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ARTICLE

Iodine promoted dual oxidative C (sp^3) –H amination of 2-methyl-3-arylquinazolin-4(3*H*)-ones: A facile route to 1,4-diarylimidazo [1,5-*a*]quinazoline-5(4*H*)-ones

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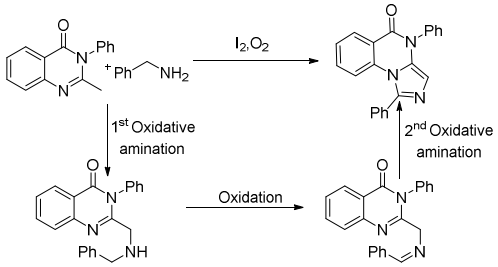
An iodine promoted tandem oxidative condensation of benzyl amines and 2-methylquinazolin-4-(3*H*)-ones was developed to yield imidazo[1,5-*a*]quinazolin-5(4*H*)-ones *via* dual C (sp^3)–H amination under metal free conditions in a greener way using molecular oxygen as terminal oxidant. This tandem transformation provides an efficient approach to construct various functionalized imidazo[1,5-*a*]quinazolin-5(4*H*)-ones in a straightforward manner *via* a sequential amination-oxidation-annulation-aromatisation.

Introduction

Nitrogen-containing fused heterocycles are valuable structural motifs in numerous biologically active compounds and pharmaceuticals.[1] In particular, imidazoquinazolinones and their derivatives are among the fused heterocycles that represent an important class of compounds which exist in wide variety of natural as well as synthetic drug molecules.[2] This privileged motif is gifted with a wide range of biological activities such as anti-thrombotic, anticonvulsant, antitumor, antihypertensive, $GABA_A$ receptor ligand and cardiotonic etc.[3] Thus, the development of synthetic methodologies towards these imidazoquinazolinones is a prominent area towards drug discovery and development. Consequently, a great deal of attention has been diverted towards the construction of these important and attractive scaffolds. Singh and co-workers developed a route for the synthesis of imidazoquinazolinones from 2-methylquinazolin-4-(3*H*)-ones by converting it into aminomethyl derivative and then into corresponding *N* carboxamide, followed by intramolecular cyclodehydration.[4a] Recently, Lebegue *et al.,* has reported a microwave-assisted two-step synthesis of 1,3-disubstituted-imidazo[1,5-*a*]quinazolin-5-(4*H*)-ones *via* formation of quinazolinone from anthranilamide and various Boc- or acylamino acids, followed by intramolecular cyclodehydration under acidic conditions.[4b] Eventhough, many synthetic methods have been developed for the synthesis of imidazoquinazolinones,[4] most of the conventional methods suffer from various disadvantages such as prefunctionalisation of substrates, harsh reaction conditions, limited substrate scope or of multi-step procedures. Therefore, more straightforward method for the preparation of imidazoquinazolinones from easily available substrates is highly desirable.

In the past few decades a great deal of progress has been achieved in the transition-metal-catalysis. Particularly, transition-metal-catalyzed C-N bond formation by the oxidative amination of C (sp^3)-H has attracted considerable attention for the construction of azaheterocycles.[5] However, the cost effectiveness and limited substrate scope are the major concerns associated with the practical applicability in the organic synthesis. Thus, alternative metal-free approaches are highly desirable for C-H amination. Recently, iodine has certainly attracted the researchers and appeared to be an alternative for a numerous transition-metals because of its versatility and ability to perform an array of synthetic transformations.[6] Accordingly, the versatility of iodine in activating both C (sp^2)-H and C (sp^3)-H to form C-N bond, eco-friendly nature has established and received much attention, and is appealing due to high atom economy and easy access of starting materials.[7]



Scheme 1 Synthesis of imidazo[1,5-*a*]quinazolin-5(4*H*)-ones *via* dual C (sp^3)–Hamination of 2-methyl-quinazolin-4-(3*H*)-ones and benzyl amines.

Recently 2-alkylarenes and 2-alkylazaarenes has been recognized and widely exploited as important frameworks for

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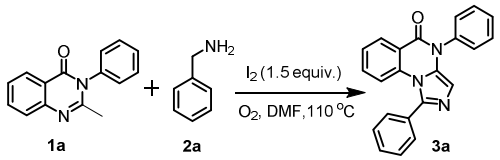
C (sp^3)-H oxidative amination because of their broad availability and inexpensive nature.[8] Chang[9a] and Zhu[9b] *et al.,* independently reported iodine promoted benzylic C-H amination. Muniz[9c] and co-workers achieved allylic C-H amination in the presence of hypervalentiodine(III) reagents. However, these approaches are limited to sulphonamides. In spite of considerable progress by many research groups towards the development of synthetic methodologies based on intramolecular and intermolecular oxidative C (sp^3)-H amination, their application in the construction of diverse aza heterocycles remain scarce. In continuation of our interest in developing domino reactions to access various pharmacologically active heterocycles,[10] we envisioned that isomerized nonaromatic enamine intermediate of 2-methyl-quinazolin-4-(3*H*)-one can be assembled into imidazo[1,5-*a*]quinazolin-5(4*H*)-ones with various benzyl amines utilizing iodine and molecular oxygen as green oxidant. Herein, we report iodine promoted domino oxidative condensation of benzyl amines and 2-methylquinazolin-4-(3*H*)-ones *via* dual C (sp^3)–H amination using oxygen as a sole oxidant to yield imidazo[1,5-*a*]quinazolin-5(4*H*)-ones.

Table 1 Optimization of the reaction conditions.[a]



1a 2a 3a

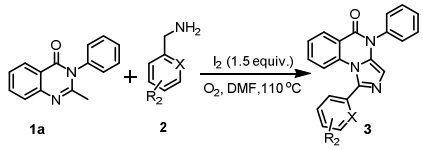
Entry	Catalyst	Equivalents	Oxidant	Solvent	Temperature(°C)	Yield(%)[b]
1	I_2	0.2	O_2	DMF	110	nd
2	I_2	0.5	O_2	DMF	110	26
3	I_2	1.0	O_2	DMF	110	55
4	I_2	1.2	O_2	DMF	110	60
5	**I_2**	**1.5**	**O_2**	**DMF**	**110**	**89**
6	I_2	2	O_2	DMF	110	88
7	I_2	1.5	TBHP	DMF	110	50
8	I_2	1.5	DTBP	DMF	110	76
9	I_2	1.5	DDQ	DMF	110	40
10	I_2	1.5	O_2	DMSO	110	trace
11	I_2	1.5	O_2	toluene	110	nd
12	I_2	1.5	O_2	ethanol	110	nd
13	NIS	1.5	O_2	DMF	110	nd
14	KI	1.5	O_2	DMF	110	nd
15	TBAI	1.5	O_2	DMF	110	nd
16	I_2	1.5	O_2	DMF	90	nd

[a]Reaction conditions: **1a** (0.5 mMol), **2a** (0.6 mMol), solvent 1.5 mL, 110 °C, 24 h. [b]Isolated yield.nd = not detected.

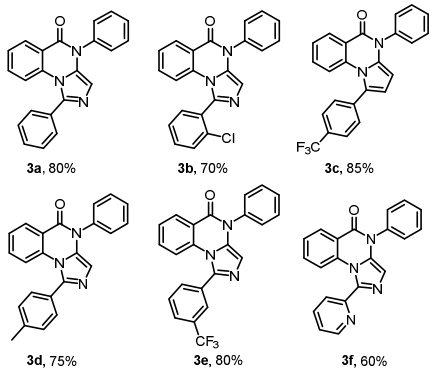
Results and discussion

Our journey towards the exploration of optimal reaction conditions for the dual C (sp^3)–H amination commenced by taking 2-methyl-3-phenylquinazolin-4-(3*H*)-one **1a** and benzyl amine **2a** as model substrates. Accordingly, 2-methyl-3-phenylquinazolin-4-(3*H*)-one (**1a)** is treated with benzyl amine**(2a)** in DMF in the presence of 0.2 equiv. of molecular iodine as a catalyst and O_2 as oxidant at 110 °C, which resulted in formation of no desired product even after stirring for more than 24 h (entry1, Table 1). To our delight, increase in the amount of iodine to 0.5 equiv. lead to formation of desired product albeit in lesser yields (entry 2, Table 1). The structure of the compound was unambiguously confirmed by the X-ray analysis. This inspiring result forced us to focus on the yields of the product. A fair improvement in the yields of the product was observed with the increase in the stoichiometry of iodine up to 1.5 equiv. (entry 3, 4 & 5, Table 1). However, no further increase in the yields was observed beyond 1.5 equiv. At this juncture, we thought to study the effect of oxidant on the reaction conditions. It is clear that O_2 was the best oxidant among the tested oxidants and inferior results were obtained with oxidants such as TBHP, DTBP and DDQ (entry 7, 8 & 9, Table 1). DMF stood as optimal solvent of choice among the studied solvents like DMSO, PhMe and EtOH (entry 10, 11 &12, Table 1). Alternate iodine sources were then investigated and it is found that NIS, KI and TBAI (entry 13, 14 & 15, Table 1) were comparably less effective under otherwise identical reaction conditions. Finally performing a reaction under inert atmosphere did not result in formation of any desired product. Temperature showed obvious effect on reaction where no product was detected at room temperature or even when the temperature was decreased to 90 °C (entry 16, Table 1).

Table 2 Substrate scope of benzyl amines[a,b]



1a 2 3



3a, 80% 3b, 70% 3c, 85%

3d, 75% 3e, 80% 3f, 60%

[a]Reaction conditions: **1a** (0.5 mMol), **2** (0.6 mMol), solvent 1.5 mL, 110 °C, 24 h.[b]Isolated yield.

With the optimal reaction conditions in hand, we next investigated the generality and substrate scope of the present protocol. As shown in Table 2, various benzylamines (**2a-f**) were treated with 2-methyl-3-arylquinazoline-4(3*H*)-one (**1a**) under the optimized reaction conditions to deliver corresponding products **3a-f** in good yields. It is observed that benzyl amines substituted with electron-withdrawing CF_3 substituent **3c, 3e** gave superior yields 85% and 80% respectively. However, comparably lesser yields were

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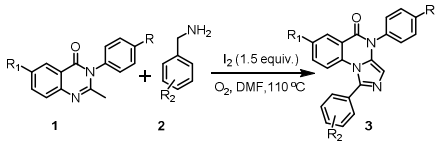
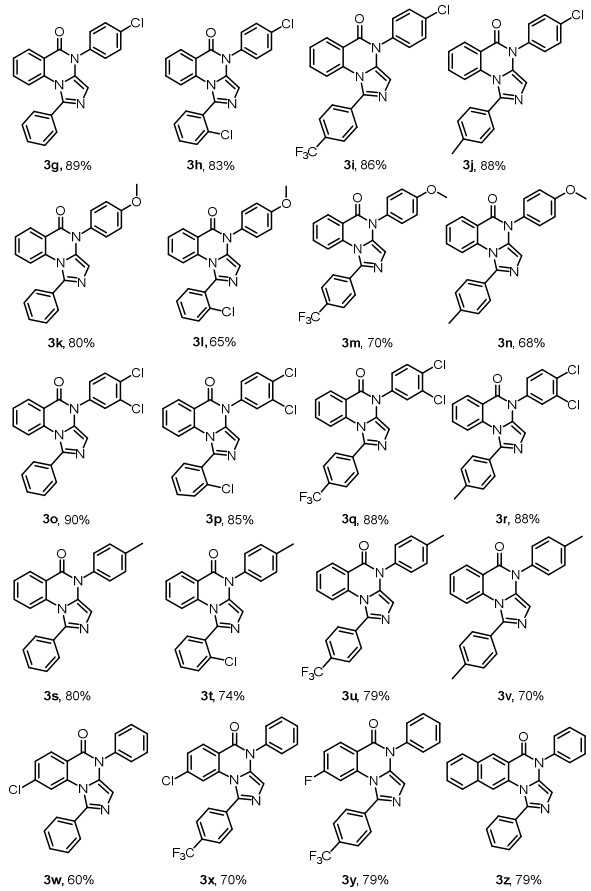
observed when electron-donating methyl substituted benzyl amine was used as amine partner **3d** (75% yield, Table 2). It is worth mention that steric factors have great influence on the reaction. Notably, *ortho*-substituted benzyl amine such as 2-chlorobenzylamine is amenable to optimized conditions and delivered corresponding products **3b** in comparably lesser yields 70%. However, as imagined, bulky methyl group at *ortho* position of benzylamine blocked the roll-over process and did not react at all even after stirring for more than 24 h.

With these fruitful results, we next focused on scope of quinazolones (with various substitutions on 3rd position) as summarized in Table 3. To our delight, electron donating and electron withdrawing substituents on phenyl ring substituted at 3rd position of quinazolones were successfully utilized in the reaction to deliver the corresponding products in good yields (**3c-d** & **3g-h**, **3k-l**, **3o-p**, **3s-t** and **3v**) the electronic effects of these groups slightly influenced the reaction efficacy. Comparably lesser yields were obtained with electron donating OMe and Me substituents at *para* position of the

Table 3 Scope of quinazolinones[a, b]



1 2 3



[a]Reaction conditions: **1** (0.5 mMol), **2** (0.6 mMol), solvent 1.5 mL, 110 °C, 24 h.
[b]Isolated yield.

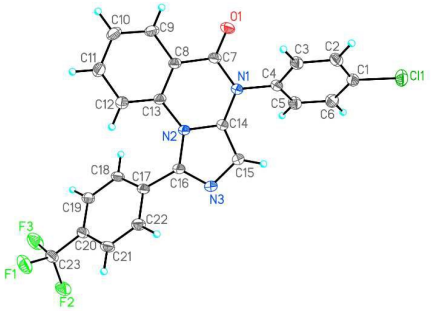
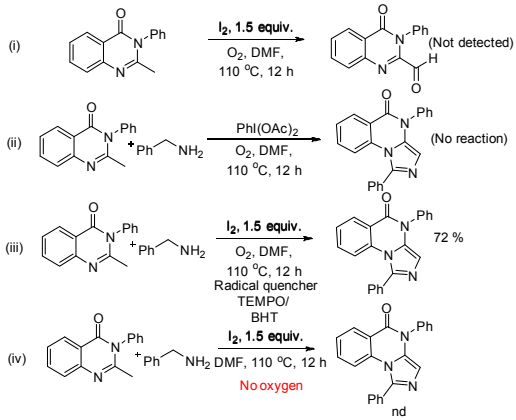


Fig .1 ORTEP diagram of **3i**

phenyl ring at 3rd position of quinazolines (**3k-n** & **3s-v**) than unsubstituted ones (Table 3). The decrease in yields is directly proportional to the electronic donating nature of the substituents as OMe substituent gave lesser yields than Me substituent. In contrast, mono and di-halo substitutions on the phenyl ring at 3rd position of quinazolones (**3g-j** & **3o-r**) gave better yields. In addition, quinazolones substituted with electron withdrawing chlorine and fluorine at 8th position were also well tolerated with benzyl amines under the optimized reaction conditions and the corresponding products (**3w**, **3x** & **3y**) were afforded in 60, 70 and 79% respectively. Moreover, 2-methyl-3-phenylbenzo[g]quinazolin-4(3*H*)-one is also a suitable substrate for this dual C (sp^3)-H amination cascade process to give the desired product (**3z**) in descent yields (79%).

To get insight in to the reaction mechanism, few control experiments were conducted (Scheme 2). Initially, **1a** in the absence of benzyl amine under optimized reaction conditions did not result in any expected aldehyde indicating that an *in situ* aldehyde intermediate based oxidative condensation process was excluded. Moreover, replacing the iodine with stoichiometric amounts of $PhI(OAc)_2$ did not result in any desired product **3a,** suggesting that the *in situ* generated hypervalent iodine intermediates are not catalyzing the reaction pathway. Finally assuming that the reaction may proceed *via* a free radical mechanism, radical trapping experiments were performed by employing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or



Scheme 2 Control experiments for proposed mechanism. nd = not detected.

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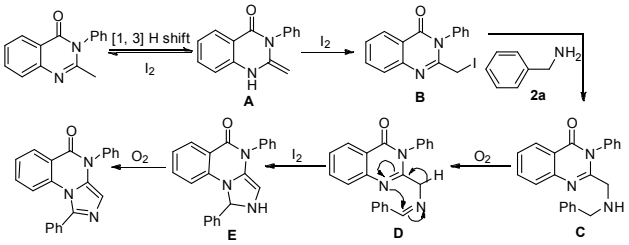
2,6-di-tert-butyl-4- methylphenol (BHT). This possibility was ruled out as the reaction did not retard in the presence of radical scavengers yielding the required product in good yields. These results conclude that reaction presumably undergoes through an *in situ* generated iodo intermediate which was generated *via* ionic pathway.

Based on the reported literature[11] and our observations, a plausible reaction mechanism for this domino oxidative condensation *via* dual C (sp^3)-H amination was outlined in Scheme 3. Since aldehyde was not formed in the reaction it is assumed that an aromatic enamine intermediate **A** is formed from 2-Methyl-3-arylquinazoline-4(3*H*)-one *via* iodine-promoted isomerization (1,3-H shift).[12] The intermediate **A** then transforms into iodo-intermediate **B**. Moreover, as toluene is not reactive under these conditions, it is clear that nitrogen is crucial for the formation of this intermediate **C**.[13] Subsequent nucleophilic amination of benzyl amine **2a** onto the intermediate **B** generates intermediate **C** which further oxidises to intermediate **D**. The intermediate **D** then directly converts into product **3a** *via* intermediate **E** through iodine promoted intramolecular cyclization followed by dehydrogenation (oxidative aromatization) in the presence of molecular oxygen[14] in a tandem process.



Scheme 3 Plausible reaction mechanism.

Conclusion

In summary, we have developed an iodine promoted domino oxidative condensation of benzyl amines and 2-methylquinazolin-4-(3*H*)-ones using oxygen as sole oxidant to yield imidazo[1,5-*a*]quinazolin-5(4*H*)-ones under metal free conditions. A domino process to construct valuable azaheterocycles by forming 2 C-N bonds *via* dual C (sp^3)–H amination. Absence of metal catalyst, operational simplicity, commercially available starting materials and avoidance of substrate prefunctionalization is the distinguished feature of the present protocol. Further studies based on iodine promoted C-H aminations for the construction of various heterocycles are underway.

Experimental section

Materials and General Methods.

Starting materials, reagents and solvents were purchased as reagent grade and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a 300, 400 and 500 MHz spectrometer at 25 °C. Chemical shifts values are given in ppm and calibrated relative to the residual signal of the TMS solvent. The peak patterns are defined as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and dd, doublet of doublets. The coupling constants *J* are reported in Hertz (Hz). Column chromatography was performed over silica gel (100–200 mesh) using a mixture of n-hexane and ethyl acetate (EtOAc) as an eluent. TLC plates (Silica gel GF254) were visualized by exposure to ultraviolet light. High resolution mass spectrometry (HRMS) was obtained on a QTOF micro spectrometer. Melting points were determined with electro thermal melting point apparatus without corrections. Organic solutions were concentrated by rotary evaporation below 45 °C in vacuum.

General procedure for synthesis of substituted 1,4-diphenyl imidazo[1,4-*a*]quinazolin-5 (4*H*)-one

2-Methyl-3-phenylquinazolin-4(3*H*)-one (1 equiv.), benzyl amine (1.2 equiv.) and iodine (1.5 equiv.) in DMF (5 mL) were taken in a sealed tube and capped with rubber septum, bubbled with O_2 via a cannula and then the septa was replaced with Teflon cap and refluxed at 110 °C. After completion of the reaction (monitored with TLC), reaction mixture was quenched with saturated solution of sodium thiosulphate (10 mL) and extracted with ethyl acetate (20 mL). Combined organic layers were dried over anhydrous sodium sulphate, filtered through funnel and solvent was removed under reduced pressure. Product obtained was further purified by column chromatography with 100-200 mesh silica gel using hexane and ethyl acetate as an eluent in increasing polarity to yield the desired imidazoquinazolinones.

1,4-Diphenylimidazo[1,5-*a*]quinazolin-5(4*H*)-one (3a): **3a** was obtained as white solid; M.p: 216-217 °C; R_f = 0.4 (30 % ethyl acetate/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38-8.36 (m, 1H), 7.64-7.60 (m, 4H), 7.59-7.57 (m, 2H), 7.55-7.52 (m, 3H), 7.45-7.43 (m, 4H), 7.24 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 142.2, 135.0, 134.4, 133.8, 131.7, 131.5, 130.5, 130.3, 130.1, 129.8, 129.7, 129.5, 129.1, 126.3, 117.9, 116.5 ppm; HRMS calculated for $[M+H]^+$ $C_{22}H_{16}N_3O$: 338.1293 found: 338.1303.

1-(2-Chlorophenyl)-4-phenylimidazo[1,5-*a*]quinazolin-5(4*H*)-one (3b): 3b was obtained as white solid; M.p: 225-226 °C; R_f = 0.4 (30% ethyl acetate/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34-8.30 (m, 1H), 7.85-7.79 (m, 2H), 7.61-7.52 (m, 3H), 7.51-7.47 (t, *J* = 6.9 Hz, 1H), 7.39-7.37 (d, *J* = 7.5 Hz, 1H), 7.35-7.31 (d, *J* = 7.0 Hz, 2H), 7.23-7.19 (d, *J* = 9.0 Hz, 2H), 7.17-7.14 (d, *J* = 7.0 Hz, 1H), 6.4 (d, *J* =15.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 151.2, 147.7, 136.9, 135.8, 134.6, 133.6, 130.3, 129.9, 129.4, 128.7, 127.7, 127.5, 127.1, 126.9, 126.8, 122.6, 121.0 ppm; HRMS calculated for $[M+H]^+$ $C_{22}H_{15}ClN_3O$: 372.0903 found: 372.0912.

4-Phenyl-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3c): 3c was obtained as creamish white solid; M.p: 170-171 °C; R_f = 0.4 (40% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (dd , *J* = 1.5, 7.7 Hz, 1H), 7.80 (s, 4H), 7.62 (t, *J* = 7.3 Hz, 2H), 7.56 (d, *J* = 7.3Hz, 1H), 7.50 (dd, *J* = 1.5, 8.3 Hz, 3H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 6.33 (s, 1H) ppm; ^{13}C NMR

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(125 MHz, $CDCl_3$): δ 157.6, 138.4, 136.0, 135.4, 134.6, 133.9, 131.5 (q, *J* = 32.3 Hz, 1C), 130.5, 130.1, 129.9, 129.5, 128.9, 128.4, 128.1, 126.3, 125.9 (q, *J* = 2.9Hz, 1C), 125.1 (q, *J* = 272.8 Hz, 1C), 116.5, 110.4 ppm; HRMS calculated for $[M+H]^+$ $C_{23}H_{14}F_3N_3O$: 406.1167 found: 406.1153.

4-Phenyl-1-*p*-tolylimidazo[1,5-*a*]quinazolin-5(4*H*)-one (3d): 3d was obtained as creamish white solid; M.p: 238-239 °C; R_f = 0.5 (40% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.36 (dd, *J* = 1.5, 7.4 Hz, 1H), 7.62-7.55 (m, 3H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.44-7.38 (m, 4H), 7.32 (d, *J* = 7.7 Hz, 2H), 7.30-7.26 (m, 2H), 2.47 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 142.4, 140.2, 35.1, 134.4, 133.8, 131.4, 130.5, 130.2, 129.8, 129.8, 129.7, 129.4, 128.7, 127.9, 126.2, 117.8, 116.5 ppm; HRMS calculated for $[M+H]^+$ $C_{23}H_{18}N_3O$: 352.1444 found: 352.1445.

4-Phenyl-1-(3-(trifluoromethyl)phenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one(3e): 3e was obtained as creamish white solid; M.p: 238-239 °C; R_f = 0.5 (40% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.33-8.30 (d, *J* = 7.8 Hz, 1H), 8.01-7.95 (d, *J* = 15.5 Hz, 1H), 7.85-7.77 (m, 2H), 7.63-7.52 (m, 5H), 7.49-7.41 (m, 2H), 7.36-7.31 (d, *J* = 6.5 Hz, 2H), 6.48-6.40 (d, *J* = 15.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 162.1, 151.0, 147.6, 138.0, 136.8, 134.7, 131.8 (q, *J* = 32.3 Hz, 1C), 130.2, 130.0, 129.3, 128.6, 127.4, 127.2, 126.9, 125.9, 125.1 (q, *J* = 272.1 Hz, 1C), 124.7 (q, *J* = 2.9 Hz, 1C), 121.7, 121.0 ppm; HRMS calculated for $[M+H]^+$ $C_{23}H_{14}F_3N_3O$: 406.1167 found: 406.1153.

4-Pheny-1-(pyridin-2-yl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3f): 3f was obtained as creamish white solid; M.p: 228-229 °C; R_f = 0.4 (40% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.82 (d, *J* = 4.5 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 7.9 Hz, 2H), 8.04-8.0 (m, 1H), 7.93-7.86 (m, 3H), 7.75 (d, *J* = 3.9 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.44-7.40 (m, 1H), 6.97 (t, *J* = 2.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.7, 148.1, 136.6, 135.2, 135.1, 132.8, 126.1, 126.0, 121.9, 121.7, 120.4, 120.4, 118.0, 113.8 ppm; HRMS calculated for $[M+H]^+$ $C_{21}H_{14}N_4O$: 339.1246 found: 352.1252.

4-(4-Chlorophenyl)-1-phenylimidazo[1,5-*a*]quinazolin-5(4*H*)-one (3g): 3g was obtained as creamish white solid; M.p: 229-230 °C; R_f = 0.4 (40% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.35 (d, *J* = 8.3 Hz, 1H), 7.62-7.57 (m, 4H), 7.56-7.51 (m, 3H), 7.44-7.38 (m, 4H), 7.26-7.23 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$):δ 158.4, 142.4, 135.9, 135.0, 134.0, 132.8, 131.8, 131.5, 131.2, 130.2, 130.2, 129.9, 129.4, 129.1, 126.4, 117.6, 116.5 ppm; HRMS calculated for $[M+H]^+$ $C_{22}H_{15}ON_3Cl$: 372.0898 found: 372.0892.

1-(2-Chlorophenyl)-4-(4-chlorophenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3h): 3h was obtained as white solid; M.p: 230-231 °C; R_f = 0.4 (40% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.37 (dd, *J* = 1.7, 7.6 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.57-7.55 (m, 2H), 7.50-7.47 (m, 3H), 7.46-7.41 (m, 3H), 7.01 (d, *J* = 8.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 138.9, 135.9, 135.0,134.9, 132.8, 132.4, 131.8, 131.4, 130.9, 130.2, 130.0,129.9, 127.7, 126.5, 117.3, 115.0 ppm; HRMS calculated for $[M+H]^+$ $C_{22}H_{14}ON_3Cl_2$: 406.0508 found: 406.0504.

4-(4-Chlorophenyl)-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3i): 3i was obtained as white solid; M.p: 207-208 °C; R_f = 0.4 (30% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.42 (dd, *J* = 1.4, 7.7 Hz, 1H), 7.80 (s, 4H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.55-7.43 (m, 4H), 7.30 (d, *J* = 8.2 Hz, 1H), 6.36 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 157.5, 138.6, 135.8, 135.4, 134.4, 134.2, 134.0, 131.9 (q, *J* = 32.7 Hz, 1C), 130.4, 130.3, 129.8, 129.3, 126.3, 125.9 (q, *J* = 2.7 Hz, 1C), 124.8 (q, *J* = 272.4 Hz, 1C), 122.7, 118.0, 116.5, 110.3 ppm; HRMS calculated for $[M+H]^+$ $C_{23}H_{14}ClF_3N_3O$: 440.0772 found: 440.0791.

4-(4-Chlorophenyl)-1-*p*-tolylimidazo[1,5-*a*]quinazolin-5(4*H*)-one (3j): **3j** was obtained as white solid; M.p: 235-236 °C; R_f = 0.4 (40% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.51-7.43 (m, 5H), 7.41-7.33 (m, 4H), 6.29 (s, 1H), 2.48 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7, 140.4, 140.0, 135.9, 135.2, 134.6, 133.9, 133.5, 131.8, 130.3, 130.2, 129.7, 129.4, 129.4, 129.4, 125.9, 117.8, 116.6, 109.5, 21.5 ppm ; HRMS calculated for $[M+H]^+$ $C_{23}H_{17}ClN_3O$: 386.1060 found: 386.1067.

4-(4-Methoxyphenyl)-1-phenylimidazo[1,5-*a*]quinazolin-5(4*H*)-one (3k): 3k was obtained as white solid; M.p: 233-234 °C; R_f = 0.4 (50% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.64-7.49 (m, 5H), 7.44-7.22 (m, 6H), 7.10 (d, *J* = 8.2 Hz, 2H), 3.90 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 158.7, 142.2, 135.0, 133.8, 131.8, 131.5, 130.3, 130.1, 130.0, 129.5, 129.1, 127.0, 126.3, 117.9, 114.8, 130.1, 55.6 ppm; HRMS calculated for $[M+H]^+$ $C_{23}H_{18}N_3O_2$: 368.1399 found: 368.1409.

1-(2-Chlorophenyl)-4-(4-methoxyphenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3l): 3l was obtained as white solid; M.p: 228-229 °C; R_f = 0.4 (40% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.34-8.29 (m, 2H), 7.83-7.77 (m, 2H), 7.50-7.46 (m, 1H), 7.39 (dd, *J* = 1.2, 7.9 Hz, 1H), 7.27-7.21 (m, 5H), 7.19-7.15 (m, 1H), 7.09-7.06 (m, 2H), 6.48 (d, *J* = 15.4 Hz, 1H), 3.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 158.6, 146.4, 138.7, 135.0. 134.5, 134.3, 132.4, 131.7, 131.5, 130.2, 130.0, 128.1, 127.6, 127.5, 127.1, 127.0, 126.4, 114.8, 55.6 ppm; HRMS calculated for $[M]^+$ $C_{23}H_{16}ClN_3O_2$: 401.0925 found: 401.0928.

4-(4-Methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3m): 3m was obtained as white solid; M.p: 178-179 °C; R_f = 0.4 (50% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.43 (d, *J* = 7.0 Hz, 1H), 7.79 (s, 3H), 7.52-7.39 (m, 4H), 7.31-7.28 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.35 (s, 1H), 3.90 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 157.9, 138.4, 136.0, 135.4, 134.9, 133.8, 131.6, 130.5, 129.8, 128.9, 128.5, 126.2, 125.9 (q, *J* = 3.7 Hz, 1C), 125.1 (q, *J* = 272.1 Hz, 1C), 118.3, 116.5, 115.3, 110.4, 55.5 ppm; HRMS calculated for $[M+H]^+$ $C_{24}H_{17}F_3N_3O_2$: 436.1267 found: 436.1263.

4-(4-Methoxyphenyl)-1-*p*-tolylimidazo[1,5-*a*]quinazolin-5 (4*H*)-one (3n): **3n** was obtained as white solid; M.p: 221-222 °C; R_f = 0.4 (40% ethyl acetate/*n*-hexane); ^1H NMR (500 MHz, $CDCl_3$): δ 8.36 (d, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 2H),7.44-7.36 (m, 2H), 7.34-7.31 (m,

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4H), 7.28-7.26 (m, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 3.90 (s, 3H), 2.47 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 158.8, 142.4, 140.2, 135.1, 133.7, 131.7, 131.5, 130.2, 129.7, 129.4, 128.8, 127.0, 126.2, 117.9, 116.5, 114.8, 55.6, 21.5 ppm; HRMS calculated for $[M+H]^+$ $C_{24}H_{20}N_3O_2$: 382.1556 found: 382.1567.

4-(3,4-Dichlorophenyl)-1-phenylimidazo[1,5-*a*]quinazolin-5(4*H*)-one (3o): 3o was obtained as white solid; M.p: 222-223 °C; R_f = 0.4 (30% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37-8.33 (s, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.65-7.55 (m, 4H), 7.56-7.52 (m, 2H), 7.46-7.39 (m, 2H), 7.32 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.27-7.22 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 145.0, 142.5, 135.0, 134.9, 134.4, 134.2, 133.7, 133.5, 132.5, 131.5, 131.2, 130.8, 130.3, 130.2, 19.9, 129.5, 126.5, 117.4, 116.5 ppm; HRMS calculated for $[M+H]^+$ $C_{22}H_{14}N_3OCl_2$: 406.0508 found: 406.0507.

1-(2-Chlorophenyl)-4-(3,4-dichlorophenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3p): 3p was obtained as white solid; M.p: 205-206 °C; R_f = 0.5 (40% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (d, *J* = 6.6 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 6.9 Hz, 2H), 7.59-7.53 (m, 3H), 7.52-7.41 (m, 4H), 7.01 (d, *J* = 7.3, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 139.1, 139.0, 135.0, 134.9, 134.8, 134.4, 133.7, 133.4, 132.5, 132.3, 131.9, 131.3, 131.2, 130.6, 130.2, 130.1, 129.9, 127.7, 126.6, 117.1, 115.0 ppm; HRMS calculated for $[M+H]^+$ $C_{22}H_{13}Cl_3N_3O$: 440.0119 found: 440.0116.

4-(3,4-Dichlorophenyl)-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3q): 3q was obtained as white solid; M.p: 182-183 °C; R_f = 0.5 (40% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (dd, *J* = 1.4, 7.7 Hz, 1H), 7.80 (t, *J* = 8.8 Hz, 4H), 7.72-7.64 (m, 2H), 7.56-7.43 (m, 2H), 7.39 (dd, *J* = 2.5, 8.5Hz, 1H), 7.32-7.27 (m, 1H), 6.40 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 138.8, 135.7, 135.4, 135.0, 134.3, 134.1, 134.0, 133.8, 131.8, 131.6, 130.5, 130.2, 129.8, 127.4, 126.5, 126.0 (q, *J* = 2.7 Hz, 1C), 124.8 (q, *J* = 272.4Hz, 1C), 117.8, 116.5, 110.3 ppm; HRMS calculated for $[M+H]^+$ $C_{23}H_{13}Cl_2F_3N_3O$: 474.0387 found: 474.0393.

4-(3,4-Dichlorophenyl)-1-*p*-tolylimidazo[1,5-*a*]quinazolin-5(4*H*)-one (3r): **3r** was obtained as white solid; M.p: 229-230 °C; R_f = 0.5 (30% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (d, *J* =7.6 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H),7.57 (s, 1H), 7.48 (d, *J* =7.8, 2H), 7.45-7.39 (m, 2H), 7.33 (d, *J* = 7.6 Hz, 3H), 7.31-7.27 (m, 2H), 2.47 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 142.7, 140.4, 135.1, 134.3, 134.2, 133.6, 133.5, 132.5, 131.2, 130.7, 130.2, 129.9, 129.8, 129.3, 128.5, 126.4, 117.4, 116.5, 21.5 ppm; HRMS calculated for $[M+H]^+$ $C_{23}H_{16}Cl_2N_3O$: 420.0664 found: 420.0672.

1-Phenyl-4-(*p*-tolyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3s): 3s was obtained as white solid; M.p: 243-244 °C; R_f = 0.5 (40% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 (dd, *J* = 1.3, 7.0 Hz, 1H), 7.62 (d, *J* = 6.4 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 3H), 7.43-7.37 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 3H), 7.27-7.22 (m, 2H), 2.48 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 142.1, 135.0, 133.7, 131.7, 131.6, 130.2, 130.1, 130.0, 129.5, 129.0, 126.2,117.9, 116.4, 21.4 ppm; HRMS calculated for $[M+H]^+$ $C_{22}H_{13}N_3O$: 352.1444 found: 352.1445.

1-(2-Chlorophenyl)-4-(*p*-tolyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3t): 3t was obtained as white solid; M.p: 252-253 °C; R_f = 0.4 (40% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 7.1 Hz, 1H), 7.58-7.52 (m, 2H), 7.50-7.27 (m, 8H), 7.02 (s, 1H), 2.47 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 140.0, 138.6, 135.0, 134.9, 134.3, 132.4, 131.7, 131.6, 131.5, 131.3, 130.3, 130.2, 130.0, 128, 127.7, 126.4, 117.6, 115 ppm; HRMS calculated for $[M+H]^+$ $C_{23}H_{17}ClN_3O$: 386.1054 found: 386.1061.

1,4-Di-*p*-tolylimidazo[1,5-*a*]quinazolin-5(4*H*)-one (3u): **3u** was obtained as white solid; M.p: 204-205 °C; R_f = 0.5 (30% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.46-7.40 (m, 2H), 7.39-7.35 (m, 4H), 7.33 (d, *J* = 7.9Hz, 3H), 6.28 (s, 1H), 2.48 (s, 3H), 2.47 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 140.1, 139.8, 139.3, 135.8, 134.0, 133.6, 130.6, 130.2, 129.7, 129.5, 127.6, 125.8, 118.1, 116.6, 109.6, 21.5, 21.3 ppm; HRMS calculated for $[M+H]^+$ $C_{24}H_{20}N_3O$: 366.1606 found: 366.1600.

4-(*p*-Tolyl)-4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3v): 3v was obtained as white solid; M.p: 198-199 °C; R_f = 0.5 (40% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.79 (s, 4H), 7.52-7.41 (m, 3H), 7.40-7.35 (m, 3H), 7.30 (d, *J* = 7.3 Hz, 1H), 6.34 (s, 1H), 2.47 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 139.5, 138.3, 136.0, 135.4, 134.7, 133.8, 133.3, 132.1 (q, *J* = 33.0 Hz, 1C), 130.7, 130.5, 129.8, 127.5, 126.2, 125.9 (q, *J* = 3.3 Hz, 1C) 125.6 (q, *J* = 272.3 Hz, 1C) 118.3, 116.4, 110.4, 21.3 ppm; HRMS calculated for $[M+H]^+$ $C_{24}H_{16}F_3N_3O$: 420.1318 found: 420.1316.

8-Chloro-1,4-diphenylimidazo[1,5-*a*]quinazolin-5(4*H*)-one (3w): **3w** was obtained as white solid; M.p: 210-211 °C; R_f = 0.5 (40% ethyl acetate/*n*-hexane); ^{1}H NMR (500MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 15.5 Hz, 1H), 7.79 (s, 1H), 7.62-7.54 (m, 3H), 7.41 (dd, *J* = 1.7, 8.4 Hz, 1H), 7.34-7.28 (m, 6H), 6.37 (d, *J* = 15.5Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 152.9,148.8, 140.7, 136.7, 135.1, 130.0, 129.9, 129.5, 128.8, 128.6, 127.9,127.1, 126.8, 119.5, 119.3 ppm; HRMS calculated for $[M+H]^+$ $C_{22}H_{15}ON_3Cl$: 372.0898 found: 372.0892.

8-Chloro-4-pheny-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3x): 3x was obtained as white solid; M.p: 220-221 °C; R_f = 0.5 (50% ethyl acetate/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.5Hz, 1H), 7.98 (d, *J* = 15.5Hz, 1H), 7.81 (d, *J* = 1.9Hz, 1H), 7.63-7.55 (m, 4H), 7.44 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.40 (d, *J* = 8.1Hz, 2H), 7.32 (dd, *J* = 1.9, 8.1 Hz, 2H), 6.43 (d, *J* = 15.5Hz , 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 152.2, 148.5, 141, 138.8, 138.4, 136.4, 130.1, 129.7, 128.6, 128.5, 127.9, 126.9, 125.8, 125.8, 121.9, 119.4 ppm; HRMS calculated for $[M+H]^+$ $C_{23}H_{14}ClF_3N_3O$: 440.0772 found: 440.0791.

8-Fluoro-4-pheny-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3y): **3y** was obtained as white solid; M.p: 202-203 °C; R_f = 0.45 (50% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (t, *J* = 8.3 Hz, 1H), 7.85-7.75 (m, 4H), 7.66-7.56 (m, 4H), 7.42 (d, *J* = 6.6 Hz, 2H), 7.15 (t, *J* = 8.4 Hz, 1H), 6.91 (d, *J* =

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9.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7 (d, *J* =256.1 Hz, 1C), 157.6, 140.6, 136.1, 136.0, 134.5, 134.0, 133.5, 133.4, 132.6, 130.4, 130.1, 129.9, 129.8, 126.2 (q, *J* =3.6 Hz, 1C), 114.8, 114.6, 104.2, 103.9 ppm; HRMS calculated for $[M]^+$ $C_{23}H_{13}F_4N_3O$: 423.0989 found: 423.0998.

1,4-Diphenylbenzo[g]imidazo[1,5-*a*]quinazolin-5(4*H*)-one (3z): **3z** was obtained as white solid; M.p: 225-226 °C; R_f = 0.5 (50% ethyl acetate/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.26 (s, 1H), 8.26 (s, 1H), 8.15-8.06 (m, 3H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.65 (t, *J* = 6.7 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 4H), 7.54-7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 145.3, 143.1, 137.6, 136.6, 132, 129.7, 129.4, 129, 128.9, 128.7, 128.1, 127.1, 126.7, 125.6 ppm; HRMS calculated for $[M+H]^+$ $C_{26}H_{18}N_3O$: 388.1449 found: 388.1456.

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