Synthesis of new 5-benzylidene-hydantoin esters

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Abstract
Compounds containing a hydantoin moiety are found in several medicines in clinical use. In this research, ethyl- and methyl-[2-(5-benzylidene)-2,4-dioxoimidazolidin-3-yl]acetyl esters are successfully synthesized over four reaction steps using conventional methods. The synthesis begins by subjecting hydantoin to a Knoevenagel condensation reaction with three different benzaldehydes to afford the penultimate products, which are further reacted with ethyl or methyl (bromoacetyl)alaninates, butanoates, valinates, and norvalinates to give the desired products as esters in low to moderate yields.

Keywords
alaninate, hydantoin, norvalinate, valinate

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Introduction
In 2020, Jonnalagadda and co-workers reported that more than 75% of drugs approved by the Food and Drug Administration (FDA) are nitrogen-containing heterocycles.¹ Among the top 25 nitrogen heterocycles in FDA-approved drugs, imidazolidine ranks as number 19 and is found in 11 approved drugs.² Imidazolidine-2,4-dione- or hydantoin-containing compounds are known to exhibit a wide range of pharmacological and biological activities and are used to treat various diseases. Both naturally occurring (Figure 1) and synthetic (Figure 2) hydantoin-containing compounds have been reported to possess biological activity. Among naturally occurring hydantoin-containing compounds, hydantocidin (1) was isolated from the Streptomyces hygroscopicus SANK 63584 and was reported to possess herbicidal activity.³ The ethanolic extract of the Red Sea sponge Hemimycale arabica was found to contain among other compounds 5-[(6-bromo-1H-indol-3-yl)methylene] hydantoin (2) which exhibits moderate antiproliferative activity against human cervical carcinoma (HeLa) cells and also displayed antimicrobial activities.⁴ Axinohydantoin (3) was isolated from the sponge Stylotella aurantium and was found to be an inhibitor of protein kinase C.⁵ Synthetic compounds containing the hydantoin moiety have also been reported to possess different biological activities. Among these are anticonvulsive agents such as phenytoin (4),⁶ antimicrobial agents such as nitrofurantoin (5),⁷ antiarrhythmic agents such as azimilide (6),⁸ and the nonsteroidal antiandrogen nilutamide (7) which has been reported for the treatment of prostate cancer.⁹ This information strengthens the necessity of synthesizing compounds containing five-membered heterocycles such

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as hydantoin. Many more hydantoin-containing compounds, both naturally occurring and synthetic, have been reported in reviews.\textsuperscript{10,11}

Encouraged by the results obtained in our previous study with 2,4-thiazolidinedione (Figure 3) in the synthesis of 5-benzylidene-2,4-thiazolidinedione esters,\textsuperscript{12} we sought to expand this study by replacing a 2,4-thiazolidinedione moiety with a hydantoin moiety for the synthesis of new 5-benzylidene hydantoin esters (Scheme 1).

The 5-benzylidene-2,4-thiazolidinedione esters synthesized in our previous work had been tested for their antidiabetic activity on the alpha-glucosidase (unpublished results). Our results indicated that compounds synthesized from para-substituted benzaldehyde had better activity than any other compounds; hence, this research also focused on the usage of 4-methoxybenzaldehyde, 4-methylbenzaldehyde, and the piperonal in the Knoevenagel condensation step.

Unlike the compounds prepared using 2,4-thiazolidinedione, this study starts with the Knoevenagel condensation of three different benzaldehydes with hydantoin as reported by Chung and co-workers.\textsuperscript{13} The resulting benzylidene hydantoins 8a–c are then reacted with ethyl or methyl (2-bromoacetyl)alaninate, -valinate, -butanoate, or -norvaline 9a–d to give the desired products 10a–o (Scheme 1).

Reagents and conditions include (1) hydantoin, piperidine, reflux, 7 h, (2) SOCl\textsubscript{2}, EtOH, or MeOH, reflux, (3) bromoacetyl chloride, H\textsubscript{2}O/DCM (1:1), K\textsubscript{2}CO\textsubscript{3}, −10 °C to r.t., (4) KOH, MeOH, reflux, 4 h.

### Results and discussion

The synthesis of the desired ethyl or methyl [2-(5-benzylidene)-2,4-dioxoimidazolidin-3-yl]acetyl esters began by reacting commercial hydantoin with different benzaldehydes to give benzylidene hydantoins 8a–c in reasonable yields.\textsuperscript{15} These compounds were characterized by NMR spectroscopy; the $^1$H NMR spectra of the three compounds exhibited the benzylidene protons signals at 6 parts per million (ppm) confirming successful condensation reactions. The same spectra also showed the presence of two singlet peaks accounting for one proton each at −10.2 ppm (assigned to the imide proton at position 3 of the hydantoin moiety) and −11.5 ppm (assigned to the amide proton at position 1 of the hydantoin moiety). In the $^{13}$C NMR spectra of compounds 8a–c, the benzylidene carbon signals were observed at 109 ppm.

Concurrently, compounds 9a–d were synthesized by first protecting the amino acids with thionyl chloride in the presence of ethanol\textsuperscript{12} or methanol\textsuperscript{14} and subsequently reacting the intermediates with bromoacetyl chloride in the presence of potassium carbonate to afford compounds 9a–d in good yields. Finally, substitution reactions between benzylidenehydantoins 8 and compounds 9 followed by crystallization from acetone afforded the targeted ethyl or methyl [2-(5-benzylidene)-2,4-dioxoimidazolidin-3-yl]acetyl esters 10a–o in low to moderate yields (Figure 4). These compounds were characterized by NMR and IR spectroscopy together with mass spectroscopic analysis. $^1$H NMR spectra of the products showed the presence of one NH signal at ~10.7 ppm consistent with mono-N-alkylation. The regioselectivity of N-alkylation of hydantoins 8 at the 3-position was established by analogy with the literature.\textsuperscript{15} Bases such as potassium hydroxide lead to selective alkylation at the more acidic 3-position; only stronger bases that effect double deprotonation give alkylation at the more hindered 1-position.\textsuperscript{16} This confirmed that the hydrogen at position 3 had been replaced by compounds 9. Also in the $^1$H NMR spectra of these compounds, doublets accounting for one proton at ~8.7 ppm were observed confirming the presence of the amide proton. The spectra were also characterized by a singlet accounting for two protons at ~4.1 ppm confirming the methylene protons adjacent to the ring nitrogen. The $^{13}$C NMR spectra of compounds 10 were characterized by four carbonyl carbon signals and a methylene carbon resonance at ~40 ppm.

### Conclusion

In summary, we have reported the synthesis of 5-benzylidenehydantoin esters. The Knoevenagel condensation of hydantoin and subsequent reactions of protected amino acids with bromoacetyl chloride afforded the desired products. Thus, this protocol provides rapid access to novel benzylidene compounds and could be of some medicinal chemistry value. Therefore, in the future, these compounds will be evaluated for their antidiabetic activities.

### Experimental

All reagents used were of analytical grade from Sigma-Aldrich and Fluka. Thin-layer chromatography (TLC) was carried out using Macherey-Nagel Alugram Sil G/UV\textsubscript{254} plates, pre-coated with 0.25 mm silica gel 60. Detection was performed under ultraviolet light at 254 nm. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-$d_6$ or...
Figure 3. A schematic diagram of reported and newly synthesized compounds.

Scheme 1. Synthesis of ethyl or methyl [2-(5-benzylidene)-2,4-dioxoimidazolidin-3-yl]acetyl esters.

Figure 4. Structures of the synthesized benzylidene-hydantoin esters, 10a–o.
CDCl₃ as the solvent and TMS (0.00 ppm) as an internal standard. The values for the chemical shifts are expressed in ppm. The following abbreviations are used: br.s, broad singlet; s, singlet; dd, doublet; d, doublet of doublets; q, quartet; quin, quinet; and m, multiplet; coupling constants (J) are measured in hertz (Hz). Melting points were determined on a Buchi B-540 melting point apparatus using capillary tubes. Infrared spectra were run on a Bruker Platinum 22 Vector Fourier Transform spectrometer (FTIR). Mass spectra (high resolution) were recorded on a Waters GCT 22 Vector Fourier Transform spectrometer (FTIR). Mass spectrometer using a Restek Rxi Wintegra Guard column (15 m, 0.25 mm ID, 0.25 µm film thickness). The samples were dissolved in acetonitrile and injected (1 µL) in mode 10:1 at a temperature of 280 °C. The source temperature was 100 °C and the desolvation temperature was set at 300 °C. Helium gas was used as the carrier gas. The software used to control the hyphenated system and to perform all data manipulation was MassLynx 4.1 (SCN 704).

**General procedure for the synthesis of (Z)-5-benzylidene hydantoin (8a–c)**

These compounds were synthesized from the reaction of hydantoin and appropriate benaldehyde as described by Chung and co-workers. Compounds 8a–c were assigned the Z-geometry by comparison with those structures reported in the literature.

**Synthesis of ethyl or methyl (2-bromoacety)esters (9a–d)**

These compounds were synthesized from their respective amino esters as described by Tshiluka et al. or Barman et al.

**General procedure for the synthesis of ethyl or methyl 2-(2,4-dioxoimidazolidin-3-yl)acetamido esters (10a–o)**

A mixture of arylidene hydantoin 8 (1 mmol) and potassium hydroxide (1 mmol) in methanol was agitated at ambient temperature for 15 min. Ethyl or methyl (2-bromoacetamido) esters (1 mmol) were added and the mixture refluxed for 2–4 h. After the mixture was allowed to cool to room temperature, a precipitate was formed and was collected by filtration. Desired products 10a–o were purified by recrystallization from acetone.

**Methyl 2-(2-(5-(4-methoxybenzylidene)-2,4-dioxoimidazolidin-3-yl)acetamido)butanoate (10b):** The reaction of 5-(4-methoxybenzylidene)hydantoin (8a) (1.00 g, 4.58 mmol) and methyl (2-bromoacetoacetamido)butanoate (0.95 g, 4.58 mmol) gave compound 10b as a yellow solid (0.71 g, 40%); m.p. = 258–262 °C. 'H NMR (400 MHz, DMSO-d6): δ 7.05 (t, 1H, =CH), 4.26 (s, 2H, CH₂N), 3.80 (s, 3H, ArOCH₃), 2.20 (s, 3H, OCH₃), 0.89 (t, 3H, CH(CH₃)₂). 13C NMR (100 MHz, DMSO-d6): δ 173.2 (C=O), 166.6 (C=O), 160.1 (ArC=O), 155.2 (C=O), 131.7 (2×ArCH), 125.7 (ArC), 125.2 (ArC), 114.8 (2×ArCH), 110.6 (ArCH), 55.8 (ArOCH₃), 53.9 (CHNH), 48.2 (OCH₃), 40.8 (CH₃N), 17.5 (CH₂CH), IR (KBr): 3286 (N–H), 2955 (C–H), 1762 (C=O), 1741 (C=O), 1601 (C=O), 1115 (C–O) cm⁻¹. HRMS (ESI-TOF): m/z [M + H]+ calcd for C₁₇H₂₀N₃O₆: 376.1247; found: 376.1234.

**Methyl 2-(2-(5-(4-methoxybenzylidene)-2,4-dioxoimidazolidin-3-yl)acetylaminate) (10a):** The reaction of 5-(4-methoxybenzylidene)hydantoin (8a) (0.50 g, 2.29 mmol) and methyl (2-bromoacetyl)alaninate (0.69 g, 3.85 mmol) gave compound 10a as a brown solid (0.82 g, 44%); m.p. = 210.8–213 °C. 1H NMR (400 MHz, DMSO-d6): δ 10.77 (s, 1H, ring-NH), 8.72 (d, 1H, J = 7.6 Hz, NH), 7.63 (d, 2H, J = 8.8 Hz, 2×ArH), 6.95 (d, 2H, J = 8.4 Hz, ArH), 6.54 (s, 1H, =CH), 4.30 (quin, 1H, J = 6.8 Hz, CHNH), 4.13 (s, 2H, CH₂N), 3.81 (s, 3H, ArOCH₃), 3.63 (s, 3H, OCH₃), 1.29 (d, 3H, J = 7.2 Hz, CH₂CH). 13C NMR (100 MHz, DMSO-d6): δ 172.2 (C=O), 166.7 (C=O), 164.4 (C=O), 160.1 (Ar-C=O), 131.7 (2×ArCH), 125.6 (ArC), 124.7 (ArC), 114.8 (2×ArCH), 110.6 (ArCH), 55.8 (ArOCH₃), 53.9 (CHNH), 52.3 (OCH₃), 40.7 (CH₂N), 25.1 (CH₂CH), 10.6 (CH₃CH). IR (KBr): 3287 (N–H), 2972 (C–H), 1758 (C=O), 1735 (C=O), 1601 (C=C), 1169 (C–O) cm⁻¹. HRMS (ESI-TOF): m/z [M + H]+ calcd for C₁₈H₂₂N₃O₆: 376.1430; found: 376.1495.

**Methyl 2-(2-(5-(4-methoxybenzylidene)-2,4-dioxoimidazolidin-3-yl)acetyl)valinate (10c):** The reaction of 5-(4-methoxybenzylidene)hydantoin (8a) (0.50 g, 2.29 mmol) and methyl (2-bromoacetyl)valinate (0.48 g, 2.29 mmol) gave compound 10c as a brown solid (0.40 g, 44%); m.p. = 259–302 °C. 1H NMR (400 MHz, DMSO-d6): δ 10.73 (s, 1H, ring-NH), 8.58 (d, 1H, J = 8.4 Hz, NH), 7.63 (d, 2H, J = 8.8 Hz, 2×ArH), 6.98 (d, 2H, J = 8.8 Hz, 2×ArH), 6.54 (s, 1H, =CH), 4.36–4.12 (m, 3H, CHNH + CH₂N), 3.81 (s, 3H, ArOCH₃), 3.66 (s, 3H, OCH₃), 2.20 (m, 1H, CH(CH₃)₂), 0.89 (t, 6H, J = 7.2 Hz, CH₂CH₃). 13C NMR (100 MHz, DMSO-d6): δ 172.2 (C=O), 166.7 (C=O), 164.4 (C=O), 160.1 (Ar-C=O), 155.2 (C=O), 131.7 (2×ArCH), 125.7 (ArC), 125.2 (ArC), 114.8 (2×ArCH), 110.6 (ArCH), 55.8 (ArOCH₃), 53.9 (CHNH), 52.3 (OCH₃), 40.7 (CH₂N), 25.1 (CH₂CH), 10.6 (CH₃CH). IR (KBr): 3296 (N–H), 2969 (C–H), 1769 (C=O), 1740 (C=O), 1604 (C=C), 1513 (C=C), 1477 (C=C), 1252 (C=O), 525 (OCH₃), 40.8 (CH₂N), 17.5 (CH₂CH). HRMS (ESI-TOF): m/z [M + H]+ calcd for C₁₉H₂₄N₃O₆: 390.1638; found: 390.1638.
2H, CH₃N), 4.13 (q, 2H, J = 3.6 Hz, OCH₂CH₃), 3.81 (s, 3H, OCH₃), 1.70–1.61 (m, 2H, CH₂CH₃), 1.29–1.21 (m, 2H, CH₂CH₃), 1.20 (t, 3H, J = 4.0 Hz, CH₃O), 0.87 (t, 3H, J = 7.2 Hz, CH₃CH₂), 13C NMR (100 MHz, DMSO-d₆): δ 173.3 (C=O), 166.6 (C=O), 164.5 (C=O), 155.3 (C=O), 138.9 (Ar-CH₃), 130.4 (Ar-C), 129.9 (2×ArCH), 128.8 (2×ArCH), 126.4 (ArC), 110.5 (ArCH), 52.9 (OCH₂CH₃), 48.17 (CHNH), 40.5 (CH₂N), 21.4 (ArCH₃), 17.5 (CH₃CH₂); IR (KBr): 3289 (N–H), 2878 (C–H), 1770 (C=O), 1718 (C=O), 1604 (C=O), 1158 (C–O) cm⁻¹. HRMS (ESI-TOF): m/z [M + H]+ calcd for C₁₉H₂₄N₃O₅: 374.1638; found: 374.1643.

Methyl (2-(5-(4-methylbenzylidene)-2,4-dioxoimidazolidin-3-yl)acetamido)butanoate (10f) (0.28 g, 1.38 mmol) and methyl (2-bromoacetoxy)alaninate (0.12 g, 0.59 mmol) gave compound 10g as a yellow solid (0.12 g, 25%); m.p. = 224–225 °C. 1H NMR (400 MHz, DMSO-d₆): δ 10.81 (s, 1H, =CH), 4.25 (quin, 1H, J = 8.0 Hz, =CH), 4.15 (s, 2H, CH₂N), 3.66 (s, 3H, OCH₃), 2.33 (s, 3H, ArCH₃), 1.20 (t, 3H, J = 7.2 Hz, CH₃CH₂); IR (KBr): 3289 (N–H), 2878 (C–H), 1770 (C=O), 1718 (C=O), 1604 (C=O), 1158 (C–O) cm⁻¹. HRMS (ESI-TOF): m/z [M + H]+ calcd for C₁₉H₂₄N₃O₅: 374.1638; found: 374.1643.

Methyl (2-(5-(4-methylbenzylidene)-2,4-dioxoimidazolidin-3-yl)acetamido)alaninate (10i) (0.12 g, 0.59 mmol) and methyl (2-bromoacetoxy)alaninate (0.12 g, 0.59 mmol) gave compound 10j as a white solid (0.12 g, 57%); m.p. = 252–257 °C. 1H NMR (400 MHz, DMSO-d₆): δ 10.81 (s, 1H, =CH), 4.25 (quin, 1H, J = 8.0 Hz, =CH), 4.15 (s, 2H, CH₂N), 3.66 (s, 3H, OCH₃), 2.33 (s, 3H, ArCH₃), 1.20 (t, 3H, J = 7.2 Hz, CH₃CH₂); IR (KBr): 3289 (N–H), 2878 (C–H), 1770 (C=O), 1718 (C=O), 1604 (C=O), 1158 (C–O) cm⁻¹. HRMS (ESI-TOF): m/z [M + H]+ calcd for C₁₉H₂₄N₃O₅: 374.1638; found: 374.1643.

Ethyl (2-(5-(4-methylbenzylidene)-2,4-dioxoimidazolidin-3-yl)acetamidono)butanoate (10k) (0.12 g, 0.59 mmol) and ethyl (2-bromoacetoxy)alaninate (0.12 g, 0.59 mmol) gave compound 10l as a white solid (0.12 g, 57%); m.p. = 252–257 °C. 1H NMR (400 MHz, DMSO-d₆): δ 10.81 (s, 1H, =CH), 4.25 (quin, 1H, J = 8.0 Hz, =CH), 4.15 (s, 2H, CH₂N), 3.66 (s, 3H, OCH₃), 2.33 (s, 3H, ArCH₃), 1.20 (t, 3H, J = 7.2 Hz, CH₃CH₂); IR (KBr): 3289 (N–H), 2878 (C–H), 1770 (C=O), 1718 (C=O), 1604 (C=O), 1158 (C–O) cm⁻¹. HRMS (ESI-TOF): m/z [M + H]+ calcd for C₁₉H₂₄N₃O₅: 374.1638; found: 374.1643.
Ethyl 2-(5-(4-methylbenzylidene)-2,4-dioxoimidazolidin-3-yl)acetoxy)valinate (10j): The reaction of 5-(4-methylbenzylidene)hydantoin (8b) (1.00 g, 4.95 mmol) and ethyl (2-bromoacetyl)valinate (0.38 g, 1.73 mmol) gave compound 10j as a white solid (0.24 g, 36%); m.p. = 252–257 °C. 1H NMR (400 MHz, DMSO-d6): δ 10.78 (s, 1H, ring-NH), 8.56 (d, 1H, J = 8.0 Hz, NH), 7.55 (d, 2H, J = 8.01 Hz, 2×ArH), 7.24 (d, 2H, J = 8.0 Hz, 2×ArH), 6.53 (s, 1H, =CH), 4.17 (quin, 1H, J = 4.0 Hz, CHNH), 4.14 (s, 2H, CH2N), 4.07 (q, 2H, J = 7.2 Hz, OCH2CH3), 2.34 (s, 3H, ArCH3), 2.06 (m, 2H, CH2CH3), 1.18 (s, 3H, J = 7.2 Hz, CH3SO2), 0.90 (t, 6H, J = 6.4 Hz, CH2CH3). 13C NMR (100 MHz, DMSO-d6): δ 170.8 (C=O), 166.7 (C=O), 164.4 (C=O), 155.2 (C=O), 130.6 (Ar-C=O), 130.4 (Ar-C), 130.2 (2×ArCH), 129.9 (2×ArCH), 110.5 (OCH2CH3), 60.4 (OCH3), 58.0 (CHNH), 40.5 (CH2N), 30.6 (CH2CH3), 21.2 (ArCH3), 19.3 (CH2CH3), 18.5 (CH2CH3), 14.5 (CH3SO2). IR (KBr): 3294 (N–H), 1727.8 (C=O), 1664.0 (C=O), 1552.0 (C=O), 1145.0 (C–O) cm−1. HRMS (ESI-TOF): m/z [M + H]+ calculated for C20H19N3O8: 388.1794; found: 388.1856.

Ethyl-2-(5-(4-methylbenzylidene)-2,4-dioxoimidazolidin-3-yl)acetoxynorvalinate (10k): The reaction of 5-(4-methylbenzylidene)hydantoin (8b) (1.00 g, 4.95 mmol) and ethyl (2-bromoacetyl)norvalinate (1.10 g, 4.95 mmol) gave compound 10k as a white solid (1.20 g, 63%); m.p. = 242–254 °C. 1H NMR (400 MHz, DMSO-d6): δ 10.80 (s, 1H, ring-NH), 8.66 (d, 1H, J = 8.01 Hz, NH), 7.55 (d, 2H, J = 7.6 Hz, 2×ArH), 7.24 (d, 2H, J = 8.0 Hz, 2×ArH), 6.53 (s, 1H, =CH), 4.23 (quin, 1H, J = 4.0 Hz, CHNH), 4.21 (s, 2H, CH2N), 4.07 (q, 2H, J = 6.0 Hz, OCH2CH3), 2.33 (s, 3H, ArCH3), 1.71–1.56 (m, 2H, CH2CH3), 1.42–1.35 (m, 2H, CH2CH3), 1.21 (t, 3H, J = 7.2 Hz, CH3SO2), 0.87 (t, 3H, J = 7.2 Hz, CH2CH3). 13C NMR (100 MHz, DMSO-d6): δ 172.4 (C=O), 166.6 (C=O), 164.5 (C=O), 155.2 (C=O), 139.0 (Ar-C=O), 130.3 (Ar-C), 130.0 (2×ArCH), 129.9 (2×ArCH), 126.3 (ArC), 110.5 (OCH2CH3), 61.0 (OCH3), 52.4 (CHNH), 41.0 (CH2N), 33.5 (CH2CH3), 21.4 (ArCH3), 18.9 (CH2CH3), 14.0 (CH3SO2), 13.9 (CH3), IR (KBr): 3291 (N–H), 2957 (C=H), 1786 (C=O), 1740 (C=O), 1119 (C–O) cm−1. HRMS (ESI-TOF): m/z [M + H]+ calculated for C20H20N3O8: 388.1794; found: 388.1864.

Ethyl-(2-[5-(benzo[d][1,3]dioxol-5-ylmethylene)-2,4-dioxoimidazolidin-3-yl)acetoxy]valinate (10l): The reaction of 5-(benzo[d][1,3]dioxol-5-ylmethylene)hydantoin (8c) (1.00 g, 4.31 mmol) and ethyl 2-(2-bromoacetyl)norvalinate (0.95 g, 4.31 mmol) gave 10l as a brown solid (0.92 g, 51%); m.p. = 221–227 °C. 1H NMR (400 MHz, DMSO-d6): δ 10.78 (s, 1H, ring-NH), 8.58 (d, 1H, J = 8.4 Hz, NH), 7.30 (d, 1H, J = 0.8 Hz, ArH), 7.18 (dd, 1H, J = 7.2, 1.2 Hz, ArH), 6.97 (d, 1H, J = 8.0 Hz, ArH), 6.51 (s, 1H, =CH), 6.08 (2H, OCH2CH3), 4.15–4.05 (m, 5H, CHNH + CH2N + OCH2CH3), 2.09–2.00 (m, 1H, CH2CH3), 1.20 (t, 3H, J = 7.2 Hz, CH2CH3O), 0.89 (t, 3H, J = 6.4 Hz, CH3SO2). 13C NMR (100 MHz, DMSO-d6): δ 171.8 (C=O), 166.6 (C=O), 164.4 (C=O), 155.2 (C=O), 148.3 (ArC), 142.8 (ArC), 127.3 (ArC), 125.5 (ArC), 110.6 (arylCH), 109.3 (arylCH), 109.2 (arylCH), 101.9 (OCH2CH3), 61.9 (OCH3), 58.0 (CHNH), 40.4 (CH2N), 30.6 (CH2CH3), 19.3 (CH2CH3), 18.6 (CH2CH3), 14.5 (CH3SO2). IR (KBr): 3294 (N–H), 2917 (C=H), 1738 (C=O), 1604 (C=O), 1293 (C–O) cm−1. HRMS (ESI-TOF): m/z [M + H]+ calculated for C19H22N4O7: 418.1536; found: 418.1595.

Methyl-(2-[5-(benzo[d][1,3]dioxol-5-ylmethylene)-2,4-dioxoimidazolidin-3-yl)acetoxy]valinate (10o): The reaction of 8c (1.00 g, 4.31 mmol) and methyl (2-bromoacetyl)norvalinate (0.95 g, 4.31 mmol) gave 10o as a brown solid (0.62 g, 34%); m.p. = 298–302 °C. 1H NMR (400 MHz, DMSO-d6): δ 10.74 (s, 1H, ring-NH), 8.64 (d, 1H, J = 7.6 Hz, NH), 7.31 (d, 1H, J = 1.2 Hz, ArH), 7.19 (dd, 1H, J = 8.0, 1.2 Hz, ArH), 6.97 (d, 1H, J = 8.4 Hz, ArH), 6.52 (s, 1H, =CH), 6.08 (2H, OCH2CH3), 4.29 (quin, 1H, J = 8.0 Hz, CHNH), 4.14 (s, 2H, CH2N), 3.64 (s, 3H, OCH3), 1.70–1.41 (m, 2H, CH2CH3),
1.38–1.25 (m, 2H, CH₂CH₃), 0.88 (t, 3H, J = 7.6 Hz, CH₃CH₂); ¹³C NMR (100 MHz, DMSO-d₆): δ 172.3 (C=O), 166.6 (C=O), 164.4 (C=O), 155.2 (C=O), 148.3 (ArC), 148.2 (ArC), 127.3 (ArC), 125.4 (ArCH), 110.7 (ArylCH), 109.3 (ArCH), 109.2 (ArCH), 101.9 (OCH₂O), 52.3 (CHNH), 52.2 (OCH₃), 40.5 (CH₂N), 33.6 (CH₂CH), 18.9 (CH₂CH₃), 13.9 (CH₂CH₃); IR (KBr): 3294 (N–H), 2971 (C–H), 1769 (C=O), 1738 (C=O), 1604 (C=C), 1293 (C–O) cm⁻¹. HRMS (ESI-TOF): m/z [M+H]⁺ calcd for C₁₉H₂₂N₃O₇: 404.1380; found: 404.1439.

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Author contributions
Ms U.T. and Mr N.R.T. are the students who executed the project and synthesized reported compounds whereas Dr M.V.B. and Dr S.S.M.-M. are the supervisors of the projects who conceived the projects.

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