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Synthesis of some novel pyrazoline-thiazole hybrids and their antimicrobial activities

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Abstract

A series of novel thiazolyl pyrazolines **7a-h**, **9a-f**, and **11a-f** have been synthesized by the reaction of thioamide derivatives **5a**,**b** with 1-aryl-2-bromoethanones **6a-d**, chloroacetones **8a-c**, and hydrazonoyl chlorides **10a-c**. Additionally, pyrazoles **15a-c** and **20** were prepared starting from enaminone **13**. These newly synthesized compounds were screened for their in vitro antibacterial activity against four bacterial species. Compound **11b** showed a moderate activity against *Klebsiella pneumoniae*. Compounds **7c** and **11c** revealed a moderate activity against *Pseudomonas aeruginosa*. In addition, the antifungal activity of the newly synthesized compounds was determined against five fungal strains. Compounds **7e**, **7g**, and **11e** showed a good activity against *Aspergillus flavus* and *Penicillium expansum*.

1 | INTRODUCTION

Recently, the dramatic increase in bacterial and fungal infections has been reported; therefore, the treatment of these infectious diseases is considered a great challenge for researchers.[1,2] For that reason, there is an urgent need to discover new effective antimicrobial agents. In addition, the designing of these agents to treat resistant bacteria becomes one of the most important areas in the antimicrobial research. Pyrazole, five-member heterocyclic ring with two adjacent nitrogen atoms, has gained a great attention in pharmaceutical and chemical industries.[3] A large number of pyrazoles showed various biological activities such as anticancer,[4,5] antihistaminic,[6] pesticidal,[7] antifungal,[8–10] anti-rheumatoid arthritis,[11] anticonvulsant,[12] antidepressant,[13] antipyretic,[14,15] antibacterial,[16,17] antituberculosis,[18] antiviral,[19] and anti-inflammatory[20] activities.

In addition, pyrazolines revealed numerous pharmacological activities including antimicrobial,[21–24] antiamoebic,[25] anti-TB,[26] anti-HIV,[27] anticancer,[28] antidepressant, and anticonvulsant activities.[29] The N—N bond in pyrazoline moiety is the main factor in their biological activity; however, the presence of N—N heterocycles is low because of the difficult construction of this bond by living organism.[30,31]

Moreover, thiazole derivatives showed a broad spectrum of biological activity, they have been reported as anticonvulsant, antibacterial, antifungal, antiviral, and anticancer agents. Recently, some thiazoles were discovered as new inhibitors of bacterial DNA gyrase B.[32–36] Thiazoles have been also used in the treatment of allergies.[37] In the light of previous data and in continuation of our interest in the synthesis of new biologically active heterocycles,[38–43] in this study, we aimed to synthesize certain pyrazoline derivatives incorporating thiazole moiety to evaluate their antimicrobial potency.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The key intermediates 1,3-*bis*(3,4-dimethoxyphenyl)prop-2-en-1-one (**3a**) and 3-(benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-

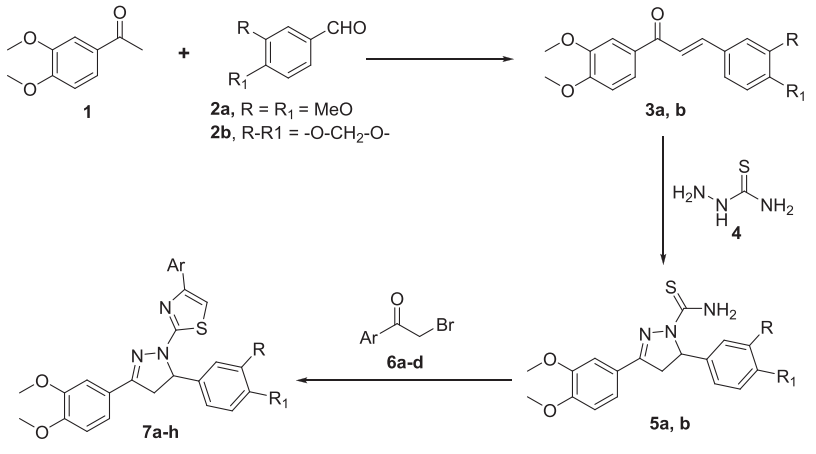
dimethoxyphenyl)prop-2-en-1-one (**3b**) were prepared by the reaction of 1-(3,4-dimethoxyphenyl)ethan-1-one (**1**) with 3,4-dimethoxybenzaldehyde (**2a**) or benzo[*d*][1,3] dioxole-5-carbaldehyde (**2b**) according to the reported methods.[44] Prop-2-en-1-ones **3a**,**b** were reacted with thiosemicarbazide (**4**), in the presence of sodium hydroxide, to give 4,5-dihydro-1*H*-pyrazole-1-carbothioamides **5a**,**b**.[45] These compounds were reacted with various 1-aryl-2-bromoethanones **6a-d** in absolute ethanol to yield the newly prepared thiazoles **7a-h**. In the latter stepwise synthesis of **7a-h**, the reaction took place via the nucleophilic sulfur atom of thioamide group to form thiohydrazonates, which underwent cyclization to give cyclic hydroxy intermediates, followed by dehydration to yield the final products **7a-h** through Hantzsch thiazole synthesis type. The structures of **7a-h** have been identified by their analytical and spectral analyses (Scheme 1). For example, their IR spectra were free of NH_2 function and they revealed the appearance of C═N bands in the region of 1580 to 1630 cm^{-1}. The ^1H NMR spectra of **7a-h** showed three signals of ABX pattern around δ 3.36, 3.95, and 5.65 ppm, each is integrated for one proton, and assigned to HA, HB, HX proton of the pyrazoline ring.

In addition, pyrazoline-thiazoles **9a-f** were obtained by the treatment of thioamide derivatives **5a**,**b** with chloroacetones **8a-c** in refluxing ethanol on the basis of their spectral data (Scheme 2). The ^1H NMR spectra of **9c** and **9f** exhibited the D_2O-exchangeable signal of NH proton at δ 8.75 and the signals of ABX pyrazoline protons. The IR spectra of **9c** and **9f** appeared the NH band at 3248 and 3284 cm^{-1}. The IR spectra of **9a-f** revealed the band of C═N function in the region 1600 to 1605 cm^{-1} and the band of C═O function at 1650 to 1724 cm^{-1}.

Similarly, the treatment of carbothioamides **5a**,**b** with hydrazonoyl chlorides **10a-c** in absolute ethanol under reflux for 4 hours gave the corresponding pyrazoline-thiazoles **11a-f**. The ^1H NMR spectra of **11a-f** showed the appearance of the characteristic signals because of the proton of methyl function around δ 2.61 to 2.66 ppm and the three signals of ABX protons of pyrazoline ring in the regions of δ 3.32 to 3.43, 3.73 to 3.85, and 5.73 to 5.97 ppm (Scheme 2). Moreover, the infrared (IR) spectra of **11a-f** showed the band of C═N function at 1600 to 1605 cm^{-1}.

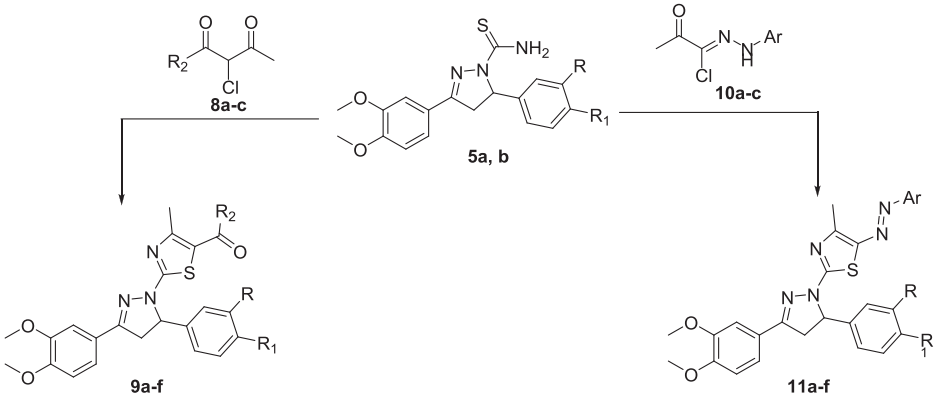
Furthermore, the reaction of enaminone **13**[46] as dipolarophile, with nitrilimines, produced in situ from hydrazonoyl chlorides **10a-c**, was realized (Scheme 3). The reaction of enaminone **13** with **10a-c** in toluene and TEA gave the pyrazoles **15a-c**. In the IR spectra of **15a-c**, the bands of C═N and C═O groups appeared at 1590 and 1689 cm^{-1}, while their ^1H NMR exhibited the methoxy singlet signals at δ 3.83 to 3.97 ppm and the multiplet signals of aromatic protons at δ 7.02 to 8.91. The reaction of **13** with **10a-c** proceeds via initial 1,3-dipolar cycloaddition of nitrilimine, derived from **10** to the enaminone double bond to give the cyclo adducts **14a-c**, which undergo in situ elimination of dimethylamine to yield pyrazoles **15a-c** as final products.[43]

On the other hand, the pyridine derivative **17** was synthesized by treatment of enaminone **13** with ethyl acetoacetate (**16**) and ammonium acetate in glacial acetic acid (Scheme 3). A mixture of the latter ester, ethyl 6-(3,4-dimethoxyphenyl)-2-methylnicotinate (**17**) and



7	R	R_1	Ar
a	OMe	OMe	Ph
b	OMe	OMe	4-F-C_6H_4
c	OMe	OMe	4-Cl-C_6H_4
d	OMe	OMe	4-Br-C_6H_4
e	-O-CH_2-O-		Ph
f	-O-CH_2-O-		4-F-C_6H_4
g	-O-CH_2-O-		4-Cl-C_6H_4
h	-O-CH_2-O-		4-Br-C_6H_4

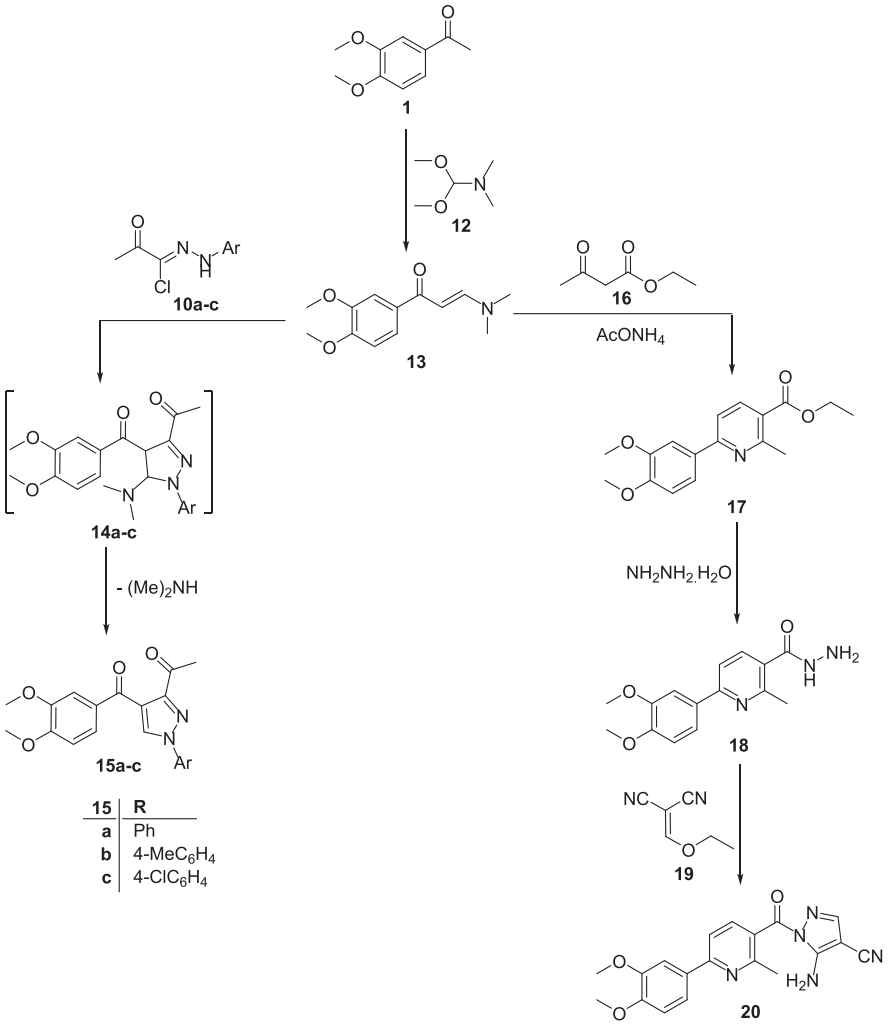
SCHEME 1 Synthesis of 4-arylthiazolyl pyrazolines **7a-h**.



9	R	R_1	R_2
a	OMe	OMe	Me
b	OMe	OMe	OEt
c	OMe	OMe	NHPh
d	-O-CH_2-O-		Me
e	-O-CH_2-O-		OEt
f	-O-CH_2-O-		NHPh

11	R	R_1	Ar
a	OMe	OMe	Ph
b	OMe	OMe	4-Me-C_6H_4
c	OMe	OMe	4-Cl-C_6H_4
d	-O-CH_2-O-		Ph
e	-O-CH_2-O-		4-Me-C_6H_4
f	-O-CH_2-O-		4-Cl-C_6H_4

SCHEME 2 Synthesis of thiazolyl pyrazolines **9a-f** and **11a-f**.



15	R
a	Ph
b	4-MeC_6H_4
c	4-ClC_6H_4

SCHEME 3 Synthesis of pyrazoles **15a-c** and **20**.

hydrazine hydrate was refluxed to give 6-(3,4-dimethoxyphenyl)-2-methylnicotinohydrazide (**18**)[47] (Scheme 3). Treatment of the hydrazide **18** with 2-(ethoxymethylene)malononitrile (**19**) gave 5-amino-1-(6-(3,4-dimethoxyphenyl)-2-methylnicotinoyl)-1*H*-pyrazole-4-carbonitrile (**20**) (Scheme 3). The IR spectrum of pyrazole **20** showed the bands of NH_2 and C≡N functions at 3300 and 2220 cm^{-1} in addition to the band of C═O at 1696 cm^{-1}. The ^1H NMR of **20** showed a broad singlet signal (D_2O-exchangeable) at 8.17 of amino group and a multiplet signal at δ 7.08 to 8.00 because of aromatic protons.

2.2 | Antimicrobial activity

The antimicrobial activity of the newly synthesized compounds was screened against two gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, and two gram-negative bacterial species *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, in addition to five different fungal strains, namely, *Candida albicans*, *Syncephalastrum racemosum*, *Aspergillus fumigatus*, *Penicillium expansum*, and *Aspergillus flavus*.The antibacterial activities of **7a-h**, **9a-f**, **11a-f**, **15a-c**, and **20** are represented in Table 1. It is noticed that compounds **11c** (R = R_1 = -OCH_3, Ar = 4-Cl-C_6H_4), **11e** (R-R_1 = -OCH_2O-, Ar = 4-Me-C_6H_4, **7e** (R-R_1 = -OCH_2O-, Ar = Ph), **9e** (R-R_1 = -OCH_2O-, R_2 = -OCH_2CH_3), and **7 g** (R-R_1 = -OCH_2O-, Ar = 4-Cl-C_6H_4) revealed a moderate antibacterial activity against *B. subtilis* with inhibition zones 1.5, 1.8, 1.5, 1.4, and 1.5 mm, respectively, when compared with that of reference drug Amoxicilline (IZ = 3.5 mm); whereas compounds **7e** (R-R_1 = -OCH_2O-, Ar = C_6H_5), **9e** (R-R_1 = -OCH_2O-, R_2 = -OCH_2CH_3), **7 g** (R-R_1 = -OCH_2O-, Ar = 4-Cl-C_6H_4), and **11c** (R = R_1 = -OCH_3, Ar = 4-Cl-C_6H_4) exhibited a moderate antibacterial activity against *S. aureus* with inhibition zones in the range of 0.9 to 1.2 mm when compared with that of reference drug Amoxicilline (IZ = 2.3 mm), which showed the role of Cl on acquiring their antibacterial activity. Additionally, compounds **11a** (R = R_1 = OCH_3, Ar = C_6H_5), **9b** (R = R_1 = OCH_3, R_2 = OCH_2CH_3), **11b** (R = R_1 = OCH_3, Ar = 4-Me-C_6H_4), and **15c** (Ar = 4-Cl-C_6H_4) exhibited a good antibacterial activities against the gram-negative bacteria *K. pneumoniae* with inhibition zones in the range of 1.2, 1.3, 2.0, and 1.2 mm, respectively, when compared with that of reference drug Amoxicilline (IZ = 2.4 mm); whereas compounds **11b** (R = R_1 = OCH_3, Ar = 4-Me-C_6H_4), **15c** (Ar = 4-Cl-C_6H_4), **7c** (R = R_1 = -OCH_3, Ar = 4-Cl-C_6H_4), **9c** (R = R_1 = -OCH_3, R_2 = -OCH_2CH_3), and **11c** (R-R_1 = -OCH_3, Ar = 4-Cl-C_6H_4) exhibited a moderate antibacterial activity against *P. aeruginosa* with inhibition zones in the range of 1.2, 1.5, 1.7, 1.0, and 1.8 mm, respectively, when compared with that of reference drug Amoxicilline (IZ = 2.2 mm).

The antifungal activities of pyrazole derivatives **7a-h**, **9a-f**, **11a-f**, **15a-c**, and **20** are represented in Table 1. From the data, it is observed that compounds **11a** (R = R_1 = -OCH_3, Ar = ph), **11b** (R = R_1 = -OCH_3, Ar = 4-Me-C_6H_4), and **11f** (R-R_1 = -OCH_2O-, Ar = 4-Cl-C_6H_4) revealed a moderate antifungal action against *C. albicans* with inhibition zones in the range of 1.3, 2.1, and 1.3 mm, respectively; whereas **7c** (R = R_1 = -OCH_3, Ar = 4-F-C_6H_4), **11b** (R = R_1 = -OCH_3, Ar = 4-Me-C_6H_4), **7 h** (R-R_1 = -OCH_2O-, Ar = 4-Br-C_6H_4), and **7e** (R-R_1 = -OCH_2O-, Ar = Ph) revealed a moderate antifungal action against *A. fumigatus* with inhibition zones 1.4, 1.2, 1.2, and 1.2 mm, respectively, when compared with that of reference drug Griseofulvin (IZ = 3.3 mm). Additionally, compounds **7e** (R-R_1 = -OCH_2O-, Ar = Ph), **7 g** (R-R_1 = -OCH_2O-, Ar = 4-Cl-C_6H_4), and **11e** (R-R_1 = -OCH_2O-, Ar = 4-Me-C_6H_4) exhibited a good antifungal activities against *A. flavus* with inhibition zones in the range of 2.3, 2.2, and 2.3 mm, respectively, when compared with IZ = 2.4 mm of reference drug Griseofulvin.

2.3 | Minimum inhibitory concentration

The results of minimum inhibitory concentration (MIC) were reported in Table 2. Pyrazoline derivatives **11b** and **11c** (MIC: 1.25 mg/mL) showed better results when compared with **7g** (MIC: 2.5 mg/mL) as revealed from their MIC values.

3 | EXPERIMENTAL

3.1 | Chemistry

Melting points are measured on an SMP3 apparatus and are uncorrected. IR spectra were recorded in KBr disc on a Perkin-Elmer 1650 spectrophotometer at Faculty of Science, Cairo University. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured in DMSO or $CDCl_3$ as solvent at room temperature using Bruker Avance (III)-400 MHz. Chemical shifts (δ) were reported in ppm to scale calibrated for tetramethylsaline (TMS), which is used as an internal standard at the Ain Shams University, Cairo, Egypt. TLCs were performed on silica gel–coated aluminum sheets (Type 60 GF_{254}, Merck) and UV lamp at λ 254 nm.

TABLE 1 The antimicrobial activity of the tested compounds against nine microbial species

Comp. (Conc. 5 mg/mL)	Inhibition Zone (IZ, mm)								
	Antibacterial activity				Antifungal activity				
	G + ve		*G − ve*						
	Staphylococcus aureus	*Bacillus subtilis*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Aspergillus fumigatus*	*Aspergillus flavus*	*Syncephlastarum. racemosum*	*Penicillium expansum*	*Candida albicans*
7a	-	-	-	-	-	-	-	-	-
7b	-	-	-	-	1.0	0.8	-	0.9	-
7c	-	-	0.9	1.7	1.4	0.8	-	-	-
7d	-	-	-	-	-	-	-	-	-
7e	0.9	1.5	-	-	1.2	2.3	-	1.0	-
7f	-	-	-	-	-	-	-	-	-
7g	1.2	1.5	-	0.9	0.8	2.2	-	2.5	-
7h	-	-	-	-	1.2		-	0.8	-
9a	-	-	-	-	-	-	-	-	-
9b	-	-	1.3	-	-	0.8	-	1.0	-
9c	-	-	-	1.0	-		-	-	-
9d	-	-	-	-	-		-	-	-
9e	1.0	1.4	-	-	-	-	-	-	-
9f	-	-	-	-	-	-	-	-	-
11a	-	-	1.2	0.8	-	-	0.9	-	1.3
11b	-	-	2	1.2	1.2	1.0	-	0.9	2.1
11c	1.2	1.5	0.9	1.8	-	1.2	-	1.3	0.9
11d	-	-	-	-	-	1.0	1.2	-	0.9
11e	0.9	1.8	-	-	1.0	2.3	-	1.3	-
11f	-	-	1.5	-	-	-	-	0.8	1.3
15a	-	-	-	-	-	-	-	-	-
15b	-	-	0.8	1.2	-	-	1.0	-	-
15c	-	-	1.2	1.5	-	0.9	-	1.2	0.8
20	1.3	1.0	-	-	-	1.0	-	-	1.2
Amoxicilline	2.3	3.5	2.4	2.2					
Griseofulvin					3.3	2.4	2.1	2.8	

Note. "-" indicates bacteria or fungi were resistant to the compound.

TABLE 2 MIC (mg/mL) of compounds **7g**, **11b**, and **11c**

Compounds	MIC (mg/mL)
11b	1.25
11c	1.25
7g	2.5

Abbreviation: MIC, mimimum inhibitory concentration.

3.2 | Synthesis of chalcone derivatives 3a,b

Into a mixture of 3,4-dimethoxyacetophenone (**1**) (1.8 g, 10.0 mmol) and vertaldehyde (**2a**) or piperonal (**2b**) (10 mmol) in ethanol (95%, 20 mL), sodium hydroxide solution (10%, 1 mL) was added. The mixture was stirred for 2 hours and the formed solid was filtered off and recrystallized from ethanol to yield **3a**,**b**.[44]

3.3 | Synthesis of 4,5-dihydro-1*H*-pyrazoles 5a,b

To a solution of NaOH (1 g, 25 mmol) and **3a**,**b** (5 mmol) in ethanol (25 mL), thiosemicarbazide (**4**) (5.5 mmol) was added under stirring. The reaction mixture was refluxed for 1 hour. The resulting solid, after cooling and addition of ice, was filtered and washed with water and ether. The solid was dried and recrystallized from ethanol to give **5a**,**b**.[45]

3.4 | General method for the synthesis of compounds 7a-h

A mixture of **5a**,**b** (1.0 mmol) and bromoethanones **6a-d** (1.0 mmol) in absolute ethanol (30 mL) was refluxed for 4 hours and then cooled at room temperature. The product was seperated out by filtration, dried under vacuum, and recrystallized from ethanol to give thiazolyl pyrazolines **7a-h**.

3.4.1 | 2-(3,5-*Bis*(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazole (7a)

Yellow powder, m.p. 181-183°C; yield 63%; IR ν_{max}/cm^{-1}: 1598 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 3.35–3.38 (m, 1H, H of pyrazole), 3.89 (s, 7H, 2 OCH_3 + H of pyrazole), 3.96 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 5.61–5.62 (m, 1H, H of pyrazole), 6.84–6.91 (m, 5H, ArHs), 7.02–7.73 (m, 7H, ArHs); Anal. Calcd. For $C_{28}H_{27}N_3O_4S$ (501.60): C, 67.05; H, 5.43; N, 8.38%; Found: C, 67.27; H, 5.51; N, 8.59%.

3.4.2 | 2-(3,5-*Bis*(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4 fluorophenyl) thiazole (7b)

White powder, m.p. 183-185°C; yield 68%; IR ν_{max}/cm^{-1}: 1597 (C=N); ^1H NMR (DMSO-d_6, 400 MHz) δ ppm: 3.34–3.38 (m, 1H, H of pyrazole), 3.71 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3) 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.97–4.04 (m, 1H, H of pyrazole), 5.56–5.61 (m, 1H, H of pyrazole), 6.88–6.94 (m, 2H, ArHs), 7.05–7.07 (m, 2H, ArHs), 7.18–7.22 (m, 2H, ArHs), 7.29–7.37 (m, 3H, ArHs), 7.78–7.82 (m, 2H, ArHs); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 43.7, 56.0, 56.1, 64.5 ($4OCH_3$), 104.2, 109.5, 111.6, 112.1, 112.3, 115.7, 115.9, 119.0, 120.6, 124.2, 127.9, 134.7, 148.7, 149.0, 149.3, 149.8, 151.1, 153.5 (Ar-C), 165.1 (C=N); Anal. Calcd. For $C_{28}H_{26}FN_3O_4S$ (519.59): C, 64.73; H, 5.04; N, 8.09%; Found: C, 64.98; H, 5.15; N, 8.18%.

3.4.3 | 2-(3,5-*Bis*(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-chlorophenyl) thiazole (7c)

Yellow powder, m.p.177-179°C; yield 62%; IR ν_{max}/cm^{-1}: 1594 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ ppm: 3.34–3.38 (m, 1H, H of pyrazole), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3) 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.96–4.04 (m, 1H, H of pyrazole), 5.57–5.59 (m, 1H, H of pyrazole), 6.88–6.94 (m, 2H, ArHs), 7.04–7.06 (m, 2H, ArHs), 7.31–7.33 (m, 1H, ArHs), 7.36–7.38 (m, 2H, ArHs), 7.42 (d, $J = 10$ Hz, 2H, ArHs), 7.77 (d, $J = 9.2$ Hz, 2H, ArHs); Anal. Calcd. For: $C_{28}H_{26}ClN_3O_4S$ (536.04): C, 62.74; H, 4.8; N, 7.84%; Found: C, 62.92; H, 4.74; N, 7.97%.

3.4.4 | 2-(3,5-*Bis*(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-bromophenyl)thiazole (7d)

Yellow powder, m.p. 184-186°C; yield 75%; IR ν_{max}/cm^{-1}: 1597 (C=N); ^1H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 3.36–3.38 (m, 1H, H of pyrazole), 3.88–4.01 (m, 13H, $4OCH_3$ + 1H of pyrazole), 5.68 (m, 1H, H of pyrazole), 6.83–7.18 (m, 6H, ArHs), 7.29–7.59 (m, 5H, ArHs); Anal. Calcd. For: $C_{28}H_{26}BrN_3O_4S$ (580.50): C, 57.93; H, 4.51; N, 7.84%; Found: C, 57.80; H, 4.35; N, 7.98%.

3.4.5 | 2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazole (7e)

Yellow powder, m.p. 177-178°C; yield 66%; IR ν_{max}/cm^{-1}: 1599(C=N). ^1H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 3.28–

3.34 (m, 1H, H of pyrazole), 3.85–3.92 (m, 1H, H of pyrazole), 3.95 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 5.68–5.73 (m, 1H, H of pyrazole), 5.94 (d, J = 3.6 Hz, 2H, -OCH_2O-), 6.80–7.00 (m, 5H, ArHs), 7.14–7.50 (m, 5H, ArHs), 7.74–7.75 (m, 2H, ArHs); Anal. Calcd. For: $C_{27}H_{23}N_3O_4S$ (485.56): C, 66.79; H, 4.77; N, 8.65%; Found: C, 66.91; H, 4.63; N, 8.85%.

3.4.6 | 2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-fluorophenyl)thiazole (7f)

White powder, m.p. 163-165°C; yield 63%; IR ν_{max}/cm^{-1}: 1601 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) δ *ppm:* 2.93–2-95 (m, 1H, H of pyrazole), 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.98–4.02 (m, 1H, H of pyrazole), 5.58–5.60 (m, 1H, H of pyrazole), 5.97 (d, J = 3.6 Hz, 2H, -OCH_2O-), 6.90–7.05 (m, 4H, ArHs), 7.19–7.36 (m, 5H, ArHs) 7.78 (m, 2H, ArHs); Anal. Calcd. For: $C_{27}H_{22}FN_3O_4S$ (503.55): C, 64.40; H, 4.40, N, 8.34%; Found: C, 64.55; H, 4.57; N, 8.49%.

3.4.7 | 2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-chlorophenyl)thiazole (7g)

Yellow powder, m.p. 187-189°C; yield 72%; IR ν_{max}/cm^{-1}: 1598 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 3.33–3.35 (m, 1H, H of pyrazole), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.95–4.02 (m, 1H, H of pyrazole), 5.58–5.62 (m, 1H, H of pyrazole), 5.98 (d, J = 3.6 Hz, 2H, -OCH_2O-), 6.90–6.91 (m, 3H, ArHs), 7.05 (d, J = 8.4 Hz, 1H, ArHs), 7.30–7.44 (m, 5H, ArHs), 7.76 (d, J = 8.8 Hz, 2H, ArHs); Anal. Calcd. For: $C_{27}H_{22}ClN_3O_4S$ (520.00): C, 62.36; H, 4.26; N, 8.08%; Found: C, 62.19; H, 4.38; N, 8.20%.

3.4.8 | 2-(5-Bbenzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-bromophenyl)thiazole (7h)

Yellow powder, m.p. 206-208°C; yield 73%; IR ν_{max}/cm^{-1}: 1623 (C=N). ^{1}H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 3.29–3.33 (m, 1H, H of pyrazole), 3.90 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.65 (m, 1H, H of pyrazole), 5.65 (m, 1H, H of pyrazole), 5.96 (d, J = 3.6 Hz, 2H, -OCH_2O-), 6.80–6.97 (m, 5H, ArHs), 7.15–7.16 (d, J = 5.2 Hz, 1H, ArHs), 7.29–7.48 (m, 3H, ArHs), 7.60–7.61 (d, J = 7.6 Hz, 2H, ArHs); Anal. Calcd. For: $C_{27}H_{22}BrN_3O_4S$ (564.45): C, 57.45; H, 3.93; N, 7.44; Found: C, 57.27; H, 4.15; N, 7.61%.

3.5 | General method for synthesis of compounds 9a-f

These compounds were prepared by the same method employed for the synthesis of **7a-h** by using chloroacetones **8a-c** instead of bromoethanones **6a-d**. The product that was separated out, in each case, after cooling was filtered, dried under vacuum, and recrystallized from ethanol to give **9a-f**.

3.5.1 | 1-(2-(3,5-*Bis*(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)ethan-1-one (9a)

Yellow powder, m.p. 174-176°C; yield 72%; IR ν_{max}/cm^{-1}: 1610 (C=O), 1509 (C=N); ^{1}H NMR ($CDCl_3$-d_6, 400 MHz) δ *ppm:* 2.46 (s, 3H, $COCH_3$), 2.53 (s, 3H, CH_3), 3.33–3.37 (m, 1H, H of pyrazole), 3.87–4.01 (m, 13H, 4OCH_3 + H of pyrazole), 5.63–5.65 (m, 1H, H of pyrazole), 6.86–6.91 (m, 3H, ArHs), 7.14–7.52 (m, 3H, ArHs); Anal. Calcd. For: $C_{25}H_{27}N_3O_5S$ (481.57): C, 62.35; H, 5.65; N, 8.73%; Found: C, 62.58; H, 5.86; N, 8.64%.

3.5.2 | Ethyl-2-(3,5-*bis*(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carboxylate (9b)

Yellow powder, m.p. 195-197°C; yield 79%; IR ν_{max}/cm^{-1}: 1701 (C=O), 1601 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 1.25 (t, 3H, -$OCH_2\underline{CH_3}$), 2.37 (s, 3H, CH_3), 3.35–3.39 (m, 1H, H of pyrazole), 3.71 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.95–4.02 (m, 1H, H of pyrazole), 4.19 (q, J = 9 Hz, 2H, $O\underline{CH_2}CH_3$), 5.62–5.63 (m, 1H, H of prazole), 6.68–6.72 (m, 1H, ArHs), 6.88–6.92 (m, 2H, ArHs), 7.02–7.05 (d, J = 9.2 Hz, 1H, ArH), 7.31–7.36 (m, 2H, ArHs); Anal. Calcd. For: $C_{26}H_{29}N_3O_6S$ (511.59): C, 61.04; H, 5.71; N, 8.21%; Found: C, 61.32; H, 5.54; N, 8.37%.

3.5.3 | 2-(3,5-*Bis*(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-N-phenylthiazole-5-carboxamide (9c)

White powder, m.p. 136-138°C; yield 66%; IR ν_{max}/cm^{-1}: 3248 (NH), 1630 (C=O), 1599 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) δ *ppm:* 2.38 (s, 3H, CH_3), 3.02–3.07 (m, 1H, H of pyrazole), 3.73 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.96–4.04 (m, 1H, H of pyrazole), 5.64–5.65 (m, 1H, H of prazole), 6.73–6.74 (m, 1H, ArHs), 6.89–6.95 (m, 2H, ArHs), 7.04–7.08 (m, 2H, ArHs), 7.30–7.36 (m, 4H, ArHs),

7.64 (d, J = 6.4 Hz, 2H, ArHs), 9.66 (s, 1H, NHPh); Anal. Calcd. For: $C_{30}H_{30}N_4O_5S$ (558.65): C, 64.50; H, 5.41; N, 10.03%; Found: C, 64.78; H, 5.31; N, 10.27%.

3.5.4 | 1-(2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)ethan-1-one (9d)

Yellow powder, m.p. 200-202°C; yield 76%; IR ν_{max}/cm^{-1}: 1615 (C=O), 1565 (C=N); ^1H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 2.45 (s, 3H, $COCH_3$), 2.51 (s, 3H, CH_3), 3.26–3.31 (m, 1H, H of pyrazole), 3.87–3.94 (m, 4H, OCH_3 + H of pyrazole), 4.00 (s, 3H, OCH_3), 5.60 (m, 1H, H of pyrazole), 5.95 (s, 2H, -OCH_2O-), 6.75–6.89 (m, 4H, ArHs), 7.12–7.14 (m, 1H, ArHs), 7.50 (s, 1H, ArHs); Anal. Calcd. For: $C_{24}H_{23}N_3O_5S$ (465.52): C, 61.92; H, 4.98; N, 9.03%; Found: C, 62.19; H, 5.16; N, 9.15%.

3.5.5 | Ethyl-2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carboxylate (9e)

Yellow powder, m.p. 165–167°C; yield 68%; IR ν_{max}/cm^{-1}: 1714 (C=O), 1604 (C=N); ^1H NMR (DMSO-d_6, 400 MHz) δ ppm: 1.25 (t, J = 7.6 Hz, 3H, -$OCH_2\underline{CH_3}$), 2.38 (s, 3H, CH_3), 3.33 (m, 1H, H of pyrazole), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.16–4.22 (m, 1H, H of pyrazole), 4.20 (q, J = 7.6 Hz, 2H, -$O\underline{CH_2}CH_3$), 5.61–5.65 (m, 1H, H of prazole), 5.99 (s, 2H, -OCH_2O-), 6.72 (d, J = 6.4 Hz, 1H, ArHs), 6.79 (s, 1H, ArH), 6.87 (d, J = 7.2 Hz, 1H, ArH), 7.04 (d, J = 8.4 Hz, 1H, ArH), 7.31 (d, J = 8.4 Hz, 1H, ArH), 7.36 (s, 1H, ArH); ^{13}C NMR: (DMSO-d_6, 100 MHz) *δ ppm:* 14.8, 18.0 ($2CH_3$), 56.0, 56.1 ($2OCH_3$), 60.6, 63.2 ($2CH_2$), 101.6, 106.7, 108.8, 109.6, 110.6, 112.0, 119.6, 121.2, 123.5, 135.7, 147.1, 148.0, 149.3, 151.6, 155.9, 159.7 (Ar-C), 162.3 (C=O), 165.2 (C=N); Anal. calcd. For: $C_{25}H_{25}N_3O_6S$ (495.55): C, 60.59; H, 5.09; N, 8.48%; Found: C, 60.81; H, 5.21; N, 8.24%.

3.5.6 | 2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-N-phenylthiazole-5-carboxamide (9f)

White solid, m.p. 200-201°C; yield 72%; IR ν_{max}/cm^{-1}: 3284 (NH), 1633 (C=O), 1507 (C=N); ^1H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 2.57 (s, 3H, CH_3), 3.27–3.31 (m, 1H, H of pyrazole), 3.79–3.85 (m, 1H, H of pyrazole), 3.88 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.59–5.61 (m, 1H, H of prazole), 5.97 (s, 2H, -OCH_2O-), 6.77–6.91 (m, 4H, ArHs), 7.13–7.38 (m, 5H, ArHs), 7.50 (s, 1H, NHPh), 7.54–7.56 (m, 2H, ArHs); Anal. calcd. For: $C_{29}H_{26}N_4O_5S$ (542.61): C, 64.19; H, 4.83; N, 10.33%; Found: C, 64.00; H, 5.94; N, 10.60%.

3.6 | General method for synthesis of compounds 11a-f

To an equimolar mixture of **5a**,**b** (1.0 mmol) and hydrazonoyl chlorides **10a-c** (1.0 mmol) in toluene (30 mL), triethylamine (1.0 mmol) was added. The reaction mixture was refluxed for 4 hours. The formed solid was filtered, washed with ethanol, dried under vacuum, and recrystallized from ethanol to afford the corresponding hydrazones **11a-f**.

3.6.1 | 2-(3,5-*Bis*(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-5-(phenyldiazenyl)thiazole (11a)

Red crystals, m.p. 240-242°C; yield 66%; IR ν_{max}/cm^{-1}: 1602(C=N); ^1H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 2.66 (s, 3H, CH_3), 3.33–3.38 (m, 1H, H of pyrazole), 3.87–3.90 (m, 7H, H of pyrazole & $2OCH_3$), 3.95 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 5.70–5.81 (m, 1H, H of prazole), 6.83–6.92 (m, 5H, ArHs), 7.15 (d, J = 8.8 Hz, 1H, ArHs), 7.30–7.55 (m, 5H, ArHs); Anal. calcd. For: $C_{29}H_{29}N_5O_4S$ (543.64): C, 64.07; H, 5.38; N, 12.88%; Found: C, 64.29; H, 5.29; N, 12.99%.

3.6.2 | 2-(3,5-*Bis*(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-5-(4-tolyldiazenyl)thiazole (11b)

Red crystals, m.p. 243-245°C; yield 77%; IR ν_{max}/cm^{-1}: 1604 (C=N); ^1H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 2.41 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.32–3.36 (m, 1H, H of pyrazole), 3.78–3.81 (m, 1H, H of pyrazole), 3.88 (s, 6H, $2OCH_3$), 3.95 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 5.72–5.75 (m, 1H, H of pyrazole), 6.83–6.90 (m, 4H, ArHs), 7.14–7.28 (m, 3H, ArHs); 7.54–7.68 (m, 3H, ArHs); Anal. calcd. For: $C_{30}H_{31}N_5O_4S$ (557.67): C, 64.61; H, 5.60; N, 12.56%; Found: C, 64.89; H, 5.75; N, 12.43%.

3.6.3 | 2-(3,5-*Bis*(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-5-((4-chlorophenyl)diazenyl)-4-methylthiazole (11c)

Red crystals, m.p. 233-235°C; yield 75%; IR ν_{max}/cm^{-1}: 1601 (C=N); ^1H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 2.66

(s, 3H, CH_3), 3.37–3.43 (m, 1H, H of pyrazole), 3.78–3.81 (m, 1H, H of pyrazole), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 5.90–4.96 (m, 1H, H of pyrazole), 6.83–6.95 (m, 4H, ArHs), 7.19 (d, J = 8.4 Hz, 1H, ArHs), 7.40 (d, J = 8.8 Hz, 2H, ArHs), 7.50–7.56 (m, 1H, ArHs), 7.71 (d, J = 8.4 Hz, 1H, ArHs); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 19.6 (CH_3), 56.0, 56.1 (4OCH_3), 110.7, 112.3, 112.4, 117.9, 123.3, 129.8, 133.3, 133.4, 140.7, 148.8, 149.3, 151.5, 151.9, 157.8, 159.9, 160.0 (Ar-C), 165.7 (C=O); Anal. calcd. For: $C_{29}H_{28}ClN_5O_4S$ (578.08): C, 60.25; H, 4.88; N, 12.12%; Found: C, 60.58; H, 4.69; N, 12.35%.

3.6.4 | 2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-5-(phenyldiazenyl) thiazole (11d)

Red crystals, m.p. 212-215°C; yield 74%; IR ν_{max}/cm^{-1}: 1603 (C=N); ^{1}H NMR (CDCl3-d_6, 400 MHz) δ ppm: 2.63 (s, 3H, CH_3), 3.28–3.33 (m, 1H, H of pyrazole), 3.73–3.80 (m, 1H, H of pyrazole), 3.96 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 5.71–5.77 (m, 1H, H of prazole), 5.96 (s, 2H, -OCH_2O-), 6.77–6.91 (m, 4H, ArHs), 7.12–7.79 (m, 7H, ArHs); Anal. calcd. For: $C_{28}H_{25}N_5O_4S$ (527.60): C, 63.74; H, 4.78; N, 13.27%; Found: C, 63.87; H, 4.99; N, 13.13%.

3.6.5 | 2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-5-(4-tolyldiazenyl) thiazole (11e)

Red crystals, m.p. 205-207°C; yield 71%; IR ν_{max}/cm^{-1}: 1605 (C=N); ^{1}H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 2.41 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 3.26–3.32 (m, 1H, H of pyrazole), 3.84–3.92 (m, 1H, H of pyrazole), 3.95 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 5.70–5.71 (m, 1H, H of pyrazole), 5.96 (s, 2H, -OCH_2O-), 6.78–6.89 (m, 4H, ArHs), 7.11–7.53 (m, 4H, ArHs), 7.67 (d, J = 8.4 Hz, 2H, ArHs); Anal. calcd. For: $C_{29}H_{27}N_5O_4S$ (541.63): C, 64.31; H, 5.02; N, 12.93%; Found: C, 64.62; H, 4.86; N, 13.08%.

3.6.6 | 2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-5-((4-chlorophenyl)diazenyl)-4-methylthiazole (11f)

Red crystals, m.p. 242-244°C; yield 75%; IR ν_{max}/cm^{-1}: 1605 (C=N); ^{1}H NMR ($CDCl_3$-d_6, 400 MHz) δ ppm: 2.62 (s, 3H, CH_3), 3.31–3.34 (m, 1H, H of pyrazole), 3.74–3.80 (m, 1H, H of pyrazole), 3.95 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 5.70–5.78 (m, 1H, H of pyrazole), 5.97 (s, 2H, -OCH_2O-), 6.78–6.90 (m, 4H, ArHs), 7.14–7.40 (m, 3H, ArHs), 7.53–7.71 (m, 3H, ArHs); Anal. calcd. For: $C_{28}H_{24}ClN_5O_4S$ (562.04): C, 59.84; H, 4.30; N, 12.46%; Found: C, 60.05; H, 4.51; N, 12.32%.

3.7 | General method for synthesis of compounds 15a-c

To an equimolar mixture of enaminone **13**[46] (0.235 g, 1.0 mmol) and the appropriate hydrozonoyl chloride **10a-c** (1.0 mmol) in toluene (50 mL), triethylamine (2.0 mmol) was added and the mixture was refluxed for 8 hours. The precipitated solid was filtered, washed with absolute ethanol, dried, and recrystallized from ethanol to give the corresponding pyrazole derivatives **15a-c**.

3.7.1 | 1-(4-(3,4-Dimethoxybenzoyl)-1-phenyl-1*H*-pyrazol-3-yl)ethan-1-one (15a)

White solid, m.p. 180-182°C; yield 72%; IR ν_{max}/cm^{-1}: 1689 (C=O), 1590 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) *δ ppm:* 2.60 (s, 3H, $COCH_3$), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 7.02–7.04 (d, J = 10 Hz, 1H, ArHs), 7.12–7.27 (m, 1H, ArHs), 7.36–7.39 (d, J = 9.2 Hz, 1H, ArHs), 7.46–7.62 (m, 4H, ArHs), 7.99–8.01 (d, J = 7.2 Hz, 2H, ArHs); Anal. calcd. For: $C_{20}H_{18}N_2O_4$ (350.37): C, 68.56; H, 5.18; N, 8.00%; Found: C, 68.79; H, 5.30; N, 7.88%.

3.7.2 | 1-(4-(3,4-Dimethoxybenzoyl)-1-(4-tolyl)-1*H*-pyrazol-3-yl)ethan-1-one (15b)

White solid, m.p. 191-193°C; yield 76%; IR ν_{max}/cm^{-1}: 1685 (C=O), 1590 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 2.39 (s, 3H, $COCH_3$), 2.58 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 7.03 (d, J = 9.2 Hz, 1H, ArHs), 7.35–7.44 (m, 4H, ArHs), 7.88 (d, J = 8.4 Hz, 2H, ArHs), 8.91 (s, 1H, ArHs); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 21.0, 27.6 (2CH_3), 56.0, 56.2 (2OCH_3), 111.1, 119.8, 123.3, 125.5, 130.6, 130.7, 131.2, 136.9, 138.0, 149.2, 150.1 (Ar-C), 153.9 (C=O), 188.3 (C=N), 193.1 (Ar-C); Anal. calcd. For: $C_{21}H_{20}N_2O_4$ (364.40): C, 69.22; H, 5.53; N, 7.69%; Found: C, 69.43; H, 5.41; N, 7.85%.

3.7.3 | 1-(1-(4-Chlorophenyl)-4-(3,4-dimethoxybenzoyl)-1*H*-pyrazol-3-yl)Ethan-1-one (15c)

White solid, m.p. 213-215°C; yield 72%; IR ν_{max}/cm^{-1}: 1682 (C=O), 1588 (C=N); ^{1}H NMR (CDCl3-d_6,

400 MHz) δ ppm: 2.60 (s, 3H, $COCH_3$), 3.90 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.84 (d, J = 10.8 Hz, 1H, ArHs), 7.33 (d, J = 7.2 Hz, 1H, ArHs), 7.53 (d, J = 8.4 Hz, 2H, ArHs), 7.61 (s, 1H, ArHs), 7.76 (d, J = 8.4 Hz, 2H, ArHs), 8.15 (s, 1H, ArHs); Anal. calcd. For: $C_{20}H_{17}ClN_2O_4$ (384.82): C, 62.42; H, 4.45; N, 7.28%; Found: C, 62.65; H, 4.33; N, 7.39%.

3.8 | Synthesis of ethyl 2-methyl-6-(3,4-dimethoxyphenyl)nicotinate (17)

This compound was synthesized in 77% yield by the reaction of enaminone **13** with ethyl acetoacetate and ammonium acetate in refluxing glacial acetic acid according to the reported method.[47]

3.9 | Synthesis of 6-(3,4-dimethoxyphenyl)-2-methylnicotinohydrazide (18)

A mixture of the ester **17** (0.301 g, 1 mmol) and hydrazine hydrate (99%, 5 mL) was refluxed for 3 hours and then left to cool. The formed solid was filtered and recrystallized from dioxan to give hydrazide **18** in 85% yield and m.p. 204-205°C.[47]

3.10 | Synthesis of 5-amino-1-(6-(3,4-dimethoxyphenyl)-2-methylnicotinoyl)-1*H*-pyrazole-4-carbonitrile (20)

To a stirred solution of the hydrazide **18** (0.287 g, 1.0 mmol) in ethanol (20 mL), 2-(ethoxymethylene) malononitrile (0.122 g, 1.0 mmol) and catalytic amount of glacial acetic acid were added. The reaction mixture was heated under reflux for 6 hours. The precipitate formed was collected by filtration while hot, washed with hot ethanol, dried, and crystallized from ethanol to give compound **20** as white solid, m.p. 251-253°C; yield 64%; IR ν_{max}/cm^{-1}: 3300 (NH_2), 2220 (CN), 1696 (C=O), 1632 (C=N); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 2.51 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 7.09 (d, J = 9.2 Hz, 1H, ArHs), 7.72–7.90 (m, 4H, ArHs), 7.99 (d, J = 10 Hz, 1H, ArHs), 8.17 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 23.6 (CH_3), 56.0 ($2OCH_3$), 73.2, 110.6, 112.2 (Ar-C), 114.1 (CN), 116.4, 120.3, 130.8, 138.6, 145.1, 149.4, 150.9, 155.9, 157.4, 158.3 (Ar-C), 165.7 (C=O), 170.5 (C=N); Anal. calcd. For: $C_{19}H_{17}N_5O_3$ (363.38): C, 62.80; H, 4.72; N, 19.27%; Found: C, 62.98; H, 4.92; N, 19.14%.

3.11 | Antimicrobial activities

3.11.1 | Microorganisms

Nine clinical strains employed for this study include two gram-positive bacteria (*S. aureus* and *B. subtilis*), two gram-negative bacteria (*K. pneumoniae* and *P. aeruginosa*), four filamentous fungi (*A. fumigatus*, *A. flavus*, *Syncephlastarum racemosum*, and *P. expansum*) and one yeast (*C. albicans*). All strains were provided from culture collection of the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Cairo, Egypt.

3.11.2 | Antimicrobial assay

By diffusion agar technique, the antimicrobial activities against the tested species were expressed as the measurement of diameter of their inhibition zone. Hole-plate diffusion method was used; six equidistant (1 cm diameter) holes were made using sterile cork borer in malt extract agar and nutrient agar sterile plates (10 cm), which had previously been seeded with tested fungal and bacterial species. Holes were filled with 100 uL of three concentrations 5, 2.5, and 1 mg/mL of each of the tested compounds in ethyl acetate. Control holes were filled with ethyl acetate solvent.

Plates were kept in a cooled incubator at 4 (±2) °C for 1 hour and then incubated at 37 (±2) °C for bacterial species and incubated at 28 (±2) °C for fungal species. Inhibition zones were measured after 24 to 48 hours. Amoxicilline was used as reference antibacterial drug while Griseofulvin was used as reference antifungal drug.[48]

3.11.3 | MIC assays

Determination of MIC was performed by a serial dilution technique. Appling ethyl acetate solvent of the synthesized compounds started with a maximum concentration of 500 mg/mL and then reduced it by successive twofold dilutions. MIC of the sample determination was carried out by inoculation of their serial dilutions with test organisms and measurement of inhibition zones using diffusion agar technique. MIC was expressed as the lowest concentration inhibiting test

Microbial cells (70 mL, 10^6 CFU/mL) of each tested pathogen were spread onto the nutrient agar plates. The wells (6 mm diameter) were dug on the inoculated agar plates and 100 μL of the newly synthesized target molecule was suspended in DMSO at 200 mg/mL and subsequently was poured in the wells. The plates were

allowed to stand at 4°C for 2 hours before incubation for the diffusion. The plates were incubated at 37°C for 24 hours except for the yeast strains which were incubated at 28°C. Incubation step was followed by measuring the diameter of inhibition zone (IZ) in mm and three replicates were averaged.[49]

4 | CONCLUSIONS

Herein, we have reported the synthesis and characterization of a new series of thiazole-based pyrazolines. Compounds **11b**, **7c**, and **11c** revealed a moderate activity against bacterial strains *K. pneumoniae* and *P. aeruginosa*. In addition, compounds **7e**, **7g**, and **11e** showed a good activity against the antifungal strains *A. flavus* and *P. expansum*. These obtained results suggest that the new pyrazolines bearing thiazole scaffold may be considered for further investigation in the design of new antimicrobial agents.

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REFERENCES AND NOTES

[1] K. D. Olczak, M. Daszkiewicz, K. Slawinska, D. B. Baginska, D. Gozdowski, P. Daszkiewicz, B. Fronc, K. Semczuk, *J. Oral. Pathol. Med.* **2012**, *41*, 568.

[2] N. C. Desai, N. Bhatt, H. Somani, A. Trivedi, *Eur. J. Med. Chem.* **2013**, *67*, 54.

[3] (a) S. Fustero, M. Sanchez-Rosello, P. Barrio, A. Simon-Fuentes, *Chem. Rev.* **2011**, *111*, 6984; (b) A. Ansari, A. Ali, M. Asif, *New. J. Chem.* **2017**, *41*, 16.

[4] A. Balbi, M. Anzaldi, C. Maccio, C. Aiello, M. Mazzei, R. Gangemi, P. Castagnola, M. Miele, C. Rosano, M. Viale, *Eur. J. Med. Chem.* **2011**, *46*, 5293.

[5] A. Kamal, A. B. Shaik, N. Jain, C. Kishor, A. Nagabhushana, B. Supriya, S. S. Chourasiya, Y. Suresh, K. R. Mishra, A. Addlaganatta, *Eur. J. Med. Chem.* **2015**, *92*, 501.

[6] P. D. Mishra, S. Wahidullah, S. Y. Kamat, *Indian. J. Chem. Soc.* **1998**, *37*, 199.

[7] F. Colliot, K. A. Kukorowski, D. W. Hawkins, D. A. Roberts, *Brighton Crop. Prot. Conf. Pests. Dis.* **1992**, *1*, 29.

[8] H. S. Chen, Z. M. Li, Y. F. Han, *J. Agric. Food Chem.* **2000**, *48*, 5312.

[9] M. Ramiz, I. Hafiz, S. Abdel, M. Reheim, A. M. Abdel, H. M. Gaber, *J. Chin. Chem.* **2012**, *59*, 72.

[10] C. B. Vicentini, C. Romagnoli, E. Andreotti, D. Mares, *J. Agric. Food Chem.* **2007**, *55*, 10331.

[11] M. Kurowski, A. Dunky, M. Geddawi, *Eur. J. Clin. Pharmacol.* **1986**, *31*, 307.

[12] F. Lepage, B. Hublot, *Chem. Abstr.* **1992**, *116*, 128917.

[13] D. M. Bailey, P. E. Hansen, A. G. Hlavac, E. R. Baizman, J. Pearl, A. F. DeFelice, M. E. Feigenson, *J. Med. Chem.* **1985**, *28*, 256.

[14] R. H. Wiley, P. Wiley, *Pyrazolones, Pyrazolidones and Derivatives*, John Wiley and sons, New York **1964** 102.

[15] D. David do CarmoMalvar, R. T. Ferreira, R. A. De Castro, L. L. De Castro, A. C. C. Freitas, E. A. Costa, F. A. Vanderlinde, *Life Sci.* **2014**, *95*, 81.

[16] S. Mert, R. Kasımoğulları, T. Iça, F. Çolak, A. Altun, S. Ok, *Eur. J. Med. Chem.* **2014**, *78*, 86.

[17] Y. R. Li, C. Li, J. C. Liu, M. Guo, T. Y. Zhang, L. P. Sun, H. R. Piao, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5052.

[18] S. P. Satasia, P. N. Kalaria, D. K. Raval, *Org. Biomol. Chem.* **2014**, *12*, 1751.

[19] S. S. Jadav, N. B. Sinha, B. Pastorino, X. de Lamballerie, R. Hilgenfeld, V. Jayaprakash, *Lett. Drug Des. Discov.* **2015**, *12*, 292.

[20] A. A. Farag, M. F. El Shehry, S. Y. Abbas, A. A. Atrees, Y. A. Ammar, *Naturforsch* **2015**, *70*, 519.

[21] S. Kini, A. M. Gandhi, *Indian J. Pharm. Sci.* **2008**, *70*, 105.

[22] E. M. Sharshira, N. M. Hamada, *Molecules* **2012**, *17*, 4962.

[23] M. Baseer, F. L. Ansari, Z. Ashraf, *Pak. J. Pharm. Sci.* **2013**, *26*, 67.

[24] S. Kumar, K. S. Meenakshi, P. Kumar, *Med. Chem. Res.* **2013**, *22*, 433.

[25] M. Abid, A. R. Bhat, F. Athar, A. Azam, *Eur. J. Med. Chem.* **2009**, *44*, 417.

[26] S. Sharma, P. K. Sharma, N. Kumar, R. Dudhe, *Biomed. Pharmacother* **2011**, *65*, 244.

[27] S. U. F. Rizvi, H. L. Siddiqui, M. Johns, M. Detorio, R. F. Schinazi, *Med. Chem. Res.* **2012**, *21*, 3741.

[28] (a) R. Bashir, S. Ovais, S. Yaseen, H. Hamid, M. S. Alam, M. Samim, S. Singh, K. Javed, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4301; (b) A. S. Hassan, T. S. Hafez, M. M. Ali, T. K. Khatab, *Res. J. Pharm. Biol. Chem. Sci.* **2016**, *7*, 417.

[29] Z. Ozdemir, H. B. Kandilci, B. Gumusel, U. Calis, A. A. Bilgin, *Eur. J. Med. Chem.* **2007**, *42*, 373.

[30] N. M. Abunada, H. M. Hassaneen, N. G. Kandile, O. A. Miqdad, *Molecules* **2008**, *13*, 1011.

[31] M. R. Shaaban, A. S. Mayhoub, A. M. Farag, *Expert. Opin. Ther. Pat.* **2012**, *22*, 253.

[32] M. A. Raslan, M. A. Khalil, *Heteroatom Chem.* **2003**, *14*, 114.

[33] J. Banothu, K. Vaarla, R. Bavantula, P. A. Crooks, *Chin. Chem. Lett.* **2014**, *25*, 172.

[34] K. A. Milinkevich, L. Ye, M. Kurth, *J. J. Comb. Chem.* **2008**, *10*, 521.

[35] M. A. Gouda, M. A. Berghot, G. E. Abd El-Ghani, A. M. Khalil, *Eur. J. Med. Chem.* **2010**, *45*, 1338.

[36] P. C. Lv, K. R. Wang, Y. Yang, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6750.

[37] A. Zablotskaya, I. Segal, A. Geronikaki, *Eur. J. Med. Chem.* **2013**, *70*, 846.

[38] M. Fares, S. R. Abd El Hadi, R. A. Eladwy, A. A. Shoun, M. M. Abdel-Aziz, W. M. Eldehna, H. A. Abdel-Aziz, P. A. Keller, *Org. Biomol. Chem.* **2018**, *16*, 3389.

[39] W. M. Eldehnaa, A. Nocentini, S. T. Al-Rashood, G. S. Hassan, H. M. Alkahtani, A. A. Almehizia, A. M. Reda, H. A. Abdel-Aziz, C. T. Supuranb, *Bioorg. Chem.* **2018**, *81*, 425.

[40] W. M. Eldehnaa, R. I. Al-Wabli, M. S. Almutairi, A. B. Keeton, G. A. Piazza, H. A. Abdel-Aziz, M. I. Attia, *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 867.

[41] M. T. El Sayed, H. A. Hussein, N. M. Elebiary, G. S. Hassan, S. M. Elmessery, A. R. Elsheakh, M. Nayel, H. A. Abdel-Aziz, *Bioorg. Chem.* **2018**, *78*, 312.

[42] H. A. Abdel-Aziz, W. M. Eldehna, A. B. Keeton, G. A. Piazza, A. A. Kadi, M. W. Attwa, A. S. Abdelhameed, M. I. Attia, *Drug Des. Develop. Ther.* **2017**, *11*, 2333.

[43] M. A. Bhat, A. F. Ahmed, Z.-H. Wen, M. A. Al-Omar, H. A. Abdel-Aziz, *Med. Chem. Res.* **2017**, *26*, 1557.

[44] M. T. L. Sheeja, A. Mathew, J. Varkey, *Asian J. Pharm.* **2012**, *2*, 257.

[45] A. Mathew, M. T. L. Sheeja, A. T. Kumar, K. Radha, *Hygeia. J. D. Med.* **2011**, *3*, 48.

[46] B. Al-Saleh, M. M. Abdel-Khalik, A. M. Eltoukhy, M. H. Elnagdi, *J. Heterocyclic Chem.* **2002**, *39*, 1035.

[47] W. M. Eldehna, M. Fares, M. M. Abdel-Aziz, H. A. Abdel Aziz, *Molecules* **2015**, *20*, 8800.

[48] H. A. Abdel-Kader, S. R. Seddkey, *Assiut. Vet. Med. J.* **1995**, *34*, 67.

[49] J. Fagbemi, L. Ferdinand, T. Adenipekun, *Afr. J. Biotechnol.* **2009**, *8*, 1176.

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