Maleic acid derivatives in the synthesis of 3-substituted 3,4-dihydroquinoxalin-2(1*H*)-ones*

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A process for preparing 3-substituted 3,4-dihydroquinoxalin-2(1*H*)-ones is proposed. It is based on the reaction of *o*-phenylenediamine with amides, di- and mono-esters of maleic acid as well as (*E*)-3-(5-phenyl-1,3,4-oxadiazol-2-yl)acrylic acid in the presence of *N*,*N*′-carbonyldiimidazole.

Key words: Michael reaction, 3,4-dihydroquinoxalin-2(1*H*)-one, maleimide, maleic acid monoamide, *o*-phenylenediamine.

Compounds containing dihydroquinoxalin-2(1*H*)-one fragment are widely used in a number of scientific and technical areas. They have antibacterial,[1] antimycotic,[2] and antidepressant[3] activities, antiphlogistic and analgesic action,[4] they are used as dyes, electroluminescent materials, and organic semiconductors.[5]

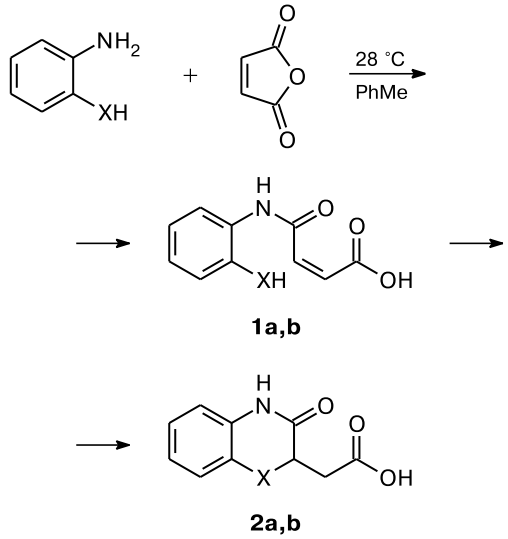
Little attention is given to the synthesis of 3,4-dihydroquinoxalin-2(1*H*)-ones with the use of maleic acid derivatives in the literature; however, their sulfur- and oxygen-containing analogs are known to be obtained in high yields. For instance, reaction of *o*-aminothiophenol or *o*-aminophenol with maleic anhydride leads to (3,4-dihydro-3-oxo-2*H*-1,4-benzothiazin-2-yl)acetic or (3,4-dihydro-3-oxo-2*H*-1,4-benzoxalin-2-yl)acetic acids (**2a** and **2b** respectively)[6] *via* the formation of corresponding intermediate **1a** or **1b** (Scheme 1).

Since *o*-phenylenediamine readily reacts with maleic anhydride to give products of mono- and diacylation, *N*-arylmaleimides **3** are used as substrates (Scheme 2). Apparently, the reaction proceeds *via* the formation of substituted succinimide **4**, which is then subjected to intramolecular acylation to afford arylamides of (1,2,3,4-tetrahydro-2-oxoquinoxalin-3-yl)acetic acid **5** in 72—80% yields (see Refs **7** and **8**).

It can be seen from the data mentioned above that the ring formation in both cases includes different sequences of acylation reaction and Michael-type *N*-alkylation.

Maleic acid esters and amides are well-known as Michael acceptors; however, there are no published examples of their use in 3,4-dihydroquinoxalin-2(1*H*)-one synthesis.

Scheme 1



X = S (**a**), O (**b**)

Initially we tried to synthesize substituted 3,4-dihydroquinoxalin-2(1*H*)-ones by the reaction between *o*-phenylenediamine and aromatic maleic acid monoamides, namely, (*Z*)-4-oxo-4-arylamino-2-butenoic acids **6**, which happen to be starting materials in the synthesis of maleimides[9] (Scheme 3). The reaction proceeds smoothly at reflux in isopropyl alcohol with DMF additive for better solubility. The yield of target 3,4-dihydroquinoxalin-2(1*H*)-ones **7** was 55—72%.

This approach seems to be more convenient than the one depicted in Scheme 2, because synthesis becomes one stage shorter: formation of *N*-arylmaleimides **3** from corresponding amides **6** is eliminated.

* According to data of cluster of conferences in organic chemistry "OrgChem-2013" (June 17—21, 2013, St. Petersburg, Repino).

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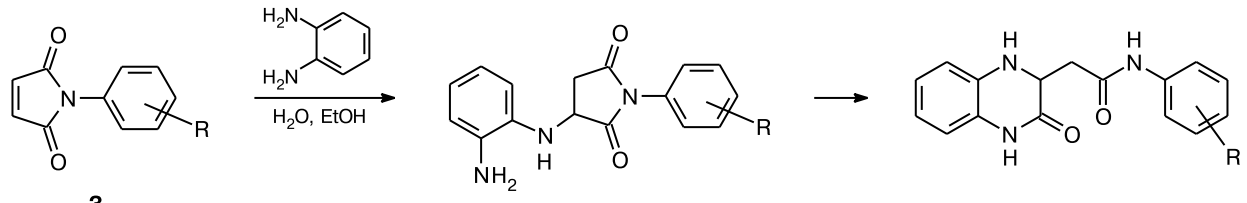
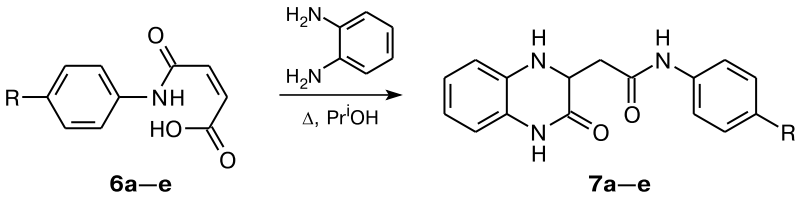
Scheme 2



R = H, 4-Me, 4-OMe, 4-Et, 2-Cl, 2-NO_2

Scheme 3



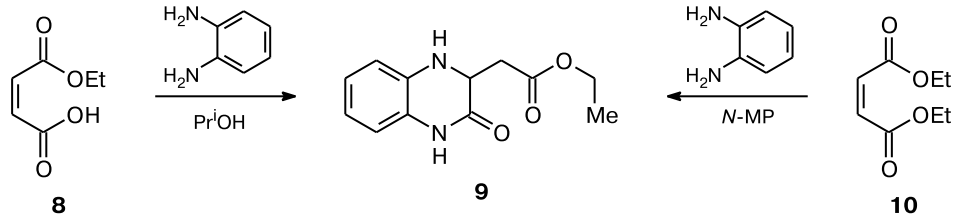
R = H (**a**), Me (**b**), OMe (**c**), Cl (**d**), NO_2 (**e**)

Since compounds structurally similar to maleic acid monoamides have to behave in a similar way, monoethyl and diethyl maleates and (*E*)-3-(5-phenyl-1,3,4-oxadiazol-2-yl)acrylic acid were chosen as the starting materials for the synthesis of 3,4-dihydroquinoxalin-2(1*H*)-one derivatives. Common structural fragment for all mentioned compounds is double bond conjugated with two electron-withdrawing substituents.

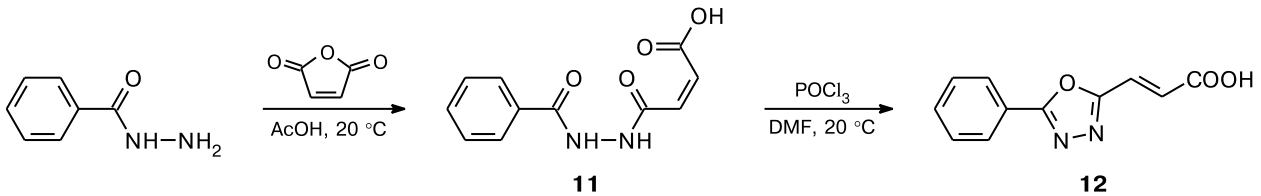
Ethyl (1,2,3,4-tetrahydro-2-oxoquinoxalin-3-yl)acetate (**9**) was synthesized *via* the reaction of *o*-phenylenediamine and monoethyl maleate **8**. The reaction was carried out at reflux in isopropyl alcohol for 1 h, the yield of product was ~30% (Scheme 4). Replacement of Pr^iOH by water, which was offered for reactions with maleimides[7] (see Scheme 2), or the use of diethyl maleate **10** in *N*-methylpyrrolidone (*N*-MP) as the substrate did not lead to any increase in product **9** yield. There are reported examples of ethyl (1,2,3,4-tetrahydro-2-oxoquinoxalin-3-yl)acetate synthesis according to more complex two-stage routes.[10,11]

(*E*)-3-(5-Phenyl-1,3,4-oxadiazol-2-yl)acrylic acid **12** has been synthesized[12] in two successive stages with the isolation of intermediate (*Z*)-4-(*N*′-benzhydrazido)-4-oxo-2-butenoic acid **11**. The first stage was acylation of benzoic acid hydrazide by maleic anhydride in glacial acetic acid. Then intramolecular dehydration of resulting acid **11** in DMF induced by phosphoryl chloride took place (Scheme 5). Formation of highly acidic medium during

Scheme 4



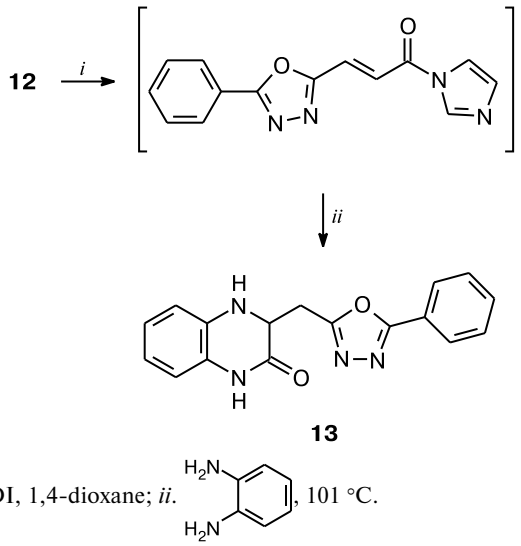
Scheme 5



the last reaction, apparently, promotes configuration change, and as a result only the more thermodynamically stable *E*-isomer is isolated. Moreover, similar (*E*)-3-(5-aryl-1,3,4-oxadiazol-2-yl)acrylic acids can be obtained by the reaction between 5-aryltetrazoles and fumaryl chloride.[13]

Refluxing the mixture of (*E*)-3-(5-phenyl-1,3,4-oxadiazol-2-yl)acrylic acid **12** and *o*-phenylenediamine in isopropyl alcohol for 1 h led to resinification or reaction mixture. The use of *N*,*N*′-carbonyldiimidazole (CDI) allowed us to successfully synthesize 3-[(5-phenyl-1,3,4-oxadiazol-2-yl)-methyl]-3,4-dihidroquinoxalin-2(1*H*)-one (**13**), presumably, due to the replacement of the first alkylation stage by acylation. The yield of the target product was 62% (Scheme 6).

Scheme 6



i. CDI, 1,4-dioxane; *ii*. , 101 °C.

To sum up, we have investigated synthetic approaches to 3-substituted 3,4-dihidroquinoxalin-2(1*H*)-ones starting from maleic anhydride and aromatic *o*-diamines. The way to obtain 3-substituted 3,4-dihidroquinoxalin-2(1*H*)-ones is proposed, it is based on reaction of *o*-phenylenediamine with amides, di- and mono-esters of maleic acid as well as with (*E*)-3-(5-phenyl-1,3,4-oxadiazol-2-yl)acrylic acid in the presence of *N*,*N*′-carbonyldiimidazole.

Experimental

^{1}H и ^{13}C NMR spectra were recorded on Bruker MSL-300 and Bruker AM-300 spectrometers, respectively, in solutions in DMSO-d_6. IR spectra were recorded on a Spectrum RX1 FT-IR spectrometer in KBr plates as mineral oil mulls. Melting points were determined on a NAGEMA PHMK-05 instrument. Elemental analysis was performed on a Perkin Elmer Instruments Series II CHNS/O Analyzer 2400. High resolution mass spectra were obtained on a MicrOTOF II (Bruker Daltonics) instrument, using electrospray ionization (ESI). Commercially available *o*-phenylenediamine, maleic anhydride, benzhydrazide (JSC Vekton), *N*,*N*′-carbonyldiimidazole (Sigma-Aldrich Co.) were used as starting materials. (*Z*)-4-Oxo-4-arylamino-2-butenoic acids,[14] diethyl[15] and monoethyl[16] esters of maleic acid were synthesized according to literature procedures.

Synthesis of arylamides of (1,2,3,4-tetrahydro-2-oxoquinoxalin-3-yl) acetic acid (7a—e). (*Z*)-4-Oxo-4-arylamino-2-butenoic acid **6** (0.024 mol) was dissolved at slight heating in a mixture of isopropyl alcohol (30 mL) and DMF (2 mL). Then *o*-phenylenediamine (2.83 g, 0.024 mol) was added and the solution was refluxed for 1 h. The reaction mixture was cooled and mixed with 200 mL of cold water. The resulting crystalline precipitate was filtered off and washed with isopropyl alcohol.

***N*-Phenyl-(1,2,3,4-tetrahydro-2-oxoquinoxalin-3- yl)acetamide (7a).** The yield was 55%, m.p. 218—221 °C (see Ref. 7: 220—223 °C). IR, ν/cm^{-1}: 3386, 3349, 3275, 3144 (NH); 1669 (C=O); 1645 (C=O (IA)); 1604 (Ar); 1551 (C=O (IIA)); 749, 690 (1,2- and monosubstituted Ar). ^{1}H NMR δ: 2.59 (dd, 1 H, CH_2, J = 15.5 Hz, J = 8.0 Hz); 2.90 (dd, 1 H, CH_2, J = 15.5 Hz, J = 4.2 Hz); 4.24 (m, 1 H, CH); 5.93 (s, 1 H, NH); 6.61 (m, 1 H, Ar); 6.76 (m, 3 H, Ar); 7.08 (t, 1 H, Ar, J = 7.9); 7.30 (t, 2 H, Ar, J = 7.6 Hz); 7.62 (d, 2 H, Ar, J = 7.7 Hz); 10.20 (s, 1 H, NHCO); 10.45 (s, 1 H, NHCO).

***N*-(*p*-Tolyl)-(1,2,3,4-tetrahydro-2-oxoquinoxalin-3- yl)-acetamide (7b).** The yield was 62%, m.p. 240—242 °C (see Ref. 7: 251—253 °C). IR, ν/cm^{-1}: 3385, 3280, 3203, 3066 (NH); 1678 (C=O); 1649 (C=O (IA)); 1540 (C=O (IIA)); 1517 (Ar); 816 (1,4-substituted Ar); 737 (1,2-substituted Ar). ^{1}H NMR δ: 2.30 (s, 3 H, CH_3); 2.60 (dd, 1 H, CH_2, J = 15.6 Hz, J = 8.5 Hz); 2.89 (dd, 1 H, CH_2, J = 15.6 Hz, J = 4.8 Hz); 4.20 (m, 1 H, CH); 5.85 (s, 1 H, NH); 6.60 (m, 1 H, Ar); 6.74 (m, 3 H, Ar); 7.06, 7.46 (both d, each 2 H, Ar, J = 8.1 Hz); 9.85 (s, 1 H, NHCO); 10.20 (s, 1 H, NHCO).

***N*-(4-Methoxyphenyl)-(1,2,3,4-tetrahydro-2-oxoquinoxalin-3-yl)acetamide (7c).** The yield was 67%, m.p. 209—211 °C (see Ref. 7: 212—215 °C). IR, ν/cm^{-1}: 3380, 3328, 3260, 3069 (NH); 1682 (C=O); 1640 (C=O (IA)); 1547 (C=O (IIA)); 1513 (Ar); 1252, 1034 (C—O—C); 830 (1,4-substituted Ar); 737 (1,2-substituted Ar). ^{1}H NMR δ: 2.59 (dd, 1 H, CH_2, J = 15.2 Hz, J = 7.9 Hz); 2.89 (dd, 1 H, CH_2, J = 15.3 Hz, J = 4.1 Hz); 3.75 (s, 3 H, OMe); 4.19 (m, 1 H, CH); 5.9 (s, 1 H, NH); 6.58 (m, 1 H, Ar); 6.71 (m, 3 H, Ar); 6.88, 7,54 (both d, each 2 H, Ar, J = 8.6 Hz); 9.78 (s, 1 H, NHCO); 10.22 (s, 1 H, NHCO).

***N*-(4-Chlorophenyl)-(1,2,3,4-tetrahydro-2-oxoquinoxalin-3-yl)acetamide (7d).** The yield was 73%, m.p. 225—227 °C. IR, ν/cm^{-1}: 3386, 3350, 3272, 3069 (NH); 1680 (C=O); 1648 (C=O (IA)); 1545 (C=O (IIA)); 1511 (Ar); 836 (1,4-substituted Ar); 735 (1,2-substituted Ar). ^{1}H NMR δ: 2.62 (dd, 1 H, CH_2, J = 15.1 Hz, J = 7.8 Hz); 2.91 (dd, 1 H, CH_2, J = 15.1 Hz, J = 4.2 Hz); 4.23 (m, 1 H, CH); 6.01 (s, 1 H, NH); 6.62 (m, 1 H, Ar); 6.75 (m, 3 H, Ar); 7.35, 7.65 (both d, each 2 H, Ar, J = 8.2 Hz); 10.17 (s, 1 H, NHCO); 10.33 (s, 1 H, NHCO). ^{13}C NMR (δ): 38.5 (CH_2); 52.4 (CH); 113.6, 114.6, 117.8, 120.5, 122.6, 125.7, 126.4, 128.3, 133.6, 137.83 (Ar); 166.2, 168.4 (C=O).

***N*-(4- Nitrophenyl)-(1,2,3,4- tetrahydro- 2- oxoquinoxalin-3- yl)acetamide (7e).** The yield was 72%, m.p. 227—230 °C. IR, ν/cm^{-1}: 3389, 3355, 3278, 3070 (NH); 1687 (C=O); 1651 (C=O (IA)); 1599 (Ar); 1549 (C=O (IIA)); 1503, 1346 (NO_2); 854, 735 (1,4- and 1,2-substituted Ar). ^{1}H NMR δ: 2.66 (dd, 1 H, CH_2, J = 15.6 Hz, J = 8.2 Hz); 2.98 (dd, 1 H, CH_2, J = 15.6 Hz, J = 4.3 Hz); 4.3 (m, 1 H, CH); 6.07 (s, 1 H, NH); 6.67 (m, 1 H, Ar); 6.82 (m, 3 H, Ar); 7.87, 8.20 (both d, each 2 H, Ar, J = 8.5 Hz); 10.20 (s, 1 H, NHCO); 10.45 (s, 1 H, NHCO). ^{13}C NMR (δ):

39.0 (CH_2); 52.5 (CH); 113.8, 114.8, 118.1, 118.8, 122.8, 124.9, 125.9, 133.9, 142.1, 145.2 (Ar); 166.7, 169.4 (C=O).

Synthesis of ethyl (1,2,3,4-tetrahydro-2-oxoquinoxalin-3-yl) acetate (9). ***A.*** **Procedure with the use of monoethyl maleate.** *o*-Phenylenediamine (2 g, 0.0185 mol) was dissolved in isopropyl alcohol (5 mL) (water can also be used as a solvent, 5 mL). Monoethyl maleate **8** (2.93 g, 0.0203 mol) was added to the resulting mixture and it was refluxed for 1 h. Cooled reaction mixture was mixed with 100 mL of cold water. The product precipitated as a resin, which crystallized when washed with water. The product was purified by recrystallization from ethyl or isopropyl alcohol. The yield was 34%.

B. **Procedure with the use of diethyl maleate.** *o*-Phenylenediamine (2 g, 0.0185 mol) and *N*-methylpyrrolidone (1 mL) were mixed. Diethyl maleate **10** (3.49 g, 0.0203 mol) was added to the resulting mixture and the solution was heated for 5 h at 80 °C. On heating the mixture was wholly dissolved. Cooled reaction mixture was mixed with 100 mL of cold water. The product precipitated as a resin, which crystallized when washed with water. The product was purified by recrystallization from ethyl or isopropyl alcohol. The yield was 29%, m.p. 115—117 °C (106—108 °C (see Ref. 10), 103—105 °C (see Ref. 11). IR, ν/cm^{-1}: 3365, 3200, 3059 (NH); 1712, 1673 (C=O); 1506 (Ar); 1200, 1034 (C—O—C); 742 (1,2-substituted Ar). ^{1}H NMR, δ: 1.21 (t, 3 H, Me, J = 7.5 Hz); 2.60 (dd, 1 H, CH_2, J = 15.6 Hz, J = 6.9 Hz); 2.75 (dd, 1 H, CH_2, J = 15.6 Hz, J = 5.3 Hz); 4.05—4.15 (m, 3 H, OCH_2, CH); 5.91 (s, 1 H, NH); 6.58 (t, 1 H, Ar, J = 7.2 Hz); 6.7 (m, 3 H, Ar); 10.25 (s, 1 H, NHCO). ^{13}C NMR (δ): 14.0 (CH_3); 36.7 (CH_2); 52.5 (CH); 60.1 (OCH_2); 113.5, 114.8, 118.0, 122.8, 125.8, 133.8 (Ar); 166.4, 170.3 (C=O).

(*Z*)-4-(*N*′-Benzhydrazido)-4-oxo-2-butenoic acid (11). A solution of benzoic acid hydrazide (13.6 g, 0.1 mol) in glacial acetic acid (35 mL) was added to a solution of maleic anhydride (10.8 g, 0.11 mol) in glacial acetic acid (30 mL) at intensive stirring. After the end of addition, precipitate was formed immediately from the reaction mixture. 20 min later the precipitate was filtered off and washed with glacial acetic acid. The yield was 91%, m.p. 177—179 °C. IR, ν/cm^{-1}: 3210 (NH); 2720 (OH); 1707 (C=O); 1651 (C=O (IA)); 1628 (C=C); 1588 (Ar); 1538 (N—C=O (IIA)); 920 (OH); 714 (monosubstituted Ar). ^{1}H NMR, δ: 6.35 (d, 1 H, CH=CH, J = 12.2 Hz); 6.41 (d, 1 H, CH=CH, J = 12.3 Hz); 7.48 (t, 2 H, Ar, J = 7.5 Hz); 7.56 (t, 1 H, Ar, J = 7.4 Hz); 7.90 (d, 2 H, Ar, J = 7.5 Hz); 10.65 (s, 1 H, NHCO); 10.90 (s, 1 H, NHCO); 13.20 (s, 1 H, OH).

(*E*)-3-(5-Phenyl-1,3,4-oxadiazol-2-yl) acrylic acid (12). Acid **11** (2.34 g, 0.01 mol) was dissolved in DMF (10 mL), and phosphoryl chloride (1.1 mL, 0.012 mol) was gradually added at intensive stirring, the temperature being maintained below 40 °C, and the reaction mixture was left for 1 h at room temperature. Then the reaction mixture was poured into a mixture of water and ice. The white precipitate that formed was filtered off and washed with water. Recrystallization from ethyl alcohol was carried out for purification. The yield was 64%, m.p. 191—193 °C. IR, ν/cm^{-1}: 2627, 2541 (OH); 1714 (C=O); 1650 (C=C); 1604 (Ar); 1520 (C=N); 1262, 1175, 1022 (C—O—C); 964 (*trans*-CH=CH); 927 (OH); 688 (monosubstituted Ar). ^{1}H NMR, δ: 6.94 (d, 1 H, CH=CH, J = 15.9 Hz); 7.47 (d, 1 H, CH=CH, J = 16.2 Hz); 7.61 (m, 3 H, Ar); 8.09 (d, 2 H, Ar, J = 8.4 Hz); 13.19 (s, 1 H, OH).

3-[(5-Phenyl-1,3,4-oxadiazol-2-yl)-methyl]-3,4-dihydroquinoxalin-2(1*H*)-one (13). Anhydrous 1,4-dioxane (10 mL) was added to (*E*)-3-(5-phenyl-1,3,4-oxadiazol-2-yl)acrylic acid **12** (2 g, 0.009 mol). CDI (2.26 g, 0.014 mol) was added to the resulting suspension. The gas started to evolve at approximately 50 °C heating, and it was followed with suspension dissolution. The solution was heated for 30 min. Then *o*-phenylenediamine was added and the mixture was refluxed for 2 h. After that, the reaction mixture was cooled and poured into water. The precipitate formed was filtered off, washed with water and ethyl alcohol. Recrystallization from ethyl alcohol was carried out for purification. The yield was 62%, m.p. 189—191 °C. IR, ν/cm^{-1}: 3338, 3203 (NH); 1667 (C=O (IA)); 1601 (Ar); 1548 (N—C=O (IIA)); 1532 (C=N); 1277, 1127, 1032 (C—O—C); 749, 707, 688 (1,2- and monosubstituted Ar). ^{1}H NMR, δ: 2.84 (m, 2 H, CH_2); 5.30 (m, 1 H, CH); 6.01 (s, 1 H, NH); 6.89 (m, 1 H, Ar); 6.97 (m, 3 H, Ar); 7.62 (m, 3 H, Ar); 7.95 (d, 2 H, Ar, J = 7.8 Hz); 9.69 (s, 1 H, NHCO). ^{13}C NMR (δ): 37.6 (CH_2); 53.7 (CH); 121.5, 121.8, 121.9, 123.3, 124.8, 126.5, 129.5, 129.6, 132.1, 137.6 (Ar), 164.1, 166.8, 169.8 (C—O—C, C=O). Found (%): C, 66.18; H, 4.34; N, 18.14. $C_{17}H_{14}N_4O_2$. Calculated (%): C, 66.66; H, 4.61; N, 18.29. Found: m/z 306.1111 $[M]^+$; $C_{17}H_{14}N_4O_2$; calculated: M = 306.1117.

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