Fang Dong and Xiang-Shan Wang*

Synthesis of spiro[pyrazole-4,8′-pyrazolo [3,4-*f*]quinolin]-5(1*H*)-ones by the reaction of aldehydes with 1*H*-indazol-6-amine and 1*H*-pyrazol-5(4*H*)-one

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Abstract: A four-component reaction including two equivalents of aldehyde, 1*H*-indazol-6-amine and 1*H*-pyrazol-5(4*H*)-one proceeds smoothly to afford a series of spiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-ones in high yields under catalyst-free conditions.

Keywords: 1*H*-indazol-6-amine; 1*H*-pyrazol-5(4*H*)-one; pyrazoloquinoline; spiro.

Introduction

Due to unique antimalarial activity, quinoline derivatives have received considerable attention in recent years [1–3] and some of them including chloroquine [4] and plasmoquine [5] (Figure 1) are clinical drugs to treat malaria. Pyrazole exhibits a wide range of biological applications. A typical example is analgesic and antipyretic drug antipyrine [6]. Pyrazole fused quinoline (pyrazoloquinoline) is also a useful heterocycle whose derivatives show various bioactivities including antimalarial [7], analgesic [8], antipsychotic [9], and antimicrobial activities [10]. Many procedures have been reported to synthesize these active compounds in the past few years [11–14].

In our previous paper, the reactions of aldehyde, 1*H*-indazol-6-amine and 3-phenylisoxazol-5(4*H*)-one were performed in refluxing EtOH, giving spiro[isoxazole-4,8′-pyrazolo[3,4-*f*]quino-lin]-5-ones or ring-opening products of pyrazoloquinolines depending on the activity of the aldehyde. In view of the importance of pyrazole, the aldehyde **1** was allowed to react with 1*H*-indazol-6-amine **2** and 1*H*-pyrazol-5(4*H*)-one **3** under similar reaction conditions (Scheme 1). This reaction gave exclusively spiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-ones **4** regardless of the type of substituents on the substrates. This report describes a continuation of our research devoted to the development of new methods for the preparation of heterocycles containing nitrogen atoms under catalyst-free conditions [15–18].

Results and discussion

The initial reaction involved two equivalents of 4-nitrobenzaldehyde (**1a**, 2.0 mmol), 1*H*-indazol-6-amine (**2**, 1.0 mmol) and 1,3-dimethyl-1*H*-pyrazol-5(4*H*)-one (**3**, 1.0 mmol) in refluxing EtOH (Scheme 1). This reaction furnished 1,3-dimethyl-7′,9′-bis(2-nitrophenyl)-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (**4a**) in an 89% yield. This model reaction was conducted in various solvents including THF, MeOH, EtOH, dioxane, toluene, and DMF. It was found that under catalyst-free conditions the use of EtOH is optimal.

Subsequently, various aldehydes **1** were allowed to react with **2** and **3** in EtOH under reflux conditions. All products **4a**–**n** were obtained in 84%–91% yields. The presence of electron-donating (alkyl) or electron-withdrawing (halide, nitro, and cyano) group on the substrates does not affect the high efficiency of the reaction.

Conclusion

The efficient synthesis of spiro[pyrazole-4,8′-pyrazolo [3,4-*f*]quinolin]-5(1*H*)-one derivatives **4** by the reaction of two equivalents of aldehyde **1** with 1*H*-indazol-6-amine **2** and 1*H*-pyrazol-5(4*H*)-one **3** is described. The

***Corresponding author: Xiang-Shan Wang,** School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou Jiangsu 221116, P.R. China, e-mail: xswang1974@yahoo.com
Fang Dong: School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou Jiangsu 221116, P.R. China

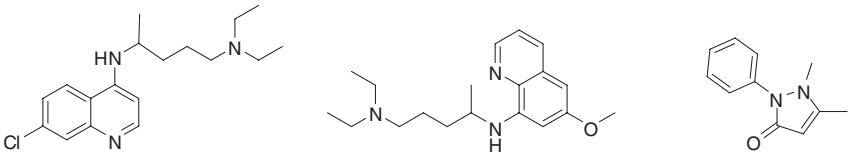
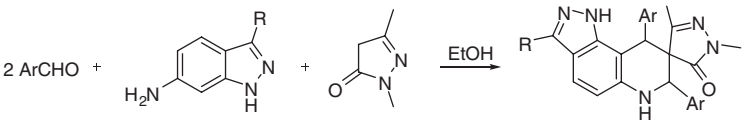


Figure 1 The marketed drugs containing pyrazole or quinoline.



4a: Ar = 4-$NO_2C_6H_4$; R = H
4b: Ar = 4-ClC_6H_4; R = H
4c: Ar = 2-$NO_2C_6H_4$; R = H
4d: Ar = 3-$NO_2C_6H_4$; R = H
4e: Ar = 4-Cl-2-$NO_2C_6H_3$; R = H
4f: Ar = 5-Br-2-$NO_2C_6H_3$; R = H
4g: Ar = 2-$CF_3C_6H_4$; R = H
4h: Ar = 4-$CF_3C_6H_4$; R = H
4i: Ar = 4-Br-2-$NO_2C_6H_3$; R = H
4j: Ar = 4-BrC_6H_4; R = H
4k: Ar = 4-$CH_3C_6H_4$; R = H
4l: Ar = 4-$MeOC_6H_4$; R = H
4m: Ar = 3-BrC_6H_4; R = H
4n: Ar = 4-$NO_2C_6H_4$; R = Me

Scheme 1 The synthetic route for the products **4**.

four-component reaction proceeds smoothly in refluxing EtOH in the absence of any catalysts.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr pellets. ^{1}H NMR spectra were obtained in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer (400 MHz). HR-MS analyses were carried out using a Bruker-micro- TOF-Q-MS analyzer.

General procedure for the synthesis of 4

A mixture of aromatic aldehyde **1** (2.0 mmol), 1*H*-indazol-6-amine **2** (1.0 mmol), 1*H*-pyrazol-5(4*H*)-one **3** (112 mg, 1.0 mmol), and EtOH (10.0 mL) was stirred at reflux for 6–10 h. After the completion of the reaction as indicated by TLC analysis, the pure product **4** was obtained by simple filtration after cooling the mixture to room temperature.

1,3-Dimethyl-7′,9′-bis(4-nitrophenyl)-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4a) Yield 89%; mp 254–255°C; ^{1}H NMR: δ_H 1.95 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 4.83 (s, 1H, CH), 5.09 (s, 1H, CH), 6.90 (m, 2H, ArH), 7.04 (s, 1H, NH), 7.36 (m, 1H, ArH), 7.60 (m, 3H, ArH), 7.89 (s, 1H, ArH), 7.96 (m, 1H, ArH), 8.19 (s, 1H, ArH), 8.24 (d, J = 8.8 Hz, 2H, ArH), 11.27 (s, 1H, NH); IR: ν 3311, 2930, 1685, 1624, 1597, 1529, 1492, 1437, 1404, 1348, 1291, 1256, 1093, 1059, 1014, 931, 871, 859, 838, 820, 795, 719 cm^{-1}. ESI-HR-MS. Calcd for $C_{26}H_{20}N_7O_5$ ([M − H]$^-$): *m/z* 510.1520. Found: *m/z* 510.1537.

7′,9′-Bis(4-chlorophenyl)-1,3-dimethyl-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4b) Yield 91%, mp 272–274°C; ^{1}H NMR: δ_H 1.97 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 4.61 (s, 1H, CH), 4.90 (s, 1H, CH), 6.58 (m, 1H, ArH), 6.82 (s, 1H, NH), 6.82 (d, J = 8.8 Hz, 1H, ArH), 7.10 (m, 1H, ArH), 7.14 (m, 1H, ArH), 7.35 (m, 3H, ArH), 7.42 (m, 2H, ArH), 7.53 (d, J = 8.4 Hz, 1H, ArH), 7.85 (s, 1H, ArH), 11.14 (s, 1H, NH); IR: ν 3377, 3253, 3063, 2926, 1697, 1621, 1589, 1524, 1489, 1428, 1376, 1354, 1255, 1173, 1089, 1057, 1014, 968, 927, 841, 730, 706 cm^{-1}. ESI-HR-MS. Calcd for $C_{26}H_{20}Cl_2N_5O$ ([M − H]$^-$) : *m/z* 488.1039. Found: *m/z* 488.1066.

1,3-Dimethyl-7′,9′-bis(2-nitrophenyl)-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4c) Yield 86%; mp 226–228°C; ^{1}H NMR: δ_H 1.94 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 5.26 (s, 1H, CH), 5.37 (s, 1H, CH), 6.82 (d, J = 8.8 Hz, 1H, ArH), 7.16 (d, J = 8.0 Hz, 1H, ArH), 7.30 (s, 1H, NH), 7.47 (d, J = 8.8 Hz, 2H, ArH), 7.57 (m, 4H, ArH), 7.62 ~ 7.72 (m, 2H, ArH), 8.24 (d, J = 8.0 Hz, 1H, ArH), 12.56 (s, 1H, NH); IR: ν 3395, 3166, 2971, 2929, 1698, 1630, 1576, 1527, 1463, 1429, 1377, 1343, 1322, 1226, 1187, 1045, 1018, 936, 874, 862, 850, 789, 730 cm^{-1}. ESI-HR-MS. Calcd for $C_{26}H_{20}N_7O_5$ ([M − H]$^-$) : *m/z* 510.1520. Found: *m/z* 510.1543.

1,3-Dimethyl-7′,9′-bis(3-nitrophenyl)-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4d) Yield 84%; mp > 300°C; ^{1}H NMR: δ_H 2.02 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.83 (s, 1H, CH), 5.07 (s, 1H, CH), 6.91 (d, J = 8.8 Hz, 1H, ArH), 7.06 (d, J = 9.6 Hz, 2H, ArH), 7.32 (s, 1H, NH), 7.41 (m, 1H, ArH), 7.60 (d, J = 9.6 Hz, 1H, ArH), 7.69 (m, 2H, ArH), 7.79 (d, J = 8.0 Hz, 2H, ArH), 7.88 (s, 1H, ArH), 8.13 (m, 1H, ArH), 11.27 (s, 1H, NH); IR: ν 3419, 3309, 3084, 2927, 1695, 1623, 1600, 1531, 1498, 1438, 1373, 1351, 1258, 1225,

1075, 1056, 1001, 929, 845, 811, 798, 781, 760, 740, 715 cm^{-1}. ESI-HR-MS. Calcd for $C_{26}H_{20}N_7O_5$ ([M – H]$^-$): *m/z* 510.1520. Found: *m/z* 510.1526.

7′,9′-Bis(4-chloro-2-nitrophenyl)-1,3-dimethyl-1′,6′,7′,9′-tetrahydrospiro [pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4e) Yield 86%; mp 211–212°C; ^{1}H NMR: δ_H 1.93 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 5.22 (s, 1H, CH), 5.25 (s, 1H, CH), 7.16 (d, *J* = 8.4 Hz, 2H, ArH), 7.36 (s, 1H, NH), 7.58 (m, 2H, ArH), 7.81 (m, 3H, ArH), 7.96 (d, *J* = 2.4 Hz, 1H, ArH), 8.30 (s, 1H, ArH), 12.59 (s, 1H, NH); IR: *ν* 3409, 3176, 3098, 3042, 2970, 1694, 1659, 1624, 1566, 1530, 1459, 1434, 1421, 1388, 1378, 1354, 1342, 1332, 1325, 1102, 1065, 932, 894, 852, 841 cm^{-1}. ESI-HR-MS. Calcd for $C_{26}H_{18}Cl_2N_7O_5$ ([M – H]$^-$) : *m/z* 578.0740. Found: *m/z* 578.0697.

7′,9′-Bis(5-bromo-2-nitrophenyl)-1,3-dimethyl-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4f) Yield 90%; mp 216–218°C; ^{1}H NMR: δ_H 1.92 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 5.24 (s, 1H, CH), 5.36 (s, 1H, CH), 6.82 (d, *J* = 8.8 Hz, 1H, ArH), 7.21 (s, 1H, NH), 7.42 (s, 1H, ArH), 7.62 (m, 2H, ArH), 7.80 (m, 3H, ArH), 7.88 (s, 1H, ArH), 8.19 (d, *J* = 8.8 Hz, 1H, ArH), 12.70 (s, 1H, NH); IR: *ν* 3342, 3175, 3066, 2926, 1696, 1659, 1626, 1597, 1566, 1522, 1496, 1462, 1421, 1377, 1339, 1290, 1256, 1182, 1099, 932, 875, 843 cm^{-1}. ESI-HR-MS. Calcd for $C_{26}H_{18}Br_2N_7O_5$ ([M – H]$^-$): *m/z* 665.9730. Found: *m/z* 665.9690.

1,3-Dimethyl-7′,9′-bis(2-(trifluoromethyl)phenyl)-1′,6′,7′,9′-tetrahydrospiro [pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4g) Yield 87%; mp 264–265°C; ^{1}H NMR: δ_H 1.97 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.76 (s, 1H, CH), 5.21 (s, 1H, CH), 6.77 (d, *J* = 8.8 Hz, 1H, ArH), 7.07 (s, 1H, NH), 7.32 (s, 1H, ArH), 7.37 (d, *J* = 8.0 Hz, 1H, ArH), 7.52 (m, 3H, ArH), 7.67 (m, 3H, ArH), 7.97 (s, 2H, ArH), 11.01 (s, 1H, NH); IR: *ν* 3297, 2921, 1709, 1669, 1625, 1595, 1513, 1497, 1437, 1378, 1344, 1310, 1291, 1258, 1157, 1135, 1061, 1038, 929, 858, 770 cm^{-1}. ESI-HR-MS. Calcd for $C_{28}H_{20}F_6N_5O$ ([M – H]$^-$): *m/z* 556.1566. Found: *m/z* 556.1546.

1,3-Dimethyl-7′,9′-bis(4-(trifluoromethyl)phenyl)-1′,6′,7′,9′-tetrahydrospiro [pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4h) Yield 84%; mp 244–245°C; ^{1}H NMR: δ_H 1.74 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.65 (s, 1H, CH), 5.07 (s, 1H, CH), 7.06 (m, 3H, ArH), 7.44 (d, *J* = 8.8 Hz, 2H, ArH), 7.59 (m, 1H, ArH), 7.69 (s, 1H, NH), 7.75 (d, *J* = 2.4 Hz, 1H, ArH), 8.22 (s, 1H, ArH), 8.54 (s, 1H, ArH), 8.69 (s, 2H, ArH), 12.32 (s, 1H, NH); IR: *ν* 3196, 3083, 1715, 1633, 1604, 1550, 1524, 1470, 1447, 1380, 1346, 1239, 1202, 1135, 1092, 1072, 950, 893, 859, 825, 786 cm^{-1}; ESI-HR-MS. Calcd for $C_{28}H_{20}F_6N_5O$ ([M – H]$^-$): *m/z* 556.1566. Found: 556.1543.

7′,9′-bis(4-bromo-2-nitrophenyl)-1,3-dimethyl-1′,6′,7′,9′-tetrahydrospiro [pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4i) Yield 89%; mp 271–272°C; ^{1}H NMR: δ_H 2.09 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.06 (s, 1H, CH), 5.70 (s, 1H, CH), 6.60 (s, 3H, ArH), 7.67 ~ 7.71 (m, 1H, ArH), 7.80 (m, 2H, ArH), 7.96 (s, 1H, NH), 8.09 (m, 2H, ArH), 8.18 (d, *J* = 8.0 Hz, 1H, ArH), 12.25 (s, 1H, NH); IR: *ν* 3196, 3083, 1715, 1633, 1604, 1550, 1524, 1470, 1447, 1380, 1346, 1239, 1202, 1135, 1092, 1072, 950, 893, 859, 825, 786 cm^{-1}. ESI-HR-MS. Calcd for $C_{26}H_{18}Br_2N_7O_5$ ([M – H]$^-$): *m/z* 665.9730. Found *m/z* 665.9685.

7′,9′-Bis(4-bromophenyl)-1,3-dimethyl-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4j) Yield 85%; mp 272–273°C; ^{1}H NMR: δ_H 2.09 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.68 (s, 1H, CH), 4.94 (s, 1H, CH), 6.18 (s, 1H, ArH), 6.53 (s, 1H, NH), 6.75 (m, 1H, ArH), 7.07 (d, *J* = 8.0 Hz, 1H, ArH), 7.20 ~ 7.23 (m, 2H, ArH), 7.39 (m, 4H, ArH), 7.57 ~ 7.60 (m, 1H, ArH), 7.95 ~ 7.98 (m, 1H, ArH), 12.83 (s, 1H, NH); IR: *ν* 3367, 3208, 2924, 1693, 1672, 1620, 1588, 1487, 1428, 1407, 1378, 1326, 1254, 1169, 1089, 1073, 1009, 926, 842, 860, 797, 756, 729, 704 cm^{-1}. ESI-HR-MS. Calcd for $C_{26}H_{20}Br_2N_5O$ ([M – H]$^-$): *m/z* 576.0035. Found: *m/z* 576.0002.

1,3-Dimethyl-7′,9′-di-*p*-tolyl-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo [3,4-*f*]quinolin]-5(1*H*)-one (4k) Yield 84%; mp 267–268°C; ^{1}H NMR: δ_H 1.96 (s, 3H, CH_3), 2.30 (s, 3H, CH_3). 2.40 (s, 3H, CH_3). 2.66 (s, 3H, CH_3), 4.52 (s, 1H, CH), 4.86 (s, 1H, CH), 6.45 (d, *J* = 8.0 Hz, 1H, ArH), 6.68 (s, 1H, NH), 6.84 ~ 6.88 (m, 2H, ArH), 6.99 ~ 7.03 (m, 1H, ArH), 7.10 (m, 1H, ArH), 7.12 ~ 7.21 (m, 4H, ArH), 7.49 (d, *J* = 8.4 Hz, 1H, ArH), 7.80 (s, 1H, ArH), 10.85 (s, 1H, NH); IR: *ν* 3403, 3250, 3061, 3028, 2918, 2865, 1686, 1617, 1588, 1487, 1432, 1375, 1327, 1259, 1225, 1060, 1021, 929, 846, 801, 733, 701 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{28}H_{26}N_5O$ [M – H]$^-$ 448.2131, found 448.2122.

7′,9′-bis(4-methoxyphenyl)-1,3-dimethyl-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4l) Yield 86%; mp 258–259°C; ^{1}H NMR: δ_H 1.99 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.53 (s, 1H, CH), 4.84 (s, 1H, CH), 6.40 (s, 1H, NH), 6.48 ~ 6.51 (m, 1H, ArH), 6.62 ~ 6.65 (m, 1H, ArH), 6.68 (s, 1H, ArH), 6.84 (d, *J* = 2.4 Hz, 1H, ArH), 6.97 (d, *J* = 8.8 Hz, 1H, ArH), 7.03 ~ 7.05 (m, 1H, ArH), 7.10 ~ 7.12 (m, 1H, ArH), 7.42 (d, *J* = 8.4 Hz, 1H, ArH), 7.49 (d, *J* = 8.4 Hz, 1H, ArH), 7.72 ~ 7.76 (m, 1H, ArH), 7.80 (s, 1H, ArH), 10.76 (s, 1H, NH); IR: *ν* 3412, 3234, 3038, 3004, 2956, 2927, 2838, 1686, 1618, 1584, 1512, 1489, 1462,1382, 1305, 1253, 1177, 1107, 1060, 1030, 964, 832, 803, 739, 703 cm^{-1}. ESI-HR-MS. Calcd for $C_{28}H_{26}N_5O_3$ ([M – H]$^-$): *m/z* 480.2108. Found: *m/z* 480.2082.

7′,9′-Bis(3-bromophenyl)-1,3-dimethyl-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4m) Yield 84%; mp 287–288°C; ^{1}H NMR: δ_H 1.84 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.52 (s, 1H, CH), 4.78 (s, 1H, CH), 6.47 (d, *J* = 8.0 Hz, 1H, ArH), 6.53 (s, 1H, NH), 6.78 (m, 3H, ArH), 7.14 (s, 1H, ArH), 7.23 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.23 (s, 1H, ArH), 7.41 (s, 1H, ArH), 7.42 (m, 1H, ArH), 7.76 (s, 1H, ArH), 11.22 (s, 1H, NH); IR: *ν* 3447, 3196, 2923, 1694, 1622, 1591, 1565, 1510, 1474, 1428, 1374, 1302, 1234, 1091, 1069, 1030, 995, 925, 836, 799, 786, 754, 721 cm^{-1}. ESI-HR-MS. Calcd for $C_{26}H_{20}Br_2N_5O$ ([M – H]$^-$): *m/z* 576.0010. Found: *m/z* 576.0006.

1,3,3′-Trimethyl-7′,9′-bis(4-nitrophenyl)-1′,6′,7′,9′-tetrahydrospiro[pyrazole-4,8′-pyrazolo[3,4-*f*]quinolin]-5(1*H*)-one (4n) Yield 89%; mp 271–272°C; ^{1}H NMR: δ_H 2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.04 (s, 1H, CH), 5.12 (s, 1H, CH), 6.74 (d, *J* = 8.4 Hz, 2H, ArH), 7.00 (s, 1H, NH), 7.41 (d, *J* = 8.4 Hz, 1H, ArH), 7.65 (m, 3H, ArH), 7.97 (m, 2H, ArH), 8.22 (d, *J* = 8.8 Hz, 2H, ArH), 12.25 (s, 1H, NH); IR: *ν* 3396, 3082, 2934, 1704, 1618, 1604, 1604, 1513, 1470, 1428, 1377, 1345, 1263, 1224, 1153, 1107, 1012, 976, 956, 860, 810, 735, 745 cm^{-1}. ESI-HR-MS. Calcd for $C_{27}H_{22}N_7O_5$ ([M – H]$^-$): *m/z* 524.1676. Found: *m/z* 524.1686.

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