Condensation of 4-hydroxy-2-thiazolines with 1,2-phenylenediamine as a novel effective route to thiazolo[3,4-a]quinoxalines

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CONDENSATION OF 4-HYDROXY-2-THIAZOLINES WITH 1,2-PHENYLENEDIAMINE AS A NOVEL EFFECTIVE ROUTE TO THIAZOLO[3,4-*a*]QUINOXALINES

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Abstract - Thiazolo[3,4-*a*]quinoxalin-4-ones were prepared in two steps starting from methyl phenylchloropyruvate using a new strategy for the construction of the ring system. A key step in this new method involves the reaction of 4-hydroxytetrahydrothiazoles with 1,2-phenylendiamines.

Synthetic potential of 4-hydroxy-2-thiazolines,[1,2] which are the unstable intermediates in the Hantzsch synthesis of thiazoles by condensation of α-halo ketones with thioureas, is insufficiently studied. Recently we have reported that the reaction of methyl phenylchloropyruvate with *N,N'*-diphenylthiourea proceeds with the formation of anomalously stable Hantzschs reaction intermediate, 2-phenylimino-3,5-diphenyl-4-methoxycarbonyl-4-hydroxythiazolidine (**1a**) in high yield, dehydration of which is going with the formation of 4-thiazoline (**2a**) only under very strong dehydrating agents as PPA and SOCl$_2$.[3,4]
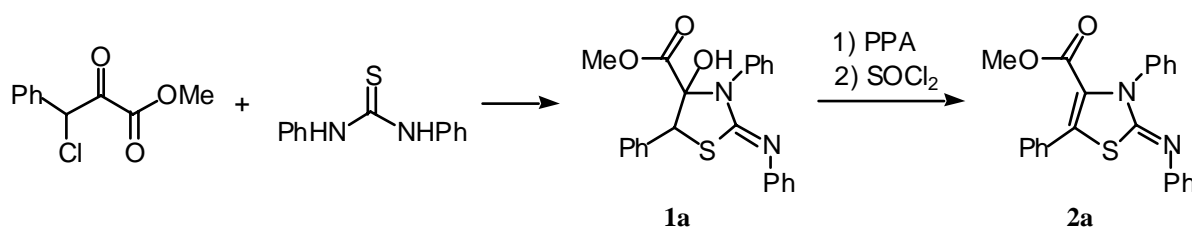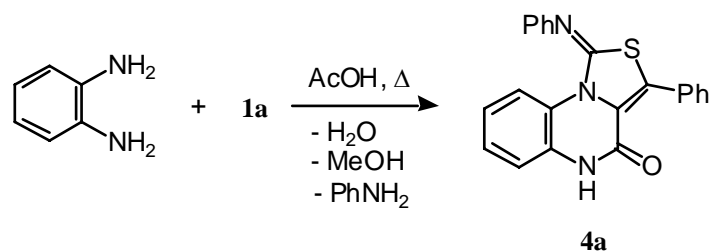

Scheme 1

It was established that 4-hydroxythiazolidine (**1a**) in solutions (DMSO, DMF, DMF+acetone) exists as a mixture of diastereomers (**1α**) and (**1β**), which most probably convert into each other through open chain intermediate (**3**).[4] Though this intermediate was not recorded by spectral methods, the interconversion between **1α** and **1β** is not possible without intermediate (**3**).

Chart 1
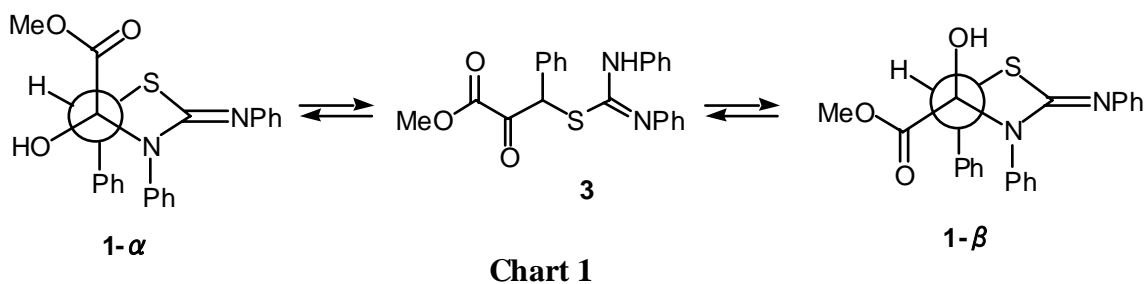
Therefore for the analysis of possible synthetic usage of 4-hydroxythiazolidine (**1a**) it is necessary to take into account not only its cyclic structures (**1**) but also an open-chain structure (**3**), which contains various types of electrophilic and nucleophilic reaction centers. In this paper we report the results of our study of synthetic potential of 4-hydroxythiazolidine (**1a**).

To clarify the scope of synthetic potential of 4-hydroxythiazolidine (**1a**), we carried out the reaction of these compounds with various 1,2-phenylenediamines, giving heterocyclic systems in which the thiazolidine residue is fused to a quinoxaline nucleus at the 1,2-position. Heterocyclic compounds in which the thiazolidine residue is fused to the quinoxaline nucleus at the 1,2-positions are few. As far as we know only three examples are available: Talukdar *et al.*[5,6] and Fedotov *et al.*[7] who have obtained some mesoionic thiazolo[3,2-*a*]quinoxalines along with several other compounds by intramolecular cyclization of 2-carboxymethylthioquinoxaline, and Adegoke *et al.*[8] obtained some dihydrothiazolo[3,4-*a*]quinoxalin-4-ones by metal-acid reductive cyclization of *N*-nitrophenyl- and *N*-dinitrophenylthiazolidine-4-carboxylic acids.

We have found that condensation of 4-hydroxy-3-aryl-5-phenyl-2-phenylimino-4-methoxy-carbonylthiazolidine (**1a**) with 1,2-phenylenediamine in boiling acetic acid takes place unexpectedly resulting in the formation of thiazolo[3,4-*a*]quinoxaline system (**4a**) (Scheme 2).

Scheme 2

Formation of thiazolo[3,4-*a*]quinoxaline system (**4a**) can be presented both from cyclic tautomer 4-hydroxythiazolidine (**1a**) (*path a* and *b*) and open chain tautomer 3-phenyl-3-isothioureidopyruvate (**3**) (*path c*) (Scheme 3).
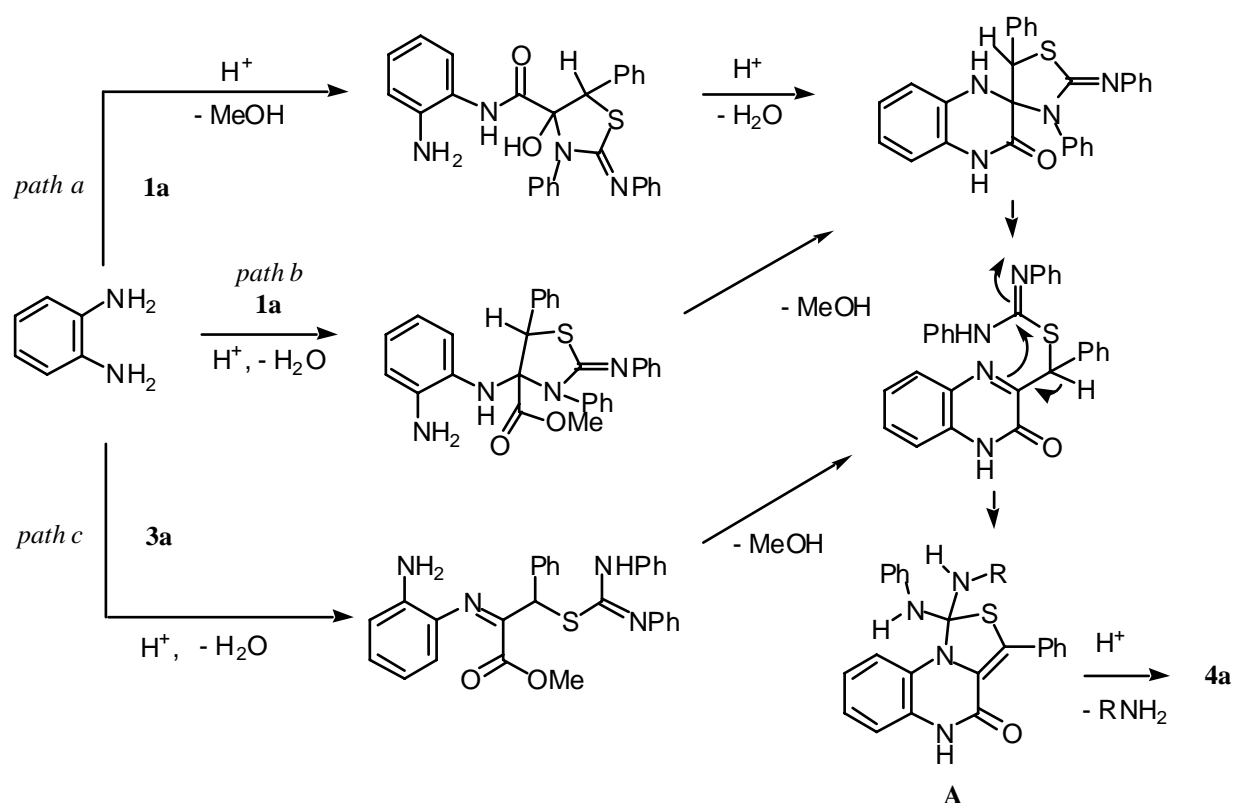
Scheme 3

In order to clarify that the formation of thiazolo[3,4-*a*]quinoxaline (**4a**) from the above mentioned paths is most probable, we have carried out a similar reaction of 4-hydroxythiazolidine with 4-nitro-1,2-phenylenediamine. We assume that the first amino group is disactivated by a nitro-group, more active second amino group in a *meta*-position in relation to nitro group is responsible for the first stage of reaction. It should be noted that there is no difference whether it is amidation, amination or imination. The structure of the final product, in particular, the position of nitro-group in the benzofragment in most probable products is different: in the first case (*path a*) it is a seventh position (**4b**), in the second (*path b*) and third (*path c*) cases – the eighth (**4c**). The formation of a single product from the reaction of 4-hydroxythiazolidine and 4-nitro-1,2-phenylenediamine is confirmed by the identity of NMR spectra of a

crude product and the product obtained after recrystallization (it is necessary to note that recrystallization from DMSO is going with the participation of a solvate molecule).

The structures assigned to all the compounds synthesized were based on IR and NMR spectra, elemental analysis and X-Ray analysis. The ^{1}H NMR spectrum of **4b** contains the broad singlet signal from carbamoyl NH group at downfield δ 11.69, aromatic multiplets between δ 7.21 and 7.62 of six protons, as well as a doublet at δ 10.50 (*J*=2.28 Hz) and doublet of doublets at δ 8.18 (*J*=8.89, 2.28 Hz), which are characteristic of two separate protons of the benzofragment. However, only on the basis of these spectral and IR spectral data it is impossible to unambiguously distinguish between these two (**4b** and **4c**) structures, because both of them have practically the same proton-containing fragments (Chart 2).
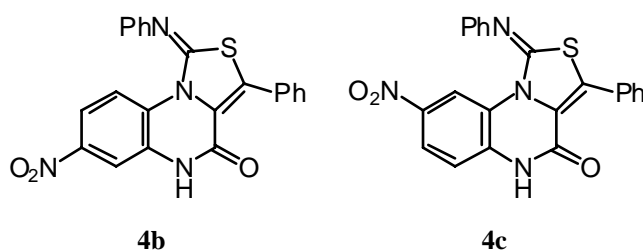

4b   **4c**

Chart 2

The fact that the studied reaction results in 4,5-dihydro-8-nitro-3-phenyl-1-phenylimino-1H-thiazolo[3,4-*a*]quinoxalin-4-one (**4c**) as a single product, and not in 7-nitro isomer (**4b**) is shown by X-Ray single crystal diffraction (Figure 1).
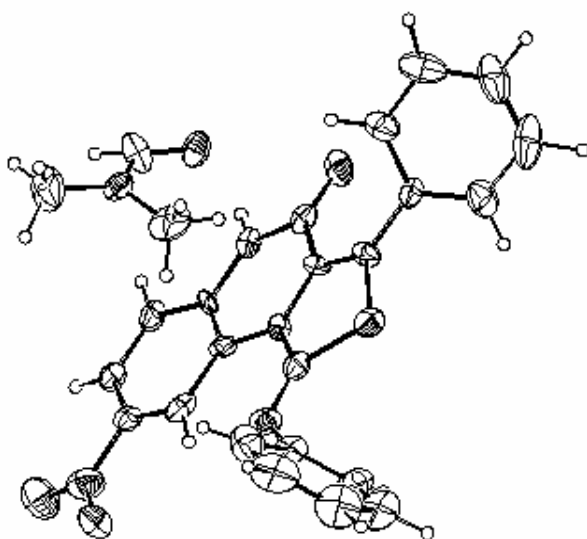
Figure 1. Geometry of the compound (**4c**) with solvate DMFA molecule in crystal.

The formation of compound (**4c**) as a single product of this reaction allows us to eliminate *path a* from the discussion. Most probable among the rest options of possible paths of formation of thiazolo[3,4-*a*]quinoxaline to our mind, is *path c* with formation of imino structure as the intermediate product, instead of amino (*path b*), which requires rather unfavorable nucleophilic substitution of hydroxy group at spatially hindered fourth carbon atom of thiazolidine cycle.

According to the above-stated reasons the structure of the single product of the reaction of 4-hydroxytetrahydrothiazole with 3,4-diaminotoluene on the basis of spectral (IR, NMR) data was established as 4,5-dihydro-7-methyl-3-phenyl-1-phenylimino-1*H*-thiazolo[3,4-*a*]quinoxalin-4-one (**4d**) (Chart 3), that was also later confirmed by X-Ray analysis.
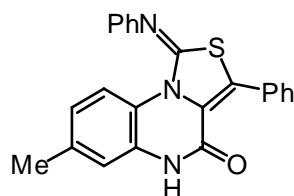

4d

Chart 3

It is necessary to note, that the reaction of 4-hydroxythiazolidines (**1b-d**), obtained from unnsymmetrically substituted thiourea, which can exist at least in four cyclic and two open-chain tautomeric forms, in contrast to 4-hydroxythiazolidine (**1a**)**,** obtained with the use of *N,N′*-diphenylthiourea, with 1,2-phenylenediamine, results in the formation of mixtures of thiazolo[3,4-*a*]quinoxalines, and the ratio of products in these mixtures is determined by the leaving ability of two various arylamino-groups in the compound of type A, formed in the last but one stage of the reaction (Scheme 4).

As it is evident from the data listed in Table 1 in two of three cases (reactions 1 and 3) aniline is the better leaving group, than tolylamine and thiazol-2-ylamine, and in the third case (the reaction 2) naphthylamine as a nucleophile successfully competes with aniline, which points out a yield of naphthylaminothiazolo[3,4-*a*]quinoxaline (**4f**), which is higher by 10%, than thiazolo[3,4-*a*]quinoxaline (**4a**) containing 1-phenylimino group.

The solubility of thiazolo[3,4-*a*]quinoxalines (**4e-g**) in various solvents differs from solubility of **4a**, containing 1-phenylimino group, which allows to separate them with the help of fractional recrystal-lization.
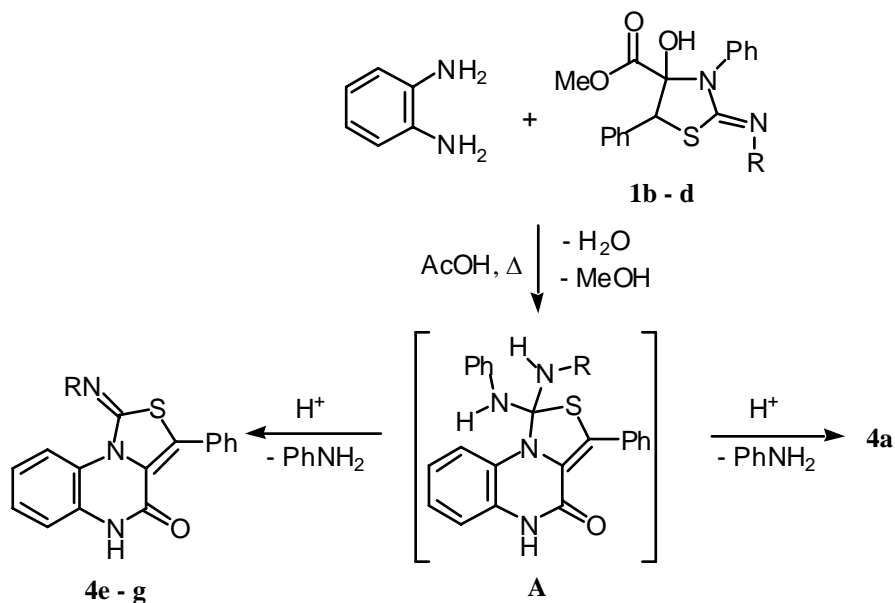
R = Tolyl (**1b**, **4e**); Naphthyl (**1c**, **4f**); Thiazol-2-yl (**1d**, **4g**)

Reaction	Ratio* of products, %	Separated yield, %
1) **1b** + PhDA	**4a**(8) **4e**(91)	**4a**(5) **4e**(86)
2) **1c** + PhDA	**4a**(34) **4f**(66)	**4a**(28) **4f**(61)
3) **1d** + PhDA	**4a**(0) **4g**(100)	**4a**(0) **4g**(96)

* Ratios of products are calculated from ^{1}H NMR spectra of crude products.

Scheme 4

The composition and structure of compounds (**4e-g**) is proved with the help of IR and ^{1}H NMR spectroscopies and of the element analysis. The characteristic feature of these compounds, as well as of compound (**4a**) is the presence of a doublet signal of a proton H9, at 9.2 ± 0.2 ppm in ^{1}H NMR spectra besides other signals.

In summary, a novel method has been developed for the preparation of thiazolo[3,4-*a*]quinoxalin-2-ones. A key step in this newly developed method involves an efficiant thiazoloquinoxaline ring system formation by reaction of 4-hydroxytetrahydrothiazoles with 1,2-phenylendiamines. The application of this new synthetic sequence to the preparation of novel biologically active compounds will be reported in due course.

EXPERIMENTAL

Melting points were determined with a Kofler hot plate apparatus and are uncorrected. IR spectra were obtained on an Infra-Red Spectrophotometer Model "UK-28" samples being run as potassium bromide pellets. The NMR spectra were measured with a Bruker MSL-400 spectrometer at 400.13 MHz for ^{1}H and 100.6 MHz for ^{13}C using tetramethylsilane as an internal standard, the chemical shifts are given in δ ppm down-field. Microanalyses were performed with an elemental analyzer.

Preparation of starting materials: The 4-hydroxytetrahydrothiazoles (**1a,b**) were prepared by the method reported in the literature.[3]

Typical procedure for preparation of 1-arylimino-3-phenyl-4,5-dihydro-2-oxo-thiazolo[3,4-*a*]quinoxalines (4a,c-g)(Table 1).

A solution of 1,2-phenylenediamine (0.54 g, 5 mmol) and 4-hydroxytetrahydrothiazole (**1a**) (2.02 g, 5 mmol) in acetic acid (20 ml) was refluxed in an oil bath for 30 minutes to precipitate yellow needles (**4a**). After cooling to rt, the yellow needles of **4a** were collected by suction filtration and then washed with isopropanol to give an analytically pure sample (3.11g). Evaporation of the filtrate in *vacuo* provided additional yellow crystals of **4a**, which were collected by suction filtration (0.39 g), total yield (3.5 g, %). Compounds (**4c**) and (**4d**) were prepared from the reaction of 4-nitro-1,2-phenylenediamine and 3,4-diaminotoluene with 4-hydroxytetrahydrothiazole. In these cases evaporation of the solvent from reaction mixture after continuously refluxing during 5 h in *vacuo* gave an oily product, which after recrystallization from dimethylformamide gave analytically pure samples as yellow needles.

The compounds (**4e**-**g**) are obtained by fractional recrystallization of mixtures formed from a reactions of 1,2-phenylenediamine with 4-hydroxytetrahydrothiazole (**2b-d**). In all these three cases the crystalline residues obtained after evaporation of a reaction mixture are boiled during the three minutes in a mixture of solvents *i*-PrOH and MeOH (1:1), then were filtered. This procedure was repeated once again with the rest crystals. The crystals, which remained after this repeated operation, were crystallized from DMSO and gave analytically pure sample of compound (**4a**). Mixed samples which with compound obtained from symmetrical *N,N'*-diphenylthiourea, did not give the reduction of melting point. Recrystallization of

the semi-crystalline mass which remained after the evaporation of alcoholic filtrate from acetic acid gives analytically pure samples of compounds (**4a**-**g**) (Table 1).

X-Ray structure determination: The X-Ray diffraction data for the crystal of **4c** were collected on a CAD4 Enraf-Nonius automatic four-circle diffractometer (graphite monochromator, MoK$_\alpha$ radiation (0.71073 Å), ω/2θ scan method, θ≤ 21.9°). Twenty five centered reflections gave a refined monoclinic unit cell of dimensions *a*= 9.602(2)*, b*= 8.781(3)*, c*= 28.069(4)Å*, β*= 92.64(1)°*, V*= 2364(1)Å^3*, Z= 4*, ρ= 1.70 (g cm^{-3}). A total of 4701 reflections were measured, of which 1216 were unique with I>3σ. The stability of crystals and of experimental conditions was checked every 2 h using three control reflections, while the orientation was monitored every 200 reflections by centering two standards. No significant decay was observed. Corrections for Lorentz and polarization effects were applied. Absorption correction was not applied (μ =1.68 cm^{-1}). The structure was solved in the uniquely assignable space group *P 2$_1$/n* by direct methods and difference Fourier synthesis using SIR[9] and MolEN[10] packages. All non-hydrogen atoms were refined anisotropically, H-atoms were located in ΔF maps and were included into structure factor calculations with fixed positional and thermal parameters. The final R values were R=0.046, R$_\omega$=0.046 for 1216 unique reflections with F^2≥3σ. All calculations were carried out on a DEC Alpha Station 200 computer, all figures were made using the program PLATON.[11] Crystallographic data (excluding structure factors) for the structures **4e**, **4c** and **4d** reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 181759 - 181761 respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Table 1. Elemental Analyses, Yields, Melting Points of 1-Arylimino-3-phenyl-4,5-dihydro-1*H*-thiazolo[3,4-*a*]quinoxalin-4-ones

Comp-ound	Yield %	Mp, °C	Molecular Formula	Found/Calcd (%)			
				C	H	N	S
4a	95	301-301.5	$C_{22}H_{15}N_3OS \cdot C_2H_6SO$	69.40	5.06	10.11	15.45
		(DMSO)		69.87	4.89	10.46	15.40
4c	89	333-334	$C_{22}H_{14}N_4O_3S \cdot C_3H_7NO$	61.61	4.31	14.36	6.58
		(DMF)		61.77	4.38	14.53	6.73
4d	86	275-277	$C_{23}H_{17}N_3OS$	72.06	4.44	10.97	8.36
		(DMF)		71.86	4.14	10.58	8.29

4e	86	257-259	$C_{23}H_{17}N_3OS$	72.06	4.44	10.97	8.36
		(DMSO)		71.87	4.16	11.12	8.19
4f	61	265-270	$C_{26}H_{17}N_3OS$	74.81	3.21	9.87	7.71
		(AcOH)		74.46	4.06	10.02	7.64
4g	96	345-345.5	$C_{19}H_{12}N_4OS_2$	60.61	3.25	14.50	17.41
		(AcOH)		60.64	3.19	14.89	17.02

Table 2. IR and NMR Spectral Data of Thiazolo[3,4-*a*]quinoxalines.

Com-pound	IR ν (cm^{-1})	^{1}H NMR (DMF-d$_7$) δ, ppm, J (Hz)
4a*	3200-2700 (NH); 1680 (C=O); 1620 (C=N)	7.0-7.46 (13H, m, 2 x C$_6$H$_5$+ H^6 + H^7 + H^8), 9.39 (1H, d, J = 7.36, H^9), 11.13 (1H, br. s, NH)
4c	3250-2600 (NH); 1680 (C=O); 1630 (C=N); 1210 (N=O)	7.21-7.62 (11H, m, 2 x C$_6$H$_5$ + H^6), 8.18 (1H, dd, J = 8.89, 2.28), 10.50 (1H, d, J = 2.28, H^9), 11.69 (1H, br. s, NH)
4d	3230-2600 (NH); 1665 (C=O); 1615 (C=N)	2.40 (3H, s, CH$_3$), 7.02-7.59 (13H, m, 2 x C$_6$H$_5$+ H^7 + H^8), 9.38 (1H, d, J = 8.88), 11.06 (1H, br.s, NH)
4e	3220-2700 (NH); 1685 (C=O); 1635 (C=N)	2.38 (3H, s, CH$_3$), 7.05-7.59 (12H, m, C$_6$H$_5$+ C$_6$H$_4$ + H^6 + H^7 + H^8), 9.371 (1H, d, J = 7.74, H^9), 11.12 (1H, br.s, NH)
4f	3250-2550 (NH); 1670 (C=O); 1625 (C=N)	7.07-7.54 (12H, m, C$_6$H$_5$ + 4H of Naphthyl + H^6 + H^7 + H^8), 7.70 (1H, d, J = 8.14, H of Naphthyl), 7.93 (1H, d, J = 7.32, H of Naphthyl), 8.09 (1H, d, J = 8.14, H of Naphthyl), 9.60 (1H, d, J = 8.13, H^9), 11.10 (1H, br.s, NH)
4g	3220-2600 (NH); 1685 (C=O); 1610 (C=N)	7.21-7.29, 7.42-o7.59 (8H, m, C$_6$H$_5$ + H^6 + H^7 + H^8), 7.31 (1H, d, J = 3.75, H^4 of thiazole), 7.61 (1H, d, J = 3.75, H^2 of thiazole), 9.66 (1H, d, J = 7.92, H^9), 11.25 (1H, br.s, NH)

*^{13}C NMR (100.6 MHz, δ/ppm, J/Hz) spectrum data for **4a** (DMSO-d$_6$); 115.61 (dd, J = 162.7; 8.0; C^6), 118.43 (bd, J = 167.6; C^7 or C^8), 121.17 (dt, J = 158.5; 7.9; C^o), 121.93 (t, J = 4.57, C^{3a}), 122.50 (bc, C^3), 122.82 (bd, J = 160.0; C^8 or C^7), 124.51 (dt, J = 164.4; 7.1; C^p), 125.46 (bs, C^i), 125.70 (dd, J = 163.2; 8.4; C^9 or C^6), 126.21 (m, C^{ia} or C^{i2}), 128.16 (d, bd, J = 159.9; 7.3; C^m), 129.07 (dt, J = 160.9; 6.3;

C^p), 130.39 (dd, J = 158.75; 8.05; C^m), 130.58 (dt, J = 161.3; 8.1; C^o), 131.42 (c, C^{i2} or C^{i1}), 151.25 (t, J = 8.4; C^N), 153.25 (c, C=O), 154.60 (c, C=N).

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