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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, antimicrobial and antioxidant activities of 2-[1-{3,5-diaryl-4,5-dihydro-1*H*-pyrazolenyl}]-4-(4-nitrophenyl)-[1,3]-thiazoles

Prajwal Lourdes Lobo · Boja Poojary · Manjunatha Kumsi · Vinaya Chandra · Nalilu Sucheta Kumari · K. R. Chandrashekar

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Abstract In this study, various substituted chalcones, prepared by condensing substituted acetophenones with substituted aldehydes/arylfurfurals, were treated with thiosemicarbazide in basic media to produce 1-thiocarbonyl-3,5-disubstituted pyrazolines which on further reaction with substituted phenacyl bromides afforded the title compounds in good yield. Structures of the newly synthesized compounds were assigned on the basis of elemental analyses, IR, ^{1}H NMR, and mass spectral studies. The newly synthesized compounds were tested for their in vitro antibacterial and antifungal activities against a variety of microorganisms and antioxidant activities by diphenylpicrylhydrazyl radical scavenging assay. Among the derivatives, compounds **3b**, **3e**, **6a**, and **6h** were identified as potent antioxidants. Compounds 3**d**, **3e**, and **6a–f** have emerged as the most promising antimicrobial agents displaying the maximum activity against all the tested microorganisms.

P. L. Lobo · B. Poojary (✉)
Department of Chemistry, Mangalore University, Mangalagangothri 575199, Karnataka, India
e-mail: bojapoojary@gmail.com

M. Kumsi
Department of Chemistry, Nagarjuna College of Engineering and Technology, Devanahalli, Bangalore 562110, Karnataka, India

V. Chandra · K. R. Chandrashekar
Department of Applied Botany, Mangalore University, Mangalagangothri 575199, Karnataka, India

N. S. Kumari
Department of Biochemistry, K. S. Hegde Medical Academy, Deralakatte 574162, Karnataka, India

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Introduction

Heterocyclic synthesis has emerged as powerful technique for generating new molecules that are useful for drug discovery. Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs. Thiazoles are familiar group of heterocyclic compounds possessing a wide variety of biological activities, and their utility as medicine is very firmly established. Thiazole nucleus is also an integral part of all the available penicillins which have revolutionized the therapy of bacterial diseases (Onca *et al*., 2004). [1,3]-Thiazoles have attracted continuing interest because of their varied biological activities (Quiroga *et al*., 2002), which have recently found applications in the development of drugs used for the treatment of allergies (Hargrave *et al*., 1983), hypertension (Patt *et al*., 1992), inflammation (Manjunatha *et al*., 2010), schizophrenia (Jean *et al*., 1990), microbial (Lobo *et al*., 2010) and human immunodeficiency virus (HIV) infections (Bell *et al*., 1995), and more recently for the treatment of pain (Carter *et al*., 1999).

Pyrazole and their derivatives could be considered as possible antimicrobial agents (Lee *et al*., 2003); antidepressants (Erhan *et al*., 2001); inhibitors of protein kinases; antiaggregating, antiarthritic (Nugen and Megan, 1993), and cerebroprotectors (Kawazura *et al*., 1997). Some aryl pyrazoles were reported to have non-nucleoside HIV-I reverse transcriptase inhibitory activity (Jamode *et al*., 2003), COX-2 inhibitory activity (Sakya and Rast, 2003), and soluble guanylate cyclase activity (David and Selwood, 2001).

Following the successful introduction of antimicrobial agents, inspired by the biological profiles of thiazoles, pyrazoles, and in the design of new drugs, the development of hybrid molecules through the combination of different pharmacophores in one frame may lead to compounds with interesting biological profiles, it was thought worthwhile to accommodate thiazole and pyrazole moieties in a single molecular framework for enhancing biological activity. The present investigation deals with the use of chalcones in the synthesis of 2-[1-{3,5-diaryl-4,5-dihydro-1*H*-pyrazolenyl}]-4-(4-nitrophenyl)-[1,3]-thiazole and studying their antioxidant, antibacterial, and antifungal properties.

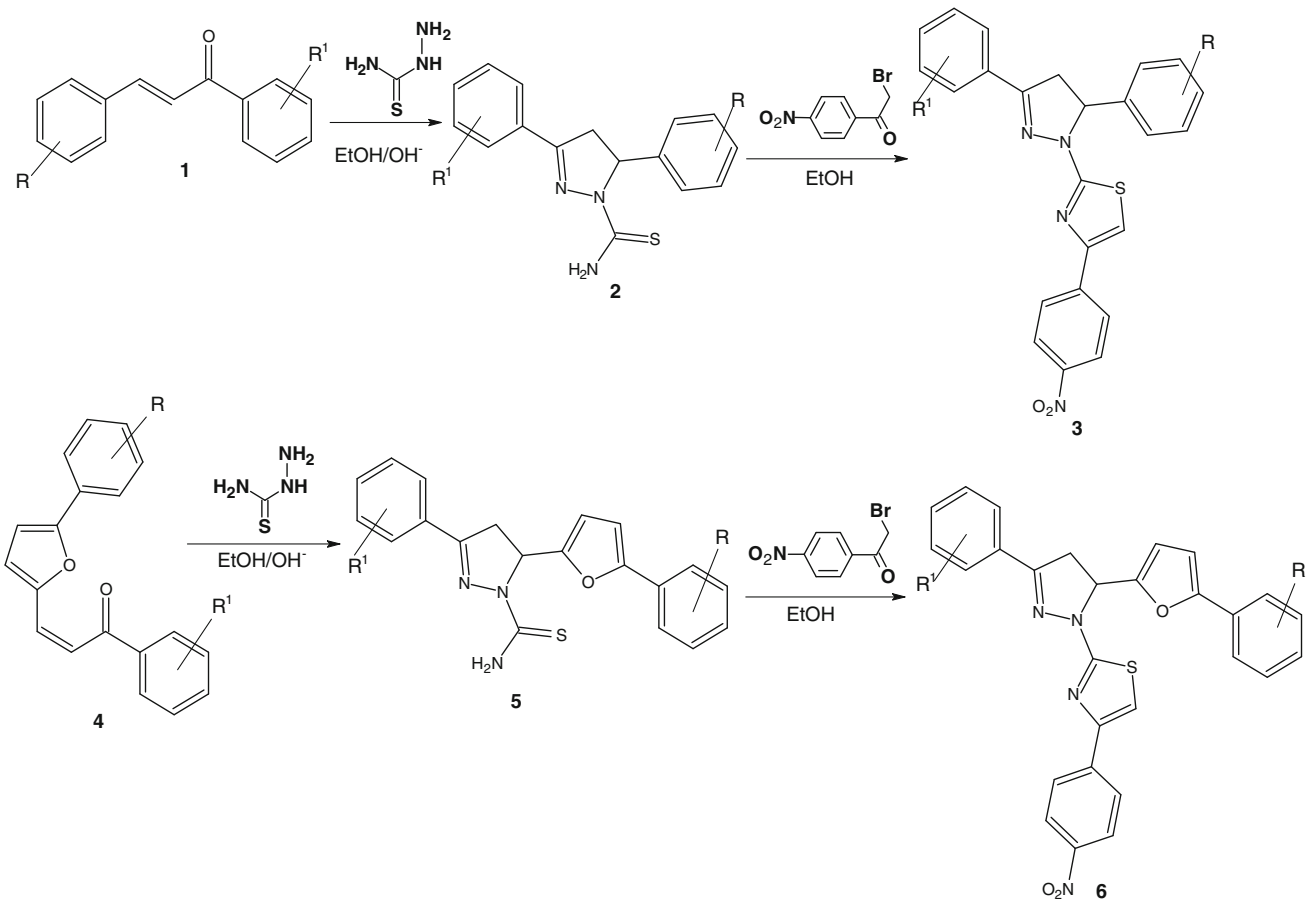
Results and discussion

Chemistry

The synthetic pathway for compounds described was achieved by a sequence of reactions starting from aldehydes and is illustrated in Scheme 1. In the first step, commercially available acetophenones were treated with various simple aryl aldehydes and aryl furfurals by Claisen–Schmidt reaction to obtain the 1,3-diaryl prop-2-en-1-ones (chalcones) **1** and **4**, respectively. Their further condensation with thiosemicarbazides in alcohol medium led to the formation of intermediate 3,5-disubstituted-4,5-dihydro-1*H*-pyrazole-1-carbothioamides **2** and **5** which were further treated with 4-nitrophenacyl bromides in alcohol medium to obtain the title compounds **3a–e** and **6a–k**.

All new compounds were characterized on the basis of complementary spectroscopic (^{1}H NMR, IR and MS) and analytical data. The physicochemical properties and spectral data of synthesized compounds are presented in Table 1.

In the ^{1}H NMR spectra of the compounds **3a–e** and **6a–k** protons of CH_2–CH fragment of pyrazolines ring showed characteristic splitting patterns of an ABX system. The chemical shifts of the protons H_A, H_B, and H_X have been assigned to about $\delta \sim 3.40$–3.80, $\delta \sim 3.70$–4.00, and $\delta \sim 5.20$–6.40, respectively and appeared as three doublets of doublets (dd) and indicate that the methylene protons



Scheme 1 R = 4-SCH_3; 2,4-Cl_2; 3-Cl-4-F; 2,4,5-Cl_3; 4-NO_2; 2-CH_3-4-NO_2; 4-Cl; 2-CH_3-6-NO_2; 4-OCH_3-2-NO_2; 4-Br; 4-Cl-2-NO_2. R′ = 4-OCH_3; 3,4-$(OCH_3)_2$; 4-NO_2; 4-Cl; 2,4-Cl_2; 3,4-$(OCH_3)_2$; H

Table 1 Characterization data of compounds (**2a–e**) and (**5a–k**)

Compounds	R	R′	Molecular formula	Melting point (°C)	Yield (%)
2a	4-SCH_3	4-OCH_3	$C_{18}H_{19}N_3OS_2$	162–164	88
2b	4-SCH_3	3,4-$(OCH_3)_2$	$C_{19}H_{16}N_3O_2S_2$	132–134	85
2c	4-SCH_3	4-NO_2	$C_{17}H_{16}N_4O_2S_2$	198–199	77
2d	4-SCH_3	4-Cl	$C_{17}H_{16}N_3S_2Cl$	140–142	89
2e	4-SCH_3	2,4-Cl_2	$C_{17}H_{15}N_3S_2Cl_2$	176–178	70
5a	2,4-Cl_2	3,4-$(OCH_3)_2$	$C_{22}H_{19}N_3O_3SCl_2$	183–185	83
5b	3-Cl,4-F	3,4-$(OCH_3)_2$	$C_{22}H_{19}N_3O_3SClF$	124–127	75
5c	2,4,5-Cl_3	3,4-$(OCH_3)_2$	$C_{22}H_{18}N_3O_3SCl_3$	158–160	78
5d	4-NO_2	3,4-$(OCH_3)_2$	$C_{22}H_{20}N_4O_5S$	173–175	77
5e	2-CH_3-4-NO_2	3,4-$(OCH_3)_2$	$C_{23}H_{22}N_4O_5S$	189–191	79
5f	4-Cl	3,4-$(OCH_3)_2$	$C_{22}H_{20}N_3O_3SCl$	139–141	85
5g	2-CH_3-6-NO_2	3,4-$(OCH_3)_2$	$C_{23}H_{22}N_4O_5S$	188–190	69
5h	4-OCH_3-2-NO_2	3,4-$(OCH_3)_2$	$C_{23}H_{22}N_4O_6S$	186–188	82
5i	4-Br	3,4-$(OCH_3)_2$	$C_{22}H_{20}BrN_3O_3S$	154–156	72
5j	4-Cl-2-NO_2	3,4-$(OCH_3)_2$	$C_{22}H_{19}N_4O_5SCl$	192–193	78
5k	4-Cl	H	$C_{20}H_{16}N_3OSCl$	167–169	83

adjacent to an asymmetric centered are magnetically non-equivalent. The large values of J_{AB} (approximate coupling constants of $J_{AB} = 17.0–18.0$, $J_{Ax} = 11.0–12.0$, and $J_{Bx} = 3.0–4.0$ Hz) were observed. The protons belonging to aryl groups were observed at expected chemical shifts and integral values. The H5-proton of thiazole ring was observed as a singlet between δ 6.9 and 7.3 ppm. The LC mass of the compounds was also in agreement with the assigned structure.

In compound **3a**, the –SMe protons appeared as a singlet at δ 3.30 and the –OMe protons appeared as a singlet at δ 3.89. The thiazole ring proton appeared at δ 7.3. The aromatic protons appeared in the region from 6.93 to 8.18. In compound **6k**, the two protons of furan ring appeared as two doublets at δ 6.82 and δ 7.24 with the coupling constant $J = 3.3$ Hz.

The IR spectra of the compounds **3a–e** and **6a–k** showed the absence of NH_2 peak confirming their formation. In compounds containing NO_2 group, two characteristic absorption maxima in the region 1,507–1,515 and 1,330–1,370 cm^{-1} reveal its presence.

Antimicrobial activity studies

The antibacterial and antifungal screening data of the newly synthesized compounds revealed that the most of the compounds synthesized were very active against all the bacterial (listed in Table 2) and fungal strains (listed in Table 3). The compounds **3d**, **3e**, and **6a–f** showed the maximum activity against all the bacterial and fungal strains. The good activity may be attributed to the presence of 4-chloro, 4-bromo, or 4-nitro group attached to any of the phenyl rings of pyrazolynyl moiety. However, the compounds **6g–k** exhibited moderate activity compared to the activity of the standard drug. Compounds **3a**, **3b**, and **3c** did not show any significant activity.

More extensive study is in progress to determine additional physicochemical and biological parameters to have a deeper insight into structure–activity relationship and to optimize the effectiveness of this series of molecules.

DPPH radical scavenging activity

Antioxidants are very interesting, particularly in terms of prevention of the presumed deleterious effects of free radicals in the human body and in fats or other constituents of food stuffs. There is therefore a parallel increase in the use of methods for estimating the efficiency of such substances as antioxidants.

One such method that is currently popular is based on the use of the stable, free radical diphenylpicrylhydrazyl (DPPH). The purpose of our study is to examine the percentage inhibition of DPPH, compared with ascorbic acid as standard. When a solution of DPPH is mixed with that of the substance that can donate a hydrogen atom, then this gives rise to the reduced form along with the loss of its violet color. Representing the DPPH radical by $Z^{\bullet}$ and the donor molecule by AH, the primary reaction is given by

$$Z^{\bullet} + AH = ZH + A^{\bullet} \quad (1)$$

where ZH is the reduced form, and $A^{\bullet}$ is the free radical produced in the first step. This latter radical will then

Table 2 Antibacterial activities of the newly synthesized compounds (**3a–e**) and (**6a–k**), expressed as MIC (1.56–25 μg/mL) and zone of inhibition (mm)

	MIC (1.56–25 μg/mL) and zone of inhibition (mm)			
Bacterial strain	*S. aureus*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
Compounds				
3a	25(<10)	25(<10)	25(<10)	25(<10)
3b	25(<10)	25(<10)	25(<10)	25(<10)
3c	25(<10)	25(<10)	25(<10)	25(<10)
3d	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
3e	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6a	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6b	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6c	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6d	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6e	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6f	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6g	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
6h	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
6i	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
6j	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
6k	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
Standard (amphicillin)	1.56(22–30)	6.25(30–40)	6.25(25–33)	6.25(23–27)

Table 3 Antifungal activities of the newly synthesized compounds (**3a–e**) and (**6a–k**), expressed as MIC (1.56–25 μg/mL) and zone of inhibition (mm)

	MIC (1.56–25 μg/mL) and zone of inhibition (mm)			
Fungal strain	*P. marneffei*	*T. mentagrophytes*	*A. flavus*	*A. fumigatus*
Compounds				
3a	25(<10)	25(<10)	25(<10)	25(<10)
3b	25(<10)	25(<10)	25(<10)	25(<10)
3c	25(<10)	25(<10)	25(<10)	25(<10)
3d	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
3e	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6a	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6b	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6c	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6d	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6e	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6f	6.25(16–20)	6.25(16–20)	6.25(16–20)	6.25(16–20)
6g	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
6h	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
6i	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
6j	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
6k	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
Standard (itraconazol)	6.25(25–33)	6.25(23–27)	1.56(22–30)	6.25(30–40)

undergo further reactions which control the overall stoichiometry that is the number of molecules of DPPH reduced by one molecule of the reductant. The DPPH molecule $Z^{\bullet}$ is thus intended to represent the free radicals formed in the system, activity of which is to be suppressed by the substance AH. The free radical $A^{\bullet}$ evidently then reacts with another molecule of the same kind that was produced by a parallel reaction to (1)

$$A^{\bullet} + A^{\bullet} = A - A$$

Table 4 DPPH radical scavenging activities of compounds **3a–e** and **6a–k**, tested in dose 4,000 μg/mL and expressed as percent of inhibition

Compounds	Percentage inhibition
3a	79
3b	86
3c	75
3d	38
3e	88
6a	86
6b	74
6c	57
6d	62
6e	14
6f	35
6g	66
6h	86
6i	69
6j	82
6k	45
Ascorbic acid	96

This therefore leads to the observed reduction of two molecules of DPPH by two molecules of the reductant, that is, a 1:1 stoichiometry.

The DPPH radical scavenging activity in terms of percentage inhibition exhibited by the title compounds are summarized in Table 4.

In this assay **3a**, **3b**, **3c**, **3e**, **6a**, **6b**, **6h**, and **6j** are the best DPPH radical scavengers. They showed significant radical scavenging activity, compared with ascorbic acid as standard. Among these compounds **3b**, **3e**, **6a**, and **6h** were as active as ascorbic acid, while other tested compounds expressed lower scavenging effect. Except compound **3e**, the other three compounds have O–CH_3 function.

Conclusion

In conclusion, we have reported a convenient protocol for the synthesis of novel 2-[1-{3,5-diaryl-4,5-dihydro-1*H*-pyrazolenyl}]-4-(4-nitrophenyl)-[1,3]-thiazole in good yield. The antioxidant properties of the new compounds were evaluated using DPPH radical scavenging assay. Compounds **3b**, **3e**, **6a**, **and 6h** were identified as potent antioxidants. They have OCH_3 substitution in one of the phenyl ring attached to pyrazole moiety. Antioxidant activities of these compounds against the stable, free radical DPPH showed that these species could help in increasing the overall antioxidant capacity of an organism. However, further detailed study on activity and long-term toxicity needs to be carried out before any final conclusion can be drawn.

The antibacterial and antifungal screening data of the newly synthesized compounds revealed that the most of the compounds synthesized were very active against all the bacterial and fungal strains. Compounds **3d**, **3e**, and **6a–f** showed maximum activity against all the tested microorganisms.

Experimental part

Materials and methods

Melting points were determined by an open capillary method and are uncorrected (melting point apparatus: Sewell instruments inc., India).The purity of the compounds was checked by thin layer chromatography on a silica-coated aluminum sheet (silica gel F_{254}) using *n*-hexane and ethyl acetate (4:1, v/v). The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. The ^{1}H NMR spectra were recorded on a BRUKER AVANCE II-400 (400 MHz) spectrometer using TMS as an internal standard. Mass spectra were recorded in Finnigan MAT8230 mass spectrometer. Elemental analysis was carried out using CHNS elemental analyzer. Solvents and reagents were purchased in the appropriate grade from commercial vendors and were used without purification. 5-Aryl-furan-2-carboxaldehydes were prepared through Meerwein reaction (Holla *et al.*, 2005). Chalcones were prepared from substituted aldehydes and substituted acetophenones according to the procedure in the literature (Rai *et al.*, 2008).

General procedure for the synthesis of 3,5-disubstituted-4,5-dihydro-1H-pyrazole-1-carbothioamides (**2a–e**) and (**5a–k**)

To a suspension of chalcones (0.01 mol) and sodium hydroxide (0.025 mol) in ethanol, thiosemicarbazide (0.01) was added. The mixture was refluxed, and after completion of the reaction, the solution was poured into ice water. The resulting precipitate was filtered off and recrystallized from ethanol.

*3-(4-Methoxyphenyl)-5-(4-methylthiophenyl)-4,5-dihydro-1H-pyrazole-1-carbothio-amide (**2a**)*

Light yellow solid (yield 88 %) mp 162–164 °C. IR (KBr, ν in cm^{-1}): 3414 (N–H), 3243 (N–H), 3023 (ArC–H), 2943 (C–H), 1593 (C=N), 1249 (C–O), 1155 (C=S); ^{1}H NMR ($CDCl_3$, δ): 2.48 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 3.15 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 3.5$ Hz, pyrazole–CH_2), 3.82 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 11.3$ Hz, pyrazole–CH_2), 4.68 (bs, 2H, NH_2), 6.01 (dd, 1H, $J = 11.3$, 3.5 Hz, pyrazole–CH),

6.97 (d, 2H, $J = 7.4$ Hz, 4-methoxyphenyl), 7.19 (d, 2H, $J = 8.3$ Hz, 4-methylthiophenyl), 7.22 (d, 2H, $J = 8.3$ Hz, 4-methylthiophenyl), 7.69 (d, 2H, $J = 7.4$ Hz, 4-methoxyphenyl); LC–MS (*m/z*, %): 358 (M+1, 92); anal. calcd. for $C_{18}H_{19}N_3OS_2$: C, 60.47; H, 5.36; N, 11.75; S, 17.94 %; found: C, 60.47; H, 5.36; N, 11.75; S, 17.9 %.

*5-(4-Methylthiophenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**2c**)*

Light yellow solid (yield 85 %) mp 132–134 °C. IR (KBr, *v* in cm^{-1}): 3387 (N–H), 3246 (N–H), 3023 (ArC–H), 2943 (C–H), 1593 (C=N), 1592.4 (C=C), 1550 (NO_2asym), 1362 (NO_2sym), 1237 (C–O), 1153 (C=S); ^{1}H NMR ($CDCl_3$, δ): 2.48 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 3.15 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 3.5$ Hz, pyrazole–CH_2), 3.82 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 11.3$ Hz, pyrazole–CH_2), 4.66 (bs, 2H, NH_2), 6.01 (dd, 1H, $J_1 = 11.3$ Hz, $J_2 = 3.5$ Hz, pyrazole–CH), 7.17 (d, 2H, $J = 8.3$ Hz, 4-thiomethylphenyl), 7.22 (d, 2H, $J = 8.3$ Hz, 4-thiomethylphenyl), 7.83 (d, 2H, $J = 7.4$ Hz, 4-nitrophenyl), 8.1 (d, 2H, $J = 7.4$ Hz, 4-nitrophenyl); LC–MS (*m/z*, %): 373 (M+1, 95); anal. calcd. for $C_{19}H_{21}N_3O_2S_2$: C, 54.82; H, 4.33; N, 15.04; S, 17.22 %; found: C, 54.85; H, 4.37; N, 15.07; S, 17.24 %.

*5-(3,4-Dimethoxylthiophenyl)-3-(5-(4-chlorophenyl)-furan-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**5f**)*

Yellow solid (yield 85 %) mp 139–141 °C. IR (KBr, *v* in cm^{-1}): 3394 (N–H), 3248 (N–H), 3024 (ArC–H), 2945 (C–H), 1640 (C=N), 1237 (C–O), 1250 (C–O), 1299 (C–O), 1162 (C=S), 755 (C–Cl); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.71 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 6.3$ Hz, pyrazole–CH_2), 4.70 (bs, 2H, NH_2) 3.85 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 11.3$ Hz, pyrazole–CH_2), 5.85 (m, 1H, pyrazole–CH), 7.23 (d, 1H, $J = 7.9$ Hz, 3,4-dimethoxyphenyl), 7.49 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.53 (d, 1H, $J = 2.0$ Hz, 3,4-dimethoxyphenyl), 6.62 (s, 1H, $J = 3.3$ Hz, furan), 6.92 (s, 1H, $J = 3.3$ Hz, furan), 8.16 (d, 2H, $J = 7.2$ Hz, 4-chlorophenyl), 8.35 (d, 2H, $J = 7.2$ Hz, 4-chlorophenyl); LC–MS (*m/z*, %): 442 (M+1, 96); anal. calcd. for $C_{22}H_{20}ClN_3O_3S$: C, 59.79; H, 4.56; N, 9.51; S, 7.26 %; found: C, 59.63; H, 4.57; N, 9.54; S, 7.28 %.

*3-(5-(4-Chlorophenyl)-furan-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**5k**)*

Yellow solid (yield 83 %) mp 167–169 °C. IR (KBr, *v* in cm^{-1}): 3391 (N–H), 3246 (N–H), 3030 (ArC–H), 2957 (C–H), 1592 (C=C), 1167 (C=S), 752 (C–Cl), 1589 (C=N), 1299 (C–O); ^{1}H NMR ($CDCl_3$, δ): 3.66 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 6.3$ Hz, pyrazole–CH_2), 4.70 (bs, 2H, NH_2), 3.85 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 11.3$ Hz, pyrazole–CH_2), 5.74 (m, 1H, pyrazole–CH), 7.06 (s, 1H, thiazole), 7.45 (m, 5H, phenyl), 6.52 (s, 1H, $J = 3.4$ Hz, furan), 6.63 (s, 1H, $J = 3.4$ Hz, furan), 7.21 (d, 2H, $J = 7.2$ Hz, 4-chlorophenyl), 7.68 (d, 2H, $J = 7.2$ Hz, 4-chlorophenyl); LC–MS (*m/z*, %): 382 (M+1, 92); anal. calcd. for $C_{20}H_{16}ClN_3OS$: C, 62.90; H, 4.22; N, 11.00; S, 8.40 %; found: C, 62.93; H, 4.25; N, 11.04; S, 8.43 %.

General procedure for the synthesis of 2-[1-{3,5-diaryl-4,5-dihydro-1*H*-pyrazolenyl}]-4-(4-nitrophenyl)-[1,3]-thiazoles (**3a**–**e**) and (**6a**–**k**)

To a suspension of the compound **2** or **5** (0.01 mol) in ethanol, 4-nitrophenacyl bromide (0.01 mol) was added and heated to reflux for 1 h. After completion of the reaction, the reaction mixture was cooled, and the solid separated was collected by suction filtration. The crude product was purified by recrystallization from suitable solvents.

*2-[1-{3-(4-Methoxyphenyl)-5-(4-methylthiophenyl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitro-phenyl)-[1,3]-thiazole (**3a**)*

Yellow solid (yield 73 %) mp 153–154 °C. IR (KBr, *v* in cm^{-1}): 3053 (ArC–H), 2949 (C–H), 1594 (C=N), 1512 (NO_2asym), 1327 (NO_2sym), 1262 (C–O); ^{1}H NMR ($CDCl_3$, δ): 2.46 (s, 3H, SCH_3), 3.85 (s, 3H, OCH_3), 3.30 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 6.6$ Hz, pyrazole–CH_2), 3.91 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 11.8$ Hz, pyrazole–CH_2), 5.59 (dd, 1H, $J_1 = 11.8$ Hz, $J_2 = 6.6$ Hz, pyrazole–CH), 7.01 (s, 1H, –CH, thiazole), 6.95 (d, 2H, $J = 8.8$ Hz, 4-methoxyphenyl), 7.23 (d, 2H, $J = 8.4$ Hz, 4-thiomethylphenyl), 7.34 (d, 2H, $J = 8.4$ Hz, 4-thiomethylphenyl), 7.70 (d, 2H, $J = 8.8$ Hz, 4-methoxyphenyl), 7.80 (d, 2H, $J = 8.9$ Hz, 4-nitrophenyl), 8.17 (d, 2H, $J = 8.9$ Hz, 4-nitrophenyl); LC–MS (*m/z*, %): 503 (M+1, 96); anal. calcd. for $C_{26}H_{22}N_4O_3S$: C, 66.38; H, 4.68; N, 11.91 %; found: C, 66.41; H, 4.72; N, 11.94 %.

*2-[1-{3-(3,4-Dimethoxyphenyl)-5-(4-methylthiophenyl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitrophenyl)-[1,3]-thiazole (**3b**)*

Yellow solid (yield 78 %) mp 159–161 °C. IR (KBr, *v* in cm^{-1}): 3053 (ArC–H), 2943 (C–H), 1592 (C=N), 1507 (NO_2asym), 1330 (NO_2sym), 1297 (C–O), 1262 (C–O), 1239 (C–O); ^{1}H NMR ($CDCl_3$, δ): 2.45 (s, 3H, SCH_3), 3.96 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 3.33 (dd, 1H, $J_1 = 17.4$ Hz, $J_2 = 6.2$ Hz, pyrazole–CH_2), 3.75 (dd, 1H, $J_1 = 17.4$ Hz, $J_2 = 11.2$ Hz, pyrazole–CH_2), 5.75 (m, 1H, pyrazole–CH), 7.01 (s, 1H, –CH, thiazole), 6.89 (d, 1H, $J = 8.4$ Hz,

3,4-dimethoxyphenyl), 7.15 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 3,4-dimethoxyphenyl), 7.47 (d, 1H, $J = 2.0$ Hz, 3,4-dimethoxyphenyl), 7.24 (d, 2H, $J = 8.4$ Hz, 4-thiomethylphenyl), 7.36 (d, 2H, $J = 8.4$ Hz, 4-thiomethylphenyl), 7.83 (d, 2H, $J = 8.9$ Hz, 4-nitrophenyl), 8.19 (d, 2H, $J = 8.9$ Hz, 4-nitrophenyl); LC–MS (*m/z*, %): 533 (M+1, 95); anal. calcd. for $C_{26}H_{22}ClN_3OS$: C, 67.97; H, 4.79; N, 9.14 %; found: C, 67.99; H, 4.77; N, 9.17 %.

*2[1-{5-(4-(Methylthio)phenyl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitro-phenyl)-[1,3]-thiazole (**3c**)*

Yellow solid (yield 75 %) mp 172–175 °C. IR (KBr, *v* in cm^{-1}): 3054 (ArC–H), 2952 (C–H), 1594 (C=N), 1512 (NO_2asym), 1327 (NO_2sym), 1262 (C–O); ^{1}H NMR ($CDCl_3$, δ): 2.46 (s, 3H, SCH_3), 3.30 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 6.7$ Hz, pyrazole–CH_2), 3.88 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 12.1$ Hz, pyrazole–CH_2), 5.60 (dd, 1H, $J_1 = 12.1$ Hz, $J_2 = 6.7$ Hz, pyrazole–CH), 7.04 (s, 1H, –CH, thiazole), 7.92 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl), 7.23 (d, 2H, $J = 8.2$ Hz, 4-thiomethylphenyl), 7.34 (d, 2H, $J = 8.2$ Hz, 4-thiomethylphenyl), 7.84 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl), 7.88 (d, 2H, $J = 8.9$ Hz, 4-nitrophenyl), 8.21 (d, 2H, $J = 8.9$ Hz, 4-nitrophenyl); LC–MS (*m/z*, %): 519 (M+1, 90); anal. calcd. for $C_{25}H_{19}N_5O_4S_2$: C, 58.01; H, 3.72; N, 13.53 %; found: C, 58.03; H, 3.75; N, 13.56 %.

*2-[1-{3-(4-Chlorophenyl)-5-(4-(methylthio)phenyl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitro-phenyl-[1,3]-)thiazole (**3d**)*

Light red solid (yield 87 %) mp 157–159 °C. IR (KBr, *v* in cm^{-1}): 3057 (ArC–H), 2950 (C–H), 1594 (C=N), 1512 (NO_2asym), 1327 (NO_2sym), 1262 (C–O), 758 (C–Cl); ^{1}H NMR ($CDCl_3$, δ): 2.46 (s, 3H, SCH_3), 3.32 (dd, 1H, $J_1 = 18.2$ Hz, $J_2 = 7.1$ Hz, pyrazole–CH_2), 3.95 (dd, 1H, $J_1 = 18.2$ Hz, $J_2 = 11.8$ Hz, pyrazole–CH_2), 5.63 (dd, 1H, $J_1 = 11.8$ Hz, $J_2 = 7.1$ Hz, pyrazole–CH), 7.02 (s, 1H, –CH, thiazole), 7.42 (d, 2H, $J = 8.3$ Hz, 4-chlorophenyl), 7.27 (d, 2H, $J = 8.4$ Hz, 4-thiomethylphenyl), 7.48 (d, 2H, $J = 8.4$ Hz, 4-thiomethylphenyl), 7.67 (d, 2H, $J = 8.3$ Hz, 4-chlorophenyl), 7.80 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl), 8.17 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl); LC–MS (*m/z*, %): 508 (M+1, 96); anal. calcd. for $C_{25}H_{19}N_4O_2S_2Cl$: C, 59.22; H, 3.78; N, 11.05 %; found: C, 59.26; H, 3.80; N, 11.08 %.

*2-[1-{3-(2,4-Dichlorophenyl)-5-(4-(methylthio)phenyl)-4,5-dihydro-1H-pyrazolyl)}]-4-(4-nitrophenyl)-[1,3]-thiazole (**3e**)*

Light red solid (yield 78 %) mp 162–164 °C. IR (KBr, *v* in cm^{-1}): 3053 (ArC–H), 2950 (C–H), 1597 (C=N), 1517 (NO_2asym), 1330 (NO_2sym), 1262 (C–O); ^{1}H NMR ($CDCl_3$, δ): 2.46 (s, 3H, SCH_3), 3.34 (dd, 1H, $J_1 = 17.7$ Hz, $J_2 = 6.4$ Hz, pyrazole–CH_2), 3.90 (dd, 1H, $J_1 = 17.7$ Hz, $J_2 = 11.3$ Hz, pyrazole–CH_2), 5.72 (dd, 1H, $J_1 = 11.3$ Hz, $J_2 = 6.4$ Hz, pyrazole–CH), 7.04 (s, 1H, –CH, thiazole), 7.32 (d, 2H, $J = 8.4$ Hz, 4-thiomethylphenyl), 7.45 (d, 2H, $J = 8.4$ Hz, 4-thiomethylphenyl), 7.67–7.70 (m, 3H, 2, 4-dichlorophenyl), 7.83 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl), 8.12 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl); LC–MS (*m/z*, %): 543 (M+1, 82); anal. calcd. for $C_{25}H_{18}N_4O_2S_2Cl_2$: C, 55.45; H, 3.35; N, 11.05 %; found: C, 55.48; H, 3.32; N, 11.04 %.

*2-[1-{5-(5-(2,4-Dichlorophenyl)furan-2-yl)-3-(2,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitrophenyl)-[1,3]-thiazole (**6a**)*

Yellow solid (yield 82 %) mp 155–157 °C. IR (KBr, *v* in cm^{-1}): 3051 (ArC–H), 2948 (C–H), 1592 (C=N), 1557 (NO_2asym), 1380 (NO_2sym), 1307 (C–O), 1262 (C–O), 1239 (C–O), 743 (C–Cl); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.71 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 6.3$ Hz, pyrazole–CH_2), 3.85 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 11.3$ Hz, pyrazole–CH_2), 5.85 (m, 1H, pyrazole–CH), 7.06 (s, 1H, thiazole), 6.89 (d, 1H, $J = 7.9$ Hz, 3,4-dimethoxyphenyl), 7.20 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.49 (d, 1H, $J = 2.0$ Hz, 3,4-dimethoxyphenyl), 7.31 (s, 1H, $J = 3.3$ Hz, furan), 7.54 (s, 1H, $J = 3.3$ Hz, furan), 7.91 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 8.17 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 7.72–7.87 (m, 3H, 4-chlorophenyl); LC–MS (*m/z*, %): 623 (M^++1, 89); anal. calcd. for $C_{30}H_{22}Cl_2N_4O_5S$: C, 57.98; H, 3.57; N, 9.01 %; found: C, 57.94; H, 3.60; N, 9.04 %.

*2-[1-{5-(5-(3-Chloro-4-fluorophenyl)furan-2-yl)-3-(2,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitrophenyl)-[1,3]-thiazole (**6b**)*

Yellow solid (yield 82 %) mp 155–157 °C. IR (KBr, *v* in cm^{-1}): 3051 (ArC–H), 2948 (C–H), 1592 (C=N), 1557 (NO_2asym), 1380 (NO_2sym), 1307 (C–O), 1262 (C–O), 1239 (C–O), 743 (C–Cl); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.71 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 6.3$ Hz, pyrazole–CH_2), 3.85 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 11.3$ Hz, pyrazole–CH_2), 5.85 (m, 1H, pyrazole–CH), 7.06 (s, 1H, thiazole), 6.89 (d, 1H, $J = 7.9$ Hz, 3,4-dimethoxyphenyl), 7.20 (dd, 1H, $J = 7.9$, 1.9 Hz, 3,4-dimethoxyphenyl), 7.49 (d, 1H, $J = 2.0$ Hz, 3,4-dimethoxyphenyl), 7.31 (s, 1H, $J = 3.3$ Hz, furan), 7.54 (s, 1H, $J = 3.3$ Hz, furan), 7.91 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 8.17 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 7.72–7.87 (m, 3H, 4-chlorophenyl); LC–MS (*m/z*, %): 623 (M^++1, 89); anal. calcd. for $C_{20}H_{16}ClN_3OS$: C,

57.98; H, 3.57; N, 9.01 %; found: C, 57.94; H, 3.60; N, 9.04 %.

*2-[1-{3-(2,4-Dimethoxyphenyl)-5-(5-(2,4,5-trichlorophenyl)furan-2-yl)-4,5-dihydro-1H-pyrazole)}]-4-(4-nitrophenyl)-[1, 3]-thiazole (**6c**)*

Yellow solid (yield 65 %) mp 167–169 °C. IR (KBr, *v* in cm^{-1}): 3051 (ArC–H), 2953 (C–H), 1592 (C=N), 1560 (NO_2asym), 1389 (NO_2sym), 1308 (C–O), 1268 (C–O), 1242 (C–O), 760 (C–Cl); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.73 (dd, 1H, $J_1 = 17.7$ Hz, $J_2 = 6.3$ Hz, pyrazole–CH_2), 3.87 (dd, 1H, $J_1 = 17.7$ Hz, $J_2 = 11.5$ Hz, pyrazole–CH_2), 5.85 (m, 1H, pyrazole–CH), 7.04 (s, 1H, thiazole), 6.73 (d, 1H, $J = 8.1$ Hz, 3,4-dimethoxyphenyl), 7.20 (dd, 1H, $J_1 = 8.1$, $J_2 = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.53 (d, 1H, $J = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.33 (s, 1H, $J = 3.4$ Hz, furan), 7.47 (s, 1H, $J = 3.4$ Hz, furan), 7.89 (d, 2H, $J = 8.4$ Hz, 4-nitrophenyl), 8.21 (d, 2H, $J = 8.4$ Hz, 4-nitrophenyl), 7.78 (s, 1H, 2,4,5-trichlorophenyl), 7.93 (s, 1H, 2,4,5-trichlorophenyl); LC–MS (*m/z*, %): 657 (M^++1, 82); anal. calcd. for $C_{30}H_{21}Cl_3N_4O_5S$: C, 54.93; H, 3.23; N, 8.54 %; found: C, 54.98; H, 3.27; N, 8.57 %.

*2-[1-{3-(2,4-Dimethoxyphenyl)-5-(5-(4-nitrophenyl)furan-2-yl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitrophenyl)-[1,3]-thiazole (**6d**)*

Yellow solid (yield 73 %) mp 182–184 °C. IR (KBr, *v* in cm^{-1}): 3055 (ArC–H), 2957 (C–H), 1594 (C=N), 1558 (NO_2asym), 1392 (NO_2sym), 1309 (C–O), 1267 (C–O), 1247 (C–O); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.70 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 6.3$ Hz, pyrazole–CH_2), 3.81 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 11.5$ Hz, pyrazole–CH_2), 5.88 (m, 1H, pyrazole–CH), 7.04 (s, 1H, thiazole), 6.74 (d, 1H, $J = 8.2$ Hz, 3,4-dimethoxyphenyl), 7.20 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 2.0$ Hz, 3,4-dimethoxyphenyl), 7.53 (d, 1H, $J = 2.0$ Hz, 3,4-dimethoxyphenyl), 7.33 (s, 1H, $J = 3.4$ Hz, furan), 7.47 (s, 1H, $J = 3.4$ Hz, furan), 7.84 (d, 2H, $J = 8.4$ Hz, 4-nitrophenyl), 8.11 (d, 2H, $J = 8.4$ Hz, 4-nitrophenyl), 7.92 (d, 2H, 4-nitrophenyl), 8.08 (d, 2H, 4-nitrophenyl); LC–MS (*m/z*, %): 599 (M^++1, 84); anal. calcd. for $C_{30}H_{23}N_5O_7S$: C, 60.29; H, 3.88; N, 11.72 %; found: C, 60.32; H, 3.91; N, 11.75 %.

*2-[1-{3-(2,4-Dimethoxyphenyl)-5-(5-(2-methyl-4-nitrophenyl)furan-2-yl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitrophenyl)-[1,3]-thiazole (**6e**)*

Light red solid (yield 73 %) mp 173–175 °C. IR (KBr, *v* in cm^{-1}): 3051 (ArC–H), 2948 (C–H), 1592 (C=N), 1557 (NO_2asym), 1380 (NO_2sym), 1307 (C–O), 1262 (C–O), 1239 (C–O); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3), 3.74 (dd, 1H, $J_1 = 17.2$ Hz, $J_2 = 6.6$ Hz, pyrazole–H_2), 3.85 (dd, 1H, $J_1 = 17.2$ Hz, $J_2 = 11.3$ Hz, pyrazole–CH_2), 5.88 (m, 1H, pyrazole–CH), 7.06 (s, 1H, thiazole), 6.95 (d, 1H, $J = 7.8$ Hz, 3,4-dimethoxyphenyl), 7.27 (dd, 1H, $J_1 = 7.8$, $J_2 = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.49 (d, 1H, $J = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.23 (s, 1H, $J = 3.3$ Hz, furan),7.38 (s, 1H, $J = 3.3$ Hz, furan), 7.83 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 8.09 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 7.72–7.74 (m, 3H, 2-methyl-4-nitrophenyl); LC–MS (*m/z*, %): 613 (M^++1, 91); anal. calcd. for $C_{31}H_{25}N_5O_7S$: C, 60.88; H, 4.12; N, 11.45 %; found: C, 60.71; H, 4.16; N, 11.48 %.

*2-[1-{2-(5-(4-Chlorophenyl)-furan-2-yl)-5-[1-{3-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazolenyl}]-4-(4-nitrophenyl)-[1,3]-thiazole (**6f**)*

Yellow red solid (yield 83 %) mp 167–169 °C. IR (KBr, *v* in cm^{-1}): 3051 (ArC–H), 2948 (C–H), 1592 (C=N), 1557 (NO_2asym), 1380 (NO_2sym), 1302 (C–O), 1262 (C–O), 1239 (C–O), 743 (C–Cl); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.71 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 6.3$ Hz, pyrazole–CH_2), 3.85 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 11.3$ Hz, pyrazole–CH_2), 5.85 (m, 1H, pyrazole–CH), 7.06 (s, 1H, thiazole), 6.89 (d, 1H, $J = 7.9$ Hz, 3,4-dimethoxyphenyl), 7.20 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.49 (d, 1H, $J = 2.0$ Hz, 3,4-dimethoxyphenyl), 7.31 (s, 1H, $J = 3.3$ Hz, furan), 7.54 (s, 1H, $J = 3.3$ Hz, furan), 7.93 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl), 8.19 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl), 8.16 (d, 2H, $J = 7.2$ Hz, 4-chlorophenyl), 8.35 (d, 2H, $J = 7.2$ Hz, 4-chlorophenyl); LC–MS (*m/z*, %): 587(M^++1, 89); anal. calcd. for $C_{30}H_{23}ClN_4O_5S$: C, 61.38; H, 3.95; N, 9.54 %; found: C, 61.31; H, 3.97; N, 9.58 %.

*2-[1-{3-(2,4-Dimethoxyphenyl)-5-(5-(2-methyl-6-nitrophenyl)furan-2-yl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitrophenyl)-[1,3]-thiazole (**6g**)*

Light red solid (yield 70 %) mp 169–171 °C. IR (KBr, *v* in cm^{-1}): 3051 (ArC–H), 2948 (C–H), 1592 (C=N), 1557 (NO_2asym), 1380 (NO_2sym), 1307 (C–O), 1262 (C–O), 1239 (C–O); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 2.42 (s, 3H, CH3), 3.74 (dd, 1H, $J_1 = 17.2$ Hz, $J_2 = 6.6$ Hz, pyrazole–CH_2), 3.85 (dd, 1H, $J_1 = 17.2$ Hz, $J_2 = 11.3$ Hz, pyrazole–CH_2), 5.88 (m, 1H, pyrazole–CH), 7.06 (s, 1H, thiazole), 6.95 (d, 1H, $J = 7.8$ Hz, 3,4-dimethoxyphenyl), 7.27 (dd, 1H, $J_1 = 7.8$, $J_2 = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.49 (d, 1H, $J = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.23 (s, 1H, $J = 3.3$ Hz,

furan), 7.38 (s, 1H, $J = 3.3$ Hz, furan), 7.83 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 8.09 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 7.72–7.74 (m, 3H, 2-methyl-6-nitrophenyl); LC–MS (*m/z*, %): 613 (M^++1, 91); anal. calcd. for $C_{31}H_{25}N_5O_7S$: C, 60.88; H, 4.12; N, 11.45 %; found: C, 60.71; H, 4.16; N, 11.48 %.

*2-[1-{3-(2,4-Dimethoxyphenyl)-5-(5-(4-methoxy-2-nitrophenyl)furan-2-yl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitrophenyl)-[1,3]-thiazole (**6h**)*

Light yellow solid (yield 81 %) mp 175–177 °C. IR (KBr, *v* in cm^{-1}): 3053(ArC–H), 2948 (C–H), 1592 (C=N), 1557 (NO_2asym), 1380 (NO_2sym), 1307 (C–O), 1262 (C–O), 1239 (C–O); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.82 (dd, 1H, $J_1 = 17.4$ Hz, $J_2 = 7.0$ Hz, pyrazole–CH_2), 3.85 (dd, 1H, $J_1 = 17.4$ Hz, $J_2 = 11.4$ Hz, pyrazole–CH_2), 5.88 (m, 1H, pyrazole–CH), 7.06 (s, 1H, thiazole), 6.99 (d, 1H, $J =$ 7.8 Hz, 3,4-dimethoxyphenyl), 7.27 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.49 (d, 1H, $J =$ 1.9 Hz, 3,4-dimethoxyphenyl), 7.23 (s, 1H, $J = 3.3$ Hz, furan), 7.41 (s, 1H, $J = 3.3$ Hz, furan), 7.77 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 8.13 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 7.97 (s, 1H, 4-methoxy-2-nitrophenyl), 7.82 (d, 1H, 2-methyl-4-nitrophenyl),7.88 (d, 1H, 2-methyl-4-nitrophenyl); LC–MS (*m/z*, %): 629 (M^++1, 91); anal. calcd. for $C_{31}H_{25}N_5O_8S$: C, 59.32; H, 4.01; N, 11.16 %; found: C, 59.35; H, 4.04; N, 11.18 %.

*2-[1-{5-(5-(4-Bromophenyl)furan-2-yl)-3-(2,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitropenyl)-[1,3]-thiazole (**6i**)*

Light yellow solid (yield 76 %) mp 163–165 °C. IR (KBr, *v* in cm^{-1}): 3053(ArC–H), 2948 (C–H), 1592 (C=N), 1560 (NO_2asym), 1382 (NO_2sym), 1307 (C–O), 1262 (C–O), 1239 (C–O); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.82 (dd, 1H, $J_1 = 17.4$ Hz, $J_2 = 7.0$ Hz, pyrazole–CH_2), 3.87 (dd, 1H, $J_1 = 17.4$ Hz, $J_2 = 11.4$ Hz, pyrazole–CH_2), 5.93 (m, 1H, pyrazole–CH), 7.05 (s, 1H, thiazole), 6.99 (d, 1H, $J = 7.8$ Hz, 3,4-dimethoxyphenyl), 7.27 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.39 (d, 1H, $J = 1.9$ Hz, 3,4-dimethoxyphenyl), 7.23 (s, 1H, $J = 3.3$ Hz, furan), 7.42 (s, 1H, $J = 3.3$ Hz, furan), 7.67 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 8.13 (d, 2H, $J = 8.6$ Hz, 4-nitrophenyl), 7.52 (d, 2H, $J = 8.3$ Hz, 4-bromophenyl), 7.46 (d, 2H, $J = 8.6$ Hz, 4-bromophenyl); LC–MS (*m/z*, %): 633 (M^++1, 87); anal. calcd. for $C_{30}H_{23}BrN_4O_5S$: C, 57.06; H, 3.67; N, 8.87 %; found: C, 57.09; H, 3.70; N, 8.88 %.

*2-[1-{5-(5-(4-Chloro-2-nitrophenyl)furan-2-yl)-3-(2,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazolyl}]-4-(4-nitrophenyl)-[1,3]-thiazole (**6j**)*

Yellow solid (yield 75 %) mp 153–155 °C. IR (KBr, *v* in cm^{-1}): 3053 (ArC–H), 2948 (C–H), 1597 (C=N), 1563 (NO_2asym), 1384 (NO_2sym), 1307 (C–O), 1262 (C–O), 1240 (C–O), 762(C–Cl); ^{1}H NMR ($CDCl_3$, δ): 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.73 (dd, 1H, $J_1 = 17.4$ Hz, $J_2 = 6.6$ Hz, pyrazole–CH_2), 3.89 (dd, 1H, $J_1 = 17.4$ Hz, $J_2 = 11.4$ Hz, pyrazole–CH_2), 6.12 (m, 1H, pyrazole–CH), 7.05 (s, 1H, thiazole), 6.93 (d, 1H, $J = 7.4$ Hz, 3,4-dimethoxyphenyl), 7.27 (dd, 1H, $J = 7.4$, 2.0 Hz, 3,4-dimethoxyphenyl), 7.39 (d, 1H, $J = 2.0$ Hz, 3,4-dimethoxyphenyl), 7.32 (s, 1H, $J = 3.3$ Hz, furan),7.42 (s, 1H, $J = 3.3$ Hz, furan), 7.67 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl), 8.11 (d, 2H, $J = 8.8$ Hz, 4-nitrophenyl), 7.92 (s, 1H, 4-chloro-2-nitrophenyl), 7.57 (d, 1H, $J = 8.3$ Hz, 4-chloro-2-nitrophenyl), 7.62 (d, 1H, $J = 8.3$ Hz, 4-chloro-2-nitrophenyl); LC–MS (*m/z*, %): 678 (M^++1, 83); anal. calcd. for $C_{30}H_{22}N_5O_7SCl$: C, 63.81; H, 3.63; N, 10.63 %; found: C, 63.84; H, 3.67; N, 10.67 %.

*2-[1-{3-(5-(4-Chlorophenyl)-furan-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazolenyl}]-4-(4-nitrophenyl)-[1,3]-thiazole (**6k**)*

Yellow solid (yield 83 %) mp 167–169 °C. IR (KBr, *v* in cm^{-1}): 3058 (ArC–H), 2952 (C–H), 1594 (C=N), 1552 (NO_2asym), 1374 (NO_2sym), 1297 (C–O), 747 (C–Cl); ^{1}H NMR ($CDCl_3$, δ): 3.66 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 =$ 6.8 Hz, pyrazole–CH_2), 3.85 (dd, 1H, $J_1 = 17.6$ Hz, $J_2 = 12.0$ Hz, pyrazole–CH_2), 5.74 (m, 1H, pyrazole–CH), 6.89 (d, 1H, $J = 3.4$ Hz, furan), 7.09 (d, 1H, $J = 3.4$ Hz, furan), 7.19 (m, 2H, phenyl), 7.06 (s, 1H, thiazole), 7.26 (d, 2H, $J = 8.1$ Hz, 4-chlorophenyl), 7.44 (m, 3H, phenyl), 7.50 (d, 2H, $J = 8.1$ Hz, 4-chlorophenyl), 7.68 (d, 2H, $J = 7.8$ Hz, 4-nitrophenyl), 7.90 (d, 2H, $J = 7.8$ Hz, 4-nitrophenyl); LC–MS (*m/z*): 527 (M^++1, 94); anal. calcd. for $C_{20}H_{16}ClN_3OS$: C, 62.90; H, 4.22; N, 11.00; S, 8.40 %; found: C, 62.93; H, 4.25; N, 11.04; S, 8.43 %.

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activities against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATTC-27853), and *Klebsiella pneumoniae* (recultured) bacterial strains by the serial plate dilution method. The minimum inhibitory concentration (MIC) was noted by observing the lowest concentration of the tested compound at which there was no visible growth. Antibacterial activity was determined by measuring the

diameter of inhibition zone. Activity of each compound was compared with ciprofloxacin as standard (Davis and Marham, 1996). Zone of inhibition was determined for all the tested compounds (**3a–e**) and (**6a–k**) The results are summarized in Table 3.

Antifungal activity

The newly prepared compounds were also screened for their antifungal activities against *Aspergilus flavus* (NCIM No. 524), *Aspergilus fumigatus* (NCIM No. 902), *Penicillium maneffei* (recultured), and *Trichophyton mentagrophytes* (recultured) in DMSO by the serial plate dilution method (Arthington-Skaggs *et al*., 2000). Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with cyclopiroxolamine as standard. Zones of inhibition were determined for the tested compounds **(3a–e)** and **(6a–k)**. The results are summarized in Table 4.

DPPH radical scavenging assay

The DPPH assay was based on the method reported by Kokura *et al*. (2005). In brief, the DMSO solutions containing 4,000 μg/mL of the tested compounds were made. Then, they were diluted to 5 mL using acetone. To these solutions, 0.1 mL of 1,1-diphenyl-2-picryl-hydrazyl (DPPH) solution (10 mg/10 mL acetone) in acetone was added.. The mixed solutions were incubated at room temperature for 15 min. The absorbance of stable DPPH was read at 517 nm using UV–Vis spectrophotometer, and the remaining DPPH was calculated. Decrease in the absorbance of DPPH solution indicated an increase in the radical scavenging activity. The DPPH solution without sample was used as control. Ascorbic acid was used as standard. The experiments were carried out in triplicate. The activity was expressed as percentage DPPH radical scavenging that was calculated from the following equation:

$$\text{DPPH scavenging activity}\,(\%) = \frac{[A_c - A_s]}{[A_c - A_b]} \times 100$$

where A_c was the absorbance of the control, A_s for the sample and A_b for the blank (MeOH). Each sample was assayed at 4,000 μg/mL, and all the experiments were carried out in triplicate, and the % RSC is shown in Table 4.

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