (0.91 ± 0.05 μM) and SMA (0.77 ± 0.03 μM) cell lines. Screening of these analogues against the normal breast cell line, MCF10A, revealed a similar level of toxicity suggesting that differentiation in toxicity between cancer cells and normal cells did not occur with these analogues. While in cell measures of toxicity is a poor model of animal or human toxicity, it does provide a note of caution in the development of these analogues as potential cytotoxic agents.

While the amide analogues **13a**-**l** were inactive, this most probably results from the different cellular hydrolysis rates between amide and esters, with the esterase action more facile than that of the corresponding amidase.[27] Notwithstanding this, these data suggest that the amide linked scaffold may offer future potential as a scaffold for use in the development of small molecules for other biological targets where cytotoxicity is not desired.

Conclusions

A simple sequence of flow reactions has allowed rapid access to two libraries of 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazines analogues (**12a**-**l** and **13a**-**l**) in modest to excellent yields. We were not able to uses these protocols to access the corresponding 2-*N*-aliphatic analogues.

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Screening of **10**, **11** and **12a**-**l** and **13a**-**l** against a panel of 11 cancer and one normal cell line revealed that the parent hemiaminals **10** and **11** and the amide linked library **13a**-**l** were essentially devoid of toxicity (ESI†). This positions both the synthesis and the scaffolds as potentially interesting as rapidly modified scaffolds are highly sought after in medicinal chemistry studies. The ester based library, **12a**-**l**, showed higher levels of toxicity consistent with the esterase cleavage of the free carboxylate on entry to the cells. Of the analogues that proceeded to GI_{50} determination, **12j** and **12l** were the most potent across all the cell lines examined. All the active analogues displayed high levels of cytotoxicity against the ovarian cell line, A2780, suggesting that the analogues developed herein may be valuable lead analogues for the development of A2780 ovarian carcinoma specific cytotoxic agents with GI_{50} values from 3.8 – 0.34 μM.

Experimental Section

Materials and methods

All reagents were purchased from Sigma Aldrich and were used without purification, with the exception of furfural, which was distilled from glass prior to use. Solvents were bulk, and distilled from glass prior to use.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance™ AMX 400 at 400.13 and 100.62 MHz, respectively and Advance™ AMX 600 at 600.21 and 150.92, respectively. Chemical shifts (δ) are reported in parts per million (ppm) measured relative to the internal standards. Coupling constants (*J*) are expressed in Hertz (Hz). Mass spectra were recorded on a Shimadzu LCMS 2010 EV and Agilent 6100 series single quadrupole LCMS using a mobile phase of 1:1 acetonitrile:H_2O with 0.1 % formic acid. Gas chromatography-mass spectrometry (GC-MS) was performed on a Shimadzu GC-MS QF2010 EI/NCI System equipped with a ZB-5MS capillary column of 5% phenyl-arylene stationary phase.

Melting points (M.P.) were recorded on a Büchi Melting Point M-565. IR spectra were recorded on a PerkinElmer Spectrum Two™ FTIR Spectrometer. Thin layer chromatography (TLC) was performed on Merck 60 F_{254} pre-coated aluminium plates with a thickness of 0.2 mm. Column chromatography was performed under 'flash' conditions on Merck silica gel 60 (230-400 mesh).

Hydrogenations were performed using a ThalesNano H-Cube Pro™ (H-Cube®) continuous-flow hydrogenation reactor. All reactions were passed through the H-Cube® reactor once, unless otherwise specified. Flow reactions were carried out using Vapourtec RS-400 fitted with V3 pumps and Vapourtec easy-MedChem fitted with V3 pumps.

Ethyl 4-hydroxy-3-nitrobenzoate (5)

Batch synthesis

A magnetically stirred solution of 4-hydroxy-3-nitrobenzoate (**4**, 10 g, 54.6 mmol) in absolute ethanol (100 mL), maintained at 18 °C, was charged with concentrated sulphuric acid (2 drops). The ensuing mixture was heated to reflux and permitted to stir at this temperature for 16 h. After cooling to room temperature, the reaction was diluted with Et_2O (100 mL) and, then, washed with saturated $NaHCO_3$ (1 × 50 mL). The separated organic layer was dried ($MgSO_4$), filtered and then concentrated to give a dark yellow solid (7.05 g, 63%).

Flow Synthesis

A solution of 4-hydroxy-3-nitrobenzoate (**4**, 1.02 g, 5.10 mm9l) and concentrated H_2SO_4 (1.04 g) in ethanol (15 mL) was pumped and recirculated through a Vapourtec easy-MedChem, fitted with 2 × 10 mL PFA coils at 140 °C, at 0.5 mL.min^{-1} and 8 bar of backpressure. After 2 h, the resulting reaction liquor was concentrated under reduced pressure to afford a bright yellow solid. The solid was washed with water, filtered through cellulose paper and air dried to afford a yellowish-pink crystalline solid (0.90 g, 69%). m.p. 66.9–68.0°C, %); R_f 0.2 (2:98 v/v MeOH/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.82 (d, *J* = 2.1 Hz, 1H), 8.25 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.3, 158.1, 138.0 133.2, 127.3, 123.1, 120.2, 61.7, 14.3; Mass spectrum (ESI, +ve) m/z 212 [$(M+H)^+$, (ESI, –ve) m/z 210 [$(M–H)^–$, 100%]; HRMS (ESI^+) calcd. for $C_9H_{10}NO_5$ $(M+H)^+$ 212.0553, found 212.0554; IR ν_{max} (cm^{-1}) 3252, 3092, 2987, 1717, 1627, 1583, 1539, 1423, 1363, 1330, 1283, 1261, 1151, 1020, 925, 860, 758, 687, 633, 574, 533, 501, 428.

N-Ethyl-4-hydroxy-3-nitrobenzamide (6)

Two solution streams, one comprising 4-hydroxy-3-benzoate (4, 0.92 mg, 5.0 mmol), COMU (2.6 g, 6.05 mmol) and iPr_2NEt (1.76 ml, 10.1 mmol) in CH_3CN (25 mL); and the second solution ethylamine (0.28 ml, 10.1 mmol of a 70% aqueous solution) in DMF (15 mL) were pumped through a Vapourtec R4 fitted with one 10 mL PFA coil, maintained at 60 °C at 1 mL.min^{-1} (residence time: 10 min) with a backpressure of 5 bar. The resulting product stream was concentrated in vacuo and adsorbed on SiO_2 and, then, subjected to column chromatography (SiO_2) with a gradual elution of 0:1 to 1:0 v/v EtOAc/n-Hexane. Concentration of the relevant fractions (R_f: 0.3 – 1:1 v/v EtOAc/n-Hexane) afforded a yellow solid (340 mg, 32 %). m.p. = 122–124°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.51 (d, *J* = 2.2 Hz, 1H), 8.06 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 6.17 (s, 1H), 3.55 – 3.48 (m, 2H), 1.28 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 157.2, 136.3, 133.1, 127.3, 123.8, 120.6, 35.4, 15.0; Mass spectrum (ESI, +ve) *m/z* 211 [$(M+H)^+$, 100%]; HRMS (ESI) calcd. for $C_9H_{11}N_2O_4$ (M+H) 211.0713, found 211.0714; IR ν_{max} (cm^{-1}) 3301, 3279, 2996, 1626, 1615, 1520, 1418, 1250, 1240, 1162, 1076, 756, 658, 618, 582, 487, 425.

Ethyl 3-amino-4-hydroxybenzoate (7)

A solution of ethyl 4-hydroxy-3-nitrobenzoate (**5**, 130 mg, 0.62 mmol) in CH_3CN (12 mL) was passed through a ThalesNano H-Cube Pro® using a 30 mm 10% Pd/C CatCart® catalyst at 3 mL.min^{-1} (residence time: 4 min) at 50 °C and 50 bar of pressure. The resulting product stream was concentrated under reduced pressure to afforded a creamy

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white solid (110 mg, 98 %). m.p. 65.5–67.8 °C, R_f 0.15 (1:9 *v*/*v* CH_3OH/CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 1.8 Hz, 1H), 7.43 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.74 (broad s, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.2, 149.0, 134.4, 422.7, 122.0, 117.5, 114.5, 60.8, 14.4; Mass spectrum (ESI, +ve) m/*z* 265 [(M+*i*PrOH+Na+H)$^+$, 100%], 182 [(M+H)$^+$, 100%], (ESI, –ve) m/*z* 180 [(M–H)$^-$, 100%]; HRMS (ESI) calcd. for $C_9H_{10}NO_3$ $(M–H)^-$ 181.1885, found 181.0499; IR ν_{max} (cm^{-1}) 3386, 3100, 2985, 1687, 1602, 1520, 1365, 1302, 1285, 1202, 1151, 1094, 1022, 893, 764, 637, 453.

3-Amino-*N*-ethyl-4-hydroxybenzamide (8)

A solution of *N*-ethyl-4-hydroxy-3-nitrobenzamide (**6**, 51 mg, 0.3 mmol) in EtOAc (12 mL) was passed through a ThalesNano H-Cube Pro® using a 70 mm 10% Pd-C CatCart® catalyst at 3 mL.min^{-1} (residence time: 4 min) at 50 °C and 50 bar of pressure. The resulting product stream was concentrated under reduced pressure to afford light brown solid (41 mg, 95 %). m.p. 183–185 °C, R_f 0.1 (1:1 *v*/*v* EtOAc/*n*-henxane), ^{1}H NMR (400 MHz, CD_3OD) δ 7.19 (d, *J* = 2.2 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 3.36 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 170.6, 149.7, 136.5, 127.3, 119.4, 115.9, 114.7, 35.7, 15.0; Mass spectrum (ESI, +ve) 181.2 [(M), 100%]; HRMS (ESI); $(M–H)^-$ 180.0899; IR ν_{max} (cm^{-1}) 3398, 3328, 2878, 1576, 1509, 1403, 1384, 1285, 1219, 1138, 870, 751, 686, 510, 451.

Ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (10)

Three solution streams, one comprising ethyl 3-amino-4-hydroxybenzoate (**7**, 68 mg, 0.04 mmol) in CH_3CN (7.5 mL); the second, $NaHCO_3$ in H_2O (0.5 M); and the third dichloroacetyl chloride in dichloroethane (0.055 M) w ere pumped through a Vapourtec easy-MedChem fitted with two 4 mL PFA coils, maintained at 18 °C, followed by two 10 mL PFA coils, maintained at 100 °C at 1 mL.min^{-1} (residence time: 14 min) with a backpressure of 8 bar. The resulting biphasic product stream was diluted with H_2O (1 × 50 mL) and extracted with EtOAc (4 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL), dried ($MgSO_4$), filtered and then concentrated *in vacuo* to give a black solid. This material was recrystallised with CH_2Cl_2 to give a light pink crystalline solid (30 mg, 44%), m.p. 175.4–177.7 °C, R_f 0.23 (1:19 *v*/*v* $MeOH/CH_2Cl_2$), ^{1}H NMR (600 MHz, d_6-DMSO): δ 10.96 (s, 1H), 8.16 (d, *J* = 6.6 Hz, 1H), 7.58 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 5.56 (d, *J* = 6.6 Hz, 1H), 4.29 (d, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, d_6-DMSO) δ 165.6, 162.6, 145.3, 127.3, 125.1, 124.6, 118.0, 116.8, 91.0, 61.1, 14.7; Mass spectrum (ESI, –ve) m/*z* 236 [(M–H)$^-$, 100%]; calcd. for $C_{11}H_{12}NO_5$ $(M+H)^+$ 238.0710 found 238.0710; IR ν_{max} (cm^{-1}) 3283, 2990, 2878, 1712, 1679, 1615, 1485, 1403, 1290, 1213, 1136, 1075, 1018, 969, 898, 764, 716, 606, 540, 449.

***N*-Ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4,]oxazine-6-carboxamide (11)**

Three solution streams, one comprising 3-amino-*N*-ethyl-4-hydroxybenzamide (80 mg, 0.44 mmol) in CH_3CN (9 mL); the second, $NaHCO_3$ in H_2O (0.5 M); and the third dichloroacetyl chloride in dichloroethane (0.05 M) were pumped through a Vapourtec easy-MedChem fitted with two 4 mL PFA coils, maintained at 18 °C, and two 10 mL PFA coils, maintained at 100 °C at 1 mL.min^{-1} (residence time: 14 min) with a backpressure of 5 bar. The resulting biphasic product stream was separated; the aqueous washed with EtOAc (2 × 30 mL), dried ($MgSO_4$), filtered and then concentrated *in vacuo* to give a pale yellow solid (54 mg, 52%); m.p. 222.9–239.1 °C; R_f 0.25 (1:9 *v*/*v* CH_3OH/CH_2Cl_2), ^{1}H NMR (600 MHz, d_6-DMSO): δ 10.91 (s, 1H), 8.37 (t, *J* = 5.3 Hz, 1H), 8.05 (d, *J* = 6.5 Hz, 1H), 7.44 – 7.43 (m, 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 5.52 (d, *J* = 6.5 Hz, 1H), 3.32 – 3.23 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 168.2, 163.0, 151.3, 125.7, 125.3, 124.5, 121.0, 114.3, 66.6, 34.4, 13.6; Mass spectrum (ESI, +ve) *m*/*z* 235.1 $[(M–H)^–$, 65%), (ESI, +ve) *m*/*z* 237 [(M+H)$^+$, 30%); HRMS (ESI) calcd. for $C_{22}H_{25}N_4O_8$ $(2M+H)^+$ 473.1667, found 473.1667; IR ν_{max} (cm^{-1}) 3363, 3095, 1684, 1635, 1550, 1495, 1389, 1282, 17, 1087, 1001, 965, 890, 763, 716, 632, 535, 472, 445.

General procedure for the synthesis of 2-anilo substituted benzoxazinones

Batch Synthesis:

A magnetically stirred slurry of ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**11a**) or *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11b**) (1.0 mmol, 1 eq.) in 1:4 *v*/*v* EtOAc/Et_2O (3 mL), was charged with the corresponding aniline (1.5 eq., 1.5 mmol) and anhydrous Na_2SO_4 (10.0 mmol, 10 eq.). The ensuing slurry was stirred at 30 °C for 19 h. After cooling to room temperature, the mixture was adsorbed onto SiO_2 and then subjected to flash chromatography (silica, 0:1 → 2:98 *v*/*v* $MeOH/CH_2Cl_2$ gradient elution) and concentration of the relevant fractions afforded the titled product.

Flow Synthesis:

Two solutions streams, one comprising of ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**11a**) or *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11b,** 1.0 mmol, 1 eq.) in EtOAc (200 µL); and the second stream of aniline (1.01 mmol, 1 eq.) in EtOAc (200 µL), were pumped through a Vapourtec easy-MedChem fitted with one 10 mL PFA coil, maintained 100 °C, and an Omnifit® column containing anhydrous Na_2SO_4, maintained at 100 °C, at 1mL.min^{-1} with a back pressure of 4 bar. The product stream was recirculated for 19 h, before it was concentrated under reduced pressure to afford the title product.

Library 1 – Ethyl ester analogues

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Ethyl 3-oxo-2-(phenylamino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (12a)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**10**, 40.0 mg, 0.17 mmol), aniline (19.0 µL, 0.20 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **12a** was isolated as a white solid (44.0 mg, 82%); R_f: 0.4 (1:19 *v/v* CH_3OH/CH_2Cl_2), m.p. 197.6–200.2 °C; ^{1}H NMR (600 MHz, d_6-acetone) δ 9.98 (bs, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.67 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.22 (dd, *J* = 8.4, 7.5 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 2H), 6.81 (t, *J* = 7.5 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.94 – 5.93 (m, 1H), 4.35 – 4.31 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 165.2, 161.5, 146.3, 144.9, 129.1 (2 overlapping signals), 127.8, 125.2 (rotamer A), 125.2 (rotamer B), 119.4, 117.7, 116.9, 114.0, 114.0, 81.6 (rotamer A), 81.5 (rotamer B), 78.3, 60.5, 13.7; Mass spectrum (ESI, –ve) m/z 311 [$(M–H)^-$, 100%]; HRMS (ESI) *Compound **12a** hydrolysed to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ $(M+H)^+$ 238.0710, found 238.0810; IR ν_{max} (cm^{-1}): 3310, 3191, 3101, 3045, 2995, 2885, 1717, 1477, 1603, 1526, 1494, 1449, 1400, 1289, 1208, 1127, 1098, 1015, 951, 916, 764, 746, 690, 507, 473.

*Rotamer exists through the free rotation of the *N*-phenyl group.

Ethyl 2-(3-bromophenylamino)-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (12b)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**10**, 40 mg, 0.17 mmol), 3-bromoaniline (21 µL, 0.18 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **12b** was isolated as a white solid (49 mg, 73%); m.p. 182.2–188.9 °C; R_f 0.45 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-acetone) δ 10.08 (s, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 7.69 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.20 (t, *J* = 2.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.00 – 6.99 (m, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.01 – 5.99 (m, 1H), 4.34 (q, *J* = 7.0 Hz, 2H), 1.36 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 165.1, 161.3, 146.7, 146.1, 130.9, 127.7, 125.3, 125.2, 122.6, 122.0, 117.7, 117.0, 116.6, 113.0, 81.0, 60.6, 13.7; Mass spectrum (ESI, +ve) *m/z* 391 [$(M+H)^+$, 100%], 393 [$(M+2+H)^+$, 100%], (ESI, –ve) *m/z* 389 [$(M–H)^-$, 100%], 391 [$(M+2–H)^-$, 100%]; HRMS (ESI) *Compound **12a** hydrolysed to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ $(M+H)^+$ 238.0710, found 238.0709; IR ν_{max} (cm^{-1}) 3191, 2989, 2390, 1714, 1678, 1674, 1597, 1479, 1368, 1306, 1254, 1215, 1170, 1123, 1070, 1018, 954, 846, 765, 680, 492, 467, 433.

Ethyl 2-(4-bromophenylamino)-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (12c)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**11a**, 40 mg, 0.17 mmol), 4-bromoaniline (32 mg, 0.18 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **12c** was isolated as a white solid (48.3 mg, 72%); m.p. 225.5–230.9 °C; R_f 0.38 – 1:19 *v/v* MeOH/CH_2Cl_2; ^{1}H NMR (600 MHz, d_6-acetone) δ 9.99 (s, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.67 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.37 – 7.35 (m, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.97 – 6.95 (m, 2H), 6.70 (d, *J* = 8.2 Hz, 1H), 5.94 – 5.93 (m, 1H), 4.35 – 4.30 (m, 2H), 1.35 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 165.1, 161.3, 146.1, 144.3, 131.9 (2 overlapping signals), 127.7, 125.2, 117.7, 117.0, 116.0 (2 overlapping signals), 110.8, 81.23 (rotamer A), 81.16 (rotamer B), 60.6, 13.7; Mass spectrum (ESI, –ve) m/*z* 389 [$(M–H)^-$, 95], 391 [$(M+2-H)^-$, 100%]; HRMS (ESI) *Compound **12c** hydrolysed to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ $(M+H)^+$ 238.0710, found 238.0711; IR ν_{max} (cm^{-1}) 3276, 1703, 1679, 1592, 1379, 1284, 1208, 1101, 1012, 921, 812, 765, 710, 658, 539, 504, 434.

3-(6-(Ethoxycarbonyl)-3-oxo-3,4-dihydro-2*H* benzo[*b*][1,4]oxazin -2-ylamino)benzoic acid (12d)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**10**, 40 mg, 0.17 mmol), 3-aminobenzoic acid (28 mg, 0.20 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **12d** was isolated as a white solid (49.0 mg, 80%); m.p. 163.3–201.6; R_f 0.15 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-DMSO) δ 12.78 (s, 1H), 11.15 (s, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.57 – 7.54 (m, 2H), 7.45 (s, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.14 – 7.12 (m, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.06 (d, *J* = 8.5 Hz, 1H), 4.32 – 4.28 (m, 2H), 1.31 (t, *J* = 6 Hz, 3H); ^{13}C NMR (151 MHz, d_6-DMSO) δ 168.0, 165.6, 161.9, 146.2, 145.5, 132.2, 129.7, 128.0, 125.3, 124.5, 120.2, 118.3, 118.1, 117.1, 114.8, 81.0, 61.1, 14.7; Mass Spectrum (ESI, –ve) 355 [$(M-H)^-$, 100%]; (ESI, +ve) 357 [$(M+H)^+$, 100%], 379 [(M+Na), 20%]; HRMS (ESI) *Compound **12d** hydrolysed to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ $(M+H)^+$ 238.0710, found 238.0711; IR ν_{max} (cm^{-1}) 3267, 2979, 1705, 1688, 1611, 1597, 1439, 1292, 1209, 1132, 1119, 960, 938, 901, 768, 754, 680, 647, 536, 492, 446.

4-(6-(Ethoxycarbonyl)-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-ylamino)-3-methoxybenzoic acid (12e)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**11a**, 40 mg, 0.17 mmol), 4-aminobenzoic acid (28 mg, 0.20 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **12e** was isolated as a white solid (53 mg, 87%); m.p. 238.1–246.7 °C; R_f 0.14 (1:19 *v/v* MeOH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-DMSO) δ 12.33 (s, 1H), 11.19 (s, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.56 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.11 (d, *J* = 8.8 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, d_6-DMSO) δ 167.7, 165.6, 161.8, 149.5, 146.1, 131.5 (2 overlapping signals), 127.9, 125.3, 124.7, 121.1 118.1, 117.2, 113.4 (2 overlapping signals), 80.3, 61.1, 14.7; Mass spectrum (ESI, –ve) *m/z* 355 [$(M–H)^-$, 100%]; HRMS (ESI) *Compound **12e** hydrolysed to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ $(M+H)^+$ 238.0710, found 238.0710; IR ν_{max} (cm^{-1}) 3267, 2978,

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1688, 1611, 1596, 1529, 1484, 1426, 1377, 1310, 1292, 1209, 1132, 1090, 959, 768, 753, 680, 535, 445.

Ethyl 2-(2-methoxyphenylamino)-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (12f)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**11a**, 40 mg, 0.17 mmol), 2-anisidine (21 µL, 0.18 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v*/*v* EtOAc/Et_2O (10 mL) were reacted in EtOAc (10 mL). The titled product **12f** was isolated as a white solid (38 mg, 65%); m.p. 168.2–176.8 °C; R_f 0.33 (1:19 *v*/v CH_3OH/CH_2Cl_2); ^{1}H NMR (400 MHz, d_6-Acetone) δ 10.0 (s, 1H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.70 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.93 – 6.90 (m, 2H), 6.82 (t, *J* = 7.9 Hz, 1H), 6.12 (d, *J* = 6.8 Hz, 1H), 5.83 (d, *J* = 6.8 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 162.4, 147.3, 146.5, 133.7, 126.4, 125.3, 121.2, 120.1, 117.8, 117.4, 112.0, 110.1, 81.9, 65.9, 61.3, 55.5, 14.3; Mass spectrum (ESI, +ve) *m/z* 343 $[(M+H)^+$, 100%], (ESI, –*ve*) *m/z* 341 $[(M-H)^-$, 100%]; HRMS (ESI) *Compound **12f** hydrolysed to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ $(M+H)^+$ 238.0710, found 238.0709; IR ν_{max} (cm^{-1}) 3412, 3305, 2978, 1723, 1695, 1600, 1527, 1483, 1329, 1288, 1212, 1182, 1103, 1022, 917, 760, 732, 632, 462, 475, 435.

Ethyl 2-(3-methoxyphenylamino)-3-oxo-3,4-dihydro-2*H*-benzo [*b*][1,4]oxazine-6-carboxylate (12g)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxylate (10, 40 mg, 0.17 mmol), 3-anisidine (21 µL, 0.18 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 v/v EtOAc/Et_2O (10 mL). The titled product **12g** was isolated as a white solid (30 mg, 51 %); m.p. 169.9–180.0 °C; R_f 0.2 (1:19 v/v CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$+CD_3OD (drop)) δ 8.91 (s, 1H), 7.76 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.17 (t, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.51 – 6.47 (m, 3H), 5.67 (d, *J* = 7.0 Hz, 1H), 5.44 (d, *J* = 7.0 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$+CD_3OD (drop)) δ 165.8, 162.3, 160.8, 146.6, 145.2, 130.3, 126.5, 126.4, 125.5, 117.8, 117.5, 107.1, 105.6, 100.6, 82.0, 61.3, 55.2, 14.3; Mass spectrum (ESI, –ve) *m/v* 340 $[(M-H)^-$, 100%]; HRMS (ESI) *Compound **12g** cleaved to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ $(M+H)^+$ 238.0710, found 238.0709; IR ν_{max} (cm^{-1}) 3333, 3261, 2984, 1704, 1699, 1679, 1601, 1486, 1369, 1293, 1200, 1165, 1118, 917, 823, 763, 686, 652, 540, 491, 439.

*Rotamer exists through the free rotation of the *N*-methoxyphenyl group.

Ethyl 2-(4-methoxyphenylamino)-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (12h)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**10**, 40 mg, 0.17 mmol), 4-anisidine (23 mg, 0.18 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v*/*v* EtOAc/Et_2O (10 mL). The titled product **12h** was isolated as a white solid (35 mg, 60%); m.p. 182.2–184.0 °C; R_f 0.3 (1:19 *v*/*v* MeOH/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$ + d_4-MeOD (drop)) δ 8.83 (s, 1H), 7.76 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.87 – 6.83 (m, 4H), 5.62 (d, *J* = 6.8 Hz, 1H), 5.16 (d, *J* = 6.8 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, d_6-Acetone) δ 165.1, 161.6, 153.7, 146.3, 138.5, 127.9, 125.1, 125.0, 117.7, 116.9, 115.4 (2 overlapping signals), 114.6 (2 overlapping signals), 82.6, 60.5, 54.8, 13.7; Mass spectrum (ESI, –ve) 341 $[(M–H)^-$, 100%]; (ESI, +ve) 343 $[(M+H)^+$, 100%]; HRMS (ESI) *Compound **12h** hydrolysed to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ $(M+H)^+$ 238.0710 found, 238.0710; IR ν_{max} 3309, 2989, 1710, 1674, 1601, 1512, 1490, 1408, 1366, 1303, 1252, 1229, 1201, 1033, 956, 927, 820, 764, 650, 556, 472, 432.

Ethyl 3-oxo-2-(*o*-tolylamino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (12i)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**10**, 40 mg, 0.17 mmol), 2-toluidine (19 mg, 0.18 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v*/*v* EtOAc/Et_2O (10 mL). The titled product **12i** was isolated as a white solid (40 mg, 72%); m.p. 199.8–200.7 °C; R_f 0.4 (1:19 *v*/*v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-acetone) δ 10.03 (s, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.71 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.12 – 7.10 (m, 3H), 6.80 (td, *J* = 7.5, 0.8 Hz, 1H), 5.90 (d, *J* = 7.4 Hz, 1H), 5.85 (d, *J* = 7.4 Hz, 1H), 4.35 (q, *J* = 7.0 Hz, 2H), 2.19 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.0, 162.9, 147.5, 143.7 (rotamer A), 143.7 (rotamer B), 131.2, 128.7, 127.9, 126.2, 126.15 (rotamer A), 126.07 (rotamer B), 124.43 (rotamer A), 124.40 (rotamer B), 120.6, 118.4, 118.0, 113.6, 83.02 (rotamer A), 82.98 (rotamer B), 61.4, 17.5, 14.6; Mass spectrum (ESI, +ve) *m/z* 327 $[(M+H)^+$, 100%], (ESI, –ve) 325 $[(M–H)^–$, 100%]; HRMS *Compound **12i** cleaved to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ $(M+H)^+$ 238.0710, found 238.0710; IR ν_{max} (cm^{-1}) 3331, 3273, 2978, 1721, 1674, 1606, 1489, 1290, 1216, 1154, 1098, 1023, 950, 913, 840, 760, 743, 711, 539, 448.

*Rotamer exists through the free rotation of the *N*-tolyl group.

Ethyl 3-oxo-2-(*m*-tolylamino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (12j)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**11a**, 40 mg, 0.17 mmol), 3-toluidine (19 µL, 0.18 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v*/*v* EtOAc/Et_2O (10 mL). The titled product **12j** was isolated as a white solid (39 mg, 70%); m.p. 205.4–207.7 °C; R_f 0.32 (1:19 *v*/*v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.76 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.15 – 7.11 (m, 2H), 6.74 – 6.70 (m, *3*H), 5.68 (d, *J* = 7.0 Hz, *1*H), 5.36 (d, *J* = 7.0 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.8, 162.4, 146.7, 143.8, 139.4, 129.3, 126.5, 126.4, 125.5, 121.4, 117.8, 117.53 (rotamer A), 117.47 (rotamer B), 115.1, 111.4, 82.2, 61.3, 21.6,

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14.3; Mass spectrum (ESI, +ve) *m/z* 327 [(M+H)$^+$, 100%], (ESI, –*ve*) *m/z* 325 [(M-H)$^-$, 100%]; HRMS (ESI) *Compound **12j** cleaved to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ (M+H)$^+$ 238.0710, found 238.0709 IR ν_{max} (cm^{-1}) 3304, 3270, 3191, 2986, 1678, 1609, 1488, 1387, 1295, 1217, 1177, 1122, 1026, 954, 922, 761, 690, 645, 537, 447, 437.

*Rotamer exists through the free rotation of the *N*-tolyl group.

Ethyl 3-oxo-2-(*p*-tolylamino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (12k)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**11a**, 40 mg, 0.17 mmol), 4-toluidine (19 µL, 0.18 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **12k** was isolated as a white solid (37 mg, 67%); m.p. 182.2–184.4 °C, R_f 0.4 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-acetone) δ 9.97 (s, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.68 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.37 (d, *J* = 8.4 Hz, 1H), 5.92 – 5.90 (m, 1H), 4.36 – 4.32 (m, 2H), 2.24 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 165.2, 161.6, 146.3, 142.5, 129.6 (2 overlapping signals), 128.3, 127.9, 125.2 (rotamer A), 125.0 (rotamer B), 117.7, 116.9, 114.1 (2 overlapping signals), 81.95 (rotamer A), 81.89 (rotamer B), 60.5, 29.7, 19.6, 13.7; Mass spectrum (ESI, -+ve) *m/z* 327 [(M+H)$^+$, 100%], (ESI, –ve) *m/*z 325 [(M–H)$^-$, 100%]; HRMS (ESI) *Compound **12k** cleaved to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ (M+H)$^+$ 238.0710, found 238.0710 IR ν_{max} (cm^{-1}) 3280, 2433, 1700, 1675, 1602, 1527, 1506, 1489, 1367, 1329, 1287, 1251, 1209, 1122, 1018, 899, 807, 765, 509, 468, 439.

*Rotamer exists through the free rotation of the *N*-tolyl group.

Ethyl 2-(2-hydroxyphenylamino)-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (12l)

Employing the procedure described above, ethyl 2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxylate (**11a**, 40 mg, 0.17 mmol), 2-aminophenol (22 mg, 0.18 mmol) and anhydrous Na_2SO_4 (241 mg, 1.70 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **12l** was isolated as a white solid (36 mg, 64%); m.p. 166.2–176.3; R_f 0.3 (5:95 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-acetone) δ 10.03 (s, 1H), 8.56 (s, 1H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.71 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.83 – 6.81 (m, 2H), 6.69 (td, *J* = 7.7, 1.3 Hz, 1H), 6.01 (d, *J* = 6.8 Hz, 1H), 5.84 (d, *J* = 6.8 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 165.1, 162.1, 146.7, 144.6, 133.4, 127.9, 125.3, 125.2, 120.3, 119.6, 117.5, 117.1, 114.3, 112.8, 81.9, 60.6, 13.7; Mass spectrum (ESI, +ve) *m/*z 329 [(M+H)$^+$, 100], 370 [(M+ACN+H), 5]$^+$, 392 [(M+ACN+Na)$^+$, 1]; *m/z* (ESI, –ve) 327 [(M–H)$^-$, 100], 363 [(M+Cl)$^-$, 5], 441[(M+TFA)$^-$, 3], 655 [(2M–H)$^-$, 10]; HRMS (ESI) *Compound **12l** cleaved to hemiacetal **7*** calcd. for $C_{11}H_{12}NO_5$ (M+H)$^+$ 238.0710, found 238.0709 IR ν_{max} 3257, 2981, 1700, 1674, 1600, 1525, 1490, 1456, 1287, 1223, 1200, 1123, 1105, 1020, 975, 952, 901, 872, 823, 765, 732, 633, 572, 477, 432.

Library 2 – Ethyl amide analogues

6-(1-Iminopropyl)-2-(phenylamino)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (13a)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (11, 35 mg, 0.15 mmol), aniline (15 µL, 0.16 mmol) and anhydrous Na_2SO_4 (220 mg, 1.5 mmol) were reacted in 1:4 v/v EtOAc/Et_2O (10 mL). The titled product **13a** was isolated as a white solid (18 mg, 38%); R_f 0.25 (1:19 v/v CH_3OH/CH_2Cl_2); m.p. 197.6–200.2 °C; ^{1}H NMR (600 MHz, d_6-acetone) δ 9.98 (s, 1H), 7.68 (s, 1H), 7.64 (s, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 2H), 7.00 – 6.97 (m, 3H), 6.81 (t, *J* = 7.3 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 5.88 (d, *J* = 8.0 Hz, 1H), 3.43–3.38 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 165.3, 161.7, 145.0, 144.6, 130.1, 129.1 (2 overlapping peaks), 127.7, 122.0, 119.3, 117.2, 115.7, 114.0 (2 overlapping peaks), 81.4, 34.2, 14.3; Mass spectrum (ESI, +ve) *m/z* 312 [(M+H)$^+$, 100%], (ESI, –ve) *m/z* 310 [(M–H)$^-$, 100%]; HRMS (ESI) calcd. for $C_{18}H_{18}N_3O_5$ (M+formic acid–H)$^-$ 356.1252, found 356.1256; IR ν_{max} (cm^{-1}) 3586, 3326, 2971, 1674, 1634, 1594, 1544, 1489, 1398, 1300, 1212, 1139, 1120, 1077, 1005, 927, 880, 850, 754, 688, 646, 509, 468, 448.

2-((3-Bromophenyl)amino)-6-(1-iminopropyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (13b)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11**, 35 mg, 0.15 mmol), 3-bromoaniline (21 µL, 0.18 mmol) and anhydrous Na_2SO_4 (210 mg, 1.50 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **13b** was isolated as a white solid (48 mg, 81%); m.p. 162.9–170 °C; R_f 0.4 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (400 MHz, d_6-acetone) δ 9.98 (s, 1H), 7.67 (s, 1H), 7.62 (s, 1H), 7.50 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.19 (t, *J* = 1.8 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.99 – 6.96 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 5.93 – 5.91 (m, 1H), 3.43 – 3.36 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, d_6-DMSO) 167.7, 162.7, 146.6, 144.7, 130.3, 129.2, 127.1, 122.5, 121.8, 117.3, 116.5, 115.4, 112.5, 80.8, 34.5, 13.5; Mass spectrum (ESI, +ve) *m/*z 390 [(M+H)$^+$, 100%], 392 [(M+2+H)$^+$, 100%], (ESI, -ve) *m/*z 388 [(M-H)$^-$, 100%], 390 [(M+2-H)$^-$, 100]; HRMS (ESI) *Material decomposed*; IR ν_{max} (cm^{-1}) 3252, 3125, 2979, 1687, 1583, 1564, 1380, 1332, 1308, 1215, 1147, 1118, 1088, 951, 923, 853, 763, 701, 763, 701, 680, 574, 470.

2-((4-Bromophenyl)amino)-6-(1-iminopropyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (13c)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11**, 35 mg, 0.15 mmol), 4-bromoaniline (32 mg, 0.18 mmol) and anhydrous Na_2SO_4 (210 mg, 1.50 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **13c** was isolated as a white solid (48 mg, 81%); m.p. 205.7–218.8 °C; R_f 0.58 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (400 MHz, d_6-acetone) δ 9.98 (s, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.49 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.00 (d, *J* =

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8.4 Hz, 1H), 6.96 – 6.94 (m, 2H), 6.67 (d, *J* = 8.2 Hz, 1H), 5.88–5.86 (m, 1H), 3.43 – 3.36 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, d_6-acetone) δ 165.3, 161.5, 144.39 (rotamer A), 144.35 (rotamer B), 131.8 (2 overlapping signals), 130.1, 127.6, 122.0, 117.2, 115.9 (2 overlapping signals), 115.7, 110.7, 81.0, 78.3, 34.2, 14.3; Mass spectrum (ESI, +ve) *m/z* 390 [(M+H)$^+$, 100%], 392 [(M+2+H)$^+$, 100%], (ESI, -ve) *m/z* 389 [(M-H)$^-$, 100%], 390 [(M+2-H)$^-$, 100%]; HRMS (ESI) *Material decomposed*; IR ν_{max} (cm^{-1}) 3320, 3056, 2974, 1679, 1616, 1579, 1563, 1489, 1386, 1408, 1294, 1212, 1143, 1110, 985, 923, 846, 815, 679, 525, 506, 469, 442.

3-((6-(Ethylcarbamoyl)-3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-2-yl)amino)benzoic acid (13d)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11**, 35 mg, 0.15 mmol), 3-aminobenzoic acid (22 mg, 0.16 mmol), anhydrous Na_2SO_4 (210 mg, 1.48 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **13d** was isolated as a white solid (29 mg, 55%); m.p. 210.1–212 °C; R_f 0.2 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-DMSO) δ 12.79 (s, 1H), 11.09 (s, 1H), 8.36 (t, *J* = 5.3 Hz, 1H), 7.50 – 7.49 (m, 2H), 7.44 – 7.33 (m, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 6.9 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 5.97 (d, *J* = 8.3 Hz, 1H), 3.33–3.23 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, d_6-DMSO) δ 168.0, 165.6, 162.1, 145.7, 144.4, 132.1, 129.7 (rotamer A), 129.6 (rotamer B), 127.8, 122.4, 120.1, 118.3, 117.4, 116.1, 114.8, 80.9, 34.5, 31.2, 15.3; Mass spectrum (ESI, –ve) *m/z* (ESI, -ve) 354 [(M-H)$^-$, 100%], 390 [(M+Cl)$^-$, 45], 709 [(2M-H)$^-$, 40]; HRMS (ESI) calcd. for $C_{18}H_{15}N_3NaO_5$ (M+Na–H)$^-$ 376.0915, found 376.2785; IR ν_{max} (cm^{-1}) 3344, 3145, 2979, 1689, 1652, 1610, 1594, 1495, 1382, 1311, 1244, 1211, 1116, 964, 937, 810, 753, 446.

4-((6-(Ethylcarbamoyl)-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)amino)benzoic acid (13e)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11**, 35 mg, 0.15 mmol), 4-aminobenzoic acid (22 mg, 0.16 mmol), anhydrous Na_2SO_4 (210 mg, 1.48 mmol) were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **13e** was isolated as a white solid (34 mg, 64%); m.p. 209.6–214.7 °C; R_f 0.18 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-DMSO) δ 12.31 (s, 1H), 11.14 (s, 1H), 8.37 (t, *J* = 5.2 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.49 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.03 (d, *J* = 8.6 Hz, 1H), 3.29 – 3.22 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, d_6-DMSO) δ 166.6, 164.5, 160.9, 148.6, 143.1, 130.4 (2 overlapping signals), 128.7, 126.6, 121.4, 119.9, 116.3, 115.0, 112.3 (2 overlapping signals), 79.1, 33.4, 14.2; Mass spectrum *m/z* 354 [(M–H)$^-$, 100%]; HRMS (ESI) calcd. for $C_{18}H_{15}N_3NaO_5$ (M+Na–H)$^-$ 376.0915, found 376.2785; IR ν_{max} (cm^{-1}) 3322, 3056, 2974, 2543, 1683, 1606, 1575, 1490, 1426, 1307, 1292, 1213, 1178, 1145, 1102, 931, 845, 530, 468.

N-Ethyl-2-((2-methoxyphenyl)amino)-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (13f)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11**, 40 mg, 0.17 mmol), 2-anisidine (26 µL, 0.19 mmol) and anhydrous Na_2SO_4 (270 mg, 1.7 mmol) were reacted in 1:4 v/v EtOAc/Et2O (10 mL). The titled product **13f** was isolated as a white solid (49 mg, 85%); m.p. 232.0–244.5 °C; R_f 0.18 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-acetone) δ 10.04 (s, 1H), 7.69 (s, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.92–6.89 (m, 2H), 6.81 (m, 1H), 6.10 (d, *J* = 6.6 Hz, 1H), 5.77 (d, *J* = 6.6 Hz, 1H), 3.84 (s, 3H), 3.43 – 3.39 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 167.1, 164.0, 149.1, 146.8, 136.1, 132.1, 129.6, 124.0, 122.8, 121.2, 118.8, 117.6, 113.8, 112.0, 83.4, 56.8, 36.1, 16.1; Mass spectrum (ESI, +ve) *m/z* 342 [(M+H)$^+$, 10], 683 [(2M+H)$^+$, 5], (ESI, -ve) 340 [(M-H)$^-$, 100%], 454 [(M+TFA-H)$^-$, 5], 681 [(2M-H)$^-$, 10]; HRMS (ESI) calcd. for $C_{18}H_{18}N_3O_4$ (M–H)$^-$ 340.1303, found 340.1302; IR ν_{max} (cm^{-1}) 3409, 3305, 2972, 2873, 1710, 1634, 1616, 1599, 1526, 1493, 1390, 1336, 1225, 1151, 1033, 927, 853, 767, 742, 683, 647, 528.

N-Ethyl-2-((3-methoxyphenyl)amino)-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (13g)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11**, 35 mg, 0.15 mmol), 3-anisidine (20 µL, 0.17 mmol), anhydrous Na_2SO_4 (210 mg, 1.48 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **13g** was isolated as a white solid (37 mg, 73%); m.p. 214.7–217.0 °C; R_f 0.46 (1:19 *v/v* CH_3OH/CH_2Cl_2), ^{1}H NMR (600 MHz, d_6-acetone) δ 9.97 (s, 1H), 7.68 (s, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.49 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.10 (t, *J* = 8.3 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.56–6.55 (m, 2H), 6.48 (d, *J* = 8.3 Hz, 1H), 6.40–6.39 (m, 1H), 5.87 (d, *J* = 8.2 Hz, 1H), 3.75 (s, 3H), 3.42–3.39 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 165.4, 161.8, 160.9, 146.4, 144.6, 130.1, 129.9, 127.8, 121.9, 117.2, 115.7, 106.64 (rotamer A), 106.60 (rotamer B), 104.8, 100.03 (rotamer A), 100.00 (rotamer B), 81.4, (rotamer A) 81.3 (rotamter B), 54.4, 34.3, 14.3; Mass spectrum (ESI, +ve) *m/z* 342 [(M+H)$^+$, 100], 383 [(M+2NA+H)$^+$, 20], 683 [(2M+H)$^+$, 50], (ESI, ve) *m/z* 340 [(M-H)$^-$, 100%], 386 [(M+formic acid-H)$^-$, 5], 454 [(M+TFA-H)$^-$, 5], 681 [(2M-H)$^-$, 10]; HRMS (ESI) calcd. for $C_{18}H_{18}N_3O_4$ (M–H)$^-$ 340.1303, found 340.1302; IR ν_{max} (cm^{-1}) 3299, 2973, 1687, 1683, 1605, 1558, 1382, 1310, 1203, 1177, 1043, 924, 813, 766, 687, 514, 495, 474, 436.

*Rotamer exists through the free rotation of the *N*-arylmethoxy group.

N-Ethyl-2-((4-methoxyphenyl)amino)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide (13h)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11**, 35 mg, 0.14 mmol), 4-anisidine (20 mg, 0.17 mmol) and anhydrous Na_2SO_4 (210 mg, 1.48 mmol), were

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reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **13h** was isolated as a white solid (35 mg, 69%); m.p. 207.4–209.3 °C; R_f 0.55 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-acetone) δ 9.90 (s, 1H), 7.65 (s, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.49 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 6.18 (d, *J* = 8.4 Hz, 1H), 5.79 (d, *J* = 8.4 Hz, 1H), 3.73 (s, 3H), 3.42 – 3.37 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 167.2, 163.7, 155.4, 146.4, 140.5, 131.8, 129.6, 123.7, 119.0, 117.4, 117.1 (2 overlapping signals), 116.3 (2 overlapping signals), 84.2, 56.7, 36.1, 16.1; Mass spectrum (ESI, +ve) *m/z* 342 [$(M+H)^+$, 100], 383 [$(M+2NA+H)^+$, 10], 683 [$(2M+H)^+$, 50], (ESI, –ve) *m/z* 340 [$(M-H)^-$, 100%], 386 [(M+formic acid-H)$^-$, 5], 454 [(M+TFA-H)$^-$, 5], 681 [(2M-H)$^-$, 10]; HRMS (ESI) calcd. for $C_{18}H_{18}N_3O_4$ $(M-H)^-$ 340.1303, found 340.1302; IR ν_{max} (cm^{-1}) 3446, 3274, 3139, 2971, 1684, 1644, 1599, 1504, 1393, 1307, 1280, 1238, 1211, 1030, 954, 927, 818, 760, 536, 471.

_N_-Ethyl-3-oxo-2-(*o*-tolylamino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (13i)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11**, 35 mg, 0.15 mmol), 2-toluidine (18 μL, 0.19 mmol) and anhydrous Na_2SO_4 (210 mg, 1.48 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **13i** was isolated as a white solid (23 mg, 41%); m.p. 208–212 °C; R_f 0.6 (1:19 *v/v* $MeOH/CH_2Cl_2$); ^{1}H NMR (600 MHz, d_6-acetone) δ 10.02 (s, 1H), 7.70 (s, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.09–7.08 (m, 2H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 5.81 (s, 1H), 3.43–3.39 (m, 2H), 2.18 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H) (Proton due to NH-Ar not observed); ^{13}C NMR (151 MHz, d_6-acetone) δ 166.3 (rotamer A), 166.2 (rotamer B), 163.1, 145.8, 143.8 (rotamer A), 143.8 (rotamer B), 131.2, 131.0, 128.7, 127.9, 124.3, 123.0, 120.5, 117.9, 116.7, 113.6, 82.9 (rotamer A), 82.9 (rotamer B), 35.2 (rotamer A), 35.1 (rotamer B), 17.5, 15.2; Mass spectrum (ESI, +ve) *m/z* 326 [$(M+H)^+$, 100%], 367 [(M+CAN+H)$^+$, 25], 651 [$(2M+H)^+$, 50], (ESI, –ve) 324 [$(M-H)^-$, 100%], 438 [(M+TFA–H)$^-$, 20]; HRMS (ESI) calcd. for $C_{18}H_{18}N_3O_4$ $(M-H)^-$ 340.1303, found 340.1302; IR ν_{max} (cm^{-1}) 3419, 3291, 2976, 2421, 1706, 1631, 1519, 1495, 1455, 1393, 1326, 1151, 1051, 926, 854, 750, 689, 466.

_N_-Ethyl-3-oxo-2-(*m*-tolylamino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (13j)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11**, 35 mg, 0.15 mmol), *m*-toluidine (18 μL, 0.19 mmol) and anhydrous Na_2SO_4 (210 mg, 1.48 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **13j** was isolated as a white solid (36 mg, 73%); m.p. 199.0–201.0 °C; R_f 0.46 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-acetone) δ 9.99 (s, 1H), 7.70 (s, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.49 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.08 (t, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.80 (s, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.39 (d, *J* = 8.3 Hz, 1H), 5.86 (d, *J* = 8.3 Hz, 1H), 3.43–3.39 (m, 2H), 2.26 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 165.4, 161.8, 145.0, 144.6, 138.6, 130.0, 129.0, 127.8, 121.9, 120.1, 117.2, 115.8, 114.7, 111.2, 81.5 (rotamer A), 81.5 (rotamer B), 34.4, 20.7, 14.3; Mass spectrum (ESI, +ve) *m/z* 326 [$(M+H)^+$, 80%], 367 [(M+ACN+H)$^+$, 100], 651 [$(2M+H)^+$, 50], (ESI, –ve) 324 [$(M-H)^-$, 100%], 438 [(M+TFA–H)$^-$, 100]; HRMS (ESI) *Compound **13k** cleaved to hemiacetal **6*** calcd. for $C_{11}H_{13}N_2O_4$ $(M+H)^+$ 237.0870, found 237.0870; IR ν_{max} (cm^{-1}) 3453, 3291, 3144, 2971, 1683, 1647, 1595, 1536, 1486, 1383, 1317, 1280, 1218, 1177, 954, 919, 852, 813, 774, 755, 689, 648, 572, 535, 453, 445.

_N_-Ethyl-3-oxo-2-(*p*-tolylamino)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (13k)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11b**, 35 mg, 0.15 mmol), 4-toluidine (18 mg, 0.17 mmol) and anhydrous Na_2SO_4 (210 mg, 1.48 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **13k** was isolated as a white solid (23 mg, 47%); m.p. 221–224 °C; R_f 0.46 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-acetone) δ 9.93 (s, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.49 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.32 (d, *J* = 8.4 Hz, 1H), 5.84 (d, *J* = 8.4 Hz, 1H), 3.43–3.39 (m, 2H), 2.24 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 165.4, 161.8, 144.6, 142.6, 130.0, 129.6 (2 overlapping signals), 128.2, 127.8, 121.9, 117.2, 115.7, 114.1 (2 overlapping signals), 81.8, 34.3, 19.6, 14.3; Mass spectrum (ESI,+ve) *m/z* 326 [$(M+H)^+$, 10], (ESI, –ve) *m/z* 324 [$(M-H)^-$, 100%], 438 [(M+TFA-H)$^-$, 10]; HRMS (ESI) *Compound **13k** cleaved to hemiacetal **6*** calcd. for $C_{11}H_{13}N_2O_4$ $(M+H)^+$ 237.0870, found 237.0870; IR ν_{max} (cm^{-1}) 3453, 3291, 3144, 2971, 1683, 1647, 1595, 1536, 1486, 1383, 1317, 1280, 1218, 1177, 954, 919, 852, 813, 774, 755, 689, 648, 572, 535, 453, 445.

_N_-ethyl-2-((2-hydroxyphenyl)amino)-3-methylene-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (13l)

Employing the procedure described above, *N*-ethyl-2-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-carboxamide (**11b**, 35 mg, 0.15 mmol), 2-aminophenol (18 mg, 0.16 mmol) and anhydrous Na_2SO_4 (210 mg, 1.48 mmol), were reacted in 1:4 *v/v* EtOAc/Et_2O (10 mL). The titled product **13k** was isolated as a white solid (39 mg, 80%); m.p. 181.4–191.5 °C; R_f 0.21 (1:19 *v/v* CH_3OH/CH_2Cl_2); ^{1}H NMR (600 MHz, d_6-acetone) δ 10.05 (s, 1H), 8.56 (s, 1H), 7.72 (s, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.54 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 7.03 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.68 (td, *J* = 7.9, 1.2 Hz, 1H), 5.99 (d, *J* = 6.7 Hz, 1H), 5.77 (d, *J* = 6.7 Hz, 1H), 3.44–3.39 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, d_6-acetone) δ 165.4, 162.3, 145.1, 144.6, 133.5, 130.2, 127.8, 122.2, 120.3, 119.5, 117.0, 115.8, 114.3, 112.7, 81.8, 34.4, 14.3; Mass spectrum (ESI, +ve) *m/z* 328 [$(M+H)^+$, 5], (ESI, –ve) *m/z* 326 [$(M-H)^-$, 100], 362 [(M+Cl)$^-$, 33], 440 [(M+TFA–H)$^-$, 50], 653 [(2M–H), 45]; HRMS (ESI) *material decomposed*; IR ν_{max} (cm^{-1}) 3376, 3063, 2977, 2876, 1695, 1635, 1611, 1532,

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1489, 1457, 1386, 1315, 1207, 1121, 981, 909, 877, 797, 740, 634, 536, 481, 456, 446, 407.

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