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Reactions of 2-amino-5-arylazopyrimidine derivatives and phenyl isocyanate

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Abstract: 3-Arylhydrazono-2,4-pentanediones and 3,3'-(phenylene-1,4-dihydrazono)bis(pentane-2,4-dione) was synthesized by azo coupling of the acetylacetone with aryldiazonium chlorides and phenylene-1,4-bis(diazonium) dichloride. 2-Amino-4,6-dimethyl-5-arylazopyrimidines and 5,5'-(phenylene-1,4-diazo)bis(2-amino-4,6-dimethylpyrimidine) have been prepared from the same diketones and guanidinium carbonate. 2-Aminopyrimidine derivatives add phenyl isocyanate to give the *N,N'*-disubstituted ureas. The structure of the resulted products was confirmed by determination of the melting point and spectrophotometric techniques such as IR and ^{1}H-NMR, in some cases by using ^{13}C-NMR spectroscopy.

Keywords: Arylhydrazone, 2-Amino-5-arylazopyrimidine, 5,5'-(Phenylene-1,4-diazo)bis(2-aminopyrimidine), Phenyl isocyanate, *N,N'*-Disubstituted urea.

Introduction

It is know that acetylacetone react with each of aryldiazonium chlorides (**1a-c**) and phenylene-1,4-bis(diazonium) dichloride (**1d**) to form the corresponding 3-arylhydrazonoacetylacetone (**2a-c**) [1,2] and 3,3'-(phenylene-1,4-dihydrazono)bis(pentane-2,4-dione) (**2d**), respectively (Scheme **1**) [3].

One of the widely used synthesis methods for pyrimidine derivatives is condensation of 1,3-diketones (or their analogues) with different derivatives of guanidine and urea. Thus, condensation of guanidinium carbonate with each of 3-arylhydrazonoacetylacetone and 3,3'-(phenylene-1,4-dihydrazono)bis(pentane-2,4-dione) at heating in ethanol results in the formation of 2-amino-4,6-dimethyl-5-arylazopyrimidine (**3a-c**) and 5,5'-(phenylene-1,4-diazo)bis(2-amino-4,6-dimethyl pyrimidine) (**3d**), respectively (Scheme 1) [4-8].

2-Aminopyrimidine derivatives exhibiting a C-NH_2-moiety, which should apply to several subsequent reactions. In particular following the improved method to synthesize substituted ureas by adding amines to isocyanates, pyrimidinyl-aryl urea derivatives should be available [9,10]. Main chemical transformations of functionalized 2-aminopyrimidines and their application in the synthesis of modern pharmaceuticals are reported [11].

The ureides are compounds which essentially incorporate urea as substructure unit either in open or cyclic form. These are an important class of compounds since out of the five nucleobases, the three pyrimidine bases cytosine, thymine and uracil incorporates urea as a substructural component. The ureides per say have been associated with several bioactivities as evident from the MDDR database which incorporates more than 6000 compounds having urea scaffold [12]. Some of the important pharmacological activities ascribed to ureides are antiinfectives, antitumor, anticancer and for various metabolic disorders including diabetes and hyperlipidemia [13].

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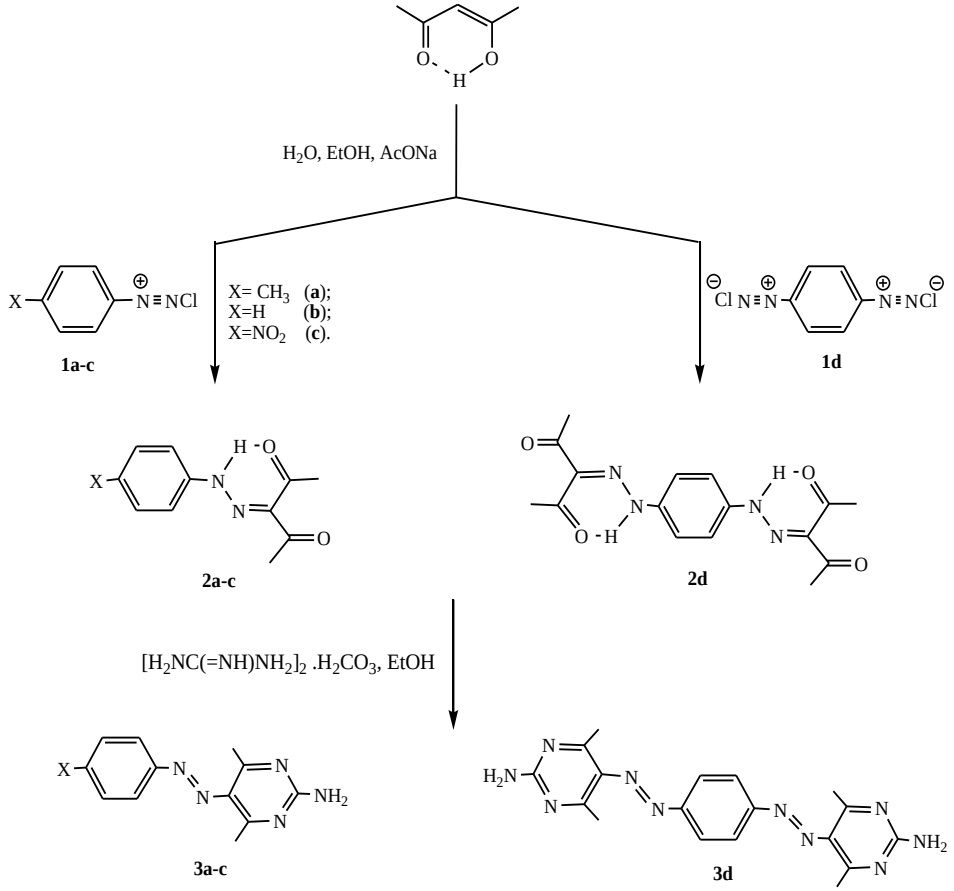
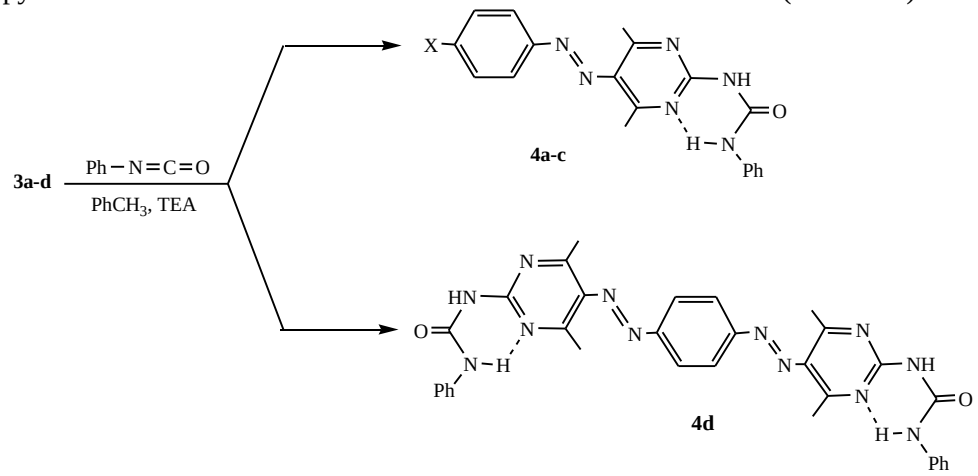
Heteroaryl aryl ureides to treat diseases mediated by the VEGF induced signal transduction pathway characterized by abnormal angiogenesis or hyperpermeability processes [14-16]. Heteroaryl aryl ureides use in the manufacture of pharmaceutical formulations useful in the treatment of protein kinase dependent diseases [17-20].



Scheme 1: Preparation of 2-Amino-4,6-dimethyl-5-arylazopyrimidines (**3a-c**) and 5,5'-(phenylene-1,4-diazo)bis(2-amino-4,6-dimethylpyrimidine) (**3d**).

Herein, we report a simple reaction between 2-amino-5-arylazopyrimidine derivatives **3a-d** and phenyl isocyanate leading to 1-pyrimidinyl-3-phenyl urea derivatives **4a-d** (Scheme **2**).



Scheme 2: Reactions **3a-d** with phenyl isocyanate**.**

Results and discussion

*Synthesis of 3-arylhydrazono-2,4-pentanediones (**2a-c**):*

It is know that the acetylacetone react with aryldiazonium chlorides in water-methanol medium in presence of AcONa to give the corresponding 3-arylhydrazono-2,4-pentanediones (**2a-c**) (Scheme **1**) [1].

*Synthesis of 3,3'-(phenylene-1,4-dihydrazono)bis(pentane-2,4-dione) (**2d**):*

The compound **2d** was synthesized by azo coupling of the acetylacetone with phenylene-1,4-bis(diazonium) dichloride (Scheme **1**) [3]. It was proved by IR and ^{1}H-NMR spectroscopies that the obtained compound **2d**. The ^{1}H-NMR spectrum of product **2d** the resonance signal of a methine proton was absent. In the ^{1}H-NMR spectrum of **2d** it can be seen that the chemical shift of the methyl of the acetyl group involved in intramolecular hydrogen bond (δ 2.62) is slightly further than the free acetyl group (δ 2.50). Its IR spectrum showed two strong absorption bands in the region 1680, 1635 cm^{-1}. This may be due to the presence of two nonequivalent carbonyl groups in its molecule. The low-frequency shift of the carbonyl bands, results from conjugation with the C=N bond, as well as participation of the C=O group in an intramolecular hydrogen bond with the amino group of arylhydrazone fragment.

*Reactions of the compounds **2a-d** with guanidinium carbonate:*

The direct synthesis of an 2-amino-5-arylazopyrimidine is obtained by the condensation of arylazoacetylacetone or phenylene-1,4-bis(azoacetylacetone) with guanidine on refluxing in absolute ethanol to give respectively 2-amino-4,6-dimethyl-5-arylazopyrimidine derivatives (**3a-c**) or 5,5'-(phenylene-1,4-diazo)bis(2-amino-4,6-dimethyl pyrimidine) (3**d**) (Scheme **1**) [5]. Structures **3a-c** was assigned on the basis of their IR, ^{1}H, and ^{13}C NMR spectra. For example, the IR spectrum of compound **3a** showed six characteristic absorption bands at 3320, 3151, 1652, 1561, 1542, 1483 cm^{-1} attributable to two bands for NH_2, NH bending, C=C, pyrimidine ring C=N and N=N, respectively. In the ^{1}H NMR spectra of **3a** we observed signals for CH_3 and $2CH_3$ protons at δ 2.45 and 2.63 ppm. Its ^{1}H NMR spectrum displayed a broad singlet at δ 5.40 ppm for the NH_2 protons and doublet of doublet signals integrated for 4 protons at δ 7.32 and 7.75 ppm (aromatic protons). On shaking the compounds **3a** with D_2O, the broad band signal attributable to NH_2 disappeared. The ^{13}C NMR spectrum of **3a** revealed three signals at δ 163.27, 160.50 and 151.15 ppm to the C_2, C_4 and C_5 carbons, respectively of the pyrimidine, besides four signals at δ 141.20, 137.11, 129.74 and 122.29 ppm attributable to the aromatic carbons and two signal at δ 22.65 and 21.46 ppm for $2CH_3$ and CH_3 carbons.

*Reactions of 2-amino-5-arylazopyrimidine derivatives **3a-d** with phenyl isocyanate:*

Functionalized pyrimidines **3a-d** attracted our attention as potential starting compounds for the synthesis of new pyrimidine derivatives (Scheme **2**). 2-amino-5-arylazopyrimidine derivatives **3a-d** reacts with phenyl isocyanate in refluxing dry toluene. Thus, 1-pyrimidinyl-3-phenyl urea derivatives **4a-d** was obtained in 79-65% isolated yields (Scheme **2**). Structures **4a-d** were confirmed by the data from IR, ^{1}H NMR and ^{13}C NMR spectra. For example, the IR spectrum of compound **4a** showed five characteristic absorption bands at 3225, 1678, 1600, 1556, 1486 cm^{-1} attributable to NH, C=O, C=C, pyrimidine ring C=N and N=N, respectively.

In the ^{1}H NMR spectrum of **4a** we observed two singlets at δ 2.45 ppm CH_3 and δ 2.63 ppm $2CH_3$, which correspond to the aromatic and pyrimidine ring. Also, two singlets at δ 10.06 ppm -NH-CO- and δ 11.35 ppm -CO-NH-Ph, a set of aromatic proton signals in the region δ 6.88-7.51 ppm were present. On shaking the compound **4a** with D_2O, the broad band signals attributable to 2NH disappeared. The ^{13}C NMR spectrum of **4a** revealed two signals at δ 21.03, 22.60 for $3CH_3$ and three signals at δ 150.94 (C_5), 160.21 (C_4 and C_6), 163.35 (C_2) ppm due to the carbons of the pyrimidine, besides eight signals at δ 119.82-139.05 ppm attributable to the aromatic carbons and a signal at δ 153.46 ppm for the amidic carbonyl carbon were identified.

Conclusion

We report a facile route for the formation of 1-pyrimidinyl-3-phenyl urea derivatives **4a-d** based on 2-amino-5-arylazopyrimidine derivatives **3a-d**.

Experimental

Methods:

The chemicals were purchased from Merck and used without further purification. Melting points were

measured with an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. These results agreed favorably with the calculated values. Infrared spectra were measured from KBr disk using a FT-IR Perkin Elmer GX spectrometer and frequencies are reported in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Ultra Shield^{TM}-500MHz instrument using TMS as an internal standard. Chemical shifts are reported in ppm. Column chromatography was performed on silica gel L 100/250. Thin-layer chromatography was performed on "Silufol-UV 254" plates.

*Synthesis of 3-arylhydrazono-2,4-pentanediones (**2a-c**):*

3-Arylhydrazono-2,4-pentanediones (**2a-c**) have been prepared by the coupling of acetylacetone with aryldiazonium chlorides [1].

*Synthesis of 3,3'-(phenylene-1,4-dihydrazono)bis(pentane-2,4-dione) (**2d**, $C_{16}H_{18}N_4O_4$):*

A solution of 0.514 g (2.0 mmol) of phenylene-1,4-diamine in dilute HCl (prepared by diluting 6.7 ml of concentrated HCl with 21 ml of water) was cooled to 0°C, and a solution of 0.276 g (4.0 mmol) of $NaNO_2$ in 1.2 ml of water was added under vigorous stirring. Solutions of 1.82 g of NaOAc in 16 ml of water and of 0.4 g (4.0 mmol) of acetylacetone in 13 ml of ethanol were mixed separately, and the above diazonium salt solution was slowly added under stirring, maintaining the temperature at 10°C. The precipitate was filtered off, recrystallized from ethanol, and dried [3].

Red crystal (Yield 83%), m.p. 269-271 °C; FT-IR (KBr): $\bar{\nu}$ = 3082 (NH), 1680, 1635 (C=O), 1596 (NH), 1525 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.50 (6H, s, CH_3), 2.62 (6H, s, CH_3), 7.47 (4H, s, C_6H_4), 13.62 (2H, br.s, 2NH) ppm.

*Synthesis of 2-amino-4,6-dimethyl-5-arylazo pyrimidines (**3a-c**) and 5,5'-(phenylene-1,4-diazo)bis(2-amino-4,6-dimethylpyrimidine) (**3d**). General Procedure:*

These were prepared by refluxing a mixture of 2.0 mmol 1,3-diketones **2a-d** with guanidinium carbonate (0.36 g (2.0 mmol) for **3a-c** and 0.72 g (4.0 mmol) for **4d**) in absolute ethanol (15 ml) for 24-30 h. The progress of the reaction was monitored by TLC (eluent AcOEt/hexane 1:1). The ethanol was evaporated, the solid that separated in each case was filtered off and was crystallized from ethanol to give **3a-d** [5].

*2-Amino-4,6-dimethyl-5-(4-methylphenyl) azo pyrimidine (**3a**, $C_{13}H_{15}N_5$):*

Orange crystal (Yield 83%), m.p. 244-246 °C; FT-IR (KBr): $\bar{\nu}$ = 3320, 3151 (NH_2), 1652 (NH), 1561 (C=C), 1542 (C=N), 1483 (N=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.45 (3H, s, CH_3), 2.63 (6H, s, $2CH_3$), 5.40 (2H, br.s, NH_2), 7.32 (2H, d, $^3J_{HH}$=8.2 Hz, $2CH_{ortho}$ of Ph-CH_3), 7.75 (2H, d, $^3J_{HH}$=8.2 Hz, $2CH_{ortho}$ of Ph-N=N) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.46 (CH_3), 22.65 ($2CH_3$), 122.29 ($2C_{ortho}$ of Ph-N=N), 129.74 ($2C_{ortho}$ of Ph-CH_3), 137.11 (C_{ipso} of Ph-CH_3), 141.20 (C_{ipso} of Ph-N=N), 151.15 (C_5), 160.50 (C_4 and C_6), 163.27 (C_2) ppm.

*2-Amino-4,6-dimethyl-5-phenylazopyrimidine (**3b**, $C_{12}H_{13}N_5$):*

Brown red powder (Yield 63%), m.p. 232-234 °C (decomp.); FT-IR (KBr): $\bar{\nu}$ = 3380, 3200 (NH_2), 1660 (NH), 1575 (C=C), 1555 (C=N), 1490 (N=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.61 (6H, s, $2CH_3$), 5.42 (2H, br.s, NH_2), 7.41 (1H, t, $^3J_{HH}$=7.3 Hz, CH_{para} of Ph-N=N), 7.50 (2H, t, $^3J_{HH}$=7.3 Hz, $2CH_{meta}$ of Ph-N=N), 7.82 (2H, d, $^3J_{HH}$=7.3 Hz, $2CH_{ortho}$ of Ph-N=N) ppm.

*2-Amino-4,6-dimethyl-5-(4-nitrophenyl)azopyrimidine (**3c**, $C_{12}H_{12}N_6O_2$):*

Red crystal (Yield 70%), m.p. 224-226 °C; FT-IR (KBr): $\bar{\nu}$ = 3334, 3158 (NH_2), 1657 (NH), 1565 (C=C), 1560 (C=N), 1556, 1331 (NO_2), 1485 (N=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.65 (6H, s, $2CH_3$), 5.44 (2H, br.s, NH_2), 7.91 (2H, d, $^3J_{HH}$=8.5 Hz, $2CH_{ortho}$ of Ph-N=N), 8.22 (2H, d, $^3J_{HH}$=8.5 Hz, $2CH_{ortho}$ of Ph-NO_2) ppm.

*5,5'-(Phenylene-1,4-diazo)bis(2-amino-4,6-dimethy lpyrimidine) (**3d**, $C_{18}H_{20}N_{10}$):*

Brown red powder (Yield 83%), m.p. 286-288 °C; FT-IR (KBr): $\bar{\nu}$ = 3336, 3150 (NH_2), 1655 (NH), 1575 (C=C), 1551 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.54 (12H, s, $4CH_3$), 5.36 (4H, br.s, $2NH_2$), 7.88 (4H, s, C_6H_4) ppm.

*Synthesis of 1-(4,6-dimethyl-5-arylazopyrimidine-2-yl)-3-phenylureas (**4a-c**)and 5,5'-(phenylene-1,4-diazo)bis1-(4,6-dimethylpyrimidine-2-yl)-3-phenylurea (**4d**).*

General Procedure:

A mixture of 1.0 mmol of 2-amino-5-arylazopyrimidine derivatives **3a-d** and of 0.119 g (1.0 mmol) of phenyl isocyanate in dry toluene (15 ml)

containing a few drops of TEA was refluxed for 3 h. The progress of the reaction was monitored by TLC (eluent AcOEt/hexane 2:1). The toluene was evaporated, the residue was separated by silica gel column chromatography (Merck 230–400 mesh) using AcOEt/hexane (1:4) as eluent to give **4a-d**. The purification was done by recrystallization of isopropyl alcohol, and dried.

*1-(4,6-Dimethyl-5-(4-methylphenyl)azopyrimidine-2-yl)-3-phenylurea (**4a**, $C_{20}H_{20}N_6O$):*

Light brown powder (Yield 74%), m.p. 286-288 °C; FT-IR (KBr): $\bar{\nu}$ = 3225 (NH), 1678 (C=O), 1600 (C=C), 1556 (C=N), 1486 (N=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.45 (3H, s, CH_3), 2.63 (6H, s, $2CH_3$), 6.88 (2H, d, $^3J_{HH}$=8.2 Hz, $2CH_{ortho}$ of Ph-CH_3), 7.01 (1H, t, $^3J_{HH}$=7.0 Hz, CH_{para} of Ph-NH), 7.04 (2H, t, $^3J_{HH}$=7.0 Hz, $2CH_{meta}$ of Ph-NH), 7.39 (2H, d, $^3J_{HH}$=7.0 Hz, $2CH_{ortho}$ of Ph-NH), 7.51 (2H, d, $^3J_{HH}$=8.2 Hz, $2CH_{ortho}$ of Ph-N=N), 10.06, 11.35 (2H, 2br.s, 2NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 21.03 (CH_3), 22.60 ($2CH_3$), 119.82, 120.75, 122.66, 124.01, 129.06, 129.81, 137.20, 139.05 (12C, 2Ph), 150.94 (C_5), 153.46 (C=O), 160.21 (C_4 and C_6), 163.35 (C_2) ppm.

*1-(4,6-Dimethyl-5-phenylazopyrimidine-2-yl)-3-phenylurea (**4b**, $C_{19}H_{18}N_6O$):*

Light brown powder (Yield 65%), m.p. 275-277 °C; FT-IR (KBr): $\bar{\nu}$ = 3233 (NH), 1676 (C=O), 1605 (C=C), 1561 (C=N), 1488 (N=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.59 (6H, s, $2CH_3$), 6.91-7.65 (10H, m, $2C_6H_5$), 10.11, 11.39 (2H, 2br.s, 2NH) ppm.

*1-(4,6-Dimethyl-5-(4-nitrophenyl)azopyrimidine-2-yl)-3-phenylurea (**4c**, $C_{19}H_{17}N_7O_3$):*

Light brown powder (Yield 69%), m.p. 267-269 °C; FT-IR (KBr): $\bar{\nu}$ = 3229 (NH), 1681 (C=O), 1605 (C=C), 1554 (C=N), 1556, 1334 (NO_2), 1490 (N=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.61 (6H, s, $2CH_3$), 7.06 (1H, t, $^3J_{HH}$=7.3 Hz, CH_{para} of Ph-NH), 7.10 (2H, t, $^3J_{HH}$=7.3 Hz, $2CH_{meta}$ of Ph-NH), 7.41 (2H, d, $^3J_{HH}$=7.3 Hz, $2CH_{ortho}$ of Ph-NH), 7.79 (2H, d, $^3J_{HH}$=8.0 Hz, $2CH_{ortho}$ of Ph-N=N), 8.12 (2H, d, $^3J_{HH}$=8.0 Hz, $2CH_{ortho}$ of Ph-NO_2), 10.17, 11.46 (2H, 2br.s, 2NH) ppm.

*5,5'-(Phenylene-1,4-diazo)bis1-(4,6-dimethyl pyrimidine-2-yl)-3-phenylurea (**4d**, $C_{32}H_{30}N_{12}O_2$):*

Light brown powder (Yield 79%), m.p. 306-308 °C; FT-IR (KBr): $\bar{\nu}$ = 3232 (NH), 1680 (C=O), 1602 (C=C), 1552 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.53 (12H, s, $4CH_3$), 7.04 (2(1H), t, $^3J_{HH}$=7.2 Hz, $2CH_{para}$ of Ph-NH), 7.12 (2(2H), t, $^3J_{HH}$=7.2 Hz, $4CH_{meta}$ of Ph-NH), 7.35 (2(2H), d, $^3J_{HH}$=7.2 Hz, $4CH_{ortho}$ of Ph-NH), 7.67 (4H, s, C_6H_4), 10.17, 11.46 (4H, 2br.s, 4NH) ppm.

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