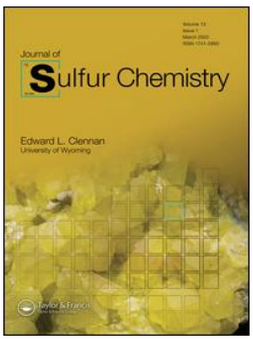

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New potential fungicides pyrazole-based heterocycles derived from 2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl) acryloyl isothiocyanate

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ABSTRACT

New series of pyrazole-based heterocyclic systems were synthesized using 2-cyanopropenoyl isothiocyanate derivative as an intermediate through treating with some nucleophilic reagents. Therefore, derivatives of carbamothioate, acylthiourea, pyrimidinethione, benzothiazole, triazolopyrimidine, pyrimidobenzothiazine, and pyrimidothiadiazepine were obtained. Structures of the obtained compounds were elucidated according to their elemental analyses and compatible spectral data. The fungicidal activity of the title compounds was evaluated against five plant pathogens belonging to both airborne and soil-borne strains using the radial growth rate method and the pyrazole derivative **13** was the most potent one that showed better fungicidal activity against *F. Solani* and *R. Solani* soil-borne fungi than the standard fungicide and moderate activity against airborne fungi. Also, pyrazole derivative **16** displayed better activity than the two standard fungicides against *B. cinerea* airborne fungus. Both *A. Alternata* and *S. Sclerotiorum* airborne fungi showed more resistance to the new pyrazoles than the standard fungicides. This means, fungicidal activity of the synthesized pyrazoles is remarkably diversified and affected by the heterocyclic ring or functional group attached to the core pyrazole.

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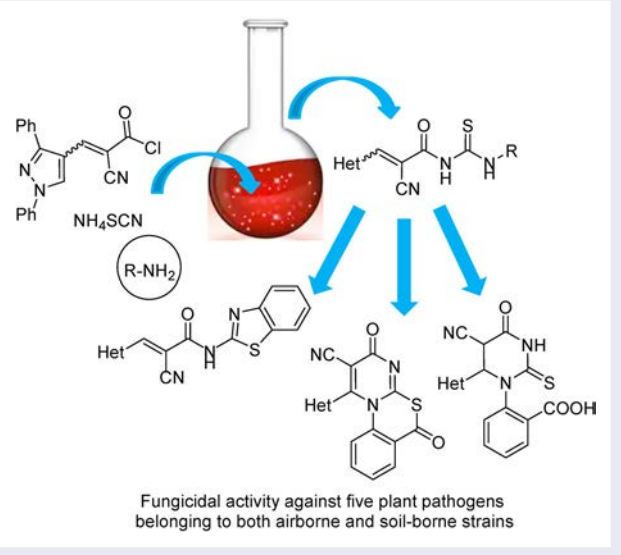


Introduction

Aroyl isothiocyanates have been extensively transformed into various nitrogen heterocycles in addition to thiosemicarbazide derivatives.[1–3] Also, owing to the diverse chemotherapeutic effects, pyrazole tethered heterocycles have received great attention.[4–16] As a result, many pharmaceutical and agrochemical active pyrazole derivatives were published (cf. Figure 1).[11,17–27] Otherwise, fungal diseases attacking plants are a serious problem worldwide due to their severe effect on crop quality and yield. About 16% of annual crop losses due to plant microbial diseases, fungal diseases represent 70-80% of these losses.[28,29] Enthused by these fascinating results and in continuation of our work on the pharmacological as well as agrochemical active heterocyclic systems,[30–37] 2-cyano-3-pyrazolylpropenoyl isothiocyanate derivative **2** was utilized as a key material for the synthesis of acylthiourea, pyrimidinethione, benzothiazole, triazolopyrimidine, and pyrimidothiadiazepine derivatives integrated with the core pyrazole, to may enhance its expected biological effect through the coexistence of more than one pharmacophore. Our strategy aimed to design new pyrazole derivatives that may have better fungicidal activity than the commercially applied fungicides that showed some resistant problems.[38]

Results and discussion

Chemistry

Herein, the key material, 2-cyano-3-pyrazolylpropenoyl chloride derivative **1** [6,7] was treated with ammonium thiocyanate in dry acetonitrile to produce the corresponding isothiocyanate derivative **2** (Scheme 1). Treatment of **2** with ethanol or aminoacetic acid in

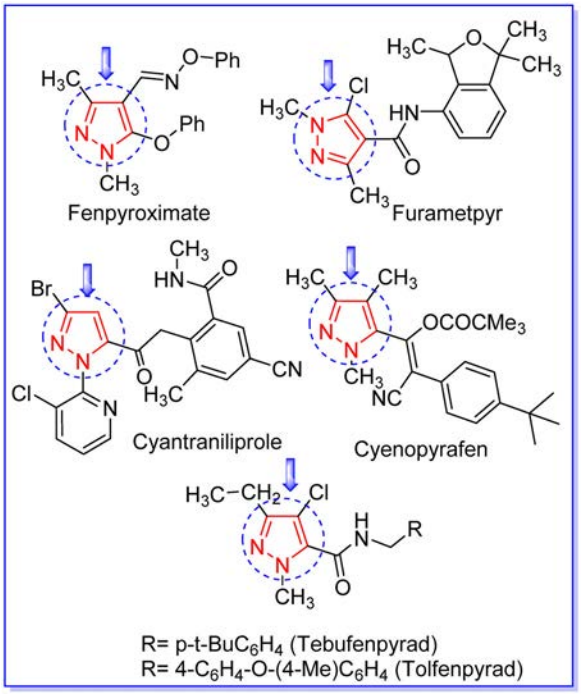
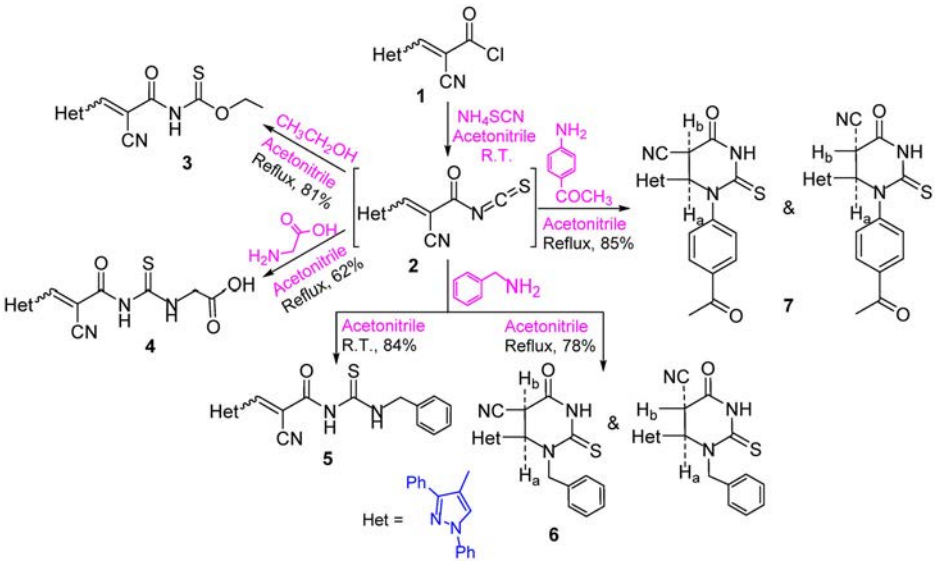
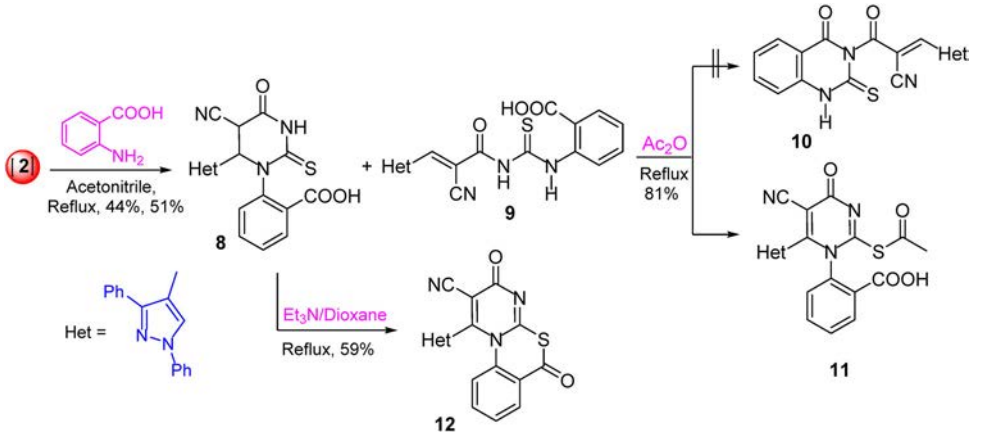


Figure 1. Some agrochemical pyrazole-based molecules.

boiling acetonitrile achieved carbamothioate and acylthiourea derivatives **3** and **4**, respectively (Scheme 1). IR spectrum of **3** disclosed the following bands: 3399 (NH), 2204 (C≡N), 1721 (C = O). Its ^{1}H NMR spectrum (DMSO-d_6) revealed singlet signals for NH at δ 12.05 ppm, C5-H pyrazole at δ 9.16 ppm, the olefinic proton at δ 8.09 ppm, and quartet signal for CH_2 protons at δ 3.44 ppm ($J = 6.9\,Hz$), triplet signal for CH_3 protons at δ 1.06 ppm ($J = 6.9\,Hz$), in addition to the aromatic protons at $\delta \sim$ 8.04-7.45 ppm. IR spectrum of **4** displayed the absorption bands for OH, NH groups at ν 3462, 3316, 3155 cm^{-1}, C≡N at ν 2225 cm^{-1}, C = O acid at ν 1703cm^{-1}, and C = O amide at ν 1670 cm^{-1}. Further, its ^{1}H NMR spectrum supported its structure as it provided the following signals: 13.50 (*br*.s, 1H, COOH, exchangeable), 11.29 (*br*.s, 1H, NH, exchangeable), 9.60 (*br*.s, 1H, NH, exchangeable), 9.17 (s, 1H, C5-H pyrazole), 8.22 (s, 1H, CH=), 8.09-7.36 (m, 10H, Ar-H), 4.40 (s, 2H, CH_2). On contrary, the interaction of **2** with benzylamine at ambient temperature furnished the acylthiourea derivative **5** in a good yield while at boiling conditions, the pyrimidinethione derivative **6** was acquired as a mixture of cis and trans isomers in a ratio of 1:1. Chromatography and recrystallization of the mixture obtained of cis- and trans-isomers were not successful for their separation. IR spectrum of **5** displayed the bands for NH, C≡N, C = O, and C = S groups at ν 3286, 2217, 1715, and 1231 cm^{-1}, respectively. Further support for its structure was the ^{1}H NMR spectrum as it exhibited a singlet signal for methylene protons at δ 4.04 ppm, a singlet signal for C5-H pyrazole at δ 9.06 ppm, a singlet signal for olefinic proton at δ 7.92 ppm, and an exchangeable singlet signal at δ 8.50 ppm integrated to two protons corresponding to two NH protons, as well as multiplet signals for the aromatic protons. The ^{1}H NMR spectrum of **6** displayed a singlet



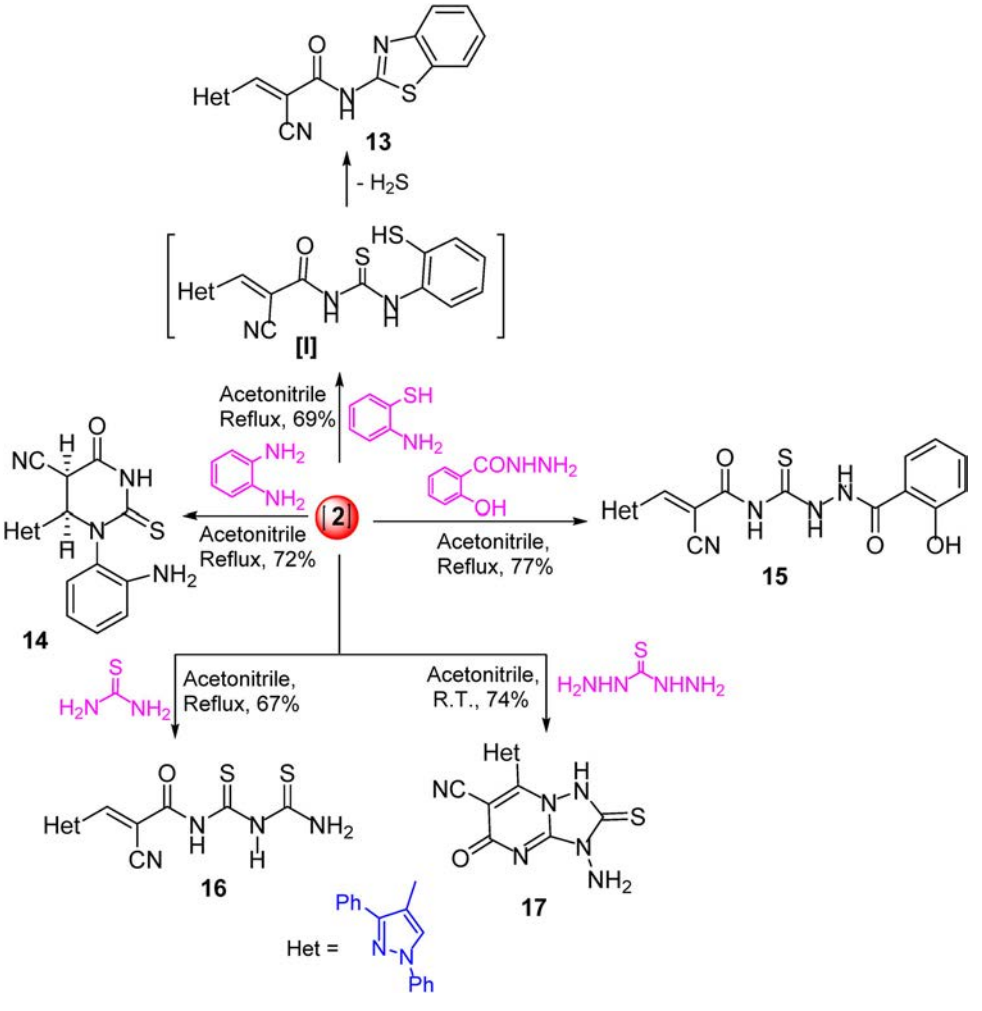
Scheme 1. Synthesis of compounds **3-7**.



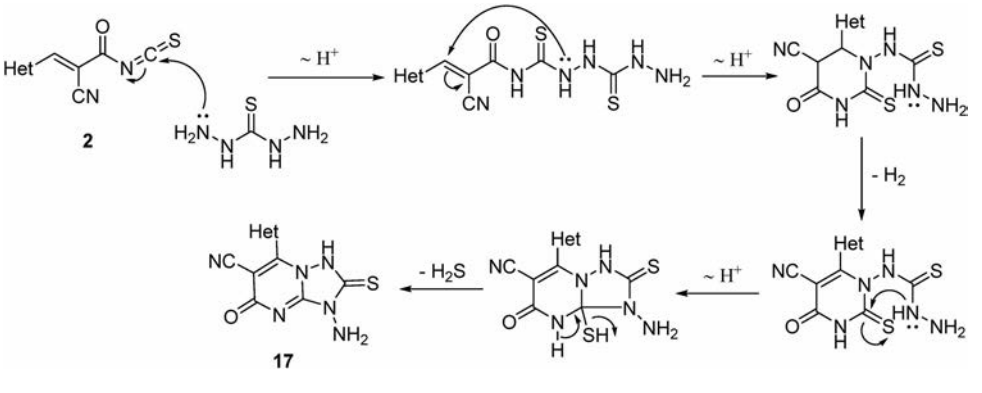
Scheme 2. Synthesis of compounds **8-12**.

signal for the methylene protons at δ 4.84 ppm, two doublet signals for CH_a, and two doublet signals for CH_b. Formation of pyrimidinethione derivative **6** can be extrapolated by 1,6-endo-trig cyclization of **5** *via* aza-Michael addition on the activated β-carbon. In a similar manner, pyrimidinethione derivative **7** was furnished as a mixture of cis and trans isomers in a ratio of 1:1, upon conducting **2** with 4-aminoacetophenone. Ample evidence for the assigned structure of **7** was its ^{1}H NMR spectrum which exhibited two doublet signals for vicinal CH–CH protons (cf. Experimental).

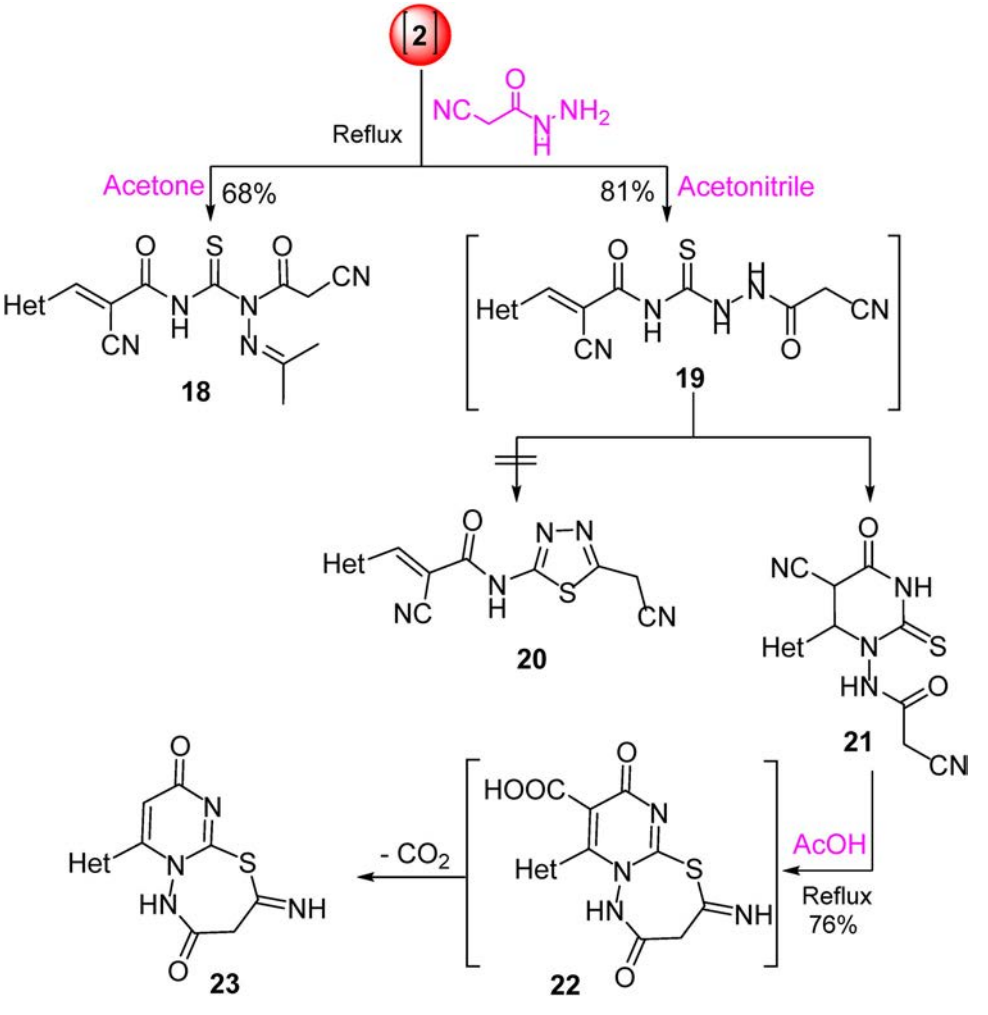
Treatment of **2** with 2-aminobenzoic acid afforded a mixture of pyrimidinethione derivative **8** and acylthiourea derivative **9** which were separated by the fractional recrystallization (cf. Experimental). The ^{1}H NMR spectrum of **8** lacked the olefinic singlet which was conserved in compound **9**. Refluxing the latter in acetic anhydride failed to produce



Scheme 3. Synthesis of compounds **13-17**.



Scheme 4. A plausible pathway for compound **17**.



Scheme 5. Reaction of **[2]** with 2-cyanoethanohydrazide.

quinazoline derivative **10** and achieved the pyrimidine derivative **11** (Scheme 2). The IR spectrum of **11** displayed carbonyl functionality at ν 1656 cm^{-1} which ruled out the structure **10**. Ample evidence for structure **11** was acquired from its ^{1}H NMR spectrum as it disclosed one exchangeable singlet signal at δ 11.87 ppm corresponding to the carboxylic proton, in addition to a singlet signal in the upfield region at δ 2.13 ppm integrated for three protons corresponding to the acetyl group. Cyclocondensation of **8** in boiling dioxane including triethylamine afforded pyrimidobenzothiazine derivative **12**. The ^{1}H NMR spectrum of **12** was devoid of any labile hydrogen.

Interaction of isothiocyanate derivative **2** with 2-aminothiophenol, 2-aminoaniline, 2-hydroxybenzoylhydrazine, and thiourea in boiling acetonitrile achieved benzothiazole, pyrimidinethione, and acylthiourea derivatives **13-16**, respectively (Scheme 3). The IR spectrum of **13** showed NH, C≡N, and C = O absorptions at ν 3142, 2216, and 1677 cm^{-1}, respectively. Also, its ^{1}H NMR spectrum disclosed two singlet signals for C5-H pyrazole (at δ 9.19 and 9.15 ppm), and two singlet signals for olefinic proton (at δ 8.32 and

8.08 ppm) which showed its existence as a mixture of *E*- and *Z*-isomers in a ratio of 1:1. Furthermore, its mass spectrum displayed the molecular ion peak at *m/z* 447 (53%) and the base peak fragment at *m/z* 77 corresponding to phenyl cation, as well as some important fragments. Formation of benzothiazole derivative **13** was distinctly interpreted *via* cyclization of thiourea intermediate [**I**] by removing gaseous hydrogen sulfide molecule, as detected by the change in color of lead acetate paper into black. The ^{1}H NMR spectrum of **14** displayed an exchangeable singlet integrated to two protons of the primary amino group and showed its existence as a mixture of cis and trans isomers in a ratio of 1:1 by showing four doublet signals corresponding to vicinal CH–CH protons. The IR spectrum of **15** showed OH, NH, C≡N, and C = O absorptions at ν 3403, 3203, 2205, and 1686 cm^{-1}, respectively. Moreover, its ^{1}H NMR spectrum displayed four exchangeable singlet signals corresponding to one OH and three NH protons at δ 12.32, 11.80, 11.20, and 10.91 ppm. The IR spectrum of **16** retained the nitrile and carbonyl functionalities. Its ^{1}H NMR spectrum exhibited three exchangeable singlet signals corresponding to two NH and NH_2 protons. In contrast, treating **2** with hydrazinecarbothiohydrazide at room temperature furnished the triazolopyrimidine derivative **17** which can be visualized *via* Scheme 4. The IR spectrum of **17** conserved both nitrile and carbonyl functionalities. The existence of exchangeable singlet signals for NH and NH_2 protons and the absence of singlet signal of the olefinic proton in its ^{1}H NMR spectrum supported the assigned structure. Furthermore, its mass spectrum displayed the $M^{+\cdot}$ peak at *m/z* 426 (6%) and a fragment at *m/z* 77 as a base peak corresponding to phenyl cation (cf. Experimental).

Noteworthy, the interaction of **2** with 2-cyanoethanohydrazide was dependent on the reaction conditions. Therefore, execution of the reaction in dry acetone as a solvent afforded the hydrazone derivative **18** while using acetonitrile yielded the pyrimidinethione derivative **21** instead of thiadiazole derivative **20** through the intermediate **19** as depicted in Scheme 5. Formation of **18** can be viewed *via* the first condensation of 2-cyanoethanohydrazide with acetone to give a non-isolable hydrazone intermediate followed by aza-Michael addition on the isothiocyanate functionality. The IR spectrum of **21** exhibited the following bands (ν, cm^{-1}): 3227, 3121 (NH), 2260, 2224 (C≡N), 1695, 1663 (C = O). Compelling support for structure **21** was its ^{1}H NMR spectrum as it provided the following signals (300 *MHz*, DMSO-d_6): 12.25, 10.88 (br.s, exchangeable, 2 NH), 8.75 (s, C5-H pyrazole), 7.88-7.37 (m, Ar-H), 5.92 (d, CH_a, $J = 6.5\,Hz$), 5.43 (d, CH_b, $J = 6.4\,Hz$), 3.47 (s, CH_2). Its mass spectrum showed the $M^{+\cdot}$ peak at *m/z* 455 (7%) and a fragment at *m/z* 77 as a base peak corresponding to phenyl cation. Interestingly, boiling **21** in glacial acetic acid afforded the pyrimidothiadiazepine derivative **23** as orange crystals. The reaction can be explained *via* intramolecular cyclization of **21** to give **22** which subsequently underwent decarboxylation (cf. Scheme 5). The IR spectrum of **23** was devoid of nitrile functionality. Its ^{1}H NMR spectrum provided two exchangeable singlet signals in the downfield region for two NH protons, in addition to a singlet signal for methylene protons. Further support was its mass spectrum showed the molecular ion peak at *m/z* 428 (28%) as well as some of the important fragments (cf. Experimental).

Fungicidal activity

Most of the newly synthesized pyrazoles were evaluated for their *in vitro* antifungal activity against the five targeted fungi namely, *Fusarium Solani* and *Rhizoctonia Solani* soil-borne

Table 1. Fungicidal activity of the synthesized pyrazoles against *F. Solani* and *R. Solani* soil-borne fungi.

Fungus	F. Solani			R. Solani		
Compound No.	**EC_{50}∗(mg/L)**	Slope of toxicity line	T.I∗∗	**EC_{50}∗(mg/L)**	Slope of toxicity line	T.I∗∗
3	905.0	2.61	34.3	316.8	2.16	60.9
4	771.9	1.24	40.2	278.6	1.93	69.3
6	506.5	2.64	61.2	275.6	2.88	70.0
7	633.9	2.88	48.9	640.2	6.83	30.1
8	739.2	2.40	41.9	707.2	6.22	27.3
9	393.9	2.14	78.7	254.8	3.78	75.7
13	310.0	2.18	100.0	192.9	3.27	100.0
14	685.4	3.01	45.2	617.8	3.59	31.2
15	629.5	2.93	49.3	575.9	1.62	33.5
16	721.4	1.56	42.7	206.9	3.78	93.2
17	529.5	2.37	58.5	205.8	3.55	93.7
18	829.6	3.31	37.4	195.9	3.51	98.5
Pencycuron	490.7	2.14	63.2	230.8	2.75	83.6

∗ The EC_{50} is the effective concentration that gives 50% of the radial growth inhibition of the fungus.
∗∗ Toxicity index (T.I) is the % of EC_{50} of the tested compound related to the most potent one that having the lowest such value.

fungi that cause damping-off and wilt incidence of different plants,[28] as well as, *Botrytis cinerea, Sclerotinia Sclerotiorum,* and *Alternaria Alternata* airborne pathogenic fungi attacking plants and crops causing many pre- and post-harvest diseases like grey mold, white mold, leaf blight, leaf blotch, and rust.[39–41] Data in Table 1 represent the fungicidal activity of screened pyrazoles against *F. Solani* and *R. Solani* soil-borne fungi. Pencycuran (Monceren 25% WP) was used as a positive control or standard fungicide. Looking closely at the toxicity parameters (EC_{50} and T.I values), synthesized pyrazoles showed differentiated behavior with good activities against the targeted strains. Particularly, the activities of pyrazole derivatives **9** and **13** were found to be more active than the standard fungicide against *F. Solani* fungus with EC_{50} values 310.0, 393.9, and 490.7 mg/L for compounds **13**, **9,** and standard fungicide, respectively. Besides, compounds **13**, **16**, **17,** and **18** displayed high activities against *R. Solani* fungus whereas, their EC_{50} values ranged from 192.9–206.9 mg/L comparing to 230.8 mg/L of the standard fungicide. Data also show that *F. Solani* fungus possessed high resistance to pyrazole derivatives **3** and **18** while, *R. Solani* fungus possessed a notable resistance to pyrazoles **7**, **8**, **14,** and **15**. EC_{50} values of such compounds were found to be double or more double than that of the standard fungicide. According to the values of the toxicity index, we can descendingly arrange the activity of the highest three potent new pyrazoles as **13**, **9,** and **6** against *F. Solani* fungus and **13**, **18,** and **17** against *R. Solani* fungus.

Data in Tables 2 illustrate the fungi toxic effects of the screened pyrazoles against *B. cinerea, S. Sclerotiorum,* and *A. Alternata* airborne pathogens. A perusal of activity data indicates that all the synthesized pyrazoles have stronger activity than the standard fungicide Metalaxyl against the three tested fungi, as the latter showed no inhibition activity up to 500 mg/L treatment. As in Table 2, *B. cinerea* fungus was found to be highly resistant to both standard fungicides (Metalaxyl and Mancozeb) but it showed notable sensitivity to the tested pyrazoles especially compounds **16**, **9**, **4**, **13,** and **17**. The EC_{50} values of these compounds respectively are 178.4, 209.5, 240.1, 250.0, and 273.4 mg/L and their toxicity indexes ranged from 100.0–60.3. In turn, the activity of the synthesized pyrazoles against *A. Alternata* and *S. Sclerotiorum* fungi is higher than that of the standard fungicide Metalaxyl

but less than that of the standard fungicide Mancozeb. The most active pyrazoles against *A. Alternata* fungus are **16**, **9,** and **13** while those against *S. Sclerotiorum* are **13**, **16,** and **9**, respectively. Introducing benzothiazole nucleus (compound **13**) and thiourea group (compound **16**) remarkably increases the activity of pyrazole core which is compatible with the published works.[42–46] Addition of benzothiazole nucleus increases the activity against soil-borne fungi while linking with thiourea group increases the activity towards most of the tested fungi especially *B. cinerea* fungus. Oppositely, linking the core pyrazole with pyrimidinthione derivatives (compounds **6**, **7,** and **8**) highly reduces the activity towards all tested strains, especially the airborne fungi (see more details in the supplemental Tables I–V).

Conclusion

A propenoyl isothiocyanate derivative was utilized for the synthesis of pyrimidinethione, benzothiazole, pyrimidothiadiazepine, pyrimidobenzothiazine, and acylthiourea derivatives encompassing a 1,3-diphenylpyrazole core. The synthesized compounds were evaluated for their antifungal activity against five pathogenic fungi belonging to both soil-borne and airborne strains. Generally based on data obtained, pyrazole derivative **13** is the most potent one that showed better fungicidal activity against *F. Solani* and *R. Solani* soil-borne fungi than the standard fungicide and moderate activity against airborne fungi. In the same boat, pyrazole derivative **16** showed better activity than the two standard fungicides against *B. cinerea* airborne fungus. Both *A. Alternata* and *S. Sclerotiorum* airborne fungi showed more resistance to the new pyrazoles than the standard fungicides. This means, fungicidal activity of the synthesized pyrazoles is remarkably diversified and affected by the heterocyclic ring or functional group attached to the core pyrazole.

Experimental

Chemistry

Melting points were measured on a GALLENKAMP electric melting point apparatus and are uncorrected. IR spectra (ν, cm^{-1}) were run using KBr disks on Fourier Transform Infrared Thermo Electron Nicolet iS10 Spectrometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) at Chemistry Department, Faculty of Science, Ain Shams University. The ^{1}H NMR and ^{13}C NMR spectra (δ, ppm) were recorded at 300 and 75 *MHz* on a Varian GEMINI (GEMINI, Manufacturing & Engineering Inc., Anaheim, CA, USA) utilizing tetramethylsilane as an internal standard in deuterated dimethyl sulfoxide (DMSO-d_6) at Faculty of Science, Cairo University. Mass spectra were carried out on direct probe controller inlet part to single quadrupole mass analyzer in (Thermo Scientific GCMS) MODEL (ISQ LT) using Thermo X-CALIBUR software at the regional center for mycology and biotechnology (RCMB), Al-Azhar University, Cairo, Egypt. Elemental analyses were recorded at Faculty of Science, Ain Shams University using Perkin-Elmer 2400 CHN elemental analyzer, and satisfactory analytical data (± 0.4) were obtained for all compounds. Reagents and solvents were purified and dried by standard techniques. The reactions were monitored by thin-layer chromatography (TLC) using Merck Kiesel gel $60F_{254}$ obtained from Fluka, Switzerland. The starting acid chloride **1** was previously reported by us.[6,7]

Table 2. Fungicidal activity of the newly synthesized pyrazoles against *B. cinerea, S. Sclerotiorum,* and *A. Alternata* airborne fungi.

Fungus	B. cinerea			A. Alternata			S. Sclerotiorum		
Compound No.	EC_{50}* (mg/L)	Slope of toxicity line	T.I**	EC_{50}* (mg/L)	Slope of toxicity line	T.I**	EC_{50}* (mg/L)	Slope of toxicity line	T.I**
3	444.8	2.46	40.1	384.2	2.03	19.2	217.5	1.91	49.8
4	240.1	2.17	74.3	860.5	2.63	8.6	288.6	1.99	37.6
6	514.7	3.89	34.7	348.4	1.29	21.2	304.9	2.20	35.6
7	900.8	337	19.8	666.0	2.58	11.1	605.0	3.72	17.9
8	620.4	1.84	28.8	930.2	2.30	7.9	239.3	2.56	45.3
9	209.5	3.41	85.2	223.6	2.09	32.9	208.8	2.27	51.9
13	250.0	2.42	71.4	229.6	2.08	32.1	179.6	2.40	60.4
14	1343.1	3.13	13.3	1084.3	1.44	6.8	936.8	3.81	11.6
15	844.8	3.29	21.1	887.2	2.11	8.3	519.8	1.90	20.9
16	178.4	3.27	100.0	188.9	2.25	39.0	197.3	3.07	54.9
17	273.4	3.56	65.3	289.3	2.02	25.5	301.1	2.77	36.0
18	567.4	1.87	31.4	542.8	1.84	13.6	294.1	1.90	36.9
Metalaxyl	*	*	*	*	*	*	*	*	*
Mancozeb	*	*	*	73.7	3.23	100.0	108.4	4.03	100.0

* The EC_{50} is the effective concentration that gives 50% of the radial growth inhibition of the fungus.
** Toxicity index (T.I) is the % of EC_{50} of the tested compound related to the most potent one that has the lowest such value.

2-Cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acryloyl Isothiocyanate (2)

Ammonium thiocyanate (5.2 mmol) was added to a stirred solution of the acid chloride **1** (5 mmol) in dry acetonitrile (10 mL), and the reaction mixture was further stirred for 20 min at room temperature to give the isothiocyanate intermediate **2** which was then used in the following reactions.

General procedure for the synthesis of compounds 3–7

The appropriate reagent namely, ethanol, aminoacetic acid, benzylamine, and 4-aminoacetophenone (5 mmol) was added to a suspension of isothiocyanate derivative **2** (5 mmol) in acetonitrile, prepared *in situ*. The reaction mixture was heated under reflux for 2-4 h and/or stirred at an ambient temperature for 1 h in the case of benzylamine. The deposited solid was collected and recrystallized from the suitable solvent to furnish compounds **3-7**.

O-Ethyl (2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acryloyl)carbamothioate (3)

Canary-yellow crystals, mp. 178–180°C (Ethanol), yield 81%. IR: 3399 (NH), 2204 (C≡N), 1721 (C = O), 1292 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 12.05 (br.s, 1H, NH, exchangeable), 9.16 (s, 1H, C5-H pyrazole), 8.09 (s, 1H, CH=), 8.04-7.45 (m, 10H, Ar-H), 3.44 (q, 2H, CH_2, J = 6.9 *Hz*), 1.06 (t, 3H, CH_3, J = 6.9 *Hz*). MS, *m/z* (%): 404 (M+2, 3), 402 ($M^{+\cdot}$, 11), 343 (100), 314 (11), 298 (21), 270 (37), 242 (7), 140 (5), 94 (4), 77 (10). Anal. Calcd. for $C_{22}H_{18}N_4O_2S$ (402.47): C, 65.65; H, 4.51; N, 13.92. found: C, 65.40; H, 4.39; N, 13.87%.

((2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acryloyl)carbamothioyl)glycine (4)

Yellow crystals, mp. 232–234°C (Benzene), yield 62%. IR: 3462 (br.OH), 3316, 3155 (NH), 2225 (C≡N), 1703 (C = O acid), 1670 (C = O amide), 1232 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 13.50 (br.s, 1H, COOH, exchangeable), 11.29 (br.s, 1H, NH, exchangeable), 9.60 (br.s, 1H, NH, exchangeable), 9.17 (s, 1H, C5-H pyrazole), 8.22 (s, 1H, CH=), 8.09-7.36 (m, 10H, Ar-H), 4.40 (s, 2H, CH_2). Anal. Calcd. for $C_{22}H_{17}N_5O_3S$ (431.47): C, 61.24; H, 3.97; N, 16.23. found: C, 61.09; H, 3.88; N, 16.25%.

N-(Benzylcarbamothioyl)-2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylamide (5)

Yellow crystals, mp. 246–248°C (Ethanol), yield 84%. IR: 3286 (NH), 2217 (C≡N), 1715 (C = O), 1231 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 9.06 (s, 1H, C5-H pyrazole), 8.50 (br.s, 2H, NH, exchangeable), 7.92 (s, 1H, CH=), 7.91-7.38 (m, 15H, Ar-H), 4.04 (s, 2H, CH_2). Anal. Calcd. for $C_{27}H_{21}N_5OS$ (463.56): C, 69.96; H, 4.57; N, 15.11. found: C, 69.79; H, 4.43; N, 15.06%.

1-Benzyl-6-(1,3-diphenyl-1H-pyrazol-4-yl)-4-oxo-2-thioxohexahydropyrimidine-5-carbonitrile (6)

Yellow crystals, mp. 190–192°C (Ethanol), yield 78%. IR: 3228 (NH), 2225 (C≡N), 1758 (C = O), 1227 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): (cis and trans isomers, 1:1), 9.21

(s, 1H, C5-H pyrazole), 8.30-7.03 (m, 15H, Ar-H), 4.84 (s, 2H, CH_2); for trans isomer: 12.00 (br.s, 1H, SH thiolactim form, exchangeable), 11.46 (br.s, 1H, NH, exchangeable), 5.70 (d, 1H, CH_a, $J = 6.2\,Hz$), 5.38 (d, 1H, CH_b, $J = 6.3\,Hz$); for cis isomer: 11.98 (br.s, 1H, SH thiolactim form, exchangeable), 10.80 (br.s, 1H, NH, exchangeable), 5.50 (d, 1H, CH_a, $J = 3.2\,Hz$), 5.22 (d, 1H, CH_b, $J = 3.2\,Hz$). MS, *m/z* (%): 465 (M+2, 11), 464 (M+1, 31), 463 ($M^{+\cdot}$, 100), 462 (28), 461 (8), 430 (21), 403 (63), 356 (6), 299 (2), 297 (15), 231 (2), 140 (4), 106 (12), 91 (8), 77 (13). Anal. Calcd. for $C_{27}H_{21}N_5OS$ (463.56): C, 69.96; H, 4.57; N, 15.11. found: C, 69.81; H, 4.44; N, 15.09%.

1-(4-Acetylphenyl)-6-(1,3-diphenyl-1H-pyrazol-4-yl)-4-oxo-2-thioxohexahydropyrimidine-5-carbonitrile (7)

Canary-yellow crystals, mp. 230–232°C (dioxane), yield 85%. IR: 3375 (NH), 2208 (C≡N), 1680 (C = O), 1229 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): (cis and trans isomers, 1:1), 9.25 (s, 1H, C5-H pyrazole), 7.95-7.00 (m, 14H, Ar-H), 2.47 (s, 3H, CH_3); for trans isomer: 12.25 (br.s, 1H, SH thiolactim form, exchangeable), 12.16 (br.s, 1H, NH, exchangeable), 6.22 (d, 1H, CH_a, $J = 6.3\,Hz$), 5.64 (d, 1H, CH_b, $J = 6.3\,Hz$); for cis isomer: 12.20 (br.s, 1H, SH thiolactim form, exchangeable), 11.80 (br.s, 1H, NH, exchangeable), 5.68 (d, 1H, CH_a, $J = 3.1\,Hz$), 5.50 (d, 1H, CH_b, $J = 3.2\,Hz$). Anal. Calcd. for $C_{28}H_{21}N_5O_2S$ (491.57): C, 68.42; H, 4.31; N, 14.25. found: C, 68.27; H, 4.26; N, 14.20%.

Reaction of 2 with 2-aminobenzoic acid

2-Aminobenzoic acid (5 mmol) was added to a suspension of isothiocyanate derivative **2** (5 mmol) in acetonitrile, prepared *in situ*. The reaction mixture was heated under reflux for 4 h. The deposited solid was collected and fractionally recrystallized from benzene to furnish pyrimidine derivative **8**. The insoluble part was recrystallized from ethanol to produce compound **9**.

2-(5-Cyano-6-(1,3-diphenyl-1H-pyrazol-4-yl)-4-oxo-2-thioxotetrahydropyrimidin-1(2H)-yl)benzoic Acid (8)

Yellow crystals, mp. 228–230°C, yield 44%. IR: 3441 (br.OH), 3237 (NH), 2223 (C≡N), 1709 (C = O), 1280 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 12.18 (br.s, 1H, COOH, exchangeable), 11.20 (br.s, 1H, NH, exchangeable), 9.18 (s, 1H, C5-H pyrazole), 7.94-7.36 (m, 14H, Ar-H), 3.17 (d, 1H, CH-N, $J = 6.3\,Hz$), 2.65 (d, 1H, CH-CN, $J = 6.2\,Hz$). MS, *m/z* (%): 493 ($M^{+\cdot}$, 3), 461 (14), 416 (11), 338 (29), 298 (54), 270 (61), 268 (100), 242 (28), 146 (16), 138 (20), 91 (32), 77 (73). Anal. Calcd. for $C_{27}H_{19}N_5O_3S$ (493.54): C, 65.71; H, 3.88; N, 14.19. found: C, 65.52; H, 3.74; N, 14.21%.

2-(3-(2-Cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acryloyl)thioureido)benzoic Acid (9)

Yellow crystals, mp. 258–260°C, yield 51%. IR: 3444 (*br*.OH,NH), 2211 (C≡N), 1695 (C = O acid), 1658 (C = O amide), 1231 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 12.79 (br.s, 1H, COOH, exchangeable), 12.67 (br.s, 1H, NH, exchangeable), 12.43 (br.s, 1H, NH,

exchangeable), 9.22 (s, 1H, C5-H pyrazole), 8.31 (s, 1H, CH=), 7.99-7.28 (m, 14H, Ar-H). Anal. Calcd. for $C_{27}H_{19}N_5O_3S$ (493.54): C, 65.71; H, 3.88; N, 14.19. found: C, 65.54; H, 3.77; N, 14.20%.

2-(2-(Acetylthio)-5-cyano-6-(1,3-diphenyl-1H-pyrazol-4-yl)-4-oxopyrimidin-1(4H)-yl)benzoic Acid (11)

A suspension of compound **9** (2 mmol) in acetic anhydride (5 mL) was heated under reflux for 2 h. The solid obtained was filtered off and recrystallized from ethanol to acquire yellow crystals, mp. 284–286°C, yield 81%. IR: 3441 (br.OH), 3167 (NH), 2220 (C≡N), 1656 (C = O), 1274 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 11.87 (br.s, 1H, COOH, exchangeable), 9.22 (s, 1H, C5-H pyrazole), 8.04-7.48 (m, 14H, Ar-H), 2.13 (s, 3H, CH_3). MS, *m/z* (%): 535 (M+2, 52), 534 (M+1, 22), 491 (20), 469 (22), 452 (75), 435 (100), 434 (99), 433 (56), 407 (64), 377 (53), 310 (51), 265 (83), 212 (55), 196 (59), 140 (61), 119 (34), 106 (27). Anal. Calcd. for $C_{29}H_{19}N_5O_4S$ (533.56): C, 65.28; H, 3.59; N, 13.13. found: C, 65.14; H, 3.48; N, 13.17%.

1-(1,3-Diphenyl-1H-pyrazol-4-yl)-3,6-dioxo-3H,6H-benzo[d]pyrimido[2,1-b][1,3]thiazine-2-carbonitrile (12)

A solution of **8** (2 mmol) in dioxane (10 mL) including triethylamine (0.1 mL) was heated under reflux for 4 h. The solid obtained after cooling was collected and recrystallized from ethanol to furnish dark-yellow crystals, mp. 300–302°C, yield 59%. IR: 2216 (C≡N), 1695, 1670 (C = O). ^{1}H NMR (300 *MHz*, DMSO-d_6): 9.05 (s, 1H, C5-H pyrazole), 8.01-7.41 (m, 14H, Ar-H). MS, *m/z* (%): 473 ($M^{+\cdot}$, 11), 434 (17), 388 (7), 351 (8), 314 (15), 271 (26), 269 (13), 194 (8), 91 (14), 77 (100). Anal. Calcd. for $C_{27}H_{15}N_5O_2S$ (473.51): C, 68.49; H, 3.19; N, 14.79. found: C, 68.32; H, 3.11; N, 14.81%.

General procedure for the synthesis of compounds 13–17

The appropriate reagent namely, 2-aminothiophenol, 2-aminoaniline, 2-hydroxybenzoyl hydrazine, thiourea, or hydrazinecarbothiohydrazide (5 mmol) was added to a suspension of isothiocyanate derivative **2** (5 mmol) in acetonitrile, prepared *in situ*. The reaction mixture was heated under reflux for 3-4 h or stirred at ambient temperature for 1 h in the case of hydrazinecarbothiohydrazide. The solid obtained was collected and recrystallized from the suitable solvent to produce compounds **13-17**.

N-(Benzo[d]thiazol-2-yl)-2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylamide (13)

Yellow crystals, mp. 298–300°C (dioxane), yield 69%. IR: 3142 (NH), 2216 (C≡N), 1677 (C = O). ^{1}H NMR (300 *MHz*, DMSO-d_6): (*E*- and *Z*-isomers, 1:1), 13.40 (br.s, 1H, NH, exchangeable), 9.19, 9.15 (s, 1H, C5-H pyrazole), 8.32, 8.08 (s, 1H, CH=), 7.93-7.31 (m, 14H, Ar-H). MS, *m/z* (%): 449 (M+2, 4), 448 (M+1, 57), 447 ($M^{+\cdot}$, 53), 446 (96), 387 (13), 315 (29), 270 (59), 269 (66), 191 (10), 104 (43), 77 (100). Anal. Calcd. for $C_{26}H_{17}N_5OS$ (447.52): C, 69.78; H, 3.83; N, 15.65. found: C, 69.61; H, 3.75; N, 15.59%.

1-(2-Aminophenyl)-6-(1,3-diphenyl-1H-pyrazol-4-yl)-4-oxo-2-thioxohexahydropyrimidine-5-carbonitrile (14)

Orange crystals, mp. 210–212°C (Ethanol), yield 72%. IR: 3346, 3229 (NH,NH_2), 2208 (C≡N), 1679 (C = O), 1231 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): (cis and trans isomers, 1:1), 8.74 (s, 1H, C5-H pyrazole), 7.94-6.61 (m, 14H, Ar-H), 5.71 (br.s, 2H, NH_2, exchangeable); for trans isomer: 12.05 (br.s, 1H, NH, exchangeable), 6.18 (d, 1H, CH_a, J = 6.4 *Hz*), 5.36 (d, 1H, CH_b, J = 6.3 *Hz*); for cis isomer: 11.98 (br.s, 1H, NH, exchangeable), 6.10 (d, 1H, CH_a, J = 3.1 *Hz*), 5.06 (d, 1H, CH_b, J = 3.1 *Hz*). MS, *m/z* (%): 464 ($M^{+\cdot}$, 18), 449 (22), 418 (13), 387 (14), 346 (16), 303 (10), 252 (20), 201 (28), 139 (50), 136 (100), 102, 92 (21), 78 (24). Anal. Calcd. for $C_{26}H_{20}N_6OS$ (464.55): C, 67.22; H, 4.34; N, 18.09. found: C, 67.17; H, 4.28; N, 18.10%.

2-Cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-(2-(2-hydroxybenzoyl)hydrazine-1-carbonothioyl)acrylamide (15)

Yellow crystals, mp. 272–274°C (dioxane), yield 77%. IR: 3403 (OH), 3203 (NH), 2205 (C≡N), 1686 (C = O), 1223 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 12.32 (br.s, 1H, OH, exchangeable), 11.80 (br.s, 1H, NH, exchangeable), 11.20 (br.s, 1H, NH, exchangeable), 10.91 (br.s, 1H, NH, exchangeable), 9.19 (s, 1H, C5-H pyrazole), 8.30 (s, 1H, CH=), 7.93-6.03 (m, 14H, Ar-H). Anal. Calcd. for $C_{27}H_{20}N_6O_3S$ (508.56): C, 63.77; H, 3.96; N, 16.53. found: C, 63.64; H, 3.88; N, 16.55%.

N-(Carbamothioylcarbamothioyl)-2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylamide (16)

Yellow crystals, mp. 242–242°C (Ethanol), yield 67%. IR: 3315, 3250, 3130 (NH), 2229 (C≡N), 1698 (C = O), 1270, 1232 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 11.28 (br.s, 1H, NH, exchangeable), 9.60 (br.s, 1H, NH, exchangeable), 9.52 (br.s, 2H, NH_2, exchangeable), 9.13 (s, 1H, C5-H pyrazole), 8.21 (s, 1H, CH=), 8.07-7.03 (m, 10H, Ar-H). ^{13}C NMR (75 *MHz*, DMSO-d_6): 181.36, 163.32, 155.11, 154.14, 144.83, 141.53, 138.60, 130.94, 129.80, 129.32, 128.98, 128.28, 128.03, 127.81, 119.69, 116.96, 114.34. Anal. Calcd. for $C_{21}H_{16}N_6OS_2$ (432.08): C, 58.32; H, 3.73; N, 19.43. found: C, 58.20; H, 3.65; N, 19.40%.

3-Amino-7-(1,3-diphenyl-1H-pyrazol-4-yl)-5-oxo-2-thioxo-1,2,3,5-tetrahydro-[1,2,4]-triazolo[1,5-a]pyrimidine-6-carbonitrile (17)

Yellow crystals, mp. 224–226°C (Ethanol), yield 74%. IR: 3350, 3200 (NH,NH_2), 2239 (C≡N), 1734 (C = O), 1235 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 11.30 (br.s, 1H, NH, exchangeable), 9.18 (s, 1H, C5-H pyrazole), 8.09-7.44 (m, 10H, Ar-H), 5.40 (br.s, 2H, NH_2, exchangeable). MS, *m/z* (%): 426 ($M^{+\cdot}$, 6), 400 (6), 315 (40), 270 (32), 269 (20), 242 (10), 193 (8), 139 (12), 104 (13), 77 (100). Anal. Calcd. for $C_{21}H_{14}N_8OS$ (426.46): C, 59.15; H, 3.31; N, 26.28. found: C, 59.01; H, 3.24; N, 26.31%.

2-Cyano-N-(1-(2-cyanoacetyl)-2-(propan-2-ylidene)hydrazine-1-carbonothioyl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylamide (18)

2-Cyanoethanohydrazide (5 mmol) was added to a suspension of isothiocyanate derivative **2** (5 mmol) in dry acetone, prepared *in situ*. The reaction mixture was heated under reflux for 3 h. The solid obtained was collected and recrystallized from ethanol to afford yellow crystals, mp. 206–208°C, yield 68%. IR: 3237 (NH), 2223 (C≡N), 1708 (C = O), 1280 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 12.15 (br.s, 1H, NH, exchangeable), 9.19 (s, 1H, C5-H pyrazole), 8.10 (s, 1H, CH=), 8.03-7.36 (m, 10H, Ar-H), 4.04 (s, 2H, CH_2), 3.17 (s, 6H, 2 CH_3). MS, *m/z* (%): 495 ($M^{+\cdot}$, 32), 477 (24), 416 (31), 377 (76), 316 (56), 270 (94), 268 (100), 237 (34), 165 (72), 131 (49), 113 (62), 104 (52), 102 (42), 74 (81). Anal. Calcd. for $C_{26}H_{21}N_7O_2S$ (495.56): C, 63.02; H, 4.27; N, 19.79. found: C, 62.91; H, 4.12; N, 19.72%.

2-Cyano-N-(5-cyano-6-(1,3-diphenyl-1H-pyrazol-4-yl)-4-oxo-2-thioxotetrahydropyrimidin-1(2H)-yl)acetamide (21)

2-Cyanoethanohydrazide (5 mmol) was added to a suspension of isothiocyanate derivative **2** (5 mmol) in dry acetonitrile, prepared *in situ*. The reaction mixture was further stirred at ambient temperature for 2 h or heated under reflux for 30 min. The solid obtained was collected and recrystallized from ethanol to produce yellow crystals, mp. 304–306°C, yield 81%. IR: 3227, 3121 (NH), 2260, 2224 (C≡N), 1695, 1663 (C = O), 1230 (C = S). ^{1}H NMR (300 *MHz*, DMSO-d_6): 12.25 (br.s, 1H, NH, exchangeable), 10.88 (br.s, 1H, NH, exchangeable), 8.75 (s, 1H, C5-H pyrazole), 7.88-7.37 (m, 10H, Ar-H), 5.92 (d, 1H, CH_a, $J = 6.5$ *Hz*), 5.43 (d, 1H, CH_b, $J = 6.4$ *Hz*), 3.47 (s, 2H, CH_2). MS, *m/z* (%): 455 ($M^{+\cdot}$, 7), 454 (9), 437 (7), 355 (8), 299 (44), 298 (98), 297 (97), 296 (23), 270 (11), 269 (31), 239 (14), 140 (20), 77 (100). Anal. Calcd. for $C_{23}H_{17}N_7O_2S$ (455.50): C, 60.65; H, 3.76; N, 21.53. found: C, 60.52; H, 3.67; N, 21.50%.

7-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-imino-2,3-dihydro-9H-pyrimido[2,1-b][1,3,4]thiadiazepine-4,9(5H)-dione (23)

A solution of compound **19** (2 mmol) in glacial acetic acid (10 mL) was heated under reflux for 1 h. The separated solid while hot was collected and recrystallized from dioxane to achieve orange crystals, mp. > 360°C, yield 76%. IR: 3166, 3134 (NH), 1678 (C = O). ^{1}H NMR (300 *MHz*, DMSO-d_6): 13.33 (br.s, 1H, NH, exchangeable), 10.52 (br.s, 1H, NH, exchangeable), 8.17 (s, 1H, C5-H pyrazole), 8.06-7.47 (m, 11H, Ar-H + CH pyrimidine), 4.59 (s, 2H, CH_2). MS, *m/z* (%): 428 ($M^{+\cdot}$, 28), 426 (5), 387 (11), 361 (60), 358 (39), 338 (45), 309 (50), 284 (45), 280 (100), 249 (55), 223 (88), 194 (55), 176 (58), 164 (95), 115 (55), 104 (50), 90 (21), 77 (64). Anal. Calcd. for $C_{22}H_{16}N_6O_2S$ (428.47): C, 61.67; H, 3.76; N, 19.61. found: C, 61.54; H, 3.61; N, 19.57%.

Evaluation of the fungicidal activity

The *in vitro* antifungal activity of the synthesized pyrazoles against targeted fungi was evaluated using mycelium growth rate method. Potato-dextrose agar (PDA) was used as food in the molten stage. Fifty milliliters of the medium were poured into 150 mL conical flasks

and autoclaved at 121°C for 20 min. Three drops of 25% lactic acid were added to prevent bacterial contamination. Dilutions for each of the tested compounds were carried out (v/v) by dissolving appropriate amounts of each compound in 10 mL DMSO. Equal volumes of DMSO containing diluted compounds were added to sterile molten (40°C) PDA to get a series of concentrations of 500, 400, 300, 200, and 100 mg/L for each compound in PDA.[47] A zero (o) concentration treatment was prepared for each fungus, which contains an equivalent volume of solvent only, and used as control. Compounds-amended PDA was dispensed aseptically into 9 cm diameter Petri-dishes. Plugs of mycelium (4 mm diameter) were cut from the margins of actively growing cultures of the *F. Solani*, *R. Solani*, *B. cinerea, S. sclerotiorum,* and *A. Alternata* fungi and placed in the center of compound-amended and unamended PDA plates with 3 replicate plates for each fungus. All plates were incubated at 25 ± 1°C. Colony diameter (in millimeters) was measured after complete growth of the control (5 - 7 days). Percentages of mycelial growth inhibition were calculated from the formula: Mycelial growth inhibition = [(DC-DT)/DC] ×100, where DC and DT are average diameters of a fungal colony of control and treatment, respectively. The estimated effective concentration (EC_{50}) values, which give 50% inhibition of fungi radial growth, toxicity index (T.I), and slopes of toxicity lines for each compound under investigation were calculated by using the LDP line program and tabulated in Tables 1 and 2 (see more details in the supplemental Tables I-V). Standard fungicides used are Metalaxyl (technical grade with 95% CL), Mancozeb (Casette MZ, 69% WP formulation) and Pencycuran (Monceren, 25% WP formulation). In formulated standards, concentrations were calculated based on the % of active ingredients and carried out in distilled water.

Disclsosure statement

The authors declare no conflict of interest.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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