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Synthesis of a novel series of 1,2-dihydroquinoline-8-glyoxylamide derivatives

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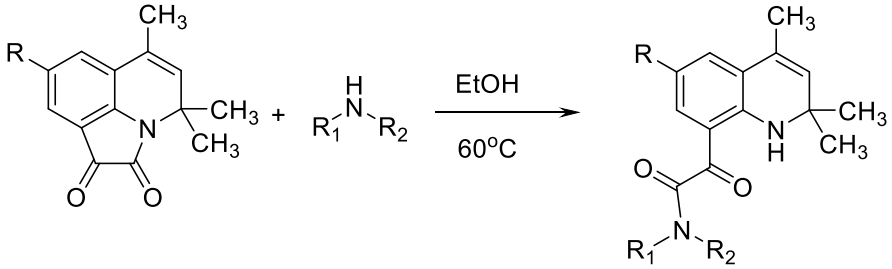
Dedicated to Prof. Girolamo Cirrincione in recognition of his outstanding contributions to the fields of organic and medicinal chemistry

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Abstract

A series of new derivatives of 1,2-dihydroquinoline-8-glyoxylamides have been synthesized via nucleophilic opening of the pyrrolidine-2,3-dione ring of 4,4,6-trimethyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones by a variety of amines. This method is an efficient synthetic strategy for introducing substituents at the *o*-position of the amine function of the 1,2-dihydroquinolines. The obtained compounds are of interest as potentially physiologically active substances.



excess amine ; mild conditions ; 7 examples 71-85 %

Keywords: 2,2,4-Trimethyl-1,2-dihydroquinoline, glyoxylamides, 4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione, amine, ring opening

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Introduction

Quinolines are widely found in natural compounds and are important biochemicals. They are successfully used in medicine as antimalarial, antiasthma, antihypertensive and antibacterial agents, as well as tyrosine kinase inhibitors.[1-4] In addition, some quinoline derivatives are part of a class of promising compounds for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus*, as well as compounds with photoantiproliferative activity.[5-7]

It should also be noted that fully or partially hydrogenated quinolines - 2,2,4-trialkyl-1,2,3,4-tetra- and 1,2-dihydroquinolines - have attracted the increasing attention of researchers in recent decades. These compounds are characterized by their high reactivity and associated variety of chemical transformations, which has been confirmed by a number of studies.[8-16] The biological significance of this class of compounds is also important. For example, derivatives of this particular series exhibit antibacterial,[17,18] anticancer,[19] anti-inflammatory,[20] and antitrypanosomal[21] activities. In particular, 2,2,4-trimethyl-1,2-dihydroquinoline and its derivatives are used as antagonists of receptors of follicle-stimulating hormone[22] and plant growth stimulators.[23,24] Furthermore, derivatives of 2,2,4-trisubstituted 1,2,3,4-tetra- and 1,2-dihydroquinolines are well known as lipid peroxidation inhibitors,[25] glucocorticoid receptor modulators,[26-28] dyes[29,30] and antioxidants.[31-33]

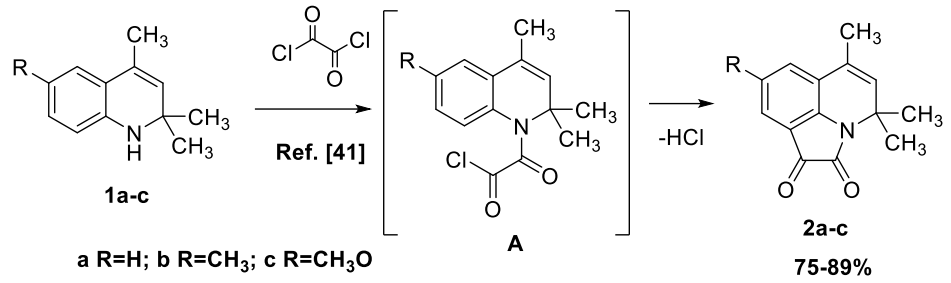
It is known that glyoxylamides are of great interest for organic chemistry and are part of many biologically active molecules. Thus, a large number of publications are devoted to indole-containing glyoxylamides, which have a wide range of antitumor properties,[34-37] as well as antimicrobial, antiasthmatic, antiallergic, and immunomodulatory effects.[38] To our surprise, there are practically no examples of the synthesis of glyoxylamides containing a quinoline fragment in the literature. At the same time, the synthesis of new structurally different glyoxylamides is of undoubted interest for studying their properties, for instance by comparying them with their indole-containing glyoxylamides.

Thus, continuing research in the field of chemistry of 2,2,4-trimethyl-1,2-dihydroquinolines[16,39,40] with the aim of searching for new derivatives with potential biological activity, we report herein the synthesis of new 8-substituted 2,2,4-trimethyl-1,2-dihydroquinolines by nucleophilic opening of the pyrroledione ring of 8-substituted 4,4,6-trimethyl-4*H*-pyrrolo[3,2,1-*ij*]quinolone-1,2-diones[41] under the action of secondary amines. This type of reaction is well known in the literature for isatin.[42-46] Here, we have demonstrated that the opening of the pyrroledione ring can be extended beyond isatin and applied to obtain a quinoline backbone with a glyoxylamide moiety.

Results and Discussion

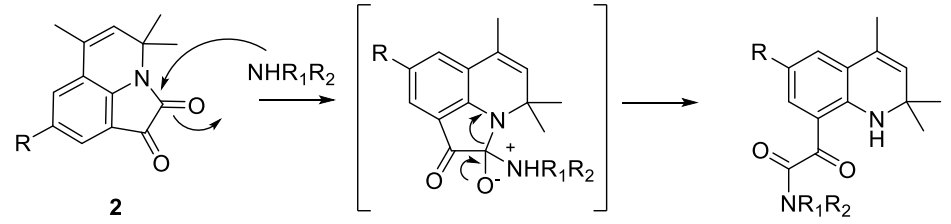
The preparation of the 4,4,6-trimethyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones were carried out following the procedure detailed in the literature,[41] starting from acylation of the amino group of the substituted 2,2,4-trimethyl-1,2-dihydroquinolines **1a-c** with oxalyl chloride, followed by an intramolecular Friedel-Craft acylation to afford compounds **2a-c** (Scheme 1).

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Scheme 1. Synthesis of the starting 4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones **2a-c**.

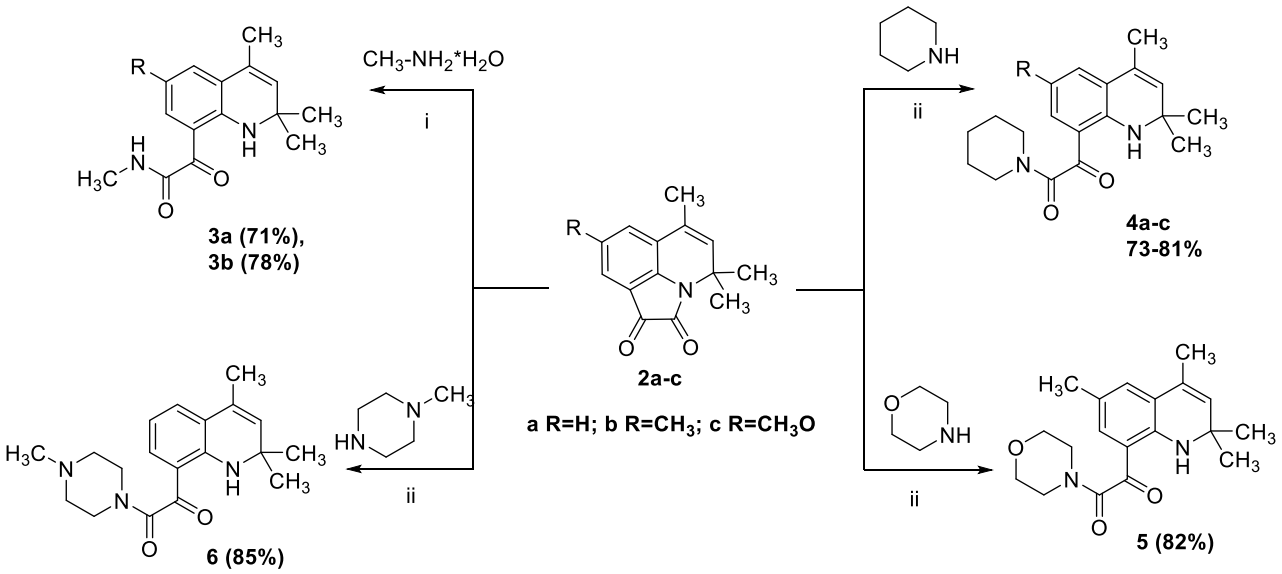
In this study, it was found that 4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones, as also shown for isatin,[42-46] participate in reactions based on the nucleophilic opening of the pyrrolidine-2,3-dione ring to form heterocyclic amides. In this manner, the nucleophilic opening of the pyrrolidine-2,3-dione ring of 4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones **2** by the attack of an amine at C2-carbonyl group of 4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones proceeds with the formation of the previously unknown 1,2-dihydroquinoline-8-glyoxylamides (Scheme 2).



Scheme 2. General mechanism for the reaction of 4,4,6-trimethyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones (**2a-c**) with amines.

Commercially available methylamine 40% solution, piperidine, morpholine and *N*-methylpiperazine were used as amines. Furthermore, by heating of 4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones **2a-b** in a 40% solution of methylamine *N*-methyl-2-oxo-2-(1,2-dihydroquinolin-8-yl) acetamides **3a-b** were obtained. In addition, the reactions of 4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones **2** with piperidine, morpholine, and *N*-methylpiperazine in ethanol resulted in 1,2-dihydroquinoline-8-glyoxylamides **4-6**. The thus obtained products were isolated as yellow solids in good yields (71-85%) (Scheme 3).

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Scheme 3. Synthesis of 1,2-dihydroquinoline-8-glyoxylamides **3a-b, 4a-c, 5-6**. Reagents and conditions: (i) CH_3NH_2 (40% solution), EtOH, 60°C, 30 min, 71-78%; (ii) secondary amines (5 eq), EtOH, 60°C, 4-10 h, 73-85%.

The formation of the ring-opened products (**3–6**) was confirmed by NMR and IR spectroscopy. The ^{1}H NMR spectra of compounds **3a,b** showed an additional doublet due to the methyl group at 2.74 ppm with J = 4.7 Hz, as well as a doublet at δ 8.65–8.68 ppm with J = 4.5–4.6 Hz, and a singlet at δ 8.75–8.87 ppm for the amino groups of the acetamide proton and dihydroquinoline fragment, respectively. In addition, the ^{13}C NMR spectra contained characteristic signals for the C=O groups at δ ~166 and ~192 ppm. As an example, the IR spectrum of *N*-methyl-2-oxo-2-(2,2,4-trimethyl-1,2-dihydroquinolin-8-yl)acetamide **3a** was characterized by the presence of absorption bands at 3735-3392 cm^{-1}, characteristic of stretching vibrations of the N–H bonds, as well as for the carbonyl groups at 1659 (C=O) and 1615 (NCO) cm^{-1}.

The ^{1}H NMR spectra of products **4a-c**, **5** and **6** contained characteristic multiplets for the methylene groups of the piperidine, morpholine and piperazine fragments in the ranges δ 1.42–3.59, 3.20–3.68, and 2.21–3.59 ppm respectively, and the signals at δ 8.70-8.82 ppm corresponded to the amino dihydroquinoline structure. In addition, the ^{13}C NMR spectra of glyoxylamides **4-6** contained signals at δ 165 and 193 ppm, characteristic of the carbon atoms of the carbonyl groups. In the IR spectra of these products, stretching vibrations of the N-H group were observed at ν 3296-3387 cm^{-1} and for the carbonyl groups in the form of an absorption band of strong intensity at ν 1615-1660 cm^{-1}.

Conclusions

In summary, we have demonstrated the possibility of functionalizing the aromatic phenyl ring of 2,2,4-trimethyl-1,2-dihydroquinolines *ortho* to the amine function via nucleophilic opening of the pyrroledione ring of 4,4,6-trimethyl-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-diones by the action of various amines. As a result, we have prepared a series of new derivatives of the 1,2-dihydroquinoline-8-glyoxylamides, which are potentially of interest as physiologically active compounds.

Experimental Section

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General. ^{1}H NMR spectra were recorded for solutions in DMSO-d_6, on Bruker Avance 400 and Bruker DRX-500 (400 and 500 MHz, respectively) spectrometers, internal standard is TMS. ^{13}C NMR were recorded for solutions in DMSO-d_6 on Bruker Avance 400 and Bruker DRX-500 (101 and 125 MHz), internal standard is TMS. High-resolution mass spectra were recorded on an Agilent Technologies LCMS 6230B instrument; the ionization method is double electrospray in a nitrogen atmosphere (ESI). Chromatographic conditions: mobile phase 0.1% formic acid in MeCN (eluent A) / 0.1% formic acid in water (eluent B), gradient 0–100%: A, 3.5 min, 50%; A, 1.5 min, 50-100%; B, 3.5 min, 50%; B, 1.5 min, 50–0%; flow 0.4 ml / min, column - Poroshell 120 EC-C18 (4.6 × 50 mm, 2.7 μm), thermostat 28 ° C, electrospray ionization (capillary –3.5 kV; fragmentator +191 V; OctRF +66 V - positive polarity). Melting points were determined on a STUART Melting point SMP30 instrument. Preparative chromatographic separation was performed on silica gel L columns (100 - 250 μm), eluent - chloroform, chloroform / ethyl acetate (10/1). The reaction progress and purity of the obtained compounds were controlled by TLC method on Merck TLC Silica gel 60 F254 plates, eluents – individual solvents (chloroform, ethyl acetate, methanol) and their mixtures in various ratios. Visualization of the chromatograms was achieved with UV light or in iodine vapor.

Pyrrolo[3,2,1-*ij*]quinoline-1,2-diones (**2a-c**) were prepared according to the reported procedure.[37]

General procedure for the synthesis of *N*-methyl-2-oxo-2-(2,2,4-trimethyl-1,2-dihydroquinolin-8-yl)acetamide 3a-b. To a solution of compound **2a-b** (2.1 mmol) in ethyl alcohol (5 mL) was added 40% solution of methylamine (2 mL). The reaction mixture was stirred at 60 °C for 30 min. A yellow precipitate formed. The crude product was collected by filtration and purified by recrystallization from a mixture of hexane-ethyl acetate (4:1).

***N*-Methyl-2-oxo-2-(2,2,4-trimethyl-1,2-dihydroquinolin-8-yl)acetamide (3a).** Yellow solid (0.38 g, 71%); mp 152-154 °C (hexane – ethyl acetate (4:1)). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ_H 1.33 (s, 2-$(CH_3)_2$, 6H), 1.93 (d, *J* 1.3 Hz, 4-CH_3, 3H), 2.74 (d, *J* 4.7 Hz, NH-CH_3, 3H), 5.49 (s, H-3, 1H), 6.49 (t, *J* 7.7 Hz, H-6, 1H), 7.20 (d, *J* 7.2 Hz, H-5, 1H), 7.37 (d, *J* 8.2 Hz, H-7, 1H), 8.68 (d, *J* 4.6 Hz, NH-CH_3, 1H), 8.87 (s, NH, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ_C 18.6, 25.1, 32.5, 52.0, 111.1, 114.0, 121. 6, 126.6, 128.4, 129.3, 132.8, 147.8, 166.6, 192.2. IR (KBr, cm $^{-1}$): *v* 3735 (NH), 3392(NH), 2360, 2342 (C-N), 1659 (C=O), 1615 (C=O), 1489 (C=C), 1206, 1174, 742. HRMS (ESI): Calc'd for $C_{15}H_{18}N_2O_2$ $[M+H]^+$ 259.1556; found 259.1558.

***N*-Methyl-2-oxo-2-(2,2,4,6-tetramethyl-1,2-dihydroquinolin-8-yl)acetamide (3b).** Yellow solid (0.45 g, 78%); mp 132-134 °C (hexane – ethyl acetate (4:1)). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ_H 1.31 (s, 2-$(CH_3)_2$, 6H), 1.93 (d, *J* 1.2 Hz, 4-CH_3, 3H), 2.14 (s, 6-CH_3, 3H), 2.74 (d, *J* 4.7 Hz, NH-CH_3, 3H), 5.49 (s, H-3, 1H), 7.06 (d, *J* 1.6 Hz, H-5, 1H), 7.16 (s, H-7, 1H), 8.65 (d, *J* 4.5 Hz, NH-CH_3, 1H), 8.75 (s, NH, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ_C 18.6, 20.1, 25.2, 32.4, 51.9, 111.0, 121.8, 122.2, 126.6, 128.7, 130.8, 131.6, 146.2, 166.7, 192.7. HRMS (ESI): Calc'd for $C_{16}H_{20}N_2O_2$ $[M+H]^+$ 273.1589; found 273.1580.

General procedure for the synthesis of compounds 4a-c, 5, 6. A mixture of compound **2a-c** (2.1 mmol) and corresponding amine (10.5 mmol) in ethanol (10 ml) was stirred at 60 °C for 4-10 h. The reaction mixture was left to cool at room temperature and the solid product was filtered and recrystallized from from a mixture of hexane-ethyl acetate (4:1).

1-(Piperidin-1-yl)-2-(2,2,4-trimethyl-1,2-dihydroquinolin-8-yl)ethane-1,2-dione (4a). Yellow solid (0.48 g, 73%); mp 109-111 °C (hexane - ethylacetate (4:1)). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ_H 1.34 (s, 2-$(CH_3)_2$, 6H), 1.42-1.44 (m, CH_2, 2H), 1.56-1.58 (m, CH_2, 2H), 1.60-1.63 (m, CH_2, 2H), 1.93 (d, *J* 0.8 Hz, 4-CH_3, 3H), 3.18-3.20 (m, CH_2, 2H), 3.54-3.57 (m, CH_2, 2H), 5.51 (s, H-3, 1H), 6.53 (t, *J* 7.7 Hz, H-6, 1H), 7.15 (dd, *J* 8.7, 1.1 Hz, H-5, 1H), 7.22 (d, *J* 7.1 Hz, H-7, 1H), 8.82 (s, NH, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ_C 18.5, 23.8, 25.1,

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25.8, 32.4, 41.1, 46.4, 52.1, 111.3, 114.4, 121.8, 126.5, 128.7, 129.4, 132.1, 147.5, 164.6, 193.7. IR (KBr, cm^{-1}): *v* 3287 (NH), 1638 (C=O), 1615 (C=O), 1581 (C=C), 1201, 1162, 760, 644 (cm^{-1}). HRMS (ESI): Calc'd for $C_{19}H_{24}N_2O_2$ $[M+H]^+$ 313.1912; found 313.1917.

1-(Piperidin-1-yl)-2-(2,2,4,6-tetramethyl-1,2-dihydroquinolin-8-yl)ethane-1,2-dione (4b). Yellow solid (0.55 g, 81%); mp 149-151 °C (hexane – ethyl acetate (4:1)).^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ_H 1.32 (s, 2-$(CH_3)_2$, 6H), 1.42-1.45 (m, CH_2, 2H), 1.56-1.58 (m, CH_2, 2H), 1.61-1.63 (m, CH_2, 2H), 1.93 (d, *J* 1.2 Hz, 4-CH_3, 3H), 2.15 (s, 6-CH_3, 3H), 3.17-3.20 (m, CH_2, 2H), 3.55-3.58 (m, CH_2, 2H), 5.51 (s, H-3, 1H), 6.91 (d, *J* 0.7 Hz, H-5, 1H), 7.08 (d, *J* 1.6 Hz, H-7, 1H), 8.69 (s, NH, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ_C 18.6, 20.1, 23.9, 25.2, 25.9, 32.3, 41.1, 46.4, 51.9, 111.2, 122.1, 126.6, 122.7, 126.5, 129.0, 130.7, 131.0, 145.9, 164.7, 193.5. IR (KBr, cm^{-1}): *v* 3277 (NH), 1639 (C=O), 1570 (C=C), 1203, 1176, 1127, 988, 733, 665 (cm^{-1}). HRMS (ESI): Calc'd for $C_{20}H_{26}N_2O_2$ $[M+H]^+$ 327.2868; found 327.2865.

1-(6-Methoxy-2,2,4-trimethyl-1,2-dihydroquinolin-8-yl)-2-(piperidin-1-yl)ethane-1,2-dione (4c). Yellow solid (0.56 g, 78%); mp 142-144 °C (hexane – ethyl acetate (4:1)). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ_H 1.33 (s, 2-$(CH_3)_2$, 6H), 1.42-1.46 (m, CH_2, 2H), 1.55-1.58 (m, CH_2, 2H), 1.61-1.64 (m, CH_2, 2H), 1.94 (d, *J* 0.9 Hz, 4-CH_3, 3H), 3.20-3.23 (m, CH_2, 2H), 3.57-3.59 (m, CH_2, 2H), 3.66 (s, 8-CH_3O, 3H), 5.59 (s, H-3, 1H), 6.57 (d, *J* 2.8 Hz, H-5, 1H), 6.93 (d, *J* 2.8 Hz, H-7, 1H), 8.63 (s, NH, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ_C 18.4, 23.7, 25.2, 25.9, 32.1, 41.1, 46.3, 51.9, 55.5, 110.5, 111.7, 119.9, 123.8, 126.3, 130.3, 143.4, 148.3, 164.6, 192.9. IR (KBr, cm^{-1}): *v* 3272 (NH), 1634 (C=O), 1605 (C=O), 1579 (C=C), 1497, 1192, 1060, 753, 732 (cm^{-1}). HRMS (ESI): Calc'd for $C_{20}H_{26}N_2O_3$ $[M+H]^+$ 343.2018; found 343.2015.

1-Morpholino-2-(2,2,4,6-tetramethyl-1,2-dihydroquinolin-8-yl)ethane-1,2-dione (5). Yellow solid (0.56 g, 82%); mp 125-127 °C (hexane – ethyl acetate (4:1)). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ_H 1.30 (s, 2-$(CH_3)_2$, 6H), 1.91 (s, 4-CH_3, 3H), 2.15 (s, 6-CH_3, 3H), 3.20-3.24 (m, CH_2, 2H), 3.48-3.52 (m, CH_2, 2H), 3.58-3.62 (m, CH_2, 2H), 3.64-3.68 (m, CH_2, 2H), 5.49 (s, H-3, 1H), 6.95 (s, H-5, 1H), 7.06 (s, H-7, 1H), 8.70 (s, NH, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, ppm): δ_C 19.0, 20.4, 32.7, 41.3, 46.3, 52.4, 66.4, 66.6, 111.4, 122.5, 123.2, 126.9, 129.4, 131.1, 131.6, 146.5, 165.4, 193.1. IR (KBr, cm^{-1}): *v* 3283 (NH), 2359 (C-N), 1645 (C=O), 1615 (C=O), 1574 (C=C), 1205, 1175, 1110, 993, 792, 582. HRMS (ESI): Calc'd for $C_{19}H_{24}N_2O_3$ $[M+H]^+$ 329.1967; found 329.1970.

1-(4-Methylpiperazin-1-yl)-2-(2,2,4-trimethyl-1,2-dihydroquinolin-8-yl)ethane-1,2-dione (6). Yellow solid (0.58 g, 85%); mp 180-182 °C (hexane – ethyl acetate (4:1)). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ_H 1.33 (s, 2-$(CH_3)_2$, 6H), 1.91 (d, *J* 1.2 Hz, 4-CH_3, 3H), 2.18 (s, N-CH_3, 3H), 2.21-2.24 (m, CH_2, 2H), 2.34-2.38 (m, CH_2, 2H), 3.19-3.22 (m, CH_2, 2H), 3.56-3.59 (m, CH_2, 2H), 5.49 (s, H-3, 1H), 6.52 (t, *J* 8.1 Hz, H-6, 1H), 7.13 (dd, *J* 8.0, 1.2 Hz, H-5, 1H), 7.19 (d, *J* 7.2 Hz, H-7, 1H), 8.80 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ_C 18.5, 32.5, 40.4, 45.4, 45.6, 52.1, 54.0, 54.5, 111.2, 114.5, 121.9, 126.5, 128.7, 129.5, 132.1, 147.6, 164.8, 193.3. IR (KBr, cm^{-1}): *v* 3296 (NH), 1660 (C=O), 1598 (C=C), 1383, 1103, 730 (cm^{-1}). HRMS (ESI): Calc'd for $C_{19}H_{25}N_3O_2$ $[M+H]^+$ 328.1771; found 328.1773.

Acknowledgements

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Supplementary Material

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IR, ^{1}H and ^{13}C NMR spectra and data LCMS for compounds **3a-b**, **4a-c**, **5**, **6** are available in the supplementary file accompanying this paper.

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