Synthesis and Antibacterial Activity of Some Novel 6-(1*H*-Benz[*d*]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines

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A new series of novel 6-(1*H*-benz[*d*]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines 8a—d has been synthesized. These compounds were evaluated for their efficiency as antibacterial agents against two Gram-positive and Gram-negative strains of bacteria along with antifungal activity against two fungal organisms. The antibacterial and antifungal activities of the present compounds were not comparable with those of the standard drugs employed. But, however, all the test compounds could exhibit notable activities only at higher concentrations (250, 500 μg/ml). The chemical structures of these compounds were confirmed on the basis of spectral data.

Key words benzimidazole; triazole; thiadiazepine; antimicrobial activity

Benzimidazoles show significant activity against several viruses such as human cytomegalovirus (HCMV),[1] human immunodeficiency virus (HIV),[2] herpes (HSV-1),[3] RNA[4] and influenza.[5] In view of the tremendous activities of benzimidazoles, their preparation has gained considerable attention. While many strategies are available for benzimidazole synthesis.[6—9] Almost all benzimidazoles with their two ring systems bear different functional substituents and this leads to essential modification of the physico-chemical, metabolic and pharmacokinetic properties of drugs.

The benzodiazepine nucleus is a pharmacophoric scaffold and represents a class of heterocycles with a wide range of biological applications.[10] Many of them are widely used as anticonvulsant, antianxiety, sedative, antidepressive, hypnotic and neuroleptic agents.[11—14] Some heterocycles containing benzodiazepines moiety were reported to possess anti inflammatory,[15] antiviral,[16] anti-HIV-1,[17] antimicrobial[18] and antitumor[19] activities. It has been noticed that introduction of an extra ring to the benzodiazepine core tends to exert profound influence in conferring novel biological activities in these molecules.[20—24] Although many methods for synthesizing benzodiazepine ring systems have been reported, they continue to receive a great deal attention.[25—27]

Another class of heterocycles used as scaffolds in medicinal chemistry is devoted to benzotriazole derivatives. They exhibit useful pharmacological properties and clinical applications.[28—31] In addition to these considerable biological applications, benzotriazoles are important intermediates, protecting groups and final products in organic synthesis.[32]

Inspired with biological profile of benzimidazoles, traizoles and diazepines and their increasing importance in pharmaceutical and biological fields, and in connection with our research on the design and synthesis of biologically active and pharmacologically important new heterocycles,[33—38] it was thought worthwhile to synthesize the title compounds with a view to obtain certain new chemical entities with three active pharmacophores in a single molecular frame work in order to prepare molecules having with potentially enhanced biological activities and to have them evaluated for their antimicrobial activity. On the other hand, to the best of our knowledge, previously there is no report, on the synthesis of 6-(1*H*-benz[*d*]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines **8a**—**d** skeleton system represented in Chart 1.

The key intermediate 4-amino-5-(4-pyridyl)-4*H*-1,2,4-triazol-3-ylhydrosulfide **7**, required for the synthesis of the title compounds was prepared by the cyclocondensation of 4-pyridinecarbohydrazide with hydrazine hydrate and CS_2 in presence of potassium hydroxide and ethanol.[39] 2-(α-Hydroxy)ethyl-benzimidazoles **3a**—**d** was prepared by the reaction of substituted *o*-phenylenediamines **1** with α-hydroxy propionic acid **2** in presence of hydrochloric acid under reflux, followed by oxidation of compounds **3a**—**d** in presence of potassium dichromate and sulfuric acid at room temperature yields 2-acetyl benzimidazoles **4** which on condensation reaction with 5-nitro furfural **5** at room temperature in presence of concentrated sulfuric acid and glacial acetic acid provides the formation of (*E*)-1-(1*H*-benzo[*d*]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-ones **6a**—**d**. These compounds **6a**—**d** on cyclocondensation reaction with 4-amino-5-(4-pyridyl)-4*H*-1,2,4-triazol-3-ylhydrosulfide **7** in presence of polyphosphoric acid afforded the compounds 6-(1*H*-benz[*d*]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines **8a**—**d**. The synthetic route leading to the title compounds is summarized in Chart 1. The chemical structures of all the newly synthesized compounds were confirmed by their IR, ^{1}H-NMR, and MS analysis and further the compounds were screened for their antibacterial and antifungal activities.

Antibacterial Activity The antibacterial activity of the synthesized compounds was evaluated against two Gram-positive bacteria *viz*., *Bacillus subtilus* and *Staphylococcus aureus*, and two Gram-negative bacteria *viz*., *Escherichia coli* and *Klebsiella pneumoniae* using streptomycin and benzyl penicillin as standard drugs, respectively by the 'cup-plate method'[40] using dimethyl sulfoxide (DMSO) as the solvent and the results are given in Table 1. The results of the test compounds could not be directly compared with those of the standard drugs, employed for a very simple reason that they vary greatly in their test concentrations, that is, 250 μg/ml and 500 μg/ml of test compounds against 40 μg/ml only of reference drugs. Hence, this data was used to compare the

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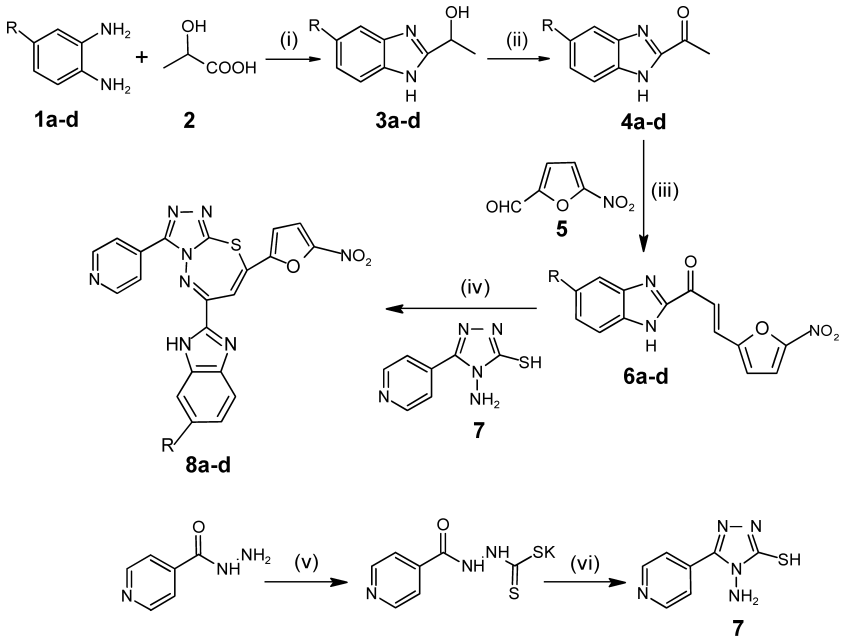

(i) 4N HCl, reflux, 24 h; (ii) $K_2Cr_20_7$, H_2SO_4, 2.5 h; (iii) 5-nitrofurfural, AcOH, con. H_2SO_4, 40 °C, 24 h; (iv) 4-amino-5-(4-pyridyl)-4*H*-1,2,4-triazol-3-ylhydrosulfide, ethanol, reflux, 7 h; (v) CS_2, KOH, EtOH, reflux, 4 h; (vi) NH_2-NH_2 H_2O, EtOH, reflux, 2 h.

1—8 R= a) H; b) 4-CH_3; c) 4-Cl; d) 4-NO_2.

Chart 1

Table 1. Antibacterial and Antifungal Activity of 6-(1*H*-Benz[*d*]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines **8a**—**d**

Compound	Antibacterial activity[a,b]			Antifungal activity[a,b]		
	B. subtilus	*S. aureus*	*E. coli*	*K. pneumoniae*	*F. oxysporum*	*A. niger*
8a	08/06	08/07	05/04	06/05	03/02	03/02
8b	13/12	14/13	14/12	12/11	04/03	03/02
8c	14/13	13/12	13/12	14/13	05/04	04/03
8d	15/14	13/12	14/13	13/12	05/04	05/04
Streptomycin[c]	—	—	16	16	—	—
Benzyl penicillin[c]	16	16	—	—	—	—
Fluconazole[c]	—	—	—	—	06	06

a) Zone of inhibition in mm at 500 μg/ml concentration. *b*) Zone of inhibition in mm at 250 μg/ml concentration. *c*) Zone of inhibition in mm at 40 μg/ml concentration.

relative antibacterial potencies of the test compounds only. Though all of the test compounds could cause inhibition of both Gram (+)ve and Gram (−)ve bacteria employed, effectively at a concentration of 500 μg/ml, the compound **8d** with two nitro groups was found to be relatively more potent among the test compounds.

Antifungal Activity The newly prepared compounds were also screened for their antifungal activity against two fungi, *viz.*, *Fusarium oxysporum* and *Aspergillus niger* by the 'cup-plate method'[40] using Fluconazole as a standard drug and DMSO as the solvent and the results are summarized in Table 1. Similar to antibacterial activity the antifungal activity of the present compounds was also not comparable to that of the standard drug Fluconazole because of the concentration variation. But, however, the test compounds could also exhibit antifungal activity against both the fungi employed. Table 1 indicates once again the compound **8d** with two nitro groups as the superior, relatively among the present new series.

Experimental

General All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60—120 mesh. IR spectra were obtained on a Perkin Elmer BX serried FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for ^{1}H-NMR. The chemical shifts were reported as ppm down field using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Typical Procedure 2-(α-Hydroxy)ethyl Benzimidazoles (3) *o*-Phenylenediamine (0.01 mol) was mixed with lactic acid (0.01 mol) in presence of 4 N hydrochloric acid (5 ml) and refluxed for 24 h. After completion of the reaction, (monitored by TLC) the reaction mixture was cooled and neutralized with NH_3 solution. The solid was separated through filter and recrystallized from ethanol.

2-Acetyl Benzimidazoles (4) To a solution of 2-(α-hydroxy)ethyl benzimidazoles **3** (0.01 mol) in dil. H_2SO_4 (5%, 40 ml) was drop wise added the solution of $K_2Cr_2O_7$ (0.15 mol) and aqueous H_2SO_4 (25%, 80 ml) with constant stirring at room temperature over a period of 20 min. Further the reac-

tion mixture was stirred at room temperature for 2 h. After completion of the reaction, (monitored by TLC), the reaction mixture neutralized with NH_3 solution (1 : 1) and formed orange solid was filtered, washed with water and dried, recrystallized from ethyl acetate.

(*E*)-1-(1*H*-benzo[*d*]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-ones (6) To a solution of 2-acetyl benzimidazoles **4** (0.01 mol) and 5-nitrofurfural (0.01 mol) in glacial acetic acid (20 ml) was added con. sulfuric acid (2 ml). Then the reaction mixture stirred at 40 °C for 24 h. The solid formed was filtered and recrystallized form ethylacetate.

4-Amino-5-(4-pyridyl)-4*H*-1,2,4-triazol-3-ylhydrosulfide (7) 4-Pyridine carbohydrazide (0.01 mol) was dissolved in 10% alcoholic potassium hydroxide (25 ml) and stirred with an equimolar quantity of CS_2, slowly while cooling in an ice both. The resultant bulk potassium dithiacarbazate was filtered and subjected to a reaction with excess of hydrazine hydrate. The product was filtered and recrystallized from alcohol to get a colorless crystalline solid. mp 250—254 °C.

6-(1*H*-benz[*d*]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazepines (8) The compounds (*E*)-1-(1*H*-benz[*d*]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-ones **6** (0.01 mol) and 4-amino-5-(4-pyridyl)-4*H*-1,2,4-triazol-3-ylhydrosulfide **7** (0.01 mol) were rapidly mixed with help of mortar and converted into paste form. The resulting mixture was then refluxed in presence of polyphosphoric acid for 7 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature poured into ice cold water. The formed pale brown precipitate was separated by using ether, dried and recrystallized from ethylacetate.

1-(1*H*-Benz[*d*]imidazol-2-yl)-1-ethanol (**3a**): Yellow solid, yield 90%, mp 180—182 °C. IR (KBr) cm^{-1}: 2971, 1623, 1458, 1215, 1103. ^{1}H-NMR ($CDCl_3$) δ: 10.30 (1H, br s), 7.52 (2H, m, J=7.8 Hz), 7.12 (2H, m, J=7.6 Hz), 4.8 (1H, s), 3.05 (1H, q, J=7.4 Hz), 1.62 (3H, d, J=7.2 Hz). MS *m*/*z*: 163 (M^++1).

1-(5-Methyl-1*H*-benz[*d*]imidazol-2-yl)-1-ethanol (**3b**): Dark yellow solid, yield 90%, mp 160—162 °C. IR (KBr) cm^{-1}: 3038, 2701, 1629, 1449, 1316, 1101. ^{1}H-NMR ($CDCl_3$) δ: 9.61 (1H, br s), 7.32 (3H, m, J=8.0 Hz), 4.85 (1H, s), 3.05 (1H, q, J=7.8 Hz), 1.62 (3H, d, J=7.4 Hz). MS *m*/*z*: 177 (M^++1).

1-(5-Chloro-1*H*-benz[*d*]imidazol-2-yl)-1-ethanol (**3c**): Brown solid, yield 65%, mp 171—173 °C. IR (KBr) cm^{-1}: 2981, 1623, 1444, 1210, 1082. ^{1}H-NMR ($CDCl_3$) δ: 12.50 (1H, s), 7.55 (2H, d, J=7.2 Hz), 7.20 (1H, d, J=7.4 Hz), 4.91 (1H, m, J=6.8 Hz), 1.52 (3H, d, J=7.0 Hz). MS *m*/*z*: 197 (M^++1).

1-(5-Nitro-1*H*-benz[*d*]imidazol-2-yl)-1-ethanol (**3d**): Brown solid, yield 75%, mp 148—150 °C. IR (KBr) cm^{-1}: 3342, 3215, 3024, 2865, 2240, 1420, 1248. ^{1}H-NMR ($CDCl_3$) δ: 8.63 (1H, s), 7.91 (1H, d, J=7.0 Hz), 76 (1H, d, J=7.2 Hz), 6.64 (1H, s), 6.59 (1H, d, J=7.4 Hz), 5.16 (1H, m, J=7.6 Hz), 1.77 (1H, d, J=7.8 Hz). MS *m*/*z*: 208 (M^++1).

1-(1*H*-Benz[*d*]imidazol-2-yl)-1-ethanone (**4a**): Yellow solid, yield 78%, mp 189—191 °C. IR (KBr) cm^{-1}: 3289, 3059, 3015, 1674, 1580, 1445, 1235, 1147. ^{1}H-NMR ($CDCl_3$) δ: 13.02 (1H, s), 7.85 (1H, d, J=7.8 Hz), 7.52 (1H, d, J=7.6 Hz), 7.32 (2H, t, J=7.4 Hz), 2.74 (3H, s). MS *m*/*z*: 161 (M^++1).

1-(5-Methyl-1*H*-benz[*d*]imidazol-2-yl)-1-ethanone (**4b**): Yellow solid, yield 80%, mp 170—172 °C. IR (KBr) cm^{-1}: 3365, 2919, 2852, 1693. ^{1}H-NMR ($CDCl_3$) δ: 11.23 (1H, s), 7.65 (1H, d, J=8.0 Hz), 7.48 (1H, d, J=7.8 Hz), 7.24 (1H, s), 3.42 (3H, s), 2.45 (3H, s). MS *m*/*z*: 174 (M^++1).

1-(5-Chloro-1*H*-benz[*d*]imidazol-2-yl)-1-ethanone (**4c**): Yellow solid, yield 65%, mp 185—187 °C. IR (KBr) cm^{-1}: 3294, 3066, 3021, 1677, 1574, 1335, 1219, 1060. ^{1}H-NMR ($CDCl_3$) δ: 10.70 (1H, s), 7.82 (1H, t, J=7.6 Hz), 7.51 (1H, m, J=7.4 Hz), 7.30 (1H, m, J=7.2 Hz), 2.81 (3H, s). MS *m*/*z*: 195 (M^++1).

1-(5-Nitro-1*H*-benz[*d*]imidazol-2-yl)-1-ethanone (**4d**): Pale yellow solid, yield 70%, mp 155—157 °C. IR (KBr) cm^{-1}: 3360, 3040, 2865, 2160, 1720, 1356, 1240. ^{1}H-NMR ($CDCl_3$) δ: 8.91 (1H, s), 8.77 (1H, s), 8.13 (1H, d, J=7.2 Hz), 8.09 (1H, d, J=7.4 Hz), 2.79 (3H, s). MS *m*/*z*: 206 (M^++1).

(*E*)-1-(1*H*-Benz[*d*]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-one (**6a**): Yellow solid, yield 40%, mp 205—207 °C. IR (KBr) cm^{-1}: 3289, 3014, 2917, 1674, 1508, 1021, 1005, 871. ^{1}H-NMR ($CDCl_3$) δ: 8.77 (1H, s), 8.11 (2H, d, J=7.8 Hz), 7.76 (2H, dd, J=7.4 Hz) 7.64 (1H, d, J=7.2 Hz), 7.43 (1H, d, J=7.6 Hz), 7.08 (1H, d, J=8.0 Hz), 6.87 (1H, d, J=8.2 Hz). MS *m*/*z*: 284 (M^++1).

(*E*)-1-(5-Methyl-1*H*-benz[*d*]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-one (**6b**): Yellow solid, yield 50%, mp 195—197 °C. IR (KBr) cm^{-1}: 3276, 3021, 2915, 1682, 1524, 1025, 1011, 875. ^{1}H-NMR ($CDCl_3$) δ: 8.77 (1H, s), 7.71 (1H, d, J=8.0 Hz), 7.66 (1H, s), 7.64 (1H, d, J=7.2 Hz), 7.43 (1H, d, J=7.6 Hz), 7.39 (1H, d, J=7.2 Hz), 7.08 (1H, d, J=7.8 Hz), 6.87 (1H, d, J=7.6 Hz), 2.43 (3H, s). MS *m*/*z*: 298 (M^++1).

(*E*)-1-(5-Chloro-1*H*-benz[*d*]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-one (**6c**): Yellow solid, yield 40%, mp 208—210 °C. IR (KBr) cm^{-1}: 3278, 3026, 2919, 1687, 1526, 1032, 1014, 875. ^{1}H-NMR ($CDCl_3$) δ: 8.77 (1H, s), 7.78 (1H, s), 7.79 (1H, d, J=7.8 Hz), 7.64 (1H, d, J=7.6 Hz), 7.58 (1H, d, J=7.4 Hz), 7.43 (1H, d, J=7.2 Hz), 7.08 (1H, d, J=8.0 Hz), 6.87 (1H, d, J=7.8 Hz). MS *m*/*z*: 318 (M^++1).

(*E*)-1-(5-Nitro-1*H*-benz[*d*]imidazol-2-yl)-3-(5-nitro-2-furyl)-2-propen-1-one (**6d**): Yellow solid, yield 30%, mp 193—195 C. IR (KBr) cm^{-1}: 3279, 3012, 2921, 1669, 1512, 1018, 1012, 879. ^{1}H-NMR ($CDCl_3$) δ: 9.09 (1H, s), 8.77 (1H, s), 8.30 (1H, d, J=7.8 Hz), 8.19 (1H, d, J=7.6 Hz), 7.64 (1H, d, J=7.4 Hz), 7.43 (1H, d, J=7.6 Hz), 7.08 (1H, d, J=7.8 Hz), 6.87 (1H, d, J=7.4 Hz). MS *m*/*z*: 329 (M^++1).

6-(1*H*-Benz[*d*]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine (**8a**): Yellow solid, yield 90%, mp 192—194 °C. IR (KBr) cm^{-1}: 3420, 3025, 2925, 1560, 1410, 1124, 1214. ^{1}H-NMR ($CDCl_3$) δ: 10.17 (1H, s), 9.17 (2H, d, J=8.0 Hz), 8.62 (2H, d, J=7.8 Hz), 7.50 (2H, d, J=7.6 Hz), 7.41 (2H, d, J=7.4 Hz), 7.21 (1H, d, J=7.6 Hz), 5.91 (1H, d, J=7.8 Hz), 4.99 (1H, t, J=7.6 Hz), 2.15 (2H, d, J=8.2 Hz). MS *m*/*z*: 459 (M^++1).

6-(6-Methyl-1*H*-benz[*d*]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine (**8b**): Yellow solid, yield 75%, mp 195—197 °C. IR (KBr) cm^{-1}: 3437, 3032, 2932, 1542, 1436, 1132, 1236. ^{1}H-NMR ($CDCl_3$) δ: 10.17 (1H, s), 9.17 (2H, d, J=7.8 Hz), 8.62 (2H, d, J=7.6 Hz), 7.24 (1H, d, J=7.4 Hz), 7.21 (1H, d, J=7.6 Hz), 7.12 (1H, d, J=7.8 Hz), 7.09 (1H, s), 5.91 (1H, d, J=7.4 Hz), 4.99 (1H, t, J=8.0 Hz), 2.43 (3H, s), 2.15 (2H, d, J=7.8 Hz). MS *m*/*z*: 473 (M^++1).

6-(6-Chloro-1*H*-benz[*d*]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine (**8c**): Yellow solid, yield 65%, mp 201—203 °C. IR (KBr) cm^{-1}: 3456, 3015, 2939, 1525, 1436, 1142, 1246, 746. ^{1}H-NMR ($CDCl_3$) δ: 10.17 (1H, s), 9.17 (2H, d, J=7.8 Hz), 8.62 (2H, d, J=7.6 Hz), 7.38 (1H, s), 7.36 (1H, d, J=8.0 Hz), 7.28 (1H, d, J=7.6 Hz), 7.21 (1H, d, J=7.8 Hz), 5.91 (1H, d, J=7.6 Hz), 4.99 (1H, t, J=8.0 Hz), 2.15 (2H, d, J=7.8 Hz). MS *m*/*z*: 493 (M^++1).

6-(6-Nitro-1*H*-benz[*d*]imidazol-2-yl)-8-(5-nitro-2-furyl)-3-(4-pyridyl)-7,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine (**8d**): Yellow solid, yield 45%, mp 189—191 °C. IR (KBr) cm^{-1}: 3412, 3014, 2945, 1542, 1425, 1136, 1224. ^{1}H-NMR ($CDCl_3$) δ: 10.17 (1H, s), 9.17 (2H, d, J=7.8 Hz), 8.62 (2H, d, J=7.6 Hz), 8.39 (1H, d, J=7.8 Hz), 8.13 (1H, d, J=8.0 Hz), 7.79 (1H, d, J=7.6 Hz), 7.21 (1H, d, J=7.8 Hz), 5.91 (1H, d, J=7.6 Hz), 4.99 (1H, t, J=8.0 Hz), 2.15 (2H, d, J=7.8 Hz). MS *m*/*z*: 504 (M^++1).

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