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Direct Access to Highly Functionalised Benzimidazoles and Benzoxazoles from a Common Precursor

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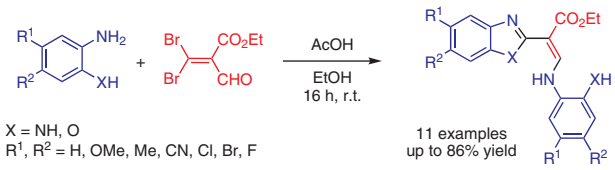

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Abstract Benzoxazole and benzimidazole are commonly encountered heterocycles in medicinal chemistry and their functionalisation around 1-, 2-, 5-, and/or 6-positions provides a wide range of molecules of biological interest. In this manuscript, a straightforward preparation of diversely and highly substituted benzimidazoles and benzoxazoles on these positions, from a common starting material, a 3,3-dibromoacrolein, is described. Such acrolein derivatives are almost never described in the literature or used as 'building-block' for organic synthesis. The double electrophilicity of this substrate was found to be advantageous for condensation with two equivalents of various 1,2-diaminobenzene or 2-aminophenol derivatives. This one-pot reaction performed under metal-free and mild conditions allows the creation of three new carbon–heteroatom bonds and affords the desired heterocycles.

Key words aldehydes, nucleophilic addition, heterocycles, cyclisation, benzimidazoles, benzoxazoles

Planar heterocycles as benzoxazoles and benzimidazoles define an important class of chemical entities in medicinal chemistry. They play a crucial role in modern drug design by improving physicochemical properties and ligand affinity of drug candidates. Over 80% of top small molecule drugs by US retail sales in 2010 contain at least one heterocyclic fragment in their structures. In fact, heterocyclic moieties are present in the structures of all of the top 10 brand-name small molecule drugs.

Benoxaprofen was one of nonsteroidal anti-inflammatory benzoxazole drug example assigned to treat arthritic pain. Released in 1980 by Eli Lilly, it was removed the same year because of adverse side effects (Figure 1).[1] Failing to withstand, benzoxazoles remain a privileged framework because of its abundance in many natural products that suggest its plausible application in pharmaceutical discipline. Currently, benzoxazole applications lie in a drug design where this scaffold is often incorporated in molecules to modulate their activities.[2]

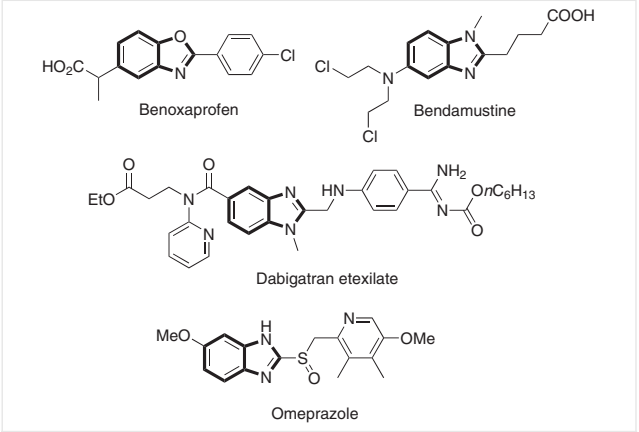

Figure 1 Selected drugs containing the benzoxazole and benzimidazole structures

Benzimidazole is a well-known heterocyclic ring commonly encountered in medicinal chemistry.[3] Its functionalisation around 1-, 2-, 5-, and/or 6- positions provides a wide range of molecules of biological interest as anticancer (Bendamustine),[4] anticoagulant (Dabigatran etexilate),[5] antiulcer (Omeprazole),[6] antihypertensive, antiviral, anthelmintic,

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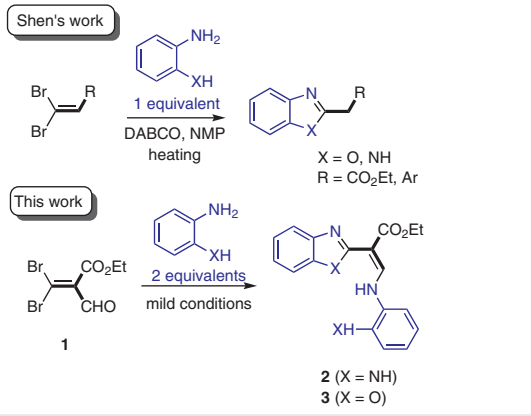
among others. All these outstanding achievements strongly reflect the plethoric pharmacological activities of benzimidazole framework (Figure 1).

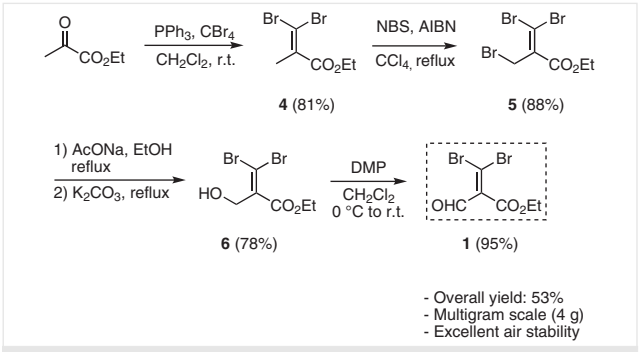
Among several synthesis routes reported, one of stands out: the condensation of 1,2-diaminobenzene or 2-aminophenol on various electrophiles, such as carboxylic acids, nitriles, imidates, orthoesters, and others.[7] However, these synthetic protocols suffer from one or more disadvantages, such as the use of dangerous or toxic oxide reagents, high temperature, strong acid conditions, prolonged reaction times, cumbersome multi-step processes, or the formation of side products. In the last decade, Shen and co-workers used a similar strategy and described 1,1-dibromoalkenes as versatile precursors, which were used, for instance, to prepare both benzimidazoles and benzoxazoles by condensation of various 2-aminophenol or diaminobenzene derivatives under heating and basic conditions (Scheme 1).[8,9] In light of these works, we assumed 3,3-dibromoacrolein **1** could be employed as a strong 1,1-dibromoalkenes Michael acceptor[10] for the preparation of both heterocycles, with higher functionalisation. Indeed, the aldehyde function could be easily transformed into the corresponding enamine by a second equivalent of 1,2-diaminobenzene or 2-aminophenol. It is noteworthy that such 3,3-dibromoacrolein **1** was never described in the literature until then, only few examples of close structures are reported.[11]



Scheme 1 Approaches for the preparation of benzimidazoles and benzoxazoles

Herein, we report in this paper a new straightforward approach for the preparation of highly functionalised benzimidazole **2** and benzoxazole **3** moieties by condensing two equivalents of 2-aminophenol or 1,2-diaminobenzene derivatives in acidic conditions on the common precursor **1** (Scheme 1).

First, the non-commercial acrolein **1** had to be prepared in large amount. With this goal in mind, a four-step protocol was developed starting from commercial ethyl pyruvate. The latter was transformed into the dibromoalkene **4** according to a literature procedure.[12] Free-radical bromination of the allylic position with *N*-bromosuccinimide in refluxing carbon tetrachloride led to the tribrominated ester **5**.[13] The allylic bromine was cleanly displaced by an acetate, this step was followed by the in situ saponification in presence of potassium carbonate to afford the corresponding alcohol **6** in good overall yield. The expected 3,3-dibromoacrolein **1** was finally obtained by oxidation with the Dess–Martin periodinane (Scheme 2). This compound was synthesised in multigram scale and was found to be stable for months by storing at 4 °C.



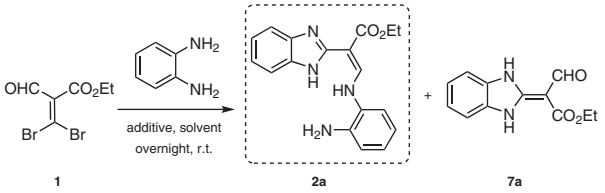
Scheme 2 Synthesis of dibromoacrolein **1**

Our first attempt for the preparation of the target heterocycles was undertaken by keeping **1** in the presence of an excess of 1,2-diaminobenzene (3 equiv) in dichloromethane at room temperature overnight (Table 1, entry 1). We were pleased to observe the formation of the expected benzimidazole **2a**, which could be isolated in a low yield of 25%. During this attempt, we were also surprised to isolate the stable intermediate **7**, obtained after the condensation of one equivalent of 1,2-diaminobenzene on **1**. According to the condition of Shen and co-workers, we decided to add an organic base in order to trap the in situ generated HBr.[8] An assay was performed with one equivalent of triethylamine as additive (entry 2). In such conditions, no traces of **2a** were found in the crude mixture but only the intermediate **7a**. The replacement of dichloromethane by a protic solvent as ethanol, keeping the same conditions, improved the yield in **2a** to 40% (entry 3). The replacement of triethylamine by an organic acid such as *p*-TsOH slightly increased the yield to 44% in **2a** and considerably improved the ratio **2a**/**7a** (entry 4). Acetonitrile as solvent did not improve the yield (entry 5), but the acid additive was optimised (entries 6 and 7) and the best conditions was found to be ethanol in presence of one equivalent of acetic acid, leading to 60% yield in **2a**.

The structure and the double bond configuration of **2a** were unambiguously confirmed by X-ray diffraction (Figure 2).[14] It should be noted that the *E*-enamine was isolated as a single diasteroisomer after column chromatography. Nevertheless, few traces of *Z*-enamine were observed in the ^{1}H NMR spectrum of the crude sample.

The scope was explored through the preparation of various benzimidazoles **2a–f** (Scheme 3) and benzoxazoles **3a–e** (Scheme 4) applying the optimised conditions. Indeed, 4-bromobenzene-1,2-diamine was employed as reagent leading to a mixture of regioisomeric benzimidazoles **2b** with a moderate yield of 36%. The replacement of bromine by a strong electron-withdrawing group such as a cyano afforded a single regioisomer **2c** in a good yield. Interestingly, NMR spectra revealed a mixture of two rotamers for this particular case, which was confirmed by variable-

Table 1 Optimisation of Reaction Conditions[a]



Entry	Additive[b]	Solvent	Ratio **2a**/**7a**[c]	**2a** Yield (%)[d]
1	none	CH_2Cl_2	65/35	25
2	Et_3N	CH_2Cl_2	0/100	0
3	Et_3N	EtOH	55/45	40
4	*p*-TsOH	EtOH	74/26	44
5	*p*-TsOH	MeCN	53/47	36
6	CF_3CO_2H	EtOH	83/17	43
7	**AcOH**	**EtOH**	**85/15**	**60**

[a] Reactions were typically performed with 0.35 mmol of dibromoacrolein **1**.
[b] 1,2-Diaminobenzene (3 equiv), additive (1 equiv).
[c] Determined by ^1H NMR analysis of the crude mixture.
[d] Isolated yield after column chromatography.

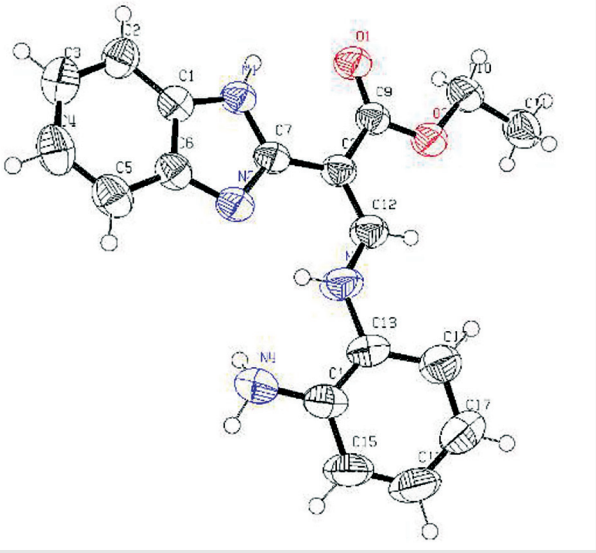
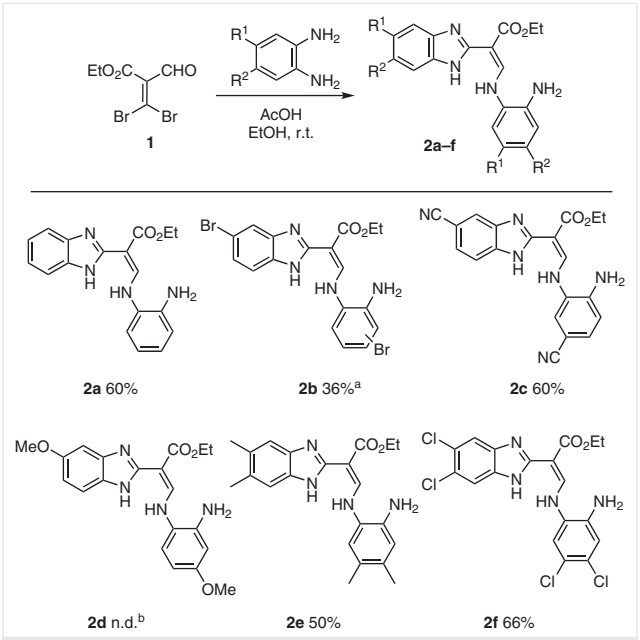
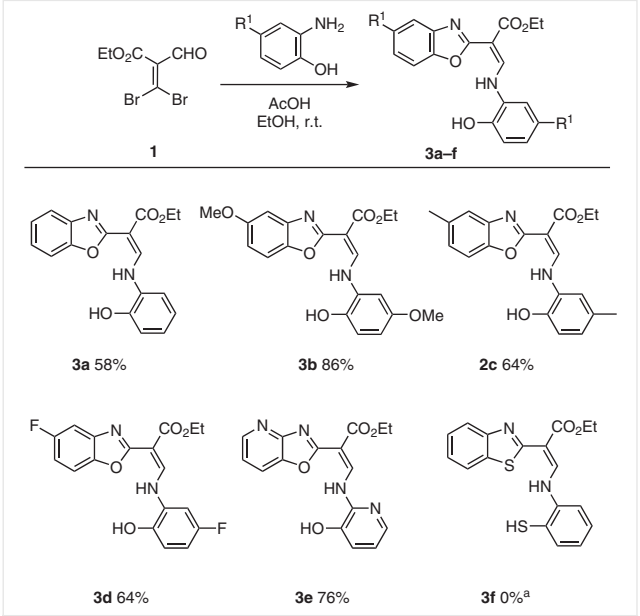


Figure 2 X-ray crystal structure of compound **2a**



Scheme 3 Synthesis of benzimidazoles **2a–f** from **1**. *Reagents and conditions*: The reactions were performed with **1** (0.35 mmol), AcOH (0.35 mmol), and 1,2-diaminobenzene (1.03 mmol) in EtOH (10 mL) at r.t., overnight. Isolated yields are shown. [a] Mixture of regioisomers. [b] Intermediate **7d** was obtained as the major compound, only traces of **2d** (yield not determined) were observed.



Scheme 4 Synthesis of benzoxazoles **3a–e** from **1**. *Reagents and conditions*: The reactions were performed with **1** (0.35 mmol), AcOH (0.35 mmol), and 2-aminophenol (1.03 mmol) in EtOH (10 mL) at r.t., overnight. Isolated yields are shown. [a] Complex mixture.

temperature NMR experiments. The coalescence for the signals of both rotamers was observed at 383 K (Figure 3). Surprisingly, 4-methoxybenzene-1,2-diamine did not afford the expected compound **2d**, but the intermediate **7d** as the major product. We assume the mesomer donor effect of methoxy group decreased the electrophilicity of the aldehyde function and therefore prevented the addition of the second equivalent of the reagent. Finally, symmetrical diamines were employed and afforded the corresponding benzimidazoles **2e** and **2f** in good yields.

The reaction was also performed with a wide range of 1,2-aminophenols. The corresponding benzoxazoles **3a–d** were obtained in good to excellent yields. Contrary to what has been observed with benzimidazole, it should be noted that methoxy substituent in the diaminobenzene furnished the best yield (86%) for this benzoxazole series. The reaction could be extended to the preparation of the oxazolo[4,5-*b*]pyridine **3e**, which could be obtained in good yield (76%). However, the extension of this methodology for the preparation of benzo[*d*]thiazole **3f** was unsuccessful as a complex mixture was obtained when 2-aminothiophenol was used as reagent.

Concerning the stereoselectivity aspects, the *E*-enamine was isolated as a single isomer for the benzimidazole series or as *E*/*Z* mixture 82/18 to 100/0 for the benzoxazole series. Interestingly, we observed the increase in the proportion of (*Z*)-**2c** from 8% to 23% at 383 K during variable-temperature NMR experiments (Figure 3).

The reaction was also attempted with non-aromatic nucleophiles such as 1,2-diaminoethane and 2-aminoethanol leading in both cases to complex mixtures, in which the expected heterocycles were never observed.

According to our results and the observations made, we propose the following mechanism (Scheme 5). Nucleophilic substitution of the first equivalent of diaminobenzene on the *gem*-dibromocarbon of **1** affords 1*H*-hydrobenzimidazole **7a**, which was fully characterised (see SI). We assumed the presence of another equivalent of 1,2-diaminobenzene (or 2-diaminophenol) is crucial at this stage, playing the role of an organic base in order to trap the generated HBr and shift the equilibrium. We considered that the external acid proton from acetic acid promotes the addition of the third equivalent of 1,2-diaminobenzene on the carbonyl

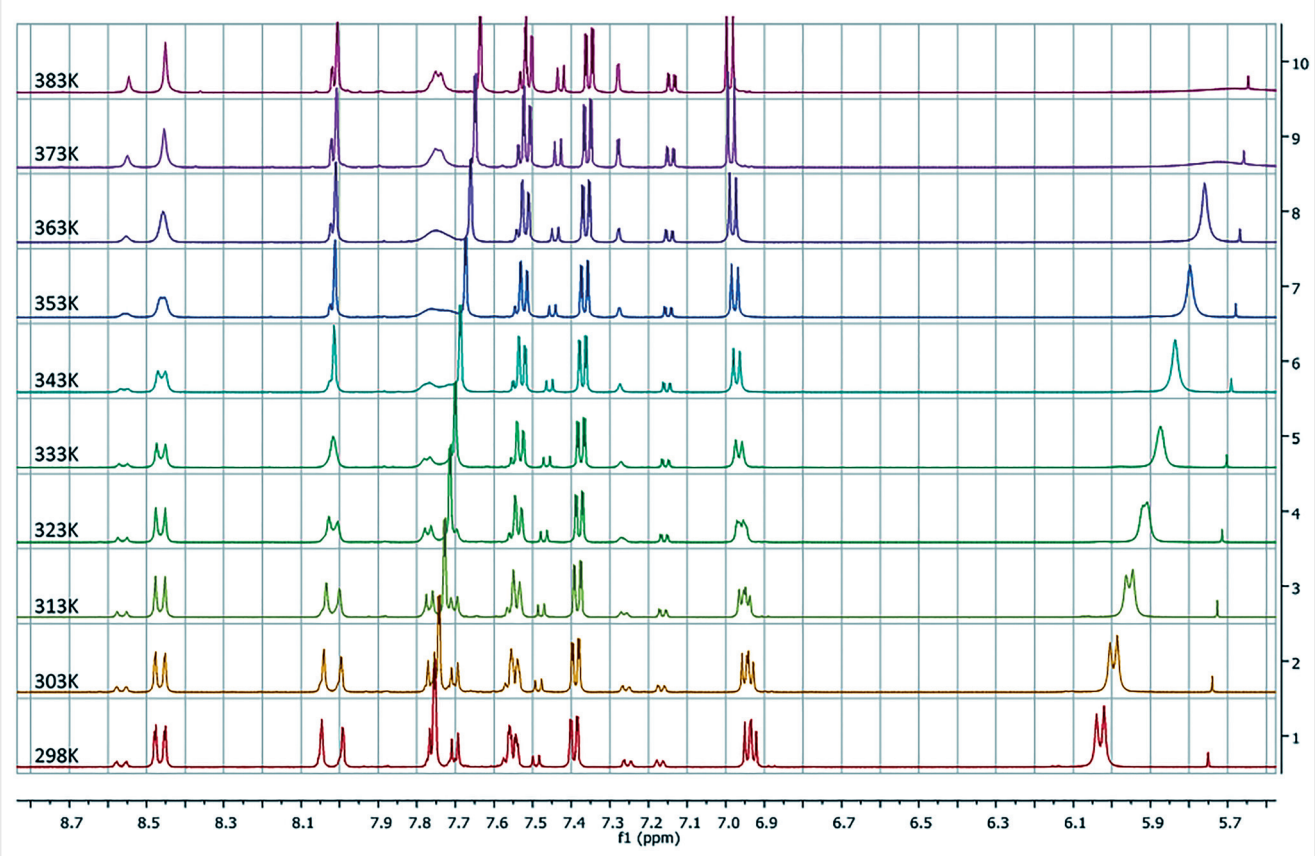
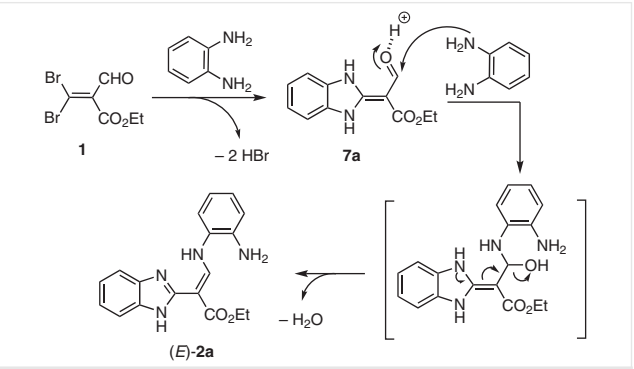


Figure 3 Variable-temperature ^{1}H NMR for compound **2c**. The coalescence for the signals of both rotamers was observed at 383 K. At this temperature an increase of the *Z*-isomer proportion to 23% was also observed.

group of **7a**, affording the intermediate hemiaminal. The later undergoes concomitant aromatisation and elimination of water to generate benzimidazole **2a**.



Scheme 5 Proposed mechanism

In conclusion, we have synthesised highly functionalised benzimidazoles **2** and benzoxazoles **3** moieties starting from the original 3,3-dihalogenoacrolein **1** with various diaminobenzenes or 2-aminophenols. The originality of this work lies in a 'one pot' metal-free and mild reaction while creating three new C–heteroatom bonds. Our effort are currently focused on the preparation of new 3,3-dibromoacroleins (with a substituent different from an ester), and the development of a multi-component version of this reaction: the amine condensed on the aldehyde of **1** would be different from the 1,2-diaminobenzene or 2-aminophenol, in order to enlarge the diversity and the prepared heterocycles.

All reactions were carried out under argon atmosphere. TLC spots were examined under UV light. Most of the chemicals were purchased from commercial suppliers and were used without further purification. 4-Methoxybenzene-1,2-diamine was purchased as the dihydrochloride salt (Acros Organics) and had to be dissolved in CH_2Cl_2, washed several times with sat. aq Na_2CO_3, evaporated and dried under vacuum prior to use. NBS was recrystallised from H_2O, and Dess–Martin periodinane was prepared in two steps starting from 2-iodobenzoic acid according to literature procedure.[15] Silica gel (Geduran Si 60, 40–63 μm by Merck) was used for column chromatography. CH_2Cl_2 was distilled from CaH_2. CCl_4 and absolute EtOH were obtained from commercial sources and were used without further purification. NMR spectra were recorded at 300 MHz for ^{1}H, 75 MHz for ^{13}C, and 282 MHz for ^{19}F on a Bruker Avance 300 spectrometer. Chemical shifts are given in parts per million (δ) relative to the residual $CHCl_3$ peak (7.26 ppm) or DMSO peak (2.50 ppm). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of ^{1}H-^{1}H COSY, HMBC, and HSQC spectra. Variable-temperature analysis were recorded on a Bruker Avance AVIII-600 NMR spectrometer equipped with Bruker variable-temperature (BVT) unit in combination with a Bruker cooling unit (BCU-05) to provide chilled air. Electrospray ionisation mass spectrometry experiments (HRMS) were obtained on a hybrid tandem quadrupole/time-offlight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, U.K.) operated in positive mode. Melting points were recorded on a Stuart™ melting point apparatus SMP3.

Ethyl 3,3-Dibromo-2-methylacrylate (4)[13]

Compound **4** was prepared by a modified procedure from literature.[12] To a solution of PPh_3 (36.1 g, 128 mmol) in CH_2Cl_2 (160 mL) cooled at 0 °C was added a solution of CBr_4 (22.9 g, 69 mmol) in CH_2Cl_2 (40 mL). The solution was stirred for 30 min at 0 °C and a solution of ethyl pyruvate (4.0 g, 34.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise. Ice bath was removed and the reaction mixture was stirred for 4 days at r.t. Petroleum ether (PE, 300 mL) was added to the mixture and after trituration, the precipated triphenylphosphine oxide was removed by a filtration over a pad of Celite. The filtrate was concentrated under reduced pressure to afford a slurry crude residue, which was purified by a simple filtration over a plug of silica gel using PE/Et_2O (80/20) as eluent; light yellow liquid; yield: 7.64 g (81%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.34 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.05 (s, 3 H, CH_3), 4.27 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3).

Characterisation data of the product match with that reported in the literature.[15]

Ethyl 3,3-Dibromo-2-(bromomethyl)acrylate (5)[13]

To a solution of **4** (7.85 g, 28.9 mmol) in CCl_4 (100 mL) were successfully added NBS (5.39 g, 30.3 mmol) and AIBN (0.241 g, 1.44 mmol). The reaction mixture was refluxed overnight, then cooled and stirred at r.t. for an additional hour. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (2 × 100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$) and the solvent were evaporated under reduced pressure. The residue was purified by a simple filtration over a plug of silica gel using PE/Et_2O (90/10) as eluent; lachrymatory light yellow liquid; yield: 8.90 g (88%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.36 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 4.32 (s, 2 H, CH_2Br), 4.34 (q, *J* = 7.1 Hz, 2 H OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0, 30.8, 62.5, 103.6, 135.7, 163.9.

Ethyl 3,3-Dibromo-2-(hydroxymethyl)acrylate (6)

A solution of **5** (8.7 g, 24.8 mmol) and AcONa (6.1 g, 74.5 mmol) in absolute EtOH (200 mL) was refluxed overnight. K_2CO_3 (3.42 g, 24.8 mmol) was added in one portion and the reaction mixture was refluxed for an additional hour. EtOH was evaporated and the residue was diluted with H_2O (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using PE/EtOAc (80/20 → 60/40) as eluent; colourless oil; yield: 5.57 g (78%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.36 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.30 (t, *J* = 7.1 Hz, 1 H, OH), 4.33 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.46 (d, *J* = 7.1 Hz, 2 H, CH_2OH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.1, 62.2, 64.6, 98.3, 139.1, 164.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_8Br_2O_4$: 286.89130; found: 286.88958.

Ethyl 3,3-Dibromo-2-formylacrylate (1)

To a solution of alcohol **6** (3.61 g, 12.5 mmol) in CH_2Cl_2 (100 mL) cooled at 0 °C was added Dess–Martin periodinane (6.40 g, 15.0 mmol) in one portion. The ice bath was removed and the reaction mixture was stirred for 2 h at r.t. The mixture was hydrolysed with

H_2O (50 mL) and the white precipitate (DMP by-product) was removed by a filtration over a pad of Celite. After decantation of the filtrate, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by a short column chromatography on silica gel using PE/EtOAc (70/30) as eluent. Aldehyde **1** was obtained as a light orange oil, which crystallised at room temperature to give a light yellow solid; yield: 3.40 g (95%); mp 55–58 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.35 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 4.35 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 9.72 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.9, 62.8, 115.8, 140.5, 162.9, 186.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_6Br_2O_4$: 284.87565; found: 284.87041.

Benzimidazoles 2a–f, 7a, 7d and Benzoxazoles 3a–e; General Procedure

To a solution of **1** (0.35 mmol) in absolute EtOH (10 mL) cooled at 0 °C were successively added glacial AcOH (20 µL, 0.35 mmol) and the 1,2-diaminobenzene or the *o*-aminophenol derivative (3 equiv). Ice bath was removed and the reaction mixture was stirred overnight at r.t. EtOH was evaporated, the residue was diluted with EtOAc (50 mL), washed with H_2O (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Ethyl (*E*)-3-[(2-Aminophenyl)amino]-2-(1*H*-benzo[*d*]imidazol-2-yl)acrylate (2a)

Following the above procedure using 1,2-diaminobenzene (113 mg, 1.03 mmol), chromatography on silica gel with PE/EtOAc (80/20) as eluent afforded **2a**; yield: 66 mg (60%); yellow solid; mp 159–162 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.40 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 3.94 (br s, 2 H, NH_2), 4.35 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 6.83–6.90 (m, 2 H_{arom}), 7.05 (td, *J* = 7.6, 1.3 Hz, 1 H_{arom}), 7.20–7.26 (m, 3 H_{arom}), 7.41–7.48 (m, 1 H_{arom}), 7.61–7.68 (m, 1 H_{arom}), 8.46 (s, 1 H, =C*H*NH), 11.2 (br s, 1 H, NH), 12.9 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.6, 60.2, 90.5, 110.5, 116.9, 117.6, 118.5, 119.6, 121.8, 122.1, 125.8, 128.1, 131.7, 138.0, 141.9, 147.3, 152.0, 168.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}N_4O_2$: 323.15025; found: 323.14843.

Ethyl 2-(1,3-Dihydro-2*H*-benzo[*d*]imidazol-2-ylidene)-3-oxopropanoate (7a)

This stable compound was identified during the optimisation process. It was isolated by column chromatography and was fully characterised; beige solid; mp 246–249 °C.

IR (ATR): 3221, 2982, 2852, 1659, 1628, 1614, 1529, 1567, 1525 cm^{-1}.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.29 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 4.24 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 7.26 (dd, *J* = 6.0, 3.2 Hz, 2 H_{arom}), 7.66 (dd, *J* = 6.0, 3.2 Hz, 2 H_{arom}), 9.70 (s, 1 H, CHO), 12.72 (br s, 2 H, NH).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 15.1, 59.1, 87.2, 113.0 (2 × CH_{arom}), 123.7 (2 × CH_{arom}), 130.1 (2 × Cq), 150.3, 167.9, 183.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}N_2O_2$: 233.09207; found: 233.09078.

Ethyl (*E*)-3-[(2-Amino-5-bromophenyl)amino]-2-(5-bromo-1*H*-benzo[*d*]imidazol-2-yl)acrylate (2b)

Following the above procedure using 4-bromobenzene-1,2-diamine (192 mg, 1.03 mmol), chromatography on silica gel with PE/EtOAc (80/20) as eluent afforded **2b** as a mixture of regioisomers; yield: 66 mg (36%); yellow solid; mp 160–164 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.37–1.44 (m, 3 H, OCH_2CH_3), 3.97 (br s, 2 H, NH_2), 4.30–4.40 (m, 2 H, OCH_2CH_3), 6.72 (d, *J* = 8.4 Hz, minor regioisomer, H_{arom}), 6.94–6.99 (m, 2 H), 7.13 (dd, *J* = 8.4, 2.1 Hz, minor regioisomer, H_{arom}), 7.30–7.32 (m, 2 H_{arom}), 7.40–7.62 (m, 1 H_{arom}), 7.74–7.83 (m, 1 H_{arom}), 8.37 (s, 1 H, =C*H*NH), 8.49 (br s, minor regioisomer, =C*H*NH), 11.0–11.3 (m, 1 H, NH), 12.71 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.6, 60.5, 90.7, 106.8, 110.6, 111.2, 111.6, 118.2, 119.4, 119.7, 122.4, 125.2, 127.0, 128.8, 129.2, 139.3, 147.1, 167.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}Br_2N_4O_2$: 478.96917; found: 478.96917.

Ethyl (*E*)-3-[(2-Amino-5-cyanophenyl)amino]-2-(6-cyano-1*H*-benzo[*d*]imidazol-2-yl)acrylate (2c)

Following the above procedure using 3,4-diaminobenzonitrile (140 mg, 1.05 mmol), chromatography on silica gel with CH_2Cl_2/EtOAc (100/0 → 98/2) as eluent was performed to get the desired compound **2c**; yield: 78 mg (60%). Compound **2c** was obtained as a mixture of *E*-(92%) and *Z*-isomers (8%). Both isomers are also a mixture of rotamers, determined by VT NMR (see spectra); yellow solid; mp 159–162 °C.

^{1}H NMR (DMSO-d_6, 300 MHz, 298 K): δ = 1.35 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 4.32 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 6.04 (m, 2 H, NH_2), 6.93 (m, 1 H_{arom}), 7.40 (m, 1 H_{arom}), 7.56 (m, 1 H_{arom}), 7.75 (m, 2 H_{arom}), 8.01 (m, 1 H_{arom}), 8.47 (m, 1 H, =C*H*NH), 12.5 (m, 2 H, 2 NH).

^{13}C NMR (DMSO-d_6, 75 MHz, 298 K): δ = 14.5 (rotamer 1 & 2), 59.9 (rotamer 1 & 2), 90.3 (rotamer 1), 90.4 (rotamer 2), 97.9 (rotamer 1 & 2), 102.9 (rotamer 1), 103.3 (rotamer 2), 113.1 (rotamer 1), 116.0 (rotamer 1 & 2), 116.2 (rotamer 1), 118.1 (rotamer 2), 119.8 (rotamer 1 & 2), 120.2 (rotamer 1 & 2), 121.5 (rotamer 2), 123.4 (rotamer 1), 123.5 (rotamer 2), 125.2 (rotamer 1), 125.3 (rotamer 2), 126.4 (rotamer 1), 126.5 (rotamer 2), 130.38 (rotamer 1), 130.44 (rotamer 2), 132.5 (rotamer 1), 136.0 (rotamer 1), 141.0 (rotamer 2), 144.5 (rotamer 2), 145.1 (rotamer 1), 145.2 (rotamer 2), 148.5 (rotamer 1), 148.9 (rotamer 2), 153.4 (rotamer 1), 154.1 (rotamer 2), 166.17 (rotamer 1), 166.21 (rotamer 2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}N_6O_2$: 373.14075; found: 373.13995.

Ethyl 2-(5-Methoxy-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-ylidene)-3-oxopropanoate (7d)

Following the above procedure using 4-methoxybenzene-1,2-diamine (142 mg, 1.05 mmol)**7d** was obtained as a single isomer. The stereochemistry of the olefin could not be determined; yield: 89 mg (97%); brown solid; mp >250 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 3.77 (s, 3 H, OCH_3), 4.23 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 6.87 (dd, *J* = 8.8, 2.5 Hz, 1 H_{arom}), 7.24 (d, *J* = 2.5 Hz, 1 H_{arom}), 7.53 (d, *J* = 8.8 Hz, 1 H_{arom}), 9.66 (s, 1 H, CHO), 12.60 (br s, 2 H, NH).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 15.1, 56.0, 59.0, 87.3, 97.4, 111.8, 113.6, 124.3, 131.0, 150.2, 156.7, 167.9, 183.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}N_2O_4$: 263.10485; found: 263.10263.

Ethyl (*E*)-3-[(2-Amino-4,5-dimethylphenyl)amino]-2-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)acrylate (2e)

Following the above procedure using 4,5-dimethylbenzene-1,2-diamine (95 mg, 0.70 mmol), chromatography on silica gel with PE/EtOAc (95/5) as eluent was performed to get the desired compound **2e**; yield: 66 mg (50%); beige solid; mp 169–173 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.26 (s, 2 H, NH_2), 1.39 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.20 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 2.35 (m, 6 H, 2 × CH_3), 4.34 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 6.65 (s, 1 H_{arom}), 6.96 (s, 1 H_{arom}), 7.19 (s, 1 H_{arom}), 7.41 (s, 1 H_{arom}), 8.39 (s, 1 H, =C*H*NH), 10.98 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.8, 19.2, 19.5, 20.4, 20.5, 60.2, 90.3, 110.9, 118.0, 118.5, 119.8, 126.1, 127.8, 130.4, 130.3, 131.0, 134.2, 135.7, 140.7, 147.1, 151.6, 168.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{26}N_4O_2$: 379.21285; found: 379.21088.

Ethyl (*E*)-3-[(2-Amino-4,5-dichlorophenyl)amino]-2-(5,6-dichloro-1*H*-benzo[*d*]imidazol-2-yl)acrylate (2f)

Following the above procedure using 4,5-dichlorobenzene-1,2-diamine (186 mg, 1.05 mmol), chromatography on silica gel with CH_2Cl_2/EtOAc (100/0 → 80/20) as eluent was performed to get the desired compound **2f**, yield: 107 mg (66%); yellow solid; mp 222–226 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.34 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 4.31 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 5.38 (br s, 2 H, NH_2), 7.10 (s, 1 H_{arom}), 7.58 (s, 1 H_{arom}), 7.79 (s, 1 H_{arom}), 7.80 (s, 1 H_{arom}), 8.44 (d, *J* = 12.6 Hz, 1 H, C=*H*NH), 12.26 (br s, 1 H, NH), 12.52 (d, *J* = 12.7 Hz, 1 H, C=HN*H*).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 14.4, 59.9, 90.6, 113.0, 117.0, 118.1, 118.6, 119.5, 123.6, 123.9, 126.9, 127.3, 132.4, 140.1, 141.1, 147.2, 153.0, 166.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}Cl_4N_4O_2$: 458.99436; found: 459.00015.

Ethyl (*E*)-2-(Benzo[*d*]oxazol-2-yl)-3-[(2-hydroxyphenyl)amino]-acrylate (3a)

Following the above procedure using 2-aminophenol (112 mg, 1.03 mmol), chromatography on silica gel with PE/EtOAc (70/30) as eluent afforded **3a** as an 85/15 mixture of *E*/*Z*-isomers; yield: 65 mg (58%); beige solid; mp 179–183 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.34 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 4.27 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 6.85–7.05 (m, 3 H_{arom}), 7.27–7.42 (m, 2 H), 7.50 (d, *J* = 7.8 Hz, 1 H_{arom}), 7.60–7.75 (m, 2 H_{arom}), 8.68 (d, *J* = 14.0 Hz, 1 H, =C*H*NH), 10.49 (s, 1 H, OH), 11.96 (d, *J* = 14.0 Hz, 1 H, =CHN*H*).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 14.9, 60.2, 89.7, 110.9, 115.7, 116.2, 118.3, 120.4, 124.7, 125.0, 125.4, 127.8, 140.5, 146.3, 147.2, 148.8, 162.8, 164.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_2O_4$: 325.11828; found: 325.11654.

Ethyl (*E*)-3-[(2-Hydroxy-5-methoxyphenyl)amino]-2-(5-methoxybenzo[*d*]oxazol-2-yl)acrylate (3b)

Following the above procedure using 2-amino-4-methoxyphenol (143 mg, 1.03 mmol), chromatography on silica gel with PE/EtOAc (50/50) as eluent afforded **3b** as an 87/13 mixture of *E*/*Z*-isomers; yield: 115 mg (86%); yellow solid; mp 201–205 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.33 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 3.75 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.27 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 6.60 (dd, *J* = 8.8, 2.5 Hz, 1 H_{arom}), 6.82–6.95 (m, 2 H_{arom}), 7.06 (d, *J* = 2.5 Hz, 1 H_{arom}), 7.12 (d, *J* = 2.5 Hz, 1 H_{arom}), 7.60 (d, *J* = 8.8 Hz, 1 H_{arom}), 8.63 (d, *J* = 14.0 Hz, 1 H, =C*H*NH), 9.95 (s, 1 H, OH), 11.91 (d, *J* = 14.0 Hz, =CHN*H*).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 14.9, 56.07, 56.15, 60.2, 90.1, 101.8, 102.0, 110.2, 111.1, 112.6, 116.7, 128.4, 141.0, 141.4, 143.3, 146.2, 153.5, 157.4, 163.5, 164.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}N_2O_6$: 385.13941; found: 385.13744.

Ethyl (*E*)-3-[(2-Hydroxy-5-methylphenyl)amino]-2-(5-methylbenzo[*d*]oxazol-2-yl)acrylate (3c)

Following the above procedure using 2-amino-4-methylphenol (86 mg, 0.70 mmol); chromatography on silica gel with PE/EtOAc (80/20) as eluent afforded **3c** as an 87/13 mixture of *E*/*Z*-isomers; yield: 79 mg (64%); beige solid; mp 199–203 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.32 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.24 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 4.21–4.32 (m, 2 H, OCH_2CH_3), 6.71 (d, *J* = 8.1 Hz, 1 H_{arom}), 6.78 (s, 1 H_{arom}), 7.18 (d, *J* = 6.0 Hz, 1 H_{arom}), 7.35 (d, *J* = 8.2 Hz, 1 H_{arom}), 7.48 (d, *J* = 6.0 Hz, 1 H_{arom}), 7.51 (s, 1 H_{arom}), 8.61 (d, *J* = 14.0 Hz, 1 H, =C*H*NH), 10.35 (br s, 1 H, OH), 11.86 (d, *J* = 14.1 Hz, 1 H, =CHN*H*).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 14.4, 20.7, 21.2, 59.7, 88.8, 110.5, 115.0, 116.3, 117.2, 120.6, 125.0, 125.6, 134.1, 134.4, 137.9, 145.6, 146.7, 148.6, 161.9, 164.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}N_2O_4$: 353.14958; found: 353.14777.

Ethyl (*E*)-3-[(5-Fluoro-2-hydroxyphenyl)amino]-2-(5-fluorobenzo[*d*]oxazol-2-yl)acrylate (3d)

Following the above procedure using 2-amino-4-fluorophenol (89 mg, 0.70 mmol), chromatography on silica gel with PE/EtOAc (70/30) as eluent afforded **3d** as an 80/20 mixture of *E*/*Z*-isomers; yield: 79 mg (64%); beige solid; mp 246–250 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.33 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 4.27 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 6.83 (td, $^3J_{H,F}$ = $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.8 Hz, 1 H_{arom}), 6.93 (dd, $^3J_{H,H}$ = 8.8 Hz, $^4J_{H,F}$ = 5.3 Hz, 1 H_{arom}), 7.20 (td, $^3J_{H,F}$ = $^3J_{H,H}$ = 9.0 Hz, $^4J_{H,H}$ = 2.7 Hz, 1 H_{arom}), 7.43 (dd, $^3J_{H,F}$ = 8.7 Hz, $^4J_{H,F}$ = 2.5 Hz, 1 H_{arom}), 7.53 (dd, $^3J_{H,F}$ = 8.6 Hz, $^4J_{H,H}$ = 2.5 Hz, 1 H_{arom}), 7.75 (dd, $^3J_{H,H}$ = 8.9 Hz, $^4J_{H,F}$ = 4.4 Hz, 1 H_{arom}), 8.68 (d, *J* = 6.6 Hz, 1 H, =C*H*NH), 10.47 (br s, 1 H, OH), 11.86 (d, *J* = 14.0 Hz, 1 H, =CHN*H*).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 14.4, 59.9, 90.1, 102.8 (d, $^2J_{C,F}$ = 28.0 Hz), 104.3 (d, $^2J_{C,F}$ = 26.0 Hz), 110.6 (d, $^2J_{C,F}$ = 20.3 Hz), 111.2, 111.4 (d, $^3J_{C,F}$ = 7.5 Hz), 112.0, 116.1 (d, $^3J_{C,F}$ = 9.0 Hz), 128.2 (d, $^3J_{C,F}$ = 10.5 Hz), 141.0 (d, *J* = 13.8 Hz), 143.1, 144.9, 146.3, 156.2 (d, $^1J_{C,F}$ = 266.2 Hz), 159.3 (d, $^1J_{C,F}$ = 269.6 Hz), 164.1.

^{19}F NMR (282 MHz, DMSO-d_6): δ = –122.8, –117.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}F_2N_2O_4$: 361.09944; found: 361.09749.

Ethyl (*E*)-3-[(3-Hydroxypyridin-2-yl)amino]-2-(oxazolo[4,5-*b*]-pyridin-2-yl)acrylate (3e)

Following the above procedure using 2-aminopyridin-3-ol (77 mg, 0.70 mmol), the desired compound was purified by washing with hexane; yield: 86 mg (76%); beige solid; mp >300 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.34 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 4.31 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 7.10 (dd, J = 7.8, 4.9 Hz, 1 H_{arom}), 7.34 (dd, J = 7.9, 1.1 Hz, 1 H_{arom}), 7.39 (dd, J = 8.1, 5.0 Hz, 1 H_{arom}), 7.92 (dd, J = 4.6, 0.9 Hz, 1 H_{arom}), 8.18 (dd, J = 8.1, 1.2 Hz, 1 H_{arom}), 8.48 (dd, J = 4.9, 1.2 Hz, 1 H_{arom}), 9.31 (d, J = 13.4 Hz, 1 H, =C*H*NH), 11.03 (br s, 1 H, OH), 12.08 (d, J = 13.2 Hz, 1 H, =CHN*H*).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 14.4, 60.1, 90.7, 118.3, 119.8, 120.9, 122.7, 138.2, 139.9, 140.7, 142.0, 144.8, 146.0, 154.3, 163.8, 164.6

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_4O_4$: 327.10878; found: 327.10709.

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Supporting Information

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References

(1) Dahl, S. L.; Ward, J. R. *Pharmacotherapy* **1982**, *2*, 354.
(2) (a) Demmer, C. S.; Bunch, L. *Eur. J. Med. Chem.* **2015**, *97*, 778. (b) Zhang, H.-Z.; Zhao, Z.-L.; Zhou, C.-H. *Eur. J. Med. Chem.* **2018**, *144*, 444.
(3) (a) Bansal, Y.; Silakari, O. *Bioorg. Med. Chem.* **2012**, *20*, 6208. (b) Rajasekhar, S.; Maiti, B.; Balamurali, M.; Chanda, K. *Curr. Org. Synth.* **2016**, *14*, 40.
(4) Derenzini, E.; Zinzani, P. L.; Cheson, B. D. *Leuk. Lymphoma* **2014**, *55*, 1471.
(5) Wang, S.; Dai, P.; Xu, Y.; Chen, Q.; Zhu, Q.; Gong, G. *Arch. Pharm.* **2015**, *348*, 595.
(6) Roche, V. F. *Am. J. Pharm. Educ.* **2006**, *70*, 101.
(7) (a) Chanda, K.; Rajasekhar, S.; Maiti, B. *Synlett* **2017**, *28*, 521. (b) Bakthadoss, M.; Mushaf, M. *RSC Adv.* **2018**, *8*, 12152. (c) Bakthadoss, M.; Selvakumar, R.; Srinivasan, J. *Tetrahedron Lett.* **2014**, *55*, 5808. (d) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Green Chem.* **2013**, *15*, 2713.
(8) Shen, W.; Kohn, T.; Fu, Z.; Jiao, X.; Lai, S.; Schmitt, M. *Tetrahedron Lett.* **2008**, *49*, 7284.
(9) (a) Tao, K.; Zheng, J.; Liu, Z.; Shen, W.; Zhang, J. *Tetrahedron Lett.* **2010**, *51*, 3246. (b) Fan, X.; He, Y.; Zhang, X.; Guo, S.; Wang, Y. *Tetrahedron* **2011**, *67*, 6369.
(10) For a synthetic application of activated dibromoalkene, see: Taylor, R.; Beltrán-Rodil, S.; Edwards, M.; Pugh, D.; Reid, M. *Synlett* **2010**, 602.
(11) (a) Roedig, A.; Degener, E. *Chem. Ber.* **1953**, *86*, 1469. (b) Kundiger, D. G.; Morris, G. F. *J. Am. Chem. Soc.* **1958**, *80*, 5988. (c) Roedig, A.; Manger, R.; Schodel, S. *Chem. Ber.* **1960**, *93*, 2294. (d) Bovonsombat, P.; McNelis, E. *Tetrahedron Lett.* **1992**, *33*, 7705. (e) Paterson, I.; Kan, S. B.; Gibson, L. J. *Org. Lett.* **2010**, *12*, 3724. (f) Kamptmann, S. B.; Brückner, R. *Eur. J. Org. Chem.* **2013**, 6584.
(12) Knochel, P.; Vu, V. A.; Marek, I. *Synthesis* **2003**, 1797.
(13) McFadden, H. G.; Harris, R. L. N.; Jenkins, C. L. D. *Aust. J. Chem.* **1989**, *42*, 301.
(14) CCDC 1892877 contains the supplementary crystallographic data for **2a**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
(15) (a) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4357. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.