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Facile synthesis of novel fluorine containing pyrazole based thiazole derivatives and evaluation of antimicrobial activity

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ABSTRACT

A series of compounds 2-(5-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-(aryl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-ones (**4a**–**q**) were synthesized and structures of these compounds were elucidated by spectral (IR, ^{1}H NMR, ^{13}C NMR, mass spectra) analysis. Synthesized compounds were screened for *in vitro* antibacterial activity against the representative panel of Gram-positive (*Staphylococcus aureus*, *Streptococcus pyogenes*) and Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) bacteria. These compounds were also tested for their inhibitory action against strains of fungi (*Candida albicans*, *Aspergillus niger*, *Aspergillus clavatus*). The synthesized compounds showed potent inhibitory action against the test organisms.

1. Introduction

The chemistry of fluorine-containing compounds has been tremendously developed. Intrinsic properties of the fluorine atom, such as high electronegativity, small atomic radius, and low polarisability of the C–F bond, impart significant improvement on the biological activity of fluorinated molecules [1]. Fluorinated compounds have proved invaluable as antibacterial and antifungal agents, and have been used for the treatment of obesity and various diseases associated with the cardiovascular and central nervous systems [2–5]. Thus, fluorine substitution remains an attractive means in the development of more active and selective pharmaceutical drug molecules.

Pyrazoles and several *N*-substituted pyrazoles are known to possess numerous chemical, biological and medicinal, applications because of their versatile biological activities such as antimicrobial [6], antitumor [7], antileukemia [8], antidepressant [9], anticonvulsant [10], antifungal [11] and antitubercular [12]. It is considered a typical model of pyrazole containing, diaryl-heterocyclic template that is known to selectively inhibit (cyclooxygenase enzyme) COX-2 [13]. Celecoxib (Fig. 1) is shown to be potent and gastrointestinal (GI) safe anti-inflammatory and analgesic agent. Much attention is given to pyrazoles as antimicrobial agents after the discovery of the natural pyrazole C-glycoside, pyrazofurin (Fig. 1) which demonstrated a broad spectrum of antimicrobial activity [14,15]. In addition, 1-unsubstituted-3,5-diaryl-2-pyrazolines are reported to exhibit human Acyl CoA cholesterol acyltransferase activity [16] as well as activity of low-density lipoprotein oxidation inhibitors [17]. Thiazoles and their derivatives have found applications in drug development for the treatment of allergies [18], hypertension [19], inflammation [20], schizophrenia [21], bacterial infections [22], HIV infections [23], hypnotics [24] and more recently for the treatment of pain [25], as fibrinogen receptor antagonists with antithrombotic activity [26] and as new inhibitors of bacterial DNA gyrase B [27]. Thiazole nucleus is also an integral part of all the available penicillins which have revolutionized the therapy of bacterial diseases [28]. Several thiazole containing drugs are available such as; nizatidine is a histamine H_2-receptor antagonist that inhibits stomach acid production, and commonly used in the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD), niridazole as schistosomicidal, sulfathiazole as antibiotic, fanetizole as anti-inflammatory, combendazole as fungicidal. Structures of commercially available drugs containing pyrazole, pyrazoline and thiazole nucleus are shown in Fig. 1.

As a result of remarkable pharmacological efficiency of pyrazole and thiazole, derivatives, our studies have been focused toward the synthesis and bio-evaluation of these derivatives by hybrid approach as possible bioactive molecules. Earlier our research group has synthesized different heterocyclic derivatives as potential antimicrobial agents [29–33]. In continuation to this, we synthesized 2-(5-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-(aryl)-4-5-dihydro-1H-pyrazol-1-yl)thiazol-4(5*H*)-ones

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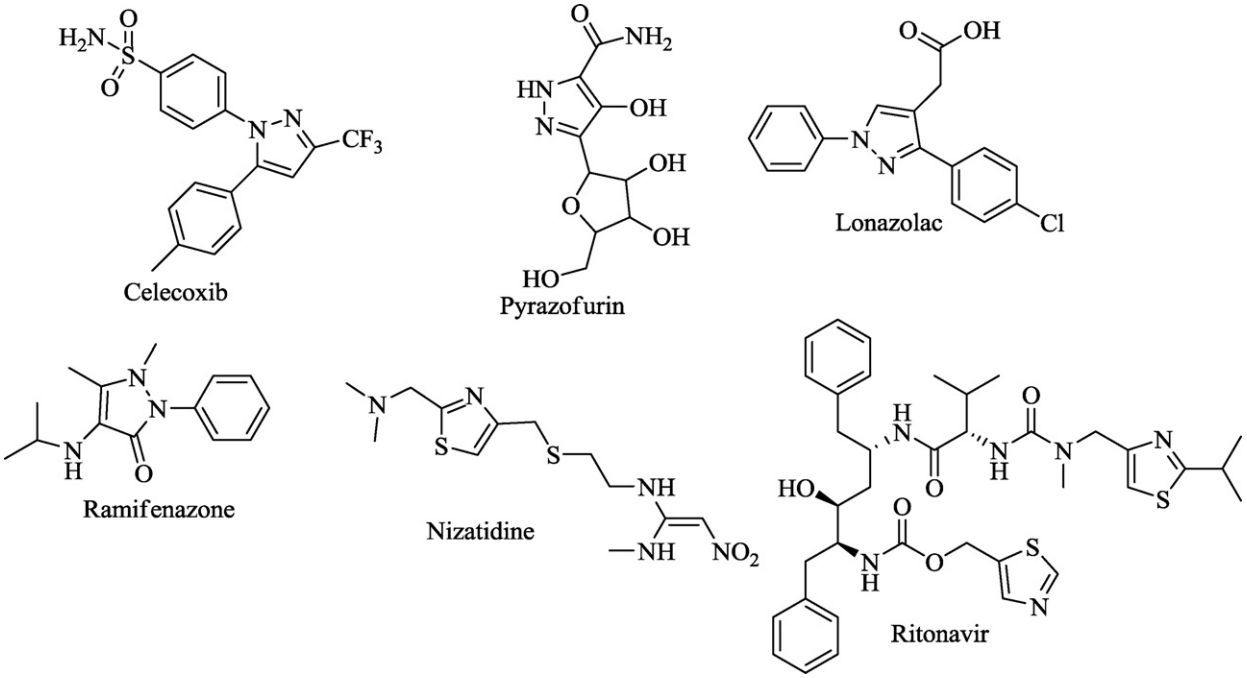


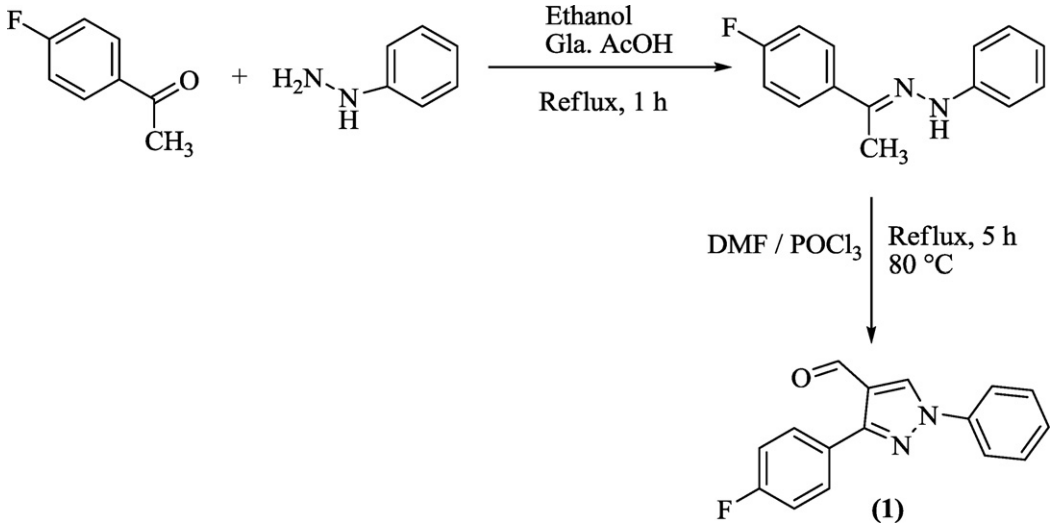
Fig. 1. Commercially available drug candidates containing pyrazole, pyrazoline and thiazole nucleus.

(**4a**–**q**) derivatives and screened then for their antimicrobial activity. The synthesized compounds (**4a**–**q**) were characterized by IR, NMR and mass spectra.

2. Results and discussion

2.1. Chemistry

Synthesis of intermediates and target compounds were accomplished according to the steps illustrated in Schemes 1 and 2. One of the most important feature of this synthetic route is the use of 3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**) as a key starting material for further transformations. Compound (**1**) was prepared in two steps. In the first step, reaction took place between 1-(4-fluorophenyl)ethanone and phenyl hydrazine. Then the resulted product hydrazone derivative was treated with the Vilsmeier–Haack reagent (DMF–$POCl_3$) leading to the corresponding 4-carboxaldehyde functionalized pyrazole ring. It was furnished in mild operating conditions to obtain the 3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**) in good yield. The key chalcone intermediates (**2a**–**q**) were synthesized through the Claisen–Schmidt condensation of equimolar amounts of acetophenone derivatives and (**1**) through stirring the reactants in aqueous alcoholic solution containing 20% sodium hydroxide at room temperature for 24 h in accordance with the method described in the literature [34]. The newly synthesized compounds 5-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-(aryl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides (**3a**–**q**) were obtained by heating at reflux equimolar amounts of thiosemicarbazide and the corresponding α,β-unsaturated ketones (**2a**–**q**) in hot ethanolic sodium hydroxide solution for 8 h (Scheme 1). This 1-thiocarbamoyl pyrazole derivative (**3a**) was characterized using IR and NMR spectra. IR spectra showed strong absorption bands at 3370 and 3442 cm^{-1} due to primary amine group. The characteristic signals



Scheme 1. Synthetic route for the preparation of compound **1**.

in ^{1}H NMR of 1-thiocarbamoyl pyrazole derivative (**3a**) was of three pyrazoline protons which displayed doublet of doublet. Methine proton of pyrazolines displayed signal at δ = 6.11 ppm as a doublet of doublet with coupling constants of nearly 11.04 Hz and 3.01 Hz. The two methylene protons displayed two signals; a doublet of doublet at δ = 3.86 ppm with coupling constants of nearly 17.35 Hz and 11.04 Hz and a doublet of doublet at δ = 3.09 ppm with coupling constants of nearly 17.34 Hz and 3.01 Hz. Furthermore, ^{13}C NMR spectra displayed a signal at 176.3 ppm assignable to thiocarbamoyl carbon (C=S). Carbon of methine showed a chemical shift at δ = 63.1 ppm. Carbon of methylene displayed a chemical shift at δ = 43.2 ppm. The mass spectrum of (**3a**) showed a molecular ion peak at m/z = 441 (M^+) corresponding to a molecular formula $C_{25}H_{20}FN_5S$. Moreover, the aforementioned 1-thiocarbamoyl pyrazole derivatives (**3a**–**q**) were cyclized (**4a**–**q**) through their reaction with ethyl bromoacetate in hot ethanol for 1 h. Compound (**4a**) showed strong absorption band at 1694 cm^{-1} due to carbonyl group in IR spectra. In addition to this, ^{1}H NMR spectra revealed the appearance of singlet peak at δ = 4.11 ppm integrating two protons of the thiazolone ring. ^{13}C NMR confirmed the proposed structure due to the appearance of signal at δ = 187.5 ppm due to carbonyl carbon as well as the appearance of signal around δ = 39.4 ppm assignable to methylene group of the thiazolone ring. Moreover, the mass spectrum of (**4a**) showed a molecular ion peak at m/z = 481 (M^+) corresponding to a molecular formula $C_{27}H_{20}FN_5OS$.

2.2. Antimicrobial activity

Compounds **4a**–**q** were evaluated against Gram-positive, Gram-negative bacterial and fungal strains. The individual minimum inhibitory concentration (MIC, μg/mL) obtained for compounds **4a**–**q** are presented in (Table 1). It was observed that compounds **4b** (2-Cl), **4d** (4-Cl), **4e** (2-F), **4f** (3-F), **4g** (4-F), **4h** (2-NO_2) and **4j** (4-NO_2) were most active compounds. On the basis of antibacterial screening, compounds **4d** (4-Cl), **4e** (2-F) and **4j** (4-NO_2) were found to show very good activity against *E. coli* at MIC = 50 μg/mL. Compound **4b** (2-Cl) showed excellent activity at MIC = 25 μg/mL, while compound **4h** (2-NO_2) exhibited highest inhibition against *E. coli* at MIC = 12.5 μg/mL as compared to standard ampicillin (MIC = 100 μg/mL). Compounds **4c** (3-Cl), **4g** (4-F) and **4h** (2-NO_2) displayed very good activity at MIC = 50 μg/mL, whereas compounds **4e** (2-F) and **4j** (4-NO_2) displayed excellent inhibitory activity against *P. aeruginosa* at MIC = 25 μg/mL as compared to ampicillin (MIC = 100 μg/mL). Compounds **4b** (2-Cl), **4d** (4-Cl) and **4g** (4-F) were found to exhibit activity at MIC = 100 μg/mL, while compound **4h** (2-NO_2) showed highest inhibition at MIC = 50 μg/mL against *S. aureus* as compared to standard ampicillin (MIC = 250 μg/mL). Compounds **4b** (2-Cl), **4e** (2-F) and **4j** (4-NO_2) showed very good activity (MIC = 50 μg/mL), while compounds **4d** (4-Cl), **4f** (3-F) and **4h** (2-NO_2) have shown excellent activity against *S. pyogenes* as compared to ampicillin (MIC = 100 μg/mL).

Antifungal activity showed that compounds **4c** (3-Cl), and **4j** (4-NO_2) were found to have very good activity at MIC = 250 μg/mL, while compounds **4b** (2-Cl), **4e** (2-F), **4g** (4-F) and **4h** (2-NO_2) showed enhanced activity and displayed excellent activity against *C. albicans* at MIC = 100 μg/mL as compared to griseofulvin (MIC = 500 μg/mL). Compounds **4b** (2-Cl), **4c** (3-Cl) and **4h** (2-NO_2) exhibited very good activity against *A. niger* at MIC = 50 μg/mL, whereas compounds **4e**, **4g** and **4j** bearing 2-F, 4-F and 4-NO_2 groups showed excellent activity against *A. niger* at MIC = 25 μg/mL as compared to griseofulvin (MIC = 100 μg/mL). Compounds **4b** (2-Cl) and **4j** (4-NO_2) displayed very good activity at MIC = 50 μg/mL, and compounds **4d** (4-Cl), **4g** (4-F) were found to have activity at MIC = 25 μg/mL whereas compound **4h** (2-NO_2) was found to exhibit highest activity at MIC = 12.5 μg/mL against *A. clavatus* as compared to griseofulvin (MIC = 100 μg/mL).

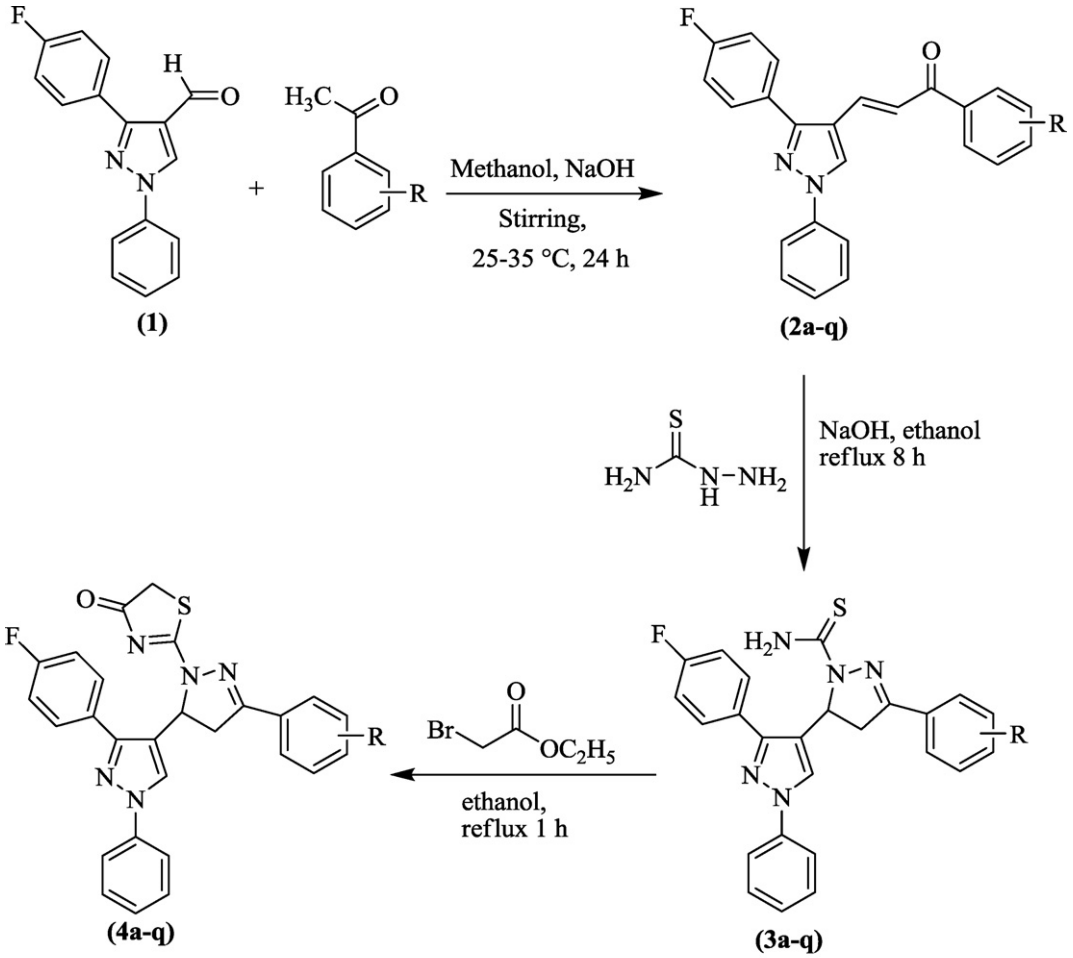
2.3. Structure–activity relationship

The structure–activity relationship (SAR) of compounds **4a**–**q** was determined using the data presented in Table 1. SAR studies revealed that the presence of an electron-withdrawing group on

Table 1
Results of antibacterial and antifungal screening of compounds (**4a**–**q**).

Entry	-R	Minimum inhibitory concentration for bacteria (μg/mL) ± SD				Minimum inhibitory concentration for fungi (μg/mL) ± SD		
		Gram-negative		Gram-positive				
		E. coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
4a	-H	250 ± 3.05	250 ± 1.00*	250 ± 4.04*	100 ± 3.46*	500 ± 4.04***	250 ± 3.70*	100 ± 1.00
4b	-2-Cl	25 ± 2.64*	100 ± 1.00**	100 ± 3.21**	50 ± 3.60**	100 ± 2.88*	50 ± 4.04*	50 ± 4.16
4c	-3-Cl	100 ± 3.21	50 ± 2.88	250 ± 2.05**	250 ± 2.05*	250 ± 3.60	50 ± 1.20***	100 ± 4.50**
4d	-4-Cl	50 ± 1.60**	100 ± 2.04**	100 ± 3.05*	25 ± 3.21*	500 ± 4.35***	250 ± 4.16*	25 ± 3.46
4e	-2-F	50 ± 3.61*	25 ± 4.04	250 ± 1.16*	50 ± 3.21*	100 ± 2.72*	25 ± 2.58***	100 ± 1.50**
4f	-3-F	100 ± 3.60	100 ± 1.60**	250 ± 1.05***	25 ± 4.16*	500 ± 2.18**	100 ± 4.04*	100 ± 4.04
4g	-4-F	250 ± 1.20**	50 ± 3.60*	100 ± 2.04*	100 ± 1.92*	100 ± 4.60***	25 ± 1.60**	25 ± 2.05**
4h	-2-NO_2	12.5 ± 1.78*	50 ± 2.21**	50 ± 1.16***	12.5 ± 3.78**	100 ± 1.16**	50 ± 1.18*	12.5 ± 3.78*
4i	-3-NO_2	100 ± 3.78*	100 ± 3.78	250 ± 2.04*	250 ± 3.46	500 ± 1.52*	500 ± 1.60*	100 ± 3.52*
4j	-4-NO_2	50 ± 2.44*	25 ± 1.21*	100 ± 4.16***	50 ± 1.78	250 ± 2.05**	25 ± 3.78	50 ± 3.78
4k	-2-OH	500 ± 4.40	500 ± 3.26	500 ± 3.78**	500 ± 4.61*	1000 ± 4.72	250 ± 1.60*	500 ± 3.60*
4l	-3-OH	100 ± 2.19*	100 ± 1.04***	500 ± 4.60*	250 ± 3.78*	500 ± 2.56*	500 ± 4.16**	500 ± 4.72**
4m	-4-OH	250 ± 1.60***	500 ± 3.78*	500 ± 2.64*	500 ± 2.64**	1000 ± 2.88*	500 ± 2.64*	1000 ± 1.00**
4n	-2-CH_3	500 ± 3.78*	500 ± 3.60*	500 ± 4.04	500 ± 4.04	500 ± 2.05	250 ± 2.05	250 ± 2.05
4o	-4-CH_3	50 ± 2.21**	500 ± 3.78**	500 ± 3.60*	250 ± 2.06	500 ± 3.21*	250 ± 3.21*	250 ± 3.21*
4p	-2-OCH_3	250 ± 1.52*	250 ± 2.04**	500 ± 4.04*	500 ± 2.05***	1000 ± 4.61**	500 ± 4.16	1000 ± 3.21*
4q	-4-OCH_3	500 ± 3.60	500 ± 1.16*	500 ± 2.50*	250 ± 3.60*	500 ± 4.04	250 ± 4.16*	1000 ± 1.86**
	Ampicillin	100 ± 2.05	100 ± 1.0	250 ± 1.52	100 ± 2.06	–	–	–
	Griseofulvin	–	–	–	–	500 ± 0.52	100 ± 1.0	100 ± 1.18

±*SD*, standard deviation. All values are presented as mean of 6 experiments (n = 6). All significant differences are considered from control value 0.00.
* $P < 0.05$ significant.
** $P < 0.01$ moderately significant.
*** $P < 0.001$ extremely significant.



R = -H, -2-Cl, -3-Cl, -4-Cl, -2-F, -3-F, -4-F, -2-NO_2, -3-NO_2, -4-NO_2, -2-OH, -3-OH, -4-OH, 2-CH_3, -4-CH_3, -2-OCH_3, -4-OCH_3

Scheme 2. Synthetic route for the preparation of title compounds **4a–q**.

the benzene ring increased the antimicrobial activity, and activity decreased in the presence of electron-releasing atoms or groups. Specifically, compounds with a nitro group in either position 2 or position 4 of the benzene ring significantly increased potency against different panel of microbial strains. The dependence of compounds efficacy (biological activity) on the position of the nitro group did not appear to be important. In this case, the use of electron withdrawing group on the benzene ring in basic structures was worthy. Compounds bearing 2-Cl, 4-Cl, 2-F, 3-F, 4-F, 2-NO_2 and 4-NO_2 exhibited more pronounced activity.

3. Conclusion

The new compounds (**4a–q**) presented here clearly differ in their corresponding antimicrobial activity depending on the type of substituent. In course of this study, particular derivatives possessing electron withdrawing groups such as halogen and nitro are identified as exhibiting potent antimicrobial activity against microbial strains. These results, combined with potential benefits or at least differences in pharmacokinetics make the titled pyrazole congeners not only interesting simplified leads for further chemical optimization of this class but also potentially interesting for future scope to study their mechanism of action and would be worthy of additional structure–activity relationship investigation.

4. Materials and methods

4.1. General

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. Melting points were determined on an electro thermal melting point apparatus and were reported uncorrected. TLC on silica gel plates (Merck, 60, F_{254}) was used for purity checking and reaction monitoring. Column chromatography on silica gel (Merck, 70–230 mesh and 230–400 mesh ASTH for flash chromatography) was applied when necessary to isolate and purify the reaction products. Elemental analysis (%C, H, N) was carried out by a Perkin-Elmer 2400 CHN analyzer. IR spectra of all compounds were recorded on a Perkin-Elmer FT-IR spectrophotometer in KBr. ^{1}H NMR spectra were recorded on Varian Gemini 300 MHz and ^{13}C NMR spectra on Varian Mercury-400 100 MHz in DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. All chemical shifts were expressed in ppm, coupling constants (J) were given in Hz. ^{19}F NMR spectra were obtained on Bruker AM 300 (282 MHz) spectrometer in $CDCl_3$ with $CFCl_3$ as external standard, downfield shifts being designated as negative. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. Anhydrous reactions were carried out in oven-dried glassware in nitrogen atmosphere.

4.2. Antibacterial assay

The newly synthesized compounds (**4a**–**q**) were screened for their antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* (MTCC-96), *Streptococcus pyogenes* (MTCC-442)) and Gram-negative bacteria (*Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688)). All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh. The activity of compounds was determined as per National Committee for Clinical Laboratory Standards (NCCLS) protocol using Mueller Hinton Broth (Becton Dickinson, USA) [35,36]. Compounds were screened for their antibacterial activity as primary screening in six sets against *E. coli*, *S. aureus*, *P. aeruginosa* and *S. pyogenes* at different concentrations of 1000, 500, 250 μg/mL. The compounds found to be active in primary screening were similarly diluted to obtain 200, 125, 100, 62.5, 50, 25 and 12.5 μg/mL concentrations for secondary screening to test in a second set of dilution against all microorganisms. Inoculum size for test strain was adjusted to 10^8 CFU/mL (Colony Forming Unit per milliliter) by comparing the turbidity (turbidimetric method). Mueller Hinton Broth was used as nutrient medium to grow and dilute the compound suspension for test bacteria. 2% DMSO was used as a diluent/vehicle to obtain the desired concentration of synthesized compounds and standard drugs to test upon standard microbial strains. Synthesized compounds were diluted to 1000 μg/mL concentration, as a stock solution. The control tube containing no antibiotic was immediately subcultured [before inoculation] by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of test organisms. The tubes were then put for incubation at 37 °C for 24 h for bacteria. 10 μg/mL suspensions were further inoculated on an appropriate media and growth was noted after 24 h and 48 h. The highest dilution (lowest concentration) preventing appearance of turbidity was considered as minimum inhibitory concentration (MIC, μg/mL) *i.e.* the amount of growth from the control tube before incubation (which represents the original inoculum) was compared. A set of tubes containing only seeded broth and solvent controls were maintained under identical conditions so as to make sure that the solvent had no influence on strain growth. The result of this is greatly affected by the size of inoculum. The test mixture should contain 10^8 CFU/mL organisms. Standard drug used in the present study was 'ampicillin' for evaluating antibacterial activity which showed 100, 100, 250 and 100 μg/mL MIC against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* respectively.

4.3. Antifungal assay

The same compounds (**4a**–**q**) were tested for antifungal activity as primary screening in six sets against *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* at various concentrations of 1000, 500, 250 μg/mL. The compounds found to be active in primary screening were similarly diluted to obtain 200, 125, 100, 62.5, 50, 25 and 12.5 μg/mL concentrations for secondary screening to test in a second set of dilution against all microorganisms. Griseofulvin was used as a standard drug for antifungal activity, which showed 500, 100 and 100 μg/mL MIC against *C. albicans*, *A. niger* and *A. clavatus*. For fungal growth, in the present protocol, we have used Sabourauds dextrose broth at 22 °C in aerobic condition for 72 h.

4.4. Statistical analysis

Standard deviation value was expressed in terms of ±SD. On the basis of calculated value by using one-way ANOVA method followed by independent two sample *t*-test, it has been observed that differences below 0.001 level were considered as statistically significant.

5. Experimental

5.1. Synthesis of 1-(1-(4-fluorophenyl)ethylidene)-2-phenylhydrazine

Glacial acetic acid (1 mL) and phenylhydrazine (0.01 mol) were added to a solution of 1-(4-fluorophenyl)ethanone (0.01 mol) in 30 mL of ethanol. Then, the reaction mixture was refluxed for 1 h at room temperature. The precipitate was filtered and washed with ethanol (95%). Then it was dried in vacuum over P_2O_5. Light yellow crystal, yield: 82%; m.p.: 134–136 °C; IR (KBr, cm^{-1}): 3354 (N–H stretching, secondary amine), 3024 (C–H stretching, CH=N linkage), 3063, 3045 (C–H stretching, aromatic ring), 2935 (C–H stretching, $-CH_3$), 1611, 1582, 1518 (C=N, C=C stretching, aromatic ring), 1383 (C–H bending, $-CH_3$), 1431 (C–H bending, –CH=N linkage), 1152 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.28 (s, 3H), 7.37 (s, 1H, NH), 6.76–7.83 (m, 9H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 17.8 (CH_3), 113.7–145.3 (Ar–C), 163.1 (C–F), 167.3 (–C=N); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.37 (s, 1F, 4-F); LCMS (*m*/*z*): 228 (M^+); Anal. Calcd. For $C_{14}H_{13}FN_2$: C-73.66, H-5.74, N-12.27; Found: C-73.60, H-5.79, N-12.36%.

5.2. Synthesis of 3-(4-fluorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (**1**)

Dimethylformamide and phosphorus oxychloride were separately cooled at 0 °C before being stirred at same temperature. A solution of 1-(1-(4-fluorophenyl)ethylidene)-2-phenylhydrazine (0.01 mol) in dimethylformamide was added dropwise to the reaction mixture which was then warmed at room temperature and heated at 70–80 °C for 5 h. After cooling at room temperature, the mixture was basified with a cool saturated K_2CO_3 solution. The precipitate was filtered, strongly washed with water and crystallized from ethanol (95%). Light yellow crystal; yield: 68%; m.p.: 173–175 °C; IR (KBr, cm^{-1}): 3072, 3054 (C–H stretching, aromatic ring), 1711 (C=O stretching, carbonyl group), 1613, 1581, 1510 (C=N, C=C stretching, aromatic ring), 1145 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.28 (m, 10H, Ar–H), 10.11 (s, 1H, HC=O); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 113.6–150.3 (Ar–C), 162.4 (C–F), 183.7 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.32 (s, 1F, 4-F); LCMS (*m*/*z*): 266 (M^+). Anal. Calcd. For $C_{16}H_{11}FN_2O$: C-72.17, H-4.16, N-10.52; Found: C-72.22, H-4.11, N-10.48%.

5.3. General procedure for the preparation of 3-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(aryl)prop-2-en-1-ones (**2a**–**q**)

Compounds were prepared according to literature method [34]. A mixture of 3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**) (0.01 mol) and acetophenone (0.01 mol) was stirred in methanolic sodium hydroxide for 24 h at room temperature. The yellow crystals formed were filtered off, washed with water and crystallized from ethanol (95%).

5.3.1. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one (**2a**)

Yield: 72%; m.p.: 194–196 °C; IR (KBr) ν_{max}/cm^{-1}: 3068 (C–H, aromatic), 3011 (C–H stretching), 1587 (C=N), 1521 (C=C), 1148 (C–F), 961 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.21–8.23 (m, 15H, Ar–H), 7.63 (d, 1H, J = 14.1, H-α), 8. 08 (d, 1H, J = 14.1, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 114.4–150.5 (Ar–C), 127.4 (CH of alkene attched to carbonyl carbon), 148.3 (CH of alkene attched to pyrazole), 162.7 (C–F of fluorophenyl ring), 183.6 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.24 (s, 1F, 4-F); LCMS (*m*/*z*): 368 (M^+); Anal. Calcd. For $C_{24}H_{17}FN_2O$: C-78.24, H-4.65, N-7.60; Found: C-78.30, H-4.61, N-7.66%.

*5.3.2. 1-(2-Chlorophenyl)-3-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (**2b**)*

Yield: 76%; m.p.: 194–196 °C; IR (KBr) ν_{max}/cm^{-1}: 3061 (C–H, aromatic), 3006 (C–H stretching), 1580 (C=N), 1517 (C=C), 1155 (C–F), 977 (C–H bending), 756 (C–Cl stretching); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.18–8.19 (m, 14H, Ar–H), 7.67 (d, 1H, *J* = 14.3, H-α), 8. 05 (d, 1H, *J* = 14.3, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 114.3–150.7 (Ar–C), 127.1 (CH of alkene attched to carbonyl carbon), 148.3 (CH of alkene attched to pyrazole), 162.3 (C–F of fluorophenyl ring), 183.2 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.31 (s, 1F, 4-F); LCMS (*m*/*z*): 402 (M^+); Anal. Calcd. For $C_{24}H_{16}ClFN_2O$: C-71.55, H-4.00, N-6.95; Found: C-71.63, H-4.07, N-6.89%.

*5.3.3. 1-(3-Chlorophenyl)-3-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (**2c**)*

Yield: 74%; m.p.: 217–219 °C; IR (KBr) ν_{max}/cm^{-1}: 3077 (C–H, aromatic), 3014 (C–H stretching), 1580 (C=N), 1524 (C=C), 1144 (C–F), 967 (C–H bending), 752 (C–Cl stretching); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.21–8.24 (m, 14H, Ar–H), 7.61 (d, 1H, *J* = 14.0, H-α), 8.11 (d, 1H, *J* = 14.0, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 114.7–150.8 (Ar–C), 127.6 (CH of alkene attched to carbonyl carbon), 148.2 (CH of alkene attched to pyrazole), 162.6 (C–F of fluorophenyl ring), 183.7 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.27 (s, 1F, 4-F); LCMS (*m*/*z*): 402 (M^+); Anal. calcd. for $C_{24}H_{16}ClFN_2O$: C-71.55, H-4.00, N-6.95; Found: C-71.62, H-3.95, N-6.88%.

*5.3.4. 1-(4-Chlorophenyl)-3-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (**2d**)*

Yield: 76%; m.p.: 187–189 °C; IR (KBr) ν_{max}/cm^{-1}: 3064 (C–H, aromatic), 3007 (C–H stretching), 1584 (C=N), 1517 (C=C), 1153 (C–F), 985 (C–H bending), 746 (C–Cl Stretching); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.20–8.29 (m, 14H, Ar–H), 7.64 (d, 1H, *J* = 14.6, H-α), 8. 11 (d, 1H, *J* = 14.6, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 114.7–150.4 (Ar–C), 127.8 (CH of alkene attched to carbonyl carbon), 148.5 (CH of alkene attched to pyrazole), 162.4 (C–F of fluorophenyl ring), 183.2 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.33 (s, 1F, 4-F); LCMS (*m*/*z*): 402 (M^+); Anal. calcd. for $C_{24}H_{16}ClFN_2O$: C-71.55, H-4.00, N-6.95; Found: C-71.49, H-3.94, N-7.02%.

*5.3.5. 1-(2-Fluorophenyl)-3-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (**2e**)*

Yield: 71%; m.p.: 197–199 °C; IR (KBr) ν_{max}/cm^{-1}: 3055 (C–H, aromatic), 3010 (C–H stretching), 1581 (C=N), 1515 (C=C), 1152 (C–F), 981 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.26–8.45 (m, 14H, Ar–H), 7.63 (d, 1H, *J* = 14.5, H-α), 8. 08 (d, 1H, *J* = 14.5, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 113.8–150.8 (Ar–C), 127.7 (CH of alkene attched to carbonyl carbon), 148.7 (CH of alkene attched to pyrazole), 160.4 (C–F of 2-fluorophenyl ring), 162.7 (C–F of fluorophenyl ring), 183.8 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.31 (s, 1F, 4-F); LCMS (*m*/*z*): 386 (M^+); Anal. calcd. for $C_{24}H_{16}F_2N_2O$: C-74.60, H-4.17, N-7.25; Found: C-74.52, H-4.08, N-7.29%.

*5.3.6. 1-(3-Fluorophenyl)-3-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (**2f**)*

Yield: 74%; m.p.: 185–187 °C; IR (KBr) ν_{max}/cm^{-1}: 3058 (C–H, aromatic), 3010 (C–H stretching), 1582 (C=N), 1522 (C=C), 1157 (C–F), 974 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.26–8.47 (m, 14H, Ar–H), 7.64 (d, 1H, *J* = 14.1, H-α), 8. 06 (d, 1H, *J* = 14.1, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 113.8–150.8 (Ar–C), 127.7 (CH of alkene attched to carbonyl carbon), 148.8 (CH of alkene attched to pyrazole), 162.3 (C–F of fluorophenyl ring), 163.1 (C–F of 3-fluorophenyl ring), 183.6 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.17 (s, 1F, 4-F); LCMS (*m*/*z*): 386 (M^+); Anal. calcd. for $C_{24}H_{16}F_2N_2O$: C-74.60, H-4.17, N-7.25; Found: C-74.66, H-4.12, N-7.20%.

*5.3.7. 1-(4-Fluorophenyl)-3-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one (**2g**)*

Yield: 79%; m.p.: 204–206 °C; IR (KBr) ν_{max}/cm^{-1}: 3054 (C–H, aromatic), 3007 (C–H stretching), 1585 (C=N), 1511 (C=C), 1147 (C–F), 983 (C–H bending), 746 (C–Cl Stretching); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.22–8.43 (m, 14H, Ar–H), 7.69 (d, 1H, *J* = 14.3, H-α), 8. 05 (d, 1H, *J* = 14.3, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 114.5–150.9 (Ar–C), 127.7 (CH of alkene attched to carbonyl carbon), 148.5 (CH of alkene attched to pyrazole), 162.4 (C–F of fluorophenyl ring), 168.1 (C–F of 4-fluorophenyl ring), 183.8 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.30 (s, 1F, 4-F); LCMS (*m*/*z*): 386 (M^+); Anal. calcd. for $C_{24}H_{16}F_2N_2O$: C-74.60, H-4.17, N-7.25; Found: C-74.54, H-4.24, N-7.30%.

*5.3.8. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(2-nitrophenyl)prop-2-en-1-one (**2h**)*

Yield: 79%; m.p.: 196–198 °C; IR (KBr) ν_{max}/cm^{-1}: 3074 (C–H, aromatic), 3015 (C–H stretching), 1584 (C=N), 1519 (C=C), 1482, 1356 (NO_2), 1157 (C–F), 985 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.26–8.45 (m, 14H, Ar–H), 7.63 (d, 1H, *J* = 14.5, H-α), 8. 08 (d, 1H, *J* = 14.5, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 113.8–150.8 (Ar–C), 127.7 (CH of alkene attched to carbonyl carbon), 148.7 (CH of alkene attched to pyrazole), 160.4 (C–F of 2-fluorophenyl ring), 162.7 (C–F of fluorophenyl ring), 183.8 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.31 (s, 1F, 4-F); LCMS (*m*/*z*): 413 (M^+); Anal. calcd. for $C_{24}H_{16}FN_3O_3$: C-69.73, H-3.90, N-10.16; Found: C-69.77, H-3.96, N-10.23%.

*5.3.9. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(3-nitrophenyl)prop-2-en-1-one (**2i**)*

Yield: 76%; m.p.: 218–220 °C; IR (KBr) ν_{max}/cm^{-1}: 3058 (C–H, aromatic), 3011 (C–H stretching), 1578 (C=N), 1528 (C=C), 1477, 1352 (NO_2), 1151 (C–F), 974 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.26–8.52 (m, 14H, Ar–H), 7.61 (d, 1H, *J* = 14.1, H-α), 8. 09 (d, 1H, *J* = 14.1, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 114.1–150.1 (Ar–C), 127.2 (CH of alkene attched to carbonyl carbon), 148.1 (C–NO_2), 148.4 (CH of alkene attched to pyrazole), 162.7 (C–F of fluorophenyl ring), 183.8 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.27 (s, 1F, 4-F); LCMS (*m*/*z*): 413 (M^+); Anal. calcd. for $C_{24}H_{16}FN_3O$: C-69.73, H-3.90, N-10.16; Found: C-69.67, H-4.00, N-10.20%.

*5.3.10. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-nitrophenyl)prop-2-en-1-one (**2j**)*

Yield: 74%; m.p.: 188–190 °C; IR (KBr) ν_{max}/cm^{-1}: 3068 (C–H, aromatic), 3008 (C–H stretching), 1588 (C=N), 1517 (C=C), 1481, 1358 (NO_2), 1147 (C–F), 983 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.25–8.48 (m, 14H, Ar–H), 7.65 (d, 1H, *J* = 14.0, H-α), 8. 11 (d, 1H, *J* = 14.0, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 114.7–150.4 (Ar–C), 127.3 (CH of alkene attched to carbonyl carbon), 148.7 (CH of alkene attched to pyrazole), 162.8 (C–F of fluorophenyl ring), 153.7 (C–NO_2), 183.6 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.30 (s, 1F, 4-F); LCMS (*m*/*z*): 413 (M^+); Anal. calcd. for $C_{24}H_{16}FN_3O$: C-69.73, H-3.90, N-10.16; Found: C-69.78, H-4.00, N-10.20%.

*5.3.11. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**2k**)*

Yield: 76%; m.p.: 221–223 °C; IR (KBr) ν_{max}/cm^{-1}: 3416 (O–H stretching), 3062 (C–H, aromatic), 3009 (C–H stretching), 1578 (C=N), 1523 (C=C), 1480, 1351 (NO_2), 1154 (C–F), 980 (C–H

bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.92–8.14 (m, 14H, Ar–H), 7.67 (d, 1H, J = 14.2, H-α), 8. 04 (d, 1H, J = 14.2, H-β), 9.13 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 113.4–150.7 (Ar–C), 127.9 (CH of alkene attched to carbonyl carbon), 148.4 (CH of alkene attched to pyrazole), 162.7 (C–F of fluorophenyl ring), 163.4 (C–OH), 183.3 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.27 (s, 1F, 4-F); LCMS (m/z): 384 (M^+); Anal. calcd. for $C_{24}H_{17}FN_2O_2$: C-74.99, H-4.46, N-7.29; Found: C-74.92, H-4.40, N-7.37%.

*5.3.12. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(3-hydroxyphenyl)prop-2-en-1-one (**2l**)*

Yield: 76%; m.p.: 202–204 °C; IR (KBr) ν_{max}/cm^{-1}: 3410 (O–H stretching), 3056 (C–H, aromatic), 3012 (C–H stretching), 1584 (C=N), 1534 (C=C), 1483, 1357 (NO_2), 1157 (C–F), 984 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.19–8.43 (m, 14H, Ar–H), 7.65 (d, 1H, J = 14.4, H-α), 8. 03 (d, 1H, J = 14.4, H-β), 9.17 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 113.8–150.6 (Ar–C), 127.4 (CH of alkene attched to carbonyl carbon), 148.4 (CH of alkene attched to pyrazole), 162.4 (C–F of fluorophenyl ring), 164.2 (C–OH), 183.7 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.32 (s, 1F, 4-F); LCMS (m/z): 384 (M^+); Anal. calcd. for $C_{24}H_{17}FN_2O_2$: C-74.99, H-4.46, N-7.29; Found: C-75.05, H-4.53, N-7.22%.

*5.3.13. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-hydroxyphenyl)prop-2-en-1-one (**2m**)*

Yield: 79%; m.p.: 180–182 °C; IR (KBr) ν_{max}/cm^{-1}: 3419 (O–H), 3070 (C–H, aromatic), 3011 (C–H stretching), 1587 (C=N), 1526 (C=C), 1482, 1353 (NO_2), 1150 (C–F), 987 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.87–8.44 (m, 14H, Ar–H), 7.61 (d, 1H, J = 14.7, H-α), 8. 07 (d, 1H, J = 14.7, H-β), 9.15 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 113.8–150.8 (Ar–C), 127.4 (CH of alkene attched to carbonyl carbon), 148.5 (CH of alkene attched to pyrazole), 162.5 (C–F of fluorophenyl ring), 164.2 (C–OH), 183.6 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.35 (s, 1F, 4-F); LCMS (m/z): 384 (M^+); Anal. calcd. for $C_{24}H_{17}FN_2O_2$: C-74.99, H-4.46, N-7.29; Found: C-74.93, H-4.52, N-7.36%.

*5.3.14. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-o-tolylprop-2-en-1-one (**2n**)*

Yield: 77%; m.p.: 194–196 °C; IR (KBr) ν_{max}/cm^{-1}: 3062 (C–H, aromatic), 3009 (C–H stretching), 2932 (C–H stretching), 1578 (C=N), 1523 (C=C), 1385 (C–H bending), 1154 (C–F), 980 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.41 (s, 3H, −CH_3), 7.21–8.46 (m, 14H, Ar–H), 7.63 (d, 1H, J = 14.5, H-α), 8. 07 (d, 1H, J = 14.5, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 19.2 (CH_3), 113.8–150.4 (Ar–C), 127.6 (CH of alkene attched to carbonyl carbon), 148.4 (CH of alkene attched to pyrazole), 162.5 (C–F of fluorophenyl ring), 184.6 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.27 (s, 1F, 4-F); LCMS (m/z): 382 (M^+); Anal. calcd. for $C_{25}H_{19}FN_2O$: C-78.52, H-5.01, N-7.33; Found: C-78.58, H-5.08, N-7.26%.

*5.3.15. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-p-tolylprop-2-en-1-one (**2o**)*

Yield: 72%; m.p.: 183–185 °C; IR (KBr) ν_{max}/cm^{-1}: 3075 (C–H, aromatic), 3010 (C–H stretching), 2924 (C–H stretching), 1585 (C=N), 1517 (C=C), 1382 (C–H bending), 1157 (C–F), 964 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.36 (s, 3H, –CH_3), 7.31–8.48 (m, 14H, Ar–H), 7.67 (d, 1H, J = 14.2, H-α), 8. 10 (d, 1H, J = 14.2, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 19.2 (CH_3), 114.2–150.6 (Ar–C), 127.3 (CH of alkene attched to carbonyl carbon), 148.6 (CH of alkene attched to pyrazole), 162.8 (C–F of fluorophenyl ring), 184.6 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.27 (s, 1F, 4-F); LCMS (m/z): 382 (M^+); Anal. calcd. for $C_{25}H_{19}FN_2O$: C-78.52, H-5.01, N-7.33; Found: C-78.46, H-4.94, N-7.27%.

*5.3.16. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(2-methoxyphenyl)prop-2-en-1-one (**2p**)*

Yield: 78%; m.p.: 176–178 °C; IR (KBr) ν_{max}/cm^{-1}: 3070 (C–H, aromatic), 3008 (C–H stretching), 2937 (C–H stretching), 1580 (C=N), 1514 (C=C), 1383 (C–H bending), 1159 (C–F), 986 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.52 (s, 3H, –OCH_3), 7.13–8.44 (m, 14H, Ar–H), 7.64 (d, 1H, J = 14.2, H-α), 8.13 (d, 1H, J = 14.2, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 54.7 (OCH_3), 111.7–150.4 (Ar–C), 127.4 (CH of alkene attched to carbonyl carbon), 148.8 (CH of alkene attched to pyrazole), 157.3 (OCH_3), 162.8 (C–F of fluorophenyl ring), 184.3 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.25 (s, 1F, 4-F); LCMS (m/z): 398 (M^+); Anal. calcd. for $C_{25}H_{19}FN_2O_2$: C-75.36, H-4.81, N-7.03; Found: C-75.30, H-4.87, N-7.09%.

*5.3.17. 3-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (**2q**)*

Yield: 75%; m.p.: 165–167 °C; IR (KBr) ν_{max}/cm^{-1}: 3087 (C–H, aromatic), 3014 (C–H stretching), 2920 (C–H stretching), 1585 (C=N), 1520 (C=C), 1386 (C–H bending), 1150 (C–F), 961 (C–H bending); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.57 (s, 3H, –OCH_3), 7.18–8.48 (m, 14H, Ar–3H), 7.67 (d, 1H, J = 14.5, H-α), 8. 10 (d, 1H, J = 14.5, H-β); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 54.3 (OCH_3), 113.8–150.6 (Ar–C), 127.8 (CH of alkene attched to carbonyl carbon), 148.6 (CH of alkene attched to pyrazole), 162.8 (C–F of fluorophenyl ring), 166.2 (C–OCH_3), 184.6 (C=O); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.34 (s, 1F, 4-F); LCMS (m/z): 398 (M^+); Anal. Calcd. for $C_{25}H_{19}FN_2O_2$: C-75.36, H-4.81, N-7.03; Found: C-75.42, H-4.74, N-6.94%.

*5.4. General procedure for the preparation of 5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(aryl)-4,5-dihydro-1H-pyrazole-1-carbothioamides (**3a**–**q**)*

A suspension of chalcones (0.01 mol), sodium hydroxide (0.025 mol) in ethanol (99.5%) (50 mL) and thiosemicarbazide (0.01 mol) was added. The mixture was refluxed for 8 h. The products were poured into crushed ice and the solid mass which separated out was filtered, dried and crystallized from ethanol (95%).

*5.4.1. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3a**)*

Yield: 63%; m.p.: 156–158 °C; IR (KBr) ν_{max}/cm^{-1}: 3442, 3370 (NH_2), 3064 (C–H, aromatic), 1579 (C=N), 1513 (C=C), 1330 (C=S), 1150 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.09 (dd, 1H, J = 17.34 Hz, 3.01 Hz, C_4-H pyrazoline), 3.86 (dd, 1H, J = 17.35 Hz, 11.04 Hz, C_4-H pyrazoline), 6.11 (dd, 1H, J = 11.04 Hz, 3.01 Hz, C_5-H pyrazoline), 6.88–8.17 (m, 14H, Ar–H), 8.31 (s, 1H, pyrazole-H), 8.53 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.2 (C_4 of pyrazoline), 63.1 (C_5 of pyrazoline), 115.8–150.1 (Ar–C), 156.7 (C=N of pyrazoline), 162.1 (C–F of fluorophenyl ring), 176.3 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.38 (s, 1F, 4-F); LCMS (m/z): 441 (M^+); Anal. Calcd. For $C_{25}H_{20}FN_5S$: C-68.01, H-4.57, N-15.86; Found: C-68.08, H-4.64, N-15.80%.

*5.4.2. 3-(2-Chlorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3b**)*

Yield: 67%; m.p.: 198–200 °C; IR (KBr) ν_{max}/cm^{-1}: 3450, 3365 (NH_2), 3061 (C–H, aromatic), 1583 (C=N), 1518 (C=C), 1322 (C=S), 1147 (C–F), 715 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.19 (dd, 1H, J = 17.44 Hz, 3.08 Hz, C_4-H pyrazoline), 3.92 (dd, 1H,

J = 17.45 Hz, 11.13 Hz, C_4-H pyrazoline), 6.02 (dd, 1H, J = 11.12 Hz, 3.08 Hz, C_5-H pyrazoline), 6.90–8.21 (m, 13H, Ar–H), 8.29 (s, 1H, pyrazole-H), 8.53 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.4 (C_4 of pyrazoline), 63.0 (C_5 of pyrazoline), 115.3–150.4 (Ar–C), 156.2 (C=N of pyrazoline), 162.3 (C–F of fluorophenyl ring), 176.2 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.09 (s, 1F, 4-F); LCMS (m/z): 475 (M^+); Anal. Calcd. For $C_{25}H_{19}ClFN_5S$: C-63.09, H-4.02, N-14.71; Found: C-63.01, H-4.08, N-14.64%.

*5.4.3. 3-(3-Chlorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3c**)*

Yield: 62%; m.p.: 177–179 °C; IR (KBr) ν_{max}/cm^{-1}: 3444, 3362 (NH_2), 3068 (C–H, aromatic), 1577 (C=N), 1523 (C=C), 1327 (C=S), 1151 (C–F), 725 (C–Cl); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.14 (dd, 1H, J = 17.48 Hz, 3.07 Hz, C_4-H pyrazoline), 3.83 (dd, 1H, J = 17.48 Hz, 11.12 Hz, C_4-H pyrazoline), 6.07 (dd, 1H, J = 11.11 Hz, 3.07 Hz, C_5-H pyrazoline), 6.96–8.28 (m, 13H, Ar–H), 8.27 (s, 1H, pyrazole-H), 8.51 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.2 (C_4 of pyrazoline), 63.2 (C_5 of pyrazoline), 115.1–150.5 (Ar–C), 156.6 (C=N of pyrazoline), 162.1 (C–F of fluorophenyl ring), 176.5 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.68 (s, 1F, 4-F); LCMS (m/z): 475 (M^+); Anal. Calcd. For $C_{25}H_{19}ClFN_5S$: C-63.09, H-4.02, N-14.71; Found: C-62.94, H-4.11, N-14.80%.

*5.4.4. 3-(4-Chlorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3d**)*

Yield: 60%; m.p.: 189–191 °C; IR (KBr) ν_{max}/cm^{-1}: 3456, 3371 (NH_2), 3067 (C–H, aromatic), 1581 (C=N), 1525 (C=C), 1326 (C=S), 1156 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.18 (dd, 1H, J = 17.52 Hz, 3.02 Hz, C_4-H pyrazoline), 3.67 (s, 3H, –OCH_3), 3.87 (dd, 1H, J = 17.52 Hz, 11.16 Hz, C_4-H pyrazoline), 6.04 (dd, 1H, J = 11.16 Hz, 3.03 Hz, C_5-H pyrazoline), 6.92–8.20 (m, 13H, Ar–H), 8.29 (s, 1H, pyrazole-H), 8.54 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.6 (C_4 of pyrazoline), 63.0 (C_5 of pyrazoline), 115.5–150.8 (Ar–C), 156.5 (C=N of pyrazoline), 162.3 (C–F of fluorophenyl ring), 176.2 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.88 (s, 1F, 4-F); LCMS (m/z): 475 (M^+); Anal. Calcd. For $C_{25}H_{19}ClFN_5S$: C-63.09, H-4.02, N-14.71; Found: C-63.16, H-4.07, N-14.77%.

*5.4.5. 3-(2-Fluorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3e**)*

Yield: 60%; m.p.: 177–179 °C; IR (KBr) ν_{max}/cm^{-1}: 3459, 3378 (NH_2), 3077 (C–H, aromatic), 1575 (C=N), 1518 (C=C), 1331 (C=S), 1152 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.23 (dd, 1H, J = 17.44 Hz, 3.10 Hz, C_4-H pyrazoline), 3.90 (dd, 1H, J = 17.44 Hz, 11.12 Hz, C_4-H pyrazoline), 6.10 (dd, 1H, J = 11.12 Hz, 3.09 Hz, C_5-H pyrazoline), 6.92–8.20 (m, 13H, Ar–H), 8.29 (s, 1H, pyrazole-H), 8.54 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.1 (C_4 of pyrazoline), 63.5 (C_5 of pyrazoline), 115.2–150.5 (Ar–C), 156.6 (C=N of pyrazoline), 159.3 (C–F of fluorophenyl ring), 162.3 (C–F of fluorophenyl ring), 176.5 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.02 (s, 1F, 4-F), −121.40 (s, 1F, 2-F); LCMS (m/z): 459 (M^+); Anal. Calcd. For $C_{25}H_{19}F_2N_5S$: C-65.34, H-4.17, N-15.24; Found: C-65.40, H-4.01, N-15.33%.

*5.4.6. 3-(3-Fluorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3f**)*

Yield: 69%; m.p.: 211–213 °C; IR (KBr) ν_{max}/cm^{-1}: 3442, 3383 (NH_2), 3062 (C–H, aromatic), 1571 (C=N), 1511 (C=C), 1337 (C=S), 1158 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.26 (dd, 1H, J = 17.47 Hz, 3.07 Hz, C_4-H pyrazoline), 3.94 (dd, 1H, J = 17.47 Hz, 11.18 Hz, C_4-H pyrazoline), 6.16 (dd, 1H, J = 11.18 Hz, 3.07 Hz, C_5-H pyrazoline), 7.12–8.24 (m, 13H, Ar–H), 8.37 (s, 1H, pyrazole-H), 8.59 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.4 (C_4 of pyrazoline), 63.2 (C_5 of pyrazoline), 114.2–150.2 (Ar–C), 156.3 (C=N of pyrazoline), 159.6 (C–F of fluorophenyl ring), 162.7 (C–F of fluorophenyl ring), 163.1 (C–F of fluorophenyl ring), 176.5 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.15 (s, 1F, 4-F), −119.82 (s, 1F, 3-F); LCMS (m/z): 459 (M^+); Anal. Calcd. For $C_{25}H_{19}F_2N_5S$: C-65.34, H-4.17, N-15.24; Found: C-65.28, H-4.11, N-15.30%.

*5.4.7. 3-(4-Fluorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3g**)*

Yield: 61%; m.p.: 180–182 °C; IR (KBr) ν_{max}/cm^{-1}: 3461, 3370 (NH_2), 3064 (C–H, aromatic), 1585 (C=N), 1520 (C=C), 1336 (C=S), 1146 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.28 (dd, 1H, J = 17.40 Hz, 3.01 Hz, C_4-H pyrazoline), 3.97 (dd, 1H, J = 17.40 Hz, 11.14 Hz, C_4-H pyrazoline), 6.14 (dd, 1H, J = 11.14 Hz, 3.02 Hz, C_5-H pyrazoline), 7.10–8.22 (m, 13H, Ar–H), 8.35 (s, 1H, pyrazole-H), 8.57 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.7 (C_4 of pyrazoline), 63.5 (C_5 of pyrazoline), 115.4–151.0 (Ar–C), 156.6 (C=N of pyrazoline), 163.3 (C–F of fluorophenyl ring), 165.1 (C–F of fluorophenyl ring), 176.8 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.02 (s, 1F, 4-F), −118.13 (s, 1F, 4-F); LCMS (m/z): 459 (M^+); Anal. Calcd. For $C_{25}H_{19}F_2N_5S$: C-65.34, H-4.17, N-15.24; Found: C-65.41, H-4.11, N-15.19%.

*5.4.8. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(2-nitrophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3h**)*

Yield: 66%; m.p.: 156–158 °C; IR (KBr) ν_{max}/cm^{-1}: 3458, 3366 (NH_2), 3054 (C–H, aromatic), 1588 (C=N), 1517 (C=C), 1485, 1352 (NO_2), 1333 (C=S), 1158 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.24 (dd, 1H, J = 17.36 Hz, 3.13 Hz, C_4-H pyrazoline), 3.92 (dd, 1H, J = 17.36 Hz, 11.08 Hz, C_4-H pyrazoline), 6.11 (dd, 1H, J = 11.08 Hz, 3.13 Hz, C_5-H pyrazoline), 7.08–8.30 (m, 13H, Ar–H), 8.33 (s, 1H, pyrazole-H), 8.54 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.4 (C_4 of pyrazoline), 63.7 (C_5 of pyrazoline), 116.0–151.4 (Ar–C), 156.3 (C=N of pyrazoline), 163.1 (C–F of fluorophenyl ring), 176.4 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.73 (s, 1F, 4-F); LCMS (m/z): 486 (M^+); Anal. Calcd. For $C_{25}H_{19}FN_6O_2S$: C-61.72, H-3.94, N-17.27; Found: C-61.77, H-4.01, N-17.17%.

*5.4.9. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(3-nitrophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3i**)*

Yield: 62%; m.p.: 188–190 °C; IR (KBr) ν_{max}/cm^{-1}: 3474, 3355 (NH_2), 3070 (C–H, aromatic), 1576 (C=N), 1527 (C=C), 1480, 1354 (NO_2), 1333 (C=S), 1160 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.23 (dd, 1H, J = 17.50 Hz, 3.08 Hz, C_4-H pyrazoline), 3.90 (dd, 1H, J = 17.50 Hz, 11.04 Hz, C_4-H pyrazoline), 6.13 (dd, 1H, J = 11.04 Hz, 3.07 Hz, C_5-H pyrazoline), 7.06–8.53 (m, 13H, Ar–H), 8.37 (s, 1H, pyrazole-H), 8.60 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.2 (C_4 of pyrazoline), 63.4 (C_5 of pyrazoline), 115.8–151.7 (Ar–C), 156.5 (C=N of pyrazoline), 163.7 (C–F of fluorophenyl ring), 176.2 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.12 (s, 1F, 4-F); LCMS (m/z): 486 (M^+); Anal. Calcd. For $C_{25}H_{19}FN_6O_2S$: C-61.72, H-3.94, N-17.27; Found: C-61.63, H-3.88, N-17.20%.

*5.4.10. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3j**)*

Yield: 68%; m.p.: 167–169 °C; IR (KBr) ν_{max}/cm^{-1}: 3479, 3358 (NH_2), 3062 (C–H, aromatic), 1580 (C=N), 1523 (C=C), 1479, 1348 (NO_2), 1327 (C=S), 1153 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.25 (dd, 1H, J = 17.38 Hz, 3.06 Hz, C_4-H pyrazoline), 3.94 (dd, 1H, J = 17.37 Hz, 11.18 Hz, C_4-H pyrazoline), 6.15 (dd, 1H, J = 11.18 Hz, 3.07 Hz, C_5-H pyrazoline), 7.09–8.36 (m, 13H, Ar–H),

8.40 (s, 1H, pyrazole-H), 8.59 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.6 (C_4 of pyrazoline), 63.8 (C_5 of pyrazoline), 115.3–151.4 (Ar–C), 156.3 (C=N of pyrazoline), 163.3 (C–F of fluorophenyl ring), 176.6 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.07 (s, 1F, 4-F); LCMS (m/z): 486 (M^+); Anal. Calcd. For $C_{25}H_{19}FN_6O_2S$: C-61.72, H-3.94, N-17.27; Found: C-61.64, H-4.00, N-17.21%.

*5.4.11. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(2-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3k**)*

Yield: 60%; m.p.: 191–193 °C; IR (KBr) ν_{max}/cm^{-1}: 3473, 3388 (NH_2), 3411 (O–H), 3061 (C–H, aromatic), 1589 (C=N), 1522 (C=C), 1337 (C=S), 1145 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.25 (dd, 1H, J = 17.52 Hz, 3.02 Hz, C_4-H pyrazoline), 3.94 (dd, 1H, J = 17.52 Hz, 11.16 Hz, C_4-H pyrazoline), 6.15 (dd, 1H, J = 11.15 Hz, 3.02 Hz, C_5-H pyrazoline), 6.87–8.20 (m, 13H, Ar–H), 8.30 (s, 1H, pyrazole-H), 8.50 (s, 2H, NH_2, D_2O exch.), 9.10 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.1 (C_4 of pyrazoline), 63.9 (C_5 of pyrazoline), 115.3–151.2 (Ar–C), 152.7 (C–OH), 156.1 (C=N of pyrazoline), 163.7 (C–F of fluorophenyl ring), 176.4 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.84 (s, 1F, 4-F); LCMS (m/z): 457 (M^+); Anal. Calcd. For $C_{25}H_{20}FN_5OS$: C-65.63, H-4.41, N-15.31; Found: C-65.69, H-4.31, N-15.23%.

*5.4.12. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(3-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3l**)*

Yield: 61%; m.p.: 170–172 °C; IR (KBr) ν_{max}/cm^{-1}: 3469, 3361 (NH_2), 3415 (O–H), 3075 (C–H, aromatic), 1574 (C=N), 1513 (C=C), 1329 (C=S), 1155 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.22 (dd, 1H, J = 17.38 Hz, 3.13 Hz, C_4-H pyrazoline), 3.91 (dd, 1H, J = 17.38 Hz, 11.14 Hz, C_4-H pyrazoline), 6.12 (dd, 1H, J = 11.14 Hz, 3.13 Hz, C_5-H pyrazoline), 7.01–8.12 (m, 13H, Ar–H), 8.33 (s, 1H, pyrazole-H), 8.54 (s, 2H, NH_2, D_2O exch.), 9.14 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.4 (C_4 of pyrazoline), 63.3 (C_5 of pyrazoline), 114.7–151.5 (Ar–C), 156.1 (C=N of pyrazoline), 158.3 (C–OH), 163.5 (C–F of fluorophenyl ring), 176.7 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.09 (s, 1F, 4-F); LCMS (m/z): 457 (M^+); Anal. Calcd. For $C_{25}H_{20}FN_5OS$: C-65.63, H-4.41, N-15.31; Found: C-65.71, H-4.33, N-15.38%.

*5.4.13. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3m**)*

Yield: 67%; m.p.: 145–147 °C; IR (KBr) ν_{max}/cm^{-1}: 3456, 3348 (NH_2), 3410 (O–H), 3063 (C–H, aromatic), 1581 (C=N), 1524 (C=C), 1332 (C=S), 1151 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.20 (dd, 1H, J = 17.40 Hz, 3.10 Hz, C_4-H pyrazoline), 3.87 (dd, 1H, J = 17.41 Hz, 11.18 Hz, C_4-H pyrazoline), 6.17 (dd, 1H, J = 11.18 Hz, 3.11 Hz, C_5-H pyrazoline), 6.83–8.17 (m, 13H, Ar–H), 8.29 (s, 1H, pyrazole-H), 8.58 (s, 2H, NH_2, D_2O exch.), 9.11 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.2 (C_4 of pyrazoline), 63.7 (C_5 of pyrazoline), 115.2–151.4 (Ar–C), 156.5 (C=N of pyrazoline), 160.3 (C–OH), 163.2 (C–F of fluorophenyl ring), 176.3 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.92 (s, 1F, 4-F); LCMS (m/z): 457 (M^+); Anal. Calcd. For $C_{25}H_{20}FN_5OS$: C-65.63, H-4.41, N-15.31; Found: C-65.58, H-4.47, N-15.26%.

*5.4.14. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-o-tolyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3n**)*

Yield: 62%; m.p.: 188–190 °C; IR (KBr) ν_{max}/cm^{-1}: 3477, 3359 (NH_2), 3056 (C–H, aromatic), 2933 (C–H, methyl), 1588 (C=N), 1517 (C=C), 1401 (C–H bending, methyl), 1338 (C=S), 1160 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.43 (s, 3H), 3.16 (dd, 1H, J = 17.44 Hz, 3.10 Hz, C_4-H pyrazoline), 3.84 (dd, 1H, J = 17.43 Hz, 11.04 Hz, C_4-H pyrazoline), 6.15 (dd, 1H, J = 11.03 Hz, 3.09 Hz, C_5-H pyrazoline), 7.05–8.12 (m, 13H, Ar–H), 8.37 (s, 1H, pyrazole-H), 8.53 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 19.4 (CH_3), 43.5 (C_4 of pyrazoline), 63.3 (C_5 of pyrazoline), 115.6–151.8 (Ar–C), 156.3 (C=N of pyrazoline), 163.6 (C–F of fluorophenyl ring), 176.6 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.04 (s, 1F, 4-F); LCMS (m/z): 455 (M^+); Anal. Calcd. For $C_{26}H_{22}FN_5S$: C-68.55, H-4.87, N-15.37; Found: C-68.62, H-4.93, N-15.30%.

*5.4.15. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-p-tolyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3o**)*

Yield: 66%; m.p.: 211–213 °C; IR (KBr) ν_{max}/cm^{-1}: 3447, 3360 (NH_2), 3046 (C–H, aromatic), 2928 (C–H, methyl), 1580 (C=N), 1511 (C=C), 1388 (C–H bending, methyl), 1331 (C=S), 1165 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.32 (s, 3H), 3.11 (dd, 1H, J = 17.50 Hz, 3.11 Hz, C_4-H pyrazoline), 3.82 (dd, 1H, J = 17.49 Hz, 11.28 Hz, C_4-H pyrazoline), 6.12 (dd, 1H, J = 11.29 Hz, 3.10 Hz, C_5-H pyrazoline), 7.11–8.10 (m, 13H, Ar–H), 8.31 (s, 1H, pyrazole-H), 8.57 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.6 (CH_3), 43.6 (C_4 of pyrazoline), 63.1 (C_5 of pyrazoline), 115.8–151.7 (Ar–C), 156.3 (C=N of pyrazoline), 163.2 (C–F of fluorophenyl ring), 176.8 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.78 (s, 1F, 4-F); LCMS (m/z): 455 (M^+); Anal. Calcd. For $C_{26}H_{22}FN_5S$: C-68.55, H-4.87, N-15.37; Found: C-68.48, H-4.80, N-15.44%.

*5.4.16. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(2-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3p**)*

Yield: 68%; m.p.: 185–187 °C; IR (KBr) ν_{max}/cm^{-1}: 3449, 3357 (NH_2), 3059 (C–H, aromatic), 2935 (C–H, methyl), 1575 (C=N), 1522 (C=C), 1410 (C–H bending, methyl), 1333 (C=S), 1211 (C–O–C), 1154 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.56 (s, 3H), 3.14 (dd, 1H, J = 17.44 Hz, 3.02 Hz, C_4-H pyrazoline), 3.86 (dd, 1H, J = 17.43 Hz, 11.14 Hz, C_4-H pyrazoline), 6.14 (dd, 1H, J = 11.15 Hz, 3.03 Hz, C_5-H pyrazoline), 6.95–8.17 (m, 13H, Ar–H), 8.36 (s, 1H, pyrazole-H), 8.55 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.7 (C_4 of pyrazoline), 54.7 (OCH_3), 63.6 (C_5 of pyrazoline), 111.4–151.6 (Ar–C), 156.3 (C=N of pyrazoline), 160.4 (C–OCH_3), 163.5 (C–F of fluorophenyl ring), 176.3 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.16 (s, 1F, 4-F); LCMS (m/z): 471 (M^+); Anal. Calcd. For $C_{26}H_{22}FN_5OS$: C-66.22, H-4.70, N-14.85; Found: C-66.31, H-4.79, N-14.78%.

*5.4.17. 5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3q**)*

Yield: 66%; m.p.: 174–176 °C; IR (KBr) ν_{max}/cm^{-1}: 3455, 3363 (NH_2), 3050 (C–H, aromatic), 2928 (C–H, methyl), 1584 (C=N), 1517 (C=C), 1416 (C–H bending, methyl), 1324 (C=S), 1204 (C–O–C), 1143 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.53 (s, 3H), 3.11 (dd, 1H, J = 17.36 Hz, 3.01 Hz, C_4-H pyrazoline), 3.86 (dd, 1H, J = 17.37 Hz, 11.16 Hz, C_4-H pyrazoline), 6.17 (dd, 1H, J = 11.16 Hz, 3.00 Hz, C_5-H pyrazoline), 7.03–8.21 (m, 13H, Ar–H), 8.38 (s, 1H, pyrazole-H), 8.57 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 43.5 (C_4 of pyrazoline), 54.3 (OCH_3), 63.5 (C_5 of pyrazoline), 114.2–151.6 (Ar–C), 156.5 (C=N of pyrazoline), 162.6 (C–OCH_3), 163.4 (C–F of fluorophenyl ring), 176.8 (C=S); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.82 (s, 1F, 4-F); LCMS (m/z): 471 (M^+); Anal. Calcd. For $C_{26}H_{22}FN_5OS$: C-66.22, H-4.70, N-14.85; Found: C-66.17, H-4.63, N-14.78%.

*5.5. General procedure for the preparation of 2-(5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(aryl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-ones (**4a**–**q**)*

To suspension of compounds (**3a**–**q**) (0.01 mol) in ethanol (99.9%), ethyl bromoacetate (0.01 mol) was added and refluxed for 1 h. After cooling, the separated product was filtered and washed. The product was crystallized from ethanol (99.5%).

*5.5.1. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4a**)*

Yield: 52%; m.p.: 165–167 °C; IR (KBr) ν_{max}/cm^{-1}: 3067, 3041 (C–H, aromatic), 2861 (C–H, methylene), 1694 (C=O), 1573 (C=N), 1530 (C=C), 1465 (C–H bending, methylene), 1150 (C–F); LCMS (*m*/*z*): 481 (M^+); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.43 (dd, 1H, *J* = 17.52 Hz, 3.13 Hz, C_4-H pyrazoline), 3.94 (dd, 1H, *J* = 17.51 Hz, 11.12 Hz, C_4-H pyrazoline), 4.11 (s, 2H, thiazolone-C_5-H), 6.09 (dd, 1H, *J* = 11.11 Hz, 3.12 Hz, C_5-H pyrazoline), 6.88–8.13 (m, 14H, Ar–H), 8.32 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.0 (C_5 of thiazolone), 42.3 (C_4 of pyrazoline), 60.4 (C_5 of pyrazoline), 115.7–151.3 (Ar–C), 159.7 (C=N of pyrazoline), 162.6 (C–F of fluorophenyl ring), 178.1 (C=N of thiazolone), 187.5 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.18 (s, 1F, 4-F); LCMS (*m*/*z*): 481 (M^+); Anal. Calcd. For $C_{27}H_{20}FN_5OS$: C-67.34, H-4.19, N-14.54; Found: C-67.42, H-4.26, N-14.48%.

*5.5.2. 2-(3-(2-Chlorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4b**)*

Yield: 50%; m.p.: 165–167 °C; IR (KBr) ν_{max}/cm^{-1}: 3059, 3035 (C–H, aromatic), 2855 (C–H, methylene), 1689 (C=O), 1568 (C=N), 1521 (C=C), 1455 (C–H bending, methylene), 1145 (C–F), 740 (C–Cl); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.48 (dd, 1H, *J* = 17.40 Hz, 3.02 Hz, C_4-H pyrazoline), 3.97 (dd, 1H, *J* = 17.40 Hz, 11.16 Hz, C_4-H pyrazoline), 4.17 (s, 2H, thiazolone-C_5-H), 6.11 (dd, 1H, *J* = 11.17 Hz, 3.02 Hz, C_5-H pyrazoline), 6.93–8.27 (m, 13H, Ar–H), 8.34 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.4 (C_5 of thiazolone), 42.6 (C_4 of pyrazoline), 60.1 (C_5 of pyrazoline), 115.2–150.8 (Ar–C), 159.4 (C=N of pyrazoline), 162.5 (C–F of fluorophenyl ring), 178.4 (C=N of thiazolone), 187.3 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.08 (s, 1F, 4-F); LCMS (*m*/*z*): 515 (M^+); Anal. Calcd. For $C_{27}H_{19}ClFN_5OS$: C-62.85, H-3.71, N-13.57; Found: C-62.79, H-3.77, N-13.50%.

*5.5.3. 2-(3-(3-Chlorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4c**)*

Yield: 58%; m.p.: 216–218 °C; IR (KBr) ν_{max}/cm^{-1}: 3051, 3030 (C–H, aromatic), 2850 (C–H, methylene), 1697 (C=O), 1575 (C=N), 1533 (C=C), 1451 (C–H bending, methylene), 1152 (C–F), 748 (C–Cl); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.46 (dd, 1H, *J* = 17.47 Hz, 3.07 Hz, C_4-H pyrazoline), 3.91 (dd, 1H, *J* = 17.47 Hz, 11.18 Hz, C_4-H pyrazoline), 4.15 (s, 2H, thiazolone-C_5-H), 6.14 (dd, 1H, *J* = 11.18 Hz, 3.08 Hz, C_5-H pyrazoline), 6.96–8.25 (m, 13H, Ar–H), 8.31 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.2 (C_5 of thiazolone), 42.6 (C_4 of pyrazoline), 60.3 (C_5 of pyrazoline), 115.6–150.5 (Ar–C), 159.7 (C=N of pyrazoline), 162.9 (C–F of fluorophenyl ring), 178.3 (C=N of thiazolone), 187.2 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.97 (s, 1F, 4-F); LCMS (*m*/*z*): 515 (M^+); Anal. Calcd. For $C_{27}H_{19}ClFN_5OS$: C-62.85, H-3.71, N-13.57; Found: C-62.91, H-3.66, N-13.63%.

*5.5.4. 2-(3-(4-Chlorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4d**)*

Yield: 53%; m.p.: 180–182 °C; IR (KBr) ν_{max}/cm^{-1}: 3041, 3035 (C–H, aromatic), 2861 (C–H, methylene), 1700 (C=O), 1567 (C=N), 1524 (C=C), 1461 (C–H bending, methylene), 1145 (C–F), 753 (C–Cl); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.42 (dd, 1H, *J* = 17.42 Hz, 3.10 Hz, C_4-H pyrazoline), 3.94 (dd, 1H, *J* = 17.41 Hz, 11.29 Hz, C_4-H pyrazoline), 4.18 (s, 2H, thiazolone-C_5-H), 6.18 (dd, 1H, *J* = 11.28 Hz, 3.10 Hz, C_5-H pyrazoline), 6.92–8.20 (m, 13H, Ar–H), 8.36 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.6 (C_5 of thiazolone), 42.2 (C_4 of pyrazoline), 60.8 (C_5 of pyrazoline), 115.1–150.7 (Ar–C), 159.3 (C=N of pyrazoline), 162.6 (C–F of fluorophenyl ring), 178.5 (C=N of thiazolone), 187.7 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.11 (s, 1F, 4-F); LCMS (*m*/*z*): 515 (M^+); Anal. Calcd. For $C_{27}H_{19}ClFN_5OS$: C-62.85, H-3.71, N-13.57; Found: C-62.79, H-3.78, N-13.52%.

*5.5.5. 2-(3-(2-Fluorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4e**)*

Yield: 57%; m.p.: 190–192 °C; IR (KBr) ν_{max}/cm^{-1}: 3067, 3042 (C–H, aromatic), 2858 (C–H, methylene), 1688 (C=O), 1563 (C=N), 1518 (C=C), 1456 (C–H bending, methylene), 1150 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.47 (dd, 1H, *J* = 17.48 Hz, 3.10 Hz, C_4-H pyrazoline), 3.95 (dd, 1H, *J* = 17.47 Hz, 11.29 Hz, C_4-H pyrazoline), 4.14 (s, 2H, thiazolone-C_5-H), 6.16 (dd, 1H, *J* = 11.28 Hz, 3.11 Hz, C_5-H pyrazoline), 6.96–8.28 (m, 13H, Ar–H), 8.34 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.3 (C_5 of thiazolone), 42.7 (C_4 of pyrazoline), 60.4 (C_5 of pyrazoline), 114.7–151.2 (Ar–C), 159.2 (C=N of pyrazoline), 159.8 (C–F), 162.5 (C–F of fluorophenyl ring), 178.4 (C=N of thiazolone), 187.8 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.99 (s, 1F, 4-F), −121.45 (s, 1F, 2-F); LCMS (*m*/*z*): 499 (M^+); Anal. Calcd. For $C_{27}H_{19}F_2N_5OS$: C-64.92, H-3.83, N-14.02; Found: C-64.87, H-3.88, N-14.11%.

*5.5.6. 2-(3-(3-Fluorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazols-4(5H)-one (**4f**)*

Yield: 53%; m.p.: 202–204 °C; IR (KBr) ν_{max}/cm^{-1}: 3056, 3039 (C–H, aromatic), 2861 (C–H, methylene), 1692 (C=O), 1570 (C=N), 1512 (C=C), 1467 (C–H bending, methylene), 1141 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.50 (dd, 1H, *J* = 17.44 Hz, 3.18 Hz, C_4-H pyrazoline), 3.98 (dd, 1H, *J* = 17.44 Hz, 11.14 Hz, C_4-H pyrazoline), 4.17 (s, 2H, thiazolone-C_5-H), 6.21 (dd, 1H, *J* = 11.15 Hz, 3.17 Hz, C_5-H pyrazoline), 7.12–8.24 (m, 13H, Ar–H), 8.39 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.7 (C_5 of thiazolone), 42.5 (C_4 of pyrazoline), 60.7 (C_5 of pyrazoline), 114.1–151.4 (Ar–C), 159.1 (C=N of pyrazoline), 162.4 (C–F of fluorophenyl ring), 163.4 (C–F), 178.7 (C=N of thiazolone), 187.5 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.07 (s, 1F, 4-F), −119.3 (s, 1F, 3F); LCMS (*m*/*z*): 499 (M^+); Anal. Calcd. For $C_{27}H_{19}F_2N_5OS$: C-64.92, H-3.83, N-14.02; Found: C-64.99, H-3.89, N-13.95%.

*5.5.7. 2-(3-(4-Fluorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4g**)*

Yield: 56%; m.p.: 204–206 °C; IR (KBr) ν_{max}/cm^{-1}: 3050, 3037 (C–H, aromatic), 2850 (C–H, methylene), 1698 (C=O), 1566 (C=N), 1522 (C=C), 1458 (C–H bending, methylene), 1144 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.47 (dd, 1H, *J* = 17.47 Hz, 3.07 Hz, C_4-H pyrazoline), 3.95 (dd, 1H, *J* = 17.47 Hz, 11.18 Hz, C_4-H pyrazoline), 4.21 (s, 2H, thiazolone-C_5-H), 6.25 (dd, 1H, *J* = 11.18 Hz, 3.07 Hz, C_5-H pyrazoline), 7.16–8.33 (m, 13H, Ar–H), 8.37 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.5 (C_5 of thiazolone), 42.7 (C_4 of pyrazoline), 60.4 (C_5 of pyrazoline), 115.1–151.8 (Ar–C), 159.4 (C=N of pyrazoline), 162.5 (C–F of fluorophenyl ring), 165.1 (C–F), 178.5 (C=N of thiazolone), 187.3 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.03 (s, 1F, 4-F), −118.12 (s, 1F, 4-F); LCMS (*m*/*z*): 499 (M^+); Anal. Calcd. For $C_{27}H_{19}F_2N_5OS$: C-64.92, H-3.83, N-14.02; Found: C-64.87, H-3.77, N-14.09%.

*5.5.8. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(2-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4h**)*

Yield: 51%; m.p.: 184–186 °C; IR (KBr) ν_{max}/cm^{-1}: 3067, 3046 (C–H, aromatic), 2868 (C–H, methylene), 1694 (C=O), 1561 (C=N), 1512 (C=C), 1462 (C–H bending, methylene), 1481, 1359 (NO_2), 1153 (C–F); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.44 (dd, 1H, *J* = 17.34 Hz, 3.13 Hz, C_4-H pyrazoline), 3.93 (dd, 1H, *J* = 17.35 Hz, 11.04 Hz, C_4-H pyrazoline), 4.18 (s, 2H, thiazolone-C_5-H), 6.23 (dd, 1H, *J* = 11.05 Hz, 3.13 Hz, C_5-H pyrazoline), 7.06–8.27 (m, 13H,

Ar–H), 8.34 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.2 (C_5 of thiazolone), 42.4 (C_4 of pyrazoline), 60.7 (C_5 of pyrazoline), 115.7–151.2 (Ar–C), 159.7 (C=N of pyrazoline), 162.3 (C–F of fluorophenyl ring), 178.4 (C=N of thiazolone), 187.1 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.10 (s, 1F, 4-F); LCMS (m/z): 526 (M^+); Anal. Calcd. For $C_{27}H_{19}FN_6O_3S$: C-61.59, H-3.64, N-15.96; Found: C-61.67, H-3.70, N-15.90%.

*5.5.9. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4i**)*

Yield: 51%; m.p.: 176–178 °C; IR (KBr) ν_{max}/cm^{-1}: 3062, 3040 (C–H, aromatic), 2877 (C–H, methylene), 1698 (C=O), 1568 (C=N), 1517 (C=C), 1457 (C–H bending, methylene), 1485, 1352 (NO_2), 1160 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.42 (dd, 1H, J = 17.42 Hz, 3.10 Hz, C_4-H pyrazoline), 3.96 (dd, 1H, J = 17.43 Hz, 11.12 Hz, C_4-H pyrazoline), 4.21 (s, 2H, thiazolone-C_5-H), 6.20 (dd, 1H, J = 11.13 Hz, 3.10 Hz, C_5-H pyrazoline), 7.01–8.54 (m, 13H, Ar–H), 8.40 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.5 (C_5 of thiazolone), 42.1 (C_4 of pyrazoline), 60.8 (C_5 of pyrazoline), 115.7–151.7 (Ar–C), 159.6 (C=N of pyrazoline), 162.1 (C–F of fluorophenyl ring), 178.7 (C=N of thiazolone), 187.7 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.16 (s, 1F, 4-F); LCMS (m/z): 526 (M^+); Anal. Calcd. For $C_{27}H_{19}FN_6O_3S$: C-61.59, H-3.64, N-15.96; Found: C-61.54, H-3.58, N-15.89%.

*5.5.10. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4j**)*

Yield: 50%; m.p.: 152–154 °C; IR (KBr) ν_{max}/cm^{-1}: 3057, 3047 (C–H, aromatic), 2871 (C–H, methylene), 1693 (C=O), 1561 (C=N), 1519 (C=C), 1466 (C–H bending, methylene), 1488, 1357 (NO_2), 1152 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.46 (dd, 1H, J = 17.51 Hz, 3.10 Hz, C_4-H pyrazoline), 3.94 (dd, 1H, J = 17.51 Hz, 11.14 Hz, C_4-H pyrazoline), 4.17 (s, 2H, thiazolone-C_5-H), 6.18 (dd, 1H, J = 11.15 Hz, 3.10 Hz, C_5-H pyrazoline), 7.07–8.35 (m, 13H, Ar–H), 8.47 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.0 (C_5 of thiazolone), 42.4 (C_4 of pyrazoline), 60.3 (C_5 of pyrazoline), 115.5–151.2 (Ar–C), 159.4 (C=N of pyrazoline), 162.6 (C–F of fluoro phenylring), 178.3 (C=N of thiazolone), 187.6 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.95 (s, 1F, 4-F); LCMS (m/z): 526 (M^+); Anal. Calcd. For $C_{27}H_{19}FN_6O_3S$: C-61.59, H-3.64, N-15.96; Found: C-61.63, H-3.60, N-16.02%.

*5.5.11. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(2-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4k**)*

Yield: 46%; m.p.: 185–187 °C; IR (KBr) ν_{max}/cm^{-1}: 3415 (O–H), 3070, 3050 (C–H, aromatic), 2863 (C–H, methylene), 1690 (C=O), 1577 (C=N), 1523 (C=C), 1462 (C–H bending, methylene), 1144 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.38 (dd, 1H, J = 17.38 Hz, 3.02 Hz, C_4-H pyrazoline), 3.83 (dd, 1H, J = 17.39 Hz, 11.11 Hz, C_4-H pyrazoline), 4.16 (s, 2H, thiazolone-C_5-H), 6.17 (dd, 1H, J = 11.11 Hz, 3.03 Hz, C_5-H pyrazoline), 6.85–8.24 (m, 13H, Ar–H), 8.43 (s, 1H, pyrazole-H), 9.13 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.5 (C_5 of thiazolone), 42.7 (C_4 of pyrazoline), 60.6 (C_5 of pyrazoline), 115.3–151.7 (Ar–C), 159.7 (C=N of pyrazoline), 162.2 (C–F of fluorophenyl ring), 163.2 (C–OH), 178.7 (C=N of thiazolone), 187.2 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.05 (s, 1F, 4-F); LCMS (m/z): 497 (M^+); Anal. Calcd. For $C_{27}H_{20}FN_5O_2S$: C-65.18, H-4.05, N-14.08; Found: C-65.24, H-4.13, N-14.02%.

*5.5.12. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(3-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4l**)*

Yield: 53%; m.p.: 179–181 °C; IR (KBr) ν_{max}/cm^{-1}: 3411 (O–H), 3066, 3042 (C–H, aromatic), 2857 (C–H, methylene), 1696 (C=O), 1586 (C=N), 1516 (C=C), 1466 (C–H bending, methylene), 1154 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.34 (dd, 1H, J = 17.40 Hz, 3.08 Hz, C_4-H pyrazoline), 3.81 (dd, 1H, J = 17.41 Hz, 11.28 Hz, C_4-H pyrazoline), 4.14 (s, 2H, thiazolone-C_5-H), 6.12 (dd, 1H, J = 11.28 Hz, 3.07 Hz, C_5-H pyrazoline), 7.02–8.14 (m, 13H, Ar–H), 8.31 (s, 1H, pyrazole-H), 9.15 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.2 (C_5 of thiazolone), 42.4 (C_4 of pyrazoline), 60.7 (C_5 of pyrazoline), 115.3–151.6 (Ar–C), 159.5 (C=N of pyrazoline), 158.4 (C–OH), 162.2 (C–F of fluorophenyl ring), 178.3 (C=N of thiazolone), 187.6 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.11 (s, 1F, 4-F); LCMS (m/z): 497 (M^+); Anal. Calcd. For $C_{27}H_{20}FN_5O_2S$: C-65.18, H-4.05, N-14.08; Found: C-65.13, H-4.12, N-14.01%.

*5.5.13. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4m**)*

Yield: 48%; m.p.: 188–190 °C; IR (KBr) ν_{max}/cm^{-1}: 3417 (O–H), 3070, 3044 (C–H, aromatic), 2866 (C–H, methylene), 1693 (C=O), 1578 (C=N), 1521 (C=C), 1468 (C–H bending, methylene), 1158 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.31 (dd, 1H, J = 17.44 Hz, 3.00 Hz, C_4-H pyrazoline), 3.77 (dd, 1H, J = 17.45 Hz, 11.15 Hz, C_4-H pyrazoline), 4.11 (s, 2H, thiazolone-C_5-H), 6.17 (dd, 1H, J = 11.16 Hz, 3.01 Hz, C_5-H pyrazoline), 6.81–8.15 (m, 13H, Ar–H), 8.29 (s, 1H, pyrazole-H), 9.09 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.4 (C_5 of thiazolone), 42.7 (C_4 of pyrazoline), 60.3 (C_5 of pyrazoline), 115.1–151.4 (Ar–C), 159.5 (C=N of pyrazoline), 160.3 (C–OH), 162.5 (C–F of fluorophenyl ring), 178.5 (C=N of thiazolone), 187.3 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.17 (s, 1F, 4-F); LCMS (m/z): 497 (M^+); Anal. Calcd. For $C_{27}H_{20}FN_5O_2S$: C-65.18, H-4.05, N-14.08; Found: C-65.25, H-4.01, N-14.18%.

*5.5.14. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(2-methylphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4n**)*

Yield: 46%; m.p.: 220–222 °C; IR (KBr) ν_{max}/cm^{-1}: 3081, 3049 (C–H, aromatic), 2921, 2866 (C–H, methyl, methylene), 1690 (C=O), 1574 (C=N), 1515 (C=C), 1401, 1460 (C–H bending, methyl, methylene), 1155 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.41 (s, 3H), 3.34 (dd, 1H, J = 17.34 Hz, 3.15 Hz, C_4-H pyrazoline), 3.74 (dd, 1H, J = 17.34 Hz, 11.12 Hz, C_4-H pyrazoline), 4.14 (s, 2H, thiazolone-C_5-H), 6.13 (dd, 1H, J = 11.13 Hz, 3.14 Hz, C_5-H pyrazoline), 7.02–8.18 (m, 13H, Ar–H), 8.36 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 19.7 (CH_3), 39.7 (C_5 of thiazolone), 42.3 (C_4 of pyrazoline), 60.5 (C_5 of pyrazoline), 116.1–151.2 (Ar–C), 159.4 (C=N of pyrazoline), 162.5 (C–F of fluorophenyl ring), 178.6 (C=N of thiazolone), 187.2 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.07 (s, 1F, 4-F); LCMS (m/z): 495 (M^+); Anal. Calcd. For $C_{28}H_{22}FN_5OS$: C-67.86, H-4.47, N-14.13; Found: C-67.92, H-4.53, N-14.21%.

*5.5.15. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(4-methylphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4o**)*

Yield: 53%; m.p.: 195–197 °C; IR (KBr) ν_{max}/cm^{-1}: 3067, 3040 (C–H, aromatic), 2917, 2860 (C–H, methyl, methylene), 1696 (C=O), 1582 (C=N), 1524 (C=C), 1392, 1462 (C–H bending, methyl, methylene), 1148 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.44 (s, 3H), 3.28 (dd, 1H, J = 17.40 Hz, 3.18 Hz, C_4-H pyrazoline), 3.71 (dd, 1H, J = 17.41 Hz, 11.18 Hz, C_4-H pyrazoline), 4.10 (s, 2H, thiazolone-C_5-H), 6.16 (dd, 1H, J = 11.19 Hz, 3.17 Hz, C_5-H pyrazoline), 6.93–8.15 (m, 13H, Ar–H), 8.37 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.4 (CH_3), 39.4 (C_5 of thiazolone), 42.6 (C_4 of pyrazoline), 60.2 (C_5 of pyrazoline), 116.1–150.8 (Ar–C), 159.6 (C=N of pyrazoline), 162.3 (C–F of fluorophenyl ring), 178.2 (C=N of thiazolone), 187.7 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.88 (s, 1F, 4-F); LCMS (m/z):

495 (M^+); Anal. Calcd. For $C_{28}H_{22}FN_5OS$: C-67.86, H-4.47, N-14.13; Found: C-67.80, H-4.51, N-14.18%.

*5.5.16. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(2-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4p**)*

Yield: 51%; m.p.: 210–212 °C; IR (KBr) ν_{max}/cm^{-1}: 3075, 3033 (C–H, aromatic), 2937, 2867 (C–H, methyl, methylene), 1690 (C=O), 1586 (C=N), 1530 (C=C), 1418, 1467 (C–H bending, methyl, methylene), 1214 (C–O–C), 1152 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.53 (s, 3H), 3.25 (dd, 1H, J = 17.42 Hz, 3.10 Hz, C_4-H pyrazoline), 3.73 (dd, 1H, J = 17.43 Hz, 11.28 Hz, C_4-H pyrazoline), 4.13 (s, 2H, thiazolone-C_5-H), 6.18 (dd, 1H, J = 11.29 Hz, 3.11 Hz, C_5-H pyrazoline), 6.93–8.18 (m, 13H, Ar–H), 8.32 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.7 (C_5 of thiazolone), 42.3 (C_4 of pyrazoline), 54.6 (OCH_3), 60.1 (C_5 of pyrazoline), 111.3–151.4 (Ar–C), 159.5 (C=N of pyrazoline), 160.6 (C–OCH_3), 162.6 (C–F of fluorophenyl ring), 178.4 (C=N of thiazolone), 187.2 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −117.95 (s, 1F, 4-F); LCMS (m/z): 511 (M^+); Anal. Calcd. For $C_{28}H_{22}FN_5O_2S$: C-65.74, H-4.33, N-13.69; Found: C-65.81, H-4.40, N-13.63%.

*5.5.17. 2-(5-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4q**)*

Yield: 55%; m.p.: 184–186 °C; IR (KBr) ν_{max}/cm^{-1}: 3071, 3044 (C–H, aromatic), 2930, 2864 (C–H, methyl, methylene), 1695 (C=O), 1582 (C=N), 1536 (C=C), 1410, 1458 (C–H bending, methyl, methylene), 1210 (C–O–C), 1144 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.57 (s, 3H), 3.22 (dd, 1H, J = 17.50 Hz, 3.18 Hz, C_4-H pyrazoline), 3.77 (dd, 1H, J = 17.51 Hz, 11.29 Hz, C_4-H pyrazoline), 4.11 (s, 2H, thiazolone-C_5-H), 6.14 (dd, 1H, J = 11.28 Hz, 3.18 Hz, C_5-H pyrazoline), 7.02–8.24 (m, 13H, Ar–H), 8.37 (s, 1H, pyrazole-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 39.7 (C_5 of thiazolone), 42.3 (C_4 of pyrazoline), 54.8 (OCH_3), 60.4 (C_5 of pyrazoline), 114.1–151.7 (Ar–C), 159.2 (C=N of pyrazoline), 160.4 (C–OCH_3), 162.4 (C–F of fluorophenyl ring), 178.5 (C=N of thiazolone), 187.5 (C=O of thiazolone); ^{19}F NMR (282 MHz, DMSO-d_6, δ, ppm): −118.14 (s, 1F, 4-F); LCMS (m/z): 511 (M^+); Anal. Calcd. For $C_{28}H_{22}FN_5O_2S$: C-65.74, H-4.33, N-13.69; Found: C-65.69, H-4.28, N-13.75%.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2012.06.021.

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