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Synthetic Studies toward Aryl-(4-aryl-4*H*-[1,2,4]triazole-3-yl)-amine from 1,3-Diarylthiourea as Urea Mimetics

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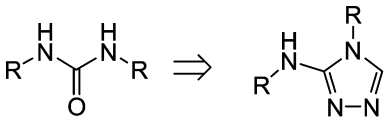

A thiophile-promoted synthesis of disubstituted 4*H*-[1,2,4]triazole-3-yl-amines as urea mimetics from the corresponding 1,3-disubstituted thioureas has been studied, and the scope and limitations of this reaction are presented. The reaction proceeds through the formation of a carbodiimide, followed by a sequential addition−dehydration with acyl hydrazides. 1,3-Branched dialkylthioureas result in the formation of the corresponding ureas. The electronic and steric effects of the substitution on the phenyl rings of the 1,3-diarylthioureas play an important role in the formation of the intermediary carbodiimde and the direction of the subsequent ring closure of the *N*-acyl hydrazide adduct.

Introduction

Several compounds that belong to the class of 1,3-disubstituted ureas are being developed as drug candidates against a variety of diseases. For example, the Raf-1 inhibitor BAY 43-9006 is developed for cancer and inflammatory disorders,[1] and the cyclic urea Mozenavir is studied for HIV.[2] 1,3-Diarylurea is frequently encountered as a privileged structure for many biological targets.[3] They constitute an essential part of pharmacophores for biological targets such as p38 and raf kinases,[4,6] vascular endothelial growth receptor 2 (VRGFR-2),[5] inosine monophosphate dehydrogenase (IMPDH),[6] highly potent and selective human A_{2B} adenosine receptor antagonists,[7] and cyclin-dependent kinase 2 (CDK2) inhibitors.[8] The mode of interaction of different 1,3-diarylureas with their targets varies. For example, while some of these urea-based inhibitors bind to an allosteric site causing a significant rearrangement of the target protein structure,[9,10] others bind to the active site such as the ATP pocket with the urea function participating in a bidentate hydrogen bond.[11]

Bioisosteric replacements of the amide and thioamide functions included heterocyclic systems such as the [1,2,4]- and [1,3,4]oxadiazoles and [1,2,4]triazoles.[12] Such

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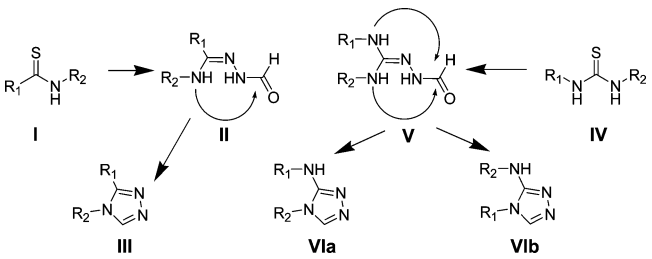

FIGURE 1. [1,2,4]Triazoles as amide mimics and 4*H*-[1,2,4]-triazol-3-yl-amine as urea mimics.

replacements led to [1,2,4]triazoles which were active antimycobacterials[13] and potent, selective 5-HT_{1D} receptor agonists.[14] Another interesting application of triazole was to employ it as a *cis*-amide bond surrogate.[15] Replacement of the Ala-NMe-Tyr(OMe) amide bond in RA-VII, a plant-origin antitumor bicyclic hexapeptide, with [1,2,4]triazole yielded the pseudopeptide.[16] As anticipated, the pseudopeptide reproduced the conformation of the minor *cis*-peptide isomer but was devoid of cytotoxic activity. Interestingly, replacement of urea function in β_3-adrenergic receptor agonists with triazole resulted in improved oral bioavailability accompanied by retention of potency, selectivity, and in vivo efficacy.[17] Replacement of the amide bond in Phe-Gly in substance P with a [1,2,4]-triazole peptide bond surrogate led to dramatic loss of affinity to the NK_1 receptor.[18] On the other hand, introduction of the same modification to dermorphin led to potent and selective pseudopeptides toward the μ-receptor subtype.[18] We anticipate that replacement of the amide/thioamide bond in the urea/thiourea with heterocyclic bioiosteric moieties such as the triazoles may increase the structural diversity and generate novel and interesting bioactive compounds of therapeutic potential.

In an effort to increase structural diversity and modify the degrees of conformational freedom of the 1,3-disubstituted moieties in the urea/thiourea, we introduced a bioisosterism used to mimic the amide/thioamide function and developed a synthetic transformation of 1,3-disubstituted thioureas to the corresponding alkyl-(4-aryl/alkyl-4*H*-[1,2,4]triazol-3-yl)-amine (Figure 1). Transformation of an amide to a thioamide using Lawesson's reagent can be applied to convert the ureas to the corresponding thioureas,[19] thus generating the starting material for the synthesis of [1,2,4]triazole. In addition, thioureas can be generated directly by the addition of amines to isothiocyanates.

Katritzky and co-workers reported on a solid-phase method to prepare [1,2,4]triazoles from acyl hydrazide resins and amidines in the presence of molecular sieves.[20] Larsen and DiPaolo converted *N*-resin-bound thioamides to amidrazones, which were then acylated by acyl halides and cyclized in the presence of acetic acid at room temperature to the triazoles of interest.[21] An efficient one-pot, three-component synthesis of substituted [1,2,4]-triazoles was reported by Stocks and co-workers.[22] Reaction of an amine with *N*′-acetyl-*N*,*N*-dimethylhydrazonoformamide and acyl hydrazides led to moderate yields when aromatic amines were employed.

We chose to employ a method used to transform the thioamide function in a thionopeptide into a [1,2,4]-triazole as a cis-amide bond surrogate by treating the thionopeptide with formic hydrazide and mercury(II) acetate as a thiophile.[15] This reaction proceeds through the formation of acyl hydrazide adduct which is cyclized to the corresponding [1,2,4]triazole under acidic conditions.

However, the problem in extending this methodology for the thiourea lies in the regioselectivity of the cyclization (Figure 1). Unlike the unidirectional cyclization of intermediary acylamidrazone (**II**) generated from the thioamides (**I**), which yields a single [1,2,4]triazole (**III**), the intermediary acylureidrazone (**V**) generated from the thiourea (**IV**) can in principle cyclize in either direction, yielding two isomeric [1,2,4]triazoles (**VIa** and **VIb**) (Figure 1). Herein we report a general method used to generate substituted [1,2,4]triazol-3-yl-amines as amide bond mimetics of corresponding ureas. Additionally, we observe interesting steric and electronic effects of the 1,3-substitutents on the thiourea that play an important role on the product distribution and regioselectivity of the cyclization.

Results and Discussion

The 1,3-disubstituted thioureas were either commercially available or were generated in good yields by the reaction of the amine with the corresponding isothiocyanate in either dichloromethane or acetonitrile. The objective was to select reagents and optimize various reaction conditions to develop a general method that can be used to generate regioselective [1,2,4]triazol-3-yl-amines as amide bond mimics of 1,3-disubstituted urea compounds. Mercury salts[23] and Mukaiyama reagent[24] have been used as thiophiles in the guanylation of amines by thioureas. Our initial objective was to identify a suitable thiophile to carry out this reaction in one-pot without isolation of intermediates. We chose to compare a variety of mercury(II) salts and the Mukaiyama reagent as our thiophile (Table 1) and monitored the formation of phenyl-(4-phenyl-4*H*-[1,2,4]triazol-3-yl)-amine (**2**) by LC−MS in a model reaction using the 1,3-diphenylthiourea **1**. On the basis of the product yield it was clear that

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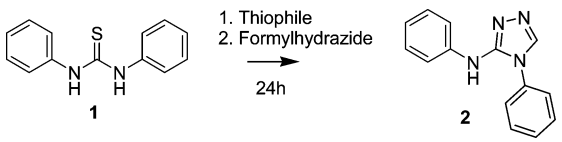
TABLE 1. Reaction of 1,3-Diphenylthiourea 1 and Formylhydrazide To Generate Phenyl-(4-phenyl-4*H*-[1,2,4]triazol-3-yl)-amine 2 Mediated by a Thiophile



	thiophile	% yield
a	$Hg(OAc)_2$	75
b	$Hg(OCOCF_3)_2$	10
c	$HgCl_2$	6
d	$HgBr_2$	11
e	HgI_2	6
f	$HgSO_4$	22
g	Mukaiyama reagent	25

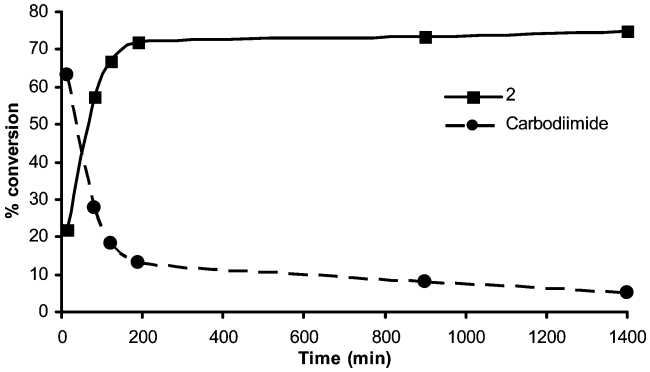


FIGURE 2. Time course for the conversion of 1,3-diphenylthiourea (**1**) to phenyl-(4-phenyl-4*H*-[1,2,4]triazol-3-yl)-amine (**2**).

$Hg(OAc)_2$ was the optimal thiophile for this model reaction, and hence we decided to use $Hg(OAc)_2$ for all subsequent reactions as the thiophile. We then turned our attention to investigate the time course for this reaction, employing equimolar amounts of **1** and formylhydrazide. In about 15 min from the start of the reaction, ~65% of the 1,3-diphenylthiourea was converted to the 1,3-diphenylcarbodiimide, which was isolated and characterized (Figure 2). Therefore, we followed the course of this reaction by monitoring the disappearance of the carbodiimide and the formation of **2** by LC−MS. We observed that in about 2 h the reaction resulted in ~70% of **2** and there was not much improvement in the product yield for the next 22 h. Hence, we decided to use 2 h as optimal time of incubation for further studies. By using 2.5 equiv of the formylhydrazide in the above reaction, we were able to increase the yield of the isolated product to 91%.

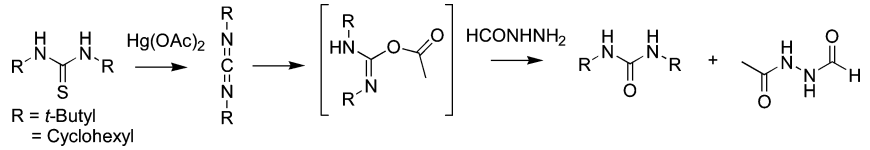
Since the [1,2,4]triazole formation is an addition−dehydration reaction, we hypothesized that the substituents on the thiourea nitrogens would play an important role in the rate of addition and the regioselectivity of ring closure. To study the substituent effect on the formation of the [1,2,4]triazole, a series of symmetrical 1,3-disubstituted thioureas were generated. A one-pot reaction was carried out with the 1,3-disubstituted thiourea, $Hg(OAc)_2$, and an acylhydrazine (1:1.05:0.95 equiv) mixed together at room temperature and incubated for 2 h. It is interesting to note that the major product from the reaction in the case of the 1,3-dialkyl substitutions viz., *tert*-butyl, cyclohexyl, and *n*-propyl thioureas (**3d**−**f**, Table 2) was the corresponding 1,3-dialkylurea. This is because the acetate, released from the thiophile $Hg(OAc)_2$ in the course of desulfurization, reacts with the intermediary 1,3-dialkylcarbodiimide faster than the addition of acylhydrazide to yield the 2-acetyl-1,3-dialkyl-isourea (Scheme 1). By using the Mukaiyama reagent (*N*-methyl 2-chloropyridinium iodide) as the thiophile and 1,3-dicylcohexylthiourea, we were able to get ~15% of the [1,2,4]triazole; longer incubation times, however, did not improve the yields. The desulfurization of the substituted 1,3-diphenylthioureas to form the corresponding carbodiimides was visually monitored based on the formation of the HgS black precipitate. HgS formation was the fastest in the thioureas in which phenyl rings substituted with electron-withdrawing groups and the slowest in those where phenyl rings were substituted with electron-donating groups. The data in Table 2 also suggest that 1,3-diphenylthioureas substituted with electron-withdrawing groups on the aromatic rings generate lower yields of [1,2,4]triazole compared to the electron-rich ring systems (cf. **3a**−**c**, Table 2). In the 4-Cl- and 3,5-di-CF_3-disubstituted phenylthioureas, a significant amount of a high molecular weight product composed of two units of carbodiimide and one unit of fromylhydrazide was observed by LC−MS. This product is generated by the addition of a second carbodiimide to the intermediary *N*-acyl hydrazide (**V**) prior to the ring closure. This pattern could be explained if the carbodiimides generated with electron-withdrawing groups on the phenyl rings are much more reactive toward the formylhydrazide compared to the one with electron-donating group on the phenyl rings; in addition these are slower to cyclize (cf. **3b** and **3c** with **3a**, Table 2). The stereoelectronic effects of the acyl group on the acylhydrazine affect the yields of the [1,2,4]triazole (**3g**−**i**, Table 2). A similar pattern is observed in the [1,2,4]triazole yields (**4g**, **4j**, and **4k**, Table 2) generated using acetylhydrazide with varying substitutions. The acid-catalyzed dehydration to generate the corresponding [1,2,4]triazole **4h** (Table 2) could be pushed to ~75% completion with a stronger acid (*p*-TsOH) and higher temperature (reflux).

To address the substituent effects on the regioselectivity of ring closure generating the [1,2,4]triazoles, we studied thioureas in which both nitrogens were differentially substituted. The corresponding [1,2,4]triazoles

TABLE 2. Substituent Effect on the Formation of [1,2,4]Triazoles from Symmetrical Thioureas

	R_1	R_2	% yield
a	4-OMe-phenyl	H	89
b	4-Cl-phenyl	H	74
c	3,5-di-CF_3-phenyl	H	36
d	*tert*-butyl	H	urea
e	cyclohexyl	H	urea
f	*n*-propyl	H	urea
g	phenyl	Me	68
h	phenyl	phenyl	12
i	phenyl	H	73
j	4-OMe-phenyl	Me	77
k	3,5-di-CF_3-phenyl	Me	60

SCHEME 1. Formation of 1,3-Dilakylurea through the 1,3-Dialkyl *O*-Acetylisourea Intermediate Formed from a 1,3-Dialkylthiourea



SCHEME 2. *N*-Benzyl Protection−Deprotection Strategy To Access Regioselective [1,2,4]Triazoles

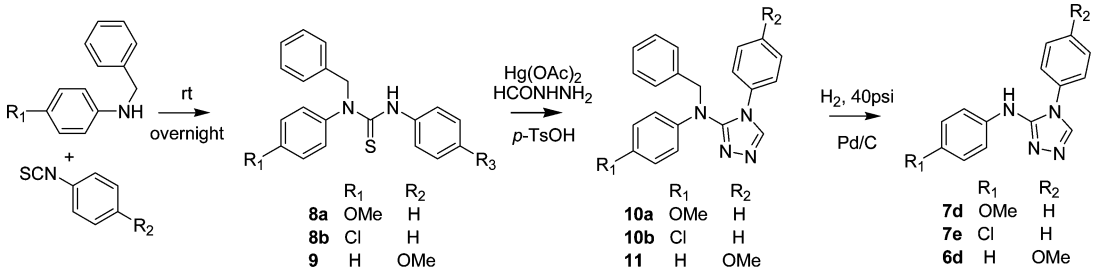
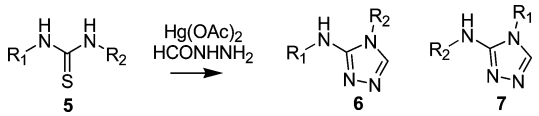


TABLE 3. Substituent Effect on the Direction of Ring Closure To Yield the [1,2,4]Triazoles Generated from Unsymmetrical 1,3-Disubstituted Thioureas (General Procedure II)[a]



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	R_1	R_2	% yield
a	cyclohexyl	phenyl	urea
b	cyclohexyl	4-OMe-phenyl	75 (**6b**)
c	3,5-di-CF_3-phenyl	cyclohexyl	44 (**6c**)
d	phenyl	4-OMe-phenyl	76 (1:5)
e	phenyl	4-Cl-phenyl	70 (2:3)
f	3,5-di-CF_3-phenyl	phenyl	84 (**6f**)
g	3,5-di-CF_3-phenyl	4-OMe-phenyl	77
h	3,5-di-CF_3-phenyl	*p*-tolyl	55
i	3,5-di-CF_3-phenyl	*o*-tolyl	50
j	3,5-di-CF_3-phenyl	2-*i*-propyl-phenyl	45
k	3,5-di-CF_3-phenyl	2-*tert*-butyl-phenyl	8

[a] Reaction times **a** − **c** = 48 h and **d** − **k** = 2 h.

were generated using the optimized procedure [1,3-disubstituted thiourea, $Hg(OAc)_2$, and an acylhydrazine (1:1.05:0.95 equiv) mixed together and incubated at room temperature], the results of which are summarized in Table 3. In the 1-cyclohexyl-3-arylthiourea (**5a**−**c**, Table 3) series, the electronic density and distribution on the phenyl ring were modified by substituting it with either an electron-donating group (**5b**, Table 3) or electron-withdrawing group (**5c**, Table 3). By LC−MS we observed a significant amount of the carbodiimide and the intermediate that results from the addition of formyl hydrazide to the carbodiimide. These reactions were allowed to proceed for 48 h at room temperature. The 1-cyclohexyl-3-phenylthiourea (**5a**, Table 3) yields the urea as a major product, while the aryl-substituted 1-cyclohexy-3-arylthioureas (**5b** and **5c**, Table 3) yield the desired products in good to moderate yields. These observations do not follow an obvious trend, and at present we can only speculate that the kinetics of the intermediate reactions might play an important role in the product ([1,2,4]triazole) formation. The reaction tolerates electron-withdrawing groups (**5e** and **5f**, Table 3), electron-donating groups (**5d** and **5h**, Table 3), and a combination of the two (**5g** Table 3), resulting in good yields of the corresponding [1,2,4]triazole. A strong electron-withdrawing group on the phenyl ring such as *m*,*m*′-di-CF_3 (**f**, Table 3) yields a regioselective product; however, with *p*-OMe and *p*-Cl substituents (**d** and **e**, Table 3) we obtain a mixture of regioisomers. In the case of a reaction wherein we get a mixture of the two regioisomers, the ratio and regioselectivity were confirmed by synthesizing exclusively a single regioisomer using a benzyl protection−deprotection strategy. In entry **5d** of Table 3 the [1,2,4]triazoles obtained were a 1:5 mixture of regioisomers **6d** and **7d**. The individual regioisomers were synthesized starting from the corresponding 1-benzyl-1,3-diphenylthioureas summarized in Scheme 2. The assignments of **6d** and **7d** were made on the basis of chemical shifts in the NMR spectra and retention times on the LC.

On the basis of ^1H and ^{13}C NMR and LC−MS, all the other unsymmetrical 1,3-disubstituted thioureas in Table 3 resulted in an overwhelming excess of single regioisomer of [1,2,4]triazole (>95:5). The regiochemistry of the compounds was assigned on the basis of the diagnostic NOESY peak. For example, Figure 3 shows the NOESY spectrum of compound **6g** displaying cross-peaks between H_b and H_c and the lack of cross-peaks between H_c and H_d (see Supporting Information for TOCSY and NOESY data for **6c**, **6f**, and **6g**).

From the symmetrical 1,3-disubstituted urea series we know that *N*-3,5-bis-trifluoromethylphenyl-substituted thioureas undergo rapid formation of the carbodiimide intermediate, thereby making the addition−dehydration the rate-limiting steps. Also, *N*-1,3-bis-substituted thioureas that have the 3,5-ditrifluoromethylphenyl substituent yield regioselective products (see **5f**−**k**, Table 3). To investigate the steric effects of substituents on the rate of the addition−dehydration reaction, we synthesized a series of mixed 1,3-disubstituted thioureas which maintain 3,5-bis-trifluoromethylphenyl on one nitrogen and a phenyl substituted with varying steric bulk on the other (**5h**−**k**, Table 3). The yields of the reactions with *N*-*p*-tolyl- and *N*-*o*-tolyl-substituted thioureas (**5h** and **5i**, Table 3) are almost equivalent. However, the 1-*p*-tolyl-3-(3,5-bis-CF_3-phenyl)thiourea (**5h**) yielded a high molecular weight compound that corresponds to the addition of two carbodiimides to one formyl hydrazide as the minor

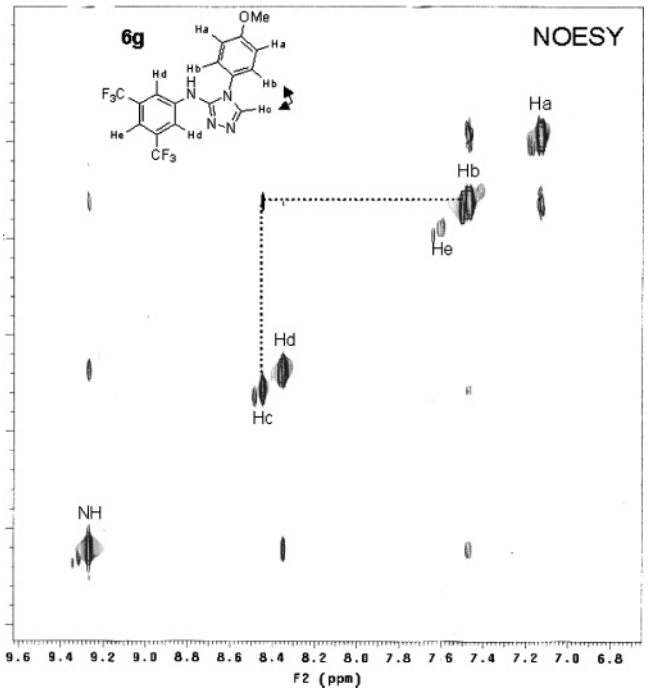

FIGURE 3. NOESY spectrum showing the diagnostic peak confirming the direction of the regioselective ring closure to yield [1,2,4]triazole **6g**.

product, while the 1-*o*-tolyl-3-(3,5-di-CF_3-phenyl)thiourea (**5i**) gave the intermediate generated by the addition of formyl hydrazide to carbodiimide as the minor product. The reactions were monitored by LC−MS, and ratios of the major to minor products were 5:1 for **h** (*N*-*p*-tolyl substitution) and 6:1 for **i** (*N*-*o*-tolyl substitution). On the basis of the product distribution, the steric hindrance in *N*-*o*-tolyl-3-(3,5-di-CF_3-phenyl)thiourea (**5i**) prevents the addition of second carbodiimde. Similar to **5i**, the steric-hindered ring closure is also compromised in the *N*-*i*-propyl (**5j**) and remarkably inhibited in the *N*-*tert*-butyl-3-(3,5-di-CF_3-phenyl)thiourea (**5k**) as shown by the lower yields of the [1,2,4]triazoles (45 and 8%, respectively) obtained under similar reaction conditions. Extending the reactions overnight, we found that these ortho-substituted phenylthiourea reactions proceed to give isolated yields of ∼70−75% of the corresponding [1,2,4]triazoles.

It is clear from the studies of the series of 1,3-disubstituted thioureas that the reaction can be fine-tuned to yield regioselective 1,3-disubstituted [1,2,4]-triazoles by modifying the substituents on the nitrogens of the thiourea. At least for the compounds described, the rate-limiting step in this reaction is the addition−dehydration step. The ring closure preferentially occurs on the nitrogen that has the electron-donating substituents. In the case where the difference between the two N-substituents is not significant leading to the formation of a mixture of regioisomeric [1,2,4]triazoles, a protection−deprotection strategy employing a benzyl group as a transient protecting group can be considered to generate the regioisomeric [1,2,4]triazole of choice. In summary, we described a new synthesis of useful 1,3-disubstituted triazoles as amide bond mimetics of urea compounds. Furthermore, the central [1,2,4]triazol-3-yl-amine scaffold under optimized conditions can be used to generate a library with four points of diversity, which is currently underway in our laboratories and will be reported in due course.

Experimental Section

Unless otherwise specified, all reagents were purchased from commercial sources and were used without further purification. Flash chromatography was carried out on silica gel (200−400 mesh). Melting points were recorded on an electrothermal melting point apparatus and are uncorrected. Mass spectra were obtained from a single quad instrument with APCI source. 1D and 2D NMR spectra were collected using standard pulse sequences.

***N*-Phenyl-(4-phenyl-4*H*-[1,2,4]triazol-3-yl)-amine (2):** (Following general procedure II) 72%, colorless solid: mp 214−216 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.50 (bs, 1H), 8.47 (s, 1H), 7.57−7.53 (m, 2H), 7.51−7.46 (m, 3H), 7.40 (d, 2H, J = 8 Hz), 7.20 (t, 2H, J = 8 Hz), 6.83 (t, 1H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 150.6, 142.6, 142.1, 134.0, 130.5, 129.4, 129.3, 126.0, 120.9, 117.3; MS$^+$(APCI) 236.9 [M + H]$^+$; Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 70.95; H, 4.89; N, 23.77.

1,3-Di-(4-methoxy-phenyl)thiourea (3a): 98%, colorless solid: mp 201−203 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.42 (s, 2H), 7.29 (d, J = 8.8 Hz, 4H), 6.87 (d, J = 8.8 Hz, 4H), 3.72 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 181.1, 157.2, 132.9, 126.8, 114.3, 55.9; MS$^+$(APCI) 288.84 [M + H]$^+$.

1,3-Bis-(3,5-bis-trifluoromethyl-phenyl)thiourea (3c): 71%, colorless solid: mp 180−181 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.65 (s, 2H), 8.19 (s, 4H), 7.85 (s, 2H); MS$^+$(APCI) 499.99 [M + H]$^+$.

(4-Methoxy-phenyl)-[4-(4-methoxy-phenyl)-4*H*-[1,2,4]-triazol-3-yl]-amine (4a): 89%, colorless solid: mp 183−184 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.29 (s, 1H), 8.13 (s, 1H), 7.43−7.39 (m, 4H), 7.09 (dd, J = 6.8, 2.0 Hz, 2H), 6.79 (dd, J = 6.8, 2.0 Hz, 2H), 3.80 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.4,153.4, 150.9, 141.1, 134.9, 127.3, 125.9, 118.4, 114.9, 113.8, 55.5, 55.2; MS$^+$(ESI) 296.30 [M + H]$^+$.

(4-Chloro-phenyl)-[4-(4-chloro-phenyl)-4*H*-[1,2,4]triazol-3-yl]-amine (4b): 74%, colorless solid: mp 226−228 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.74 (s, 1H), 8.48 (s, 1H), 7.61 (dd, J = 40.5, 9.0 Hz, 2H), 7.41 (dd, J = 125.0, 9.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 149.7, 141.2, 140.5, 133.5, 132.0, 129.8, 128.4, 127.6, 123.9, 118.3; MS$^+$(ESI) 305.5 [M + H]$^+$.

(3,5-Bis-trifluoromethyl-phenyl)-[4-(3,5-bis-trifluoromethyl-phenyl)-4*H*-[1,2,4]triazol-3-yl]-amine (4c): 36%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.49 (bs, 1H), 8.65 (s, 1H), 8.44 (s, 2H), 8.35 (s, 1H), 8.18 (s, 2H), 7.53 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 149.9,143.6, 142.2, 135.3, 132.5, 132.2, 131.6, 131.3, 128.8, 125.4, 124.8, 123.9, 122.7, 122.1, 117.3, 113.7; MS$^+$(APCI) 508.93 [M + H]$^+$.

(5-Methyl-4-phenyl-4*H*-[1,2,4]triazol-3-yl)-phenyl-amine (4g): 68%, colorless solid: mp 236−238 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.14 (s, 1H), 7.58−7.50 (m, 3H), 7.44−7.36 (m, 4H), 7.18−7.13 (m, 2H), 6.81−6.77 (m, 1H), 2.10 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 151.3, 148.3, 142.7, 133.8, 130.6, 130.0, 129.2, 128.3, 120.6, 117.1, 11.9; MS$^+$(APCI) 251.01 [M + H]$^+$; Anal. Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.78; H, 5.47; N, 22.41.

(4,5-Diphenyl-4*H*-[1,2,4]triazol-3-yl)-phenyl-amine (4h): 12%, colorless solid: mp 201−202 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.36 (s, 1H), 7.54−7.49 (m, 5H), 7.44−7.42 (m, 2H), 7.35−7.33 (m, 1H), 7.33−7.31 (m, 4H), 7.23 (t, J = 7.2 Hz, 2H), 6.89 (t, J = 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 152.5, 150.6, 141.8, 133.8, 130.7, 130.6, 130.1, 129.4, 129.2, 129.1, 128.5, 127.7, 121.7, 118.3; MS$^+$(APCI) 313.12 [M + H]$^+$.

***N*-Phenyl-(4-phenyl-4*H*-[1,2,4]triazol-3-yl)-amine (4i):** (Following general procedure II) 73%. Compound **4i** is identical to **2**, which is fully characterized.

(4,5-Diphenyl-4*H*-[1,2,4]triazol-3-yl)-phenyl-amine (4k): 60%, colorless solid; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.56 (s, 1H), 9.06 (s, 1H), 8.34 (s, 2H), 8.27 (s, 1H), 8.07 (s, 2H), 7.38 (s, 1H), 1.71 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 167.9, 149.6, 147.8, 142.9, 134.6, 132.1, 131.8, 130.8, 130.6, 129.8, 124.5, 123.9, 122.3, 121.7, 116.4, 112.8, 10.9; MS$^+$(APCI) 523.13 [M + H]$^+$.

1-Cyclohexyl-3-phenylthiourea (5a):[23] 80%, colorless solid: mp 144−145 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.29 (bs, 1H), 9.31 (s, 1H), 7.61 (s, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 7.2 Hz, 2H), 7.05 (t, J = 7.6 Hz, 1H), 4.07 (s, 1H), 1.89−1.87 (m, 2H), 1.68−1.64 (m, 2H), 1.56−1.52 (m, 1H), 1.32−1.11 (m, 5H); MS$^+$(APCI) 235.23 [M + H]$^+$.

1-Cyclohexyl-3-(4-methoxy-phenyl)thiourea (5b):[23] 84%, colorless solid: mp 138−139 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.12 (bs, 1H), 7.36 (s, 1H), 7.24 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.2 Hz, 2H), 4.04 (s, 1H), 3.72 (s, 3H), 1.86−1.82 (m, 2H), 1.70−1.66 (m, 2H), 1.54−1.52 (m, 1H), 1.30−1.09 (m, 5H); MS$^+$-(APCI) 264.89 [M + H]$^+$.

1-(3,5-Bis-trifluoromethyl-phenyl)-3-cyclohexylthiourea (5c):[25] 86%, colorless solid: mp 164−165 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 8.21 (s, 2H), 8.14 (s, 1H), 7.70 (s, 1H), 4.09 (bs, 1H), 1.91−1.87 (m, 2H), 1.69−1.66 (m, 2H), 1.57−1.54 (m, 1H), 1.34−1.14 (m, 5H); MS$^+$(APCI) 371.00 [M + H]$^+$.

1-(4-Methoxy-phenyl)-3-phenylthiourea (5d):[26] 65%, colorless solid: mp 159−161 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.61 (s, 1H), 9.59 (s, 1H), 7.46−7.43 (m, 2H), 7.32−7.27 (m, 4H), 7.10 (dt, J = 8, 1.2 Hz, 1H), 6.88 (dd, J = 8, 1.2 Hz, 2H), 3.76 (s, 3H); MS$^+$(APCI) 258.97 [M + H]$^+$.

1-(3,5-Bis-trifluoromethyl-phenyl)-3-phenylthiourea (5f): 86%, colorless solid: mp 141−143 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.29 (s, 1H), 10.20 (s, 1H), 8.23 (s, 2H), 7.79 (s, 1H), 7.43−7.34 (m, 4H), 7.17 (t, J = 7.2 Hz, 1H); MS$^+$(APCI) 364.90 [M + H]$^+$.

1-(3,5-Bis-trifluoromethyl-phenyl)-3-(4-methoxy-phenyl)thiourea (5g): 91%, colorless solid: mp 148−150 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.12 (s, 1H), 10.01 (s, 1H), 8.23 (s, 2H), 7.76 (s, 1H), 7.11 (dd, J = 144.0, 8.8 Hz, 4H), 3.73 (s, 3H); MS$^+$(APCI) 394.89 [M + H]$^+$.

1-(3,5-Bis-trifluoromethyl-phenyl)-3-*p*-tolyl-thiourea (5h): 64%, colorless solid: mp 153−154 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.22 (s, 1H), 10.10 (s, 1H), 8.23 (s, 2H), 7.76 (s, 1H), 7.22 (dd, J = 48.8, 8.0 Hz, 4H), 3.30 (s, 3H); MS$^+$(APCI) 378.89 [M + H]$^+$.

1-(3,5-Bis-trifluoromethyl-phenyl)-3-*o*-tolyl-thiourea (5i): 83%, colorless solid: mp 153−154 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.05 (s, 1H), 9.88 (s, 1H), 8.25 (s, 2H), 7.76 (s, 1H), 7.28−7.17 (m, 4H), 3.33 (s, 3H); MS$^+$(APCI) 378.92 [M + H]$^+$.

1-(3,5-Bis-trifluoromethyl-phenyl)-3-(2-isopropyl-phenyl)thiourea (5j): 82%, colorless solid: mp 148−150 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.29 (bs, 1H), 9.87 (s, 1H), 8.26 (s, 2H), 7.77 (s, 1H), 7.37−7.20 (m, 4H), 3.09 (septa, J = 7.2 Hz, 3H), 1.15 (d, J = 7.2 Hz, 6H); MS$^+$(APCI) 406.93 [M + H]$^+$.

1-(3,5-Bis-trifluoromethyl-phenyl)-3-(2-*tert*-butyl-phenyl)thiourea (5k): 65%, colorless solid: mp 137−138 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.89 (bs, 1H), 9.75 (bs, 1H), 8.30 (s, 2H), 7.77 (s, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.31−7.23 (m, 2H), 7.18 (d, J = 7.2 Hz, 1H), 1.26 (s, 9H); MS$^+$(APCI) 420.94 [M + H]$^+$.

(4-Cyclohexyl-4*H*-[1,2,4]triazol-3-yl)-(4-methoxy-phenyl)-amine (6b): 75%, colorless solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.08 (s, 1H), 7.02 (dd, J = 138.3, 9.0 Hz, 4H), 5.94 (d, J = 8.4), 3.44−3.33 (m, 1H), 1.82−1.76 (m, 2H), 1.66−1.63 (m, 2H), 1.54−1.51 (m, 1H), 1.33−1.25 (m, 2H), 1.20−1.10 (m, 3H); MS$^+$(APCI) 272.98 [M + H]$^+$.

(3,5-Bis-trifluoromethyl-phenyl)-(4-cyclohexyl-4*H*-[1,2,4]-triazol-3-yl)-amine (6c): 44%, colorless solid; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.35 (s, 1H), 8.48 (s, 1H), 8.35 (s, 2H), 7.54 (s, 1H), 4.12 (tt, J = 4.0, 11.5 Hz, 1H), 1.98−1.96 (m, 2H), 1.86−1.83 (m, 2H), 1.71−1.61 (m, 3H), 1.45−1.37 (m, 2H), 7.20 (tq, J = 4.0, 13.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 148.7, 143.2, 138.8, 130.9, 130.8, 130.6, 130.5, 126.7, 124.5, 122.37, 120.1, 116.2, 112.5, 52.5, 32.8, 25.1, 24.5; MS$^+$(APCI) 378.95 [M + H]$^+$; Anal. Calcd for $C_{16}H_{16}N_4F_6$: C, 50.80; H, 4.26; N, 14.81. Found: C, 50.89; H, 4.43; N, 15.00.

(4-Methoxy-phenyl)-(4-phenyl-4H-[1,2,4]triazol-3-yl)-amine (6d): 63%, pale yellow oil; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.77 (s, 1H), 7.65−7.60 (m, 6H), 7.15 (dd, J = 170, 8.8 Hz, 4H), 3.74 (s, 3H); MS$^+$(APCI) 267.03 [M + H]$^+$.

[4-(4-Methoxy-phenyl)-4*H*-[1,2,4]triazol-3-yl]-phenyl-amine (7d): 56%, colorless solid; mp 211−212 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.37 (s, 1H), 8.36 (bs, 1H), 7.44−7.39 (m, 4H), 7.20 (t, J = 12 Hz, 2H), 7.11−7.07 (m, 2H), 6.83 (t, J = 12 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.4, 150.3, 141.8, 141.5, 128.6, 127.1, 125.9, 120.2, 116.6, 114.9, 55.5; MS$^+$(APCI) 267.03 [M + H]$^+$.

[4-(4-Chloro-phenyl)-4*H*-[1,2,4]triazol-3-yl]-phenyl-amine (7e): 20%, colorless oil; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.68 (s, 1H), 8.49 (s, 1H), 7.59−7.56 (m, 2H), 7.52−7.49 (m, 5H), 7.26 (d, J = 8.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 158.9, 149.7, 141.5, 140.7, 133.1, 129.9, 128.9, 128.4, 125.4, 123.8, 118.3; MS$^+$(APCI) 271.4 [M + H]$^+$; Anal. Calcd for $C_{14}H_{11}ClN_4$: C, 62.11; H, 4.10; N, 20.70. Found: C, 61.68; H, 3.86; N, 20.33.

(3,5-Bis-trifluoromethyl-phenyl)-(4-phenyl-4*H*-[1,2,4]-triazol-3-yl)-amine (6f): 84%, colorless solid; mp 191−192 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.40 (s, 1H), 8.54 (s, 1H), 8.31 (s, 2H), 7.62−7.53 (m, 5H), 7.50 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 149.2, 143.1, 141.7, 132.7, 131.2, 130.8, 130.5, 130.2, 129.9, 129.3, 127.5, 126.0, 124.8, 122.1, 119.4, 116.6, 112.7; MS$^+$(APCI) 372.93 [M + H]$^+$ Anal. Calcd for $C_{16}H_{10}F_6N_4$: C, 51.62; H, 2.71; N, 15.05. Found: C, 51.57; H, 2.60; N, 14.93.

(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-methoxy-phenyl)-4*H*-[1,2,4]triazol-3-yl]-amine (6g): 77%, colorless solid; mp 212−213 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.27 (s, 1H), 8.45 (s, 1H), 8.35 (s, 2H), 7.51 (s, 1H), 7.47 (dd, J = 9.2, 2.8 Hz, 2H), 7.13 (dd, J = 9.2, 2.8 Hz, 2H), 3.82 (s, 3H); MS$^+$(APCI) 403.02 [M + H]$^+$; Anal. Calcd for $C_{14}H_{12}N_4 \cdot 0.5CH_3OH$: C, 50.25; H, 3.37; N, 13.39. Found: C, 50.49; H, 3.56; N, 13.57.

(3,5-Bis-trifluoromethyl-phenyl)-(4-*p*-tolyl-4*H*-[1,2,4]-triazol-3-yl)-amine (6h): 55%, colorless solid; mp 230−231 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.33 (s, 1H), 8.48 (s, 1H), 8.32 (s, 2H), 7.51 (s, 1H), 7.41 (dd, J = 13.6, 8 Hz, 4H), 2.39 (s, 3H); MS$^+$(APCI) 386.85 [M + H]$^+$; Anal. Calcd for $C_{17}H_{12}F_6N_4$: C, 52.86; H, 3.13; N, 14.50. Found: C, 52.62; H, 3.07; N, 14.32.

(3,5-Bis-trifluoromethyl-phenyl)-(4-*o*-tolyl-4*H*-[1,2,4]-triazol-3-yl)-amine (6i): 50%, colorless solid; mp 239−240 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.26 (s, 1H), 8.43 (s, 1H), 8.40 (s, 2H) 7.51 (s, 1H), 7.49−7.41 (m, 4H), 2.05 (s, 3H); MS$^+$(APCI) 386.97 [M + H]$^+$; Anal. Calcd for $C_{17}H_{12}F_6N_4$: C, 52.86; H, 3.13; N, 14.50. Found: C, 52.71; H, 2.92; N, 14.60.

(3,5-Bis-trifluoromethyl-phenyl)-[4-(2-isopropyl-phenyl)-4*H*-[1,2,4]triazol-3-yl]-amine (6j): 45%, colorless solid; mp 216−217 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.21 (s, 1H), 8.46 (s, 1H), 8.43 (s, 2H), 7.60 (m, 2H), 7.53 (s, 1H), 7.42−7.40 (m, 2H), 2.45 (septa, J = 6.8 Hz, 1H), 1.08 (dd, J = 6.8, 1.8 Hz, 6H); MS$^+$(APCI) 414.90 [M + H]$^+$; Anal. Calcd for $C_{19}H_{16}F_6N_4$: C, 55.08; H, 3.89; N, 13.52. Found: C, 54.82; H, 3.76; N, 13.66.

(3,5-Bis-trifluoromethyl-phenyl)-[4-(2-*tert*-butyl-phenyl)-4*H*-[1,2,4]triazol-3-yl]-amine (6k): (Following general procedure III) 49%, colorless solid; mp 249−250 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.11 (s, 1H), 8.49 (s, 2H), 8.48 (s, 1H), 7.73 (dd, J = 7.6, 1.2 Hz, 1H), 7.58 (dt, J = 6.8, 1.6 Hz, 1H), 7.52 (s, 1H), 7.40 (dt, J = 7.6, 1.2 Hz, 1H), 7.23 (dd, J = 7.6,

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1.2 Hz, 1H), 2.45 (septa, J = 6.8 Hz, 1H), 1.15 (s, 9H); MS^+-(APCI) 428.98 $[M + H]^+$; Anal. Calcd for $C_{20}H_{18}F_6N_4$: C, 56.08; H, 4.24; N, 13.08. Found: C, 55.94; H, 4.09; N, 13.00.

1-Benzyl-1-(4-methoxy-phenyl)-3-phenylthiourea (8a): 93%, off-white solid: mp 87−88 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.69 (s, 1H), 7.34−7.26 (m, 8H), 7.23 (t, J = 6.5 Hz, 1H), 7.15−7.10 (m, 1H), 7.03 (dd, J = 110, 9.0 Hz, 4H), 5.50 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 182.5, 158.3, 140.7, 137.5, 134.4, 128.7, 128.2, 127.8, 127.0, 126.3, 124.9, 114.9, 57.6, 55.2; MS^+(APCI) 348.96 $[M + H]^+$; RT = 10.84.

1-Benzyl-1-(4-chloro-phenyl)-3-phenylthiourea (8b): 85%, ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.27 (m, 10H), 7.22−7.19 (m, 1H), 7.06 (dd, J = 8.5, 2.0 Hz, 1H), 6.95 (bs, 1H), 5.55 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 181.9, 139.2, 138.9, 136.7, 134.9, 130.7, 129.4, 128.6, 128.4, 127.6, 126.2, 125.8, 58.1; MS^+(APCI) 352.98 $[M + H]^+$.

1-Benzyl-3-(4-methoxy-phenyl)-1-phenylthiourea (9): 77%, beige solid: mp 141−142 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.70 (s, 1H), 7.36−7.13 (m, 12H), 6.82 (d, J = 9 Hz, 2H), 5.49 (s, 2H), 3.69 (s, 3H); MS^+(APCI) 348.86 $[M + H]^+$; RT = 10.60.

Benzyl-(4-methoxy-phenyl)-(4-phenyl-4*H*-[1,2,4]triazol-3-yl)-amine (10a): 20%, colorless solid; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.57 (s, 1H), 7.38 (d, J = 7.2 Hz, 2H), 7.32−7.18 (m, 9H), 6.60 (dd, J = 27.0, 9.0 Hz, 4H), 4.84 (s, 2H), 3.55 (s, 3H); MS^+(APCI) 357.03 $[M + H]^+$; RT = 8.86.

Benzyl-(4-chloro-phenyl)-(4-phenyl-4*H*-[1,2,4]triazol-3-yl)-amine (10b): 24%, colorless solid; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, J = 8.0 Hz, 2H), 7.22−7.19 (m, 3H), 7.13−7.10 (m, 2H), 7.10−6.95 (m, 5H), 6.91 (m, 3H) 5.35 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 141.9, 140.1, 135.7, 134.4, 132.3, 129.5, 128.64, 128.60, 128.53, 128.52, 126.8, 126.6, 126.1, 120.5; MS^+(APCI) 361.02 $[M + H]^+$.

Benzyl-(4-methoxy-phenyl)-(4-phenyl-4*H*-[1,2,4]triazol-3-yl)-amine (11): 18%, colorless solid; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.67 (s, 1H), 7.40 (d, J = 8 Hz, 2H), 7.28−7.19 (m, 5H), 7.04 (t, J = 7.2 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.71 (t, J = 6.8 Hz, 1H), 6.61 (d, J = 8.4 Hz, 2H), 4.82 (s, 2H), 3.71 (s, 3H); MS^+(APCI) 356.89 $[M + H]^+$; RT = 9.07.

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Supporting Information Available: General procedures for synthesis, ^1H NMR of **3a**, **3c**, **4a**, **4b**, **4c**, **4k**, **6c**, **6d**, **7d**, and **6f**, ^{13}C NMR of **3a**, **4a**, **4b**, **4k**, **6c**, **7d**, and **6f**, LC−MS of **3c**, **4c**, **6d**−**7d** regioisomeric mixture and **6e**−**7e** regioisomeric mixture, and NOESY and TOCSY of **6c**, **6f**, and **6g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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