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Transformation of arylcarboxamides into 1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamides

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The synthesis of 1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamides in four steps starting from (hetero)-arylcarboxamides is described

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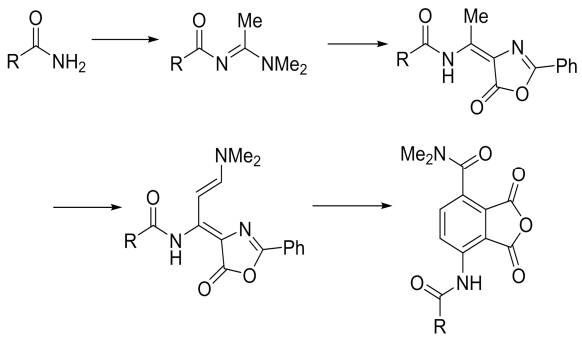

-Graphical Abstract

Transformation of arylcarboxamides into 1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamides

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Abstract

In this paper, we describe a four step synthesis of 1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamides starting from (hetero)arylcarboxamides. These are first transformed to the corresponding acetamidines followed by condensation to substituted [(oxazol-4(5*H*)-ylidene)ethyl]benzamides, which are further derivatized to substituted [(oxazol-4(5*H*)-ylidene)allyl]benzamides. The latter compounds undergo a supposed [4+2] cycloaddition with maleic anhydride, leading to the final products.

Keywords

Enaminones, Carboxamides, Aroylacetamidines, (*E*)-*N*-(1-(dimethylamino)ethylidene)-carboxamides, 1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamides

Dedicated to Professor Emeritus Dr. Miha Tišler on the occasion of his 90th birthday

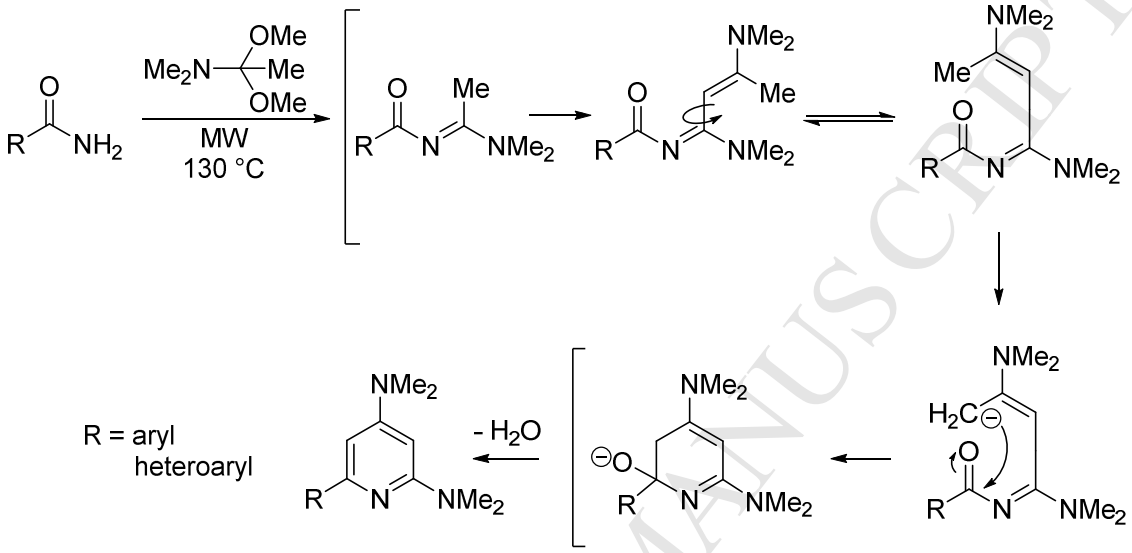
1.Introduction

In our laboratory, much work has been done on 3-dimethylaminopropenoates and related enaminones. These are a class of highly stable, readily available, versatile compounds with widespread use in organic synthesis,[1-3] including the preparation of natural products and their analogues, such as aplysinopsins,[4,5] meridianines,[6,7] and other similar compounds.[8]

Recently, we described a microwave-assisted [2+2] cycloaddition of enaminones to electron-poor acetylenes which lead to rearrangements and ring expansion reactions, as well as to polysubstituted butadienes, which were further transformed into carbocyclic and heterocyclic systems.[9,10] The expansion of the enaminone methodology, where amide acetals are used as reagents, was also demonstrated in the synthesis of polysubstituted benzene derivatives

starting from methyl ketones (acetyl compounds) and compounds with an active methylene group. In a simple, microwave-assisted reaction the formation of enaminone intermediates, which in this case were not isolated, were key in these syntheses.[11]

In an analogous manner, starting from commercially affordable carboxamides, again using *N*,*N*-dimethylacetamide dimethylacetal (DMADMA) as the building block, electron rich pyridine derivatives were prepared.[12] (Scheme 1).



Scheme 1: Transformation of carboxamides into polysusbstituted pyridines.

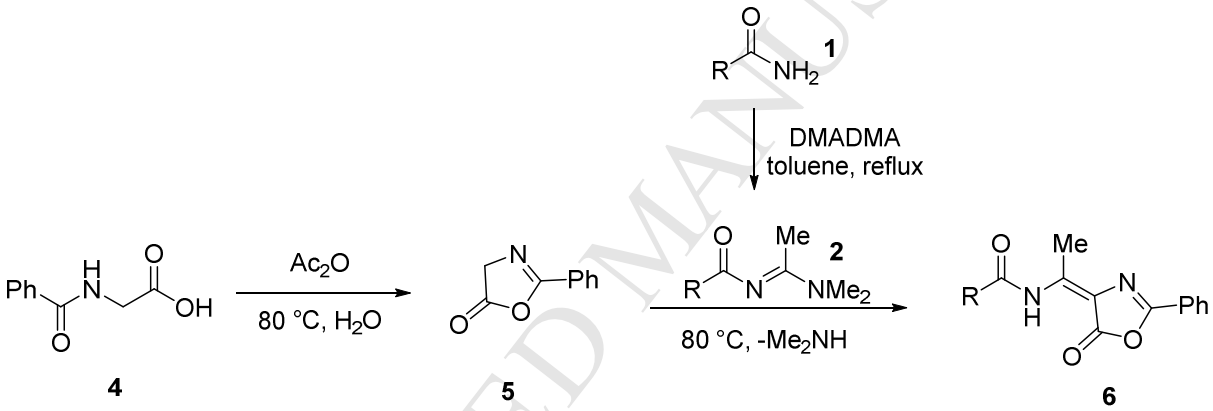
In this instance, similar as enaminones in the synthesis benzene derivatives, the amidine intermediates were key intermediates in these syntheses.

From a structural point of view, formamidines and acetamidines are nitrogen containing analogues of propenoates, and as such were interesting to us for further investigation. Amidines are also very important building blocks in organic and heterocyclic synthesis.[13,14] They also have diverse application in areas such as catalyst design,[15] material science,[16] medicinal chemistry[17] and superbase promoted reactions.[18] Starting from the general acetamidine synthesis developed by Raczynska *et al*,[19] we prepared various amidines, starting from simple, commercially available (hetero)aryl carboxamides. The reaction sequence of form/acet-amidine formation, followed by substitution of the dimethylamino group with a heterocyclic *C*-nucleophile, further elongation of the conjugated system and final reaction with maleic anhydride in a supposed [4+2] Diels-Alder reaction under microwave irradiation, resulted in formation of 1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamides. As is described

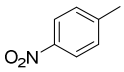
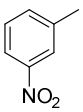
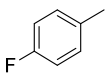
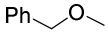
in this publication, using only elementary chemical reactions we were able to prepare a new type of system, appropriate for an ever-interesting Diels-Alder reaction which led to the final phthalic anhydride derivatives.

2. Results and discussion

Aryl and heteroaryl acetamidines **2a-j** were prepared from aryl and heteroarycarboxamides (**1**) and dimethylacetamide dimethyl acetal by heating in anhydrous toluene. After cooling, the crystalline products were separated by filtration, washed with diethyl ether and crystallized from the appropriate solvent. They reacted with 2-phenyloxazol-5(4*H*)-one (**5**) prepared *in situ* from hippuric acid (**4**) by heating in acetic anhydride to afford *N*-[1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)ethyl](hetero)arylamides **6a-g** (Scheme 2, Table 1).



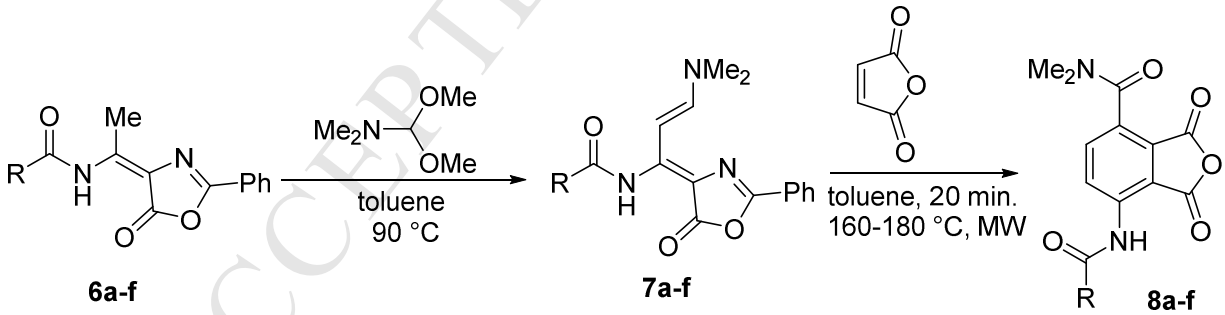
Scheme 2: Synthesis of acetamidines **2** and (hetero)arylamides **6**.

Compound	Yield 2a-g (%)	R	Compound	Yield 6a-g (%)
2a	48	Ph	**6a**	67
2b	87		**6b**	67
2c	68		**6c**	75
2d	69		**6d**	58
2e	98		**6e**	53
2f	63		**6f**	41

2g	94		**6g**	61

Table 1: (*E*)-*N*-[(dimethylamino)ethylidene]arylamides and *N*-[1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)ethyl]arylamides

The methyl group in compounds **6a-f** reacts with *N*,*N*-dimethyl formamide dimethyl acetal (DMFDMA) in toluene at 90 °C to give the corresponding *N*-((1*E*,2*E*)-3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)aryl amides **7a-f**. (Scheme 3, Table 2).



Scheme 3: Synthesis of *N*-((1*E*,2*E*)-3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)ylidene)arylamides **7a-f** and *N*,*N*-dimethyl-7-substituted-1,2,-dioxo-1,3-dihydroiso-benzofuran-4-carboxamides **8a-f**.

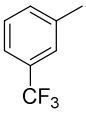
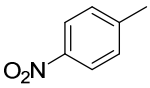
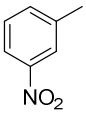
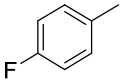
Product	R	Reaction time (h)	Yield (%)
7a	Ph-	2	85
87b		2	37
7c		1	90
7d		0.5	93
7e		2	97
7f	Ph-CH_2O-	0.5	94

Table 2: *N*-((1*E*,2*E*)-3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)aryl amides **7a-f**.

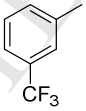
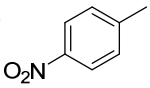
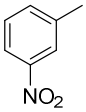
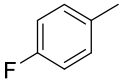
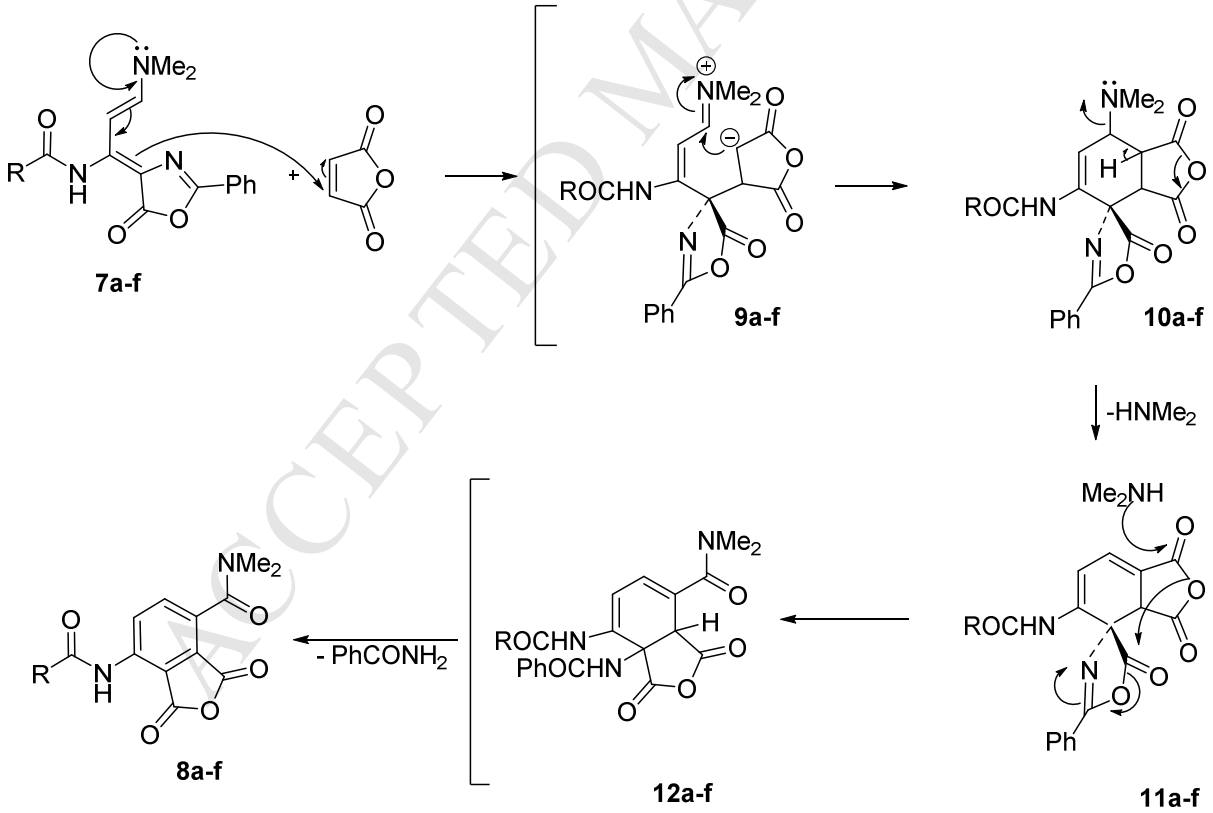
Product	R	Reaction time (min)	Yield (%)
8a	Ph-	40	48
8b		25	52
8c		50	42
8d		25	41
8e		15	50
8f	Ph-CH_2O-	20	34

Table 3: *N*,*N*-dimethyl-7-substituted-1,2,-dioxo-1,3-dihydroisobenzofuran-4-carboxamides **8a-f.**

Compounds **7a-f** exist in *s-cis* orientation and as electron-rich compounds, they are suitable for [4+2] cycloadditions with electron-poor maleic anhydride. In this connection, the reaction of compound **7a** with maleic anhydride was carried out in dry toluene under microwave irradiation for 20–40 minutes at 160–180 °C. On the basis of analytical data for C, H, and N, as well as spectroscopic data it became clear that major rearrangement was taking place during this reaction. On the basis of this evidence and on the mass spectrum, *m/e* = 338 (M^+), it was immediately evident that one of the benzamide groups had been eliminated. The starting compound **7a** contained two benzamide groups, one is the carboxamide group and the other one which originates from *N*-benzoyl glycine and is incorporated in the oxazole ring. In order to solve this problem the reaction was repeated with compounds **7b-f**, where the substituent on the starting carboxamide would help answer the question of which group is eliminated during the reaction. It turned out that benzoyl group originating from hippuric acid was eliminated during the reaction. The structure of **8a** was also confirmed by X-ray analysis.

The following reaction path was proposed for this transformation:



Scheme 4. Proposed reaction path for the formation of 1,2-dioxo-1,3-dihydroisobenzofuran-4-carboxamides **8a-f**.

3. Structure determination

The structures of new compounds were determined by ^{1}H and ^{13}C NMR, IR and HRMS spectral characteristics, and by elemental analyses for C, H, and N. The structure of compounds **2c**,**h, 6b**,**d**,**f**, **7a**,**d**,**f**, and **8a** were supported also by X–ray analysis.

The ^{1}H NMR spectra of substituted acetamidines **2a-h** show a singlet integrating for three protons for a methyl group in the range of δ =2.24–2.44 ppm and a singlet integrating for six protons for the dimethylamino group at δ = 3.04–3.24 ppm. Since the orientation around the double bond was not possible to determine on the basis of NMR spectra, the X–ray analyses for **2c**,**g** were carried out to show that this type of compounds exist in (*E*)–form.

Compound **6f** shows in ^{1}H NMR spectrum two singlets at δ = 2.84 and 2.88 ppm and two singlets for N*H* proton of the carbamate group at δ = 8.42 and 9.96 ppm indicating that it exists in solution in the (*E*)– and (*Z*)– forms. However, it crystallizes only in the (*E*)– form. All other compounds, **6a-e**,**g** exist in solution only in (*E*)– form concluded on the basis of chemical shift for the amide proton at δ = 11.33–11.50 ppm. The structures for **6b,d,f** were supported by X–ray analyses.

Compounds **7a-f** show two doublets in the range of *δ* = 7.01–7.08 and δ = 9.34–9.40 ppm with a coupling constant ^{3}J = 12.5–12.6 Hz characteristic for protons attached to the C=C double bond indicating that the orientation around the newly formed double bond is (*E*), two singlets for two methyl groups of NMe_2 group in the range of δ = 3.08–3.11 ppm and δ = 3.33–3.39 ppm, and a singlet in the range of *δ* = 11.89–12.09 ppm for the N*H* group which show no correlation in 2D NMR spectra. The structures of **7a**,**d**, **f** were confirmed by X–ray analyses (Figure 1).

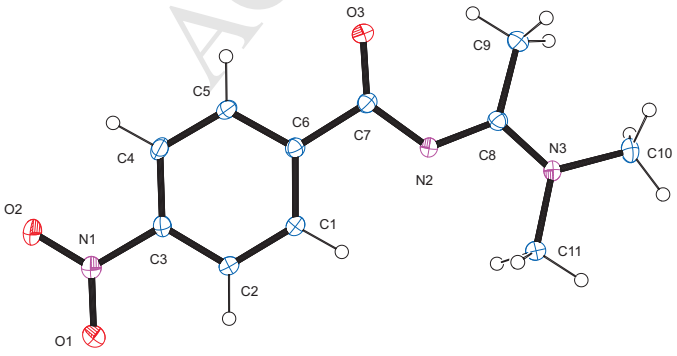
Compounds **8a-f** show two singlets in the range of δ = 2.79–2.83 ppm and δ = 3.03–3.06 ppm corresponding to two methyl groups of the *N*,*N*-dimethylamino group, two doublets in the range of δ = 7.83–7.96 ppm and δ = 8.39–8.55 ppm with a coupning constant ^{3}J = 7.8–8.4 Hz, characteristic for aromatic *ortho* protons, a multiplet for benzoyl group, and a singlet at δ = 10.14 ppm for an amide proton.

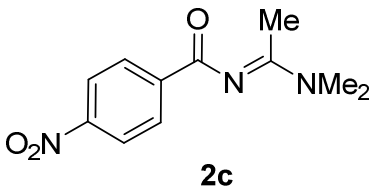
The NMR apectral data are also in agreement with the proposed structures. (Table 4).

Product	δ 5-C*H* (ppm)	δ 6-C*H* (ppm)	$J_{5H\text{-}6H}$ (Hz)	δ N*Me*$_2$ (ppm)	δ C=O (NMe$_2$) (ppm)	δ N*H* (ppm)	Solvent
8a	7.91	8.55	8.4	2.82 in 3.05	165.0	10.43	DMSO-d_6
8b	7.92	8.39	7.8	2.83 in 3.06	165.0	10.77	DMSO-d_6
8c	7.93	8.40	8.3	2.83 in 3.06	165.0	10.81	DMSO-d_6
8d	7.91-7.96	8.36	8.2	2.83 in 3.06	165.0	10.90	DMSO-d_6
8e	7.90	8.48	8.4	2.82 in 3.05	165.0	10.47	DMSO-d_6
8f	7.83	8.50	8.5	2.79 in 3.03	165.0	9.39	DMSO-d_6

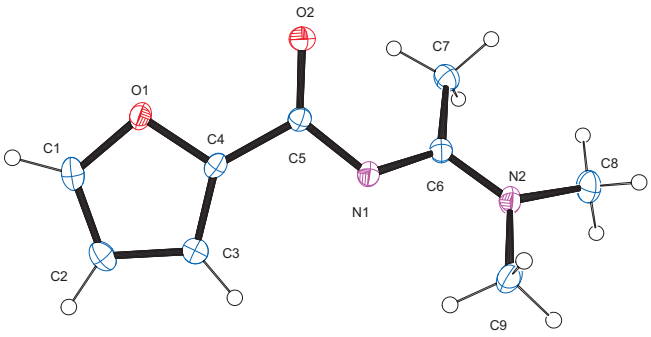
4. Conclusion

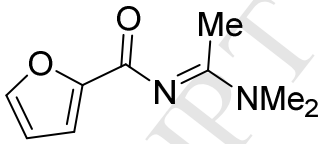
A four step synthesis of 1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamides starting from (hetero)arylcarboxamides is described. Carboxamides are first transformed to the corresponding acetamidines followed by condensation to substituted [(oxazol-4(5*H*)-ylidene)ethyl]benzamides, which are further transformed into substituted [(oxazol-4(5*H*)-ylidene)allyl]benzamides. The latter compounds undergo a [4+2] cycloaddition with maleic anhydride leading to the final products.



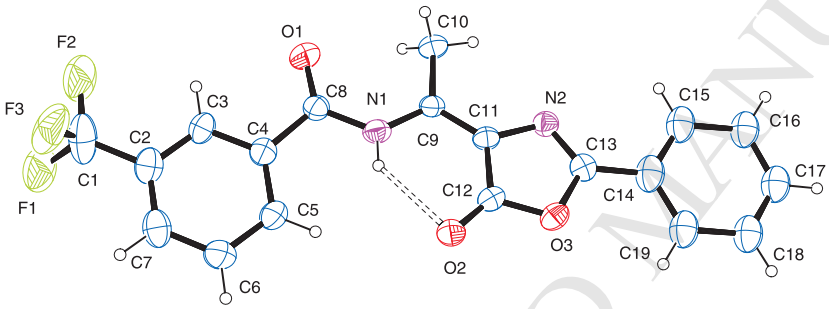


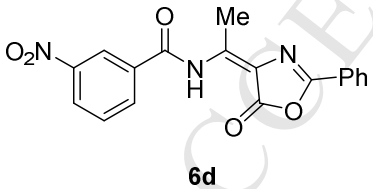
2c



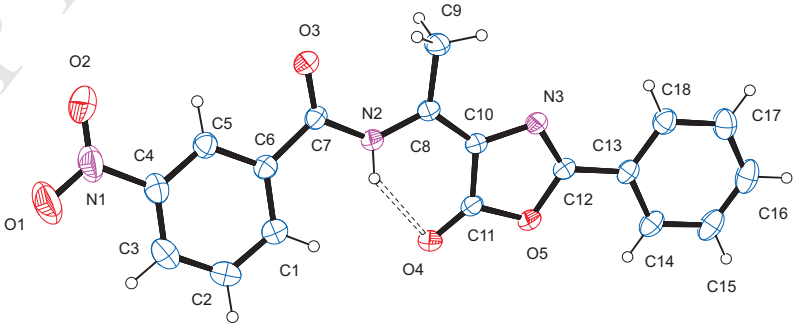


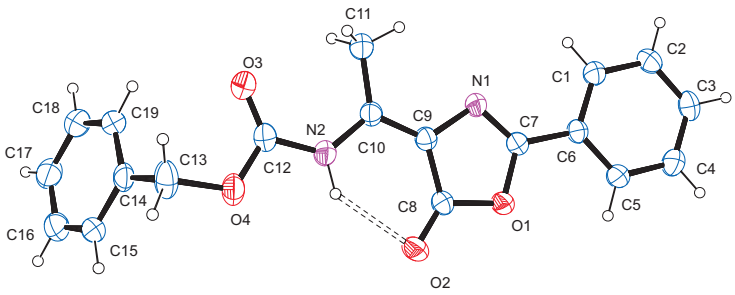
2g

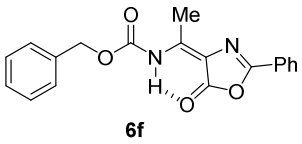




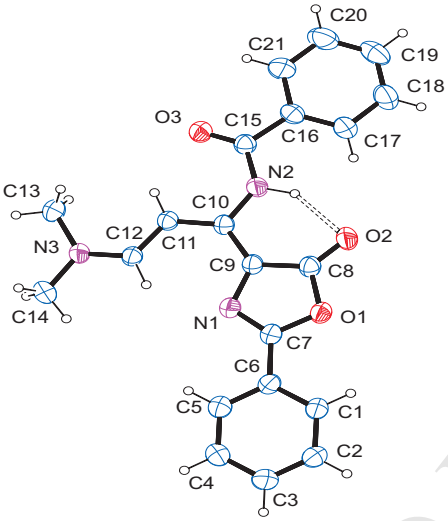
6d

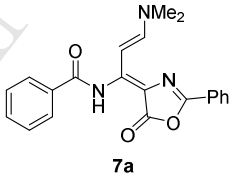




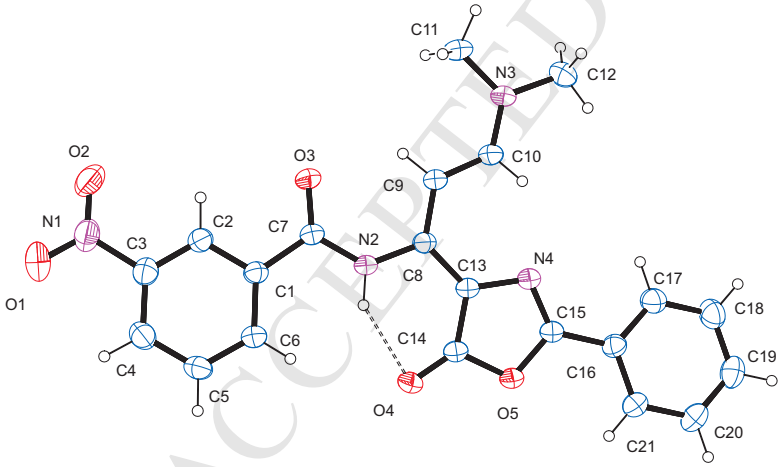


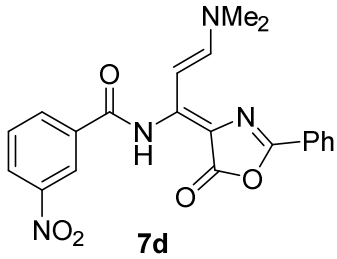
6f





7a





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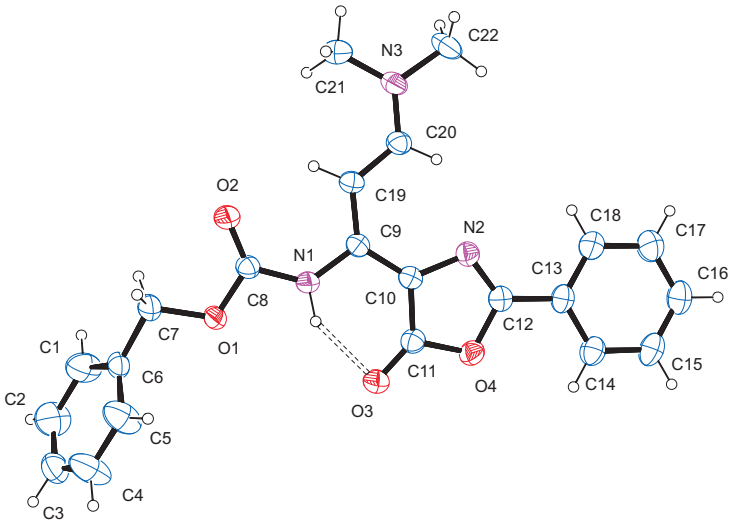

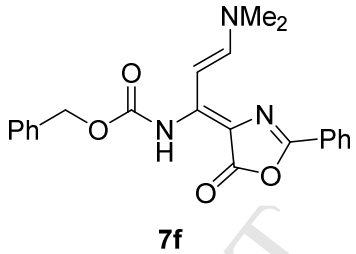

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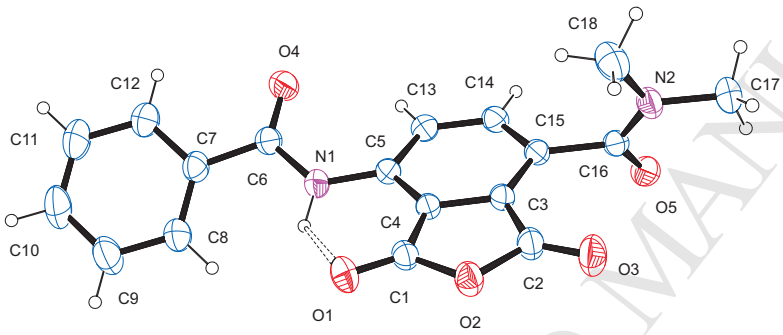
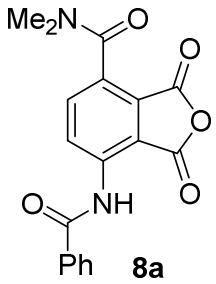




8a

Figure 1: ORTEP view of compounds **2c, 2g**, **6b**, **6d**, **6f**, **7a**, **7d**, **7f**, **8a**

5. Experimental

5.1 General

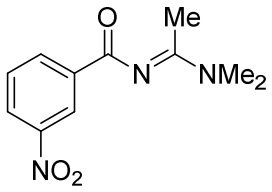
Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting point system. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C and on a Bruker Avance III UltraShield 500 plus at 500 MHz for ^{1}H and 126 MHz for ^{13}C, using $CDCl_3$ and DMSO-d_6 with Me_4Si as the internal standard, as solvents. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS spectrometer, IR spectra on a Perkin Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II. Column chromatography (CC) was performed on silica gel (Fluka, Silica gel 60, particle size 35-70 μm).

Microwave irradiations were performed on CEM Corporation Discover microwave unit. Column chromatography was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm).

5.2 General procedure for the preparation of (*E*)-*N*-(1-(dimethylamino)ethylidene)-carboxamides

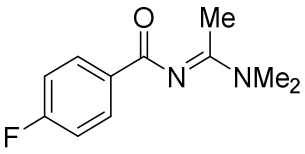
The starting amides (30.0 mmol) were suspended in toluene (40 mL) and 1.5 equivalents of *N*,*N*-dimethylacetamide dimethyl acetal (45.0 mmol) were added. The reaction mixture was refluxed for 2-10 h. The reaction mixture was then cooled. Generally, the corresponding products deposited upon cooling and were thus collected via vacuum filtration and washed with diethyl ether to remove any impurities. In other cases, the volatile components were removed under reduced pressure and the products were obtained and purified with column chromatography, using various mixtures of ethyl acetate/petroleum ether as the eluent.

*5.2.1 (E)-N-(1-(Dimethylamino)ethylidene)-3-nitrobenzamide (**2d**)*



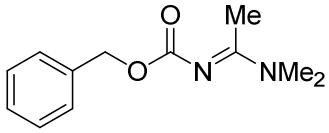
Prepared from 3-nitrobenzamide (**1d**; 4.980 g, 30.0 mmol), reflux for 8 h. The product was isolated from the reaction mixture via vacuum filtration, which was followed by washing with diethyl ether. Yield: 69% (4.871 g), off-white solid; mp = 92.7-96.4 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.40 (3H, s, CH_3); 3.19 (3H, s, N(CH_3)$_2$); 3.27 (3H, s, N(CH_3)$_2$); 7.57 (1H, t, J = 7.9 Hz, 5-C*H*); 8.30 (1H, dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 4-C*H*); 8.46-8.49 (1H, m, 6-C*H*); 8.96 (1H, br. s, 2-C*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.8, 38.7, 124.5, 125.6, 128.9, 135.1, 139,7, 148.1, 167.6, 172.8. EA $C_{11}H_{13}N_3O_3$ requires: C 56.16; H 5.57; N 17.86. Found: C 55.90; H 5.49; N 17.81. EI-HRMS: *m/z* = 236.1030 (MH^+) found; $C_{11}H_{14}N_3O_3$ calculated: *m/z* = 236.1030 (MH^+). ν_{max} 3365, 3162, 3084, 1711, 1616, 1565, 1521, 1398, 1367, 1343, 1308, 1238, 1191, 1070, 1017, 951, 822, 702.

*5.2.2 (E)-N-(1-(Dimethylamino)ethylidene)-4-fluorobenzamide (**2e**)*



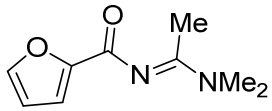
Prepared from 4-fluorobenzamide (**1e**; 330 mg, 2.37 mmol), reflux for 8 h. The product was isolated and purified with column chromatography, using a 2:1 mixture of ethyl acetate and petroleum ether as the mobile phase. Yield: 98% (493 mg), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.30 (3H, s, CH_3); 3.08 (3H, br. s, N(CH_3)$_2$); 3.16 (3H, br. s, N(CH_3)$_2$); 7.02-7.08 (2H, m, 3-C*H* and 4-C*H*); 8.12-8.18 (2H, m, 2-C*H* and 6-C*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.4, 38.2, 38.3, 114.6 (d, J = 21.5 Hz), 131.7 (d, J = 8.9 Hz), 133.9 (br. s), 164.8 (d, J = 250 Hz), 174.6. EI-HRMS: m/z = 209.1086 (MH^+) found; $C_{11}H_{14}FN_2O$ calculated: m/z = 209.1085 (MH^+). ν_{max} 3065, 2929, 2894, 1621, 1555, 1497, 1421, 1395, 1305, 1293, 1237, 1212, 1143, 1085, 1021, 936, 847, 806, 768, 685.

*5.2.3 Benzyl (E)-(1-(dimethylamino)ethylidene)carbamate (**2f**)*



Prepared from benzyl carbamate (**1f**; 3.078 g, 20.40 mmol), reflux for 4 h. The product was isolated from the reaction mixture with column chromatography, using a 4:1 mixture of ethyl acetate and petroleum ether as the mobile phase. Yield: 63% (2.816 g), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.24 (3H, s, C*H*$_3$); 3.04 (3H, br. s, N(C*H*$_3$)$_2$); 3.06 (3H, br. s, N(C*H*$_3$)$_2$); 5.14 (2H, s, C*H*$_2$); 7.25-7.30 (1H, m, 4*H*-Ph); 7.30-7.37 (2H, m, 3*H*-Ph and 5*H*-Ph); 7.39-7.43 (2H, m, 2*H*-Ph and 6*H*-Ph). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.3, 38.3, 38.6, 67.2, 127.8, 128.2, 128.3, 137.1, 162.5, 166.3. EI-HRMS: *m/z* = 221.1284 (MH^+) found; $C_{12}H_{17}N_2O_2$ calculated: *m/z* = 221.1285 (MH^+). ν_{max} 3031, 2932, 2894, 2819,1665, 1571, 1497, 1453, 1422, 1399, 1372, 1283, 1210, 1184, 1049, 1020, 809, 740, 698.

*5.2.4 (E)-N-(1-(Dimethylamino)ethylidene)furan-2-carboxamide (**2g**).*

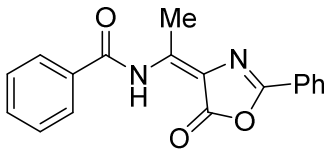


Prepared from furan-2-carboxamide (**1f**; 164 mg, 1.48 mmol), reflux for 2 h. Volatile components were removed under *vacuo*, the residue was dissolved in H_2O (20 mL) and extracted with dichloromethane (3 x 5 mL). The organic phases were collected, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the final product. Yield: 94% (250 mg), brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.35 (3H, s, C*H*$_3$); 3.12 (3H, s, N(C*H*$_3$)$_2$); 3.19 (3H, s, N(C*H*$_3$)$_2$); 6.46 (1H, dd, J_1 = 3.4 Hz, J_2 = 1.7 Hz, 4-C*H*); 7.07 (1H, dd, J_1 = 3.4 Hz, J_2 = 0.9 Hz, 3-C*H*); 7.52 (1H, dd, J_1 = 1.7 Hz, J_2 = 0.9 Hz, 5-C*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.9, 38.5, 111.6, 115.6, 144.9, 152.3, 166.7, 167.5. EA $C_9H_{12}N_2O_2$ requires: C 59.99; H 6.71; N 15.55. Found: C 59.85; H 6.83; N 15.35. EI-HRMS: *m/z* = 181.0970 (MH^+) found; $C_9H_{13}N_2O_2$ calculated: *m/z* = 181.0972 (MH^+). ν_{max} 2927, 2878, 1611, 1574, 1551, 1501, 1470, 1421, 1387, 1310, 1259, 1196, 1166, 1113, 1024, 1008, 946, 823, 763.

5.3. General procedure for the preparation of substituted-*N*-(1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)ethyl)benzamides:

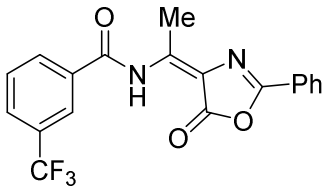
Hippuric acid (1.200 g, 6.70 mmol) was added to acetic anhydride (8 mL). The reaction mixture was heated to 85 °C and stirred vigorously until the reaction mixture became yellow in appearance, meaning that the 2-phenyloxazol-5(4*H*)-one had formed *in situ*. Immediate addition of *N*-(1-(dimethylamino)ethylidene)-carboxamides (4.44 mmol) followed. The reaction mixture was than stirred at 85 °C for 0.5-4 h. The reaction mixture was then cooled to room temperature, upon which the products participated from the reaction mixture. The products were filtered off and washed with cold ethanol.

*5.3.1. N-(1-(5-Oxo-2-phenyloxazol-4(5H)-ylidene)ethyl)benzamide (**6a**).*



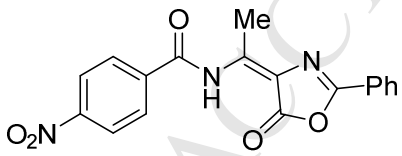
Prepared from *N*-(1-(dimethylamino)ethylidene)benzamide (**2a**; 293 mg, 1.50 mmol) and hippuric acid (415 mg, 2.30 mmol) in acetic anhydride (3 mL). Stirred at 85 °C for 1 h, then cooled to room temperature. The product was filtered and washed with cold ethanol. Yield: 67% (310 mg), white-yellowish solid; mp = 154.0-155.8 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.01 (3H, s, C*H*$_3$); 7.46-7.50 (3H, m, Ph); 7.52-7.56 (2H, m, Ph); 7.60-7.64 (1H, m, Ph); 8.02-8.06 (4H, m, Ph); 11.40 (1H, br. s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.0, 188.8, 126.1, 127.2, 127.5, 127.8, 128.9, 129.1, 132.0, 133.2, 152.3, 156.8, 165.5, 168.0. EA $C_{18}H_{14}N_2O_3$ requires: C 70.58; H 4.61; N 9.15. Found: C 70.28; H 4.73; N 9.15. EI-HRMS: *m/z* = 307.1073 (MH^+) found; $C_{18}H_{15}N_2O_3$ calculated: *m/z* = 307.1077 (MH^+). ν_{max} 3373, 3065, 3005, 1781, 1727, 1696, 1639, 1597, 1587, 1525, 1488, 1447, 1423, 1388, 1343, 1320, 1291, 1242, 1217, 1168, 1065, 1007, 871, 775.

5.3.2. *(E)-N-(1-(5-Oxo-2-phenyloxazol-4(5H)-ylidene)ethyl)-3-(trifluoromethyl)benzamide (**6b**).*



Prepared from *N*-(1-(dimethylamino)ethylidene)-3-(trifluoromethyl)benzamide (**2b**; 612 mg, 2.37 mmol) and hippuric acid (636 mg, 3.56 mmol) in acetic anhydride (4 mL). Stirred at 85 °C for 4 h, then cooled to room temperature. Volatile components were removed under reduced pressure and the product was obtained from the residue with flash chromatography, using ethyl acetate : petroleum ether = 1:5 as the mobile phase. Yield: 67% (593 mg), yellow solid; mp = 116.0-120.7 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.02 (3H, s, C*H*$_3$); 7.47-7.51 (2H, m, Ph); 7.51-7.55 (1H, m, Ph); 7.67-7.73 (1H, m, 5-C*H*); 7.86-7.90 (1H, m, 4-C*H*); 8.03-8.07 (2H, m, Ph); 8.18-8.21 (1H, m, 6-C*H*); 8.33 (1H, deg. t, J = 1.8 Hz, 2-C*H*); 11.46 (1H, br. s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.1, 119.6, 123.6 (q, J = 273 Hz), 125.5 (q, J = 3.8 Hz), 126.0, 127.5, 129.0, 129.8 (q, J = 3.6 Hz), 129.9, 130.5, 132.0 (q, J = 33 Hz), 132.3, 134.0, 151.8, 157.4, 164.2, 168.3. EA $C_{19}H_{13}F_3N_2O_3$ requires: C 60.97; H 3.50; N 7.48. Found: C 61.28; H 3.31; N 7.24. EI-HRMS: *m/z* = 375.0947 (MH^+) found; $C_{19}H_{14}F_3N_2O_3$ calculated: *m/z* = 375.0951 (MH^+). ν_{max} 3063, 3023, 2936, 1786, 1728, 1697, 1639, 1599, 1522, 1490, 1443, 1331, 1320, 1232, 1212, 1150, 1111, 1071, 1062, 997, 953, 884, 805, 771, 738, 682.

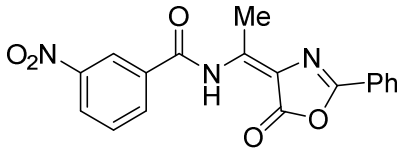
5.3.3. *4-Nitro-N-(1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)ethyl)benzamide (**6c**).*



Prepared from *N*-(1-(dimethylamino)ethylidene)-4-nitrobenzamide (**2c**; 1.040 g, 4.44 mmol) and hippuric acid (1.200 g, 6.70 mmol) in acetic anhydride (8 mL). Stirred at 85 °C for 1 h, then cooled to room temperature. The product was filtered and washed with cold ethanol. Yield: 75% (1.174 g), yellow solid; mp = 250.0-253.4 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.02 (3H, s, C*H*$_3$); 7.48-7.53 (2H, m, Ph); 7.54-7.59 (1H, m, Ph); 8.04-8.08 (2H, m, Ph); 8.19-8.23 (2H, m, 2-C*H* and 6-C*H*); 8.38-8.42 (2H, m, 3-C*H* and 5-C*H*) 11.49 (1H, br. s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.1, 120.0, 124.4, 125.9, 127.5, 129.1, 129.2, 132.5, 138.5,

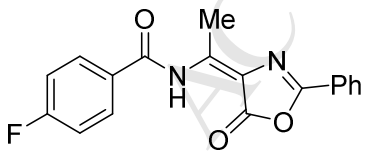
149.8, 150.6, 157.7, 166.4, 168.3. EA $C_{18}H_{13}N_3O_5$ requires: C 61.54; H 3.73; N 11.96. Found: C 61.45; H 3.52; N 11.97. EI-HRMS: *m/z* = 352.0923 (MH^+) found; $C_{18}H_{14}N_3O_5$ calculated: *m/z* = 352.0928 (MH^+). ν_{max} 3073, 1737, 1700, 1642, 1599, 1518, 1482, 1446, 1382, 1339, 1322, 1240, 1214, 1086, 1064, 1004, 871, 847, 727, 695, 670, 660.

*5.3.4. (E)-3-Nitro-N-(1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)ethyl)benzamide (**6d**).*



Prepared from *N*-(1-(dimethylamino)ethylidene)-3-nitrobenzamide (**2d**; 1.040 g, 4.44 mmol) and hippuric acid (1.200 g, 6.70 mmol) in acetic anhydride (8 mL). Stirred at 85 °C for 1 h, then cooled to room temperature. The product was filtered and washed with cold ethanol. Yield: 58% (898 mg), yellow solid; mp = 181.5-185.8 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.02 (3H, s, C*H*$_3$); 7.47-7.52 (2H, m, Ph); 7.53-7.58 (1H, m, Ph); 7.77 (1H, t, *J* = 8.0 Hz, 5-C*H*); 8.03-8.07 (2H, m, Ph); 8.32 (1H, dt, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 4-C*H*); 8.47 (1H, ddd, J_1 = 8.4 Hz, J_2 = 2.2 Hz, J_3 = 1.0 Hz, 6-C*H*); 8.91 (1H, t, *J* = 2.0 Hz, 2-C*H*); 11.50 (1H, br. s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.9, 119.8, 123.4, 125.8, 127.3, 127.4, 128.9, 130.4, 132.3, 132.8, 134.8, 148.8, 151.2, 157.5, 163.2, 168.2. EA $C_{18}H_{13}N_3O_5$ requires: C 61.54; H 3.73; N 11.96. Found: C 61.77; H 3.69; N 11.91. EI-HRMS: *m/z* = 352.0923 (MH^+) found; $C_{18}H_{14}N_3O_5$ calculated: *m/z* = 352.0928 (MH^+). ν_{max} 3033, 1787, 1734, 1698, 1644, 1597, 1518, 1448, 1381, 1322, 1292, 1236, 1224, 1179, 1113, 1077, 1064, 1004, 883, 777, 709, 697.

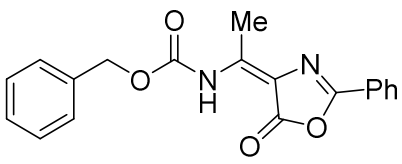
*5.3.5. 4-Fluoro-N-(1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)ethyl)benzamide (**6e**).*



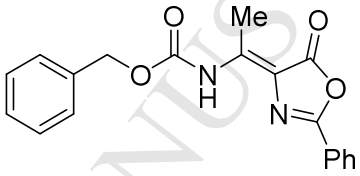
Prepared from *N*-(1-(dimethylamino)ethylidene)-4-fluorobenzamide (**2e**; 480 mg, 2.30 mmol) and hippuric acid (620 mg, 3.46 mmol) in acetic anhydride (3.5 mL). Stirred at 85 °C for 30 min, then cooled to room temperature. The product was filtered and washed with a small amount of cold ethanol. Yield: 53% (397 mg), yellow solid; mp = 167.2-168.9 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.00 (3H, s, C*H*$_3$); 7.19-7.24 (2H, m, 3-C*H* and 5-C*H*); 7.46-7.50 (2H,

m, Ph); 7.51-7.54 (1H, m, Ph); 8.02-8.07 (4H, m, 2-C*H* and 6-C*H* and Ph); 11.37 (1H, br. s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.1, 116.4 (d, J = 22 Hz), 119.0, 126.1, 127.3, 129.0, 129.3 (d, J = 3.1 Hz), 130.5 (d, J = 9.4 Hz), 132.2, 152.3, 157.0, 164.5, 165.9 (d, J = 255 Hz), 168.2. EA $C_{18}H_{13}FN_2O_3$ requires: C 66.66; H 4.04; N 8.64. Found: C 66.70; H 3.79; N 8.65. EI-HRMS: m/z = 325.0979 (MH^+) found; $C_{18}H_{14}FN_2O_3$ calculated: m/z = 325.0983 (MH^+). ν_{max} 3363, 3076, 3000, 1781, 1740, 1698, 1643, 1598, 1590, 1517, 1481, 1387, 1342, 1320, 1301, 1232, 1223, 1167, 1084, 1069, 989, 947, 877, 773, 752, 693, 680, 664, 643.

*5.3.6. Benzyl (E)-(1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)ethyl)carbamate and benzyl (Z)-(1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)ethyl)carbamate (**6f**).*



(*E*)-isomer



(*Z*)-isomer

Prepared from benzyl (*E*)-(1-(dimethylamino)ethylidene)carbamate (**2f**; 268 mg, 1.22 mmol) and hippuric acid (328 mg, 1.83 mmol) in acetic anhydride (2 mL). Stirred at 85 °C for 2 h, then cooled to room temperature. The product was filtered and washed with cold ethanol. The product was found to be a mixture of stereoisomers in a 1:1.5 ratio, based on NMR evidence, where the (*E*)-isomer was the major isomer. Yield: 41% (170 mg), white solid; mp = 122.3-124.7 °C (mixture).

EA $C_{19}H_{16}N_2O_4$ requires: C 67.85; H 4.80; N 8.33. Found: C 67.77; H 4.81; N 8.38. EI-HRMS: m/z = 337.1181 (MH^+) found; $C_{19}H_{17}N_2O_4$ calculated: m/z = 337.1183 (MH^+). ν_{max} 3363, 3304, 3037, 2973, 1778, 1747, 1729, 1651, 1597, 1490, 1426, 1394, 1320, 1295, 1257, 1193, 1158, 1058, 1043, 1031, 977, 873, 753, 689.

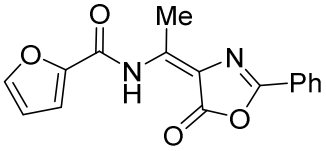
(*E*)-isomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.84 (3H, s, CH_3); 5.22 (2H, s, CH_2); 7.36-7.44 (5H, m, Ph); 7.45-7.48 (2H, m, Ph); 7.49-7.53 (1H, m, Ph); 7.99-8.03 (2H, m, Ph); 9.96 (1H, br. s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.3, 68.2, 117.5, 126.3, 127.2, 128.7, 128.8, 128.9, 129.0, 132.0, 135.1, 151.9, 152.4, 156.6, 167.5.

(*Z*)-isomer:

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.88 (3H, s, CH_3); 5.23 (2H, s, CH_2); 7.36-7.44 (5H, m, Ph); 7.45-7.48 (2H, m, Ph); 7.49-7.53 (1H, m, Ph); 7.98-8.02 (2H, m, Ph); 8.42 (1H, br. s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9, 68.3, 116.4, 126.0, 127.5, 128.8, 128.9, 129.0, 129.1, 132.3, 135.1, 148.6, 151.8, 156.7, 166.0.

*5.3.7. N-(1-(5-Oxo-2-phenyloxazol-4(5H)-ylidene)ethyl)furan-2-carboxamide (**6g**).*

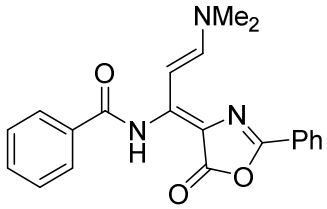


Prepared from *N*-(1-(dimethylamino)ethylidene)furan-2-carboxamide (**2g**; 180 mg, 1.00 mmol) and hippuric acid (268 mg, 1.50 mmol) in acetic anhydride (2.5 mL). Stirred at 85 °C for 2 h, then cooled to room temperature. The product was filtered and washed with a small amount of cold ethanol. Yield: 61% (182 mg), yellowish solid; mp = 136.2-143.5 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.97 (3H, s, CH_3); 6.60 (1H, dd, J_1 = 3.4 Hz, J_2 = 1.7 Hz, 3-C*H*); 7.33 (1H, dt, J_1 = 3.4 Hz, J_2 = 0.7 Hz, 4-C*H*); 7.45-7.55 (3H, m, Ph); 7.65 (1H, dd, J_1 = 1.7 Hz, J_2 = 0.7 Hz, 5-C*H*); 8.01-8.05 (2H, m, Ph); 11.33 (1H, br. s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.1, 113.0, 117.6, 118.9, 126.2, 127.4, 129.0, 132.1, 146.2, 147.0, 151.3, 156.4, 157.1, 167.6. EA $C_{16}H_{12}N_2O_4$ requires: C 64.86; H 4.08; N 9.46. Found: C 64.19; H 3.98; N 9.24. EI-HRMS: *m/z* = 297.0869 (MH^+) found; $C_{16}H_{13}N_2O_4$ calculated: *m/z* = 297.0870 (MH^+). ν_{max} 3061, 1735, 1696, 1643, 1582, 1504, 1492, 1468, 1446, 1381, 1337, 1277, 1264, 1213, 1156, 1088, 1065, 1004, 953, 882, 845, 765, 736, 693.

5.4. General procedure for the preparation of *N*-(3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)allyl)-(substituted)benzamides and benzyl (3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)allyl)carbamate:

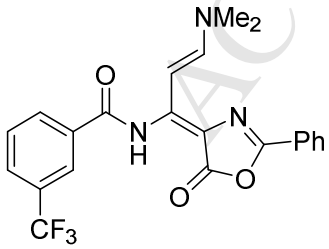
The starting compounds (1.00 mmol) were dissolved in anhydrous toluene (4 mL) and *N*,*N*-dimethylformamide dimethyl acetal (2.00 mmol) were added. The reaction mixture was heated to 90 °C and vigorously stirred for 30 min–2 h. The reaction mixture was then cooled to room temperature, upon which the products deposited from the reaction mixture as solids. The products were collected by vacuum filtration and thoroughly washed with diethyl ether, to remove any present impurities.

*5.4.1. N-((1E,2E)-3-(Dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)allyl)benzamide (**7a**).*



Prepared from *N*-(1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)ethyl)benzamide (**6a**; 2.035 g, 6.65 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (1.76 mL, 13.30 mmol) in anhydrous toluene (25 mL). Heated to 90 °C for 2 h, then cooled to room temperature. The product was filtered and washed with diethyl ether to remove any present impurities. Yield: 85% (2.040 g), crimson solid; mp = 180.4-184.2 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.11 (3H, s, N(C*H*$_3$)$_2$); 3.35 (3H, s, N(C*H*$_3$)$_2$); 7.08 (1H, d, *J* = 12.6 Hz, 2'-C*H*); 7.40-7.45 (3H, m, Ph); 7.49-7.54 (2H, m, Ph); 7.55-7.60 (1H, m, Ph); 7.93-7.98 (2H, m, Ph); 8.10-8.14 (2H, m, Ph); 9.35 (1H, d, *J* = 12.6 Hz, 3'-C*H*); 11.91 (1H, s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.2, 46.5, 90.0, 100.1, 108.5, 126.2, 128.0, 128.8, 129.0, 130.3, 132.6, 134.4, 151.7, 152.0, 159.9, 167.0, 168.6. EA $C_{21}H_{19}N_3O_3$ requires: C 69.79; H 5.30; N 11.63. Found: C 69.63; H 5.19; N 11.62. EI-HRMS: *m/z* = 362.1495 (MH^+) found; $C_{21}H_{20}N_3O_3$ calculated: *m/z* = 362.1499 (MH^+). ν_{max} 3322, 3060, 1696, 1663, 1604, 1591, 1546, 1499, 1464, 1443, 1405, 1383, 1323, 1272, 1258, 1244, 1116, 1095, 1058, 1023, 982, 899, 854, 761, 689.

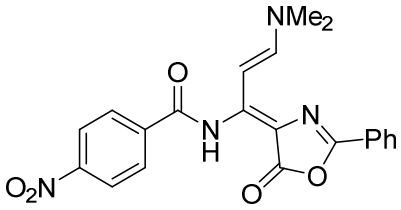
*5.4.2. N-3-(Dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)allyl)-3-(trifluoromethyl) benzamide (**7b**).*



Prepared from *N*-(1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)ethyl)-3-(trifluoromethyl)benzamide (**6b**; 300 mg, 0.80 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (212 µL, 1.60 mmol) in anhydrous toluene (4 mL). Heated to 90 °C for 2 h, then cooled to room temperature. The product was filtered and washed with diethyl ether to remove any

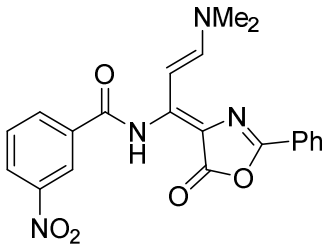
present impurities. Yield: 37% (127 mg), red solid; mp = 205.8-207.4 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.14 (3H, s, N(C*H*$_3$)$_2$); 3.39 (3H, s, N(C*H*$_3$)$_2$); 7.07 (1H, d, *J* = 12.6 Hz, 2'-C*H*); 7.44-7.49 (3H, m, Ph); 7.69 (1H, t, *J* = 7.8 Hz, 5-C*H*); 7.83-7.87 (1H, m, 4-C*H*); 7.96-8.01 (2H, m, Ph); 8.33-8.37 (1H, m, 6-C*H*); 8.43 (1H, br. s, 2-C*H*); 9.40 (1H, d, *J* = 12.6 Hz, 3'-C*H*); 12.05 (1H, s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.1, 46.5, 89.8, 108.5, 123.7 (q, *J* = 271 Hz), 125.4 (q, *J* = 3.8 Hz), 126.1, 127.2, 128.7, 128.9 (q, *J* = 3.2 Hz), 129.6, 130.3, 131.5 (q, *J* = 33 Hz), 135.1, 151.1, 152.1, 159.9, 165.3, 168.6. EA $C_{22}H_{18}F_3N_3O_3$ requires: C 61.54; H 4.23; N 9.79. Found: C 61.59; H 4.19; N 9.74. EI-HRMS: *m/z* = 430.1370 (MH^+) found; $C_{22}H_{19}F_3N_3O_3$ calculated: *m/z* = 430.1373 (MH^+). ν_{max} 3134, 3060, 1665, 1631, 1606, 1592, 1471, 1441, 1406, 1382, 1328, 1276, 1252, 1218, 1187, 1166, 1119, 1100, 1063, 982, 925, 854, 806, 761, 714, 693.

*5.4.3. N-3-(Dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)allyl)-4-nitrobenzamide (**7c**).*



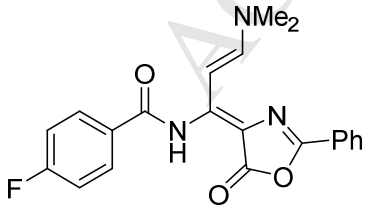
Prepared from 4-nitro-*N*-(1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)ethyl)benzamide (**6c**; 689 mg, 1.96 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (520 µL, 3.92 mmol) in anhydrous toluene (4 mL). Heated to 90 °C for 1 h, then cooled to room temperature. The product was filtered and washed with diethyl ether to remove any present impurities. Yield: 90% (717 mg), gray-greenish solid; mp = 245.4-246.7 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.13 (3H, s, N(C*H*$_3$)$_2$); 3.38 (3H, s, N(C*H*$_3$)$_2$); 7.01 (1H, d, *J* = 12.5 Hz, 2'-C*H*); 7.42-7.46 (3H, m, Ph); 7.94-7.98 (2H, m, Ph); 8.26-8.30 (2H, m, 2-C*H* and 6-C*H*); 8.34-8.37 (2H, m, 3-C*H* and 5-C*H*); 9.38 (1H, d, *J* = 12.5 Hz, 3'-C*H*); 12.07 (1H, s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.3, 46.7, 89.9, 108.8, 124.2, 126.3, 127.2, 128.9, 129.2, 130.5, 139.8, 150.2, 150.9, 152.4, 160.2, 164.8, 168.7. EA $C_{21}H_{18}N_4O_5$*$\frac{1}{15}$ H_2O requires: C 61.88; H 4.48; N 13.75. Found: C 61.59; H 4.18; N 13.59. EI-HRMS: *m/z* = 407.1341 (MH^+) found; $C_{21}H_{19}N_4O_5$ calculated: *m/z* = 407.1350 (MH^+). ν_{max} 3118, 3055, 2894, 2855, 1680, 1606, 1585, 1493, 1469, 1442, 1407, 1378, 1335, 1286, 1255, 1236, 1174, 1094, 1069, 1056, 978, 896, 859, 850, 763, 692.

*5.4.4. N-((1E,2E)-3-(Dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)allyl)-3-nitrobenzamide (**7d**).*



Prepared from (*E*)-3-nitro-*N*-(1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)ethyl)benzamide (**6d**; 90 mg, 0.26 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (70 µL, 0.52 mmol) in anhydrous toluene (2 mL). Heated to 90 °C for 30 min, then cooled to room temperature. The product was filtered and washed with diethyl ether to remove any present impurities. Yield: 93% (106 mg), red solid; mp = 224.1-227.3 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.13 (3H, s, N(C*H*$_3$)$_2$); 3.38 (3H, s, N(C*H*$_3$)$_2$); 7.01 (1H, d, J = 12.5 Hz, 2'-C*H*); 7.42-7.46 (3H, m, Ph); 7.72 (1H, t, J = 8.0 Hz, 5-C*H*); 7.92-7.96 (2H, m, Ph); 8.41 (1H, ddd, J_1 = 8.2 Hz, J_2 = 2.2 Hz, J_3 = 1.0 Hz, 6-C*H*); 8.46 (1H, dt, J_1 = 7.8 Hz, J_2 = 1.3 Hz, 4-C*H*); 8.98 (1H, t, J = 2.0 Hz, 2-C*H*); 9.37 (1H, d, J = 12.5 Hz, 3'-C*H*); 12.09 (1H, s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.3, 46.7, 89.9, 108.8, 123.7 126.3, 126.9, 127.3, 128.8, 130.3, 130.5, 133.0, 136.2, 148.8, 151.0, 152.4, 160.2, 164.4, 168.8. EA $C_{21}H_{18}N_4O_5$ requires: C 62.06; H 4.46; N 13.79. Found: C 62.00; H 4.27; N 13.76. EI-HRMS: *m/z* = 407.1345 (MH^+) found; $C_{21}H_{19}N_4O_5$ calculated: *m/z* = 407.1350 (MH^+). ν_{max} 3135, 2915, 1665, 1625, 1590, 1527, 1487, 1467, 1445, 1400, 1383, 1346, 1329, 1297, 1258, 1216, 1171, 1124, 1108, 1085, 1064, 977, 903, 850, 813, 759, 711.

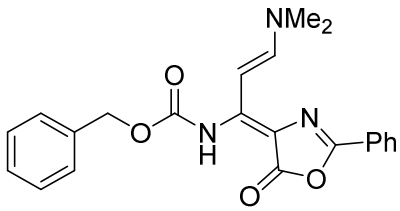
*5.4.5. N-3-(Dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)allyl)-4-fluorobenzamide (**7e**).*



Prepared from 4-fluoro-*N*-(1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)ethyl)benzamide (**6e**; 324 mg, 1.00 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (265 µL, 2.00 mmol) in anhydrous toluene (4 mL). Heated to 90 °C for 2 h, then cooled to room temperature. The product was filtered and washed with diethyl ether to remove any present impurities. Yield:

97% (370 mg), orange solid; mp = 218.1-220.0 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.08 (3H, s, N(C*H*$_3$)$_2$); 3.33 (3H, s, N(C*H*$_3$)$_2$); 7.04 (1H, d, *J* = 12.6 Hz, 2'-C*H*); 7.15-7.21 (2H, m, 3-C*H* and 5-C*H*); 7.40-7.45 (3H, m, Ph); 7.92-7.96 (2H, m Ph); 8.12-8.16 (2H, m, 2-C*H* and 6-C*H*); 9.34 (1H, d, *J* = 12.6 Hz, 3'-C*H*); 11.89 (1H, s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.2, 46.5, 89.9, 108.4, 116.1 (d, *J* = 22 Hz), 126.2, 127.4, 128.8, 130.3, 130.5 (d, *J* = 9.0 Hz), 130.6, 151.6, 151.9, 160.0, 165.6 (d, *J* = 229 Hz), 165.8, 168.6. EA $C_{21}H_{18}FN_3O_3$ requires: C 66.48; H 4.78; N 11.08. Found: C 66.41; H 4.88; N 11.06. EI-HRMS: *m/z* = 380.1396 (MH^+) found; $C_{21}H_{19}FN_3O_3$ calculated: *m/z* = 380.1405 (MH^+). ν_{max} 3123, 3072, 2922, 1659, 1622, 1590, 1508, 1459, 1448, 1375, 1259, 1228, 1164, 1117, 1095, 1055, 981, 897, 851, 844, 761, 742, 693, 672.

*5.4.6. Benzyl ((1E,2E)-3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5H)-ylidene)allyl)carbamate (**7f**).*

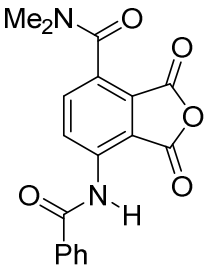


Prepared from benzyl (1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)ethyl)carbamate (**6f**; 131 mg, 0.39 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (104 µL, 0.78 mmol) in anhydrous toluene (1 mL). Heated to 90 °C for 30 min, then cooled to room temperature. The product was filtered and washed with diethyl ether to remove any present impurities. Yield: 94% (144 mg), orange solid; mp = 206.7-210.5 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.04 (3H, s, N(C*H*$_3$)$_2$); 3.31 (3H, s, N(C*H*$_3$)$_2$); 5.20 (2H, s, C*H*$_2$); 6.55 (1H, d, *J* = 12.6 Hz, 2'-C*H*); 7.33-7.45 (8H, m, Ph); 7.91-7.95 (2H, m, Ph); 9.25 (1H, d, *J* = 12.6 Hz, 3'-C*H*); 10.58 (1H, s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.1, 46.4, 67.4, 88.6, 107.4, 126.1, 127.5, 128.4, 128.5, 128.7, 128.8, 130.2, 135.8, 151.6, 151.8, 153.5, 159.3, 168.1. EA $C_{22}H_{21}N_3O_4$ requires: C 67.51; H 5.41; N 10.74. Found: C 67.73; H 5.21; N 10.74. EI-HRMS: *m/z* = 392.1602 (MH^+) found; $C_{22}H_{22}N_3O_4$ calculated: *m/z* = 392.1605 (MH^+). ν_{max} 3087, 2915, 1736, 1668, 1612, 1592, 1493, 1461, 1402, 1378, 1276, 1245, 1227, 1195, 1180, 1114, 1087, 1069, 1018, 978, 905, 850, 783, 746, 667.

5.5. General procedure for the preparation of *N*,*N*-dimethyl-7-(substituted)-1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamides and benzyl (7-(dimethylcarbamoyl)-1,3-dioxo-1,3-dihydroisobenzofuran-4-yl)carbamate:

The starting compounds (0.30 mmol) were placed in a microwave tube and were dissolved in 1 mL of anhydrous toluene. Next, 1.2 equvialents of maleic anhydride was added (0.33 mmol) and the reaction mixture was placed in a CEM Microwave unit. The reaction temperature varied from 160-180 °C, Power max option was set to OFF, maximum allowed pressure was set to 16 bar, irradiation power 300 W, reaction times were between 15-50 min. The microwave tube, along with its contents was left to cool to room temperature. Deposition of the product from the reaction mixture was assisted by scratching the walls of the cooled microwave tube with a glass stick. If the product did not participate from the reaction mixture at room temperature, additional cooling of the microwave tube and its contents was applied by immersing it in to an ice bath. The participated products were filtered and thoroughly washed with diethyl ether to remove any present impurities.

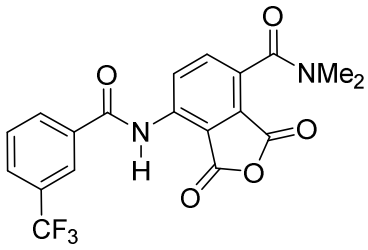
*5.5.1. 7-Benzamido-N,N-dimethyl-1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamide (**8a**)*



Prepared from *N*-((1*E*,2*E*)-3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)allyl)benzamide (**7a**; 100 mg, 0.28 mmol) and maleic anhydride (33 mg, 0.33 mmol) in anhydrous toluene (1 mL). The reaction mixture was heated under microwave irradiation at 180 °C for 40 min, cooled in an ice bath. The participated product was filtered and washed with diethyl ether. Yield: 48% (46 mg), brown solid; mp = 247.8-251.5 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.93 (3H, s, N(CH_3)$_2$); 3.21 (3H, s, N(CH_3)$_2$); 7.56-7.61 (2H, m, Ph); 7.64-7.70 (1H, m, Ph); 7.85 (1H, d, *J*= 8.6 Hz, 6-C*H*); 8.00-8.04 (2H, m, Ph); 9.18 (1H, d, *J* = 8.6 Hz, 5-C*H*); 10.14 (1H, s, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.3, 38.5, 115.6, 126.5, 126.7, 127.6, 129.4, 130.5, 132.8, 133.4, 137.3, 139.6, 160.4, 164.7, 165.4, 165.8. EA $C_{18}H_{14}N_2O_5*\frac{1}{6}H_2O$ requires: C 63.34; H 4.23; N 8.21. Found: C 63.37; H 3.89; N 7.99. EI-HRMS: *m/z* =

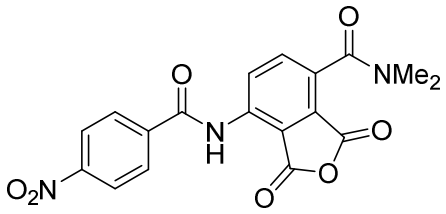
339.0976 (MH^+) found; $C_{18}H_{15}N_2O_5$ calculated: *m/z* = 339.0975 (MH^+). ν_{max} 3365, 3056, 2930, 1842, 1767, 1689, 1628, 1594, 1516, 1489, 1415, 1295, 1255, 1239, 1201, 1149, 1112, 1090, 1068, 1030, 933, 859, 701, 685.

*5.5.2. N,N-Dimethyl-1,3-dioxo-7-(3-(trifluoromethyl)benzamido)-1,3-dihydroisobenzofuran-4-carboxamide (**8b**).*



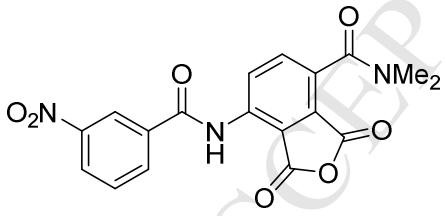
Prepared from *N*-3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)allyl)-3-(trifluoromethyl)benzamide (**7b**; 55 mg, 0.13 mmol) and maleic anhydride (19 mg, 0.20 mmol) in anhydrous toluene (0.7 mL). The reaction mixture was heated under microwave irradiation at 160 °C for 25 min, then cooled in an ice bath. The participated product was filtered and washed with diethyl ether. Yield: 52% (27 mg), brown solid; mp = 195.3-199.4 °C. ^{1}H NMR (d_6-DMSO, 500 MHz): δ 2.83 (3H, s, N(C*H*$_3$)$_2$); 3.06 (3H, s, N(C*H*$_3$)$_2$); 7.89 (1H, deg. t, *J* = 7.8 Hz, 5'-C*H*); 7.92 (1H, d, *J* = 8.3 Hz, 5-C*H*); 8.07-8.10 (1H, m, 4'-C*H*); 8.29-8.32 (1H, m, 6'-C*H*); 8.32-8.34 (1H, m, 2'-C*H*); 8.39 (1H, d, *J* = 8.3 Hz, 6-C*H*); 10.77 (1H, s, N*H*). ^{13}C NMR (d_6-DMSO, 125 MHz): δ 34.4, 37.9, 121.1, 123.7 (q, *J* = 270 Hz), 124.4 (q, *J* = 4.1 Hz), 127.4, 129.2 (q, *J* = 3.7 Hz), 129.6 (q, *J* = 32 Hz), 129.8, 130.4, 131.4, 131.8, 134.2, 135.3, 136.7, 161.3, 161.9, 164.1, 165.0. EA $C_{19}H_{13}F_3N_2O_5$ requires: C 56.17; H 3.23; N 6.89. Found: C 55.89; H 3.10; N 6.76. EI-HRMS: *m/z* = 407.0852 (MH^+) found; $C_{19}H_{14}F_3N_2O_5$ calculated: *m/z* = 407.0849 (MH^+). ν_{max} 2937, 1850, 1773, 1690, 1638, 1601, 1524, 1489, 1457, 1404, 1361, 1329, 1294, 1252, 1234, 1205, 1166, 1119, 1071, 902, 855, 841, 749, 736, 690, 643.

*5.5.3. N,N-Dimethyl-7-(4-nitrobenzamido)-1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamide (**8c**).*



Prepared from *N*-3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)allyl)-4-nitrobenzamide (**7c**; 59 mg, 0.15 mmol) and maleic anhydride (19 mg, 0.19 mmol) in anhydrous toluene (2 mL). The reaction mixture was heated under microwave irradiation at 160 °C for 50 min, then cooled to room temperature. The participated product was filtered and washed with diethyl ether. Yield: 42% (45 mg), brown-red solid; mp = 253.1-257.6 °C. ^{1}H NMR (d$_6$-DMSO, 500 MHz): δ 2.83 (3H, s, N(C*H*$_3$)$_2$); 3.06 (3H, s, N(C*H*$_3$)$_2$); 7.93 (1H, d, *J* = 8.3 Hz, 5-C*H*); 8.22-8.26 (2H, m, 2'-C*H* and 6-C*H*); 8.40 (1H, d, *J* = 8.3 Hz, 6-C*H*); 8.45-8.49 (2H, m, 3'-C*H* and 5'-C*H*); 10.81 (1H, s, N*H*). ^{13}C NMR (d$_6$-DMSO, 125 MHz): δ 34.4, 37.9, 121.2, 124.1, 127.5, 129.3, 129.8, 131.5, 135.4, 136.5, 138.7, 149.8, 161.3, 161.9, 163.9, 165.0. EA $C_{18}H_{13}N_3O_7$ requires: C 56.40; H 3.42; N 10.96. Found: C 56.95; H 3.16; N 10.65. EI-HRMS: *m/z* = 384.0825 (MH$^+$) found; $C_{18}H_{14}N_3O_7$ calculated: *m/z* = 384.0826 (MH$^+$). ν_{max} 3367, 3106, 2940, 1846, 1771, 1691, 1633, 1600, 1520, 1488, 1409, 1345, 1309, 1295, 1259, 1240, 1201, 1150, 1112, 1092, 1012, 901, 850, 757, 745, 678.

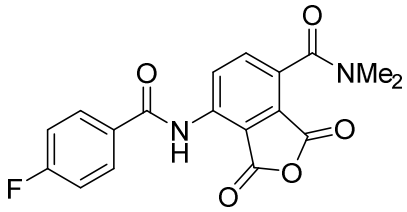
*5.5.4. N,N-Dimethyl-7-(3-nitrobenzamido)-1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamide (**8d**).*



Prepared from *N*-((1*E*,2*E*)-3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)allyl)-3-nitrobenzamide (**7d**; 50 mg, 0.12 mmol) and maleic anhydride (18 mg, 0.19 mmol) in anhydrous toluene (1 mL). The reaction mixture was heated under microwave irradiation at 160 °C for 25 min, then cooled to room temperature. The participated product was filtered and washed with diethyl ether. Yield: 41% (19 mg), brown solid; mp = 200.0-203.5 °C. ^{1}H NMR (d$_6$-DMSO, 500 MHz): δ 2.83 (3H, s, N(C*H*$_3$)$_2$); 3.06 (3H, s, N(C*H*$_3$)$_2$); 7.91-7.96 (2H, m, 5'-C*H* and 5-C*H*); 8.36 (1H, d, *J* = 8.2 Hz, 6-C*H*); 8.42-8.45 (1H, m, 6'-C*H*); 8.52-8.55 (1H, m, 4'-C*H*); 8.82 (1H, t, *J* = 1.9 Hz, 2'-C*H*); 10.90 (1H, s, N*H*). ^{13}C NMR (d$_6$-DMSO, 125

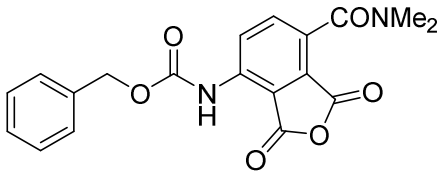
MHz): δ 34.4, 37.9, 121.4, 122.6, 127.2, 127.5, 130.1, 130.8, 131.6, 134.1, 134.6, 135.3, 136.5, 148.0, 161.3, 161.7, 163.5, 165.0. EA $C_{18}H_{13}N_3O_7*\frac{1}{6}$ toluene requires: C 57.74; H 3.62; N 10.54. Found: C 57.45; H 3.23; N 10.82. EI-HRMS: *m/z* = 384.0823 (MH^+) found; $C_{18}H_{14}N_3O_7$ calculated: *m/z* = 384.0826 (MH^+). ν_{max} 3102, 3091, 2936, 1986, 1844, 1769, 1701, 1629, 1602, 1523, 1487, 1412, 1305, 1268, 1252, 1241, 1202, 1152, 1080, 1002, 943, 905, 870, 768, 671.

*5.5.5. 7-(4-Fluorobenzamido)-N,N-dimethyl-1,3-dioxo-1,3-dihydroisobenzofuran-4-carboxamide (**8e**).*



Prepared from *N*-3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)allyl)-4-fluorobenzamide (**7e**; 53 mg, 0.14 mmol) and maleic anhydride (21 mg, 0.21 mmol) in anhydrous toluene (0.7 mL). The reaction mixture was heated under microwave irradiation at 150 °C for 15 min, then cooled to room temperature. The participated product was filtered and washed with diethyl ether. Yield: 50% (25 mg), brown solid; mp = 287.3-291.8 °C. ^{1}H NMR (d_6-DMSO, 500 MHz): δ 2.82 (3H, s, N(C*H*$_3$)$_2$); 3.05 (3H, s, N(C*H*$_3$)$_2$); 7.46-7.51 (2H, m, 2'-C*H* and 6'-C*H*); 7.90 (1H, d, *J* = 8.4 Hz, 5-C*H*); 8.06-8.11 (2H, m, 3'-C*H* and 5'-C*H*); 8.48 (1H, d, *J* = 8.4 Hz, 6-C*H*); 10.47 (1H, s, N*H*). ^{13}C NMR (d_6-DMSO, 125 MHz): δ 34.4, 37.9, 116.1 (d, *J* = 22 Hz), 120.2, 128.8, 130.5 (d, *J* = 9.4 Hz), 130.6, 130.9, 135.5, 137.2, 161.3, 162.3, 164.2, 164.7 (d, *J* = 249 Hz), 165.0. EA $C_{18}H_{13}FN_2O_5$ requires: C 60.68; H 3.68; N 7.86. Found: C 60.52; H 3.67; N 7.64. EI-HRMS: *m/z* = 357.0878 (MH^+) found; $C_{18}H_{14}FN_2O_5$ calculated: *m/z* = 357.0881 (MH^+). ν_{max} 3368, 3054, 1847, 1768, 1689, 1631, 1603, 1527, 1498, 1402, 1364, 1319, 1296, 1254, 1234, 1200, 1166, 1088, 902, 850, 755, 734, 684.

*5.5.6.Benzyl (7-(dimethylcarbamoyl)-1,3-dioxo-1,3-dihydroisobenzofuran-4-yl)carbamate (**8f**).*



Prepared from benzyl ((1*E*,2*E*)-3-(dimethylamino)-1-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)allyl)carbamate (**7f**; 59 mg, 0.15 mmol) and maleic anhydride (22 mg, 0.23 mmol) in anhydrous toluene (1 mL). The reaction mixture was heated under microwave irradiation at 160 °C for 20 min, then cooled to room temperature. The participated product was filtered and washed with diethyl ether. Yield: 34% (19 mg), brown solid; mp = 163.2-167.5 °C. ^{1}H NMR (d$_6$-DMSO, 500 MHz): δ 2.79 (3H, s, N(C*H*$_3$)$_2$); 3.03 (3H, s, N(C*H*$_3$)$_2$); 5.26 (2H, s, C*H*$_2$); 7.35-7.44 (3H, m, Ph); 7.45-7.48 (2H, m, Ph); 7.83 (1H, d, *J* = 8.5 Hz, 6-C*H*), 8.31 (1H, d, *J* = 8.5 Hz, 5-C*H*); 9.39 (1H, s, N*H*). ^{13}C NMR (d$_6$-DMSO, 125 MHz): δ 34.4, 37.8, 67.1, 118.2, 126.6, 127.2, 128.3, 128.4, 128.5, 129.8, 135.6, 135.8, 152.7, 161.3, 162.4, 165.0. EI-HRMS: *m/z* = 369.1079 (MH$^+$) found; $C_{19}H_{17}N_2O_6$ calculated: *m/z* = 369.1081 (MH$^+$). ν_{max} 3216, 3108, 3029, 2928, 1984, 1846, 1774, 1742, 1626, 1592, 1552, 1488, 1457, 1307, 1269, 1232, 1205, 1155, 1073, 1030, 907, 848, 753, 670, 646.

5.6. X-ray crystal structure determination for compounds 2c, 2g, 6b, 6d, 6f, 7a, 7d, 7f and 8a.

The Agilent SuperNova diffractometer equipped with Atlas detector was used for structural analysis of the aforementioned compounds. Diffraction data of single crystals of compounds **2c** and **2g** were collected at 150 K while diffraction data for other structures were collected at room temperature. Cu Kα (1.54184 Å) radiation was used for data collection of **7a**, **7d** and **8a**, while Mo Kα (0.71073 Å) tube was used for other compounds. Data reduction and integration were performed with the software package *CrysAlis PRO*.[20] All structures were solved by means of SIR97 or Olex2 structure solution program.[21,22] A full-matrix least-squares refinement on F^2 magnitudes with anisotropic displacement parameters for all non-hydrogen atoms using *SHELXL*2013[23] was employed. All hydrogen atoms were initially located in the difference Fourier maps. Carbon-attached hydrogens were subsequently treated as riding atoms in geometrically idealized positions with bond lengths C−H of 0.96/0.98 Å for methyl, 0.97 for methylene and 0.93/0.95 Å for aromatic C−H bonds (the first values refer to room temperature and the second to low temperature). The corresponding displacement parameters U_{iso}(H) were 1.5-times higher than those of the carrier methyl carbons and 1.2-

times higher than methylene and aromatic carbon atoms. Hydrogen of the NH group was refined isotropically and without any restraints with exception of structures **6b** and **7a** in which it was located from difference Fourrier map and refined using AFIX 3 or AFIX 4 restraint. In **6b**, the disorder of CF_3 moieties was restrained predicting the uniform C−F distance (1.28(2) Å) and uniform displacement parameter for all three F atoms disordered over two positions; only one of them is represented in the corresponding figure. Figures depicting the structures were prepared by *ORTEP*.[24] CCDC nos. 1493806−1493814 contain the supplementary crystallographic data for 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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