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ARTICLE TYPE

I₂-DMSO-PTSA: A simple and metal free oxidative cross coupling of imidazo[1,2-*a*]pyridines and methylketones

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Abstract: A simple, highly efficient and selective oxidative cross coupling of imidazo[1,2-*a*]pyridine (IP) compounds (**1**) and methylketones (**2**), promoted by molecular iodine in DMSO in presence of catalytic amount of PTSA have been realized in one pot reaction. This strategy has provided a general route for the synthesis of 1-Aryl-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)ethane-1,2-diones (**3**) with a new C-C bond formation through Kornblum oxidation followed by nucleophilic attack of IP compounds (**1**) on the *insitu* formed phenylglyoxal. Simple reaction conditions, no metal catalysts and selective product formation are the advantages of this protocol.

1. Introduction

Imidazo[1,2-*a*]pyridine compounds are prominent among N-fused heterocycles and have shown interesting biological activities.¹ Based on the diverse biological activities of these compounds *i.e.* antibacterial, antiviral, anti-inflammatory and C-X-C chemokine receptor type-4 (CXCR4) antagonists, a number of drugs from imidazo[1,2-*a*]pyridine (IP) core moiety have come into the market. For example; Nicopidem, GSK812397, Alpidem, Minodronic acid.² (Fig.1).

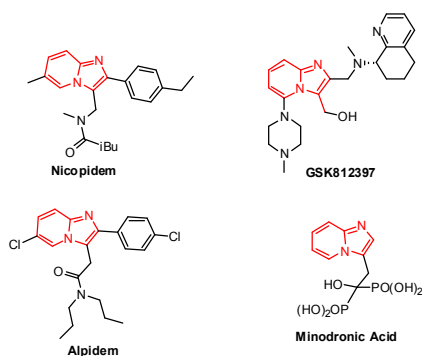


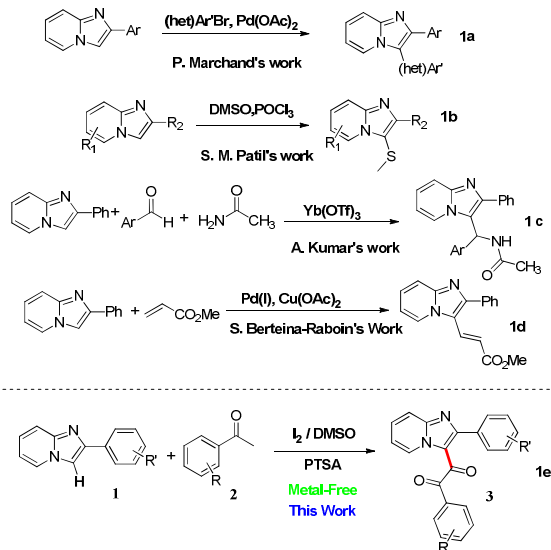
Figure 1: Some of the biological active compounds containing imidazo[1,2-*a*]pyridine frame work

In fact, several reports are available on the synthesis of imidazo[1,2-*a*]pyridine (IP) derivatives and very recently some pioneering examples of imidazo[1,2-*a*]pyridine compounds have been reported by S.Berteina-Raboin.³ However, in recent years, C-H bond functionalization, especially *sp*³ C-H bond towards the formation of C-C and C-heteroatom is one of the most attractive and powerful strategy in organic synthesis.^{4,5}

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This approach not only streamlines the existing synthesis of useful molecular entities, but also contributes to the way chemists think about chemical reactivity and plan the synthesis. Further, functionalization of imidazo[1,2-*a*]pyridines at 2 and 3 position is of very significant as substitution at these positions reported⁶ great impact in terms of biological activity. A growing repertoire of C-H bond functionalization reactions have been reported lately, including arylation, alkylation, alkenylation, insertion, amination, oxidation, borylation, and halogenation.⁷ Despite significant advances in method development, the application of C-H functionalization for the synthesis of structurally complex molecules remains a formidable challenge to the chemical community. Notably, the development of transition-metal free cross-coupling reactions is a highly topical and significant research area in organic synthesis as the transition metals add additional costs and generate stoichiometric amounts of metal salts as waste.



Scheme 1: Previous reports (**1a-d**) and present work (**1e**)

In this context, a very useful methods have been reported on Suzuki cross-coupling reaction for direct arylation of imidazole heterocycles⁸ promoted by Pd(OAc)₂ (Scheme 1a) and recently

S.M. Patil et al. reported methylthiolation of imidazo[1,2-*a*]pyridines with DMSO-POCl₃ (Scheme 1b). Most recently, A. Kumar et al. disclosed the one pot, three-component synthesis of 1-amidomethyl-imidazo[1,2-*a*]pyridines catalyzed by ytterbium triflate (Scheme 1c). Further, S. Bertein-Raboin's team described metal oxidative C–H alkenylation of imidazo[1,2-*a*]pyridines (Scheme 1d). Furthermore, An-Xin Wu and co-workers developed useful protocols for the C-H activation of methyl ketones.⁹ On the other hand iodine and its salts have gained the importance as they have turned out to be a very good alternate to transitional metals and efficient mediators in oxidative coupling reactions.^{10,11}

In view of the prominence gained by the direct C-H bond functionalization reactions coupled with significance of iodine as an alternate to metal catalysts and also our continued interest on the synthesis of bioactive heterocycles,¹² we have planned for the oxidative coupling of IP compounds and ketones in order to functionalize the imidazo[1,2-*a*]pyridines without involving any transition metal catalysts as they are known to pose environmental problem and should be avoided wherever possible. Further, it is highly desirable to develop the green protocols to access the bioactive molecules. On this account, we herein report for the first time, a simple and efficient method for the oxidative cross coupling of imidazo[1,2-*a*]pyridine (**1**) compounds with acetophenones (**2**) promoted by molecular iodine in DMSO in presence of an acid. This strategy provided a powerful and general route to the synthesis of 1-aryl-2-(2-phenylimidazo [1,2-*a*]pyridin-3-yl)ethane-1,2-diones (**3**) (Scheme 1e).

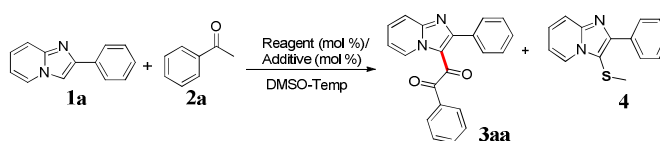
2. Results and discussion

Initially a model reaction was attempted with 2-phenylimidazo[1,2-*a*]pyridine **1a** (1.0 mmol), acetophenone **2a** (1.0 mmol) and I₂ (1.0 mmol) in DMSO (Table 1). To our delight, formation of desired oxidative cross-coupling product **3aa** was observed in 61% yield along with *S*-methylated product **4** in 24% at 100 °C in 12 h. The structure of the products was confirmed by their spectral data. When the dosage of I₂ was increased to 1.5 (equiv), a palpable increase in the yield of **3aa** to 65% was observed. However, further increase in the dosage of I₂ did not lead to significant variation. The reaction was unable to occur in the absence of I₂ indicating the presence of molecular iodine is imperative for the reaction to proceed (Table 1, entry 1-4).

It is well documented that, reaction of acetophenone with molecular iodine in DMSO result in phenylglyoxal and dimethylsulfide. Thus, the resulted phenylglyoxal and dimethylsulfide are probably competing to react with imidazo[1,2-*a*]pyridine derivative **1a** leading to products **3aa** and **4**. However, formation of **3aa** as major product may be attributed to the possible preferential nucleophilic attack of **1** on to phenylglyoxal. Further, experiments were conducted by employing the iodine in combination with bases such as KOH, Et₃N, K₂CO₃, Pyridine, DBU and DABCO in order to verify the yield improvement if any. However, there was no improvement in product yields. A range of temperature was also evaluated to see the effect on the reaction (Table 1, entries 5 and 6), where 100°C was determined as the optimal for cascade of the reaction. Next, studies were conducted by replacing the iodine with PhI(OAc)₂, TBAI, KI, NaI, NIS (Table 1, entries 7-11). However, only PhI(OAc)₂ and TBAI, promoted the reaction and gave the *S*-methylated product **4** exclusively in poor yields. In order to suppress the formation of **4**, the reaction was studied by varying the stoichiometry of acetophenone (1.5 and 2.0 equivalents).

However, these parameters induced the slight improvement in the yields of **3aa** (Table 1, entry 12 and 13). Next, our attention was diverted on to obtain the compound **3aa** exclusively, as a method for exclusive formation of *S*-methylated product **4** is already exist.¹³ Therefore, experiments were carried out by employing catalytic amount (10 mol%) of H₂SO₄, CSA (camphorsulfonic acid), PTSA along with molecular iodine in DMSO independently, presuming, presence of acid may help in activation of aldehyde group in phenylglyoxal. Dramatically, PTSA (Table 1, entry 14) has provided the exclusive formation of compound **3aa** in good yield. Whereas, H₂SO₄ and CSA (Table 1, entry 15 & 16) could not vary the product ratio of **3aa** & **4**. Excited over the formation of **3aa** as sole product, quantity of PTSA has been screened by increasing from 10 mol% to 20 and 30 mol %. However, no significant change was observed.

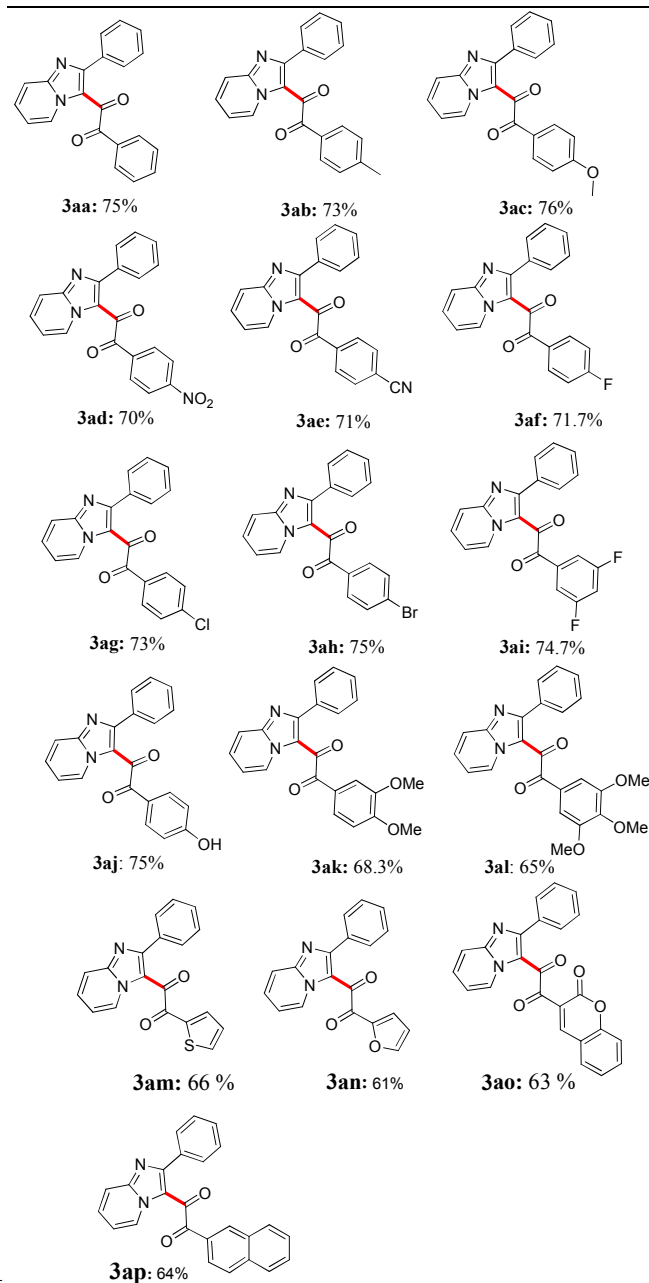
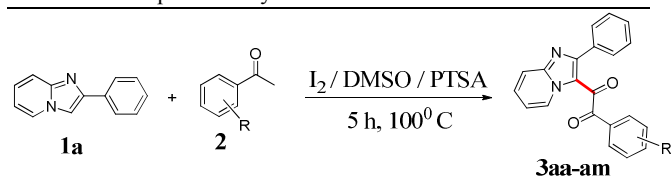
Table 1: Screening to optimize reaction condition^{a,b}



Entry	2 (mmol)	Reagent (equiv) /Additive (mol %)	Temp. (°C)	Yield (%) ^b	
				3aa	4
1	1.0	I ₂ (1.0)	100	61	24
2	1.0	I ₂ (1.5)	100	65	23
3	1.0	I ₂ (2.0)	100	65	23
4	1.0	-----	100	---	---
5	1.0	I ₂ (2.0)	110	43	35
6	1.0	I ₂ (2.0)	120	45	38
7	1.0	PhI(OAc) ₂ (1.0)	100	---	32
8	1.0	TBAI (1.0)	100	---	28
9	1.0	KI	100	---	---
10	1.0	NaI	100	---	---
11	1.0	NIS	100	---	---
12	1.5	I ₂ (1.0)	100	65	24
13	2.0	I ₂ (1.0)	100	66	22
14	1.0	I₂ (1.0)/PTSA (10)	100	75	---
15	1.0	I ₂ (1.0)/H ₂ SO ₄ (10)	100	47	28
16	1.0	I ₂ (1.0)/CSA (10)	100	42	30

^aAll the reactions were carried out using Imidazo[1,2-*a*]pyridine (**1a**) (1.0 mmol) and Acetophenone (**2a**) (1.0 mmol) in DMSO (4 mL) at above mentioned conditions. ^bIsolated yields.

With the optimized conditions in hand, the generality and scope of this protocol was next explored. To our satisfaction, this protocol demonstrated wide scope for aryl methyl ketones bearing electron neutral (*p*-H, *p*-Me), electron-releasing (*p*-OMe, 3,4-di-OMe, 3,4,5-tri-OMe) (Scheme 2, **3aa** to **3ac** & **3ak**, **3al**) and electron-withdrawing (*p*-NO₂, *p*-CN) substituents (Scheme 2, **3ad** to **3ae**). Electronic and steric nature of aromatic ketones has shown no influence on the reaction efficiency. Much to our satisfaction, the method was found to be mild enough to be compatible with halogenated (*p*-Br, *p*-Cl, *p*-F, 3,4-di-F) (Scheme 2, **3af** to **3ai**) substrates. Furthermore heterocyclic (Scheme 2, **3am** to **3ao**) and naphthyl methyl ketones (**3ap**) furnishes the oxidative products in good yields.

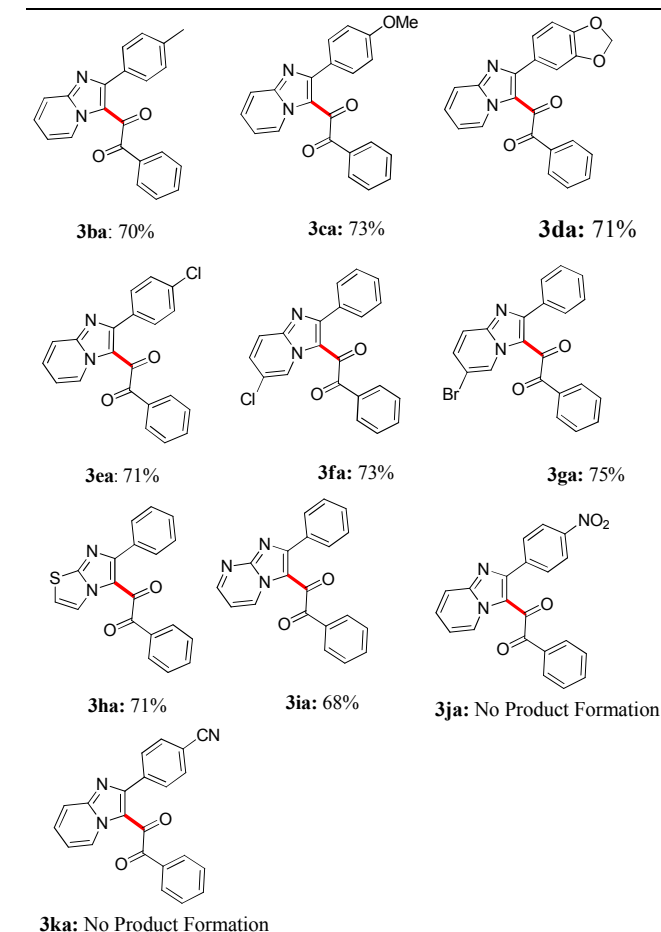
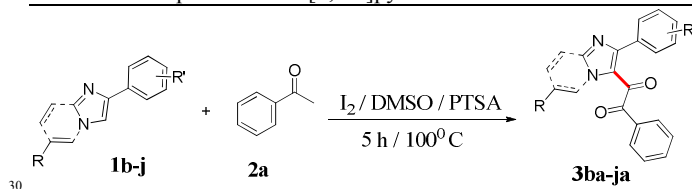
Scheme 2: Scope of methyl ketones^{a,b}

5

^aReaction conditions: Imidazo[1,2-*a*]pyridine (**1a**) (1.0 mmol), Methyl ketones (**2**) (1.0 mmol), I_2 (1.0 mmol) in DMSO (4 mL), PTSA (10 mol %) at $100^\circ C$. ^bIsolated yields.

Next, we studied the reaction with varying the substitution on compound **1**, where substituted imidazo[1,2-*a*]pyridine substrates bearing electron donating groups such as *p*-Me, *p*-OMe, 3,4-(*O*-

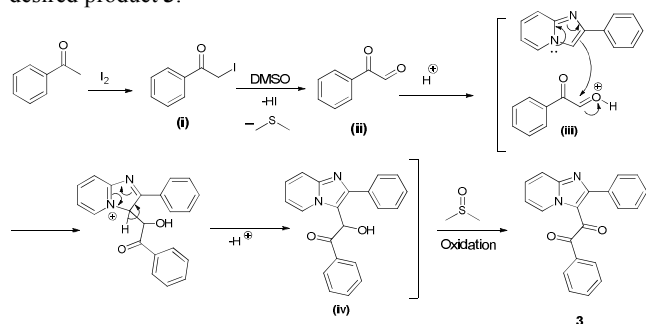
CH_2 -*O*-) on the phenyl ring (Scheme 3, **3ba** to **3da**), furnished the corresponding products in high yields. Substrates bearing halide substitution were also well tolerated and gave the corresponding products in good yields (Scheme 3, **3ea** to **3ga**). However, the substrates bearing electron withdrawing groups such as *p*-NO₂ and *p*-CN on phenyl ring were unsuccessful. This could be attributed to the delocalization of lone pair electrons on the nitrogen in the imidazopyridine ring due to the decrease in electron density on the adjacent phenyl ring. (Scheme 3, **3ja** & **3ka**). Furthermore, 6-phenylimidazo[2,1-*b*]thiazole and 2-phenylimidazo[1,2-*a*]pyrimidine when reacted with acetophenone gave the corresponding products (Scheme 3, **3ha** and **3ia**).

Scheme 3: Scope of imidazo[1,2-*a*]pyridines^{a,b}

^aReaction conditions: Imidazo[1,2-*a*]pyridine (**1b**) (1.0 mmol), acetophenone (**2a**) (1.0 mmol), I_2 (1.0 mmol) in DMSO (4 mL), PTSA (10 mol%) at $100^\circ C$. ^bIsolated yields

A plausible mechanism has been proposed for the exclusive formation of **3** based on the previous reports. Treatment of acetophenone with molecular iodine generates the

α -iodoketone (**i**), which on subsequent reaction with DMSO collapse into phenylglyoxal (**ii**) and dimethylsulfide (DMS) by Kornblum oxidation. Next, The imidazo[1,2-*a*]pyridine nucleophile could attack on the electron deficient phenylglyoxal species (**iii**) which was probably activated by iodine in presence of an acid leading to (**iv**), which on further oxidation leads to the desired product **3**.



Scheme 4: Plausible reaction mechanism for **3**.

10 3. Conclusions

In conclusion, a highly efficient and selective I₂-DMSO promoted oxidative cross-coupling in presence of PTSA has been developed with the use of imidazo[1,2-*a*]pyridines and methyl ketones for the construction of 1-phenyl-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)ethane-1,2-diones (**3**) with a new C-C bond formation. This tandem oxidative cross coupling proved easy to operate and could sequentially promote three mechanistically distinct reactions in a one pot without use of any metal catalyst.

20 4. Experimental section

4.1 General procedure for the synthesis of 1-phenyl-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)ethane-1,2-dione (**3a**)

To a suspension of imidazo[1,2-*a*]pyridine (**1**) (0.48 g, 1.0 mmol), methyl ketone (**2**) (0.300 g, 1.0 mmol), and DMSO (4 mL) in 25 mL two-neck round-bottomed flask was added iodine (0.63 g, 1.0 mmol) followed by the catalytic amount (10 mol%) of PTSA at room temperature. Then the reaction mixture was stirred at 100°C for 5 h. After completion of the reaction as indicated by TLC, the reaction mixture was allowed to cool to room temperature, quenched with saturated Na₂S₂O₃ solution, extracted into ethyl acetate (2×10 mL). The combined organic layer was dried over anhydrous sodium sulphate and evaporated to get the crude compound which was purified by column chromatography by eluting with petroleum ether / ethyl acetate (9:1 v/v) to get pure compound **3a**.

4.1.1 1-Phenyl-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)ethane-1,2-dione (**3aa**)

Isolated as a yellow solid; Yield 75%; m.p.122-123°C; IR (KBr): 2928, 2902, 1675, 1596, 1400, 1129, 859, 720 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.84 (d, *J* = 6.79 Hz, 1H), 7.85 (d, *J* = 8.87 Hz, 1H), 7.76-7.63 (m, 3H), 7.57 (t, *J* = 7.36 Hz, 1H), 7.39 (t, *J* = 7.74 Hz, 2H), 7.33-7.20 (m, 4H), 7.10 (t, *J* = 7.55 Hz, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 191.3, 184.5, 158.4, 148.2, 134.2, 133.3, 132.7, 131.1, 130.0, 129.5, 129.2, 128.5, 128.2, 127.9, 117.5, 115.9 ppm; ESI-MS:

m/z 327 [M+H]⁺; HRMS (ESI) Anal. Calcd. For C₂₁H₁₅N₂O₂ *m/z* 327.11280 [M+H]⁺, found 327.11289.

4.1.2 1-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)-2-(p-

50 tolyl)ethane-1,2-dione (**3ab**). Isolated as a light yellow solid; Yield 73%; m.p.152-155°C; IR (KBr): 3016, 1678, 1593, 1526, 1467, 1400, 1341, 730 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 9.83 (d, *J* = 6.86 Hz, 1H), 7.84 (d, *J* = 8.85 Hz, 1H), 7.67-7.61 (m, 3H), 7.31 (d, *J* = 7.01 Hz, 2H), 7.27 (t, *J* = 7.62 Hz, 1H), 7.24-7.17 (m, 3H), 7.11 (t, *J* = 7.62 Hz, 2H), 2.41 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 191.2, 184.5, 158.5, 148.1, 139.4, 133.9, 133.3, 132.7, 130.9, 129.8, 129.4, 129.1, 128.5, 128.3, 118.7, 117.3, 115.6, 21.1 ppm; ESI-MS: *m/z* 341[M+H]⁺; HRMS (ESI) Anal. Calcd. For C₂₂H₁₇N₂O₂ *m/z* 341.1305 [M+H]⁺, found 341.1290.

4.1.3 1-(4-Methoxyphenyl)-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)ethane-1,2-dione (**3ac**)

Isolated as a white yellow solid; Yield 76%; m.p.166-168°C; IR (KBr): 2930, 1658, 1599, 1460, 1260, 1180, 748, 753 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 9.83 (d, *J* = 6.86, 1H), 7.84 (d, *J* = 9.00 Hz, 1H), 7.70 (d, *J* = 9.03 Hz, 2H), 7.65 (t, *J* = 7.32 Hz, 1H), 7.32 (d, *J* = 7.01 Hz, 2H), 7.27 (t, *J* = 6.25 Hz, 1H), 7.22 (t, *J* = 6.56 Hz, 1H), 7.12 (t, *J* = 7.78 Hz, 2H), 6.86 (d, *J* = 9.00 Hz, 2H), 3.87 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 190.0, 184.8, 164.4, 158.3, 132.8, 131.9, 129.8, 129.1, 128.4, 127.7, 126.4, 124.4, 117.4, 116.8, 115.6, 113.8, 113.4, 55.5 ppm; ESI-MS: *m/z* 357 [M+H]⁺; HRMS (ESI) Anal. Calcd. For C₂₂H₁₇N₂O₃ *m/z* 357.1214 [M+H]⁺, found 357.1239.

4.1.4 1-(4-Nitrophenyl)-2-(2-phenylimidazo[1,2-*a*]pyridin-

75 3-yl)ethane-1,2-dione (**3ad**). Isolated as a light yellow solid; Yield 70%; m.p.220-224°C; IR (KBr): 3116, 3017, 1678, 1602, 1406, 1248, 764 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 9.80 (d, *J* = 6.86 Hz, 1H), 8.23 (d, *J* = 8.85 Hz, 2H), 7.89 (d, *J* = 8.39 Hz, 3H), 7.72 (t, *J* = 7.47 Hz, 1H), 7.34-7.24 (m, 4H), 7.13 (t, *J* = 7.62 Hz, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 189.3, 182.7, 159.0, 150.5, 148.6, 137.6, 131.5, 130.3, 130.0, 129.7, 129.2, 128.1, 123.6, 118.7, 117.7, 116.1 ppm; ESI-MS: *m/z* 372 [M+H]⁺; HRMS (ESI) Anal. Calcd. For C₂₁H₁₄N₂O₄ *m/z* 372.0965 [M+H]⁺, found 372.0984.

4.1.5 4-(2-Oxo-2-(2-phenylimidazo[1,2-*a*]pyridin-3-

yl)acetyl)benzotrile (**3ae**). Isolated as a light yellow solid; Yield 71%; m.p.180-185°C; IR (KBr): 3430, 2962, 2227, 1679, 1603, 1407, 1252, 763 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 9.79 (d, *J* = Hz, 1H), 7.87 (d, *J* = 8.69 Hz, 1H), 7.80 (d, *J* = 7.78 Hz,

2H), 7.70 (t, $J = 6.25$ Hz, 3H), 7.35-7.22 (m, 4H), 7.13 (t, $J = 7.32$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 189.6, 182.8, 158.9, 148.5, 136.2, 132.6, 132.2, 131.4, 130.0, 129.7, 129.6, 129.2, 128.0, 118.7, 117.7, 117.0, 116.1 ppm; ESI-MS: m/z 352 $[\text{M}+\text{H}]^+$; HRMS (ESI) Anal. Calcd. For $\text{C}_{22}\text{H}_{14}\text{N}_3\text{O}_2$ m/z 352.1061 $[\text{M}+\text{H}]^+$, found 352.1086.

4.1.6 1-(4-Fluorophenyl)-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (3af). Isolated as a light yellow solid; Yield 71.7%; m.p.165-168°C; IR (KBr): 2943, 2816, 1666, 1582, 1400, 1233, 763 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 9.82 (d, $J = 6.79$ Hz, 1H), 8.87 (s, 1H), 8.14-8.01 (m, 2H), 7.74 (t, $J = 8.68$ Hz, 2H), 7.35-7.25 (m, 2H), 7.18-7.03 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 189.4, 184.2, 169.7, 167.2, 165.2, 157.4, 147.6, 133.0, 132.6, 132.1, 131.6, 130.0, 129.1, 129.7, 127.9, 118.6, 117.2, 116.3, 116.0, 115.8, 115.4 ppm; ESI-MS: m/z 345 $[\text{M}+\text{H}]^+$; HRMS (ESI) Anal. Calcd. For $\text{C}_{21}\text{H}_{14}\text{FN}_2\text{O}_2$ m/z 345.10436 $[\text{M}+\text{H}]^+$, found 345.10442.

4.1.7 1-(4-Chlorophenyl)-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (3ag). Isolated as a white yellow solid; Yield 73%; m.p.120-125°C; IR (KBr): 2953, 2806, 1676, 1592, 1400, 1253, 753 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 9.81 (d, $J = 6.56$ Hz, 1H), 7.94 (d, $J = 8.24$ Hz, 1H), 7.67 (t, $J = 12.51$ Hz, 3H), 7.37 (d, $J = 8.24$ Hz, 2H), 7.33-7.21 (m, 4H), 7.14 (t, $J = 7.32$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 190.0, 183.8, 158.6, 148.3, 140.6, 132.6, 131.7, 131.3, 131.1, 130.7, 129.9, 129.2, 128.9, 127.9, 118.7, 117.6, 115.9 ppm; ESI-MS: m/z 361 $[\text{M}+\text{H}]^+$; HRMS (ESI) Anal. Calcd. For $\text{C}_{21}\text{H}_{14}\text{ClN}_2\text{O}_2$ m/z 361.0757 $[\text{M}+\text{H}]^+$, found 361.0743.

4.1.8 1-(4-Bromophenyl)-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (3ah). Isolated as a white solid; Yield 75%; m.p.138-140°C; IR (KBr): 3067, 2932, 1676, 1590, 1400, 1254, 753 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 9.81 (d, $J = 6.86$ Hz, 1H), 7.88 (d, $J = 8.85$ Hz, 1H), 7.69 (t, $J = 7.47$ Hz, 1H), 7.62-7.50 (m, 4H), 7.33-7.23 (m, 4H), 7.14 (t, $J = 7.62$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 190.2, 183.8, 158.6, 148.3, 132.7, 132.1, 131.9, 131.6, 131.1, 130.8, 129.9, 129.5, 129.2, 127.9, 118.8, 117.6, 115.9 ppm; ESI-MS: m/z 405 $[\text{M}+\text{H}]^+$; HRMS (ESI) Anal. Calcd. For $\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_2\text{Br}$ m/z 405.0247 $[\text{M}+\text{H}]^+$, found 405.0238.

4.1.9 1-(3,5-Difluorophenyl)-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (3ai). Isolated as a light yellow solid; Yield 74.7%; m.p.106-110°C; IR (KBr): 3088, 2925, 1685, 1595, 1407, 1315, 988, 718 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ

9.79 (d, $J = 6.79$ Hz, 1H), 7.87 (d, $J = 8.87$ Hz, 1H), 7.70 (t, $J = 7.55$ Hz, 8H), 7.38-7.13 (t, $J = 8.30$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 188.5, 182.6, 162.6 (dd, $J_1 = 251.58$, $J_2 = 10.89$ Hz) 158.9, 148.9, 148.5, 136.0 (t, $J = 7.26$ Hz), 132.68, 131.34, 129.94, 129.62, 129.18, 128.0, 118.63, 117.67, 112.13 (dd, $J_1 = 19.98$, $J_2 = 6.35$ Hz), 109.35 (t, $J = 25.4$) ppm; ESI-MS: m/z 363 $[\text{M}+\text{H}]^+$; HRMS (ESI) Anal. Calcd. For $\text{C}_{21}\text{H}_{13}\text{F}_2\text{N}_2\text{O}_2$ m/z 363.0931 $[\text{M}+\text{H}]^+$, found 363.0945.

4.1.10 1-(4-hydroxyphenyl)-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (3aj). Isolated as a white solid; Yield 68.1%; m.p.132.2°C; IR (KBr): 3444, 2925, 1682, 1596, 1450, 1215, 979, 686 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 9.71 (t, $J = 7.17$ Hz, 1H), 7.87 (s, 1H), 7.78-7.74 (m, 1H), 7.59 (q, $J_1 = 7.17$ Hz, $J_2 = 14.80$ Hz, 1H), 7.39 (d, $J = 8.54$ Hz, 1H), 7.28 (d, $J = 8.24$ Hz, 1H), 7.22-7.11 (m, 4H), 7.04-6.95 (m, 2H), 6.58-6.48 (s, 1H); ^{13}C NMR (75 MHz, $\text{CDCl}_3+\text{DMSO}-d_6$) δ 188.6, 184.0, 163.1, 147.6, 140.8, 131.8, 130.8, 130.2, 129.5, 129.1, 128.9, 127.4, 127.0, 117.0, 115.6, 115.4, 114.3 ppm; ESI-MS: m/z 343 $[\text{M}+\text{H}]^+$; HRMS (ESI) Anal. Calcd. For $\text{C}_{21}\text{H}_{15}\text{N}_2\text{O}_3$ m/z 343.1096 $[\text{M}+\text{H}]^+$, found 343.1082.

4.1.11 1-(3,4-Dimethoxyphenyl)-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (3ak). Isolated as a white solid; Yield 67.2%; m.p.118-120°C; IR (KBr): 2934, 2841, 1725, 1671, 1588, 1408, 1325, 1124, 760 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 9.83 (d, $J = 6.79$ Hz, 1H), 7.86 (d, $J = 9.06$ Hz, 1H), 7.68 (t, $J = 8.30$ Hz, 1H), 7.36-7.22 (m, 5H), 7.16 (t, $J = 7.55$ Hz, 2H), 6.98 (s, 2H) 3.82 (s, 3H), 3.54 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 190.2, 184.2, 158.5, 152.9, 148.2, 143.5, 133.0, 130.9, 129.9, 129.2, 129.1, 128.4, 127.9, 118.8, 117.6, 115.7, 106.9, 61.0, 56.2 ppm; ESI-MS: m/z 387 $[\text{M}+\text{H}]^+$; HRMS (ESI) Anal. Calcd. For $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_4$ m/z 387.1362 $[\text{M}+\text{H}]^+$, found 387.1344.

4.1.12 1-(2-phenylimidazo[1,2-a]pyridin-3-yl)-2-(3,4,5-trimethoxyphenyl)ethane-1,2-dione (3al). Isolated as a white solid; Yield 67.2%; m.p.135-140°C; IR (KBr): 2962, 2937, 1666, 1402, 1271, 1113, 761 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 9.82 (d, $J = 6.98$ Hz, 1H), 7.86 (d, $J = 8.87$ Hz, 1H), 7.67 (t, $J = 7.17$ Hz, 1H), 7.37-7.21 (m, 4H), 7.16 (t, $J = 7.55$ Hz, 2H), 6.9 (s, 2H), 3.95 (s, 3H), 3.83 (s, 6H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 190.2, 184.6, 170.9, 153.3, 149.0, 148.0, 130.9, 129.9, 129.1, 127.8, 125.5, 124.3, 121.9, 117.4, 115.7, 112.0, 110.1, 109.8, 56.0, 55.9, 55.8 ppm; ESI-MS: m/z 417 $[\text{M}+\text{H}]^+$; HRMS (ESI)

Anal. Calcd. For $C_{24}H_{21}N_2O_5$ m/z 417.1446[M+H]⁺, found 417.1450.

4.1.13 1-(2-Phenylimidazo[1,2-a]pyridin-3-yl)-2-(thiophen-2-yl)ethane-1,2-dione (3am). Isolated as a yellow solid; Yield 75%; m.p.128-130°C; IR (KBr): 2929, 2854, 1655, 1609, 1400, 1248, 729 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃): δ 9.76 (d, J = 6.86 Hz, 1H), 7.91 (d, J = 9.00 Hz, 1H), 7.74 (t, J = 4.88 Hz, 2H), 7.67 (t, J = 7.32 Hz, 1H), 7.40 (d, J = 7.01 Hz, 2H), 7.33 (t, J = 6.56 Hz, 1H), 7.25-7.17 (m, 3H), 7.14 (t, J = 4.88 Hz, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 183.4, 182.8, 165.4, 158.4, 148.2, 140.4, 136.1, 135.5, 133.9, 131.0, 129.8, 129.0, 128.3, 127.7, 118.2, 117.5, 115.8 ppm; ESI-MS: m/z 333 [M+H]⁺; HRMS (ESI) Anal. Calcd. For $C_{19}H_{13}N_2O_2S$ m/z 333.0674 [M+H]⁺, found 333.0697.

4.1.14 1-(furan-2-yl)-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (3an). Isolated as a white solid; Yield 70.2%; m.p.121°C; IR (KBr): 3134, 2927, 1663, 1568, 1461, 1250, 1027, 766 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃): δ 9.74 (d, J = 6.42 Hz, 1H), 7.85 (d, J = 8.68 Hz, 1H), 7.71-7.58 (m, 2H), 7.45-7.10 (m, 7H), 6.55 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 182.4, 178.9, 158.5, 150.3, 147.9, 132.9, 130.9, 129.5, 128.9, 127.8, 129.4, 121.0, 118.4, 117.5, 115.7, 112.7 ppm; ESI-MS: m/z 317 [M+H]⁺; HRMS (ESI) Anal. Calcd. For $C_{19}H_{13}N_2O_3$ m/z 317.09193 [M+H]⁺, found 317.09207.

4.1.15 1-(2-oxo-2H-chromen-3-yl)-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (3ao). Isolated as a white solid; Yield 62.6%; m.p.132.5°C; IR (KBr): 2930, 1731, 1607, 1562, 1404, 1250, 875, 759 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃): δ 9.76 (d, J = 6.79 Hz, 1H), 8.23 (s, 1H), 7.87 (d, J = 8.87 Hz, 1H), 7.75-7.52 (m, 5H), 7.39 (t, J = 8.49 Hz, 2H), 7.25-7.18 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 187.2, 182.2, 158.9, 157.6, 155.4, 148.4, 148.2, 135.0, 133.4, 130.3, 130.1, 129.5, 129.2, 128.1, 125.2, 121.8, 118.0, 117.4, 116.9, 115.6 ppm; ESI-MS: m/z 395 [M+H]⁺; HRMS (ESI) Anal. Calcd. For $C_{24}H_{15}N_2O_4$ m/z 395.10303 [M+H]⁺, found 395.10263.

4.1.16 1-(Naphthalen-2-yl)-2-(2-phenylimidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (3ap). Isolated as a yellow solid; Yield 65%; m.p.158-162°C; IR (KBr): 2939, 2844, 1625, 1609, 1409, 1228, 739 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃): δ 9.90 (d, J = 6.86 Hz, 1H), 8.36 (s, 1H), 7.92-7.86 (m, 3H), 7.82 (d, J = 8.69 Hz, 1H), 7.72-7.67 (m, 2H), 7.64 (t, J = 7.01 Hz, 1H), 7.56 (t, J = 7.17 Hz, 1H), 7.29 (t, J = 8.24 Hz, 3H), 7.22 (t, J = 7.47

Hz, 1H), 7.02 (t, J = 7.93 Hz, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 209.6, 202.9, 176.8, 166.5, 154.3, 151.0, 150.5, 149.5, 149.1, 148.3, 147.7, 147.5, 146.9, 146.2, 145.3, 142.3, 137.3, 135.9, 134.3 ppm; ESI-MS: m/z 378 [M+H]⁺; HRMS (ESI) Anal. Calcd. For $C_{25}H_{17}N_2O_2$ m/z 377.12965 [M+H]⁺, found 377.12975.

4.1.17 1-Phenyl-2-(2-(p-tolyl)imidazo[1,2-a]pyridin-3-yl)ethane-1,2-dione (3ba). Isolated as a light yellow solid; Yield 70%; m.p. 110°C; IR (KBr): 3065, 2921, 2841, 1674, 1605, 1229, 758 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃): δ 9.83 (d, J = 6.79 Hz, 1H), 7.87 (d, J = 8.87 Hz, 1H), 7.73 (d, J = 7.17 Hz, 1H), 7.66 (t, J = 7.36 Hz, 1H), 7.58 (t, J = 7.36 Hz, 1H), 7.48-7.36 (m, 2H), 7.28-7.14 (m, 4H), 6.89 (d, J = 7.74 Hz, 2H), 2.28 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 191.27, 184.51, 169.40, 158.51, 148.16, 139.43, 133.96, 133.30, 130.92, 129.89, 129.11, 128.51, 128.33, 117.38, 115.67, 21.16 ppm; ESI-MS: m/z 341 [M+H]⁺; HRMS (ESI) Anal. Calcd. For $C_{22}H_{17}N_2O_2$ m/z 341.1305 [M+H]⁺, found 341.1290.

4.1.18 1-(2-(4-Methoxyphenyl)imidazo[1,2-a]pyridin-3-yl)-2-phenylethane-1,2-dione (3ca). Isolated as a light brown solid; Yield 71%; m.p. 166-168°C; IR (KBr): 3060, 2933, 2751, 1684, 1615, 1239, 658 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃): δ 9.83 (d, J = 6.98 Hz, 1H), 7.86 (d, J = 8.87 Hz, 1H), 7.74-7.61 (m, 3H), 7.35-7.19 (m, 4H), 7.12 (t, J = 7.55 Hz, 2H), 6.86 (d, J = 8.87 Hz, 2H), 3.87 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 190.1, 184.9, 164.3, 158.4, 148.1, 132.9, 132.0, 130.0, 129.4, 129.3, 128.4, 128.5, 127.8, 126.6, 124.5, 117.5, 117.0, 115.8, 113.9, 113.5, 55.6 ppm; ESI-MS: m/z 357 [M+H]⁺; HRMS (ESI) Anal. Calcd. For $C_{22}H_{17}N_2O_3$ m/z 357.1271 [M+H]⁺, found 357.1239

4.1.19 1-(2-(Benzo[d][1,3]dioxol-5-yl)imidazo[1,2-a]pyridin-3-yl)-2-phenylethane-1,2-dione. (3da) Isolated as a light yellow solid; Yield 75%; m.p. 118-120°C; IR (KBr): 3110, 2983, 2861, 1694, 1625, 1229, 778 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃): δ 9.81 (d, J = 6.40 Hz, 1H), 7.85 (d, J = 8.85 Hz, 1H), 7.29 (d, J = 7.93 Hz, 2H), 7.66 (t, J = 7.78 Hz, 1H), 7.60 (t, J = 6.71 Hz, 1H), 7.43 (t, J = 7.47 Hz, 2H), 7.23 (t, J = 6.71 Hz, 1H), 6.83 (s, 1H), 6.72 (d, J = 7.78 Hz, 1H), 6.44 (d, J = 7.78 Hz, 1H), 5.91 (s, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 191.2, 184.4, 158.0, 148.8, 148.2, 147.4, 134.1, 133.3, 131.0, 129.4, 129.1, 128.5, 126.4, 124.9, 117.4, 115.7, 109.8, 107.6, 101.2 ppm; ESI-MS: m/z 371 [M+H]⁺; HRMS (ESI) Anal. Calcd. For $C_{22}H_{15}O_4N_2$ m/z 371.10301 [M+H]⁺, found 371.10263.

4.1.20 1-(2-(4-chlorophenyl)imidazo[1,2-a]pyridin-3-yl)-2-phenylethane-1,2-dione (3ea) Isolated as a white solid; Yield 73%; m.p. 122-123°C; IR (KBr): 2926, 2854, 1682, 1600, 1406, 1263, 1145, 764 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.82 (d, *J* = 6.79 Hz, 1H), 7.87 (d, *J* = 8.87 Hz, 1H), 7.77-7.55 (m, 4H), 7.42 (t, *J* = 7.55 Hz, 2H) 7.25 (t, *J* = 7.55 Hz, 3H), 7.07 (d, *J* = 8.30 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 191.4, 184.3, 157.0, 148.2, 135.7, 134.3, 133.1, 131.2, 131.1, 129.9, 129.4, 129.2, 128.6, 128.0, 118.8, 117.6, 116.0 ppm; ESI-MS: *m/z* 361 [M+H]⁺; HRMS (ESI) Anal. Calcd. For C₂₁H₁₄ClN₂O₂ *m/z* 361.0757 [M+H]⁺, found 361.0743.

4.1.21 1-(7-Chloro-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-phenylethane-1,2-dione (3fa) Isolated as a white solid; Yield 73%; m.p. 180-183°C; IR (KBr): 3160, 2923, 2851, 1624, 1505, 1239, 858 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 9.93 (s, 1H), 7.81 (d, *J* = 9.46 Hz, 1H), 7.72 (d, *J* = 8.39 Hz, 2H), 7.66-7.57 (m, 2H), 7.41 (t, *J* = 7.62 Hz, 2H), 7.30-7.25 (m, 3H), 7.10 (t, *J* = 7.17 Hz, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 190.9, 184.7, 158.6, 146.5, 134.2, 133.1, 132.4, 132.0, 129.9, 129.6, 129.5, 128.6, 128.0, 127.2, 124.0, 117.8, 119.0 ppm; ESI-MS: *m/z* 362 [M+H]⁺; HRMS (ESI) Anal. Calcd. For C₂₁H₁₄ClN₂O₂ *m/z* 362.10744 [M+H]⁺, found 362.10634.

4.1.22 1-(7-Bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-2-phenylethane-1,2-dione (3ga) Isolated as a light yellow solid; Yield 75%; m.p. 153-155°C; IR (KBr): 3160, 2963, 2851, 1644, 1615, 1239, 678 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 10.01 (s, 1H), 7.78-7.68 (m, 4H), 7.58 (t, *J* = 7.55 Hz, 1H), 7.40 (t, *J* = 7.74 Hz, 2H), 7.27 (t, *J* = 8.12 Hz, 3H), 7.10 (t, *J* = 7.17 Hz, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 190.9, 184.7, 158.5, 146.6, 134.2, 133.2, 132.4, 129.9, 129.5, 129.3, 128.6, 127.9, 118.1, 110.5 ppm; ESI-MS: *m/z* 405 [M+H]⁺; HRMS (ESI) Anal. Calcd. For C₂₁H₁₄BrN₂O₂ *m/z* 405.0256 [M+H]⁺, found 405.0238.

4.1.23 1-Phenyl-2-(6-phenylimidazo[2,1-b]thiazol-5-yl)ethane-1,2-dione (3ha) Isolated as a light yellow solid; Yield 68%; m.p. 160-162°C; IR (KBr): 3163, 2963, 2851, 1644, 1615, 1229, 658 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.56 (d, *J* = 4.52 Hz, 1H), 7.76 (d, *J* = 6.79 Hz, 2H), 7.59 (t, *J* = 7.55 Hz, 1H), 7.41 (t, *J* = 8.30 Hz, 2H), 7.33-7.23 (m, 3H), 7.13 (q, *J* = 4.53 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 191.5, 182.9, 158.4, 156.0, 134.2, 133.0, 132.6, 129.6, 129.4, 129.3, 128.5, 127.8, 121.8, 121.8, 114.9 ppm; ESI-MS: *m/z* 333 [M+H]⁺; HRMS (ESI) Anal.

Calcd. For C₁₉H₁₃N₂O₂S *m/z* 333.07015 [M+H]⁺, found 333.06922.

4.1.24 1-phenyl-2-(2-phenylimidazo[1,2-a]pyrimidin-3-yl)ethane-1,2-dione (3ia) Isolated as a white solid; Yield 76.1%; m.p. 171°C; IR (KBr): 3068, 2924, 1682, 1595, 1493, 1392, 1347, 1138, 874, 685 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 10.05 (d, *J* = 5.95 Hz, 1H), 8.91 (s, 1H), 7.75 (d, *J* = 7.32 Hz, 2H), 7.60 (t, *J* = 7.01 Hz, 1H), 7.42 (t, *J* = 7.32 Hz, 2H), 7.37 (d, *J* = 7.17 Hz, 2H), 7.29 (t, *J* = 6.25 Hz, 2H), 7.12 (t, *J* = 7.32 Hz, 2H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 190.6, 185.1, 159.3, 154.9, 150.5, 136.8, 134.4, 132.8, 131.8, 130.0, 129.9, 128.6, 128.5, 127.9, 117.0, 111.9 ppm; ESI-MS: *m/z* 328 [M+H]⁺; HRMS (ESI) Anal. Calcd. For C₂₃H₁₄N₃O₄ *m/z* 328.10792 [M+H]⁺, found 328.10805.

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