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Synthesis of a new polycyclic heterocyclic ring system. Part III. Benzo[*b*]imidazo[1,5-*d*][1,4] oxazepine-1,4(2*H*,5*H*)-diones

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Abstract: A series of novel tricyclic benzoxazepines with fused imidazolone ring was prepared in five steps starting from the corresponding benzoxazolones **1–3**. The key to the reported synthetic approach is transformation of 3-(2-oxopropyl)-2(3*H*)-benzoxazolones **4–6** to 1-(2-hydroxyphenyl)-4-methyl-1,3-dihydro-2*H*-imidazol-2-ones **7–12**, and their subsequent conversion to the phenoxyacetic acids **19–24**, which were finally acylated in polyphosphoric acid to form the oxazepine ring.

Keywords: benzoxazepine; benzoxazole; heterocycle; imidazole; ring transformation.

Introduction

Benzodiazepine and benzoxazepine ring systems are common pharmacophores, found in numerous structures with diverse biological activities. Investigations of this class of compounds started 55 years ago, when Sternbach and Reeder published their pioneering work on 1,4-benzodiazepines [1]. The discovery of 1,4-benzodiazepines has been followed by synthesis of a drug for the treatment of anxiety, sleep disorders and epilepsy [1–3]. Being structurally related to benzodiazepines, benzoxazepine derivatives have gained significant attention among several research groups [4, 5]. A number of compounds with benzoxazepine scaffolds have been described as potent antiviral [6], anticonvulsant [7] and neuroleptic [8] agents. In recent years, several tricyclic pyrrolo-1,5-benzoxazepines (PBOXs) have been studied as promising anticancer candidates due to their ability to induce microtubule depolymerization and apoptosis in numerous cell lines, e.g. human chronic myeloid leukaemia K562, ovarian carcinoma A2780 and neuroblastomas SHSY5Y and SK-N-BE(1) [9–12]. Compounds PBOX-6 and PBOX-15 (Figure 1) represent the most active PBOX members with low micromolar cytotoxicity [12]. PBOX-6 has shown efficiency in an *in vivo* mouse mammary carcinoma model, causing the inhibition of tumor growth [13].

In continuation of our previous studies on the synthesis of imidazo[5,1-c][1,4]benzothiazines and benzo[b]imidazo[1,5-d][1,5]thiazepines [14, 15], herein we present a method for the preparation of benzo[*b*]imidazo[1,5-*d*][1,4]oxazepine-1,4(2*H*,5*H*)-diones as new heterocyclic systems. These compounds were inspired by the PBOX compounds and derived by replacing the fused pyrrole ring of the PBOX scaffold with an imidazolone.

Results and discussion

As part of our research on the design and synthesis of novel heterocyclic systems with potential biomedical applications, we developed a convenient five-step approach to tricyclic benzoxazepines containing a fused imidazolone ring. The present method involves the use of benzoxazolones as easily available starting materials that undergo a series of chemical transformations leading to the target molecules.

As depicted in Scheme 1, benzoxazolone derivatives **1–3** were allowed to react with chloroacetone in *N,N*-dimethylformamide in the presence of potassium carbonate and a catalytic amount of benzyltriethylammonium chloride (TEBA). The milder reaction conditions compared to previously reported methods [16] led to yields of 82%–89%. The resulting 3-(2-oxoalkyl)-benzoxazolones are known to undergo ring transformation to 1-(2-hydroxyphenyl)-3,4-disubstituted-2-imidazolones in the presence of nucleophiles such as primary amines [17, 18]. Therefore, the reaction of compounds **4–6** with methylamine or benzylamine under reflux in *n*-propanol or 2-methoxyethanol, respectively, led

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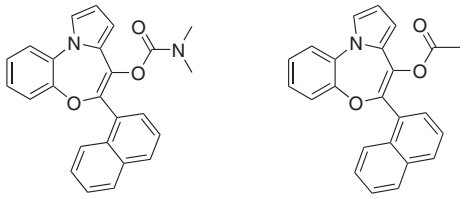


PBOX-6 PBOX-15

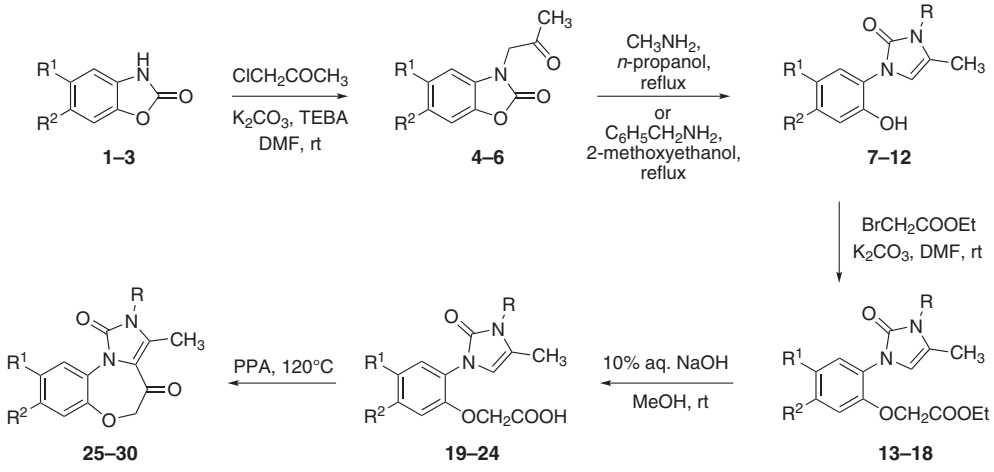
Figure 1 Structures of pyrrolo-1,5-benzoxazepines PBOX-6 and PBOX-15.

to the formation of imidazolone derivatives **7–12**. In the next step, compounds **7–12** were treated with ethyl bromoacetate under basic conditions, yielding esters **13–18** quantitatively. The corresponding carboxylic acids **19–24** were obtained after alkaline hydrolysis of the ester group. Intramolecular acylation of these compounds led to target products **25–30**. The intramolecular acylation of **19** was tested under various reaction conditions. No product formation was observed when conducting the reaction in sulfuric acid at room temperature or in a mixture of sulfolane/polyphosphoric acid. The same results were observed at higher temperature (80°C). The use of Eaton's reagent (P_2O_5-CH_3SO_3H) as a reaction medium at 80°C led to the formation of the desired product at 63% yield after 5 h. The best yield (78%) was achieved in polyphosphoric acid (PPA) at 120°C for 2 h, and these conditions were chosen for the acylation of the series of carboxylic acids **19–24**. Due to the powerful catalytic and dehydrating properties of the PPA [19], the reaction proceeds via formation of the mixed anhydride, followed by acylation of the imidazolone fragment at position 5, thus forming the seven-membered oxazepine ring.

The structure of target tricyclic benzoxazepines with fused imidazolone ring was confirmed by spectroscopic techniques. Two carbonyl bands at 1700 cm^{-1} and 1650 cm^{-1} are observed in the IR spectra of compounds **25–30**, corresponding to the CO group in the imidazolone ring and the carbonyl group of the oxazepine moiety. In the ^1H NMR spectra of compounds **19–24**, the methyl doublet appears at 1.96–2.04 ppm and the corresponding singlet for **25–30** is shifted downfield to 2.44–2.52 ppm. The intramolecular cyclization of **19–24** leading to the formation of a benzoxazepine scaffold is confirmed by the disappearance of the characteristic signal of imidazole-H5 (at 6.45–6.51 ppm in **19–24**) in the proton spectra of the final products **25–30**. The singlet for the methylene protons of the carboxylic acids is shifted from 4.78–4.81 ppm to 4.58–4.62 ppm in the benzoxazepines. The corresponding ^{13}C NMR signals are shifted from 64.8–65.3 ppm to 78.9–79.5 ppm. The carbonyl carbon signals can be seen at 169.4–170.0 ppm in the starting acids and at 188.9–189.6 ppm in the final compounds.

Conclusion

In summary, we developed a convenient five-step approach to a new tricyclic ring system containing 1,5-benzoxazepine fused with an imidazolone. The reported compounds are structural analogs of the PBOX series, with potentially interesting biological activities.



1, **4**: $R^1 = R^2 = H$
2, **5**: $R^1 = H$; $R^2 = Cl$
3, **6**: $R^1 = Cl$; $R^2 = H$

7, **13**, **19**, **25**: $R^1 = R^2 = H$; R = Me
8, **14**, **20**, **26**: $R^1 = H$; $R^2 = Cl$; R = Me
9, **15**, **21**, **27**: $R^1 = Cl$; $R^2 = H$; R = Me

10, **16**, **22**, **28**: $R^1 = R^2 = H$; R = Bn
11, **17**, **23**, **29**: $R^1 = H$; $R^2 = Cl$; R = Bn
12, **18**, **24**, **30**: $R^1 = Cl$; $R^2 = H$; R = Bn

Scheme 1 Synthesis of benzo[*b*]imidazo[1,5-*d*][1,4]oxazepine-1,4(2*H*,5*H*)-diones.

Experimental

Melting points were determined on a Böetius hot-stage microscope and are uncorrected. IR spectra were recorded on a Specord 75 or Thermo Scientific Nicolet iS10 spectrophotometer. ^{1}H NMR and ^{13}C NMR were obtained on Bruker DRX 300, Bruker DRX 400 and Bruker DRX 500 spectrometers. Chemical shifts are reported relative to the solvent peak. Elemental analyses (C, H, N) were carried out on a Vario III microanalyzer. Thin-layer chromatography (TLC) was carried out on silica gel plates (Merck 60 F_{254}), using *n*-heptane/ethyl acetate (7 : 3 v/v), toluene/chloroform/ethyl acetate (3 : 1 : 1 v/v) or chloroform/methanol (9 : 1 v/v) as eluent. Column chromatography was performed with a Merck 60 silica gel (0.040–0.063 mm, 230–400 mesh).

Synthesis of 3-(2-oxopropyl)-2(3*H*)-benzoxazolones 4–6

Powdered K_2CO_3 (75 mmol), TEBA (0.9 mmol) and chloroacetone (50 mmol) were added to a stirred solution of 2(3*H*)-benzoxazolone **1–3** (50 mmol) in *N*,*N*-dimethylformamide (20 mL). The mixture was stirred for 2–4 h (TLC) at room temperature and then poured onto water (100 mL). The resulting precipitate was collected by filtration, dried and crystallized from ethanol.

3-(2-Oxopropyl)-2(3*H*)-benzoxazolone (4) White crystals; yield 82%; mp 119–120°C (ethanol); lit mp 119–120°C [16, 20].

6-Chloro-3-(2-oxopropyl)-2(3*H*)-benzoxazolone (5) White crystals; yield 89%; mp 154–156°C (ethanol); lit mp 155–156°C [16]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, 1H, *J* = 1.9 Hz), 7.15 (dd, 1H, *J* = 8.4, 1.8 Hz), 6.70 (d, 1H, *J* = 8.4 Hz), 4.59 (s, 2H), 2.29 (s, 3H).

5-Chloro-3-(2-oxopropyl)-2(3*H*)-benzoxazolone (6) White crystals; yield 84%; mp 124–125°C (ethanol); lit mp 125–126°C [16]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, 1H, *J* = 8.5 Hz), 7.10 (dd, 1H, *J* = 8.5, 2.0 Hz), 6.79 (d, 1H, *J* = 2.0 Hz), 4.59 (s, 2H), 2.30 (s, 3H).

Synthesis of 1-(2-hydroxyphenyl)-4-methyl-1,3-dihydro-2*H*-imidazol-2-ones 7–12

Methylamine (40% aqueous solution, 50 mmol) or benzylamine (50 mmol) was added to a suspension of 3-(2-oxopropyl)-2(3*H*)-benzoxazolone **4–6** (25 mmol) in *n*-propanol (15 mL) or 2-methoxyethanol (15 mL), respectively. The mixture was heated under reflux for 4–6 h (TLC) and poured onto water (50 mL). After cooling to room temperature, the solution was acidified with concentrated HCl. The resulting precipitate was collected by filtration, washed with water, dried and purified by column chromatography using *n*-heptane/ethyl acetate (7 : 3 v/v) as eluent.

1-(2-Hydroxyphenyl)-3,4-dimethyl-1,3-dihydro-2*H*-imidazol-2-one (7) White crystals; yield 95%; mp 132–133°C (ethanol/water 2 : 1); lit mp 132–133°C [17]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.72 (s, 1H), 7.17–7.22 (m, 1H), 7.07–7.11 (m, 2H), 6.92 (td, 1H, *J* = 8.0, 1.4 Hz), 6.35 (d, 1H, *J* = 1.3 Hz), 3.30 (s, 3H), 2.13 (d, 3H, *J* = 1.2 Hz).

1-(4-Chloro-2-hydroxyphenyl)-3,4-dimethyl-1,3-dihydro-2*H*-imidazol-2-one (8) White crystals; yield 91%; mp 167–169°C (isopropanol); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.05 (s, 1H), 7.09 (d, 1H, *J* = 2.3 Hz), 6.99 (d, 1H, *J* = 8.6 Hz), 6.89 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.30 (d, 1H, *J* = 1.3 Hz), 3.29 (s, 3H), 2.13 (d, 3H *J* = 1.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.1, 151.0, 133.1, 125.2, 123.3, 122.7, 121.1, 120.8, 107.1, 27.8, 10.4. Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74. Found: C, 55.69; H, 4.44; N, 11.95.

1-(5-Chloro-2-hydroxyphenyl)-3,4-dimethyl-1,3-dihydro-2*H*-imidazol-2-one (9) White crystals; yield 90%; mp 219–220°C (ethanol); lit mp 214–215°C [17]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.15 (dd, 1H, *J* = 8.7, 2.6 Hz), 7.07 (d, 1H, *J* = 2.6 Hz), 7.01 (d, 1H, *J* = 8.7 Hz), 6.33 (d, 1H, *J* = 1.3 Hz), 3.29 (s, 3H), 2.13 (d, 3H, *J* = 1.3 Hz).

3-Benzyl-1-(2-hydroxyphenyl)-4-methyl-1,3-dihydro-2*H*-imidazol-2-one (10) White crystals; yield 96%; mp 58–60°C (ethanol/water 2 : 1); lit mp 85–86°C [17]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.72 (s, 1H), 7.33–7.36 (m, 2H), 7.26–7.30 (m, 3H), 7.22–7.24 (m, 1H), 7.12 (d, 2H, *J* = 8.3 Hz), 6.93–6.96 (m, 1H), 6.37 (d, 1H, *J* = 1.2 Hz), 4.94 (s, 2H), 2.04 (d, 3H, *J* = 1.2 Hz).

3-Benzyl-1-(4-chloro-2-hydroxyphenyl)-4-methyl-1,3-dihydro-2*H*-imidazol-2-one (11) White crystals; yield 98%; mp 117–118°C (ethanol); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.06 (s, 1H), 7.24–7.37 (m, 5H), 7.12 (d, 1H, *J* = 2.3 Hz), 7.03 (d, 1H, *J* = 8.6 Hz), 6.92 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.33 (d, 1H, *J* = 1.4 Hz), 4.93 (s, 2H), 2.04 (d, 3H, *J* = 1.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.3, 151.0, 136.4, 133.2, 129.0, 128.0, 127.2, 125.2, 123.4, 122.7, 121.1, 120.8, 107.7, 45.2, 10.6. Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 65.13; H, 4.53; N, 8.75.

3-Benzyl-1-(5-chloro-2-hydroxyphenyl)-4-methyl-1,3-dihydro-2*H*-imidazol-2-one (12) White crystals; yield 90%; mp 72–73°C (diisopropyl ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.23–7.37 (m, 5H), 7.17 (dd, 1H, *J* = 8.7, 2.5 Hz), 7.11 (d, 1H, *J* = 2.5 Hz), 7.04 (d, 1H, *J* = 8.7 Hz), 6.36 (d, 1H, *J* = 1.1 Hz), 4.93 (s, 2H), 2.04 (d, 3H, *J* = 1.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.4, 148.9, 136.4, 129.1, 128.1, 128.0, 127.2, 127.1, 125.3, 122.8, 122.6, 122.2, 107.6, 45.2, 10.6. Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.59; H, 4.73; N, 9.21.

Synthesis of 2-(2-(4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)phenoxy)acetic acids 19–24

Powdered K_2CO_3 (50 mmol) and ethyl bromoacetate (25 mmol) were added to a solution of the phenol derivative **7–12** (25 mmol) in DMF (20 mL). The mixture was stirred at room temperature for 2–6 h (TLC) and then poured onto water (50 mL). The resulting ester **13–18** was extracted with dichloromethane (3 × 15 mL). The extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The ester **13–18** was obtained in a quantitative yield and hydrolyzed in the next step without further purification. To a stirred solution of the ester **13–18** in methanol (10 mL), 10% aqueous solution of NaOH (10 mL) was added. The mixture was stirred at room temperature for 1–2 h (TLC) and acidified with concentrated HCl. The resultant precipitate of carboxylic acid **19–24** was filtered, washed with water, dried and crystallized.

2-(2-(3,4-Dimethyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)phenoxy) acetic acid (19) White crystals; yield 94%; mp 215–217°C (ethanol); ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.12 (br s, 1H), 7.36 (dd, 1H, *J* = 7.8, 1.7 Hz), 7.28 (ddd, 1H, *J* = 8.5, 7.5, 1.7 Hz), 6.99–7.08 (m, 2H), 6.46 (d,

1H, *J* = 1.4 Hz), 4.78 (s, 2H), 3.13 (s, 3H), 2.05 (d, 3H, *J* = 1.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.9, 151.8, 128.1, 127.6, 125.7, 121.1, 118.8, 113.1, 107.8, 64.8, 26.9, 9.8; IR (KBr): 3450, 3140–2500, 1740, 1650, 1620 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.86; H, 5.35; N, 10.58.

2-[5-Chloro-2-(3,4-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl) phenoxy] acetic acid (20) White crystals; yield 92%; mp 190–192°C (ethanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.16 (s, 1H), 7.40 (d, 1H, *J* = 8.5 Hz), 7.21 (d, 1H, *J* = 2.2 Hz), 7.09 (dd, 1H, *J* = 8.5, 2.2 Hz), 6.45 (d, 1H, *J* = 1.4 Hz), 3.12 (s, 3H), 4.85 (s, 2H), 2.04 (d, 3H, *J* = 1.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.8, 152.5, 151.8, 131.8, 128.7, 124.7, 120.9, 118.9, 113.8, 107.6, 65.1, 26.9, 9.8; IR (nujol): 3140–2500, 1720, 1650, 1620 cm^{-1}. Anal. Calcd for $C_{13}H_{13}ClN_2O_4$: C, 52.63; H, 4.42; N, 9.44. Found: C, 52.45; H, 4.48; N, 9.47.

2-[4-Chloro-2-(3,4-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl) phenoxy] acetic acid (21) White crystals; yield 90%; mp 225–227°C (ethanol); ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.12 (br s, 1H), 7.48 (d, 1H, *J* = 2.7 Hz), 7.32 (dd, 1H, *J* = 8.9, 2.7 Hz), 7.11 (d, 1H, *J* = 8.9 Hz), 6.52 (d, 1H, *J* = 1.4 Hz), 4.80 (s, 2H), 3.13 (s, 3H), 2.05 (d, 3H, *J* = 1.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.8, 151.7, 150.6, 127.3, 126.9, 126.7, 124.3, 119.0, 114.8, 107.5, 65.0, 26.9, 9.8; IR (nujol): 3120–2400, 1720, 1650, 1620 cm^{-1}. Anal. Calcd for $C_{13}H_{13}ClN_2O_4$: C, 52.63; H, 4.42; N, 9.44. Found: C, 52.38; H, 4.44; N, 9.52.

2-[2-(3-Benzyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl) phenoxy]acetic acid (22) White crystals; yield 85%; mp 145–146°C (toluene); ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.09 (s, 1H), 7.43 (dd, 1H, *J* = 7.8, 1.7 Hz), 7.36 (t, 2H, *J* = 7.5 Hz), 7.25–7.32 (m, 4H), 7.09 (dd, 1H, *J* = 8.4, 0.9 Hz), 7.04 (td, 1H, *J* = 7.7, 1.1 Hz), 6.51 (d, 1H, *J* = 1.4 Hz), 4.79 (s, 2H), 4.85 (s, 2H), 1.95 (d, 3H, *J* = 1.3 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.9, 152.1, 151.9, 138.1,128.7, 128.2, 127.8, 127.2, 126.8, 125.7, 121.1, 118.4, 113.3, 108.6, 64.9, 43.6, 10.0; IR (nujol): 3160–2500, 1720, 1650, 1620 cm^{-1}. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.28; H, 5.46; N, 8.44.

2-[2-(3-Benzyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-5-chlorophenoxy]-acetic acid (23) White crystals; yield 97%; mp 168–169°C (ethanol); ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.14 (s, 1H), 7.47 (d, 1H, *J* = 8.5 Hz), 7.36 (t, 2H, *J* = 7.5 Hz), 7.25–7.29 (m, 3H), 7.23 (d, 1H, *J* = 2.2 Hz), 7.11 (dd, 1H, *J* = 8.5, 2.2 Hz), 6.51 (d, 1H, *J* = 1.4 Hz), 4.86 (s, 2H), 4.84 (s, 2H), 1.94 (d, 3H, *J* = 1.3 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 152.7, 152.1, 138.0, 131.9, 128.9, 128.7, 127.3, 126.9, 124.7, 121.1, 118.7, 113.9, 108.4, 65.2, 43.7, 10.0; IR (KBr): 3450, 3150–2400, 1740, 1680, 1620 cm^{-1}. Anal. Calcd for $C_{19}H_{17}ClN_2O_4$: C, 61.21; H, 4.60; N, 7.51. Found: C, 61.48; H, 4.73; N, 7.22.

2-[2-(3-Benzyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)-4-chlorophenoxy]-acetic acid (24) White crystals; yield 90%; mp 176–178°C (ethanol); ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.13 (s, 1H), 7.55 (d, 1H, *J* = 2.7 Hz), 7.34–7.38 (m, 3H), 7.29 (d, 1H, *J* = 7.3 Hz), 7.26 (d, 2H, *J* = 7.2 Hz), 7.14 (d, 1H, *J* = 8.9 Hz), 6.58 (d, 1H, *J* = 1.4 Hz), 4.84 (s, 2H), 4.81 (s, 2H), 1.94 (d, 3H, *J* = 1.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.9, 152.1, 150.8, 138.0, 128.8, 127.7, 127.4, 127.1, 126.9, 126.7, 124.4, 118.8, 115.1, 108.4, 65.3, 43.7, 10.1; IR (KBr): 3450, 3150–2600, 1740, 1650, 1620 cm^{-1}. Anal. Calcd for $C_{19}H_{17}ClN_2O_4$: C, 61.21; H, 4.60; N, 7.51. Found: C, 61.48; H, 4.59; N, 7.82.

Synthesis of 3-methylbenzo[*b*]imidazo[1,5-*d*][1,4] oxazepine-1,4(2*H*,5*H*)-diones 25–30

The carboxylic acid **19–24** (20 mmol) was added slowly in small portions to hot (110–120°C) polyphosphoric acid (40 mL). The color of the mixture changed from pale orange to dark red. The mixture was stirred at 120°C for 2–4 h (TLC) and poured onto crushed ice (100 g). The obtained benzoxazepine was isolated by extraction with ethyl acetate (3×15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of compounds **25–30** was accomplished by column chromatography using CH_2Cl_2 as eluent.

2,3-Dimethylbenzo[*b*]imidazo[1,5-*d*][1,4]oxazepine-1,4(2*H*,5*H*)-dione (25) White crystals; yield 71%; mp 165–167°C (ethanol); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–8.02 (m, 1H), 7.18–7.28 (m, 3H), 4.59 (s, 2H), 3.38 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.4, 151.5, 150.9, 134.1, 130.9, 127.9, 125.8, 124.9, 122.2, 119.4, 79.4, 27.7, 10.8; IR (nujol): 1690, 1650 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.62; H, 4.88; N, 11.49.

8-Chloro-2,3-dimethylbenzo[*b*]imidazo[1,5-*d*][1,4]oxazepine-1,4(2*H*,5*H*)-dione (26) White crystals; yield 68%; mp 220–221°C (isopropanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, 1H, *J* = 8.7 Hz), 7.24 (dd, 1H, *J* = 8.7, 2.4 Hz), 7.21 (d, 1H, *J* = 2.3 Hz), 4.58 (s, 2H), 3.36 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 151.8, 150.7, 134.5, 132.3, 129.6, 126.0, 125.7, 122.7, 119.1, 79.3, 27.8, 10.8; IR (nujol): 1700, 1650 cm^{-1}. Anal. Calcd for $C_{13}H_{11}ClN_2O_3$: C, 56.03; H, 3.98; N, 10.05. Found: C, 56.23; H, 3.92; N, 10.14.

9-Chloro-2,3-dimethylbenzo[*b*]imidazo[1,5-*d*][1,4]oxazepine-1,4(2*H*,5*H*)-dione (27) White crystals; yield 62%; mp 202–203°C (ethanol); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, 1H, *J* = 2.5 Hz), 7.18 (dd, 1H, *J* = 8.6, 2.5 Hz), 7.10 (d, 1H, *J* = 8.6 Hz), 4.53 (s, 2H), 3.34 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.7, 150.6, 149.9, 134.6, 131.7, 130.8, 127.8, 124.8, 123.2, 119.0, 79.2, 27.8, 10.8; IR (nujol): 1700, 1650 cm^{-1}. Anal. Calcd for $C_{13}H_{11}ClN_2O_3$: C, 56.03; H, 3.98; N, 10.05. Found: C, 56.35; H, 3.99; N, 10.19.

2-Benzyl-3-methylbenzo[*b*]imidazo[1,5-*d*][1,4]oxazepine-1,4(2*H*,5*H*)-dione (28) White crystals; yield 44%; mp 167–169°C (ethanol); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, 1H, *J* = 7.3, 2.3 Hz), 7.38–7.41 (m, 2H), 7.28–7.36 (m, 5H), 7.24–7.26 (m, 1H), 5.06 (s, 2H), 4.63 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.7, 151.5, 151.1, 135.8, 133.9, 130.9, 129.2, 128.3, 128.0, 127.5, 125.8, 125.0, 122.2, 119.7, 79.5, 45.1, 11.0; IR (nujol): 1690, 1650 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.48; H, 5.23; N, 8.68.

2-Benzyl-8-chloro-3-methylbenzo[*b*]imidazo[1,5-*d*][1,4]oxazepine-1,4(2*H*,5*H*)-dione (29) White crystals; yield 63%; mp 130–132°C (ethanol); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, 1H, *J* = 8.8 Hz), 7.28–7.38 (m, 5H), 7.26 (dd, 1H, *J* = 8.8, 2.4 Hz), 7.23 (d, 1H, *J* = 2.4 Hz), 5.01 (s, 2H), 4.59 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.9, 151.9, 150.9, 135.6, 134.3, 132.5, 129.6, 129.2, 128.3, 127.5, 126.8, 126.0, 122.7, 119.3, 79.3, 45.1, 11.0; IR (nujol): 1700, 1650 cm^{-1}. Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.60; H, 4.24; N, 7.93.

2-Benzyl-9-chloro-3-methylbenzo[*b*]imidazo[1,5-*d*][1,4]oxazepine-1,4(2*H*,5*H*)-dione (30) White crystals; yield 66%; mp 175–176°C (ethanol); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, 1H, J = 2.5 Hz), 7.30–7.38 (m, 5H), 7.22 (dd, 1H, J = 8.6, 2.5 Hz), 7.14 (d, 1H, J = 8.6 Hz), 5.02 (s, 2H), 4.57 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.0, 150.9, 150.0, 135.6, 134.4, 131.7, 130.9, 129.2, 128.4, 127.9, 127.5, 124.9, 123.3, 119.4, 79.3, 45.2, 11.1; IR (nujol): 1700, 1650 cm^{-1}. Anal. Calcd for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.58; H, 4.33; N, 7.88.

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