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Transformations of enaminones. A simple one-pot synthesis of imidazolone derivatives

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ABSTRACT

Ethyl (5-benzoyl-2-oxo-3-substituted-2,3-dihydro-1*H*-imidazol-1-yl)carbamates **7** were prepared by the *Michael* addition of diethyl azodicarboxylate (**3**) to (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**2**) followed by substitution of the dimethylamino group with primary amines **5a**–**n** to afford a mixture of (*E*) and (*Z*) diethyl 1-(1-(substituted)amino)-3-oxo-3-phenylprop-1-en-2-yl)hydrazine-1,2-dicarboxylates (**6a**–**n**), followed by cyclization to give final products **7a**–**n**. The intermediate **6i** was isolated and characterized and transformed into **7i**. All imidazolones **7a**–**n** were synthesized in one pot reaction sequences with individual reactions being very clean.

1. Introduction

Nitrogen containing heterocycles[1] are of special interest in organic synthetic chemistry, since they occur in a wide variety of natural products. The imidazolone motif appears in many natural products,[2] which possess interesting biological activities.[3] They are inhibitors of V-RAF murine sarcoma viral oncogene homologue B1.[4] They are antagonists of many receptors including the neurokinin-1 receptor[5] and the dopamine receptor.[6] They were applied as intermediates in the synthesis of many natural products, such as biotin,[7] slagenins,[8] axinohydantoins,[9] oroidin-derived alkaloids,[10] aplysinopsins,[11] Lancetta-derived alkaloid carcaridine A,[12] and others. Due to their importance, many methods have been developed for the construction of the imidazole ring.[13,14] Recently, there has been great progress in copper-catalysed N-arylation.[15,16] 4-Aroyl-1,3-dihydro-2*H*-imidazol-2-ones, have been prepared by acylation of the appropriate 2*H*-imidazol-2-ones and evaluated as a new class of cardiotonic agents.[17] The most important compound in this series is 4-methyl-5-[4-(methylthio)benzoyl]-1*H*-imidazol-2(3*H*)-one (Perfan® or Enoximone®) (Fig. 1), a selective phosphodiesterase inhibitor, which has significant inotropic and vasodilating properties that have proved useful in the postoperative management of infants and children having cardiac surgery.[18,19] The effects of phosphodiesterase (III/IV)-inhibitors and cytokines on mechanical properties of neutrophilic granulocytes in neonates and adults have been studied.[20]

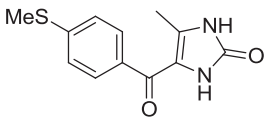

Fig. 1. 4-Methyl-5-[4-(methylthio)benzoyl]-1*H*-imidazol-2(3*H*)-one (Perfan® or Enoximone®).

In this communication we report a simple one-pot synthesis of imidazolone derivatives using enaminone methodology recently extensively studied in our laboratory. The wide applicability of 3-(dimethylamino)propenoates and related enaminones as versatile reagents in heterocyclic synthesis,[21] including natural products and their analogues[11,22] and regiospecific microwave-assisted [2+2] cycloadditions with electron-poor acetylenes and their transformations into highly substituted heterocyclic systems has been demonstrated.[23]

In this communication we report a simple one-pot synthesis of ethyl (5-benzoyl-2-oxo-3-substituted-2,3-dihydro-1*H*-imidazol-1-yl)carbamates, which were prepared by the *Michael* addition of diethyl azodicarboxylate to (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one followed by substitution of the dimethylamino group with primary amines and cyclization into imidazolone derivatives.

2. Results and discussion

First, (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**2**) prepared from acetophenone (**1**) and *N*,*N*-dimethylformamide

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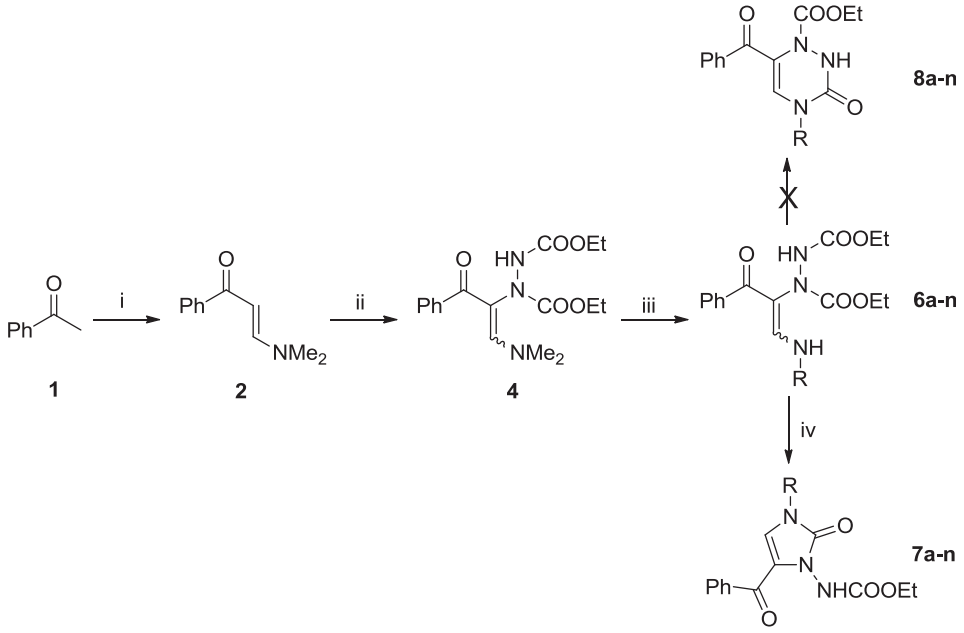
dimethylacetal (DMFDMA) according to known procedure[24] was treated with diethyl azodicarboxylate (DEAD) (**3**) in toluene for 24 h at room temperature to give a 1:1 mixture of (*E*)- and (*Z*)-1-(1-(dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)hydrazine-1,2-di carboxylate (**4**) in 95% yield. Substitution of the dimethylamino group with 3-nitroaniline (**5i**) in acetic acid under reflux for 3 h afforded a 7:3 mixture of diethyl (*E*)- and diethyl (*Z*)-[1-(3-(nitrophenyl)amino]-3-oxo-3-phenylprop-1-en-2-yl)hydrazine-1,2-dicarboxylate **6i** in 93% yield. Cyclization of **6i** was achieved by heating in an ethanol solution of NaOH for 2.5 h to give ethyl (5-benzoyl-3-(3-nitrophenyl)-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate **7i** in 93% yield. The formation of 1,2,4-triazin-3-ones (**8a**–**n**) was not observed (Scheme 1).

3. Structure determination

The cyclization can take place either at the NH group at position 3′ and the ester group at position 1 of conformer **6** to give imidazole derivative **7**, or alternatively at the NH group at position 3′ and the ester group at position 2 of conformer **6′** to give 1,2,4-triazine derivative **8** (Scheme 4).

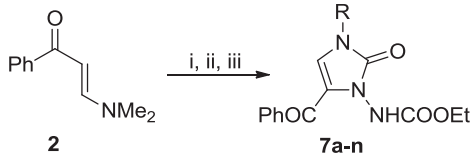
The ^{1}H NMR spectra of the products show, besides the signals characteristic for the aromatic group, the ethyl ester group at δ=1.21–1.30 ppm for the Me group and δ=4.11–4.24 ppm for the CH_2 group. Also a CH singlet in the range δ=6.83–7.97 ppm and a broad singlet originating from the primary amine in the range δ=7.03–10.11 ppm are visible in the spectra. On the basis of spectral



Scheme 1. Reagents and conditions: (i) dimethylformamide dimethylacetale, (ii) diethyl azodicarboxylate (**3**), acetonitrile, rt, (iii) primary amine **5**, acetic acid, reflux, (iv) NaOH, EtOH, reflux.

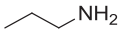
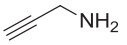
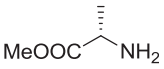
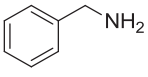
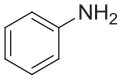
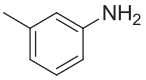
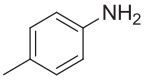
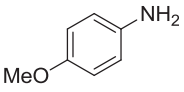
This reaction sequence can be carried out as a one-pot procedure. To a solution of **2** in ethanol, a solution of DEAD (**3**) in toluene was added and the reaction mixture was stirred at room temperature for 4 h. Primary amines **5a**–**n** and an aqueous solution of hydrochloric acid (or amine hydrochloride) were added and the reaction mixture was stirred again at room temperature for 12–240 h. The solution was made alkaline by addition of sodium hydroxide and the reaction mixture was stirred for a further 24–144 h. Then the volatile components were evaporated in vacuo. The crude products **7a**–**n** were purified by column chromatography and recrystallized from appropriate solvents. In the case of compound **7c** the methyl ester group was hydrolysed under these conditions and only the corresponding acid was isolated. (Scheme 2, Table 1).

The same reaction sequence was used for the transformation of bis enaminone **9** into bis imidazolone derivative **10** (Scheme 3).



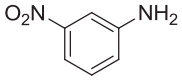
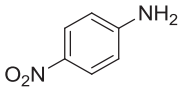
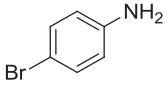
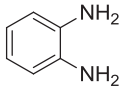
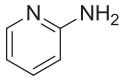
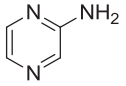
Scheme 2. Reagents and conditions: (i) diethyl azodicarboxylate (**3**), EtOH, rt, (ii) primary amine **5**, EtOH, rt, (iii) NaOH, EtOH, rt.

Table 1
Substituted (2-oxo-2,3-hihydro-1*H*-imidazol-1-yl)carbamates

Compound **7**	RNH_2 (**5**)	Yield (%)	Mp (°C)
a		74	210.5–212.5
b		35	Oil
c		94	Oil
d		82	206.9–208.5
e		74	153.4–154.6
f		75	217.1–219.2
g		78	164.5–166.1
h		92	164.7–165.3

(*continued on next page*)

Table 1 (*continued*)

Compound **7**	RNH_2 (**5**)	Yield (%)	Mp (°C)
i		85	181.2–182.1
j		68	185.3–187.6
k		92	167.6–169.7
l		68	162.4–167.6
m		49	118.9–119.7
n		69	194.7–197.0

amino)-3-oxo-3-phenylprop-1-en-2-yl)hydrazine-1,2-dicarboxylates (**6a**–**n**) in good to excellent yields.

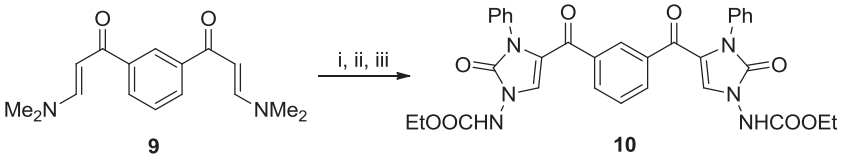
5. Experimental

5.1. General

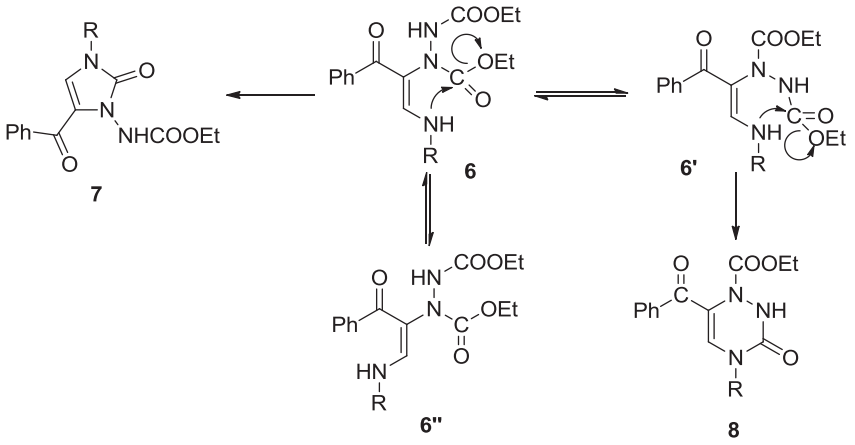
Melting points were determined on an Optimelt MPA100. ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H, and 75.5 MHz for ^{13}C and a Bruker Avance III 500 MHz at 500 MHz for ^{1}H and 126 MHz for ^{13}C, using DMSO-d_6 and $CDCl_3$ as solvents and TMS as the internal standard. Mass spectra were recorded on an AutoSpecQ and QTof-premier spectrometers, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400. Column chromatography was performed on silica gel (Fluka, Silica gel 60, 0.04–0.06 mm). (*E*)-3-(Dimethylamino)-1-phenylprop-2-en-1-one (**2**) and (2*E*,2′*E*)-1,1′-(1,3-phenylene)bis(3-(dimethylamino)prop-2-en-1-one) (**9**) were prepared according to procedures described in the literature.[24]

5.2. Diethyl 1-(1-(dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)hydrazine-1,2-dicarboxylate (4)

To a solution of (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**2**) (175 mg, 1 mmol) in MeCN (2 mL) was added a solution of



Scheme 3. Reagents and conditions: (i) diethyl azodicarboxylate (**3**), EtOH, rt, (ii) aniline hydrochloride (**5e**), EtOH, rt, (iii) NaOH, EtOH, rt.



Scheme 4.

characteristics one can not differentiate between imidazolone derivatives **7** and 1,2,4-triazine derivatives **8**, therefore the X-ray structural analysis of good monocrystals of **7i** shows that in this reaction imidazolone derivatives **7** were formed (Fig. 2).

4. Conclusion

A simple synthesis of ethyl (5-benzoyl-2-oxo-3-substituted-2,3-dihydro-1*H*-imidazol-1-yl)carbamate (**7a**–**n**) was developed from (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**2**) in a three step one-pot synthesis via (E) and (*Z*) diethyl (1-(1-(substituted) DEAD (**3**) in toluene (512 μL, *w*=39%, 1.1 mmol). The reaction mixture was stirred for 24 h at room temperature. Volatile components were evaporated in vacuo and product was purified by column chromatography (ethyl acetate/petroleum ether=1:2) to afford 1:1 as inseparable mixture of *E*/*Z* isomers. Yield: 331 mg (95%) of white oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25–1.30 (12H, m, 4× CH_3); 3.04 (6H, br s, 2× NCH_3); 3.46 (6H, br s, 2× NCH_3); 4.15–4.27 (8H, m, 4× CH_2); 6.93 (1H, s, C*H*); 6.97 (1H, s, C*H*); 7.35–7.43 (6H, m, 2× Ph); 7.45–7.50 (4H, m, 2× Ph); 7.61 (1H, br s, N*H*); 7.73 (1H, br s, N*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.6, 38.1, 48.1, 61.6, 63.2, 114.7, 128.3, 128.5, 130.2, 140.1, 151.9, 152.4,

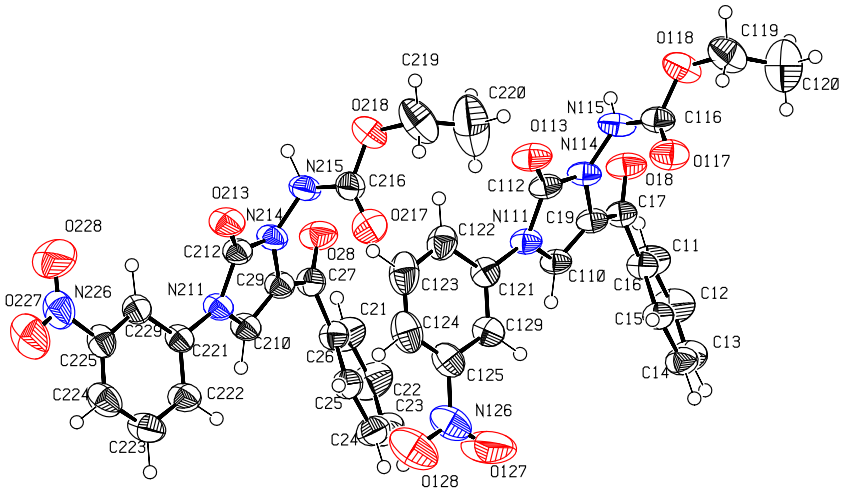


Fig. 2. Ethyl (5-benzoyl-3-(3-nitrophenyl)-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate (**7i**).

156.2, 158.3, 191.8. EI-HRMS: m/z=350.1699 (MH^+); $C_{17}H_{24}N_3O_5$ requires: m/z=350.1716 (MH^+); ν_{max} (NaCl) 2950, 1721, 1693, 1605, 1495, 1433, 1398, 1244, 1217, 1087, 1042, 979, 785, 763 cm^{-1}.

5.3. Diethyl 1-(1-((3-nitrophenyl)amino)-3-oxo-3-phenylprop-1-en-2-yl)hydrazine-1,2-dicarboxylate (6i)

To a solution of diethyl 1-(1-(dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)hydrazine-1,2-dicarboxylate (**4**) (280 mg, 0.75 mmol) in AcOH (2 mL) was added *m*-nitroaniline (**5i**) (104 mg, 0.75 mmol). The reaction mixture was refluxed for 3 h. Volatile components were evaporated in vacuo and the product was purified by column chromatography (ethyl acetate/petroleum ether=1:2) to afford a 7:3 inseparable mixture of *E*/*Z* isomers. Yield: 411 mg (93%) of white solid. Mp 127.3–155.5 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18–1.30 (6H, m, 2× CH_3); 4.17–4.30 (4H, m, 2× CH_2); 7.29 (1H, br s, *CH*); 7.43–7.59 (4H, m, Ph); 7.63–7.69 (3H, m, Ph+N*H*); 7.75–7.78 (1H, m, Ph); 7.81–7.88 (2H, m, Ph); 9.87 (0.3H, d, J=11.9 Hz, N*H*); 10.02 (0.7H, d, J=12.7 Hz, N*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.5, 63.1, 63.6, 110.2, 117.8, 120.1, 122.1, 128.5, 128.7, 130.7, 131.6, 138.6, 141.3, 142.4, 156.6, 159.6, 190.9. ($C_{21}H_{22}N_4O_7$ requires: C, 57.01; H, 5.01; N, 12.66. found C, 57.26; H, 4.74; N, 12.72); EI-HRMS: m/z=443.1550 (MH^+); $C_{21}H_{23}N_4O_7$ requires: m/z=443.1567 (MH^+); ν_{max} (NaCl) 1734, 1707, 1655, 1602, 1572, 1536, 1483, 1373, 1354, 1320, 1264, 1179, 1092, 1055, 938, 871, 797, 736 cm^{-1}.

5.4. Ethyl (5-benzoyl-3-(3-nitrophenyl)-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)carbamate (7i)

To a solution of diethyl 1-(1-((3-nitrophenyl)amino)-3-oxo-3-phenylprop-1-en-2-yl)hydrazine-1,2-dicarboxylate (**6i**) (310 mg, 0.70 mmol) in EtOH (10 mL) was added NaOH (28 mg, 0.70 mmol). The reaction mixture was refluxed for 2.5 h. Volatile components were evaporated in vacuo and product was purified by column chromatography (ethyl acetate/petroleum ether=1:1). Yield: 273 mg (95%) of white solid. Mp 181.2–182.1 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (3H, t, J=7.2 Hz, CH_3); 4.18 (2H, t, J=7.2 Hz, CH_2); 7.34 (1H, s, *CH*); 7.45–7.50 (2H, m, Ph); 7.56–7.64 (2H, m, Ph); 7.84–7.87 (2H, m, Ph); 8.03–8.10 (2H, m, Ph); 8.26 (1H, br s, N*H*); 8.42 (1H, t, J=2.1 Hz, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.2, 62.7, 116.7, 119.8, 121.6, 122.7, 127.7, 128.7, 128.9, 130.4, 133.1, 136.6, 136.7, 148.5, 150.6, 155.5, 183.0. ($C_{19}H_{16}N_4O_6$ requires: C, 57.58; H, 4.07; N, 14.14. found C, 57.62; H, 4.03; N, 14.08); EI-HRMS: m/z=397.1142 (MH^+); $C_{19}H_{17}N_3O_4$ requires: m/z=397.1148 (MH^+); ν_{max} (KBr) 3308, 3114, 3008, 1763, 1745, 1723, 1637, 1575, 1534, 1435, 1398, 1348, 1241, 1211, 1139, 1097, 1055, 960, 870, 809, 741, 717 cm^{-1}.

5.5. General procedure for the synthesis of ethyl (5-benzoyl-2-oxo-3-substituted-2,3-dihydro-1*H*-imidazol-1-yl) carbamates (7a–n)

To a solution of (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one (**2**) (175 mg, 1 mmol) in EtOH (2 mL) was added a solution of DEAD (**3**) in toluene (512 μL, w=39%, 1.1 mmol). The reaction mixture was stirred for 4 h at room temperature. Then, amine (**5a**–**n**) (1 mmol) with 4 drops of concd HCl_{aq} or amine hydrochloride (1 mmol) was added and the reaction mixture was stirred for t_1. NaOH (100 mg, 2.5 mmol) was then added and the reaction mixture was stirred for t_2. Volatile components were evaporated in vacuo and products were purified by column chromatography and crystallised from appropriate solvents.

*5.5.1. Ethyl (5-benzoyl-2-oxo-3-propyl-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7a**).* Prepared from propylamine (**5a**) (82.4 μL, 1.0 mmol), t_1=240 h, t_2=72 h, chromatography (chloroform/methanol=30:1). Crystallised from ethyl acetate/petroleum ether; yield: 236 mg (74%) of white solid. Mp 210.5–212.5 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (3H, t, J=7.2 Hz, CH_3); 1.28 (3H, t, J=6.9 Hz, CH_3); 1.75 (2H, sep, J=7.2 Hz, CH_2); 3.69 (2H, t, J=7.2 Hz, CH_2); 4.22 (2H, q, J=6.9 Hz, CH_2); 6.83 (1H, s, *CH*); 7.32 (1H, br s, N*H*); 7.45–7.51 (2H, m, Ph); 7.57–7.62 (1H, m, Ph); 7.76–7.79 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 11.1, 14.5, 22.7, 46.4, 62.8, 121.5, 123.6, 128.38, 128.9, 132.8, 137.5, 152.2, 155.6, 183.1. ($C_{16}H_{19}N_3O_4$ requires: C, 60.56; H, 6.03; N, 13.24. found C, 60.33; H, 6.08; N, 13.24); EI-HRMS: m/z=318.1455 (MH^+); $C_{16}H_{20}N_3O_4$ requires: m/z=318.1454 (MH^+); ν_{max} (KBr) 3097, 3000, 2963, 1751, 1695, 1636, 1584, 1511, 1447, 1368, 1332, 1251, 1174, 1133, 1099, 1054, 992, 895, 837, 784, 750, 721 cm^{-1}.

*5.5.2. Ethyl (5-benzoyl-2-oxo-3-(prop-2-yn-1-yl)-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7b**).* Prepared from propargylamine hydrochloride (**5b**) (92.0 mg, 1.0 mmol), t_1=168 h, t_2=144 h, chromatography (ethyl acetate/petroleum ether=1:2). yield: 111 mg (35%) of colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (3H, t, J=7.2 Hz, CH_3); 4.22 (2H, q, J=7.2 Hz, CH_2); 5.59 (2H, d, J=6.6 Hz, CH_2); 6.88 (1H, s, *CH*); 7.08 (1H, t, J=6.6 Hz, *CH*); 7.33(1H, br s, N*H*); 7.47–7.52 (2H, m, Ph); 7.59–7.64 (1H, m, Ph); 7.78–7.82 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.3, 62.9, 89.9, 94.5, 118.9, 122.4,

128.8, 128.9, 133.0, 137.0, 150.1, 155.4, 183.1, 201.2. EI-HRMS: m/z=314.1149 (MH^+); $C_{16}H_{16}N_3O_4$ requires: m/z=314.1154 (MH^+); ν_{max} (KBr), 2974, 1719, 1636, 1577, 1508, 1448, 1366, 1326, 1245, 1239, 1176, 1580, 856, 713 cm^{-1}.

*5.5.3. (S)-2-(4-Benzoyl-3-((ethoxycarbonyl)amino)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)propanoic acid (**7c**).* Prepared from L-alanine methyl ester hydrochloride (**5c**) (139.0 mg, 1.0 mmol), t_1=168 h, t_2=144 h, extraction ethyl acetate/1 M HCl. Yield: 326 mg (94%) of colourless oil; $[\alpha]_{589}^{21}$ 5.2 (c 0.58, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (3H, t, J=7.2 Hz, CH_3); 1.64 (3H, d, J=7.5 Hz, CH_3); 4.21 (2H, q, J=7.2 Hz, CH_2); 5.06 (1H, q, J=7.5 Hz, CH); 5.51 (1H, br s, COOH); 7.03 (1H, br s, NH); 7.45–7.50 (2H, m, Ph); 7.56–7.62 (2H, m, Ph+CH); 7.77–7.81 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.4, 16.9, 51.7, 63.0, 121.7, 128.8, 129.0, 132.9, 137.1, 152.2, 156.0, 172.2, 183.3. ($C_{16}H_{17}N_3O_6\times0.5H_2O$ requires: C, 53.93; H, 5.09; N, 11.79. found C, 53.92; H, 5.11; N, 11.44); EI-HRMS: m/z=346.1045 ($M-H^+$); $C_{16}H_{16}N_3O_6$ requires: m/z=346.1039 (MH^+); ν_{max} (KBr) 2996, 1723, 1635, 1576, 1520, 1493, 1447, 1405, 1374, 1327, 1238, 1176, 1095, 1060, 1021, 959, 894, 852, 831, 753, 715 cm^{-1}.

*5.5.4. Ethyl (5-benzoyl-3-benzyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7d**).* Prepared from benzylamine hydrochloride (**5d**) (143.6 mg, 1.0 mmol), t_1=48 h, t_2=24 h, chromatography (ethyl acetate/petroleum ether=1:2). Crystallised from ethyl acetate/petroleum ether; yield: 298 mg (82%) of white solid. Mp 206.9–208.5 °C ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.22 (3H, t, J=7.2 Hz, CH_3); 4.11 (2H, t, J=7.2 Hz, CH_2); 4.89 (2H, s, CH_2); 7.27–7.39 (5H, m, Ph); 7.51–7.55 (2H, m, Ph); 7.61–7.72 (4H, m, Ph+CH); 10.11 (1H, br s, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ 14.4, 47.1, 61.2, 120.2, 125.1, 127.5, 127.7, 128.4, 128.5, 128.6, 132.3, 136.6, 137.4, 151.5, 155.5, 181.6. ($C_{20}H_{19}N_3O_4$ requires: C, 65.74; H, 5.24; N, 11.50. found C, 65.84; H, 5.13; N, 11.47); EI-HRMS: m/z=366.1561 (MH^+); $C_{20}H_{20}N_3O_4$ requires: m/z=366.1454 (MH^+); ν_{max} (KBr) 3253, 3094, 2983, 1744, 1700, 1637, 1584, 1505, 1439, 1346, 1256, 1167, 1053, 990, 896, 841, 748, 716 cm^{-1}.

*5.5.5. Ethyl (5-benzoyl-2-oxo-3-phenyl-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7e**).* Prepared from aniline hydrochloride (**5e**) (129.0 mg, 1.0 mmol), t_1=48 h, t_2=24 h, chromatography (ethyl acetate/petroleum ether=1:2). Crystallised from ethyl acetate/petroleum ether; yield: 260 mg (74%) of white solid. Mp 153.4–154.6 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (3H, t, J=7.2 Hz, CH_3); 4.23 (2H, t, J=7.2 Hz, CH_2); 7.13 (1H, s, CH); 7.31–7.36 (1H, m, Ph); 7.42–7.51 (4H, m, Ph); 7.55–7.63 (4H, m, Ph+NH); 7.82–7.85 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.4, 63.0, 121.8, 122.3, 122.7, 127.7, 128.9, 129.0, 129.7, 133.1, 135.9, 137.3, 151.0, 155.6, 183.3. ($C_{19}H_{17}N_3O_4$ requires: C, 64.95; H, 4.88; N, 11.96. found C, 64.90; H, 4.76; N, 11.99); EI-HRMS: m/z=352.1290 (MH^+); $C_{19}H_{18}N_3O_4$ requires: m/z=352.1297 (MH^+); ν_{max} (KBr) 3220, 2987, 1745, 1705, 1639, 1576, 1525, 1505, 1435, 1396, 1326, 1254, 1240, 1053, 895, 822, 757, 707 cm^{-1}.

*5.5.6. Ethyl (5-benzoyl-2-oxo-3-(m-tolyl)-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7f**).* Prepared from m-toluidine (**5f**) (108.2 μL, 1.0 mmol), 4 drops of concd HCl, t_1=48 h, t_2=24 h, chromatography (ethyl acetate/petroleum ether=1:2). Crystallised from ethyl acetate/petroleum ether; yield: 261 mg (72%) of white solid. Mp 217.1–219.2 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (3H, t, J=7.2 Hz, CH_3); 2.39 (3H, s, CH_3); 4.25 (2H, t, J=7.2 Hz, CH_2); 7.11 (1H, s, CH); 7.14–7.17 (1H, m, Ph); 7.32–7.39 (4H, m, 3Ph+NH); 7.47–7.52 (2H, m, Ph); 7.59–7.64 (1H, m, Ph); 7.83–7.85 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.5, 21.6, 63.0, 119.9, 122.2, 123.5, 128.7, 128.9, 129.1, 129.5, 133.1, 135.8, 137.3, 139.9, 155.6, 183.4. ($C_{20}H_{19}N_3O_4$ requires: C, 65.74; H, 5.24; N, 11.50. found C, 65.43; H, 5.15; N, 11.43); EI-HRMS: m/z=366.1448 (MH^+); $C_{20}H_{20}N_3O_4$ requires: m/z=366.1454 (MH^+); ν_{max} (KBr) 3015, 1752, 1726, 1625, 1894, 1573, 1525, 1497, 1448, 1431, 1401, 1323, 1240, 1211, 1132, 1056, 1000, 956, 889, 859, 795, 721 cm^{-1}.

*5.5.7. Ethyl (5-benzoyl-2-oxo-3-(p-tolyl)-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7g**).* Prepared from p-toluidine hydrochloride (**5g**) (143.0 mg, 1.0 mmol), t_1=24 h, t_2=24 h, chromatography (ethyl acetate/petroleum ether=1:2). Crystallised from ethyl acetate/petroleum ether; yield: 271 mg (78%) of white solid. Mp 164.5–166.1 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (3H, t, J=7.2 Hz, CH_3); 2.35 (3H, s, CH_3); 4.20 (2H, t, J=7.2 Hz, CH_2); 7.10 (1H, s, CH); 7.19–7.22 (2H, m, Ph); 7.41–7.49 (4H, m, Ph); 7.55–7.61 (1H, m, Ph); 7.81–7.84 (2H, m, Ph); 7.88 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.5, 21.2, 62.9, 122.1, 122.2, 122.7, 128.0, 129.0, 130.2, 133.0, 133.3, 137.3, 137.8, 151.1, 155.7, 183.3. ($C_{20}H_{19}N_3O_4$ requires: C, 65.74; H, 5.24; N, 11.50. found C, 65.72; H, 4.98; N, 11.52); EI-HRMS: m/z=366.1459 (MH^+); $C_{20}H_{20}N_3O_4$ requires: m/z=366.1454 (MH^+); ν_{max} (KBr) 3021, 1746, 1709, 1637, 1575, 1519, 1478, 1433, 1399, 1328, 1253, 1218, 1052, 938, 895, 815, 779, 754 cm^{-1}.

*5.5.8. Ethyl (5-benzoyl-3-(4-methoxyphenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7h**).* Prepared from p-metoxyaniline (**5h**) (123.2 mg, 1.0 mmol), 4 drops of concd HCl, t_1=12 h, t_2=24 h, chromatography (ethyl acetate/petroleum ether=1:2). Crystallised from ethyl acetate/petroleum ether; yield: 350 mg (92%) of white solid. Mp 164.7–165.3 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (3H, t, J=7.2 Hz, CH_3); 3.79 (3H, s, OCH_3); 4.19 (2H, t, J=7.2 Hz, CH_2); 6.90–6.94 (2H, m, Ph); 7.07 (1H, s, CH); 7.40–7.48 (4H, m, Ph); 7.54–7.60 (1H, m, Ph); 7.80–7.83 (2H, m, Ph); 8.00 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.7, 55.6, 62.7, 114.6, 121.8, 122.3, 124.4, 128.6, 128.7, 128.9, 132.8, 137.2, 151.1, 155.7, 158.9, 183.0. ($C_{20}H_{19}N_3O_5$ requires: C, 62.99; H, 5.02; N, 11.02. found C, 62.72; H, 4.99; N, 11.09); EI-HRMS: m/z=382.1419 (MH^+); $C_{20}H_{20}N_3O_5$ requires: m/z=382.1403 (MH^+); ν_{max} (KBr) 1745, 1709, 1634, 1575, 1517, 1433, 1401, 1330, 1256, 1180, 1055, 940, 895, 831, 778, 738, 704 cm^{-1}.

*5.5.9. Ethyl (5-benzoyl-3-(3-nitrophenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7i**).* Prepared from m-nitroaniline (**5i**) (138.0 mg, 1.0 mmol), 4 drops of concd HCl, t_1=24 h, t_2=24 h, chromatography (ethyl acetate/petroleum ether=1:1). Crystallised from ethyl acetate/petroleum ether; yield: 337 mg (85%) of white solid.

*5.5.10. Ethyl (5-benzoyl-3-(4-nitrophenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7j**).* Prepared from p-nitroaniline (**5j**) (138.0 mg, 1.0 mmol), 4 drops of concd HCl, t_1=24 h, t_2=48 h, chromatography (ethyl acetate/petroleum ether=1:2). Crystallised from ethyl acetate/petroleum ether; yield: 268 mg (68%) of yellow solid. Mp 185.3–187.6 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (3H, t, J=7.2 Hz, CH_3); 4.19 (2H, t, J=7.2 Hz, CH_2); 7.26 (1H, s, CH); 7.48–7.53 (2H, m, Ph); 7.61–7.66 (1H, m, Ph); 7.84–7.87 (4H, m, Ph); 7.97 (1H, br s, NH); 8.25–8.28 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.7, 63.4, 119.6, 122.2, 123.6, 125.5, 129.3, 129.4, 133.8, 137.1, 141.3, 146.2, 150.9, 155.8, 183.6. ($C_{19}H_{16}N_4O_6$ requires: C, 57.58; H, 4.07; N, 14.14. found C, 57.87; H, 3.91; N, 13.98); EI-HRMS: m/z=397.1133 (MH^+); $C_{19}H_{17}N_3O_4$ requires: m/z=397.1148 (MH^+); ν_{max} (KBr) 1748, 1712, 1677, 1584, 1527, 1504, 1431, 1394, 1384, 1327, 1241, 1217, 1177, 1112, 1052, 939, 895, 856, 811, 750 cm^{-1}.

*5.5.11. Ethyl (5-benzoyl-3-(4-bromophenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7k**).* Prepared from p-bromoaniline (**5k**) (172.0 mg, 1.0 mmol), 4 drops of concd HCl, t_1=48 h, t_2=72 h, chromatography (ethyl acetate/petroleum ether=1:2). Crystallised from ethyl acetate; yield: 395 mg (92%) of white solid. Mp 167.6–169.7 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (3H, t, J=7.2 Hz, CH_3); 4.24 (2H, t, J=7.2 Hz, CH_2); 7.09 (1H, s, CH); 7.09 (1H, br s, NH);

7.45–7.53 (4H, m, Ph); 7.56–7.66 (3H, m, Ph); 7.82–7.86 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.5, 63.0, 120.9, 121.1, 122.5, 124.0, 128.9, 129.0, 132.7, 133.2, 134.9, 137.1, 150.8, 155.6, 183.2. ($C_{19}H_{16}N_3O_4Br$ requires: C, 53.04; H, 3.75; N, 9.77. found C, 53.09; H, 3.51; N, 9.71); EI-HRMS: m/z=430.0403 (MH^+); $C_{19}H_{17}N_3O_4Br$ requires: m/z=430.0402 (MH^+); ν_{max} (KBr) 3017, 1744, 1707, 1638, 1589, 1572, 1523, 1496, 1435, 1395, 1327, 1252, 1214, 1052, 1011, 895, 827, 758, 711 cm^{-1}.

*5.5.12. Diethyl (3,3′-(1,2-phenylene)bis(5-benzoyl-2-oxo-2,3-dihydro-1H-imidazole-3,1-diyl))dicarbamate (**7l**).* Prepared from *o*-diaminobenzene (**5l**) (54 mg, 0.5 mmol), 4 drops of concd HCl, t_1=240 h, t_2=24 h, chromatography (ethyl acetate/petroleum ether=2:1). Crystallised from ethyl acetate/petroleum ether; yield: 214 mg (68%) of brownish solid. Mp 162.4–167.6 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.21 (6H, br s, 2× CH_3); 4.16 (4H, br s, 2× CH_2); 7.09 (2H, s, C*H*); 7.44–7.49 (6H, m, Ph); 7.53–7.58 (4H, m, Ph); 7.82 (2H, br s, 2× N*H*); 7.89–7.91 (4H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.3, 62.8, 122.2, 124.6, 128.5, 128.8, 129.3, 130.8, 132.8, 133.2, 137.3, 150.7, 156.2, 183.5. ($C_{32}H_{28}N_6O_8$ requires: C, 61.53; H, 4.52; N, 13.46. found C, 61.14; H, 4.42; N, 13.30); EI-HRMS: m/z=625.2041 (MH^+); $C_{32}H_{29}N_6O_8$ requires: m/z=625.2047 (MH^+); ν_{max} (KBr) 3012, 1749, 1736, 1638, 1585, 1508, 1488, 1436, 1406, 1333, 1253, 1236, 1212, 1176, 1134, 1060, 935, 897, 824, 775, 715 cm^{-1}.

*5.5.13. Ethyl (5-benzoyl-2-oxo-3-(pyridin-2-yl)-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7m**).* Prepared from *o*-aminopyridine (**5m**) (94.1 mg, 1.0 mmol), 4 drops of concd HCl, t_1=24 h, t_2=24 h, chromatography (ethyl acetate/petroleum ether=1:2). Crystallised from ethyl acetate/petroleum ether; yield: 174 mg (49%) of white solid. Mp 118.9–119.7 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (3H, t, J=7.2 Hz, CH_3); 4.21 (2H, t, J=7.2 Hz, CH_2); 7.19 (1H, ddd, J_1=0.9 Hz, J_2=4.8 Hz, J_3=7.5 Hz, Py); 7.45–7.50 (2H, m, Ph); 7.56–7.62 (1H, m, Ph); 7.79 (1H, ddd, J_1=1.8 Hz, J_2=7.5 Hz, J_3=8.4 Hz, Py); 7.85–7.88 (2H, m, Ph); 7.97 (1H, s, C*H*); 8.16 (1H, br s, N*H*); 8.36 (1H, ddd, J_1=0.9 Hz, J_2=1.8 Hz, J_3=4.8 Hz, Py); 8.43 (1H, dt, J_1=0.9 Hz, J_2=8.4 Hz, Py). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.4, 62.7, 114.7, 118.9, 122.0, 122.2, 128.7, 129.0, 133.0, 137.0, 138.9, 148.0, 148.1, 150.6, 155.6, 183.6. ($C_{18}H_{16}N_4O_4$ requires: C, 61.36; H, 4.58; N, 15.90. found C, 61.19; H, 4.42; N, 15.81); EI-HRMS: m/z=353.1235 (MH^+); $C_{18}H_{17}N_4O_4$ requires: m/z=353.1250 (MH^+); ν_{max} (KBr) 2977, 1734, 1646, 1636, 1577, 1506, 1472, 1441, 1395, 1327, 1248, 1209, 1175, 1095, 1056, 944, 894, 781, 713 cm^{-1}.

*5.5.14. Ethyl (5-benzoyl-2-oxo-3-(pyrazin-2-yl)-2,3-dihydro-1H-imidazol-1-yl)carbamate (**7n**).* Prepared from *o*-aminopyrazine (**5n**) (95.1 mg, 1.0 mmol), 4 drops of concd HCl, t_1=24 h, t_2=24 h, chromatography (ethyl acetate/petroleum ether=1:1). Crystallised from ethyl acetate/petroleum ether; yield: 245 mg (69%) of white solid. Mp 194.7–197.0 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (3H, t, J=7.2 Hz, CH_3); 4.23 (2H, t, J=7.2 Hz, CH_2); 7.49–7.54 (2H, m, Ph); 7.61–7.66 (1H, m, Ph); 7.87–7.90 (4H, m, 2Ph+C*H*+N*H*); 8.36 (1H, dd, J_1=1.5 Hz, J_2=2.5 Hz, Py); 8.53 (1H, d, J=2.5 Hz, Py); 9.78 (1H, d, J=1.5 Hz, Py). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.5, 62.1, 117.7, 123.5, 128.9, 129.2, 133.4, 136.8, 137.4, 142.2, 142.6, 144.6, 150.3, 155.5, 183.7. ($C_{17}H_{15}N_5O_4$ requires: C, 57.79; H, 4.28; N, 19.82. found C, 57.88; H, 4.16; N, 19.78); EI-HRMS: m/z=354.1208 (MH^+); $C_{17}H_{16}N_5O_4$ requires: m/z=354.1202 (MH^+); ν_{max} (KBr) 3298, 3143, 2057, 2992, 1750, 1724, 1641, 1598, 1576, 1506, 1478, 1434, 1332, 1265, 1234, 1210, 1178, 1058, 1013, 899, 854, 816, 770, 714 cm^{-1}.

5.6. Diethyl (4,4′-isophthaloylbis(2-oxo-3-phenyl-2,3-dihydro-1*H*-imidazole-4,1-diyl))dicarbamate (10)

Prepared from (2*E*,2′*E*)-1,1′-(1,3-phenylene)bis(3-(dimethylamino)prop-2-en-1-one) (**9**) (272 mg, 1.0 mmol) and aniline hydrochloride (**5e**) (258.2 mg, 2.0 mmol), t_1=48 h, t_2=48 h, chromatography (ethyl acetate/petroleum ether=1:2). Crystallised from ethyl acetate/petroleum ether; yield: 244 mg (39%) of white solid. Mp 142.6–149.6 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.21 (6H, t, J=6.9 Hz, 2× CH_3); 4.15 (4H, q, J=4.15 Hz, 2× CH_2); 7.23 (2H, s, C*H*); 7.25–7.28 (2H, m, Ph); 7.31–7.37 (4H, m, Ph); 7.49–7.51 (4H, m, Ph); 7.58 (1H, t, J=7.7 Hz, Ph); 8.01 (2H, d, J=7.7 Hz, Ph); 8.25 (3H, br s, 2× N*H*+Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.3, 62.6, 121.7, 122.2, 122.4, 127.5, 128.9, 129.2, 129.4, 132.6, 135.4, 137.6, 150.7, 155.6, 181.8. ($C_{32}H_{28}N_6O_8\times0.5H_2O$ requires: C, 60.66; H, 4.61; N, 13.26. found C, 60.51; H, 4.50; N, 13.20); EI-HRMS: m/z=625.2067 (MH^+); $C_{32}H_{29}N_6O_8$ requires: m/z=625.2047 (MH^+); ν_{max} (KBr) 3240, 2982, 2925, 1719, 1637, 1596, 1577, 1499, 1438, 1400, 1329, 1252, 1216, 1095, 1053, 966, 910, 829, 799, 763 cm^{-1}.

5.7. X-ray structure analysis for compound 7i

Single crystal X-ray diffraction data were collected at room temperature on a Nonius Kappa CCD diffractometer (Mo Ka radiation was used) using the Nonius Collect Software.[25] DENZO and SCALEPACK[26] were used for indexing and scaling of the data. The structures were solved by using SIR97.[27] Refinement was performed using the Xtal3.4[28] program package and crystallographic plots were prepared with ORTEP III.[29] Structures were refined on *F* values using the full-matrix least squares procedure. The non-hydrogen atoms were refined anisotropically in both cases, while the positions of hydrogen atoms were geometrically calculated; their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina weighting scheme was used in both cases.

CCDC 834560 contains the supplementary crystallographic data for structure reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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