

Cyclization of Methyl-Coumalate Derived Methyl 1-benzamido-6-oxo-1,6-dihydropyridine-3-carboxylates: Assembly of the [1,2,4]Triazolo[1,5-a]pyridine Ring System

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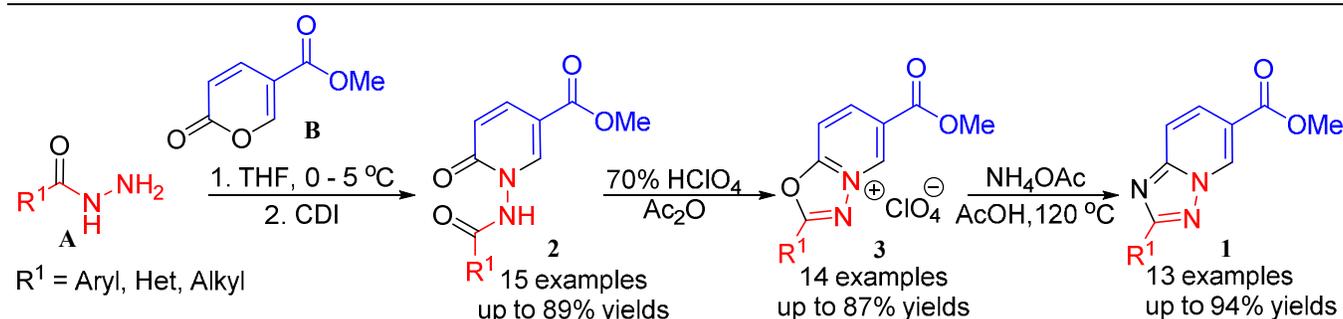
Cyclization of Methyl-Coumalate Derived Methyl 1-benzamido-6-oxo-1,6-dihydropyridine-3-carboxylates: Assembly of the [1,2,4]Triazolo[1,5-a]pyridine Ring System

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Supporting Information Placeholder



ABSTRACT: An efficient three step synthesis of a series of fused bicyclic *s*-[1,2,4]triazolo[1,5-*a*]pyridines **1** was accomplished utilizing novel intermediates derived from inexpensive commercially available hydrazides **A** and methyl coumalate **B**. A significant feature of this approach was the formation of a dihydrazide intermediate **2**, bypassing the need for oxidative N-N bond formation in the 1,2,4 triazole synthesis. Further purification of the dihydrazides **2**, beyond simple isolation, proved unnecessary due to the impurity rejection afforded by the crystalline oxadiazolium salts **3**. Additionally, the prepared oxadiazolium perchlorate salts showed excellent moisture stability, an unusual feature in compounds of this type.

1.0 INTRODUCTION

The *s*-[1,2,4]triazolo[1,5-*a*]pyridine system represents a structural core associated with a diverse range of biologically important small molecules. Reports in the scientific literature have made reference to its properties in the inhibition of JAK1,¹ JAK2,² Pi3K,³⁻⁵ as antibacterial and microbial agents⁶⁻⁹ and its association with anti-cancer properties.¹⁰ This pharmacologically active subunit is also frequently mentioned in patent literature; selected examples mention its properties of JAK2 inhibition,² mGlu 2 modulation,¹¹ treatment of cardiovascular disorders¹² and type 2 diabetes,^{13,14} in the treatment of hyperproliferative disorders,¹⁵ PDE10 inhibitors¹⁶ and for its herbicidal effects.¹⁷ Despite the plethora of therapeutic areas associated with this heterocyclic system, relatively few distinct synthetic strategies exist for its construction.¹⁸ and references contained therein The 1,2-4 triazole moiety does not contain two adjacent carbon atoms, thus to form a fused ring-system, one of the nitrogen ring atoms must also be a component of the second ring. Bearing this in mind, it is unsurprising that the most frequently encountered substrates in its production are the 2-amino pyridines. 2-Amino pyridines are industrially important feedstock chemicals however present sustainability issues due to their derivation from petroleum sources.¹⁹ Use of these starting materials results in scope limitations due to the requirement for an oxidative N-N bond formation, frequently

utilizing stoichiometric quantities of oxidant. Oxidants such as lead tetraacetate,²⁰ Cu(OAc)₂,²¹ MnO₂ (4eq.),⁶ NaClO,²² and PPA²³ have all been used to varying degrees of success to close the triazole ring via N-N bond formation. More recent examples include heterogeneous transition metal catalyzed cyclization strategies utilizing copper(I)bromide with molecular oxygen as the oxidant²¹ and a catalyzed oxidation.²⁴ A variety of hypervalent iodine mediated metal free alternatives have also been disclosed,^{25,26} though while being more environmentally friendly than aforementioned metal mediated routes, suffer from the same lack of scope on the pyridine ring.

Previously disclosed work from our medicinal chemistry laboratories¹³ has described the synthesis of a series of molecules containing the *s*-[1,2,4]triazolo[1,5-*a*]pyridine moiety under investigation for their GPR40 activation properties. The *s*-[1,2,4]triazolo[1,5-*a*]pyridine core, **4**, of these molecules is highlighted in **Figure 1**. A major drawback of the described route (**Scheme 1**) was the requirement for a high energy electrophilic aminating agent, *O*-mesitylsulfonylhydroxylamine (MSH) to synthesise key intermediate **5**. While preparation and safe use of MSH has been demonstrated,²⁷ the desire remained to move away from this method of synthesis.

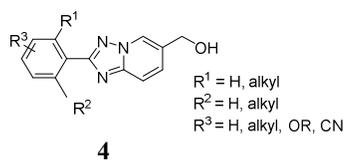
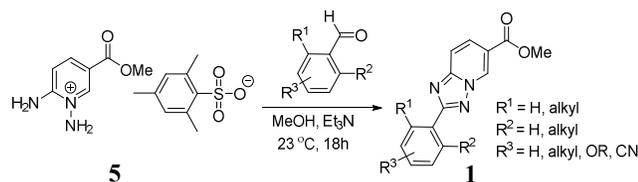


Figure 1. The 1,2,4-triazole fragment of potential activators of GPR 40 for treatment of type 2 diabetes

Scheme 1. Synthesis of **1** from MSH intermediates

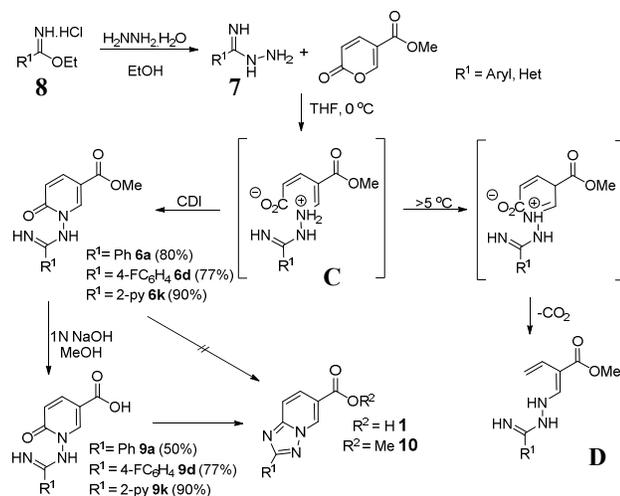


We envisioned that methyl coumalate **B**,²⁸ a renewable feedstock ultimately derived from glucose²⁹ *via* malic acid could be reacted with hydrazides to access the pyridine-ring *via* a pyridine species and facilitate the cyclization to afford the 1,2,4 triazole ring without the requirement for oxidative N-N bond formation. Presently, we disclose two complementary metal free synthetic routes to 6-methyl carboxylate substituted s-[1,2,4]triazolo[1,5-a]pyridine systems previously unknown in the literature.

2.0 RESULTS AND DISCUSSION

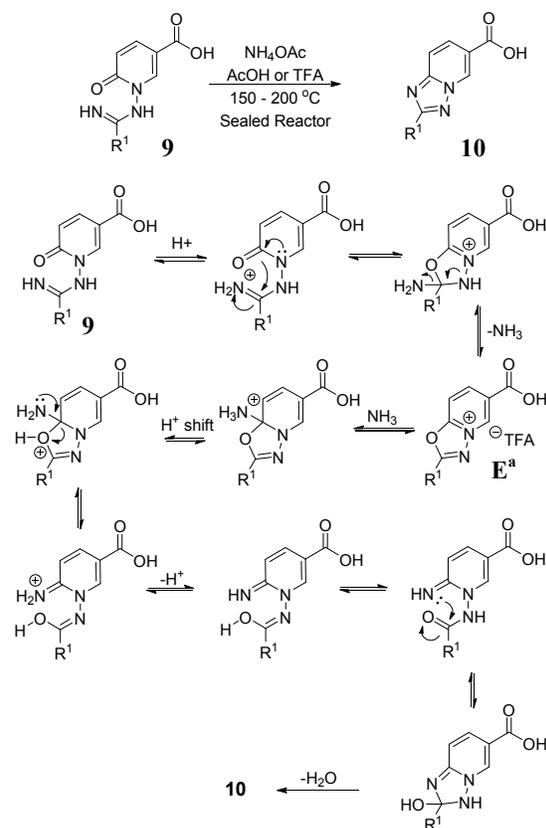
In the course of synthetic route investigations carried out by our laboratories, a number of known methods were attempted to access the desired substituted 1,2,4 triazole core **4**. Several methods involving oxidative N-N bond formation performed poorly or failed completely at the cyclization stage when applied to the substrates required for our work.^{21,30,31} Bearing this in mind, it was hoped that methyl coumalate **B** could be used as a platform chemical, reducing the overall chemical processing involved and providing a greener and more sustainable route to the biologically important pharmacophores discussed in this work. **Scheme 2** details our initial strategy using imidohydrazone pyridine (IHP) derivatives **6**, planned as potential intermediates for condensation to the 1,2,4-triazole system **1**.

Scheme 2. Initial Efforts to s-[1,2,4]Triazolo[1,5-a]pyridine Ring System



A range of iminohydrazides **7** were prepared using the methods described by Pinner³² from the corresponding nitriles *via* reaction of the Pinner salt **8** with hydrazine.³³ Preparation of the iminohydrazone pyridine ester proceeded from a Michael addition *via* a zwitterionic intermediate **C** (**Scheme 2**) which was stable at 0 °C. Careful control of temperature was important, rapid decarboxylation of the intermediate adducts **C** to **D** occurred above 5 °C. Treatment of intermediate **C** with CDI promotes cyclization to give IHP **6**. Unfortunately a range of efforts to promote a subsequent ring closure of the IHP esters, **6**, to **1** were unsuccessful, the ester moiety activating the molecule towards 1,4-addition. Conversion to the acid derivative **9** facilitated the cyclization to the desired ring system **10** though isolation issues were associated with this route due to the acid functionality of **10** and use of acetic acid or trifluoroacetic acid as solvents. In an effort to promote cyclization to **10**, additives were screened in a sealed reactor system at elevated temperature. The sealed system permitted heating beyond the solvent boiling point and ensured containment of ammonia. It was found that ammonium acetate was an effective additive though its role in the reaction mechanism was unclear. Understanding was gained when LCMS analysis of the crude reaction mixtures showed the major product of the reaction gave *m/z* +1 higher than anticipated when the reaction was carried out in TFA. Further investigation by NMR and high resolution mass spectrometry indicated that the cyclization reactions were in fact proceeding *via* an oxadiazolium cationic intermediate **E** (**Scheme 3**) initially displacing the imidohydrazone nitrogen instead of displacing the oxygen as desired.

Scheme 3. Proposed Mechanism of 1,2,4-Triazole Formation from IHP acids

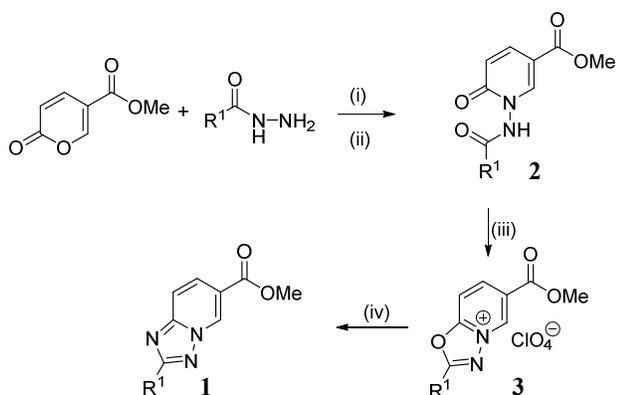


^a1-D and 2-D NMR provided in Supplementary Information

The intermediate **E** undergoes attack by ammonia, either ammonium acetate derived or from oxygen displaced ammonia. The proposed cyclization mechanism in TFA is outlined in Scheme 3. It is likely that when the reaction is carried out in acetic acid, the ion pair is insufficient to arrest the oxadiazolium **C**. Representative examples of prepared imidohydrazone esters **6** and acids **9** are provided in the experimental section for information purposes. Taking advantage of this mechanistic insight, the synthetic route was altered (Scheme 4) to proceed directly through the oxadiazolium, shortening the synthesis by 1-2 steps depending on the aromatic substitution pattern.

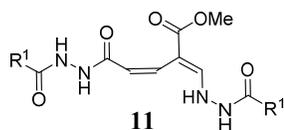
A series of novel dihydrazides of type **2** (Scheme 5) were prepared through sequential treatment of a methyl coumalate THF solution with the corresponding commercially available hydrazide followed by CDI, in good to excellent yield (40-89%). Initial addition to methyl coumalate was complete in under two hours in all cases. After addition of CDI, cyclization was complete in 3-8 h though the reactions were frequently left overnight. The addition and cyclization reactions were conducted at 0 - 5 °C to avoid the decarboxylation encountered previously at the zwitterion stage.

Scheme 4. Revised Synthetic route to the s-[1,2,4]Triazolo[1,5-a]pyridine Ring System^a



^aReagents and conditions: (i) THF, 0 - 5 °C, 15 - 60 min; (ii) CDI, 12 h, rt; (iii) 70% HClO₄, Ac₂O, <35 °C; (iv) NH₄OAc, AcOH, 120 °C, 15-90 min.

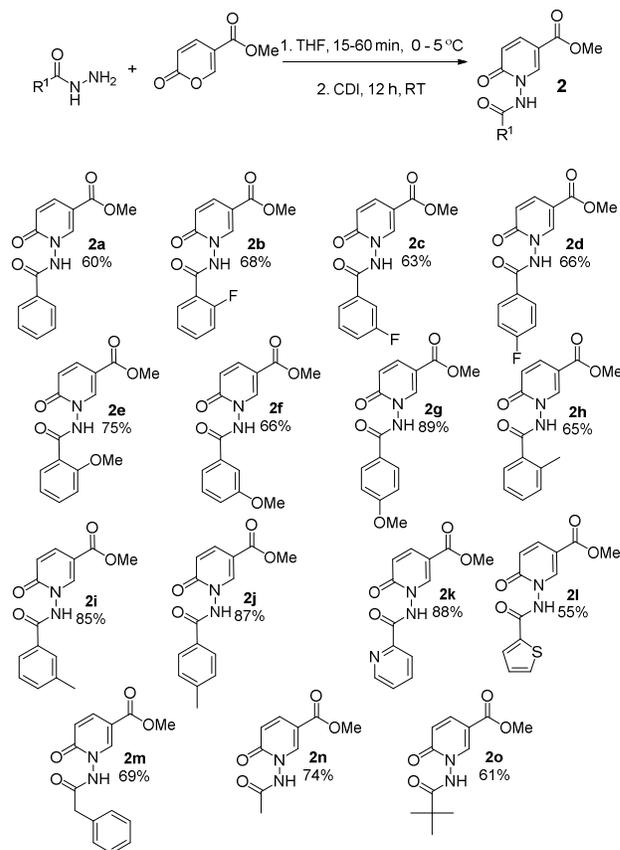
After work up, if desired, dihydrazides **2** could be used crude in the next synthetic step. Use of 1N HCl in the work up resulted in the removal of the major impurity from the crude material, residual imidazole. Dihydrazides (**2g**, **2i - k**) precipitated following cyclization with CDI, required no work-up, and lead to increased isolated yields (55 - 89%). The reaction also proceeds in EtOAc or CH₃CN as reaction solvent and this leads to more instances of product precipitation, though yields are lower by 5-10%.



An impurity commonly observed by LCMS were the double addition products **11**, likely derived from an initial 1,2 addition of **A** and **B**. These species were rejected in the work-up and could be kept to a minimum through use of a slight excess of methyl coumalate, utilized as a dilute solution when added

to the hydrazide starting material. Alkyl derivative **2n**, required storage under moisture free conditions, due to the acetate being labile to hydrolysis.

Scheme 5. Dihydrazide Synthesis Substrate Scope

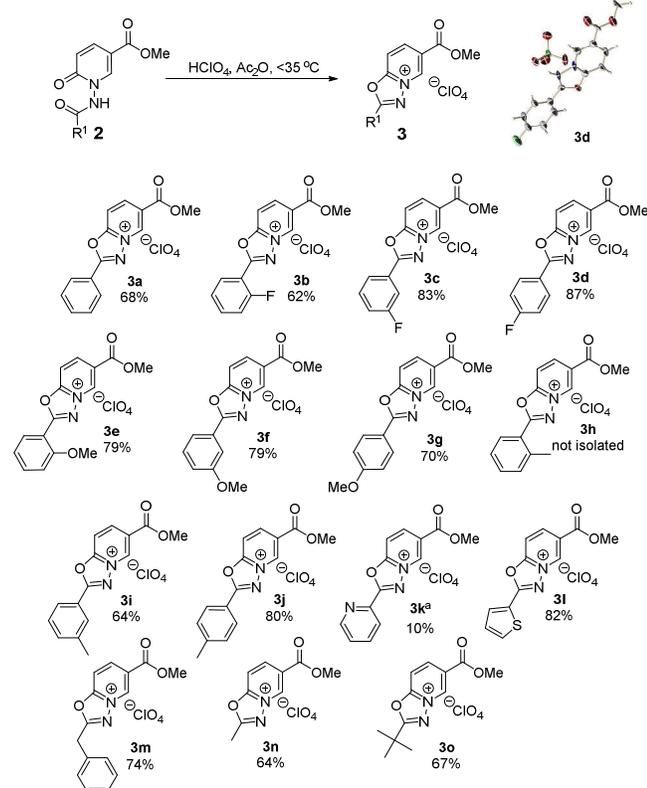


Tetrafluoroborate and perchlorate quaternary salts of simple 1,3,4-oxadiazoles were first described by Boyd³⁴ in 1967 and were noted to be very sensitive to nucleophilic attack, particularly by water. A diazapine synthesis utilizing an oxadiazolium perchlorate intermediate noted the strict requirement for dry reaction conditions due to their reactivity with even poor nucleophiles.³⁵

A selection of novel oxadiazolium perchlorate salts **3** were prepared through the action of 1.5 - 5 eq. of aq 70% perchloric acid on a slurry of the dihydrazides **2** in acetic anhydride (Scheme 6). The rate of perchloric acid addition was such that the temperature was not allowed to exceed 35 °C, the slurry becoming a solution after addition of 1.5 eq. of acid. Salts **3** containing aromatic substituents showed particular stability to water, in fact the isolation of the 2-aryl perchlorate salts could be accomplished through slowly pouring the reaction mixture into cold water (5 - 10 °C) and subsequent separation of the perchlorate salts by filtration. Hydrolytic stability was investigated through exposure of **3d** to 30 volumes of water at ambient temperature for 5 days and resulted in no loss of salt potency. Isolated yields of the perchlorate salts were in the range of 62 - 87% and were identified by the absence of the N-H signal in their ¹H NMR and the presence of their stable cations observable by mass spectrometry. Analysis of the infrared spectra showed C=N⁺ and C=N stretches at 1640 cm⁻¹ and 1610 cm⁻¹ and characteristic perchlorate stretches³⁶ were observed at 1090 cm⁻¹. The intact structure of the perchlorate salt

was firmly established by X-ray crystallographic analysis, the unit cell being composed of a 1:1 oxadiazolium:perchlorate salt, no solvent or water detected in the crystal (**Scheme 6**, **3d**).

Scheme 6. Perchlorate Salt Substrate Scope



^aAfter 36 h, not isolated

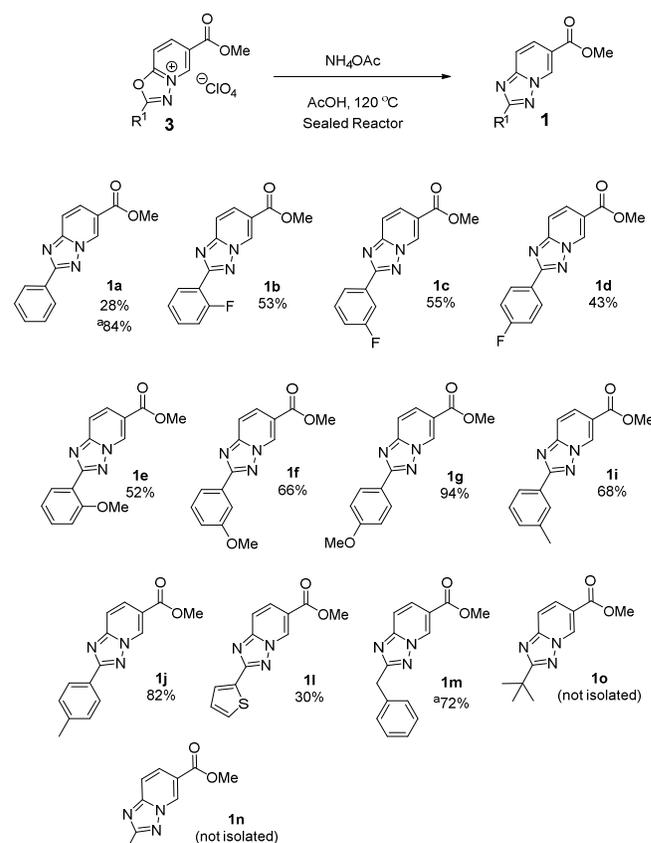
Oxadiazolium perchlorates, **3a-j**, **l** appear to be the only examples of compounds of this type with this degree of water stability under ambient conditions and affording them greater synthetic utility than literature examples due to their relative ease of use and stability. When R^1 = benzyl or alkyl isolation was achieved through trituration with cold MTBE, though hydrolytic instability ($2 - 5^\circ\text{C}$) was not observed. Difficulties were encountered in the preparation of a 2-pyridyl derivative **3k**, low conversion ($\sim 10\%$) to the oxadiazolium was observed by LCMS even after long reaction times (36 h). Evidence for the formation of *o*-tolyl derivative **3h** was obtained by LCMS and HRMS, however all attempts at isolation were unsuccessful. Perchlorate **3n** showed substantially less thermal stability than other analogues in this series, decomposing above 100°C .

The perchlorate salts, **3**, were combined with ammonium acetate in hot acetic acid in a sealed reactor to yield the desired products in moderate to excellent yields in 15 - 90 mins (Scheme 7). Despite the aforementioned hydrolytic stability of perchlorates, **3**, under ambient conditions, cyclization of the prepared oxadiazolium salts **3** to the bicyclic triazoles **1** was sensitive to water due to the reaction temperatures involved (120°C). The presence of water in the reaction, through association with reagents, moisture in the system, or, from the resulting cyclization condensation, leads to a competing hydrolysis returning oxadiazolium salts, **3**, to the dihydrazides **2**. Use of molecular sieves gave minor improvements in yield, water trapping possibly poor due to the presence of relatively

large quantities of ammonium, swamping the ability of the sieves to store water.³⁷ Addition of 2 - 4 eq. of acetic anhydride as a water scavenger achieved a substantial improvement in product yield ($\sim 55\%$ for **1a**). Even without the addition of acetic anhydride, isolated yield of **1g** was near quantitative, highest yields in the series observed when R^1 was electron rich.

Isolation of the triazole products **1a-l** was relatively straightforward, the presence of the ester greatly facilitated isolation and purification relative their acid derivatives **10**. Simple cooling of the reaction mixture post-reaction to $5 - 10^\circ\text{C}$ and addition of cold water ($2 - 5^\circ\text{C}$) resulted in precipitation of the desired products with complete rejection of impurities into the mother liquor. Triazole **1m** was triturated with cold MTBE to isolate. Alkyl derivatives **1n** and **1o** were successfully synthesized, however attempts to isolate **1n** were hampered by its general instability. Reactions to produce **1o** resulted in poor yields, significant quantities of dihydrazide **2o** present, even with the addition of acetic anhydride.

Scheme 7. Synthetic Strategy Towards s-[1,2,4]Triazolo[1,5-a]pyridine Ring System



^a Ac_2O (3 eq) 130°C .

3.0 CONCLUSIONS

In summary, a cost effective synthesis of novel s-[1,2,4]triazolo[1,5-a]pyridine **1** compounds has been accomplished from methyl coumalate and commercially available hydrazides in three linear steps by a chromatography free process. Our new synthetic strategy using methyl coumalate as the primary starting material provides a useful alternative to literature methods and is particularly effective for the synthe-

sis of aryl substituted derivatives. The synthesis is metal free, shows good substrate scope and initial pyridine dihydrazide **2** generation removes the requirement for N-N bond formation in the strategy. Additionally, the oxadiazolium perchlorate salts generated in the course of the synthesis are unusually water stable and may be stored for many months without any sign of degradation.

4.0 EXPERIMENTAL SECTION

General.

All reagents were reagent grade, obtained from commercial suppliers and used without further purification. All solvents were HPLC grade and used as supplied. Reaction monitoring was accomplished by TLC or LCMS using an Agilent 6130 Quadropole LCMS fitted with photo diode array detection and an XBridge C18 2.5 μm , 1.0 x 75mm column at 30 °C. TLC plates were visualized under UV light (254 nm). Flash chromatography was carried out with silica gel 60 (230–400 ASTM mesh) on a Teledyne Isco CombiFlash Rf+ Purlon with hexane:ethyl acetate as the solvent gradient system. ^1H and ^{13}C NMR spectra were obtained on a Varian spectrometer at 400 and 100 MHz respectively. Proton fine splitting reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), dd = doublet of doublets, dt = doublet of triplets. Chemical shifts were referenced on residual solvent peaks: CDCl_3 (δ = 7.26 ppm for ^1H NMR and 77.00 ppm for ^{13}C NMR), $\text{DMSO} (\text{CD}_3)_2\text{SO}$ (δ = 3.33 ppm for ^1H NMR and 39.51 ppm for ^{13}C NMR). Structural assignment of resonances have been performed with the help of 2D NMR gradients experiments (COSY, multiplicity edited ^1H - ^{13}C HSQC, ^1H - ^{13}C HMBC, and ^1H - ^{15}N HMBC). High-resolution mass spectra were measured on Thermo Scientific LTQ-Orbitrap Discovery with electrospray ionization mode (ESI+) with mass accuracy greater than 2 ppm, applied mass range from 75 to 1500 Da. IR spectra (4000–400 cm^{-1}) were collected performed by ATR-FTIR (Attenuated Total Reflectance) on a Nicolet 6700 FT-IR with a Smart OMNI sampler on neat solid samples. DSC was performed on a TA SA+ Discovery series instrument running TRIOS Explorer software (10 °C/min).

General Procedures.

General Procedure for Products **6a,d** and **k**

To a solution of methyl-6-oxopyran-3-carboxylate (6.79 g, 44 mmol) in THF (60 ml) at 0 °C under a nitrogen atmosphere was added a solution of the appropriate imidohydrazide **7** (44 mmol) in THF (48 ml) *via* cannula over 5 mins. The mixture was stirred until complete consumption of the methyl-coumalate occurred-indicated by TLC or LCMS (<2h). 1,1'-carbonyldiimidazole was added, solution proceeding through a number of colour changes to eventually yield a black solution which was slowly allowed warm to room temperature overnight. The reaction mixture was diluted with EtOAc (50 ml), transferred to a separator funnel and washed with water (3 x 70 ml), brine (50 ml), dried with sodium sulphate and concentrated by rotary evaporation to yield a brown solid which was used without further purification in the production of **9**.

General Procedure for Products **9a,d** and **k**

To a suspension of **6** (3.6 mmol) in methanol (5 mL) was added 4mL 1N *aq* NaOH (4 mmol, 1.1 equiv). The mixture was

allowed stir until LCMS/TLC analysis indicated the complete consumption of the starting material. The reaction slowly became homogenous as the reaction progressed. When reaction was complete, the solution was acidified to pH 4 with saturated aqueous citric acid. A white precipitate formed which was isolated by filtration and washed with water (2 x 5 ml)

Procedure for synthesis of oxadiazolium intermediate **E** ($R = 4\text{-F C}_6\text{H}_4$)

A solution of **9d** (20 mg (0.07 mmol) and ammonium acetate (27 mg, 0.35 mmol, 5 equiv.) in TFA- d_1 (0.75 ml) was placed in a 2 ml Hastelloy port connector reactor and placed inside a modified GC oven. The reaction was heated at 200 °C for 2 hours, cooled to room temperature and the full contents of the reactor analysed by NMR spectroscopy.

General Procedure for Products **2a-o**

To a suspension of the appropriate hydrazide (16.4 mmol, 1.1 equiv) in THF (20 ml) at 0 °C under a nitrogen atmosphere was added a solution of methyl-6-oxopyran-3-carboxylate (2.3 g, 15 mmol) in THF (20 ml) dropwise over 10 -30 mins. The mixture was stirred until complete consumption of the methyl-coumalate occurred-indicated by TLC or LCMS (15-60 mins). 1,1'-carbonyldiimidazole (21.3 mmol, 1.3 equiv) was added, solution proceeding through a number of colour changes to eventually yield a black solution which was slowly allowed warm to room temperature overnight. The reaction mixture was diluted with EtOAc (50 ml), transferred to a separator funnel and washed with 1N HCl (2x 30 ml), water (40 ml), brine (40 ml), dried with sodium sulphate and concentrated by rotary evaporation to yield a brown solid. The products could be forward processed in their crude form for use in the oxadiazolium synthesis. Isolated yields were determined on analytically pure samples after, if required, the product was isolated as a white solid by column chromatography, hexane:ethyl acetate (40:60) as eluents.

General Procedure for Products **3a-o**

A suspension of dihydrazide (**1a-o**) (3 mmol) in acetic anhydride (6 ml) was cooled on an ice bath and purged with nitrogen. 70% Perchloric acid solution (9 mmol, 1.5-5 equiv) was added dropwise at such a rate that the temperature of the reaction mixture never exceeded 35 °C. Upon acid addition the contents of the reaction pot slowly went into solution. After complete acid addition the reaction was removed from the ice bath and allowed stir for 1-2 hours until complete consumption of the starting material was indicated by TLC or LCMS. The reaction mixture (**3a-j,l**) was slowly poured into water (20 ml), the resulting crystals filtered and washed with water (2 x 5 ml). Compounds **3m-o** were isolated by trituration with MTBE (10 ml), filtration and washing with cold ether (5ml). The solids were dried in a vacuum oven at 35 °C and used without further purification.

General Procedure for Products **1a-o**

A mixture of oxadiazolium perchlorate salt (1 mmol) (**3a-o**) and ammonium acetate (3.5 - 5 equiv) was dissolved in acetic acid (2.5 ml) in a 20 ml thick walled screw-capped tube, flushed with nitrogen and heated to 120 °C for 15-90 min. The reaction was monitored by LCMS and deemed complete when the dihydrazide **2** was consumed. The tube was cooled to room

temperature and the contents slowly poured into 20 ml of water (5 – 10 °C). The desired triazole was isolated as a solid by filtration and the solids washed with water (2 x 10 ml). Where noted, 2-4 eq. of acetic anhydride was also added to the reaction in order to suppress hydrolysis of **3** to **2**.

Methyl 1-benzamido-6-oxo-1,6-dihydropyridine-3-carboxylate (2a) White solid. Yield: 8.46 g (60%). m.p. (DSC) (10 °C/min) onset 183.42 °C, maximum 183.86 °C. IR (ATR) ν_{\max} 3259, 1720, 1687, 1668, 1604, 1528, 1492, 1447, 1314, 1293, 1266, 1120, 1108 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.79 (s, 3H), 6.63 (d, J = 9.6 Hz, 2H), 7.56 (m, 2H), 7.66 (m, 1H), 7.93 (m, 3H), 8.48 (d, J = 2.4 Hz, 1H), 11.85 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 52.5, 109.1, 120.2, 128.3, 129.1, 131.7, 133.1, 139.5, 146.7, 159.9, 164.3, 166.4. m/z 271.1. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_4$ [$\text{M}+\text{H}^+$] 273.0870, found 273.0871.

Methyl 1-(2-fluorobenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (2b) White solid. Yield 1.30 g (68%). m.p. (DSC) (10 °C/min) onset 129.41 °C, maximum 132.10 °C. IR (ATR) ν_{\max} 3177, 1719, 1660, 1614, 1541, 1447, 1316, 1279, 1260, 1122, cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.79 (s, 3H), 6.64 (d, J = 10 Hz, 1H), 7.37 (m, 2H), 7.64 (m, 1H), 7.87 (m, 2H), 8.49 (d, J = 2.4 Hz, 1H), 11.71 (brs, 1H). ^{19}F δ_{F} : -112.1. ^{13}C NMR (100 MHz, DMSO) δ_{C} : 52.5, 109.1, 116.9 (d, J = 21 Hz), 120.3, 120.9 (d, J = 14 Hz), 125.1, 131.1, 134.5 (d, J = 7.2 Hz), 139.5, 146.5, 159.7, 160.1 (d, J = 252 Hz), 163.7, 164.2. m/z 291.1. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_4\text{F}$ [$\text{M}+\text{H}^+$] 291.0776, found 291.0779.

Methyl 1-(3-fluorobenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (2c) White solid Yield 1.27 g (63%). m.p. (DSC) (10 °C/min) onset 188.85 °C, maximum 190.27 °C. IR (ATR) ν_{\max} 3186, 1723, 1696, 1658, 1608, 1591, 1445, 1311, 1283, 1263, 1208, 1124 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.79 (s, 3H), 6.64 (d, J = 9.6 Hz, 1H), 7.51 (td, J = 6.4 Hz, 2.4 Hz, 1H), 7.62 (q, J = 8 Hz, 1H), 7.73 (d, J = 9.6 Hz, 1H), 7.79 (d, J = 6.8 Hz, 1H), 7.89, (dd, J = 7.2, 2.4 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 11.98 (br s, 1H). ^{19}F δ_{F} : -112.1; ^{13}C NMR (100 MHz, DMSO) δ_{C} : 52.5, 109.2, 115.1 (d, J = 24 Hz), 120.1 (d, J = 21 Hz), 120.3, 124.5 (d, J = 3 Hz), 131.4 (d, J = 8 Hz), 134.0 (d, J = 8 Hz), 139.5, 146.6, 159.8, 162.5 (d, J = 245 Hz), 164.2, 165.2 (d, J = 3 Hz); m/z 291.1; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_4\text{F}$ [$\text{M}+\text{H}^+$] 291.0776, found 291.0779

Methyl 1-(4-fluorobenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (2d) White solid. Yield 0.95 g (66%). m.p. (DSC) (10 °C/min) onset 260.04 °C, maximum 260.31 °C. IR (ATR) ν_{\max} 3242, 1718, 1680, 1660, 1603, 1535, 1502, 1446, 1294, 1263, 1223, 1129, 1114 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.79 (s, 3H), 6.65 (d, J = 9.6 Hz, 1H), 7.41 (t, J = 8.8 Hz, 2H), 7.90 (dd, J = 2.4, 9.6 Hz, 1H), 8.02 (m, 2H), 8.50 (d, J = 2.4 Hz, 1H). ^{19}F δ_{F} : -106.8. ^{13}C NMR (100 MHz, DMSO) δ_{C} : 52.5, 109.1, 116.2 (d, J = 24 Hz), 120.2, 128.3, 131.1, 131.2, 139.5, 146.7, 160.0, 164.2, 165.5; m/z 291.1; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_4\text{F}$ [$\text{M}+\text{H}^+$] 291.0776, found 291.0782.

Methyl 1-(2-methoxybenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (2e) White solid. Yield 2.5 g (75%). m.p. (DSC) (10 °C/min) onset 130.24 °C, maximum 139.42 °C. IR (ATR) ν_{\max} 3278, 1710, 1697, 1675, 1602, 1500, 1477, 1452, 1317, 1301, 1275, 1117, 1104, 1015 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.78 (s, 3H), 3.92 (s, 3H), 6.61, (d, J = 10 Hz, 1H), 7.08 (m, 1H), 7.30 (m, 1H), 7.59 (m, 1H), 7.87 (m, 2H), 8.35 (d, J = 2.4 Hz, 1H), 11.16 (s, 1H). ^{13}C

NMR (100 MHz, DMSO) δ_{C} : 52.5, 56.5, 108.7, 112.8, 119.9, 120.3, 121.1, 131.5, 133.4, 139.2, 146.7, 158.1, 159.7, 164.3, 164.9. m/z 303.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_5$ [$\text{M}+\text{H}^+$] 303.0975, found 303.0979.

Methyl 1-(3-methoxybenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (2f) White solid. Yield 2.2 g (66%). m.p. (DSC) (10 °C/min) onset 186.65 °C, maximum 186.87 °C. IR (ATR) ν_{\max} 3234, 1720, 1670, 1661, 1597, 1527, 1490, 1444, 1304, 1293, 1275, 1233, 1120, 1035 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.78 (s, 3H), 3.82, (s, 3H), 6.63 (d, J = 9.2 Hz, 1H), 7.20 (dd, J = 2.4, 5.6 Hz, 1H), 7.49 (m, 3H), 7.89 (dd, J = 2.4, 9.6 Hz, 1H), 8.48 (d, J = 2.4 Hz, 1H), 11.94 (br s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 52.5, 55.8, 109.1, 113.3, 119.0, 120.2, 120.5, 130.0, 133.0, 139.5, 146.7, 159.7, 159.9, 164.2, 166.2. m/z 303.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_5$ [$\text{M}+\text{H}^+$] 303.0975, found 303.0982.

Methyl 1-(4-methoxybenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (2g) Isolated by filtration, no work-up. White solid. Yield 4.0 g (89%). m.p. (DSC) (10 °C/min) onset 193.02 °C, maximum 193.72 °C. IR (ATR) ν_{\max} 3219, 1722, 1679, 1659, 1606, 1535, 1507, 1445, 1312, 1295, 1271, 1253, 1196, 1128, 1105, 1025 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.78 (s, 3H), 3.84 (s, 3H), 6.62 (d, J = 9.6 Hz, 1H), 7.09 (d, J = 9.6 Hz, 2H), 7.90 (m, 3H), 7.43 (d, J = 2.4 Hz, 1H), 11.69 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 52.5, 56.0, 109.0, 114.4, 120.2, 123.7, 130.3, 139.4, 146.9, 160.1, 163.1, 164.3, 166.0. m/z 303.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_5$ [$\text{M}+\text{H}^+$] 303.0975, found 303.0982

Methyl 1-(2-methylbenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (2h) White solid. Yield 2.30 g (65%). m.p. (DSC) (10 °C/min) onset 166.41 °C, maximum 169.01 °C. IR (ATR) ν_{\max} 3209, 1724, 1684, 1663, 1603, 1544, 1513, 1444, 1311, 1286, 1259, 1121, 1101 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 2.41 (s, 3H), 3.80 (s, 3H), 6.62 (d, J = 9.6 Hz, 1H), 7.31 (m, 2H), 7.44 (m, 1H), 7.65 (m, 1H), 7.88 (dd, J = 9.2, 2.4 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 11.60 (br s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 19.7, 52.5, 109.0, 120.3, 126.0, 128.4, 131.1, 131.2, 133.5, 136.9, 139.5, 146.7, 159.8, 164.3, 168.7; m/z 287.1; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_4$ [$\text{M}+\text{H}^+$] 287.1026, found 287.1032

Methyl 1-(3-methylbenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (2i) White solid. Isolated by filtration, no work-up. Yield 3.30 g (85%). m.p. (DSC) (10 °C/min) onset 175.59 °C, maximum 177.84 °C. IR (ATR) ν_{\max} 3176, 1724, 1702, 1660, 1607, 1533, 1443, 1311, 1268, 1125, 1106, 1069 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 2.38 (s, 3H), 3.78 (s, 3H), 6.63 (d, J = 9.6 Hz, 1H), 7.45 (m, 2H), 7.75 (m, 2H), 7.88 (dd, J = 2.4, 9.2 Hz, 1H), 8.46 (d, J = 2.4 Hz, 1H), 11.80 (br s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 21.3, 52.5, 109.1, 120.2, 125.4, 128.8, 129.0, 131.7, 133.7, 138.5, 139.4, 146.7, 159.92, 164.2, 166.6. m/z 287.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_4$ [$\text{M}+\text{H}^+$] 287.1026, found 287.1031.

Methyl 1-(4-methylbenzamido)-6-oxo-1,6-dihydropyridine-3-carboxylate (2j) White solid. Isolated by filtration, no work-up. Yield 5.15 g (87%). m.p. (DSC) (10 °C/min) onset 192.50 °C, maximum 193.74 °C. IR (ATR) ν_{\max} 3210, 1701, 1663, 1610, 1531, 1503, 1445, 1315, 1288, 1270, 1122 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 2.38 (s, 3H), 3.78 (s, 3H), 6.63 (d, J = 9.6 Hz, 1H), 7.35 (d, J = 8 Hz, 2H), 7.85 (m, 3H), 8.45 (d, J = 2 Hz, 1H), 11.77 (br s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 21.5, 52.5, 109.1, 120.2, 128.3, 129.6, 139.4,

143.3, 146.8, 159.9, 164.25, 166.35. m/z 287.1. HRMS (ESI) calcd for C₁₅H₁₅N₂O₄ [M+H⁺] 287.1026, found 287.1031.

Methyl 6-oxo-1-(picolinamido)-1,6-dihydropyridine-3-carboxylate (2k) White solid. Isolated by filtration, no work-up. Yield 3.4 g (87%). m.p. (DSC) (10 °C/min) onset 222.11 °C, maximum 222.76 °C. IR (ATR) ν_{\max} 3301, 1727, 1712, 1682, 1543, 1483, 1443, 1317, 1295, 1281, 1103, 999 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ_{H} : 3.78 (s, 3H), 6.61 (d, J = 9.6 Hz, 1H), 7.72 (m, 1H), 7.87 (dd, J = 9.6 Hz, 2.8 Hz, 1H), 8.07 (m, 2H), 8.41 (d, J = 2.4 Hz, 1H), 8.74 (d, J = 4.4 Hz, 1H), 11.95 (br s, 1H). ¹³C NMR (100 MHz, DMSO) δ_{C} : 52.5, 109.0, 120.3, 123.3, 128.2, 138.5, 139.3, 146.7, 148.4, 149.3, 159.6, 163.8, 164.2. m/z 275.1. HRMS (ESI) calcd for C₁₃H₁₂N₃O₄ [M+H⁺] 274.0822, found 274.0828

Methyl 6-oxo-1-(thiophene-2-carboxamido)-1,6-dihydropyridine-3-carboxylate (2l) White solid. Yield 1.69 g (55%). m.p. (DSC) (10 °C/min) onset 239.60 °C, maximum 239.88 °C. IR (ATR) ν_{\max} 3226, 3096, 1715, 1660, 1610, 1536, 1512, 1443, 1419, 1357, 1314, 1272, 1121, 882, 859 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ_{H} : 3.78 (s, 3H), 6.63 (d, J = 10 Hz, 1H), 7.26 (t, J = 4 Hz, 1H), 7.89 (m, 1H), 7.95 (m, 2H), 8.46 (d, J = 2 Hz, 1H), 11.91 (br s, 1H). ¹³C NMR (100 MHz, DMSO) δ_{C} : 52.5, 109.2, 120.2, 128.8, 131.0, 133.5, 135.9, 139.6, 146.7, 159.9, 161.4, 164.2. m/z 279.0. HRMS (ESI) calcd for C₁₂H₁₁N₂O₄S [M+H⁺] 279.0434, found 274.0439.

Methyl 6-oxo-1-(2-phenylacetamido)-1,6-dihydropyridine-3-carboxylate (2m) White solid. Yield 6.64 g (69%). m.p. (DSC) (10 °C/min) onset 107.26 °C, maximum 109.70 °C. IR (ATR) ν_{\max} 3147, 2949, 1720, 1663, 1604, 1540, 1513, 1495, 1443, 1309, 1278, 1134, 1112, 1097 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ_{H} : 3.67 (s, 2H), 3.76 (s, 3H), 6.58 (d, J = 10 Hz, 1H), 7.33 (m, 5H), 7.85 (m, 1H), 8.25 (d, J = 2.4 Hz, 1H), 11.59 (s, 1H). ¹³C NMR (100 MHz, DMSO) δ_{C} : 39.3, 52.5, 108.9, 120.2, 127.2, 128.8, 129.7, 135.1, 139.3, 146.3, 159.7, 164.2, 170.5. m/z 287.1. HRMS (ESI) calcd for C₁₅H₁₅N₂O₄ [M+H⁺] 287.1026, found 287.1032.

Methyl 1-acetamido-6-oxo-1,6-dihydropyridine-3-carboxylate (2n) White solid. Yield 6.64 g (69%). m.p. (DSC) (10 °C/min) 133 °C (decomposes). IR (ATR) ν_{\max} 3210, 3031, 1726, 1672, 1612, 1540, 1450, 1375, 1313, 1289, 1261, 1117, 1098 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ_{H} : 2.20 (s, 3H), 3.85 (s, 3H), 6.64 (d, J = 9.6 Hz, 1H), 7.95 (dd, J = 2.8, 9.2 Hz), 8.22 (d, J = 2.0 Hz, 1H), 10.12 (s, 1H). ¹³C NMR (100 MHz, DMSO) δ_{C} : 20.9, 52.3, 110.5, 119.6, 140.0, 144.5, 160.6, 163.9, 170.2. m/z 211.1; HRMS (ESI) calcd for C₉H₁₁N₂O₄ [M+H⁺] 211.0713, found 211.0718.

Methyl 6-oxo-1-pivalamido-1,6-dihydropyridine-3-carboxylate (2o) White solid. Yield 4.58 g (61%). m.p. (DSC) (10 °C/min) onset 159.47 °C, maximum 159.60 °C. IR (ATR) ν_{\max} 3270, 1719, 1669, 1536, 1497, 1443, 1309, 1284, 1225, 1139, 1113, 915 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ_{H} : 1.21 (s, 9H), 3.77 (s, 3H), 6.56 (d, J = 9.6 Hz, 1H), 7.83 (m, 1H), 8.21 (d, J = 2 Hz, 1H), 10.90 (br s, 1H). ¹³C NMR (100 MHz, DMSO) δ_{C} : 27.3, 38.4, 52.5, 108.8, 120.2, 139.3, 146.8, 159.8, 164.3, 177.7. ; m/z 253.1; HRMS (ESI) calcd for C₁₂H₁₇N₂O₄ [M+H⁺] 253.1183, found 253.1187.

Methyl 2-phenyl-4 λ^4 -[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (3a) Off-white solid. Yield 1.53 g (68%). m.p. (DSC) (10 °C/min) onset 265.21 °C, maximum 267.87 °C. IR (ATR) ν_{\max} 3112, 1729, 1646, 1610, 1567,

1452, 1437, 1302, 1286, 1209, 1089 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ_{H} : 4.01 (s, 3H), 7.81 (m, 2H), 7.93, (m, 1H), 8.28 (d, J = 7.6 Hz, 2H), 8.83 (d, J = 9.2 Hz), 9.12 (d, J = 9.2 Hz, 1H), 10.35 (s, 1H). ¹³C NMR (100 MHz, DMSO) δ_{C} : 54.2, 112.0, 120.1, 126.3, 128.9, 130.8, 135.7, 136.3, 144.7, 155.2, 162.4, 166.0. m/z 255.1. HRMS (ESI) calcd for C₁₄H₁₁N₂O₃ [M⁺] 255.0764, found 255.0766.

Methyl 2-(2-fluorophenyl)-4 λ^4 -[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (3b) Off-white solid. Yield 0.95 g (62%). m.p. (DSC) (10 °C/min) 205 °C (decomposes). IR (ATR) ν_{\max} 3088, 1744, 1641, 1625, 1597, 1484, 1462, 1308, 1290, 1089 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ_{H} : 4.02 (s, 3H), 7.66 (t, J = 8 Hz, 1H), 7.72 (t, J = 10.8 Hz, 1H), 8.00 (q, J = 6 Hz, 1H), 8.30 (t, J = 7.6 Hz, 1H), 8.88 (d, J = 9.2 Hz, 1H), 9.15 (d, J = 9 Hz, 1H). ¹⁹F δ_{F} : -106.6. ¹³C NMR (100 MHz, DMSO) δ_{C} : 54.2, 108.8 (d, J = 11 Hz), 112.0, 118.4 (d, J = 20 Hz), 126.4, 126.8 (d, J = 3 Hz), 131.2, 135.8, 138.8 (d, J = 2 Hz) 145.1, 154.7, 161.0 (d, J = 261 Hz), 162.4, 162.8 (d, J = 6 Hz). m/z 273.1. HRMS (ESI) calcd for C₁₄H₁₀N₂O₃F [M⁺] 273.0670, found 273.0673.

Methyl 2-(3-fluorophenyl)-4 λ^4 -[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (3c) Off-white solid. Yield 0.65 g (83%). m.p. (DSC) (10 °C/min) onset 257.26 °C, maximum 258.12 °C. IR (ATR) ν_{\max} 3091, 1733, 1646, 1438, 1288, 1255, 1092 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ_{H} : 4.01 (s, 3H), 7.86 (m, 2H), 8.15 (m, 2H), 8.84 (d, J = 9.2 Hz, 1H), 9.15 (m, 1H), 10.38 (s, 1H). ¹⁹F δ_{F} : -109.5. ¹³C NMR (100 MHz, DMSO) δ_{C} : 54.2, 112.1, 115.5 (d, J = 24 Hz), 122.0 (d, J = 3 Hz), 123.4 (d, J = 26 Hz), 125.4, 126.5, 133.5 (d, J = 8 Hz), 135.8, 145.8, 155.1, 162.4, 162.7 (d, J = 248 Hz), 165.0. m/z 273.1. HRMS (ESI) calcd for C₁₄H₁₀N₂O₃F [M⁺] 273.0670, found 273.0675.

Methyl 2-(4-fluorophenyl)-4 λ^4 -[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (3d) White solid. Yield 0.56 g (87%). m.p. (DSC) (10 °C/min) onset 250.22 °C, maximum 251.49 °C. IR (ATR) ν_{\max} 3100, 1733, 1647, 1615, 1503, 1433, 1301, 1240, 1087 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ_{H} : 4.01 (s, 3H), 7.67 (t, J = 8.8 Hz, 2H), 8.37 (dd, J = 5.5, 8.4 Hz, 2H), 8.82 (d, J = 9.2 Hz, 1H), 9.12 (m, 1H), 10.35 (s, 1H). ¹⁹F δ_{F} : -100.7. ¹³C NMR (100 MHz, DMSO) δ_{C} : 54.2, 112.0, 116.8, 118.4 (d, J = 22 Hz), 119.7, 126.3, 132.1 (d, J = 8 Hz), 135.7, 144.8, 155.1, 162.4, 165.2. m/z 273.1. HRMS (ESI) calcd for C₁₄H₁₀N₂O₃F [M⁺] 273.0670, found 273.0675.

Methyl 2-(2-methoxyphenyl)-4 λ^4 -[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (3e) White solid. Yield 1.01 g (79%). m.p. (DSC) (10 °C/min) onset 238.78 °C, maximum 242.63 °C. IR (ATR) ν_{\max} 3078, 1733, 1642, 1608, 1556, 1510, 1495, 1452, 1305, 1287, 1130, 1077, 1053, 1038 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ_{H} : 4.01 (s, 3H), 4.06 (s, 3H), 7.33, (t, J = 7.6 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.88 (t, J = 7.2 Hz, 1H), 8.15 (m, 1H), 8.79 (d, J = 9.2 Hz, 1H), 9.08 (m, 1H), 10.33 (s, 1H). ¹³C NMR (100 MHz, DMSO) δ_{C} : 54.1, 57.1, 108.4, 111.8, 114.1, 122.0, 126.0, 131.6, 135.6, 138.0, 144.2, 154.6, 159.8, 162.5, 164.6. m/z 285.1. HRMS (ESI) calcd for C₁₅H₁₃N₂O₄ [M⁺] 285.0870, found 285.0873

Methyl 2-(3-methoxyphenyl)-4 λ^4 -[1,3,4]oxadiazolo[3,2-a]pyridine-6-carboxylate perchlorate (3f) White solid. Yield 1.01 g (79%). m.p. (DSC) (10 °C/min) onset 211.73 °C, maximum 217.20 °C. IR (ATR) ν_{\max} 3103, 1744, 1641, 1617, 1568, 1483, 1461, 1440, 1299, 1289, 1260, 1087, 1027 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ_{H} : 3.92 (s, 3H), 4.01, (s, 3H),

7.50, (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.70 (t, $J = 2.4$ Hz, 1H), 7.74 (t, $J = 8.0$ Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 8.80 (d, $J = 9.2$ Hz, 1H), 9.12 (dd, $J = 9.2$ Hz, 1.2 Hz, 1H), 10.33 (1H, d, $J = 1.2$ Hz). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 54.2, 56.3, 109.1, 112.1, 113.1, 121.2, 122.4, 126.3, 132.3, 135.7, 144.8, 155.2, 160.5, 162.4, 165.8. m/z 285.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_4$ [M^+] 285.0870, found 285.0874

*Methyl 2-(4-methoxyphenyl)-4 λ^4 -[1,3,4]oxadiazolo[3,2-*a*]pyridine-6-carboxylate perchlorate (3g)* White solid. Yield 1.1 g (70%). m.p. (DSC) (10 °C/min) onset 244.17 °C, maximum 245.03 °C. IR (ATR) ν_{max} 3102, 1738, 1645, 1601, 1505, 1322, 1294, 1271, 1093, 1009 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.94 (s, 3H), 4.00 (s, 3H), 7.33 (d, $J = 9.0$ Hz, 2H), 8.23 (d, $J = 9.2$ Hz, 2H), 8.76 (d, $J = 9.2$ Hz, 1H), 9.06 (d, $J = 9.2$ Hz, 1H), 10.27 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 54.1, 56.5, 111.8, 116.4, 126.0, 131.2, 135.4, 139.4, 144.1, 155.1, 162.5, 165.5, 165.9. m/z 285.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_4$ [M^+] 285.0870, found 285.0873

*Methyl 2-(*m*-tolyl)-4 λ^4 -[1,3,4]oxadiazolo[3,2-*a*]pyridine-6-carboxylate perchlorate (3i)* White solid. Yield 0.83 g (64%). m.p. (DSC) (10 °C/min) onset 220.15 °C, maximum 221.48 °C. IR (ATR) ν_{max} 3090, 1746, 1645, 1611, 1565, 1611, 1565, 1480, 1431, 1302, 1197, 1088 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 2.49 (s, 3H), 4.01 (s, 3H), 7.71 (m, 2H), 8.09 (m, 2H), 8.81 (d, $J = 9.6$ Hz, 1H), 9.11 (dd, $J = 1.1$, 9.2 Hz, 1H), 10.33 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 21.2, 54.2, 112.0, 120.1, 126.2, 126.2, 128.9, 130.7, 135.7, 137.0, 140.6, 144.6, 155.2, 162.4, 166.0. m/z 269.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_3$ [M^+] 269.0921, found 269.0924

*Methyl 2-(*p*-tolyl)-4 λ^4 -[1,3,4]oxadiazolo[3,2-*a*]pyridine-6-carboxylate perchlorate (3j)* White solid. Yield 0.80 g (80%). m.p. (DSC) (10 °C/min) onset 233.77 °C, maximum 235.82 °C. IR (ATR) ν_{max} 3095, 1730, 1644, 1613, 1563, 1505, 1434, 1304, 1290, 1188, 1092 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 2.49 (s, 3H), 4.01 (s, 3H), 7.61 (d, $J = 8$ Hz, 2H), 8.09 (d, $J = 8$ Hz, 2H), 8.78 (d, $J = 9.2$ Hz, 1H), 9.09 (dd, $J = 8$ Hz, 1.2 Hz, 1H), 10.30 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 22.0, 54.2, 111.9, 117.2, 126.1, 128.9, 131.4, 135.6, 144.4, 147.4, 155.1, 162.5, 166.2. m/z 269.1; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_3$ [M^+] 269.0921, found 269.0924

*Methyl 2-(thiophen-2-yl)-4 λ^4 -[1,3,4]oxadiazolo[3,2-*a*]pyridine-6-carboxylate perchlorate (3l)* White solid. Yield 0.53 g (82%). m.p. (DSC) (10 °C/min) onset 200.90 °C, maximum 204.20 °C. IR (ATR) ν_{max} 3093, 1727, 1644, 1608, 1580, 1439, 1320, 1300, 1133, 1092, 1078, 1065 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.99 (s, 3H), 7.52, (t, $J = 8$ Hz, 1H), 8.37 (d, $J = 3.6$ Hz, 1H), 8.40 (d, $J = 4.8$ Hz, 1H), 8.78 (d, $J = 9.2$ Hz, 1H), 9.09 (dd, $J = 9.2$, 1.2 Hz, 1H), 10.29 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 54.2, 111.8, 120.5, 126.2, 130.8, 135.5, 136.9, 138.8, 144.5, 154.8, 162.2, 162.4. m/z 261.0. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_9\text{N}_3\text{O}_3\text{S}$ [M^+] 261.0328, found 261.0333

*Methyl 2-(4-methylbenzyl)-4 λ^4 -[1,3,4]oxadiazolo[3,2-*a*]pyridine-6-carboxylate perchlorate (3m)* White solid. Yield 0.35 g (74%). m.p. (DSC) (10 °C/min) onset 178.78 °C, maximum 180.26 °C. IR (ATR) ν_{max} 3083, 2954, 1743, 1636, 1604, 1598, 1495, 1456, 1402, 1324, 1304, 1169, 1084 cm^{-1} . ^1H NMR (400 MHz, DMSO) 3.98 (s, 3H), 4.75 (s, 2H), 7.33-52 (m, 5H), 8.74 (d, $J = 9.2$ Hz, 1H), 9.06 (d, $J = 9.2$ Hz, 1H), 10.25 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 31.5, 54.1, 112.0, 125.9, 128.5, 129.4, 130.2, 131.9, 135.7, 144.6, 155.3,

162.5, 169.7. m/z 269.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_3$ [M^+] 269.0921, found 269.0924

*6-(methoxycarbonyl)-2-methyl-[1,3,4]oxadiazolo[3,2-*a*]pyridin-4-ium perchlorate (3n)* Orange waxy solid. Yield 0.45 g (64%) m.p. (DSC) (10 °C/min) 104 °C (decomposes). IR (ATR) ν_{max} 3161, 1723, 1647, 1619, 1587, 1439, 1315, 1208, 1084 cm^{-1} . ^1H NMR (400 MHz, DMSO) 2.94 (s, 3H), 3.99 (s, 3H), 8.74 (d, $J = 9.2$ Hz, 1H), 9.06 (d, $J = 9.2$ Hz, 1H), 10.21 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 11.9, 54.1, 111.8, 125.9, 135.5, 144.4, 155.2, 162.5, 168.8. m/z 193.1. HRMS (ESI) calcd for $\text{C}_9\text{H}_9\text{N}_2\text{O}_3$ [M^+] 193.0608, found 193.0612

*2-(Tert-butyl)-6-(methoxycarbonyl)-[1,3,4]oxadiazolo[3,2-*a*]pyridin-4-ium (3o)* White solid. Yield 0.39 g (67%). m.p. (DSC) (10 °C/min) onset 144.76 °C, maximum 148.46 °C. IR (ATR) ν_{max} 3083, 2980, 1729, 1647, 1602, 1515, 1458, 1440, 1366, 1320, 1310, 1206, 1175, 1123, 1087 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 1.53 (s, 9H), 3.99 (s, 3H), 8.73 (d, $J = 9.2$ Hz, 1H), 9.06 (d, $J = 9.2$ Hz, 1H), 10.26 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 27.4, 33.5, 54.1, 112.1, 125.9, 135.6, 144.4, 155.5, 162.5, 176.1. m/z 235.1. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_3$ [M^+] 235.1077, found 235.1080

*Methyl 2-phenyl-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate (1a)* White solid. Yield 0.05 g (28%). With 3 eq. acetic anhydride, 130 °C, Yield 0.12 g (84%). m.p. (DSC) (10 °C/min) onset 149.27 °C, maximum 150.01 °C. IR (ATR) ν_{max} 2953, 1724, 1638, 1450, 1438, 1319, 1334, 1307, 1297, 1201, 1135 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.90 (s, 3H), 7.54 (m, 3H), 7.92 (d, $J = 9.2$ Hz, 1H), 8.04 (d, $J = 9.2$ Hz, 1H), 8.21 (m, 2H), 9.46 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 53.1, 116.1, 117.9, 127.5, 129.5, 130.1, 130.4, 131.1, 132.5, 152.9, 164.6, 165.3. m/z 254.1. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{12}\text{N}_3\text{O}_2$ [$\text{M}+\text{H}^+$] 254.0924, found 254.0926

*Methyl 2-(2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate (1b)* White solid. Yield 0.28 g (53%). m.p. (DSC) (10 °C/min) onset 157.72 °C, maximum 158.80 °C. IR (ATR) ν_{max} 2955, 1719, 1639, 1617, 1587, 1512, 1474, 1448, 1439, 1321, 1305, 1289, 1197, 1140, 1128 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.91 (s, 3H), 7.39 (q, $J = 6.8$ Hz, 2H), 7.59 (m, 1H), 7.64 (d, $J = 9.6$ Hz, 1H), 8.06 (d, $J = 9.2$ Hz, 1H), 8.19 (t, $J = 7.6$ Hz, 1H), 9.51 (br s, 1H). ^{19}F δ_{F} : -111.1. ^{13}C NMR (100 MHz, DMSO) δ_{C} : 53.2, 116.2, 117.3 (d, $J = 19$ Hz), 118.1, 118.4 (d, $J = 9$ Hz) 125.3, 130.2, 131.3 (d, $J = 3$ Hz), 132.5, 133.0 (d, $J = 9.5$ Hz), 152.2, 160.5 (d, $J = 256$ Hz), 162.0, 164.6. m/z 272.1. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_2\text{F}$ [$\text{M}+\text{H}^+$] 272.0830, found 272.0833

*Methyl 2-(3-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate (1c)* White solid. Yield 0.29 g (55%). m.p. (DSC) (10 °C/min) onset 150.20 °C, maximum 154.78 °C. IR (ATR) ν_{max} 2959, 1723, 1638, 1590, 1512, 1434, 1322, 1296, 1217, 1103 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.90 (s, 3H), 7.39 (m, 2H), 7.59 (m, 1H), 7.95 (d, $J = 9.4$ Hz, 1H), 8.06 (d, $J = 9.4$ Hz, 1H), 8.19 (t, $J = 7.2$ Hz, 1H), 9.51 (s, 1H). ^{19}F δ_{F} : -112.3. ^{13}C NMR (100 MHz, DMSO) δ_{C} : 53.2, 113.9 (d, $J = 27$ Hz), 116.3, 117.9 (d, $J = 22$ Hz), 118.2, 123.6 (d, $J = 3$ Hz), 130.3, 131.8 d, $J = 9$ Hz), 132.5, 132.8, 152.9, 161.6, 164.1, 164.6. m/z 272.1. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_2\text{F}$ [$\text{M}+\text{H}^+$] 272.0830, found 272.0832

*Methyl 2-(4-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridine-6-carboxylate (1d)* White solid. Yield 0.25 g (43%). m.p. (DSC) (10 °C/min) onset 152.21 °C, maximum 154.16 °C. IR (ATR)

ν_{\max} 2959, 1730, 1641, 1609, 1529, 1457, 1440, 1323, 1300, 1261, 1198, 1156, 1139 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.90 (s, 3H), 7.38 (t, $J = 8.8$ Hz, 2H), 7.91 (d, $J = 9.2$ Hz, 1H), 8.04 (m, 1H), 8.23 (m, 2H), 9.45 (s, 1H). ^{19}F δ_{F} : -110.1. ^{13}C NMR (100 MHz, DMSO) δ_{C} : 53.1, 116.1, 116.5 (d, $J = 21$ Hz), 118.0, 127.0 (d, $J = 3$ Hz) 129.8 (d, $J = 10$ Hz), 130.2, 132.5, 152.9, 164.0 (d, $J = 249$ Hz), 164.5, 164.6. m/z 272.1. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_2\text{F}$ $[\text{M}+\text{H}^+]$ 272.0830, found 272.0835

Methyl 2-(2-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1e) White solid. Yield 0.46 g (52%). m.p. (DSC) (10 $^{\circ}\text{C}/\text{min}$) onset 105.35 $^{\circ}\text{C}$, maximum 106.07 $^{\circ}\text{C}$. IR (ATR) ν_{\max} 3061, 2956, 1721, 1636, 1608, 1587, 1512, 1477, 1445, 1434, 1329, 1300, 1286, 1257, 1247, 1127 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.84 (s, 3H), 3.90 (s, 3H), 7.08 (t, $J = 7.6$ Hz, 1H), 7.20 (d, $J = 8.4$ Hz, 1H), 7.50 (m, 1H), 7.90 (m, 2H), 8.02 (m, 1H), 9.45 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 53.1, 56.2, 110.0, 112.8, 115.9, 117.6, 120.8, 129.7, 131.7, 132.1, 132.3, 151.9, 158.1, 164.4, 164.7. m/z 284.1.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}^+]$ 284.1030, found 284.1032

Methyl 2-(3-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1f) White solid. Yield 0.42 g (66%). m.p. (DSC) (10 $^{\circ}\text{C}/\text{min}$) onset 130.98 $^{\circ}\text{C}$, maximum 132.13 $^{\circ}\text{C}$. IR (ATR) ν_{\max} 3079, 2961, 1730, 1640, 1593, 1480, 1433, 1318, 1272, 1239, 1134 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.84 (s, 3H), 3.91 (s, 3H), 7.10 (dd, $J = 2.4, 8.4$ Hz, 1H), 7.46, (t, $J = 8$ Hz, 1H), 7.72 (s, 1H), 7.79 (d, $J = 8$ Hz, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 8.05 (d, $J = 9.6$ Hz, 1H) 9.49 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 53.2, 55.7, 112.2, 116.1, 117.1, 118.0, 119.8, 130.2, 130.7, 131.7, 132.5, 152.9, 160.0, 164.6, 165.2. m/z 284.1.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}^+]$ 284.1030, found 284.1032

Methyl 2-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1g) White solid. Yield 0.54 g (94%). m.p. (DSC) (10 $^{\circ}\text{C}/\text{min}$) onset 185.70 $^{\circ}\text{C}$, maximum 186.30 $^{\circ}\text{C}$. IR (ATR) ν_{\max} 2950, 1711, 1637, 1611, 1532, 1460, 1445, 1427, 1320, 1295, 1248, 1200, 1185, 1167, 1027, 837 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.82 (s, 3H), 3.90 (s, 3H), 7.09 (d, $J = 8.8$ Hz, 2H), 7.87 (d, $J = 9.2$ Hz, 1H), 8.02 (d, $J = 9.2$ Hz, 1H), 8.14 (d, $J = 8.8$ Hz, 2H), 9.43 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 53.1, 55.8, 114.9, 115.8, 117.6, 122.8, 129.1, 130.0, 132.3, 152.9, 161.7, 164.7, 165.3. m/z 284.1.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}^+]$ 284.1030, found 284.1032

Methyl 2-(m-tolyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1i) Off-white solid. Yield 0.44 g (68%). m.p. (DSC) (10 $^{\circ}\text{C}/\text{min}$) 142 $^{\circ}\text{C}$ (decomposes). IR (ATR) ν_{\max} 3012, 2956, 1721, 1637, 1509, 1439, 1320, 1307, 1296, 1198, 1116, 1037 cm^{-1} . ^1H NMR (400 MHz, CDCl_3 -DMSO) δ_{H} : 2.45 (s, 3H), 3.99 (s, 3H), 7.20 (m, 1H), 7.65 (d, $J = 6.4$ Hz, 1H), 7.98 (m, 3H), 9.19 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 21.4, 52.8, 115.5, 117.8, 124.7, 128.1, 128.8, 129.7, 129.8, 131.5, 131.7, 138.6, 152.7, 164.5, 166.0. m/z 268.1.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}^+]$ 268.1081, found 268.1085

Methyl 2-(p-tolyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1j) White solid. Yield 0.49 g (82%). m.p. (DSC) (10 $^{\circ}\text{C}/\text{min}$) 91 $^{\circ}\text{C}$ (decomposes). IR (ATR) ν_{\max} 3076, 2953, 1721, 1639, 1614, 1459, 1436, 1346, 1323, 1304, 1197, 1186, 1135, 960 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ_{H} : 2.42 (s, 3H), 3.98 (s, 3H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.72 (d, $J = 9.2$ Hz, 1H), 8.02 (d, $J = 9.2$ Hz, 1H), 8.16 (d, $J = 8.0$ Hz, 2H), 9.26 (s, 1H).

^{13}C NMR (100 MHz, DMSO) δ_{C} : 21.5, 52.7, 115.4, 117.5, 127.3, 127.4, 129.45, 129.5, 131.6, 140.9, 152.8, 164.5, 166.2. m/z 268.1.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}^+]$ 268.1081, found 268.1085

Methyl 2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1l) White solid. Yield 0.16 g (30%). m.p. (DSC) (10 $^{\circ}\text{C}/\text{min}$) onset 174.28 $^{\circ}\text{C}$, maximum 174.87 $^{\circ}\text{C}$. IR (ATR) ν_{\max} 3082, 2951, 1710, 1639, 1566, 1509, 1473, 1441, 1393, 1356, 1324, 1308, 1291, 1224, 1204, 1140, 1106 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ_{H} : 3.90 (s, 3H), 7.23 (m, 1H), 7.78, (d, $J = 6.7$ Hz, 1H), 7.86 (m, 2H), 8.03 (dd, $J = 9, 12$ Hz, 1H), 9.43 (s, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 53.1, 115.8, 117.9, 128.9, 130.1, 130.4, 132.3, 133.0, 139.6, 152.7, 161.4, 164.6. m/z 260.0.1. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{10}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}^+]$ 260.0488, found 260.0491

Methyl 2-benzyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1m) White solid. With 3 eq. acetic anhydride, 130 $^{\circ}\text{C}$. Isolated by trituration with MTBE. Yield 0.14 g (72%). m.p. (DSC) (10 $^{\circ}\text{C}/\text{min}$) onset 107.54 $^{\circ}\text{C}$, maximum 108.90 $^{\circ}\text{C}$. IR (ATR) ν_{\max} 3065, 3032, 2956, 1723, 1638, 1518, 1453, 1439, 1337, 1319, 1293, 1205, 1155, 1135, 1020 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ_{H} : 3.98 (s, 3H), 4.30 (s, 2H), 7.25 (m, 1H), 7.33 (t, $J = 7.6$ Hz, 2H), 7.41 (d, $J = 7.2$ Hz, 2H), 7.71 (d, $J = 8.2$ Hz, 1H), 8.07 (dd, $J = 9.8, 1.2$ Hz, 1H), 9.22 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 35.2, 52.8, 115.3, 117.8, 126.9, 128.7, 129.0, 129.8, 131.6, 136.9, 152.1, 164.4, 167.9. m/z 268.1. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}^+]$ 268.1081, found 268.1085

Methyl 2-methyl-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1n) Not isolated. m/z 192.1

Methyl 2-(tert-butyl)-[1,2,4]triazolo[1,5-a]pyridine-6-carboxylate (1o) Not isolated. m/z 234.1. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{16}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}^+]$ calcd 234.1237, found 234.1241

Methyl 1-benzimidamido-6-oxo-1,6-dihydropyridine-3-carboxylate 6a Pale yellow solid. Yield 1.21 g (80%). m.p. (DSC) (10 $^{\circ}\text{C}/\text{min}$) 183 $^{\circ}\text{C}$ (decomposes). IR (ATR) ν_{\max} 3425, 3338, 3231, 1720, 1647, 1586, 1550, 1442, 1416, 1272, 1106 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.76 (s, 3H), 6.47 (d, $J = 9.2$ Hz, 1H), 7.15 (brs, 2H), 7.47 (m, 2H), 7.54 (m, 1H), 7.73 (dd, $J = 2.4, 9.2$ Hz, 1H), 7.88 (d, $J = 9.2$ Hz, 1H), 8.10 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 52.2, 108.5, 119.9, 127.8, 128.6, 131.4, 133.3, 136.8, 142.6, 158.9, 162.1, 164.8. m/z 272.1. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{14}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}^+]$ 272.1030, found 272.1036

Methyl (Z)-1-((amino(4-fluorophenyl)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylate 6d Yellow solid. Isolated by filtration. Yield 3.67 g (77%) (DSC) (10 $^{\circ}\text{C}/\text{min}$) onset 281.76 $^{\circ}\text{C}$, maximum 283.15 $^{\circ}\text{C}$ IR (ATR) ν_{\max} 3420, 3335, 3225, 1722, 1644, 1606, 1587, 1558, 1535, 1443, 1418, 1308, 1273, 1106 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.75 (s, 3H), 6.47 (d, $J = 9.6$ Hz, 1H), 7.18 (brs, 2H), 7.31 (t, $J = 8.8$ Hz, 2H), 7.73 (d, 9.6 Hz, 1H), 7.95 (m, 2H), 8.12 (s, 1H). ^{19}F δ_{F} : -109.8. ^{13}C NMR (100 MHz, DMSO) δ_{C} : 53.2, 108.5, 115.20, 119.9, 129.7, 130.3, 136.8, 142.6, 158.9, 161.1, 164.2, 164.8; m/z 290.1; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_3\text{F}$ $[\text{M}+\text{H}^+]$ 290.0935, found 290.0940.

Methyl (Z)-1-((amino(pyridin-2-yl)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylate 6k Yellow solid. Isolated by filtration, no work-up. Yield 12.0 g (90%). m.p. (DSC) (10

°C/min) onset 237.30 °C, maximum 238.96 °C. IR (ATR) ν_{\max} 3388, 3314, 3260, 1720, 1676, 1643, 1595, 1561, 1443, 1407, 1313, 1298, 1276, 1262, 1117 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.86 (s, 3H), 6.65 (d, $J = 9.6$ Hz, 1H), 7.45 (m, 1H), 7.88 (m, 2H), 8.32 (m, 2H), 8.59 (d, $J = 3.6$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 52.1, 109.8, 119.8, 122.1, 126.1, 137.0, 137.5, 146.7, 141.9, 148.2, 148.24, 158.0, 159.1, 164.6. m/z 273.1. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{N}_4\text{O}_3$ [$\text{M}+\text{H}^+$] 273.0982, found 273.0988.

(*Z*)-1-((Amino(phenyl)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid **9a** Pale yellow solid. Yield 0.16 g (50%). m.p. (DSC) (10 °C/min) onset 263.15 °C, maximum 265.27 °C. IR (ATR) ν_{\max} 3445, 3311, 3213, 1700, 1634, 1600, 1557, 1535, 1437, 1400, 1242, 1216, 1132 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 6.45 (d, $J = 9.2$ Hz, 1H), 7.12 (brs, 2H), 7.46 (m, 2H), 7.53 (m, 1H), 7.72 (dd, $J = 2.4, 9.2$ Hz, 1H), 7.88 (d, $J = 9.2$ Hz, 1H), 8.04 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ_{C} : 109.5, 119.8, 127.8, 128.6, 131.4, 133.3, 137.2, 142.4, 159.0, 162.0, 165.8. m/z 258.1. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{12}\text{N}_3\text{O}_3$ [$\text{M}+\text{H}^+$] 258.0873, found 258.0882.

(*Z*)-1-((amino(4-fluorophenyl)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid **9d** White solid. Isolated by filtration. Yield 3.67 g (77%) (DSC) (10 °C/min) onset 281.76 °C, maximum 283.15 °C. IR (ATR) ν_{\max} 3431, 3330, 3230, 1699, 1646, 1608, 1562, 1532, 1518, 1449, 1415, 1320, 1272, 1231, 1164, 1117, 834 cm^{-1} . ^1H NMR (400 MHz, DMSO) δ_{H} : 3.75 (s, 3H), 6.44 (d, $J = 9.6$ Hz, 1H), 7.20 (brs, 1H), 7.31 (t, $J = 8.8$ Hz, 2H), 7.73 (d, 9.6 Hz, 1H), 7.94 (m, 2H), 8.04 (s, 1H). ^{19}F δ_{F} : -109.8. ^{13}C NMR (100 MHz, DMSO) δ_{C} : 109.6, 115.6, 119.7, 129.76, 130.3, 137.3, 142.4, 158.9, 161.0, 164.2, 165.9. m/z 276.1; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3\text{F}$ [$\text{M}+\text{H}^+$] 276.0779, found 276.0784.

(*Z*)-1-((amino(pyridin-2-yl)methylene)amino)-6-oxo-1,6-dihydropyridine-3-carboxylic acid **9k** White solid. Yield 0.90 g (97%). m.p. (DSC) (10 °C/min) onset 300.22 °C, maximum 300.77 °C. IR (ATR) ν_{\max} 3441, 3224, 1714, 1697.5, 1648, 1623, 1586, 1534, 1440, 1397, 1363, 1282, 1239, 1209, 1132, 770, 763 cm^{-1} . ^1H NMR (400 MHz, TFA- d_4) δ_{H} : 7.21 (d, $J = 9.5$ Hz, 1H), 8.40 (dd, 1H, $J = 8.1, 9.9$ Hz), 8.43 (d, $J = 9.5$ Hz, 1H), 8.68 (d, 1H), 8.76 (d, $J = 8.1$ Hz, 1H), 8.91 (dd, $J = 8.1, 8.1$ Hz, 1H), 9.07 (d, $J = 9.9$ Hz, 1H). ^{13}C NMR (125 MHz, TFA) δ_{C} : 115.1, 119.1, 125.8, 130.1, 141.1, 141.7, 141.8, 143.1, 148.5, 154.51, 161.7, 167.7. m/z 259.1. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{11}\text{N}_4\text{O}_3$ [$\text{M}+\text{H}^+$] 259.0831, found 259.0833.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

1-D and 2-D NMR characterization of **E**, ^1H NMR, ^{13}C NMR spectra of all other compounds (PDF)

Crystallographic information (cif)

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