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Cyclisation of 2-(2-aminophenyl)quinazolin-4(3*H*)-one reexamined: formation of isomeric angular fused quinazolinoquinazolinones and their spectroscopic identification ☆

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ABSTRACT

Cyclisation of 2-(2-aminophenyl)quinazolin-4(3*H*)-ones on to N_3 and on to N_1 leading to 6-alkyl-(8*H*)-quinazolino[4,3-*b*]quinazolin-8-one and 6-alkyl-(13*H*)-quinazolino[3,4-*a*]quinazolin-13-one, respectively was described for the first time. The differences in the IR and carbon NMR data of these isomeric fused quinazolinoquinazolinones afford a useful method for distinguishing between the two series.

Over the past decade, synthesis of the heterocyclic compounds has become the cornerstone of synthetic organic chemistry as a result of wide variety of their application in medicinal and pharmaceutical chemistry.[1] The exploration of heterocycles as privileged structures in drug discovery is the important major area in medicinal chemistry.[2] Among them, quinazoline ring system is an ubiquitous structural unit and important pharmacophore found in a number of alkaloids and many biologically active compounds.[3] The synthesis of quinazolin-4(3*H*)-ones has been extensively investigated,[4] as some of the members, for example, 4-anilinoquinazolines, are shown to possess EGFR (epidermal growth factor receptor) tyrosine kinase inhibitory effects, useful to inhibit tumour growth.[5] For example, Iressa® and Tarceva® are the two selective EGFR-TK inhibitors approved by the FDA in 2004 for locally advanced or metastatic non-small cell lung cancer (NSCLC) therapy and are currently under clinical trials. (8*H*)-Quinazolino[4,3-*b*]quinazolin-8-ones (**1**) and (13*H*)-quinazolino[3,4-*a*]quinazolin-13-ones (**2**) are two isomeric angularly fused quinazolinoquinazolinones. Although there are a few synthetic methods[6–9] reported for the synthesis of **1**, there are only two articles[10,11] in the literature for **2**. Ozaki and co-workers[10a] employed a benzoxazine as the key intermediate, whereas Marinho et al.[10b] used *o*-aminobenzonitrile as the starting material. In view of the important biological activities of the fused quinazolinones, we have investigated the synthesis and spectroscopic differentiation of the two systems **1** and **2**, and herein we present our results.

Cyclisation of 2-(2-aminophenyl)quinazolin-4(3*H*)-one (**3**) with triethyl orthoformate[12] and auto-redox based cyclisation of 2-(2-nitrophenyl)quinazolin-4(3*H*)-one with tin(II) chloride in the presence of alcohols[13] on to N_3-nitrogen to give (8*H*)-quinazolino[4,3-*b*]quinazolin-8-ones (**1**) and 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-ones, respectively, via path a, are well established. However, the cyclisation of **3** through path b, that is, on to the N_1-nitrogen for the generation of **2** is not reported in the literature (Scheme 1). The selective formation of **1** from **3**, via path a, is surprising, and prompted us to re-examine the reaction employing different reagents and conditions. The required 2-(2-aminophenyl)quinazolin-4(3*H*)-one **3** was obtained from 2-aminobenzamide and 2-nitrobenzoic acid in three steps.[13,14] Compound **3** was then treated with various reagents and the results are summarised in Table 1.

First, the reaction was examined with one-carbon equivalent reagents such as dimethylformamide–dimethylacetal (DMF–DMA), triethyl orthoformate, formic acid and ethyl formate, which resulted in the formation of only compound **1** (Table 1, entries 1–7) as reported earlier.[12] The structure of **1** has been established from the spectroscopic data and confirmed by comparing with that described in the literature.[8] In a similar manner, reaction with the two-carbon equivalent reagent such as triethyl orthoacetate, proceeded selectively through path a, and resulted in compound **1** in

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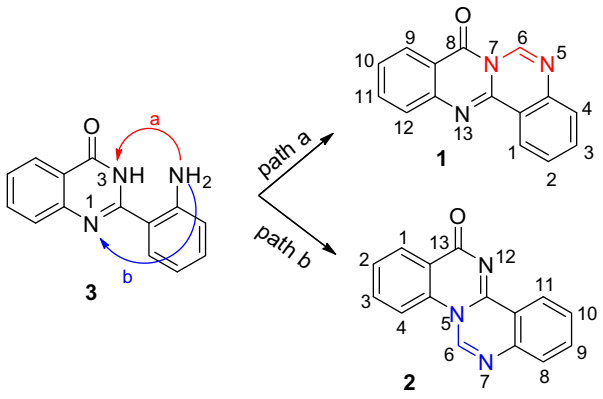


Scheme 1. Cyclisation of **3** via paths a and b.

Table 1
Reaction of **3** with various reagents[a]

Entry	Reagent	Solvent/catalyst	Conditions	Yield[b] (%)	
				1	**2**
1	DMF–DMA	Toluene/AcOH	rt, 30 min	91	—
2	DMF–DMA	Toluene/AcOH	Reflux, 10 min	86	—
3	$CH(OEt)_3$	Toluene/AcOH	rt, 24 h	50	—
4	$CH(OEt)_3$	Toluene/AcOH	Reflux, 2 h	90	—
5	HCOOH	Toluene	rt, 24 h	—	—
6	HCOOH	HCOOH	Reflux, 30 min	82	
7	HCOOEt	HCOOEt	Reflux, 24 h	86	—
8	$H_3CC(OEt)_3$	Toluene/AcOH	rt, 1.5 h	91	—
9	$H_3CC(OEt)_3$	Toluene/AcOH	Reflux, 15 min	91	—
10	AcOH	AcOH	rt, 16 h	—	—
11	AcOH	AcOH	Reflux, 4 h	—	—
12	Ac_2O	Ac_2O	Reflux, 2 h	49	32
13	Ac_2O	Ac_2O/pyridine	Reflux, 2 h	50	29
14	$(C_2H_5CO)_2O$	$(C_2H_5CO)_2O$	Reflux, 2 h	55	23

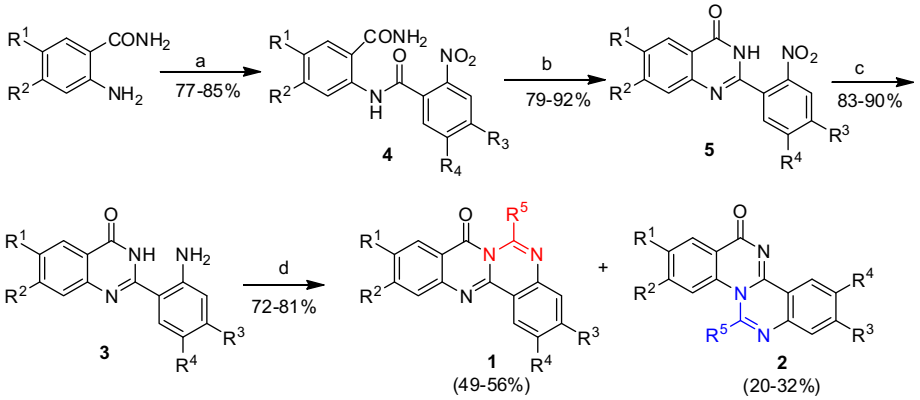
[a] All the reactions were performed with **3** (10 mmol), reagent (20 mmol) and optionally acid or base.
[b] Isolated yields.

91% yield (entries 8, 9), although no product was formed with acetic acid (entries 10, 11). Contrary to these results, we were pleased to observe that with acetic anhydride, the reaction proceeded to give both the compounds **1** and **2** in good yield (entries 12, 13).[15] Similarly with three-carbon equivalent reagent such as propionic anhydride also gave two isomeric fused quinazolinoquinazolinones **1** and **2** (entry 14). To the best of our knowledge, this is the first report on the formation of isomeric angular fused quinazolinoquinazolinones **1** and **2** by the competitive cyclisation of 2-(2-aminophenyl)quinazolin-4(3*H*)-one **3**.

Encouraged by these results, generality of the reaction was investigated with various 2-(2-aminophenyl)quinazolin-4(3*H*)-ones (**3**) with acetic anhydride as the reagent. The substituted derivatives of **3** were prepared from the corresponding 2-aminobenzamides and 2-nitrobenzoic acids as depicted in Scheme 2.

Thus, the reaction of 2-aminobenzamides with 2-nitrobenzoyl chlorides in the presence of triethylamine gave 2-[(2-nitrophenyl)carbonylamino]benzamides **4**. Ring closure of the compounds **4** using aqueous potassium hydroxide in ethanol provided 2-(2-nitrophenyl)quinazolin-4(3*H*)-ones **5**[13,14] in good yields. The nitro functionality was then reduced using iron powder to generate the key intermediates **3**. Refluxing a solution of the compounds **3** in acetic anhydride furnished a mixture of the isomeric angularly fused quinazolinoquinazolinones **1a–f** and **2a–f**, which were separated by column chromatography on silica gel. The yield of compounds **1a–f** is found to be more (49–56%) than the corresponding isomeric compounds **2a–f** (20–32%) indicating that the cyclisation on to N_3-nitrogen is more favourable, which might be due to better stability of system **1** (having complete π-conjugation from the carbonyl group to the carbon-6, which is absent in **2**). All the products have been characterized by their analytical and spectroscopic data.[16] The carbonyl absorptions in IR spectra of the isomeric fused quinazolinoquinazolinones **1** and **2** are presented in Table 2. It was found that the two compounds can easily be differentiated by the carbonyl absorption band in IR spectra; the value of **1** is between 1699 and 1709 cm^{-1} and **2** is between 1647 and 1660 cm^{-1}. Similarly, the chemical shift of the carbonyl carbon in the ^{13}C NMR spectrum (Table 3) was also found to be diagnostic. The value of **1** is in the range of δ 160.2–161.6 ppm and the corresponding carbon in **2** is in the range of δ 166.0–167.5 ppm.

A tentative mechanism is given in Scheme 3. First step is the formation of $RNHCOCH_3$ derivative **6**. Intramolecular nucleophilic



a: $R^1=R^2=R^3=R^4=H$, $R^5=CH_3$
b: $R^1=R^2=OCH_3$, $R^3=R^4=H$, $R^5=CH_3$
c: $R^1=R^2=H$, $R^3=R^4=OCH_3$, $R5=CH_3$
d: $R^1=R^3=R^4=H$, $R^2=Cl$, $R^5=CH_3$
e: $R^1=Br$, $R^2=R^3=R^4=H$, $R^5=CH_3$
f: $R^1=R^2=R^3=R^4=H$, $R^5=C_2H_5$

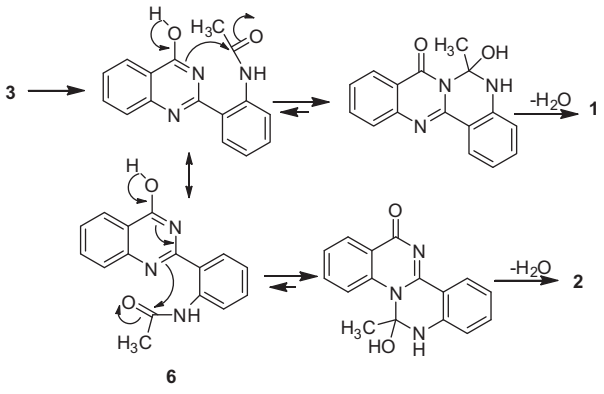
Scheme 2. Reagents and conditions: (a) 2-nitrobenzoic acids, $SOCl_2$, reflux, 2 h; THF, NEt_3, rt, 2 h; (b) 10% aq KOH, EtOH, reflux, 30 min; (c) Fe/AcOH, 60–70 °C, 1 h; (d) Ac_2O, reflux, 2 h.

Table 2
C=O absorption band of the compounds **1** and **2**

Compd No.	C=O (ν_{max}/cm^{-1})	
	1	**2**
a	1701	1660
b	1699	1651
c	1700	1647
d	1709	1651
e	1701	1655
f	1709	1658

Table 3
^{13}C NMR data of isomeric fused quinazolinones

Compd No.	C=O (δ ppm)	
	1	**2**
a	161.4	167.3
b	160.5	167.0
c	161.6	167.4
d	160.8	166.5
e	160.2	166.0
f	161.4	167.5



Scheme 3. Probable mechanism for the formation of **1** and **2**.

addition of either nitrogen N_3 or N_1 in **6** on to the amide, followed by the loss of water molecule generates **1** or **2**, respectively.

In summary, we have described an approach for the synthesis of isomeric angularly fused quinazolinoquinazolinones **1** and **2**. With acid anhydrides, 2-(2-aminophenyl)quinazolin-4(3*H*)-ones **3** were competitively cyclised to generate 6-alkyl-(8*H*)-*quinazolino[4,3-b*]quinazolin-8-ones **1** and 6-alkyl-(13*H*)-quinazolino[3,4-*a*]quinazolin-13-ones **2**, via intramolecular nucleophilic addition of either N_3-nitrogen or N_1-nitrogen, respectively. The methodology provides an entry for the isomeric angularly fused quinazolinones from a common intermediate and can be useful for the creation of libraries in a short time. The two series of compounds were found to be easily distinguishable from their IR and ^{13}C NMR data. The carbonyl absorptions in IR spectra of **1** are at higher value (between 1699 and 1709 cm^{-1}) than those of **2** (between 1647 and 1660 cm^{-1}). The carbonyl absorption in carbon NMR spectra of **1** appeared at higher field and the value is lower than that of **2** (ca. 5–6 ppm).

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15. *General procedure for **1** and **2***: A solution of **3** (500 mg) in acetic anhydride (10 mL) was refluxed for 2 h and allowed to cool to rt. The solution was poured into ice cold water and stirred for 10 min. The solution was extracted with chloroform (3 × 100 mL) and the combined layer was washed with water, brine dried over sodium sulfate and filtered. The solution was evaporated and the residue was chromatographed over silica gel column using chloroform/methanol (95:5) as eluents to give the products.
16. *Spectroscopic data*—Compound **1a**: Off-white color solid (49%), mp 180–182 °C (Lit.[12] mp 180–181 °C). IR (KBr) ν_{max} 1701, 1624, 1601, 1375, 1338, 1252, 1209, 1082, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (1H, d, J = 8.0 Hz), 8.35 (1H, d, J = 7.6 Hz), 7.79–7.86 (2H, m), 7.73 (1H, td, J = 7.6, 1.2 Hz), 7.67 (1H, d, J = 7.6 Hz), 7.55 (1H, td, J = 7.5, 1.0 Hz), 7.49 (1H, td, J = 7.4, 1.2 Hz), 3.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 150.4, 146.7, 146.2, 142.2, 135.3, 133.4, 127.9, 127.5, 127.1, 126.9, 126.3, 126.1, 121.6, 120.7, 27.3; LC–MS (positive ion mode): m/z 262 $(M+H)^+$.
Compound **2a**: Pale brown color solid (32%), mp 224–226 °C (Lit.[10a] mp 227–230 °C). IR (KBr) ν_{max} 1660, 1616, 1604, 1595, 1346, 1328, 1273, 1240, 1215, 1114, 1070, 1041, 771, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (1H, dd, J = 8.0, 0.8 Hz), 8.41 (1H, d, J = 7.6 Hz), 7.83 (1H, td, J = 7.6, 1.6 Hz), 7.74–7.76 (2H, m), 7.71 (1H, d, J = 8.0 Hz), 7.63–7.67 (1H, m), 7.58 (1H, td, J = 7.6, 1.2 Hz), 3.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 153.3, 148.2, 143.4, 136.8, 134.9, 131.9, 128.4, 128.2, 128.1, 126.8, 126.3, 123.1, 120.4, 119.9, 26.0; LC–MS (positive ion mode): m/z 262 $(M+H)^+$.
Compound **1b**: Off-white color solid (50%), mp 228–230 °C. IR (KBr) ν_{max} 1699, 1620, 1597, 1396, 1292, 1242, 1126, 1080, 1006, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (1H, d, J = 8.0 Hz), 7.68 (1H, t, J = 7.4 Hz), 7.62 (1H, d, J = 7.6 Hz), 7.59 (1H, s), 7.50 (1H, t, J = 7.2 Hz), 7.11 (1H, s), 4.04 (3H, s), 4.00 (3H, s), 3.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 156.1, 150.4, 149.0, 145.3, 143.2, 142.0, 133.0, 127.8, 126.9, 125.7, 121.6, 113.8, 107.3, 106.2, 56.4, 56.3, 27.6; LC–MS (positive ion mode): m/z 322 $(M+H)^+$; HRMS-(EI) (m/z) $(M+H)^+$ calcd for $C_{18}H_{16}N_3O_3$ 322.1192, found 322.1192.
Compound **2b**: Off-white color solid (25%), mp 282–284 °C. IR (KBr) ν_{max} 1651, 1604, 1280, 1250, 1203, 1006, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69

(1H, d, J = 8.0 Hz), 7.80 (1H, t, J = 7.4 Hz), 7.76 (1H, s), 7.68 (1H, d, J = 8.0 Hz), 7.56 (1H, t, J = 7.6 Hz), 7.15 (1H, s), 4.04 (3H, s), 4.03 (3H, s), 3.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 152.5, 152.4, 149.6, 147.6, 143.1, 134.5, 131.7, 128.0, 126.6, 126.2, 119.9, 117.1, 108.0, 103.2, 56.5, 56.5, 26.4; LC–MS (positive ion mode): m/z 322 $(M+H)^+$; HRMS-(EI) (m/z) $(M+H)^+$ calcd for $C_{18}H_{16}N_3O_3$ 322.1192, found 322.1190.

Compound **1c**: Off-white color solid (50%), mp 238–240 °C. IR (KBr) ν_{max} 1700, 1631, 1601, 1392, 1288, 1253, 1230, 1157, 1022, 864, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (1H, d, J = 8.0 Hz), 8.05 (1H, s), 7.80 (1H, t, J = 7.4 Hz), 7.74 (1H, d, J = 8.0 Hz), 7.43 (1H, t, J = 7.4 Hz), 7.08 (1H, s), 4.09 (3H, s), 4.01 (3H, s), 3.10 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 154.4, 149.7, 149.3, 147.1, 146.1, 138.3, 135.2, 127.5, 126.7, 125.6, 120.1, 114.8, 108.0, 105.8, 56.4, 56.3, 27.3; LC–MS (positive ion mode): m/z 322 $(M+H)^+$; HRMS-(EI) (m/z) (M+Na) calcd for $C_{18}H_{15}N_3O_3Na$ 344.1011, found 344.1012.

Compound **2c**: Pale brown color solid (23%), mp 292–294 °C. IR (KBr) ν_{max} 1647, 1601, 1334, 1265, 1238, 1203, 1018, 979, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (1H, d, J = 8.0 Hz), 8.04 (1H, s), 7.71–7.77 (2H, m), 7.61–7.65 (1H, m), 7.11 (1H, s), 4.05 (3H, s), 4.04 (3H, s), 3.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 155.9, 152.8, 150.0, 147.2, 140.1, 136.8, 131.7, 128.4, 128.0, 123.1, 120.4, 113.3, 107.0, 105.9, 56.7, 56.4, 26.1; LC–MS (positive ion mode): m/z 322 $(M+H)^+$. HRMS-(EI) (m/z) (M+Na) calcd for $C_{18}H_{15}N_3O_3Na$ 344.1011, found 344.1009.

Compound **1d**: Colorless solid (52%), mp 192–194 °C. IR (KBr) ν_{max} 1709, 1624, 1593, 1338, 1246, 1207, 1105, 925, 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (1H, d, J = 8.0 Hz), 8.21 (1H, d, J = 8.4 Hz), 7.70–7.74 (2H, m), 7.63 (1H, d, J = 8.0 Hz), 7.52 (1H, t, J = 7.6 Hz), 7.38 (1H, d, J = 8.0 Hz), 3.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 150.1, 147.6, 147.3, 142.4, 141.7, 133.8, 128.9, 128.0, 127.0, 126.9, 126.5, 126.2, 121.2, 119.0, 27.3; LC–MS (positive ion mode): m/z 296, 298 $(M+H)^+$; HRMS-(EI) (m/z) $(M+H)^+$ calcd for $C_{16}H_{11}ClN_3O$ 296.0591, found 296.0591.

Compound **2d**: Off-white color solid (20%), mp 216–218 °C. IR (KBr) ν_{max} 1651, 1585, 1261, 1068, 1022, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (1H, d, J = 8.0 Hz), 8.33 (1H, d, J = 8.4 Hz), 7.84 (1H, t, J = 7.4 Hz), 7.76 (1H, br s), 7.70 (1H, d, J = 8.0 Hz), 7.56–7.62 (2H, m), 3.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 153.6, 147.7, 143.3, 138.5, 137.6, 135.2, 130.0, 128.7, 128.3, 126.9, 126.4, 121.5, 120.4, 119.7, 26.0; LC–MS (positive ion mode): m/z 296, 298 $(M+H)^+$; HRMS-(EI) (m/z) $(M+H)^+$ calcd for $C_{16}H_{11}ClN_3O$ 296.0591, found 296.0594.

Compound **1e**: Colorless solid (56%), mp 190–192 °C. IR (KBr) ν_{max} 1701, 1624, 1334, 1253, 1141, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (1H, d, J = 8.0 Hz), 8.45 (1H, d, J = 1.6 Hz), 7.88 (1H, dd, J = 8.4, 1.6 Hz), 7.74 (1H, t, J = 7.2 Hz), 7.64–7.67 (2H, m), 7.55 (1H, t, J = 7.4 Hz), 3.10 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 150.0, 146.5, 145.5, 142.2, 138.4, 133.6, 129.9, 128.8, 128.1, 127.0, 126.1, 121.9, 121.3, 119.6, 27.2; LC–MS (positive ion mode): m/z 340, 342 $(M+H)^+$; HRMS-(EI) (m/z) $(M+H)^+$ calcd for $C_{16}H_{11}BrN_3O$ 340.0085, found 340.0082.

Compound **2e**: Off-white color solid (21%), mp 288–290 °C. IR (KBr) ν_{max} 1655, 1608, 1342, 1269, 1207, 1072, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (1H, d, J = 8.0 Hz), 8.55 (1H, d, J = 1.6 Hz), 7.82–7.86 (2H, m), 7.72 (1H, d, J = 8.0 Hz), 7.57–7.65 (2H, m), 2.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 153.5, 147.7, 143.5, 135.7, 135.2, 135.0, 131.1, 128.4, 126.9, 126.4, 124.5, 122.2, 122.0, 119.7, 26.0; LC–MS (positive ion mode): m/z 340, 342 $(M+H)^+$; HRMS-(EI) (m/z) $(M+H)^+$ calcd for $C_{16}H_{11}BrN_3O$ 340.0085, found 340.0087.

Compound **1f**: Colorless solid (55%), mp 162–164 °C (Lit.[12] mp 156–157 °C). IR (KBr) ν_{max} 1709, 1620, 1597, 1558, 1334, 1238, 1080, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (1H, d, J = 8.0 Hz), 8.34 (1H, d, J = 7.6 Hz), 7.77–7.84 (2H, m), 7.68–7.74 (2H, m), 7.54 (1H, t, J = 6.8 Hz), 7.48 (1H, t, J = 7.0 Hz), 3.51 (2H, q, J = 7.2 Hz), 1.42 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 154.7, 146.8, 146.4, 142.3, 135.3, 133.4, 127.9, 127.5, 127.2, 127.0, 126.3, 126.1, 121.5, 120.9, 31.9, 12.4; LC–MS (positive ion mode): m/z 276 $(M+H)^+$.

Compound **2f**: Colorless solid (23%), mp 188–190 °C. IR (KBr) ν_{max} 1658, 1620, 1593, 1342, 1240, 1188, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (1H, d, J = 8.0 Hz), 8.39 (1H, d, J = 7.6 Hz), 7.83 (1H, t, J = 7.4 Hz), 7.69–7.75 (3H, m), 7.64 (1H, t, J = 7.2 Hz), 7.57 (1H, t, J = 7.4 Hz), 3.27 (2H, q, J = 7.2 Hz), 1.45 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 153.4, 153.0, 143.7, 136.8, 134.8, 131.8, 128.4, 128.1, 128.0, 126.8, 126.6, 123.3, 120.4, 119.9, 30.7, 13.0; LC–MS (positive ion mode): m/z 276 $(M+H)^+$; HRMS-(EI) (m/z) (M+Na) calcd for $C_{17}H_{13}N_3ONa$ 298.0956, found 298.0957.