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Synthesis of isomeric angularly fused dihydroquinazolinoquinazolinones and an unusual oxidative rearrangement ☆

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ABSTRACT

Cyclization of 2-(2-aminophenyl)-2,3-dihydroquinazolin-4(1*H*)-ones onto N_1-nitrogen and onto N_3-nitrogen leading to 11b,12-dihydro-(13*H*)-quinazolino[3,4-*a*]quinazolin-13-ones and 13,13a-dihydro-(8*H*)-quinazolino[4,3-*b*]quinazolin-8-ones, respectively, is described for the first time. An unusual dehydrogenative rearrangement of 11b,12-dihydro-(13*H*)-quinazolino[3,4-*a*]quinazolin-13-one to (8*H*)-quinazolino[4,3-*b*]quinazolin-8-one is also described.

Over the past decade, the synthesis of heterocyclic compounds has become the cornerstone of synthetic organic chemistry as a result of a wide variety of their application in medicinal and pharmaceutical chemistry.[1] Exploration of heterocycles as privileged structures in drug discovery is the important major area in medicinal chemistry.[2] Quinazolin-4(3*H*)-one possess many biological activities[3] and their synthesis has been extensively investigated.[4] 4-Anilinoquinazolines are shown to possess EGFR (epidermal growth factor receptor) tyrosine kinase inhibitory effects, useful to inhibit tumor growth.[5] For example, Iressa® and Tarceva® are two selective EGFR-TK inhibitors approved by the FDA in 2004 for locally advanced or metastatic non-small cell lung cancer (NSCLC) therapy. (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 reported for the synthesis of **1**[6] and **2**,[7] synthesis of the corresponding dihydro derivatives were not reported in the literature. In view of the important biological activities of the fused quinazolinones and in continuation of our interest in this chemistry,[8] herein we describe the first synthesis of dihydroquinazolinoquinazolinones and an unusual dehydrogenative rearrangement of 11b,12-dihydro-(13*H*)-quinazolino[3,4-*a*]quinazolin-13-one.

Cyclization of 2-(2-aminophenyl)quinazolin-4(3*H*)-one (**3a**) with triethyl orthoformate[9] and auto-redox based cyclization of 2-(2-nitrophenyl)quinazolin-4(3*H*)-one (**3b**) with tin (II) chloride in the presence of alcohols[10] onto 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 (**1a**), respectively, via path a, are well established (Fig. 1). Recently, we reported the cyclization of **3a** with acetic anhydride onto N_3 and onto N_1-nitrogen leading to 6-methyl-(8*H*)-quinazolino[4,3-*b*]quinazolin-8-one (**1b**) and 6-methyl-(13*H*)-

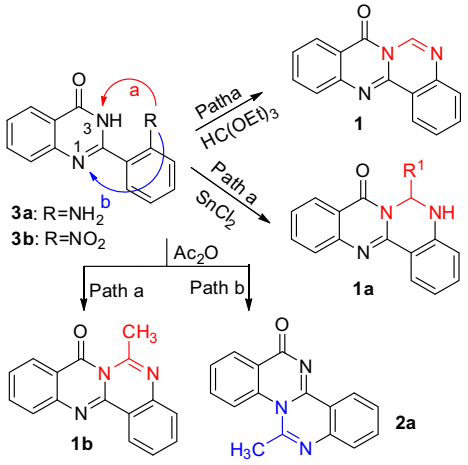

Figure 1. Known cyclization of **3** via paths a and b.

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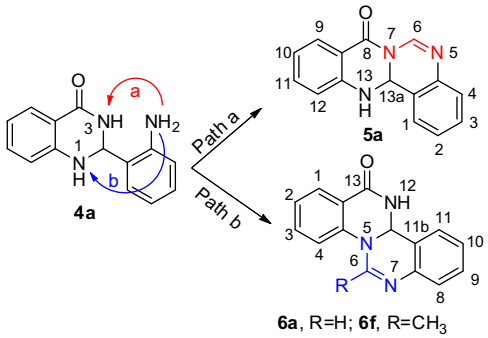
Table 1
Cyclization of **4a** with various reagents[a]



Entry	Reagent	Solvent/catalyst/conditions	Yield[b] (%)	
			5a	6a/6f
1	$HC(OEt)_3$	Toluene/rt, 16 h	—	76
2	$HC(OEt)_3$	Toluene/reflux, 2 h	—	76
3	$HC(OEt)_3$	$HC(OEt)_3$/reflux, 2 h	—	76
4	$HC(OEt)_3$	Toluene/AcOH/reflux, 2 h	—	76
5	$HC(OEt)_3$	Toluene/TEA/reflux, 2 h	—	70
6	HCOOH	HCOOH/reflux, 2 h	—	70
7	DMF–DMA	Toluene/reflux, 2 h	19	48
8	DMF–DMA	Toluene/AcOH/reflux, 2 h	—	76
9	DMF–DMA	Toluene/TEA/reflux, 2 h	22	51
10	AcOH	AcOH/reflux, 2 h	—	—
11	Ac_2O	Ac_2O/reflux, 2 h	—	—
12	$CH_3C(OEt)_3$	Toluene/reflux, 2 h	—	55
13	$CH_3C(OEt)_3$	Toluene/AcOH/reflux, 2 h	—	73
14	$CH_3C(OEt)_3$	Toluene/TEA/reflux, 2 h	—	73

[a] All the reactions were performed with **4a** (10 mmol), reagent (20 mmol), and optionally acid or base.
[b] Isolated yields.

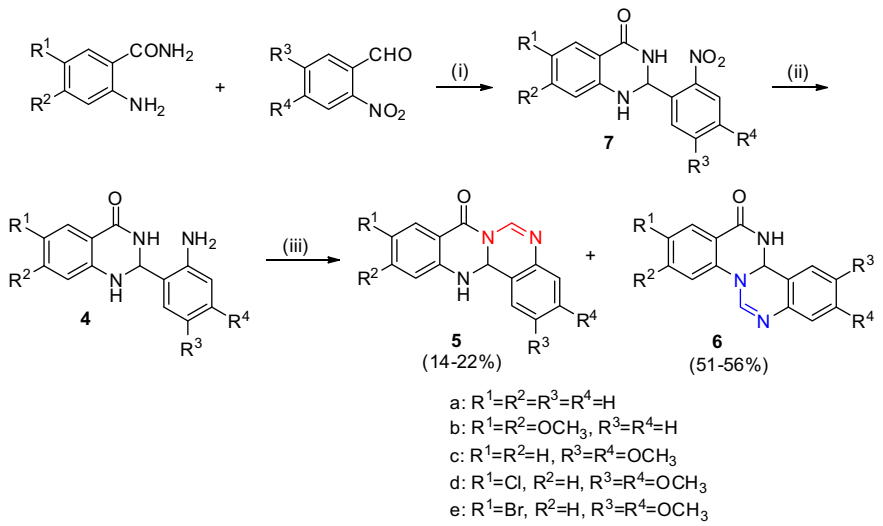
quinazolino[3,4-*a*]quinazolin-13-one (**2a**), respectively.[8] However cyclization of 2-(2-aminophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (**4a**) has not been studied. This prompted us to study this cyclization reaction. The required **4a** was obtained from anthranilamide and 2-nitrobenzaldehyde in two steps.[11] Compound **4a** was then treated with various reagents and the results are summarized in Table 1.

First, the reaction was examined under one-carbon equivalent reagents such as triethyl orthoformate and formic acid; the cyclization went smoothly and selectively to give compound **6a** (Table 1, entries 1–6) via path b. However, with dimethylformamide–dimethylacetal (DMF–DMA), the reaction proceeded competitively via paths a and b to give the compounds **5a** and **6a** in good yield (entries 7 and 9). But with the same reagent under acid catalyst, the reaction proceeded selectively through path b and gave **6a** in good yield (entry 8). The structures of **5a** and **6a** have been deduced from its spectroscopic data. Next, with the two-carbon equivalent reagents such as acetic acid and acetic anhydride, the acetylated products were obtained instead of the products, whereas with triethyl orthoacetate the reaction proceeded selectively through path b, and gave 6-methyl substituted compound **6f** in good yield (entries 13 and 14). These results indicate that the cyclization onto N_1-nitrogen is more favorable to give compound **6**, which might be due to better stability (due to the extended conjugation through amide nitrogen) of the system **6**. Calculations based on PCMODEL indicated that the compound **6a** is substantially more stable than the compound **5a**. To the best of our knowledge this is the first report on the formation of both the isomeric angular fused dihydroquinazolinoquinazolinones by the cyclization of 2-(2-aminophenyl)-2,3-dihydroquinazolin-4(1*H*)-one.

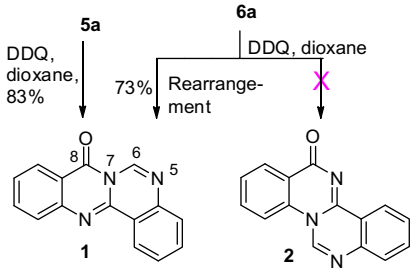
Encouraged by the above results, the reaction was tried with various 2-(2-aminophenyl)-2,3-dihydroquinazolin-4(1*H*)-ones (**4**) with DMF–DMA to check the generality of the method for generating isomeric angularly fused dihydroquinazolinoquinazolinones. The substituted **4** were obtained from the corresponding 2-aminobenzamides and 2-nitrobenzaldehydes as depicted in Scheme 1.

The synthetic methodology commenced with the synthesis of 2,3-dihydro-2-(2-nitrophenyl)quinazolin-4(1*H*)-ones (**7**) by refluxing anthranilamide and 2-nitrobenzaldehydes in the presence of water.[11] The nitro functionality was reduced using iron powder to generate **4**, which were reacted with DMF–DMA in toluene to give two isomeric angularly fused dihydroquinazolinoquinazolinones (**5** and **6**).[12] The two products were separated and characterized by their analytical and spectroscopic data.[13]

It was contemplated that the dehydrogenation reaction of **5** and **6** would lead to compounds **1** and **2**. Among the several reagents known,[14] DDQ was chosen for the aromatization reaction. Thus, dehydrogenation of 13,13a-dihydro-(8*H*)-quinazolino[4,3-*b*]quinazolin-8-one (**5a**) with 1.5 equiv of DDQ gave (8*H*)-quinazolino[4,3-*b*]quinazolin-8-one (**1**) in good yield. The structure of **1** has been deduced from its spectroscopic data and confirmed by comparing with that described in the literature.[6c] However,



Scheme 1. Reagents and conditions: (i) H_2O:AcOH, reflux, 5 h, 71–86% (ii) Fe/HCl, NH_4Cl, MeOH, reflux, 0.5 h, 70–92% (iii) DMF–DMA, Et_3N, toluene, reflux, 3 h, 68–73%.

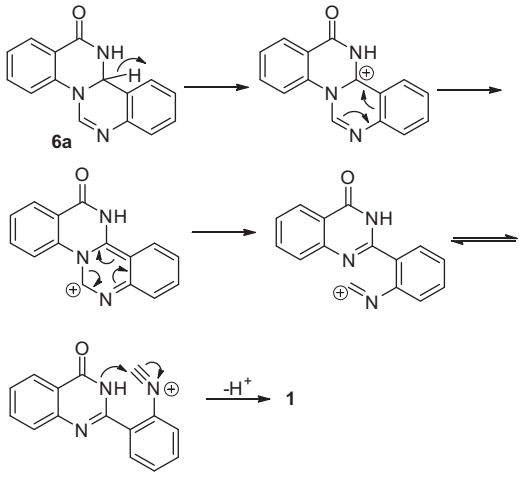


Scheme 2. Dehydrogenation of **5a** and **6a.**

Table 2
Dehydrogenation of **6a**[a]

S. no.	Reagent	Conditions	Yield[b] (**1**)
1	DDQ	Dioxane, reflux, 2 h	70%
2	—	Dioxane, reflux, 4 h	No change
3	—	Toluene, reflux, 4 h	No change
4	*p*-TSA	Toluene, reflux, 4 h	No change
5	NBS	Dioxane, pyridine, reflux, 3 h	35%
6	Pd–C	Benzene, reflux, 2 h	35%
7	S powder	DMF, reflux, 4 h	70%
8	SeO_2	AcOH, reflux, 4 h	40%

[a] All the reactions were performed with **6a** (10 mmol), reagent (15 mmol), and solvent.
[b] Isolated yields.



Scheme 3. Tentative mechanism of the rearrangement.

contrary to the expectation, dehydrogenation of 11b,12-dihydro-(13*H*)-quinazolino[3,4-*a*]quinazolin-13-one (**6a**) with DDQ under identical conditions, instead of (13*H*)-quinazolino[3,4-*a*]quinazolin-13-one (**2**), gave compound **1** in good yield as shown in Scheme 2. The product is identical in all respects (mp, mixed mp, ^{1}H, and ^{13}C NMR) with **1**.

This unusual rearrangement of **6a** prompted us to investigate with other dehydrogenative reagents and the results were summarized in Table 2. First the reaction was carried out without dehydrogenation reagent in two solvents and with *p*-TSA, an acidic catalyst (entries 2–4). However, there is no reaction confirming that the rearrangement is not acid catalyzed. With NBS and Pd–C, only rearranged product **1** was observed (entries 5 and 6). Refluxing with sulfur powder in DMF or with SeO_2 gave again the rearranged product (entries 7 and 8). Perhaps a complete π-electron delocalization from carbonyl (C-8) to the adjacent carbon-6 via two benzene rings made the rearranged product **1** more stable, which might be the driving force for the rearrangement.

The mechanism of the rearrangement is not very clear at this moment. For simplicity, the carbonium ion based tentative mechanism (an analogous free radical based mechanism can also be visualized) is depicted in Scheme 3.

In summary, we have described an approach for the synthesis of isomeric angularly fused dihydroquinazolinoquinazolinones. 2-(2-Aminophenyl)-2,3-dihydroquinazolin-4(1*H*)-one was cyclized selectively onto N_1-nitrogen to provide 11b,12-dihydro-(13*H*)-quinazolino[3,4-*a*]quinazolin-13-one using formic acid, triethyl orthoformate, and triethyl orthoacetate. However with DMF–DMA under neutral or basic conditions, the cyclization is onto N_3 and N_1-nitrogen leading to 13,13a-dihydro-(8*H*)-quinazolino[4,3-*b*]quinazolin-8-one and 11b,12-dihydro-(13*H*)-quinazolino[3,4-*a*]quinazolin-13-one, respectively. This methodology provides an entry for the isomeric angularly fused dihydroquinazolines from a common intermediate and can be extrapolated for similar kinds of heterocycles for the generation of large libraries in shorter time. Dehydrogenation of 13,13a-dihydro-(8*H*)-quinazolino[4,3-*b*]quinazolin-8-one with DDQ provided (8*H*)-quinazolino[4,3-*b*]quinazolin-8-one. Surprisingly 11b,12-dihydro-(13*H*)-quinazolino[3,4-*a*]quinazolin-13-one is rearranged to (8*H*)-quinazolino[4,3-*b*]quinazolin-8-one with the general dehydrogenating reagents such as DDQ, Pd–C, etc.

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12. *General procedure for **5** and **6**:* To a suspension of **4** (1.5 mmol) in toluene (15 mL) was added successively DMF–DMA (0.4 mL, 3.0 mmol) and triethylamine (0.2 mL, 1.5 mmol) at rt, stirred for 1 h and refluxed for 3 h. The reaction mixture was allowed to cool to rt and the precipitated product was filtered, washed with toluene and dried. The crude product was recrystallized from chloroform–methanol to give **6**. The filtrate from the reaction mixture was diluted with ice cold water (200 mL) and extracted with ethyl acetate (3 × 100 mL). The combined EtOAc layer was washed with brine, dried over sodium sulfate and filtered. The solution was evaporated and the residue was chromatographed over silica gel column using chloroform–methanol (98:2) as eluents to give **5**.
13. *Spectroscopic data - Compound **5a**:* Off-white color solid (22%), mp 226–228 °C. IR (KBr) ν_{max} 3228, 1687, 1621, 1610, 1308, 1251, 1221, 1171, 1157, 900, 760 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.17 (1H, s), 7.85 (1H, d, J = 7.6 Hz), 7.64 (1H, d, J = 7.2 Hz), 7.56 (1H, s, exchangeable with D_2O), 7.52 (1H, t, J = 7.6 Hz), 7.42 (1H, t, J = 7.2 Hz), 7.35 (1H, t, J = 7.0 Hz), 7.25 (1H, d, J = 7.2 Hz), 7.10 (1H, d, J = 8.0 Hz), 6.94 (1H, t, J = 7.2 Hz), 6.35 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.8, 147.7, 139.2, 139.1, 135.4, 129.8, 128.7, 126.9, 126.0, 125.8, 121.6, 119.4, 116.6, 114.5, 63.6; LC–MS (positive ion mode): m/z 250 $(M+H)^+$; HRMS-(EI) (m/z) $(M+Na)^+$ Calcd for $C_{15}H_{11}N_3O$ 272.0800, found 272.0804.
*Compound **6a**:* Off-white color solid (51%), mp 296–302 °C. IR (KBr) ν_{max} 3157, 3050, 1686, 1622, 1605, 1314, 1303, 1254, 1182, 760 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.76 (1H, s, exchangeable with D_2O), 7.98 (1H, d, J = 7.6 Hz), 7.78 (1H, s), 7.69 (1H, t, J = 7.8 Hz), 7.64 (1H, d, J = 7.6 Hz), 7.36–7.41 (3H, m), 7.25 (1H, t, J = 7.4 Hz), 7.20 (1H, d, J = 8.0 Hz), 6.50 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.0, 143.6, 140.8, 139.8, 133.5, 129.9, 128.1, 127.6, 125.8, 125.2, 125.1, 123.1, 118.5, 118.2, 62.0; LC–MS (positive ion mode): m/z 250 $(M+H)^+$; HRMS-(EI) (m/z) $(M+H)^+$ Calcd for $C_{15}H_{11}N_3O$ 250.0980, found 250.0977.
*Compound **5b**:* Off-white color solid (14%), mp 248–250 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (1H, s), 7.44–7.48 (2H, m), 7.39 (1H, t, J = 7.6 Hz), 7.35 (1H, t, J = 8.0 Hz), 7.27 (1H, t, J = 7.6 Hz), 6.47 (1H, s), 6.19 (1H, d, J = 7.6 Hz), 4.39 (1H, d, J = 7.2 Hz, exchangeable with D_2O), 3.94 (3H, s), 3.92 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 156.1, 145.7, 140.6, 140.1, 139.9, 130.4, 127.2, 127.0, 124.8, 121.4, 110.8, 109.9, 101.5, 64.4, 56.3, 56.2; LC–MS (negative ion mode): m/z 308 $(M-H)^-$.
Compound **6b**: Off-white color solid (52%), mp 308–310 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 8.53 (1H, s, exchangeable with D_2O), 7.80 (1H, s), 7.41 (1H, s), 7.35–7.38 (2H, m), 7.18–7.25 (3H, m), 6.42 (1H, s), 3.92 (3H, s), 3.83 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.0, 153.3, 146.7, 144.0, 139.9, 135.4, 129.8, 127.6, 125.6, 125.1, 118.6, 115.0, 109.5, 102.0, 62.3, 56.2, 55.8; LC–MS (positive ion mode): m/z 310 $(M+H)^+$; HRMS-(EI) (m/z) $(M+H)^+$ Calcd for $C_{17}H_{15}N_3O_3$ 310.1192, found 310.1194.
Compound **5c**: Off-white color solid (15%), mp 242–244 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (1H, s), 8.10 (1H, d, J = 8.0 Hz), 7.53 (1H, t, J = 7.8 Hz), 7.11 (1H, t, J = 7.6 Hz), 7.01 (1H, d, J = 8.4 Hz), 6.91 (1H, s), 6.88 (1H, s), 6.22 (1H, d, J = 6.0 Hz), 4.58–4.60 (1H, m, exchangeable with D_2O), 3.94 (3H, s), 3.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 150.4, 148.4, 144.9, 138.5, 135.5, 134.1, 129.9, 122.1, 118.6, 118.5, 112.6, 110.3, 107.5, 64.2, 56.5, 56.1; LC–MS (negative ion mode): m/z 308 $(M-H)^-$; HRMS-(EI) (m/z) $(M+Na)^+$ Calcd for $C_{17}H_{15}N_3O_3$ 332.1011, found 332.1017.
*Compound **6c**:* Off-white color solid (56%), mp 306–308 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 8.73 (1H, s), 7.98 (1H, d, J = 7.6 Hz), 7.72 (1H, s), 7.62–7.69 (2H, m), 7.37 (1H, t, J = 7.8 Hz), 6.96 (1H, s), 6.78 (1H, s), 6.43 (1H, s), 3.81 (3H, s), 3.80 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 149.7, 146.8, 141.8, 140.9, 133.5, 128.1, 124.9, 122.6, 118.0, 110.3, 109.9, 108.6, 62.2, 55.7, 55.6; LC–MS (positive ion mode): m/z 310 $(M+H)^+$.
*Compound **5d**:* Off-white color solid (15%), mp 188–190 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (1H, s), 8.06 (1H, d, J = 2.4 Hz), 7.47 (1H, dd, J = 8.6, 2.2 Hz), 6.97 (1H, d, J = 8.8 Hz), 6.90 (1H, s), 6.86 (1H, s), 6.19 (1H, d, J = 6.4 Hz), 4.60 (1H, d, J = 6.0 Hz, exchangeable with D_2O), 3.93 (3H, s), 3.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 150.5, 148.5, 143.2, 138.1, 135.5, 134.0, 129.2, 127.7, 120.3, 119.8, 112.1, 110.4, 107.5, 64.2, 56.5, 56.1; LC–MS (negative ion mode): m/z 342, 344 $(M-H)^-$; HRMS-(EI) (m/z) $(M+H)^+$ Calcd for $C_{17}H_{14}ClN_3O_3$ 344.0802, found 344.0826.
*Compound **6d**:* Off-white color solid (55%), mp 306–308 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 8.88 (1H, s), 7.91 (1H, s), 7.72 (3H, br s), 6.96 (1H, s), 6.79 (1H, s), 6.43 (1H, s), 3.81 (3H, s), 3.80 (3H, s); LC–MS (positive ion mode): m/z 344, 346 $(M+H)^+$; HRMS-(EI) (m/z) $(M+H)^+$ Calcd for, $C_{17}H_{14}ClN_3O_3$ 344.0802, found 344.0807.
*Compound **5e**:* Off-white color solid (16%), mp 220–222 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (1H, s), 8.21 (1H, d, J = 2.0 Hz), 7.60 (1H, dd, J = 8.6, 2.2 Hz), 6.91 (1H, d, J = 7.2 Hz), 6.90 (1H, s), 6.86 (1H, s), 6.19 (1H, d, J = 6.4 Hz), 4.64 (1H, d, J = 5.6 Hz, exchangeable with D_2O), 3.93 (3H, s), 3.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 150.6, 148.6, 143.6, 138.3, 138.1, 134.0, 132.3, 120.4, 120.0, 114.6, 112.1, 110.4, 107.5, 64.1, 56.5, 56.1; LC–MS (negative ion mode): m/z 386, 388 $(M-H)^-$.
*Compound **6e**:* Off-white color solid (52%), mp 324–326 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 8.88 (1H, s, exchangeable with D_2O), 8.04 (1H, d, J = 1.2 Hz), 7.85 (1H, dd, J = 8.6, 1.6 Hz), 7.72 (1H, s), 7.65 (1H, d, J = 8.4 Hz), 6.95 (1H, s), 6.79 (1H, s), 6.43 (1H, s), 3.81 (3H, s), 3.80 (3H, s); LC–MS (positive ion mode): m/z 388, 390 $(M+H)^+$; HRMS-(EI) (m/z) $(M+H)^+$ Calcd for, $C_{17}H_{14}BrN_3O_3$ 388.0297, found 388.0293.
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