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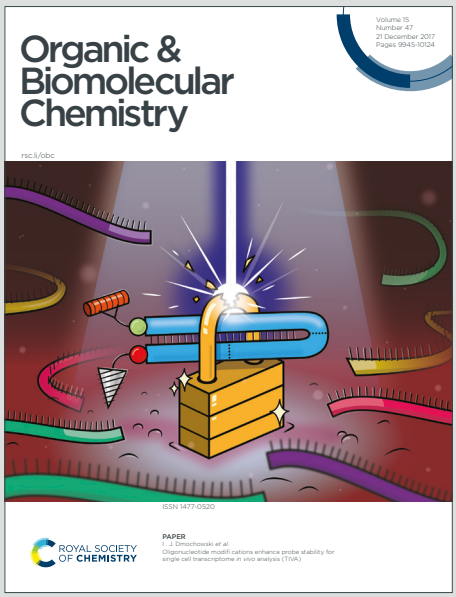

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Novel one-pot synthesis of imidazolinones from ester: A concise synthesis of GSK2137305

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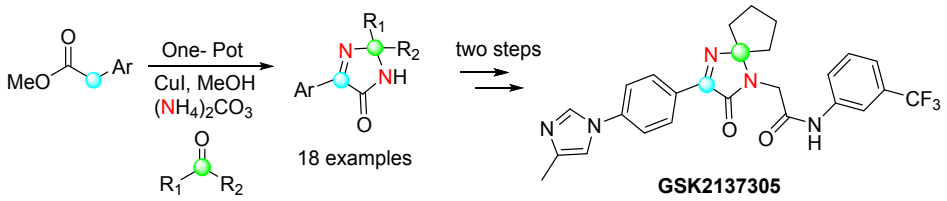

- **One-pot synthesis of imidazolinones**
- **Protocol via C-H activation,C-N formation and condensation with ketone**
- **18 samples,yields up to 85%**
- **A concise approach to obtain GSK213705**

ABSTRACT: A new copper-catalyzed one–pot reaction resulted in the practical synthesis of imidazolinones in moderate yield from the ester. The use of inexpensive copper iodide as catalyst, $(NH_4)_2CO_3$ as the nitrogen source and readily available starting materials makes this process economically viable. Applying this protocol to the synthesis of GSK213705, a concise approach was developed to obtain GSK213705 from the ester in only three steps with an overall yield of 26.9%.

Introduction

Imidazolinones are not only particularly relevant due to their abundance in the chromophoric system of the green fluorescent protein (GFP),[1] but also belong to a class of herbicides.[2] Many natural and therapeutic products with other biological activities also contain imidazolinone core,[3] such as Kottamides A-D with antitumor activity,[4] SCH900822 with hypoglycemic activity,[5] and GSK2137305, an effective and selective glycine transporter type 1 (GlyT1) inhibitor for potential treatment of neuropsychiatric disorders.[6] Some imidazolinones and complexes of imidazolinones with transition metals such as copper, rhodium, palladium and ruthenium are excellent enantioselective catalysts for carbon-carbon coupling reactions.[7,8] The importance of imidazolinones led to the versatile methods for the formation of imidazolinone core (Scheme 1).[1b,2,6,9]

In the past decade, metal-catalyzed C-H bond activation and amination have been favored.[10-11] The activation energy of C-H can be reduced by directly metal-catalyzed activation of the C-H, which makes the reaction easier and simplifies the synthetic process. We are interested in tandem metal-catalyzed transformation for the heterocyclic synthesis,[12] especially the α-amination catalyzed by transition metal complexes,[13] which is an attractive reaction for the synthesis of amine derivatives and amino-functionalized heterocycles.

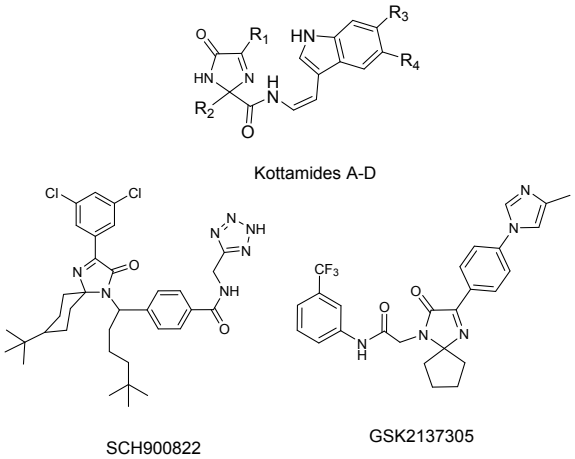

Figure 1. Structure of Bioactive Imidazolinones

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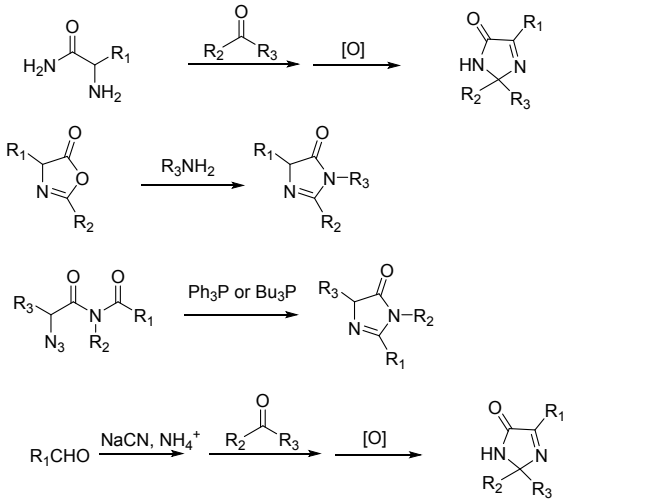
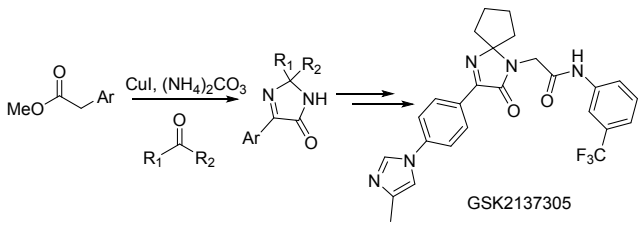
In this paper, we demonstrated that the phenylacetates, initiated by a copper salt with inorganic $(NH_4)_2CO_3$ as the nitrogen source, form the divergent imidazolinones in one-pot reaction. The approach provides a simple and rapid synthesis of imidazolinones derivatives and has certain versatility. Thus, it may provide a new convenient route to synthitic bioactive imidazolinones.

Scheme 1 Versatile Methods for Imidazolinones Synthesis

Previous works



This work



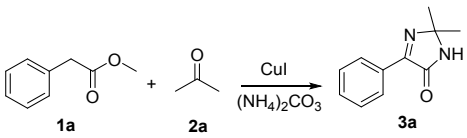
Results and discussion

Initially, we began to investigate the best reaction conditions by using methyl phenylacetate **1a**, acetone,CuI and $(NH_4)_2CO_3$ under the condition of heating (**Table 1**). The result **(Table 1**, entry 1) shows that one-pot reaction of methyl phenylacetate and acetone with $(NH_4)_2CO_3$ nitrogen source was successfully initiated by copper iodide to form the desired imidazolinone **3a**. The structure of **3a** was further confirmed by the X-ray single crystal analysis (detailed crystal data is provided in the Supporting Information).

In the meantime, we also studied the effects of solvent, temperature, and the amount of catalyst CuI on the reaction (Table 1). We replaced the methanol solvent with THF, toluene, DMSO, and DMF. The results indicate that methanol is only an effective solvent for the reaction, which may be related the good solubility of ammonia in methanol. We could not find any imidazolinone product **3a** while we used THF or toluene as solvent (Table 1, entries 4, 5). Similarly, there was only trace amounts of the product to form in the reaction with DMSO or DMF as solvent (Table 1, entries 6, 7). The effect of reaction temperature displays that the optimal temperature was 100 °C and the yield declined at higher (120 °C, Table 1, entry 11) or lower reaction temperatures (room temperature, 65 °C, and 80 °C, Table 1, entries 8-10). The catalyst CuI is necessary for the reaction (Table 1, entry 3), however, if the amount of CuI decreased from 10% to 5%, the reaction still maintain a good yield (Table 1, entry 2).

The effect of reaction time on the reaction depends on the structure of the substrate. It only takes 1 to 2 hours to get **3a** in 52% yield, prolonging the reaction time did not further improve the yield significantly. However, the product **3n** of 42% yield can be obtained by the reaction of 6 hours from dichlorophenyl acetate **1n** and a 12-hour reaction gave a yield of 60% under the same other conditions.

Table 1. Optimization of Reaction Conditions

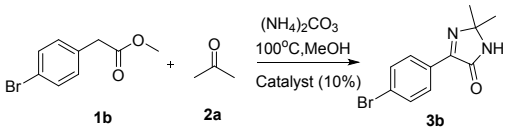


Entry	Solvent	Temperature(℃)	Amount of CuI(%)	Yield(%)
1	MeOH	100	10	52
2	MeOH	100	5	50
3	MeOH	100	0	NR
4	THF	100	10	NR
5	Toluene	100	10	NR
6	DMSO	100	10	Trace
7	DMF	100	10	Trace
8	MeOH	rt	10	NR
9	MeOH	65	10	Trace
10	MeOH	80	10	26
11	MeOH	120	10	45

Mole ratio of methyl phenylacetate, acetone, catalyst, and $(NH_4)_2CO_3$ was 1 : 1 : 0.1 : 20; NR: no product **3a** was found; rt: room temperature.

Next, maintaining other optimal reaction conditions not changed, we investigate the effect of different metal catalysts on the imidazolinone synthesis. Methyl 4-bromophenylacetate **1b** was selected as substrate for the formation of imidazolinone **3b** which is the analogous of the key intermediate **3c** for the synthesis of GSK213705. The results (Table 2) show that only copper catalysts are effective in this one-pot reaction of methyl 4-bromophenylacetate and acetone (Table 2, entries 2-7). Although dinitrato 1,10-phenanthroline copper (II) is a little better catalyst for the reaction, copper iodide is still selected for the next step study due to its low cost and environmental friendliness. As with **3a**, **3b** was not found in the reaction without the catalyst (Table 1, entry 3；Table 2, entry 1). The other metal catalysts, such as palladium, ruthenium, and silver complexes, also failed to initiate the reaction (Table 2, entries 8-11).

Table 2. Selection of Catalysts.



Entry	Catalyst	Yield(%)
1	--	NR

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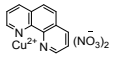
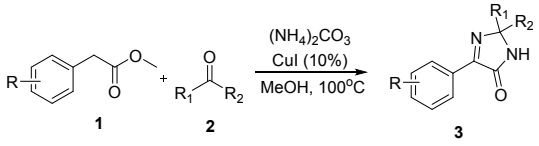
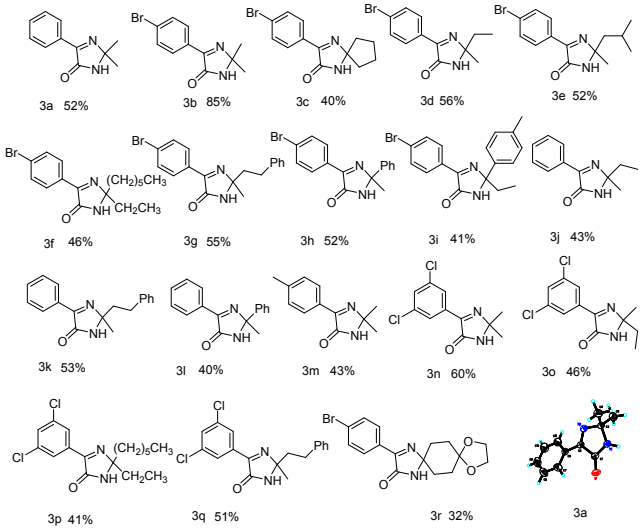
2	CuI	85
3	$CuCl_2$	84
4	$[Cu(CH_3CN)_4]ClO_4$	83
5	Cu	72
6	CuBr	82
7		87
8	$Pd(acac)_2$	NR
9	$Ru_3(CO)_{12}$	NR
10	$AgCF_3SO_3$	NR
11	$Yb(CF_3SO_3)_3$	NR

NR: no product **3b** was found

Furtherly, we explored the scope of the new imidazolinone synthesis, eighteen imidazolinones were obtained from different substrates under the optimized conditions in which the reaction for the imidazolinone synthesis was carried out in MeOH at 100 °C for 2~12h with mole ratio of methyl phenylacetate, acetone, CuI, and $(NH_4)_2CO_3$ of 1 : 1 : 0.1 : 20.We applied four different methyl phenylacetate compounds and a variety of ketones as substrates to the cyclization reaction.

Scheme 2 Formation of Divergent Imidazolinones from the Ester

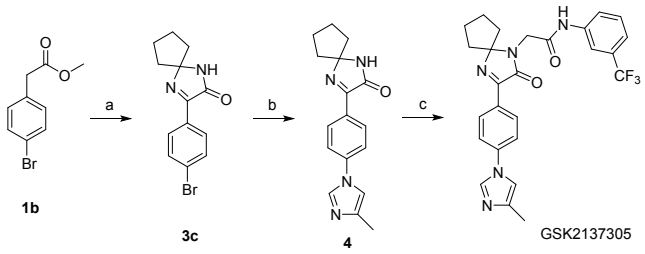




The initial eight-step synthesis of GSK2137305 provided <5% yield of crude product and must be further purified by preparative HPLC to remove a regioisomeric impurity.[6] An improved four-stage synthesis using a highly toxic reagent NaCN has an overall yield of 12% for GSK2137305,[9b] which was further optimized in its third step to increase overall yield to 25.7%, but the use of NaCN could not be excluded.[14] Zhao, et al developed a new method for the synthesis of GSK2137305, but the key imidazolinone intermediate has a yield of only 33%, resulting in only 1.4% of overall yield for the six-step synthesis approach.[15] Subsequently, we applied our new imidazolinone synthesis to the synthesis of GSK2137305 (Scheme 3).

The synthesis of GSK2137305 was completed as shown in Scheme 3. The key step in the three-step synthesis is the formation of imidazolinone **3c**, which was carried out from commercially available methyl 4-bromophenylacetate **1b** and cyclopentanone with ammonium carbonate as nitrogen source under copper iodide catalysis in 40% yield. Compared with previous synthesis of **3c**,[9b,14] the new synthesis of **3c** avoided the use of NaCN and greatly increased the yield. *N*-arylation of 4-methylimidazole with **3c** followed the reference procedure,[14] however, the less expensive bis(dibenzylidene-acetone)Pd catalyst not original $Pd_2(dba)_3$ was used to achieve nearly similar yield (85% yield). Subsequent substitution reaction of **4** easily formed GSK2137305 in DMF in 79% yield. A total yield of 26.9% was obtained for the synthesis of GSK2137305 in three steps from commercially available **1b**.

Scheme 3. Synthesis of GSK2137305



a. cyclopentanone, $(NH_4)_2CO_3$, 10%CuI, MeOH, 40% yield. *b.* 4-methyl-1*H*-imidazole,bis(dibenzylideneacetone)Pd, L1(0.2%), K_3PO_4(2.0 eq.), toluene-dioxane（1 : 1）, 85% yield. *c.* 2-chloro-*N*-(3-(trifluoromethyl) phenyl) acetamide, NaH（2.5 eq.), DMF, 79% yield.

During the imidazolinone synthesis reaction, we examined the reaction mixture and detected the presence of the intermediate **F** by LC-MS. Meanwhile, the effects of air and trace amount water on the reaction were also investigated. In the absence of air or water, only trace target product was obtained, indicating that the oxygen was beneficial to this reaction. It may also mean that α-oxidation is easier than α-amination. Therefore, we speculed a possible pathway of imidazolinone synthesis, as shown in **Scheme 4**. The novel imidazolinone synthesis possibly occurred via α-imination of the ester by C-H activation oxidation affording α-oxophenyl acetic ester in the presence of copper salt[16], followed by a formation of imino group due to the amine source, and aminolysis then a following condensation reaction with ketone.

Scheme 4. Conjecture on the formation pathway of Imidazolinone

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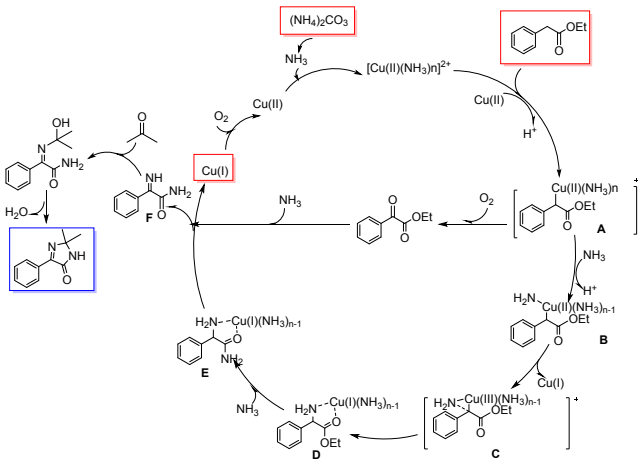

Conclusion

In summary, we have developed a novel imidazolinone synthesis process, which is carried out from commercially available esters and ketones with inorganic ammonium carbonate as nitrogen source under the catalysis of less expensive copper iodide in moderate yield. This reaction is environmentally friendly and easy to control. The method was applied to the synthesis of GSK2137305 and a concise preparation approach to GSK2137305 was developed with a much higher overall yield from readily available starting materials.

Experimental section

General Information. All reactions were carried out under air atmosphere, unless otherwise mentioned. Commercially available materials were used as received without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on commercial silica gel plates using UV light as a visualizing agent . Commercial silica gel was used for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz or 600 MHz spectrometer. ^{1}H NMR spectra were referenced to Chloroform-d (7.26 ppm) or DMSO-d_6 (2.50 ppm), and reported as follows; chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to Chloroform-d (77.23 ppm) or DMSO-d_6(39.51 ppm). Mass spectral data were obtained from Bruker Daltonics Data analysis 3.2 mass spectrometer. X-Ray data were collected on a Bruker APEX-II equipped with a CCD area detector using Mo/Kα radiation. The structures were solved by direct method using SHELXL-97.

General procedures for imidazolinones 3

A 25ml sealed tube was charged with CuI (10 mmol %), carboxylic ester (0.37 mmol), ketone (0.37 mmol), $(NH_4)_2CO_3$ (7.4 mmol), and MeOH (2 mL), the mixture was stirred at 100℃ in an oil bath for 2-12h. After disappearance of the reactant (monitored by TLC) , the reaction mixture was filtered and the filtrate was concentrated under reduced pressure.The crude residue was purified by silica gel chromatography using petroleum ether/ ethyl acetate as eluent to give pure product **3**.

2,2-Dimethyl-5-phenyl-2,3-dihydro-4*H*-imidazol-4-one (3a)

Prepared according to the general procedure. Methyl phenylacetate(55 mg, 0.37 mmol) and acetone(21 mg, 0.37 mmol) were employed to give **3a** (36 mg, 52%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.79 (s, 1H), 8.42-8.37 (m, 2H), 7.56-7.45 (m, 3H), 1.60 (s, 6H). ^{13}C NMR (100 MHz, Chloroform-d) δ 165.2, 160.9, 131.8, 130.1, 128.5, 128.5, 80.3, 27.0. HRMS (ESI) m/z calcd for $C_{11}H_{13}N_2O$ ($M+H^+$): 189.1028, found: 189.1022.

5-(4-Bromophenyl)-2,2-dimethyl-2,3-dihydro-4*H*-imidazol-4-one (3b)

Prepared according to the general procedure. Methyl 4-bromophenylacetate(85 mg, 0.37 mmol) and acetone(21 mg, 0.37 mmol) were employed to give **3b** (84 mg, 85%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.12 (s, 1H), 8.29 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 1.60 (s, 6H). ^{13}C NMR (100 MHz, Chloroform-d) δ 165.4, 160.1, 131.7, 129.9, 129.3, 126.4, 80.7, 26.9. HRMS (ESI) m/z calcd for $C_{11}H_{12}BrN_2O$ ($M+H^+$): 267.0133, found: 267.0126.

3-(4-Bromophenyl)-1,4-diazaspiro[4.4]non-3-en-2-one (3c)

Prepared according to the general procedure. Methyl 4-bromophenylacetate(85 mg, 0.37 mmol) and cyclopentanone (31 mg, 0.37 mmol. It is noted that the increase of the ratio of cyclopentanone will reduce the yield.) were employed to give **3c** (43 mg, 40%) as a taupe solid.^{1}H NMR (400 MHz, Chloroform-d) δ 8.70 (s, 1H), 8.29 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.1Hz, 2H), 2.15-2.02 (m, 4H), 1.94 (m, 4H). ^{13}C NMR (100 MHz, Chloroform-d) δ 165.3, 159.4, 131.7, 129.7, 129.5, 126.3, 90.4, 37.5, 24.4. HRMS (ESI) m/z calcd for $C_{13}H_{14}BrN_2O$ ($M+H^+$): 293.0290, found: 293.0283.

5-(4-Bromophenyl)-2-ethyl-2-methyl-2,3-dihydro-4*H*-imidazol-4-one (3d)

Prepared according to the general procedure. Methyl 4-bromophenylacetate(85 mg, 0.37 mmol) and 2-butanone (27 mg, 0.37 mmol) were employed to give **3d** (58 mg, 56%) as a yellowish solid.^{1}H NMR (400 MHz, Chloroform-d) δ 8.71 (s, 1H), 8.29 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 1.94 (q, J = 7.4 Hz, 2H), 1.57 (s, 3H), 0.86 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 165.6, 160.5, 131.7, 129.9, 129.3, 126.4, 83.1, 32.6, 25.3, 7.9. HRMS (ESI) m/z calcd for $C_{12}H_{14}BrN_2O$ ($M+H^+$): 281.0290, found: 281.0283.

5-(4-Bromophenyl)-2-isobutyl-2-methyl-2,3-dihydro-4*H*-imidazol-4-one (3e)

Prepared according to the general procedure. Methyl 4-bromophenylacetate(85 mg, 0.37 mmol) and 4-methyl-2-pentanone (37 mg, 0.37 mmol) were employed to give **3e** (59 mg, 52%) as a yellowish solid.^{1}H NMR (400 MHz, Chloroform-d) δ 9.01 (s, 1H), 8.29 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 1.88 -1.78 (m, 2H), 1.55 (s, 3H), 0.89 (m, 7H). ^{13}C NMR (100 MHz, Chloroform-d) δ 165.7, 160.2, 131.8, 129.9, 129.5, 126.4, 83.2, 48.1, 26.4, 24.3, 24.2, 23.9. HRMS (ESI) m/z calcd for $C_{14}H_{18}BrN_2O$ ($M+H^+$): 309.0603, found: 309.0595.

5-(4-Bromophenyl)-2-ethyl-2-hexyl-2,3-dihydro-4*H*-imidazol-4-one (3f)

Prepared according to the general procedure. Methyl 4-bromophenylacetate(85 mg, 0.37 mmol) and 3-nonanone (53 mg, 0.37 mmol) were employed to give **3f** (60 mg, 46%) as a yellow liquid.^{1}H NMR (400 MHz, Chloroform-d) δ 8.96 (s, 1H), 8.28 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 2.00–1.85 (m, 4H), 1.24 (m, 8H), 0.81 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-d) δ 166.0, 160.9, 131.7, 129.8, 129.3, 126.3, 85.4, 37.9, 31.5, 31.2, 29.2, 22.9, 22.5, 13.9, 7.5. HRMS (ESI) m/z calcd for $C_{17}H_{24}BrN_2O$ ($M+H^+$): 351.1072, found: 351.1065.

5-(4-Bromophenyl)-2-methyl-2-phenethyl-2,3-dihydro-4*H*-imidazol-4-one (3g)

Prepared according to the general procedure. Methyl 4-bromophenylacetate(85 mg, 0.37 mmol) and benzylacetone (55 mg, 0.37 mmol) were employed to give **3g** (73 mg, 55%) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 10.05

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(s, 1H), 8.28 (d, J = 6.9 Hz, 2H), 7.71 (d, J = 6.9 Hz, 2H), 7.24 (t, J = 7.5 Hz, 2H), 7.15 (m , 3H), 2.56-2.33 (m, 2H), 2.08 (m, 2H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*6) δ 164.3, 160.4, 141.4, 131.8, 130.1, 129.9, 128.5, 128.3, 126.0, 125.6, 81.9, 40.9, 29.5, 25.9. HRMS (ESI) m/z calcd for $C_{18}H_{18}BrN_2O$ (M+H$^+$): 357.0603, found:357.0569.

5-(4-Bromophenyl)-2-methyl-2-phenyl-2,3-dihydro-4*H*-imidazol-4-one(3h)

Prepared according to the general procedure. Methyl 4-bromophenylacetate(85 mg, 0.37 mmol) and acetophenone (45 mg, 0.37 mmol) were employed to give **3h** (63 mg, 52%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 10.70 (s, 1H), 8.32 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 7.7 Hz, 2H), 7.35 (m, 3H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*6) δ 164.1, 159.6, 141.3, 137.6, 131.7, 130.0, 129.5, 128.5, 127.9, 125.6, 83.1, 28.6. HRMS (ESI) m/z calcd for $C_{16}H_{14}BrN_2O$ (M+H$^+$): 329.0290, found: 329.0283.

5-(4-Bromophenyl)-2-ethyl-2-(p-tolyl)-2,3-dihydro-4*H*-imidazol-4-one(3i)

Prepared according to the general procedure. Methyl 4-bromophenylacetate(85 mg, 0.37 mmol) and 4-methylpropiophenone (55 mg, 0.37 mmol) were employed to give **3i** (54 mg, 41%) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 10.03 (s, 1H), 8.35 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 2.33 (s, 3H), 2.30–2.10 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 166.3, 160.0, 137.9, 137.2, 131.7, 130.0, 129.3, 129.2, 126.5, 125.9, 87.2, 34.7, 21.0, 8.1. HRMS (ESI) m/z calcd for $C_{18}H_{18}BrN_2O$ (M+H$^+$): 357.0603, found: 357.0596.

2-Ethyl-2-methyl-5-phenyl-2,3-dihydro-4*H*-imidazol-4-one (3j)

Prepared according to the general procedure. Methyl phenylacetate(55 mg, 0.37 mmol) and 2-butanone (27 mg, 0.37 mmol) were employed to give **3j** (32 mg, 43%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.38 (d, J = 6.6 Hz, 2H), 8.02 (s, 1H), 7.56-7.43 (m, 3H), 1.95 (q, J = 7.5 Hz, 2H), 1.58 (s, 3H), 0.86 (t, J = 7.5Hz, 3H). ^{13}C NMR (100 MHz, $CDCL_3$) δ 166.1, 161.5, 131.4, 130.5, 128.5, 128.3, 82.9, 32.5, 25.3, 7.9. HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2O$ (M+H$^+$): 203.1184, found: 203.1179.

2-Methyl-2-phenethyl-5-phenyl-2,3-dihydro-4*H*-imidazol-4-one (3k)

Prepared according to the general procedure. Methyl phenylacetate(55 mg, 0.37 mmol) and benzylacetone (55 mg, 0.37 mmol) were employed to give **3k** (55 mg, 53%) as a yellow solid.^{1}H NMR (400 MHz, Chloroform-d) δ 9.18 (s, 1H), 8.42 (d, J = 7.5 Hz, 2H), 7.51 (m, 3H), 7.24 (m, 2H), 7.15 (m, 3H), 2.59 (m, 2H), 2.28 (m, 2H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 166.0, 161.6, 140.9, 131.6, 130.4, 128.5, 128.4, 128.3, 128.2, 125.9, 82.5, 41.1, 29.8, 25.9. HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O$ (M+H$^+$): 279.1497, found: 279.1490.

2-Methyl-2,5-diphenyl-2,3-dihydro-4*H*-imidazol-4-one (3l)

Prepared according to the general procedure. Methyl phenylacetate(55 mg, 0.37 mmol) and acetophenone (45 mg, 0.37 mmol) were employed to give **3l** (37 mg, 40%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.77 (s, 1H), 8.50–8.42 (m, 2H), 7.62-7.44 (m, 5H), 7.42-7.30 (m, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 166.1, 160.8, 140.7, 131.7, 130.4, 128.7, 128.6, 128.5, 128.2, 125.6, 83.8, 28.7. HRMS (ESI) m/z calcd for $C_{16}H_{15}N_2O$ (M+H$^+$): 251.1184, found: 251.1177.

2,2-Dimethyl-5-(p-tolyl)-2,3-dihydro-4*H*-imidazol-4-one (3m)

Prepared according to the general procedure. Methyl 4-methylphenylacetate(61 mg, 0.37 mmol) and acetone(21 mg, 0.37 mmol) were employed to give **3m** (32 mg, 43%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.29 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 2.41 (s, 3H), 1.59 (s, 6H). ^{13}C NMR (100 MHz, Chloroform-d) δ 165.8, 160.8, 141.9, 129.2, 128.3, 127.8, 80.3, 27.0, 21.6. HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2O$ (M+H$^+$): 203.1184, found: 203.1177.

5-(3,5-Dichlorophenyl)-2,2-dimethyl-2,3-dihydro-4*H*-imidazol-4-one (3n)

Prepared according to the general procedure. Methyl 2-(3,5-dichlorophenyl)acetate (81 mg, 0.37 mmol) and acetone(21 mg, 0.37 mmol) were employed to give **3n** (57 mg, 60%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.41 (s, 1H), 8.34 (d, J = 2.0 Hz, 2H), 7.50 (t, J = 2.0 Hz, 1H), 1.62 (s, 6H). ^{13}C NMR (100 MHz, Chloroform-d) δ 164.8, 158.9, 135.2, 133.1, 131.3, 126.6, 81.1, 26.8. HRMS (ESI) m/z calcd for $C_{11}H_{11}Cl_2N_2O$ (M+H$^+$): 257.0248, found: 257.0242.

5-(3,5-Dichlorophenyl)-2-ethyl-2-methyl-2,3-dihydro-4*H*-imidazol-4-one (3o)

Prepared according to the general procedure. Methyl 2-(3,5-dichlorophenyl)acetate (81 mg, 0.37 mmol) and 2-butanone (27 mg, 0.37 mmol) were employed to give **3o** (46 mg, 46%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.05 (s, 1H), 8.33 (d, J = 1.9 Hz, 2H), 7.50 (t, J = 1.9 Hz, 1H), 1.96 (q, J = 7.6 Hz, 2H), 1.59 (s, 3H), 0.87 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 165.0, 159.3, 135.2, 133.0, 131.2, 126.6, 83.5, 32.5, 25.1, 7.85. HRMS (ESI) m/z calcd for $C_{12}H_{13}Cl_2N_2O$ (M+H$^+$): 271.0405, found: 271.0399.

5-(3,5-Dichlorophenyl)-2-ethyl-2-hexyl-2,3-dihydro-4*H*-imidazol-4-one (3p)

Prepared according to the general procedure. Methyl 2-(3,5-dichlorophenyl)acetate (81 mg, 0.37 mmol) and 3-nonanone (53 mg, 0.37 mmol) were employed to give **3p** (52 mg, 41%) as a yellow liquid.^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.90 (s, 1H), 8.34 (d, J = 1.9 Hz, 2H), 7.50 (d, J = 1.9 Hz, 1H), 2.00-1.88 (m, 4H), 1.25 (m, 8H), 0.82 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-d) δ 165.4, 159.6, 135.2, 133.0, 131.2, 126.6, 85.8, 37.9, 31.5, 31.1, 29.2, 23.0, 22.5, 13.9, 7.4. HRMS (ESI) m/z calcd for $C_{17}H_{23}Cl_2N_2O$ (M+H$^+$): 341.1187, found: 341.1179.

5-(3,5-Dichlorophenyl)-2-methyl-2-phenethyl-2,3-dihydro-4*H*-imidazol-4-one (3q)

Prepared according to the general procedure. Methyl 2-(3,5-dichlorophenyl)acetate (81 mg, 0.37 mmol) and benzylacetone (55 mg, 0.37 mmol) were employed to give **3q** (65 mg, 51%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.67 (s, 1H), 8.24 (d, J = 2.0 Hz, 2H), 7.43 (t, J = 2.0 Hz, 1H), 7.22-7.13 (m, 2H), 7.13 -7.03 (m, 3H), 2.49 (m, 2H), 2.28– 2.09 (m, 2H), 1.56 (s, 3H). ^{13}C NMR (150 MHz, Chloroform-d) δ 164.9, 159.5, 140.6, 135.3, 132.9, 131.4, 128.5, 128.2, 126.7, 126.2, 82.9, 40.8, 29.9, 25.8. HRMS (ESI) m/z calcd for $C_{18}H_{17}Cl_2N_2O$ (M+H$^+$): 347.0718, found: 347.0709.

11-(4-Bromophenyl)-1,4-dioxa-9,12-diazadispiro[4.2.48.25] tetradec-11-en-10-one (3r)

Prepared according to the general procedure. Methyl 4-bromophenylacetate(85 mg, 0.37 mmol) and 1,4-dioxaspiro[4.5]decan-8-one (58 mg, 0.37 mmol) were employed to give **3r** (43 mg, 32%) as a white solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.28 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 3.91 (s, 4H), 2.05- 1.50 (m, 8H).^{13}C NMR (101 MHz, DMSO-d_6) δ 164.1, 160.3, 131.8, 130.1, 130.0, 125.6, 107.4, 81.3, 64.0, 34.4, 31.5. HRMS (ESI) m/z calcd for $C_{16}H_{18}BrN_2O_3$ (M+H$^+$): 365.0501, found: 365.0493.

Synthetic procedures and spectra data of 3-(4-(4-methyl-1*H*-imidazol-1-yl)phenyl)-1,4-diazaspiro[4.4]non-3-en-2-one. An oven-dried vial was equipped with a magnetic stir bar and

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charged with $Pd(dba)_2$ (0.3 mg, 0.0005 mmol) and L1 (0.5 mg, 0.001 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of 3 times). Then, toluene (0.5 mL) was added via syringe. This dark purple mixture was stirred at 115 °C for 10 min. A second oven-dried vial which was equipped with stir bar was charged with 1a (30 mg, 0.1 mmol), 4-methylimidazole (17 mg, 0.2 mmol) and K_3PO_4 (42mg, 0.2 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of 3 times). 0.2 mL of the premixed catalyst solution was transferred to the second vial via syringe and then toluene (0.4 mL) and dioxane (0.6 mL) were added to the second vial. The reaction was heated at 115 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with brine, dried over $MgSO_4$, concentrated in vacuo and purified via silica gel chromatography (EtOAc) to provide the title compound as a white solid (26 mg, 85%), ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.42 (d, J = 8.4 Hz, 2H), 8.27 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.55 (s, 1H), 2.17 (s, 3H), 1.97–1.81 (m, 8H).^{13}C NMR (150 MHz, DMSO-d_6) δ 164.5, 159.2, 139.4, 139.3, 135.2, 129.9, 128.9, 119.7, 114.2, 90.1, 37.6, 24.3, 14.0.HRMS (ESI) m/z calcd for $C_{17}H_{19}N_4O$ ($M+H^+$): 295.1559, found: 295.1553

Synthesis of GSK 2137305. An oven-dried vial was equipped with a stir bar and charged with 3-(4-(4-Methyl-1H-imidazol-1-yl)phenyl)-1,4-diazaspiro[4.4]non-3-en-2-one (20mg, 0.07 mmol).The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of 3 times). Then, NaH (4mg,0.17mmol) and DMF (1 mL) was added to the vial and stirred at room temperature for 10 min. 2-chloro-*N*-(3-(trifluoromethyl)phenyl) acetamide (20mg, 0.084 mmol) was added and the reaction mixture was stirred at room temperature for 12 h , then diluted with EtOAc, washed with brine, dried over $MgSO_4$, concentrated in vacuo and purified via silica gel chromatography (n-hexane : acetone=1:1 and 1:1.2) to provide the title compound as a white solid (27 mg, 79%), Mp 258-260 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.45 (d, J = 8.5 Hz, 2H), 8.28 (d, J = 1.4 Hz, 1H), 8.11 (s, 1H), 7.78 (m, 3H), 7.61-7.52 (m, 2H), 7.43 (d, J = 7.8 Hz, 1H), 4.38 (s, 2H), 2.18 (s, 3H), 2.12–1.84 (m, 6H), 1.73–1.64 (m, 2H).^{13}C NMR (100 MHz, DMSO-d_6) δ 166.5, 162.8, 157.7, 139.7, 139.4, 139.1, 135.0, 130.4, 129.9, 129.6, 128.6, 124.3 (q, J = 272.4 Hz), 123.0, 120.1 (q, J = 3.6 Hz), 119.7, 115.5 (q, J = 3.5 Hz), 114.1, 93.5, 43.6, 34.6, 23.9, 13.8.

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Author contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally. (match statement to author names with a symbol)

Notes

Any additional relevant notes should be placed here.

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