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Synthesis of Novel Biological Active 1,2,4,-Triazole Analogues †

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Abstract: The efficient method we have developed for the synthesis of novel biologically active 1,2,4-Triazole Analogues, In case several five-membered aromatic systems having three hetero atoms at the symmetrical position have been studied because of their interesting physiological properties and have broad scope towards the organic transformation. It is also well established that various derivatives of 1,2,4-triazole. This is a convenient method that proceeded under clean, non-toxic, efficient and mild reaction conditions for synthesizing the first step as a one-pot *N*-substituted thioureas derivative in acetonitrile (CH_3CN). To the best of our knowledge, on the introduction of 1,2,4, triazoles analogs from corresponding N-aryl-N′- benzoylthioureas derivatives.

Keywords: One-Pot; *N*′- benzoylthioureas; 1,2,4 Triazoles

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1. Introduction

The 1,2,4-triazoles are important according to the various unit is one of the well-sought-out structural units and also important in various fields and various applications.

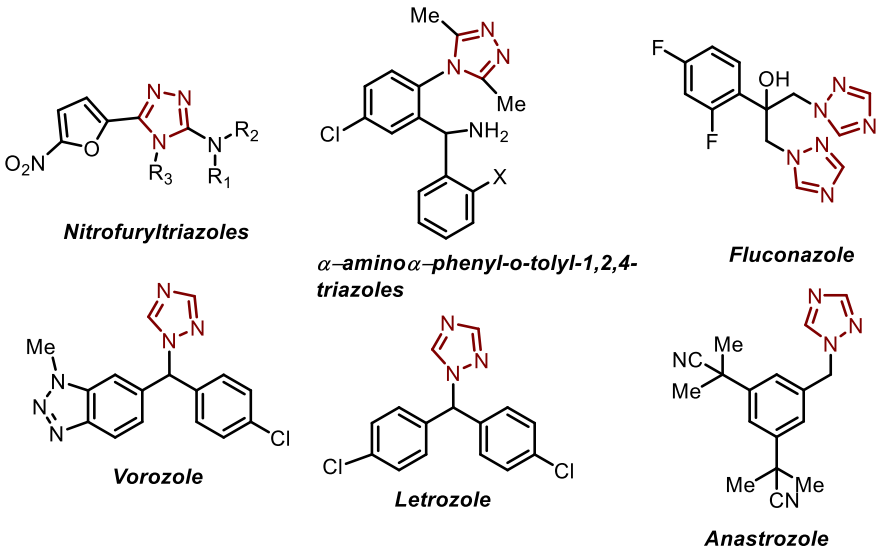


Figure 1. The relevance of 1,2,4-trizoles compounds.

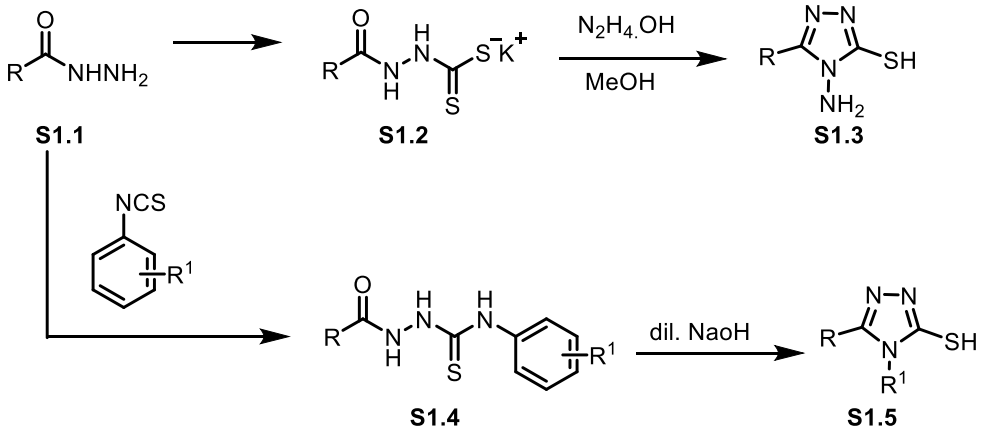
In 1,2,4,-triazoles having interesting physiological properties, also possess a broad scope of biological applications[1]. Among the nitrofuryltriazoles showing antibacterial activity [2]. and α- amino-α-phenyl-o-tolyl-1,2,4-triazoles reported as the anticonvulsant agent [3]. Furthermore, 1,2,4 Triazoles have shown their pharmaceutical activities such

drugs are fluconazole[4,5] and itraconazole[6] possess antifungal also antiviral drugs[7]. apart from this some of the 1,2,4-triazoles moieties exhibit aromatase inhibitors which are useful in breath cancers such as vorozole, letrozole, and anastrozole[8,9,10].

2. Previous Research

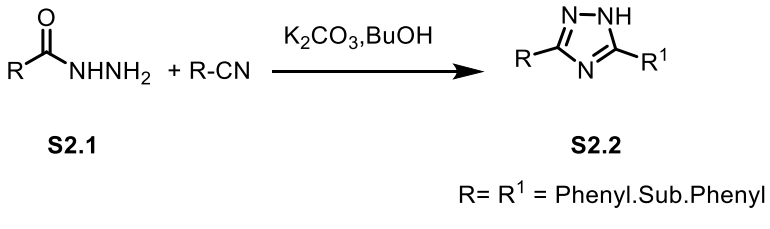
2.1. Synthesis of 3-mercapto-1,2,4-triazoles.

Several synthetic routes are available for the synthesis of 1,2,4-triazole nuclei. Some of these methods are discussed here. Cansiz et al[11] reported. Carbohydrazide S1.1 and CS2 in ethanolic potassium hydroxide give dithiocarbamate S1.2, After treatment with hydrazine hydrate yields 4-amino-5-aryl-4H-1,2,4-triazole-3-Thiol S1.3 (Scheme 1). Cyclic dehydration of thiosemicarbazide S1.4 in alkaline medium. This results in the formation of 1,2,4-triazole S4.5. Next, Maity and colleagues reported the same 4-Amino-5-mercapto 3-(substituted)-1,2,4-triazole derivatives S1.5 and their anticancer activity revealed their anticancer activity on EAC-bearing mice.[12]



2.2. Base-catalyzed synthesis of 3,5-disubstituted-1,2,4-triazoles.

A convenient and efficient one-step base-catalyzed synthesis of 3,5-disubstituted 1,2,4- triazoles S2.2 has been reported by Yeung's group.[13] The method is claimed to be a general one and tolerable for a wide range of functional groups.



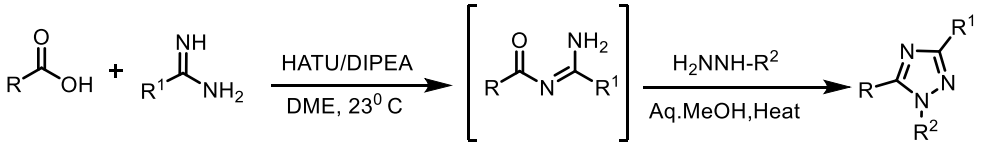
2.3. Synthesis of 1, 2, 4-triazoles using silica gel

Rostamizadeh and co-workers reported the sold-phase synthesis of 1,2,4-triazoles.[14] A three-component condensation of acylhydrazines S3.1 in the presence of S-methyl isothioamide hydroiodide S3.2, silica gel, and ammonium acetate under microwave irradiation of 900 W power afforded 1,2,4-triazole derivatives S3.3. Silica gel has been used as a solid acidic catalyst.

S3.1 **S3.2** **S3.3**

2.4. Synthesis of 1,3,5-trisubstituted 1,2,4-triazoles

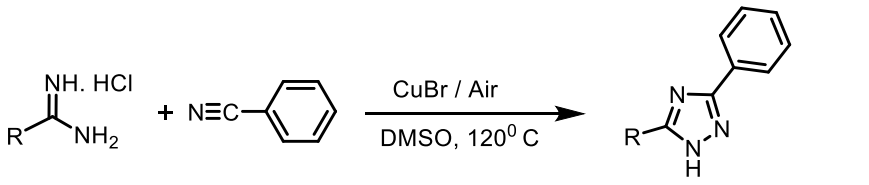
Castanedo and co-workers documented a highly regioselective one-pot process for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles S4.3. The reported method involves the condensation of carboxylic acid S4.1, primary amidine S4.2, and monosubstituted hydrazine in one pot employing HATU (2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexa fluorophosphate) as the peptide coupling reagent. This synthesis allows greater flexibility for the functional groups at the 5-position.[15]



S4.1 **S4.2** **S4.3**

2.5. Synthesis of 1,2,4-triazole derivatives using copper catalyst

A copper-catalyzed coupling of amidines S5.2 and nitriles S5.3 via sequential N–C and N–N oxidative coupling reactions have been reported by Ueda's group.[16] A wide range of functional groups are tolerated. This is based on the well-known ability of transition metals to activate nitriles.



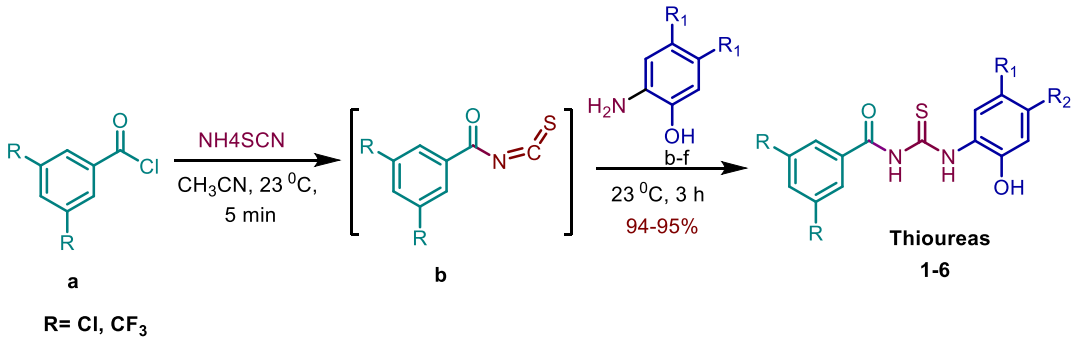
S5.1 **S5.2** **S5.3**

3. Hypothesis

Studying the above literature background, we have modified our scheme of the scope of example for the synthesis of 1,2,4 triazoles derivatives, because of the hydrazine and other basic compounds showing important role in the synthesis of the heterocyclic compounds.

4. Result and Discussion

We carried out one-pot synthesis of N-substituted thioureas in acetonitrile (CH_3CN) conditions as follows (Scheme 1). First, benzoyl isothiocyanate is formed by the reaction of 3,5- dichlorobenzoyl chloride or 3,5-Bis (Trifluoromethyl) benzoyl chloride with ammonium thiocyanate (NH_4SCN). Second, the benzoyl isothiocyanate reacts with an aminophenols (4-Nitro, 4-chloro, 5-Chloro, 4-methyl, and 5-Methyl) to afford the N-Aryl- N′-benzoylthioureas (1-6) in good yield.



Scheme 1. The overall scheme for one-pot Synthesis of Thioureas.

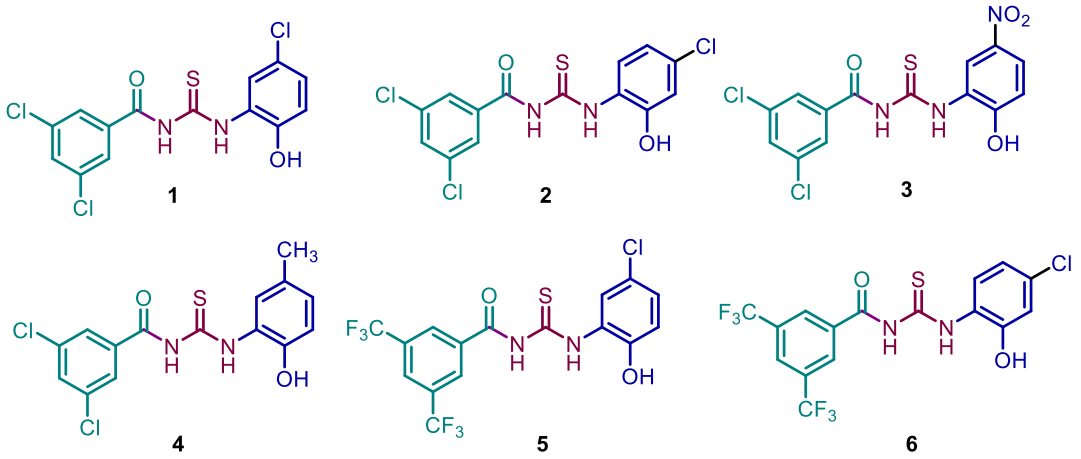
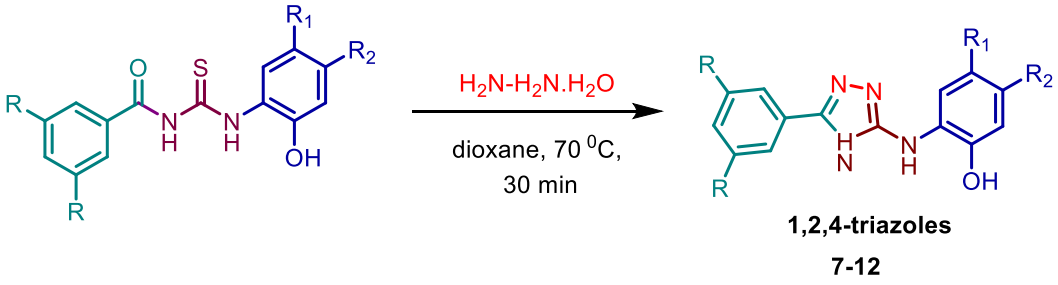


Figure 3. Structure of thiourea analogues (1–6).

The synthesis of 1,2,4,-triazole derivatives from the corresponding N-aryl-N′- benzoylthioureas (1-6) has been carried out by using hydrazine hydrate in 1,4-dioxane at 70°C for 0.5 h to afford 7–12 in 50–86% yields (Scheme 2).



Scheme 2. Synthesis of 1,2,4-triazoles.

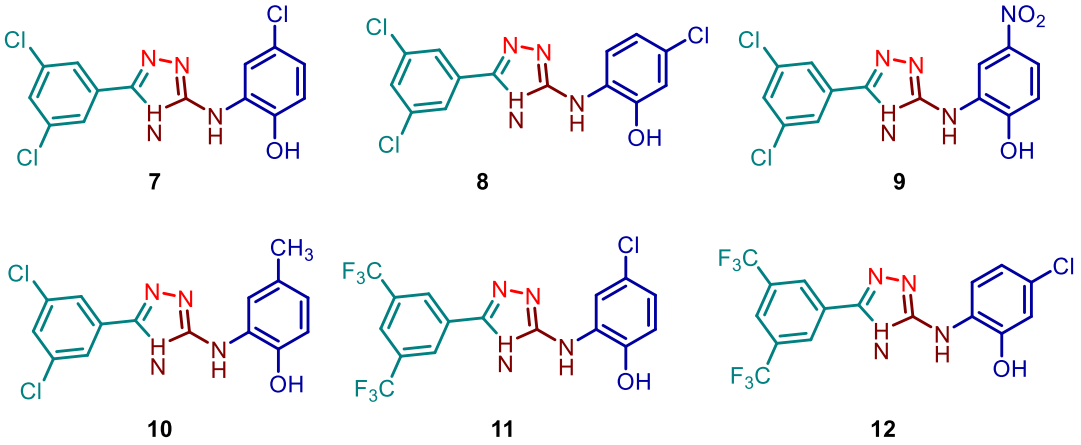


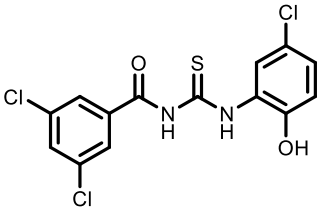
Figure 3. Synthesis of 1,2,4-Triazoles.

All synthesized 1,2,4-triazoles have been completely characterized with help of ^{1}H, ^{13}C NMR, IR and HRMS data. For example, in the ^{1}H NMR spectrum of the compounds **7**, the 3,5- Dichlorobenzoyl substituted phenyl ring aromatic protons appeared at δ 8.38 and 8.44 as two singlets integrating for 2 protons and other protons between two chloro (Cl) appeared at δ 8.07 as a triplet. At the other end, the Cl substituted phenyl ring of R1′ proton appeared at δ 7.56 (d, J = 8.8 Hz) as a doublet; the aromatic CH proton between NH and R1 appeared at δ 8.66 (d, J = 8.8 Hz) as a doublet; and the proton ortho to the hydroxyl group appeared at δ 7.94 (dd, J = 2.3, 8.8 Hz) as a doublet of the doublet. The N–H protons resonated at δ 9.53 and 11.96 ppm as broad singlets. In the ^{13}C NMR spectra of **7**, the carbons of the C=N have appeared at δ 161.2 ppm. The presence of N–H groups was also evident from the IR spectrum, where the absorption was observed at 3376 cm-1. In the ESI mass spectrum, the exact mass of the compound showed, as calculated, for (MH+) it was found to be 354.9.

5. Exprimental Data

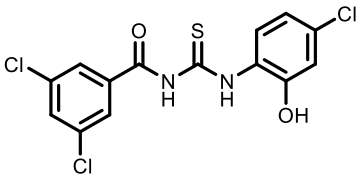
5.1 General Procedure I: Preparation of Thiourea derivatives (1) To a solution of ammonium thiocyanate (361 mg, 4.7 mmol) in 30 mL of acetonitrile, benzoyl chloride (500 mg, 2.38 mmol) was added dropwise, the mixture was stirred for 5 minutes to form white precipitate of isothiocyanate, and then a solution of corresponding amine (2.38 mmol) in acetonitrile (10 mL) was added slowly. The reaction mixture was stirred at rt for 3 h. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography with Pet. ether/EtOAc (8:2) as eluent to give thiourea derivative.

3,5-dichloro-N-((5-chloro-2-hydroxyphenyl)carbamothioyl)benzamide (1):



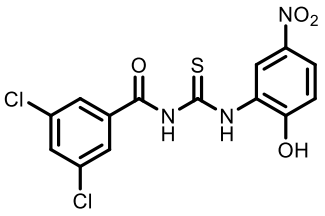
Isolated by column chromatography (pet.ether/ethyl acetate = 8:2, Rf = 0.3), The title compound was determined as yellow solid (750 mg, 94%). M. P.: 185-190 °C; IR ($CHCl_3$): ν 3220, 3020, 1658, 1602, 1565, 1543, 1263, 1179, 1108, 758, cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d^6, 200 MHz): δ 6.67 (d, J = 8.6 Hz, 1H), 6.76 (dd, J = 2.4, 8.6 Hz, 1H), 7.32 (t, J = 1.8, 3.6 Hz, 1H), 7.71(s, 1H), 7.72 (s, 1H), 8.57 (d, J = 2.4 Hz, 1H), 9.64 (s, 1H), 10.92 (s, 1H), 12.69 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 115.7, 121.9, 122.5, 125.5, 126.7, 132.1, 134.7, 147.1, 164.9, 176.6 ppm; ESI Mass (MH+) 374.8.

3,5-dichloro-N-((4-chloro-2-hydroxyphenyl)carbamothioyl)benzamide (2):



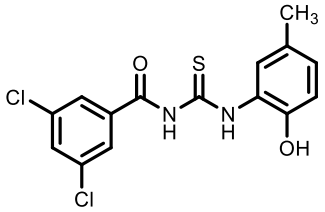
Isolated by column chromatography (pet.ether/ethyl acetate = 8:2, Rf = 0.4), The title compound was determined as yellow solid (862 mg, 94%). M. P.: 182-185 °C; IR ($CHCl_3$): ν 3480, 3220, 3082, 1659, 1603, 1541, 1498, 1424, 1262, 1181, 757 cm–1; ^1H NMR ($CDCl_3$+DMSO-d^6, 200 MHz): δ 6.52 (d, J = 8.5 Hz, 1H) 6.61 (dd, J = 2.3, 8.6 Hz, 1H), 7.19 (t, J = 1.8, 3.6 Hz, 1H), 7.58 (s, 1H), 7.59 (s, 1H), 8.44 (d, J = 2.3 Hz, 1H), 9.60 (s, 1H), 10.97 (s, 1H), 12.56 (s, 1H), ppm; ^{13}C NMR ($CDCl_3$+DMSO-d^6, 50 MHz): δ 115.4, 121.6, 122.1, 125.2, 126.6, 131.8, 134.4, 146.9, 160.8, 176.5 ppm; ESI Mass (MH+) 374.9.

3,5-dichloro-N-((2-hydroxy-5-nitrophenyl)carbamothioyl)benzamide (3):



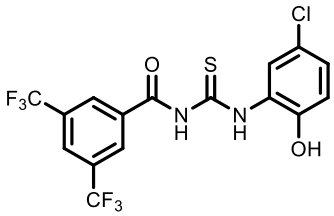
Isolate d by column chromatography (pet. ether/ethyl acetate = 8:2, Rf = 0.4), The title compound was determined as a yellow solid (852 mg, 95%). M. P.: 210-215 °C; IR ($CHCl_3$): ν 3319, 3020, 1663, 1559, 1466, 1270, 1225, 1136, 756 cm–1; ^1H NMR ($CDCl_3$+DMSO-d^6, 200 MHz): δ 6.92 (d, J = 8.6, Hz, 1H), 7.43 (t, J = 1.8, 3.6, Hz, 1H), 7.81 (s, 1H), 7.82 (s, 1H), 7.86 (dd, J = 2.3, 8.6 Hz, 1H), 9.72 (d, J = 2.3, Hz, 1H), 10.96 (s, 1H), 12.92 (s, 1H ppm; ^{13}C NMR ($CDCl_3$+DMSO-d^6, 50 MHz): δ 114.3, 118.0, 122.0, 126.1, 132.4, 134.6, 134.9, 139.1, 154.5, 165.2, 177.2 ppm; ESI Mass calcd for (MH+) 385.9.

3,5-dichloro-N-((2-hydroxy-5-methylphenyl)carbamothioyl)benzamide (4):



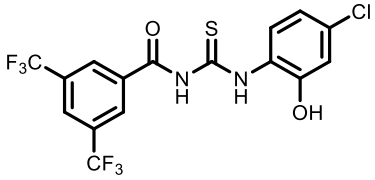
Isolated by column chromatography (pet.ether/ethyl acetate = 8:2, Rf = 0.4), The title compound was determined as yellow solid (773 mg, 91%). M. P.: 195-200 °C; IR ($CHCl_3$): ν 3318, 3042, 1675, 1623, 1514, 1312, 1270, 1206, 1147, 1074, 772 cm–1; ^1H NMR ($CDCl_3$+DMSO-d^6, 200 MHz): δ 2.3 (s, 3H), 6.69 (dd, J = 1.5, 8.3 Hz, 1H), 6.79 (d, J = 1.3 Hz, 1H), 7.62 (s, 1H), 8.01 (s, 1H), 8.01 (s, 1H), 8.40 (d, J = 8.3 Hz, 1H), 9.64 (s, 1H), 11.45 (s, 1H), 12.75 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d^6, 50 MHz): δ 19.9, 114.7, 117.9, 121.9, 122.3, 126.1, 130.9, 133.5, 134.1, 135.2, 147.7, 164.2, 175.8 ppm; HRMS ESI calcd for (MH+) $C_{15}H_{12}N_2O_2Cl_2S$ 355.0069, found 355.0066.

N-(5-chloro-2-hydroxyphenylcarbamothioyl)-3,5-bis(trifluoromethyl)benzamide (5):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, Rf = 0.3), The title compound was determined as yellow solid (149 mg, 94%). M. P.: 169 °C; IR ($CHCl_3$): ν 3362, 3020, 1734, 1674, 1542, 1496, 1278, 1185, 1139, 761, cm–1; ^1H NMR ($CDCl_3$+DMSO-d^6, 400 MHz): δ 6.79 (d, J = 8.6 Hz, 1H), 6.88 (dd, J = 2.4, 8.6 Hz, 1H), 7.91 (s, 1H), 8.46 (s, 2H), 8.66 (d, J = 2.4 Hz, 1H), 9.71 (s, 1H), 11.58 (s, 1H), 12.83 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 119.5, 121.1, 123.8, 124.5 (2C), 125.8, 127.2, 128.2 (2C), 128.5 (2C), 133.1, 133.5, 147.7, 164.8, 177.0 ppm; HRMS ESI calcd for (MH+) $C_{16}H_{10}N_2O_2ClF_6S$ 443.0050, found 443.0053.

N-(4-chloro-2-hydroxyphenylcarbamothioyl)-3,5-bis(trifluoromethyl)benzamide (6):

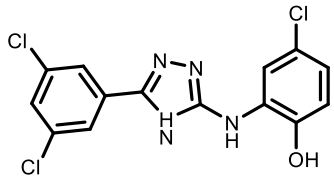


Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, Rf = 0.4), The title compound was determined as yellow solid (151 mg, 95%). M. P.: 156 °C; IR ($CHCl_3$): ν 3546, 3362, 3020, 1672, 1601, 1562, 1541, 1421, 1278, 1128, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.02 (dd, J = 2.1, 8.5 Hz, 1H), 7.08 (d, J = 2.1 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 8.18 (s, 1H), 8.35 (s, 2H), 9.34 (s, 1H), 12.40 (s, 1H) ppm; 13C NMR ($CDCl^3$+DMSO-d^6, 50 MHz): δ 115.5 118.6, 119.9, 123.8, 124.7 (2C), 125.8, 129.1 (2C), 131.1 (2C), 131.8, 134.2, 149.7, 165.1, 177.1 ppm; HRMS ESI calcd for (MH+) $C_{16}H_{10}N_2O_2ClF_6S$ 443.0056, found 443.0050.

5.2 General Procedure II: preparation of 1,2,4-Triazole derivatives (2)

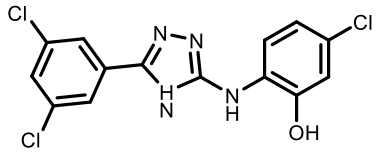
To a solution of thiourea (500 mg, 0.13 mmol) in 1, 4-dioxane (25 mL), hydrazine hydrate (1.96 mmol) was added dropwise and the reaction mixture was heated at 70°C for 0.5 h. Solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography with Pet. Ether/EtOAc (1:1) as eluent to give 1,2,4-triazole.

4-chloro-2-((5-(3,5-dichlorophenyl)-4H-1,2,4-triazol-3-yl)amino)phenol (7):



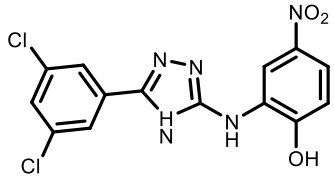
Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, Rf = 0.5), The title compound was determined as yellow solid (398 mg, 84%). M. P.: 162-170 °C; IR (Neat): ν 3376, 3186, 3077, 1629, 1571, 1565, 1463, 1262, 1190, 1167, 805 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d^6, 200MHz): δ 7.56 (d, J = 8.8 Hz, 1H), 7.94 (dd, J = 2.3, 8.8 Hz, 1H), 8.07 (t, J = 1.5, 3.4, Hz, 1H), 8.38 (s, 1H), 8.40 (s, 1H), 8.66 (d, J = 8.8 Hz, 1H), 9.53 (s, 1H), 11.96 (s, 1H) ppm;^{13}C NMR ($CDCl^3$+DMSO-d^6, 50 MHz): δ 115.3, 116.2, 118.0, 119.9, 124.0, 126.1, 130.8, 134.5, 143.2, 149.8, 161.2 ppm; ESI Mass calcd for (MH+) 354.8.

5-chloro-2-((5-(3,5-dichlorophenyl)-4H-1,2,4-triazol-3-yl)amino)phenol (8):



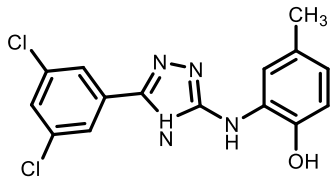
Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, Rf = 0.5), The title compound was determined as yellow solid (410 mg, 86%). M. P.: 188-200 °C; IR (Neat): ν 3443, 3376, 3076, 1706, 1617, 1571, 1552, 1499, 1275, 1197, 1131, 1023, 875 cm^{-1}; ^{13}C NMR ($CDCl_3$+DMSO-d^6, 50 MHz): δ 108.8, 115.2, 118.0, 120.0, 124.1, 126.1, 134.6, 143.2, 148.3, 155.7 ppm; ESI Mass calcd for (MH+) 354.9.

2-((5-(3,5-dichlorophenyl)-4H-1,2,4-triazol-3-yl)amino)-4-nitrophenol (9):



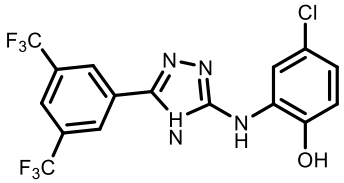
Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, Rf = 0.5), The title compound was determined as yellow solid (250 mg, 65%). M. P.: 215- 220 °C; IR (Neat): ν 3376, 3290, 3020, 1621, 1584, 1564, 1497, 1322, 1278, 1122, 901, 861 cm^{-1}; ^1H NMR ($CDCl^3$+DMSO-d_6, 200 MHz): δ 6.65 (d, J = 8.8, Hz, 1H), 7.09 (s, 1H), 7.20 (s, 1H), 7.43 (dd, J = 2.6, 8.8 Hz, 1H), 7.57 (d, J = 1.5 Hz, 1H), 7.69 (s, 1H), 7.69 (s, 1H), 8.95 (s, 1H), 11.15 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d^6 , 50 MHz): δ 113.4, 116.8, 124.3, 125.9, 127.7, 128.2, 131.1, 131.4, 134.8, 135.2, 150.2, 161.0, 164.3 ppm; ESI Mass calcd for (MH+) 365.9.

2-((5-(3,5-dichlorophenyl)-4H-1,2,4-triazol-3-yl)amino)-4-methylphenol (10):



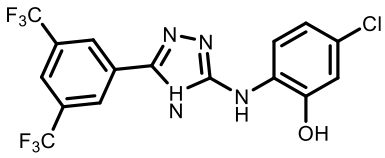
Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, Rf = 0.5), The title compound was determined as yellow solid (216 mg, 50%). M. P.: 180-188 °C; IR (Neat): ν 3324, 3019, 1625, 1511, 1285, 1217, 1149, 1089, 783 cm–1; ^{1}H NMR (CDCl$_3$+DMSO-d$_6$, 200 MHz): δ 1.89 (s, 3H), 6.40-6.53 (m, 2H), 7.10 (t, J = 1.8, 3.8 Hz, 1H), 7.42 (s, 1H), 7.47 (s, 1H), 8.41 (d, J = 2.3 Hz, 1H), 9.50 (s, 1H), 11.1 (s, 1H) ppm; ^{13}C NMR (CDCl$_3$+DMSO-d$_6$, 50 MHz): δ 19.5, 116.1, 124.7, 125.0, 125.5, 127.9, 129.7, 130.1, 133.8, 146.9, 148.9, 160.2, 163.5 ppm; ESI Mass calcd for (MH+) 335.0.

2-((5-(3,5-bis(trifluoromethyl)phenyl)-4H-1,2,4-triazol-3-yl)amino)-4-chlorophenol (11):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, Rf = 0.4), The title compound was determined as yellow solid (125 mg, 87%). M. P.: 126–127 °C; IR (Neat): ν 3421, 3121, 3021, 1645, 1614, 1571, 1451, 1273, 1189, 1131, 915 cm–1; ^{1}H NMR (CDCl$_3$+DMSO-d$_6$, 200 MHz): δ 6.82 (dd, J = 1.9, 8.5 Hz, 1H), 7.0 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 7.84 (s, 1H), 8.34 (d, J = 8.8 Hz, 2H), 10.02 (s, 1H) ppm;^{13}C NMR (CDCl$_3$+DMSO-d$_6$, 50 MHz): δ 117.9, 120.2, 120.3, 123.5, 124.8 (2C), 126.1, 127.5, 128.6 (2C), 131.0, 131.6 (2C), 136.0, 162.2, 162.7 ppm; HRMS ESI calcd for (MH+) $C_{16}H_{10}N_4OClF_6$ 423.0442, found 423.0444.

2-((5-(3,5-bis(trifluoromethyl)phenyl)-4H-1,2,4-triazol-3-yl)amino)-5-chlorophenol (12):



Isolated by column chromatography (pet. ether/ethyl acetate = 1:1, Rf = 0.4), The title compound was determined as a yellow solid (128 mg, 89%). M. P.: 124 °C; IR (Neat): ν 3199, 3082, 2359, 1639, 1607, 1571, 1539, 1275, 1197, 1131, 914 cm–1; ^{1}H NMR (CDCl$_3$, 200 MHz): δ6.82 (dd, J = 2.3, 8.5 Hz, 1H), 6.95 (d, J = 2.3 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.97 (s, 1H), 8.48 (s, 2H), 8.51 (s, 1H), 8.86 (s, 1H) ppm;^{13}C NMR (CDCl$_3$+DMSO-d$_6$, 50 MHz): δ 116.7, 119.2, 124.2 (2C), 124.9, 125.5, 126.1, 127.7 (2C), 130.8, 131.5 (2C), 134.8, 150.8, 162.3, 164.1 ppm; HRMS ESI calcd for (MH+) $C_{16}H_{10}N_4OClF_6$ 423.0446, found 423.0442.

Supplementary Materials:

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Conflicts of Interest:

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