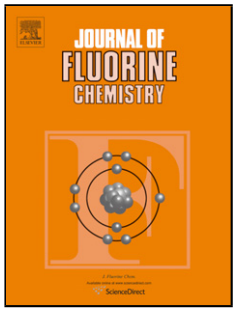

Title: Synthesis and biological activities of novel 1,2,4-triazole thiones and bis(1,2,4-triazole thiones) containing phenylpyrazole and piperazine moieties

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Synthesis and Biological Activities of Novel 1,2,4-Triazole Thiones and Bis(1,2,4-Triazole Thiones) Containing Phenylpyrazole and Piperazine Moieties

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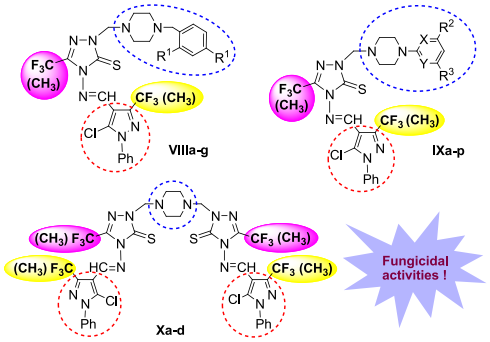
Graphical abstract

A series of novel phenylpyrazole- and piperazine-containing (bis)1,2,4-triazole thiones were synthesized *via* Mannich reaction in high yields. The compounds with two CF_3 groups exhibited excellent fungicidal activities.



Highlights

- 27 novel phenylpyrazole- and piperazine-containing (bis)1,2,4-triazole thiones were synthesized.
- Several compounds exhibited significant fungicidal activities.
- The compounds with two CF_3 groups on triazole and pyrazole rings had excellent fungicidal activities.
- **VIIIg**, **IXi**, **IXo** and **IXp** could be used as new fungicide lead compounds.

Abstract: A series of novel 1,2,4-triazole thione and bis(1,2,4-triazole thione) derivatives containing phenylpyrazole and substituted piperazine moieties have been conveniently synthesized *via* Mannich reaction using various 1,2,4-triazole thiols, substituted piperazines, and formaldehyde at room temperature in short time. Their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The preliminary bioassays for 27 new title compounds have shown that some of them possess certain herbicidal activities against *Echinochloa crusgalli* at 100 μg/mL concentration. Some of the compounds exhibited significant *in vitro* fungicidal activities, especially against *Cercospora arachidicola* and *Rhizoctonia cerealis* at the concentration of 50 μg/mL, and were comparable with that of control Triadimefon. Meanwhile, **IXp** held the control efficacy of 60% against *Puccinia sorghi* Schw. at 200 μg/mL concentration in the *in vivo* test. The SAR analysis has indicated that compounds with two CF_3 groups both on triazole and pyrazole rings are more effective than compounds with one CF_3 group or two CH_3 groups according to their fungicidal activity data. On the whole, compounds **VIIIg**, **IXi**, **IXo** and **IXp** could be used as novel lead structures for the design and discovery of new fungicides.

Keywords: Trifluoromethyl; pyrazole; triazole thione; biological activities

1. Introduction

Fluorine- and heterocycle-containing compounds play a very important role not only in the research area of organic chemistry, but also in a variety of applied chemistry areas, such as pharmaceutical chemistry, pesticidal chemistry and material science [1-9]. It is known that the introduction of fluorine atoms or trifluoromethyl groups may increase the biological activity of the parent compounds. Many trifluoromethyl-containing compounds were found to have biological activities as fungicides [10], insecticides [11], herbicides [12], COX-2 inhibitors [13], CETP inhibitors [14], anti-inflammatory agents [15, 16] and anti-cancer agents [17, 18]. For example, Flubendiamide, a new insecticide which targets the insect ryanodine recepor, found by Nippon Kayaku Co., has a heptafluoroisopropyl group (two trifluoromethyl and one fluorine atom) on one of the benzene rings of its phthalic diamide structure [19]. Furthermore, azole thiones as one kind of heterocyclic compounds have attracted much attention due to their interesting structural properties and versatile pharmacological activities; many of them have been found to possess antituberculous [20], antimalarial [21], antifungal [22] and anticancer [23] activities.

Moreover, the pyrazole and its derivatives are known to occupy an important position in the field of medicinal and pesticidal chemistry; they are always associated with various pharmacological and biological activities. As medicines, many of them possess significant antibacterial, antiviral, anticoagulant, antimicrobial, anti-inflammatory and anticancer properties [24-26]. Their pesticidal activities are manifested by their use as insecticides, fungicides, herbicides and plant growth regulators [27, 28]. For example, Fipronil, an insecticide that is used to control lepidopteran and coleopteran insects, is a kind of pyrazole derivative [29].

In our previous work, some triazole thiones with trifluoromethyl and piperazine groups were synthesized successfully and found to have favorable herbicidal and significant fungicidal activities [30, 31], which provided an important reference for us to make some further structural modifications. The preliminary SAR studies have illustrated the necessity for further optimization based on the general structure of this type of compounds, especially for the phenyl group and the substituent on the

piperazine ring part [30, 31]. Considering all that mentioned above and with our pursuit to look for novel heterocyclic compounds with pesticidal potential, in this paper we report the synthesis of a series of novel 1,2,4-triazole thione derivatives with phenylpyrazole and substituted benzylpiperazine or various arylpiperazine moieties, as well as bis(1,2,4-triazole thione) derivatives with phenylpyrazole and piperazine moieties *via* Mannich reaction. For SAR study, the methyl and trifluoromethyl groups were introduced into the structures in various combinations on both triazole and pyrazole rings. These novel compounds were further evaluated for heribicidal and fungicidal activities.

To the best of our knowledge, the synthesis and pesticidal activities of the title compounds with such structural characteristics have not been studied so far. Thus, the research in this paper may provide usful information for the synthesis and discovery of new bioactive fluorine and heterocycle-containing compounds.

2. Results and discussion

2.1 Synthesis

The synthetic routes of the intermediates and the title compounds are shown in **Scheme 1**, **Scheme 2** and **Scheme 3**.

The trifluoromethyl-containing carbonyl compounds, such as trifluoroacetophenone, ethyl trifluoroacetoacetate and 1,1,1,5,5,5-hexafluoro-2,4-pentanedione are known as important building blocks for the construction of trifluoromethyl imines or enamines in either open-chain or heterocyclic form, *via* the condensation reaction with amines [32-36]; however, the condensation of ethyl trifluoroacetoacetate (or ethyl acetoacetate) with substituted hydrazines will result in 5-trifluoromethyl(or 5-methyl)-pyrazolone compounds [37, 38]. The latter method was used to smoothly synthesize intermediate **IV**. Phenylpyrazole carbaldehyde **V** was prepared *via* Vilsmeier reaction [39] from phenylpyrazolone **IV** in $POCl_3$/DMF system in 86% ~ 92% yield, followed by the condensation with amino-triazole thiol **VI** under refluxing condition in absolute ethanol using acetic acid as a catalyst to give phenylpyrazole-containing triazole thiol (Schiff base) **VII** in 71% ~ 87% yield.

Taking the thioamide structure (C(=S)-NH-) into account, it is obvious that the intermediate **VII** can exist either in thiol or thione tautomeric forms. Based on the results of our experiment, it was found that the thione isomer undergoes subsequent Mannich reaction *via* the N-H at *α*- position of thiocarbonyl (C=S). As a result, the condensation fo intermediate **VII** with formaldehyde and 4-(substituted benzyl)piperazine **I**, or 4-(substituted pyrimidyl)/ phenyl/pyridylpiperazine **III** in ethanol at room temperature led to novel 1,2,4-triazole thiones **VIII** and **IX** in satisfactory yields (59% ~ 85%), respectively. Under the similar reaction conditions using excess formaldehyde and 2 : 1 molar ratio of Schiff base **VII** and piperazine, bis(1,2,4-triazole thione) **X** was successfully synthesized in high yield (over 82%). Overall, this approach towards the synthesis of the title compounds have noticeable advantages, such as, mild reaction conditions, high yield and short reaction time (1 ~ 3 h).

The title compounds were identified by IR, ^{1}H NMR, and ^{13}C NMR spectra. The measured elemental analyses were also consistent with the corresponding calculated values. In IR spectra of the compounds, the stretching vibration absorption peaks of C=S and C=N appeared at 1143-1177 cm^{-1} and 1577-1615 cm^{-1} respectively. In ^{1}H NMR, the -N=CH- proton showed up at δ 9.96-11.02. The piperazine ring proton signals of compounds **VIII** and **IX** were observed at two positions; however, due to the symmetrical structure of compound **X**, they were observed as a singlet at δ 2.85-2.89. In the ^{13}C NMR spectra of representive compounds, the typical carbon signal at δ 162.6-165.0 was derived from the resonance of thiocarbonyl group (C=S). The piperazine carbons of compound **X** also appeared as one signal at δ ~ 50.3 as opposed to two signals in compounds **VIII** and **IX**. In addition, due to the “F” splitting, the signals of CF_3 carbon and carbons adjacent to CF_3 group (heterocyclic carbon) were split into quartet or multiplet.

2.2 The biological activities

As shown in **Table 1** (some data are listed in **Table S1** in Supplementary Information), compared with commercial herbicide Chlorsulfuron, most of the title

compounds at the concentration of 100 μg/mL showed rather weak herbicidal activities based on the rape (*Brassica campestris*) root tests. However, in the case of barnyardgrass (*Echinochloa crusgalli*) cup tests, at the concentration of 100 μg/mL, several compounds showed higher herbicidal activities than the control Chlorsulfuron (29.9%), such as **VIIIc** (30.0%), **IXe** (40.0%) and **IXf** (50.0%). On the whole, the title compounds may be more effective against monocotyledonous weeds (*Echinochloa crusgalli*).

The *in vitro* fungicidal activity data of 1,2,4-triazole thiones **VIII**, **IX** and bis(1,2,4-triazole thiones) **X** for inhibition of mycelial growth in six test fungi are listed in **Table 2** (some data could be found in **Table S2** in Supplementary Information). It was found that at the test concentration of 50 μg/mL, most of the compounds exhibited significant fungicidal activities against *Alternaria solani Sorauer*, *Physalospora piricola* and *Rhizoctonia cerealis* while some of these results were comparable with those of the contol Triadimefon. In addition, several compounds displayed favorable actities against other test fungi, such as compound **IXg** (62.5%) against *Gibberella sanbinetti*, compounds **VIIIg** (75.0%), **IXo** (87.5%) and **IXp** (75.0%) against *Cercospora arachidicola*, were more effective than Triadimefon, respectively.

According to the *in vitro* fungicidal activity data, several trifluoromethyl-containing compounds were chosen to be tested for *in vivo* fungicidal activity against *Puccinia sorghi* Schw. at 200 μg/mL concentration. From **Table 3**, it was shown that compounds **VIIIg**, **IXm**, **IXn** and **IXp** have certain *in vivo* fungical activities, especially **IXp** exhibited good activity against *Puccinia sorghi* Schw. with control efficacy of 60%.

In general, these 1,2,4-triazole Mannich bases containing phenylpyrazole and substituted piperazine moieties held significant fungicidal activities against various

plant fungi, while the CF_3 group made an apparent influence on their fungicidal activities, which could be well reflected particularly in the results of *Rhizoctonia cerealis* test. By analyzing the SAR based on the fungicidal data against *Rhizoctonia cerealis*, it was found that in most cases trifluoromethyl-containing compounds exhibit higher activity than methyl-containing ones, and compounds with two CF_3 groups both on triazole and pyrazole rings are more effective than compounds with one CF_3 (on the triazole ring, or on the pyrazole ring) or with two CH_3 groups. In the case of compounds **VIII** (**Table 2**), when R^1 is fixed as Cl atom, the activity sequence is **VIIIg** (A=CF_3, B=CF_3) > **VIIId** (A=CF_3, B=CH_3) > **VIIIf** (A=CH_3, B=CF_3) > **VIIIb** (A=CH_3, B=CH_3); in the case of compounds **IX** (**Table 2**), when the substituent at 4- position of piperazine is fixed as pyridyl, the activity sequence is **IXn** (A=CF_3, B=CF_3) >> **IXf** (A=CF_3, B=CH_3) > **IXj** (A=CH_3, B=CF_3) > **IXb** (A=CH_3, B=CH_3). For the phenyl substituent, the sequence is similar to that of pyridyl. When the substituent at 4- position of piperazine is fixed as 4-methylpyrimidinyl, the activity sequence is **IXo** (A=CF_3, B=CF_3) > **IXg** (A=CF_3, B=CH_3) > **IXc** (A=CH_3, B=CH_3) > **IXk** (A=CH_3, B=CF_3). Compounds with 4,6-dimethylpyrimidinyl substitutient show the similar trend; in the case of compounds **X** (**Table 2**), when there are four CF_3 groups in total attached to both triazole and pyrazole rings as in the structure **Xd**, the activity sequence is **Xd** (A=CF_3, B=CF_3) >> **Xa** (A=CH_3, B=CH_3) ≈ **IXb** (A=CF_3, B=CH_3) ≈ **Xc** (A=CH_3, B=CF_3). In addition, according to the *in vivo* fungicidal test results against *Puccinia sorghi* Schw., the superiority of two-CF_3-containing compounds can also be well reflected (such as **IXp**, **IXn** vs. **VIIId**).

It was worthy of note that against some test fungi, **VIIIg**, **IXi**, **IXo** and **IXp** overall exhibited higher and wider fungicidal activities than others, and were comparable with that of control fungicide Triadimefon. Especially, **VIIIg**, **IXo** and **IXp** had excellent fungicial activities against *Rhizoctonia cerealis* that is a very popular fungus and creates big threat to the wheat yield in china and some other countries [40]. Therefore, they could be used as novel lead structures for the design and discovery of new fungicides.

3. Conclusion

In conclusion, series of novel 1,2,4-triazole thione derivatives and bis(1,2,4-triazole thione) derivatives with phenylpyrazole and substituted piperazine moieties have been synthesized *via* Mannich reaction from the intermediate pyrazole-containing 1,2,4-triazole Schiff bases at room temperature in short time. Among 27 title compounds, the preliminary bioassays for some of them showed promising herbicidal activities against *Echinochloa crusgalli* at 100 μg/mL concentration. Some of compounds exhibited significant *in vitro* fungicidal activities at 50 μg/mL concentration against six plant fungi, especially *Cercospora arachidicola* and *Rhizoctonia cerealis*. On the whole, coumpounds **VIIIg**, **IXi**, **IXo** and **IXp** showed higher and wider fungicidal activities and were comparable with that of control Triadimefon. Meanwhile, the *in vivo* fungicidal activity of **IXp** against *Puccinia sorghi* Schw. at 200 μg/mL concentration was also favourable. The SAR analysis indicated that compounds with two CF_3 groups on both triazole and pyrazole rings are more effective than those ones with one CF_3 or with two CH_3 groups according to their fungicidal activity data. Overall **VIIIg**, **IXi**, **IXo** and **IXp** could be used as novel lead structures for the design and discovery of new fungicides.

4. Experimental

4.1 Instruments and materials

The melting points were determined on a Beijing Tech X-4 binocular microscope apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet MAGNA-560 spectrophotometer as KBr tablets. ^{1}H NMR spectra were measured on a Bruker AC-P500 instrument (400MHz) using TMS as an internal standard and DMSO-d_6 or $CDCl_3$ as solvent. Elemental analysis was performed on a Vario EL elemental analyzer. Partial 4-substituted piperazine intermediates were purchased from Aladin and Alfa Aesar reagent companies. Anhydrous piperazine and other materials were purchased from Nanjing Duodian Reagent Co. Ltd. All solvents were dried in advance by using standard methods and distilled before use.

4.2 Synthetic procedures

4-Amino-5-methyl/trifluoromethyl-4*H*-1,2,4-triazole-3-thiol **VIa** and **VIb** were prepared according to the reported procedure [41].

4.2.1 Preparation of 4-(substituted benzyl)piperazine (I)

Following the method in Lit. [42], to a solution of anhydrous piperazine (50 mmol) in 95% ethanol (20 mL) was added concentrated hydrochloric acid (25 mmol). The mixture was stirred under reflux and substituted benzyl chloride (25 mmol) was added dropwise over 5 min. The mixture was refluxed for 4 ~ 8 h with TLC monitoring, then left overnight at room temperature. The solid precipitate was filtered off and washed with ethanol; the filtrate was evaporated in vacuo. The residue was dissolved in saturated K_2CO_3 aq. (30 mL) and extracted with chloroform (5 × 8 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was then distilled under reduced pressure to give compound **I** as a colorless liquid.

Ia: yield 58%, bp 131-134 ^oC/10mmHg; **Ib**: yield 37%, bp 147-150 ^oC/6 mmHg.

4.2.2 Preparation of 4-(4,6-disubstituted pyrimidin-2-yl)piperazine (III)

2-Chloro-4,6-disubstituted pyrimidines **II** were prepared by reaction of the diazonium salts of 4,6-disubstituted pyrimidin-2-amines with concentrated hydrochloric acid and $ZnCl_2$ [43]. Compounds **III** were prepared according to the known protocol [42] and the method was improved. To a stirred solution of piperazine (45 mmol) and K_2CO_3 (16.5 mmol) in water (20 mL), chloropyrimidine **II** (18 mmol) was added in small portions at 50-65 °C. The mixture was stirred for 1 h at 60-65 ^oC and cooled to 35 ^oC. The yellow solid (1,4-disubstituted piperazine byproduct), was filtered off, and the filtrate was extracted three times with chloroform, dried over Na_2SO_4, and concentrated to give **III**, which were used in the subsequent step without further purification.

IIIa: yellow solid, yield 81%, mp 45-48 ^oC; **IIIb**: yellow solid, yield 79%, mp

82-84 ºC.

4.2.3 Preparation of 5-chloro-1-phenyl-3-methyl/trifluoromethyl-1*H*-pyrazole-4-carbalde hyde (V)

2-Phenyl-5-methyl/trifluoromethyl-2,4-dihydro-3*H*-pyrazol-3-one **IV** were prepared by refluxing ethyl acetoacetate or ethyl trifluoroacetoacetate and phenylhydrazine in ethanol [37]. Intermediate pyrazole carbaldehydes **V** were prepared according to the reference [39] and the method was improved. To a violently stirred cold solution of DMF (23 mL), phosphorus oxychloride (64 mL) was added dropwise at 0-10ºC. The mixture was stirred at this temperature for 30 min; then compound **IV** (0.1 mol) was added in portions. The mixture was heated at 90-100 ºC for 3 ~ 4 h. After cooling down to room temperature, it was slowly poured into ice-water (400 mL) and stirred for 10 min. For **Va**, the resulting solid was filtered off and recrystallized from ethyl acetate/petroleum ether (60-90 °C) to give pure product; for **Vb**, the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with 10% $NaHCO_3$ solution (2 × 20 mL) and brine (2 × 20 mL) successively, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, the residue was subjected to column chromatography using petroleum ether and ethyl acetate (1:1) as solvents to give pure product.

Va: white crystals, yield 86%, mp 139-140 ºC (Lit. [44] mp 140-141ºC); **Vb**: yellow oil, yield 92% (Lit. [45] mp 34-36ºC).

4.2.4 General synthetic procedures for 4-(((5-chloro-1-phenyl-3-methyl/trifluoromethyl -1*H*-pyrazol-4-yl)methylene)amino)-5-(methyl/trifluoromethyl)-4*H*-1,2,4-triazole-3-th iol (VII)

Compound **VIa** or **VIb** (10 mmol), pyrazole carbaldehyde **V** (10.5 mmol) and acetic acid (10 drops) were mixed in absolute ethanol (25 mL). After being stirred and refluxed for 4 ~ 5 h, the reaction mixture was cooled to room temperature. The resulting solid was filtered off and recrystallized from ethanol to give Schiff base **VII**.

VIIa: colorless crystals, yield 83%, mp 224-226 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.77 (s, 1H, SH), 10.18 (s, 1H, CH), 7.69-7.49 (m, 5H, Ph-H), 2.51 (s, 3H, CH_3), 2.36 (s, 3H, CH_3).

VIIb: white crystals, yield 72%, mp 206-207 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.89 (s, 1H, SH), 10.12 (s, 1H, CH), 7.66-7.54 (m, 5H, Ph-H), 2.48 (s, 3H, CH_3).

VIIc: colorless crystals, yield 87%, mp 202-204 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.12 (s, 1H, SH), 10.91 (s, 1H, CH), 7.62-7.49 (m, 5H, Ph-H), 2.47 (s, 3H, CH_3).

VIId: colorless crystals, yield 77%, mp 195-197 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.52 (s, 1H, SH), 10.74 (s, 1H, CH), 7.60-7.50 (m, 5H, Ph-H).

4.2.5 General synthetic procedures for 4-(((5-chloro-1-phenyl-3-methyl/trifluoromethyl-1*H*-pyrazol-4-yl)methylene)amino)-2-((4-(substitutedbenzyl)piperazin-1-yl)methyl)-5-(methyl/trifluoromethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (VIII)

Schiff base **VII** (1 mmol) and 37% formalin (1.5 mmol) were dissolved in ethanol (15 mL), and the mixture was stirred at room temperature for 5 min. The solution of 4-(substituted benzyl)piperazine **I** (1 mmol) in ethanol (2 mL) was slowly added dropwise. Then the reaction mixture was stirred for 2 ~ 3 h and left at room temperature or placed in a refrigerator overnight. The resulting precipitate was filtered off and recrystallized from ethanol to give novel 1,2,4-triazole thione **VIII**.

1-((4-Benzylpiperazin-1-yl)methyl)-4-(((5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-3-methyl-1*H*-1,2,4-triazole-5(4*H*)-thione (VIIIa) White solid, yield 64%, mp 120-122 ^{o}C; IR (KBr), ν (cm^{-1}): 2935, 2805(C-H), 1612(C=N), 1596, 1537, 1500, 1454(Ar), 1167(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H, CH=N), 7.57-7.49 (m, 5H, Ph-H), 7.24-7.10 (m, 5H, Ph-H), 4.98 (s, 2H, NCH_2N), 3.37 (s, 2H, $PhCH_2$), 2.67 (bs, 4H, Piperazine-H), 2.33 (bs, 4H, Piperazine-H), 2.30 (s, 3H, Pyrazole-CH_3). Anal. calcd for $C_{26}H_{29}ClN_8S$: C, 59.93; H, 5.61; N, 21.50; found: C, 59.65; H, 5.71; N 21.29.

4-(((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(2,4-dichlorobenzyl)piperazin-1-yl)methyl)-3-methyl-1*H*-1,2,4-triazole-5(4*H*)-thione

(VIIIb) White solid, yield 67%, mp 147-149 °C; IR (KBr), ν (cm^{-1}): 2940, 2813(C-H), 1615(C=N), 1593, 1531, 1504, 1455(Ar), 1165(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H, CH=N), 7.63-7.57 (m, 6H, Ph-H), 7.46-7.38 (m, 2H, Ph-H), 5.04 (s, 2H, NCH_2N), 3.50 (s, 2H, $ArCH_2$), 2.73 (bs, 4H, Piperazine-H), 2.52 (s, 3H, Triazole-CH_3), 2.42 (bs, 4H, Piperazine-H), 2.39 (s, 3H, Pyrazole-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.6 (C=S), 153.9 (triazole), 150.4 (pyrazole), 147.7 (C=N), 137.4 (Ph), 134.8 (Ph), 134.6 (Ph), 133.1 (Ph), 131.4 (Ph), 131.1 (pyrazole), 129.2 (Ph), 129.2 (Ph), 128.9 (Ph), 126.9 (Ph), 125.0 (Ph), 112.4 (pyrazole), 68.7 (CH_2), 58.7 (CH_2), 53.0 (piperazine-C), 50.5 (piperazine-C), 15.1 (CH_3), 11.2 (CH_3). Anal. calcd for $C_{26}H_{27}Cl_3N_8S$: C, 52.93; H, 4.61; N, 18.99; found: C, 52.65; H, 4.49; N, 19.11.

1-((4-Benzylpiperazin-1-yl)methyl)-4-(((5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (VIIIc) White crystals, yield 69%, mp 100-102 °C; IR (KBr), ν (cm^{-1}): 2940, 2878(C-H), 1608(C=N), 1535, 1489, 1456(Ar), 1312, 1197(C-F), 1154(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H, CH=N), 7.65-7.54 (m, 5H, Ph-H), 7.32-7.23 (m, 5H, Ph-H), 5.17 (s, 2H, NCH_2N), 3.46 (s, 2H, $PhCH_2$), 2.77 (bs, 4H, Piperazine-H), 2.47 (bs, 4H, Piperazine-H), 2.40 (s, 3H, Pyrazole-CH_3). Anal. calcd for $C_{26}H_{26}ClF_3N_8S$: C, 54.30; H, 4.56; N, 19.49; found: C, 54.38; H, 4.34; N, 19.21.

4-(((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(2,4-dichlorobenzyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (VIIId) White solid, yield 74%, mp 128-130 °C; IR (KBr), ν (cm^{-1}): 2941, 2818(C-H), 1607(C=N), 1535, 1502, 1488, 1457(Ar), 1314, 1196(C-F), 1163(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H, CH=N), 7.66-7.55 (m, 6H, Ph-H), 7.45 (d, J = 8.3 Hz, 1H, Ph-H), 7.39 (m, 1H, Ph-H), 5.18 (s, 2H, NCH_2N), 3.51 (s, 2H, $ArCH_2$), 2.78 (bs, 4H, Piperazine-H), 2.50 (bs, 4H, Piperazine-H), 2.44 (s, 3H, Pyrazole-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.1 (C=S), 155.2 (pyrazole), 151.0 (C=N), 138.8 (q, J = 47.7 Hz, triazole), 137.3 (Ph), 134.9 (Ph), 134.2 (Ph), 133.2 (Ph), 131.8 (Ph), 131.5 (pyrazole), 129.3 (Ph), 129.2 (Ph), 129.0 (Ph), 127.0 (Ph), 125.0 (Ph), 116.9 (q, J = 271.6 Hz, CF_3), 111.9 (pyrazole), 69.9 (CH_2), 58.6 (CH_2), 52.9

(piperazine), 50.4 (piperazine), 15.0 (CH_3). Anal. calcd for $C_{26}H_{24}Cl_3F_3N_8S$: C, 48.49; H, 3.76; N, 17.40; found: C, 48.55; H, 3.61; N, 17.30.

1-((4-Benzylpiperazin-1-yl)methyl)-4-(((5-chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-3-methyl-1*H*-1,2,4-triazole-5(4*H*)-thione (VIIIe) White solid, yield 59%, mp 85-87 ^oC; IR (KBr), ν (cm^{-1}): 2938, 2813(C-H), 1596(C=N), 1533, 1492, 1452(Ar), 1315, 1191(C-F), 1150(C=S). ^1H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H, CH=N), 7.72-7.63 (m, 5H, Ph-H), 7.29-7.23 (m, 5H, Ph-H), 5.03 (s, 2H, NCH_2N), 3.42 (s, 2H, $PhCH_2$), 2.72 (bs, 4H, Piperazine-H), 2.36 (bs, 7H, Piperazine-H + Triazole-CH_3). Anal. calcd for $C_{26}H_{26}ClF_3N_8S$: C, 54.30; H, 4.56; N, 19.49; found: C, 54.17; H, 4.62; N, 19.22.

4-(((5-Chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(2,4-dichlorobenzyl)piperazin-1-yl)methyl)-3-methyl-1*H*-1,2,4-triazole-5(4*H*)-thione (VIIIf) White crystals, yield 64%, mp 99-100 ^oC; IR (KBr), ν (cm^{-1}): 2941, 2825(C-H), 1593(C=N), 1532, 1493, 1458(Ar), 1298, 1176(C-F), 1143(C=S). ^1H NMR (400 MHz, $CDCl_3$): δ 11.02 (s, 1H, CH=N), 7.68-7.41 (m, 5H, Ph-H), 7.39-7.35 (m, 2H, Ph-H), 7.18 (dd, J = 8.3, 2.1 Hz, 1H, Ph-H), 5.12 (s, 2H, NCH_2N), 3.55 (s, 2H, $ArCH_2$), 2.87 (bs, 4H, Piperazine-H), 2.53 (bs, 4H, Piperazine-H), 2.45 (s, 3H, Triazole-CH_3). Anal. calcd for $C_{26}H_{24}Cl_3F_3N_8S$: C, 48.49; H, 3.76; N, 17.40; found: C, 48.36; H, 3.78; N, 17.18.

4-(((5-Chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(2,4-dichlorobenzyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (VIIIg) White solid, yield 69%, mp 112-114 ^oC; IR (KBr), ν (cm^{-1}): 2939, 2817(C-H), 1594(C=N), 1529, 1492, 1462(Ar), 1316, 1189(C-F), 1167(C=S). ^1H NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 1H, CH=N), 7.75-7.72 (m, 2H, Ph-H), 7.66-7.63 (m, 3H, Ph-H), 7.56 (d, J = 1.9 Hz, 1H, Ph-H), 7.45 (d, J = 8.3 Hz, 1H, Ph-H), 7.38 (dd, J = 8.3, 1.9 Hz, 1H, Ph-H), 5.17 (s, 2H, NCH_2N), 3.51 (s, 2H, $ArCH_2$), 2.78 (bs, 4H, Piperazine-H), 2.44 (bs, 4H, Piperazine-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.7 (C=S), 140.0 (q, J = 39.2 Hz, triazole), 136.6 (Ph), 135.2 (Ph), 134.5 (Ph), 134.5 (pyrazole), 132.6 (Ph), 132.5 (Ph), 130.9 (pyrazole), 130.1 (Ph), 129.1 (Ph), 127.6 (Ph), 126.5 (Ph), 120.7 (q, J = 270.1 Hz, CF_3), 117.2 (q, J =

272.7 Hz, CF_3), 111.1 (pyrazole), 70.0 (CH_2), 58.4 (CH_2), 53.0 (piperazine-C), 50.0 (piperazine-C). Anal. calcd for $C_{26}H_{21}Cl_3F_6N_8S$: C, 44.74; H, 3.03; N, 16.06; found: C, 44.52; H, 3.22; N, 15.98.

4.2.6 General synthetic procedures for 4-(((5-Chloro-1-phenyl-3-methyl/trifluoromethyl-1*H*-pyrazol-4-yl)methylene)amino)-2-((4-arylpiperazin-1-yl)methyl)-5-(methyl/trifluoromethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (IX)

The procedure was similar to that of **VIII**, using 4-phenylpiperazine **IIIc**, or 4-(pyridin-2-yl)piperazine **IIId**, or 4-(4,6-disubstitutedpyrimidin-2-yl) piperazine **III(a-b)** as amine material to give corresponding novel 1,2,4-triazole thione **IX**.

4-(((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-3-methyl-1-((4-phenylpiperazin-1-yl)methyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXa) White solid, yield 72%, mp 152-154 ºC; IR (KBr), ν (cm^{-1}): 2944, 2816(C-H), 1599(C=N), 1533, 1502, 1452(Ar), 1162(C=S). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.44 (s, 1H, CH=N), 7.60-7.48 (m, 5H, Ph-H), 7.28 (t, J = 7.9 Hz, 2H, Ph-H), 6.94 (d, J = 8.3 Hz, 2H, Ph-H), 6.88 (t, J = 7.2 Hz, 1H, Ph-H), 5.22 (s, 2H, NCH_2N), 3.25-3.22 (m, 4H, Piperazine-H), 3.04-3.02 (m, 4H, Piperazine-H), 2.61 (s, 3H, Triazole-CH_3), 2.47 (s, 3H, Pyrazole-CH_3). Anal. calcd for $C_{25}H_{27}ClN_8S$: C, 59.22; H, 5.37; N, 22.10; found: C, 58.98; H, 5.29; N, 22.00.

4-(((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-3-methyl-1-((4-(pyridin-2-yl)piperazin-1-yl)methyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXb) White solid, yield 70%, mp 111-113 ºC; IR (KBr), ν (cm^{-1}): 2945, 2842(C-H), 1594(C=N), 1534, 1481(Ar), 1161(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H, CH=N), 8.07 (d, J = 3.2 Hz, 1H, Pyridine-H), 7.62-7.57 (m, 5H, Ph-H), 7.52-7.46 (m, 1H, Pyridine-H), 6.80 (d, J = 8.6 Hz, 1H, Pyridine-H), 6.60 (dd, J = 6.9, 5.0 Hz, 1H, Pyridine-H), 5.10 (s, 2H, NCH_2N), 3.52-3.43 (m, 4H, Piperazine-H), 2.87-2.73 (m, 4H, Piperazine-H), 2.50 (s, 3H, Triazole-CH_3), 2.36 (s, 3H, Pyrazole-CH_3). Anal. calcd for $C_{24}H_{26}ClN_9S$: C, 56.74; H, 5.16; N, 24.81; found: C, 56.79; H, 5.25; N, 24.85.

4-(((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-3-methyl-1-((4-(4-methylpyrimidin-2-yl)piperazin-1-yl)methyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXc) White solid, yield 80%, mp 155-157 ^{o}C; IR (KBr), ν (cm^{-1}): 2949, 2858(C-H), 1581(C=N), 1555, 1532, 1500, 1449(Ar), 1156(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H, CH=N), 8.17 (d, J = 4.8 Hz, 1H, Pyrimidine-H), 7.64-7.54 (m, 5H, Ph-H), 6.48 (d, J = 4.8 Hz, 1H, Pyrimidine-H), 5.10 (s, 2H, NCH_2N), 3.75-3.73 (m, 4H, Piperazine-H), 2.76-2.73 (m, 4H, Piperazine-H), 2.50 (s, 3H, Triazole-CH_3), 2.36 (s, 3H, Pyrazole-CH_3), 2.24 (s, 3H, Pyrimidine-CH_3). Anal. calcd for $C_{24}H_{27}ClN_{10}S$: C, 55.11; H, 5.20; N, 26.78; found: C, 54.99; H, 5.11; N, 26.53.

4-(((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(4,6-dimethylpyrimidin-2-yl)piperazin-1-yl)methyl)-3-methyl-1*H*-1,2,4-triazole-5(4*H*)-thione (IXd) White solid, yield 85%, mp 152-154 ^{o}C; IR (KBr), ν (cm^{-1}): 2947, 2847(C-H), 1577(C=N), 1538, 1483, 1449(Ar), 1161(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H, CH=N), 7.70-7.50 (m, 5H, Ph-H), 6.36 (s, 1H, Pyrimidine-H), 5.09 (s, 2H, NCH_2N), 3.74 (bs, 4H, Piperazine-H), 2.73 (bs, 4H, Piperazine-H), 2.50 (s, 3H, Triazole-CH_3), 2.35 (s, 3H, Pyrazole-CH_3), 2.19 (s, 6H, Pyrimidine-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0 (pyrimidine), 162.6 (C=S), 161.6 (pyrimidine), 153.9 (triazole), 150.4 (pyrazole), 147.6 (C=N), 137.4 (Ph), 131.1 (pyrazole), 129.2 (Ph), 128.9 (Ph), 125.0 (Ph), 112.4 (pyrazole), 108.8 (pyrimidine), 68.9 (CH_2), 50.7 (piperazine-C), 43.5 (piperazine-C), 24.1 (CH_3), 15.1 (CH_3), 11.1 (CH_3). Anal. calcd for $C_{25}H_{29}ClN_{10}S$: C, 55.91; H, 5.44; N, 26.08; found: C, 55.61; H, 5.51; N, 26.08.

4-(((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-phenylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXe) White solid, yield 71%, mp 123-125 ^{o}C; IR (KBr), ν (cm^{-1}): 2952, 2828(C-H), 1604(C=N), 1530, 1491, 1454(Ar), 1316, 1198(C-F), 1168(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H, CH=N), 7.65-7.50 (m, 5H, Ph-H), 7.19 (t, J = 7.3 Hz, 2H, Ph-H), 6.92 (d, J = 7.8 Hz, 2H, Ph-H), 6.77 (t, J = 7.0 Hz, 1H, Ph-H), 5.25 (s, 2H, NCH_2N), 3.14 (bs, 4H, Piperazine-H), 2.91 (bs, 4H, Piperazine-H), 2.48 (s, 3H,

Pyrazole-CH_3). Anal. calcd for $C_{25}H_{24}ClF_3N_8S$: C, 53.52; H, 4.31; N, 19.97; found: C, 53.36; H, 4.22; N, 19.88.

4-(((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(pyridin-2-yl)piperazin-1-yl)methyl)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXf) White solid, yield 73%, mp 114-116 ^oC; IR (KBr), ν (cm^{-1}): 2949, 2835(C-H), 1597(C=N), 1569, 1533, 1483(Ar), 1313, 1196(C-F), 1170(C=S). ^1H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H, CH=N), 8.08 (dd, J = 4.8, 1.8 Hz, 1H, Pyridine-H), 7.65-7.59 (m, 6H, Ph-H + Pyridine-H), 6.82 (d, J = 8.6 Hz, 1H, Pyridine-H), 6.60 (dd, J = 7.0, 5.0 Hz, 1H, Pyridine-H), 5.24 (s, 2H, NCH_2N), 3.52-3.49 (m, 4H, Piperazine-H), 2.86-2.83 (m, 4H, Piperazine-H), 2.47 (s, 3H, Pyrazole-CH_3). Anal. calcd for $C_{24}H_{23}ClF_3N_9S$: C, 52.93; H, 4.61; N, 18.99; found: C, 52.57; H, 4.69; N, 18.65.

4-(((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(4-methylpyrimidin-2-yl)piperazin-1-yl)methyl)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXg) White solid, yield 81%, mp 153-155 ^oC; IR (KBr), ν (cm^{-1}): 2935, 2829(C-H), 1599(C=N), 1569, 1531, 1487, 1448(Ar), 1317, 1199(C-F), 1155(C=S). ^1H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H, CH=N), 8.17 (s, J = 3.4 Hz, 1H, Pyrimidine-H), 7.65-7.50 (m, 5H, Ph-H), 6.47 (d, J = 3.7 Hz, 1H, Pyrimidine-H), 5.23 (s, 2H, NCH_2N), 3.76 (bs, 4H, Piperazine-H), 2.80 (bs, 4H, Piperazine-H), 2.46 (s, 3H, Pyrazole-CH_3), 2.24 (s, 3H, Pyrimidine-CH_3). Anal. calcd for $C_{24}H_{24}ClF_3N_{10}S$: C, 49.96; H, 4.19; N, 24.27; found: C, 49.71; H, 4.32; N, 24.07.

4-(((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(4,6-dimethylpyrimidin-2-yl)piperazin-1-yl)methyl)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXh) White solid, yield 84%, mp 168-170 ^oC; IR (KBr), ν (cm^{-1}): 2937, 2831(C-H), 1600(C=N), 1582, 1536, 1493, 1448(Ar), 1315, 1197(C-F), 1152(C=S). ^1H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H, CH=N), 7.70-7.50 (m, 5H, Ph-H), 6.36 (s, 1H, Pyrimidine-H), 5.23 (s, 2H, NCH_2N), 3.76 (bs, 4H, Piperazine-H), 2.79 (bs, 4H, Piperazine-H), 2.46 (s, 3H, Me), 2.19 (s, 6H, Pyrimidine-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1 (pyrimidine), 165.0 (C=S), 161.5 (pyrimidine), 159.4 (m, triazole), 155.3 (pyrazole), 151.0 (C=N), 137.3 (Ph), 131.9 (pyrazole),

129.3 (Ph), 129.0 (Ph), 125.0 (Ph), 116.9 (q, J = 271.9 Hz, CF_3), 111.9 (pyrazole), 109.0 (pyrimidine), 70.1 (CH_2), 50.5 (piperazine-C), 43.4 (piperazine-C), 24.1 (CH_3), 15.0 (CH_3). Anal. calcd for $C_{25}H_{26}ClF_3N_{10}S$: C, 50.80; H, 4.43; N, 23.70; found: C, 50.52; H, 4.54; N, 23.34.

4-(((5-Chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-3-methyl-1-((4-phenylpiperazin-1-yl)methyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXi) White solid, yield 73%, mp 139-141 ºC; IR (KBr), ν (cm^{-1}): 2944, 2825(C-H), 1598(C=N), 1528, 1494, 1451(Ar), 1322, 1182(C-F), 1146(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H, CH=N), 7.75-7.72 (m, 2H, Ph-H), 7.67-7.64 (m, 3H, Ph-H), 7.19 (t, J = 7.8 Hz, 2H, Ph-H), 6.91 (d, J = 8.3 Hz, 2H, Ph-H), 6.77 (t, J = 7.2 Hz, 1H, Ph-H), 5.12 (s, 2H, NCH_2N), 3.13 (bs, 4H, Piperazine-H), 2.87 (bs, 4H, Piperazine-H), 2.38 (s, 3H, Triazole-CH_3). Anal. calcd for $C_{25}H_{24}ClF_3N_8S$: C, 53.52; H, 4.31; N, 19.97; found: C, 53.37; H, 4.34; N, 19.83.

4-(((5-Chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-3-methyl-1-((4-(pyridin-2-yl)piperazin-1-yl)methyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXj) White solid, yield 75%, mp 145-147 ºC; IR (KBr), ν (cm^{-1}): 2939, 2833(C-H), 1595(C=N), 1532, 1488(Ar), 1300(C-F), 1174(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H, CH=N), 8.07 (d, J = 3.4 Hz, 1H, Pyridine-H), 7.73-7.71 (m, 2H, Ph-H), 7.65-7.63 (m, 3H, Ph-H), 7.56-7.40 (m, 1H, Pyridine-H), 6.80 (d, J = 8.6 Hz, 1H, Pyridine-H), 6.60 (dd, J = 6.8, 5.1 Hz, 1H, Pyridine-H), 5.10 (s, 2H, NCH_2N), 3.49 (bs, 4H, Piperazine-H), 2.80 (bs, 4H, Piperazine-H), 2.35 (s, 3H, Triazole-CH_3). Anal. calcd for $C_{24}H_{23}ClF_3N_9S$: C, 51.29; H, 4.12; N, 22.43; found: C, 51.25; H, 4.09; N, 22.26.

4-(((5-Chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-3-methyl-1-((4-(4-methylpyrimidin-2-yl)piperazin-1-yl)methyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXk) White solid, yield 75%, mp 203-204 ºC; IR (KBr), ν (cm^{-1}): 2937, 2861(C-H), 1577(C=N), 1530, 1492, 1450(Ar), 1296(C-F), 1177(C=S). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.00 (s, 1H, CH=N), 8.13 (d, J = 4.9 Hz, 1H, Pyri midine-H), 7.56 (m, 5H, Ph-H), 6.34 (d, J = 5.0 Hz, 1H, Pyrimidine-H), 5.16 (s, 2H, NCH_2N), 3.92-3.80 (m, 4H, Piperazine-H), 2.92-2.82 (m, 4H, Piperazine-H), 2.42 (s, 3H,

Triazole-CH_3), 2.30 (s, 3H, Pyrimidine-CH_3). Anal. calcd for $C_{24}H_{24}ClF_3N_{10}S$: C, 49.96; H, 4.19; N, 24.27; found: C, 49.65; H, 4.23; N, 24.18.

4-(((5-Chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(4,6-dimethylpyrimidin-2-yl)piperazin-1-yl)methyl)-3-methyl-1*H*-1,2,4-triazole-5(4*H*)-thione (IXl) White solid, yield 78%, mp 191-193 ºC; IR (KBr), ν (cm^{-1}): 2938, 2832(C-H), 1580(C=N), 1533, 1494, 1451(Ar), 1295, 1174(C-F), 1161(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H, CH=N), 7.57-7.53 (m, 5H, Ph-H), 6.23 (s, 1H, Pyrimidine-H), 5.16 (s, 2H, NCH_2N), 3.89-3.86 (bs, 4H, Piperazine-H), 2.88-2.85 (bs, 4H, Piperazine-H), 2.41 (s, 3H, Triazole-CH_3), 2.25 (s, 6H, Pyrimidine-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1 (pyrimidine), 162.6 (C=S), 161.6 (pyrimidine), 148.3 (triazole), 147.5 (C=N), 141.1 (q, *J* = 39.6 Hz, pyrazole), 136.7 (Ph), 132.1 (pyrazole), 130.0 (Ph), 129.5 (Ph), 125.4 (Ph), 120.4 (q, *J* = 270.3 Hz, CF_3), 112.7 (pyrazole), 108.9 (pyrimidine), 68.7 (CH_2), 50.7 (piperazine-C), 43.5 (piperazine-C), 24.1 (CH_3), 11.0 (CH_3). Anal. calcd for $C_{25}H_{26}ClF_3N_{10}S$: C, 50.80; H, 4.43; N, 23.70; found: C, 50.58; H, 4.54; N, 23.49.

4-(((5-Chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-phenylpiperazin-1-yl)methyl)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXm) White solid, yield 76%, mp 148-150 ºC; IR (KBr), ν (cm^{-1}): 2952, 2829(C-H), 1601(C=N), 1579, 1528, 1495, 1456(Ar), 1319, 1197(C-F), 1176(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 1H, CH=N), 7.73 (d, *J* = 3.6 Hz, 2H, Ph-H), 7.64 (d, *J* = 3.4 Hz, 3H, Ph-H), 7.19 (t, *J* = 7.5 Hz, 2H, Ph-H), 6.92 (d, *J* = 7.9 Hz, 2H, Ph-H), 6.76 (t, *J* = 7.0 Hz, 1H, Ph-H), 5.25 (s, 2H, NCH_2N), 3.13 (bs, 4H, Piperazine-H), 2.92 (bs, 4H, Piperazine-H). Anal. calcd for $C_{25}H_{21}ClF_6N_8S$: C, 48.82; H, 3.44; N, 18.22; found: C, 48.81; H, 3.65; N, 18.00.

4-(((5-Chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(pyridin-2-yl)piperazin-1-yl)methyl)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXn) White solid, yield 79%, mp 125-127 ºC; IR (KBr), ν (cm^{-1}): 2948, 2847(C-H), 1596(C=N), 1567, 1531, 1487(Ar), 1317, 1186(C-F), 1164(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.31 (s, 1H, CH=N), 8.08 (dd, *J* = 4.8, 1.6 Hz, 1H, Pyridine-H), 7.74 (dd, *J* = 6.5, 3.0 Hz, 2H, Ph-H), 7.65-7.63 (m, 3H, Ph-H), 7.51-7.47

(m, 1H, Pyridine-H), 6.82 (d, *J* = 8.6 Hz, 1H, Pyridine-H), 6.60 (dd, *J* = 7.0, 5.0 Hz, 1H, Pyridine-H), 5.24 (s, 2H, NCH_2N), 3.51-3.49 (m, 4H, Piperazine-H), 2.86-2.84 (m, 4H, Piperazine-H). Anal. calcd for $C_{24}H_{20}ClF_6N_9S$: C, 46.80; H, 3.27; N, 20.46; found: C, 46.59; H, 3.41; N, 20.25.

4-(((5-Chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(4-methylpyrimidin-2-yl)piperazin-1-yl)methyl)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXo) White solid, yield 73%, mp 108-110 °C; IR (KBr), ν (cm^{-1}): 2936, 2828(C-H), 1611(C=N), 1575, 1531, 1487, 1449(Ar), 1299, 1212(C-F), 1169(C=S). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 10.30 (s, 1H, CH=N), 8.17 (d, *J* = 4.9 Hz, 1H, Pyrimidine-H), 7.75-7.72 (m, 2H, Ph-H), 7.65-7.63 (m, 3H, Ph-H), 6.47 (d, *J* = 4.9 Hz, 1H, Pyrimidine-H), 5.23 (s, 2H, NCH_2N), 3.76 (bs, 4H, Piperazine-H), 2.82-2.79 (m, 4H, Piperazine-H), 2.24 (s, 3H, Pyrimidine-CH_3). Anal. calcd for $C_{24}H_{21}ClF_6N_{10}S$: C, 45.68; H, 3.35; N, 22.20; found: C, 45.41; H, 3.36; N, 22.12.

4-(((5-Chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-1-((4-(4,6-dimethylpyrimidin-2-yl)piperazin-1-yl)methyl)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (IXp) White solid, yield 83%, mp 120-122 °C; IR (KBr), ν (cm^{-1}): 2822(C-H), 1614(C=N), 1576, 1532, 1492, 1449(Ar), 1303, 1181(C-F), 1165(C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.30 (s, 1H, CH=N), 7.75-7.72 (m, 2H, Ph-H), 7.65-7.63 (m, 3H, Ph-H), 6.35 (s, 1H, Pyrimidine-H), 5.23 (s, 2H, NCH_2N), 3.76 (bs, 4H, Piperazine-H), 2.79 (bs, 4H, Piperazine-H), 2.19 (s, 6H, Pyrimidine-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1 (pyrimidine), 165.0 (C=S), 161.6 (pyrimidine), 150.4 (C=N), 141.9 (q, *J* = 39.5 Hz, triazole), 138.9 (d, *J* = 42.4 Hz, pyrazole), 136.6 (Ph), 132.4 (pyrazole), 130.1 (Ph), 129.5 (Ph), 125.4 (Ph), 120.1 (q, *J* = 270.6 Hz, CF_3),116.7 (d, *J* = 271.9 Hz, CF_3), 111.5 (pyrazole), 109.1 (pyrimidine), 70.1 (CH_2), 50.5 (piperazine-C), 43.5 (piperazine-C), 24.1 (CH_3). Anal. calcd for $C_{25}H_{23}ClF_6N_{10}S$: C, 46.55; H, 3.59; N, 21.71; found: C, 46.54; H, 3.55; N, 21.54.

4.2.7 General synthetic procedures for 1,1'-((piperazin-1,4-diyl)bis(methylene))bis(4-

((5-chloro-1-phenyl-3-methyl/trifluoromethyl-1*H*-pyrazol-4-yl)methylene)amino-3-methyl/trifluoromethyl-1*H*-1,2,4-triazole-5(4*H*)-thione) (X)

Schiff base **VII** (1.8 mmmol) and 37% formalin (2.5 mmol) were dissolved in ethanol (30 mL), and the mixture was stirred at room temperature for 5 min. A solution of piperazine (0.9 mmol) in ethanol (2 mL) was slowly added dropwise. Then the reaction mixture was stirred for 1 ~ 2 h at room temperature. The resulting precipitate was filtered off and recrystallized from ethanol to give novel bis(1,2,4-triazole thione) **X**.

1,1'-(Piperazine-1,4-diylbis(methylene))bis(4-(((5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-3-methyl-1*H*-1,2,4-triazole-5(4*H*)-thione) (Xa) White solid, yield 83%, mp 224-226°C(Dec.); IR (KBr), ν (cm^{-1}): 2936, 2815(C-H), 1597(C=N), 1539, 1504, 1485, 1451(Ar), 1169(C=S). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.39 (s, 2H, CH=N), 7.60-7.40 (m, 10H, Ph-H), 5.08 (s, 4H, NCH_2N), 2.86 (s, 8H, Piperazine-H), 2.57 (s, 6H, Pyrazole-CH_3), 2.41 (s, 6H, Triazole-CH_3). Anal. calcd for $C_{34}H_{36}Cl_2N_{14}S_2$: C, 52.64; H, 4.68; N, 25.28; found: C, 52.81; H, 4.65; N, 25.13.

1,1'-(Piperazine-1,4-diylbis(methylene))bis(4-(((5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)-3-(trifluoromethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione) (Xb) White solid, yield 87%, mp 185-187°C(Dec.); IR (KBr), ν (cm^{-1}): 2940, 2857(C-H), 1599(C=N), 1533, 1504, 1485, 1460(Ar), 1315, 1189(C-F), 1171(C=S). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.35 (s, 2H, CH=N), 7.60-7.40 (m, 10H, Ph-H), 5.18 (s, 4H, NCH_2N), 2.89 (s, 8H, Piperazine-H), 2.56 (s, 6H, Pyrazole-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.0 (C=S), 155.3 (pyrazole), 151.0 (C=N), 138.8 (q, J = 42.0 Hz, triazole), 137.3 (Ph), 131.9 (pyrazole), 129.3(Ph), 129.0(Ph), 125.0 (Ph), 116.9 (q, J = 271.6 Hz, CF_3), 111.9 (pyrazole), 69.8 (CH_2), 50.3 (piperazine), 15.0 (CH_3). Anal. calcd for $C_{34}H_{30}Cl_2F_6N_{14}S_2$: C, 46.21; H, 3.42; N, 22.19; found: C, 46.38; H, 3.61; N, 21.99.

1,1'-(Piperazine-1,4-diylbis(methylene))bis(4-(((5-chloro-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methylene)amino)-3-methyl-1*H*-1,2,4-triazole-5(4*H*)-thione) (Xc) White solid, yield 89%, mp 213-215°C(Dec.); IR (KBr), ν (cm^{-1}): 2939, 2828(C-H), 1594(C=N), 1530, 1494, 1453(Ar), 1326(C-F), 1175(C=S). ^{1}H NMR (400

MHz, $CDCl_3$): δ 10.99 (s, 2H, CH=N), 7.60-7.50 (m, 10H, Ph-H), 5.06 (s, 4H, NCH_2N), 2.85 (s, 8H, Piperazine-H), 2.42 (s, 6H, Triazole-CH_3). Anal. calcd for $C_{34}H_{30}Cl_2F_6N_{14}S_2$: C, 46.21; H, 3.42; N, 22.19; found: C, 46.08; H, 3.39; N, 22.29.

1,1'-(Piperazine-1,4-diylbis(methylene))bis(4-(((5-chloro-1-phenyl-3-(trifluoro methyl)-1*H*-pyrazol-4-yl)methylene)amino)-3-(trifluoromethyl)-1*H*-1,2,4-triazole -5(4*H*)-thione) (Xd) White solid, yield 84%, mp 197-198ºC(Dec.); IR (KBr), ν (cm^{-1}): 2945, 2851(C-H), 1597(C=N), 1535, 1493, 1462(Ar), 1322, 1186(C-F), 1164(C=S). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.82 (s, 2H, CH=N), 7.58-7.50 (m, 10H, Ph-H), 5.17 (s, 4H, NCH_2N), 2.88 (s, 8H, Piperazine-H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9 (C=S), 150.4 (C=N), 141.9 (q, *J* = 39.8 Hz, triazole), 139.0 (q, *J* = 41.8 Hz, pyrazole), 136.6 (Ph), 132.5 (pyrazole), 130.1 (Ph), 129.5 (Ph), 125.4 (Ph), 120.1 (q, *J* = 270.7 Hz, CF_3), 116.7 (q, *J* = 271.3 Hz, CF_3), 111.4 (pyrazole), 69.7 (CH_2), 50.3 (piperazine). Anal. calcd for $C_{34}H_{24}Cl_2F_{12}N_{14}S_2$: C, 41.18; H, 2.44; N, 19.77; found: C, 40.92; H, 2.48; N, 19.71.

4.3 Biological activity tests

4.3.1 Herbicidal activity test

The *in vivo* herbicidal activities were determined by the inhibition tests of the root-growth of rape (*Brassica campestris*) and the seedling-growth of barnyardgrass (*Echinochloa crusgalli*) according to the reported protocol [46]. The commercial herbicide Chlorsulfuron was used as the control.

4.3.2 Fungicidal activity test

The *in vitro* fungicidal activities against *Alternaria solani Sorauer*, *Gibberella sanbinetti*, *Fusarium omysporum*, *Cercospora arachidicola*, *Physalospora piricola* and *Rhizoctonia cerealis* were evaluated *via* the mycelium growth rate test according to the reported protocol [47]. The commercial fungicides Triadimefon, Carbendazim and Chlorothalonil were used as controls.

The *in vivo* fungicidal activities against *Puccinia sorghi* Schw. was tested according to the reported method [48], and the commercial fungicides Azoxystrobin

and Triadimefon were used as controls.

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Supplementary data

All the supplementary data associated with this article including ^{1}H NMR and IR spectra for compounds **VIII**, **IX** and **X**, ^{13}C NMR spectra for representative compounds and herbicidal and *in vitro* fungicidal activities for some of the compounds can be found in the online version.

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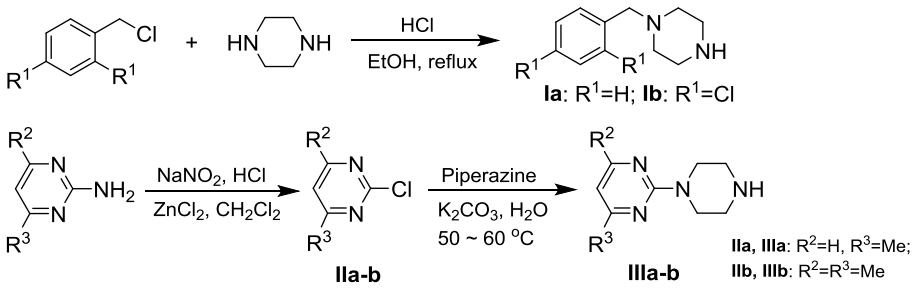
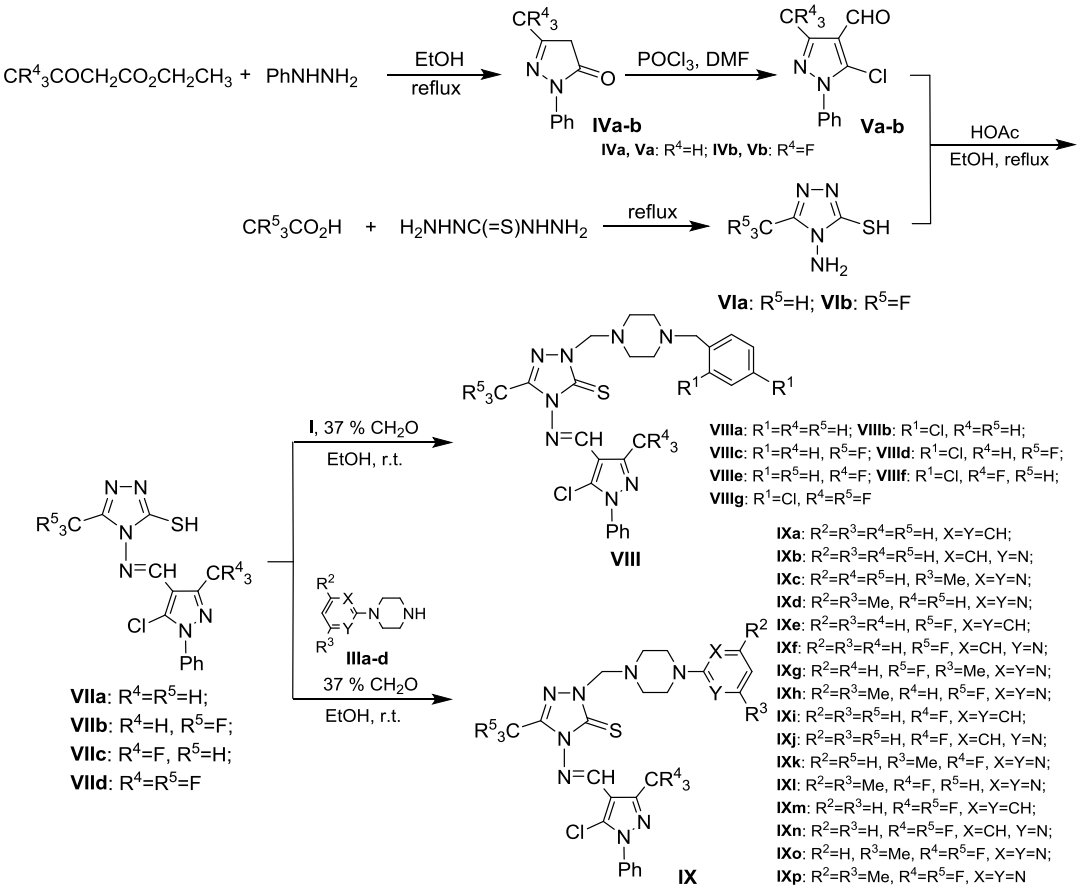
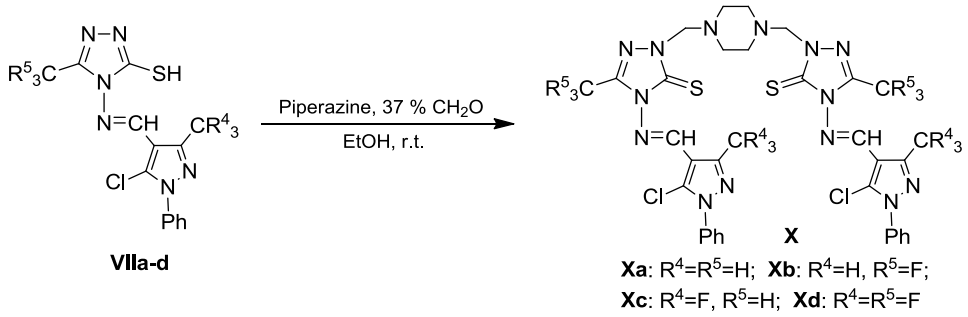


Scheme 1. The synthetic routes of the intermediates **Ia-b** and **IIIa-b**.



Scheme 2. The synthetic routes of the title compounds **VIIIa-g** ang **IXa-p**.

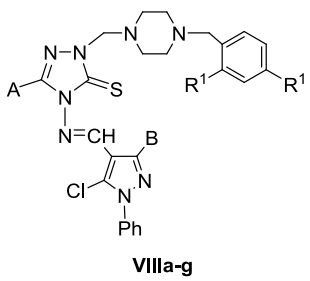


Scheme 3. The synthetic routes of the title compounds **Xa-d**.

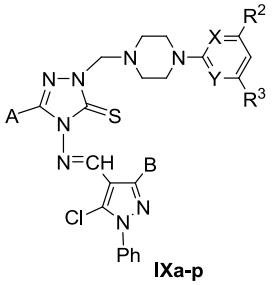
Table 1. The herbicidal activities of tested compounds at 100 μg/mL concentration (% inhibition)

Compd.	*Brassica campestris*	*Echinochloa crusgalli*
VIIIc	7.3	30.0
VIIIe	18.2	0
VIIIg	19.5	18.9
IXe	0	40.0
IXf	0	50.0
IXg	5.0	20.0
IXh	0	15.0
IXm	8.9	21.6
IXn	20.9	21.6
IXo	18.6	25.0
IXp	0	16.2
Xb	0	12.0
Xd	17.5	13.5
Chlorsulfuron	80.4	29.9

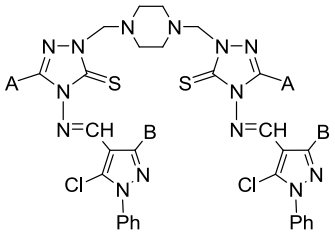
Table 2. The *in vitro* fungicidal activities of tested compounds at 50 μg/mL concentration (% inhibition)



VIIIa-g



IXa-p



Xa-d

Compd.	A	B	*Alternaria solani Sorauer*	*Gibberella sanbinetti*	*Fusarium omysporum*	*Cercospora arachidicola*	*Physalospora piricola*	*Rhizoctonia cerealis*
VIIIb	CH_3	CH_3	40.0	52.6	3.7	33.3	63.8	53.1
VIIId	CF_3	CH_3	26.7	47.4	3.7	23.8	44.7	85.7
VIIIf	CH_3	CF_3	31.6	41.5	22.6	35.0	60.5	60.7
VIIIg	CF_3	CF_3	47.6	31.0	11.1	75.0	12.5	91.8
IXb	CH_3	CH_3	33.3	21.1	3.7	33.3	34.0	53.1
IXc	CH_3	CH_3	33.3	5.3	25.9	42.9	55.3	46.9
IXf	CF_3	CH_3	46.7	21.1	7.4	33.3	44.7	65.3
IXg	CF_3	CH_3	43.8	62.5	20.7	42.1	49.0	76.5
IXi	CH_3	CF_3	47.6	58.6	55.6	62.5	75.0	61.2
IXj	CH_3	CF_3	42.9	44.8	16.7	50.0	37.5	57.1
IXk	CH_3	CF_3	31.6	14.6	29.0	25.0	48.8	35.7
IXn	CF_3	CF_3	28.6	31.0	16.7	25.0	50.0	93.9
IXo	CF_3	CF_3	33.3	44.8	5.6	87.5	25.0	98.0
IXp	CF_3	CF_3	47.6	55.2	5.6	75.0	43.8	91.8
Xa	CH_3	CH_3	23.8	37.9	11.1	50.0	75.0	63.3
Xb	CF_3	CH_3	38.1	44.8	5.6	12.5	0.0	57.1
Xc	CH_3	CF_3	23.8	44.8	11.1	50.0	6.3	57.1
Xd	CF_3	CF_3	31.6	26.8	29.0	35.0	58.1	83.9
Triadimefon			31.3	52.9	63.6	66.7	71.4	98.0
Carbendazim			100			100		
Chlorothalonil				72.2	75		100	

Table 3. The *in vivo* fungicidal activities of tested compounds at 200 μg/mL concentration (% control efficacy)

Compd.	*Puccinia sorghi* Schw.
VIIId	0
VIIIg	10
IXm	10
IXn	30
IXp	60
Azoxystrobin	99（20 μg/mL）
Triadimefon	95