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Utility of 5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide in the synthesis of heterocyclic compounds with antimicrobial activity

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Abstract

Background: Pyrazolines show different biological activities. In recent years, interest in the chemistry of hydrazonoyl halides has been renewed. 1,3,4-Thiadiazoles are one of the most common heterocyclic pharmacophores with a wide range of biological activities.

Results: Ethyl 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-thiazole-5-carboxylate, 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one, and 1-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)ethan-1-one were synthesized from the reaction of 5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide with different halogenated compounds. Thiazole, 1,3,4-thiadiazole and pyrano[2,3-*d*] thiazole derivatives were also synthesized. The structures of the newly synthesized compounds were elucidated based on elemental analysis, spectral data, and alternative synthetic routes whenever possible. Additionally, the newly synthesized compounds were screened for antimicrobial activity against various microorganisms.

Conclusions: A new series of novel functionalized 1,3,4-thiadiazoles, 1,3-thiazoles, and pyrazoline-containing moieties were synthesized using hydrazonoyl halides as precursors and evaluated for their in vitro antibacterial, and antifungal activities. The antimicrobial results of the examined compounds revealed promising results and some derivatives have activities similar to the references used.

Keywords: Thiazoles, Hydrazonoyl halides, 1,3,4-Thiadiazoles, Urea derivatives, Pyrano[2,3-*d*]thiazoles, Antimicrobials

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Introduction

Pyrazolines show a variety of biological activities. They are antimicrobial [1–4], antifungal [5], anti-depressant [6], immunosuppressive [7], anticonvulsant [8–10], anti-tumor [11], anti-amoebic [12], antibacterial [13], anti-inflammatory [14], anticancer [15], and MAO inhibitory activity [16]. Hydrazonoyl halides have been widely used as reagents for the synthesis of various heterocyclic compounds [17, 18]. Thiazoles are used in drugs developed for the treatment of allergies [19], hypertension [20], inflammation [21], schizophrenia [22], bacterial infections [23], HIV [24], sleep disorders [25] and more recently, for the treatment of pain [26]. They are also used as fibrinogen receptor antagonists with antithrombotic activity [27], and as new inhibitors of bacterial DNA gyrase B [28]. Moreover, 1,3,4-thiadiazoles are among the most common heterocyclic pharmacophores. They display a broad spectrum of biological activities, including antimicrobial [29], anticancer [30, 31], antioxidant [32], anti-depressant [33], anticonvulsant [34, 35] and anti-hypertensive activities [36], as well as acetyl cholinesterase inhibition for the treatment of Alzheimer's disease [37, 38]. In continuation of the author's research work [39–45], the synthesis of some new thiazoles, 1,3,4-thiadiazoles and pyrano[2,3-*d*]thiazole from 5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide are reported herein.

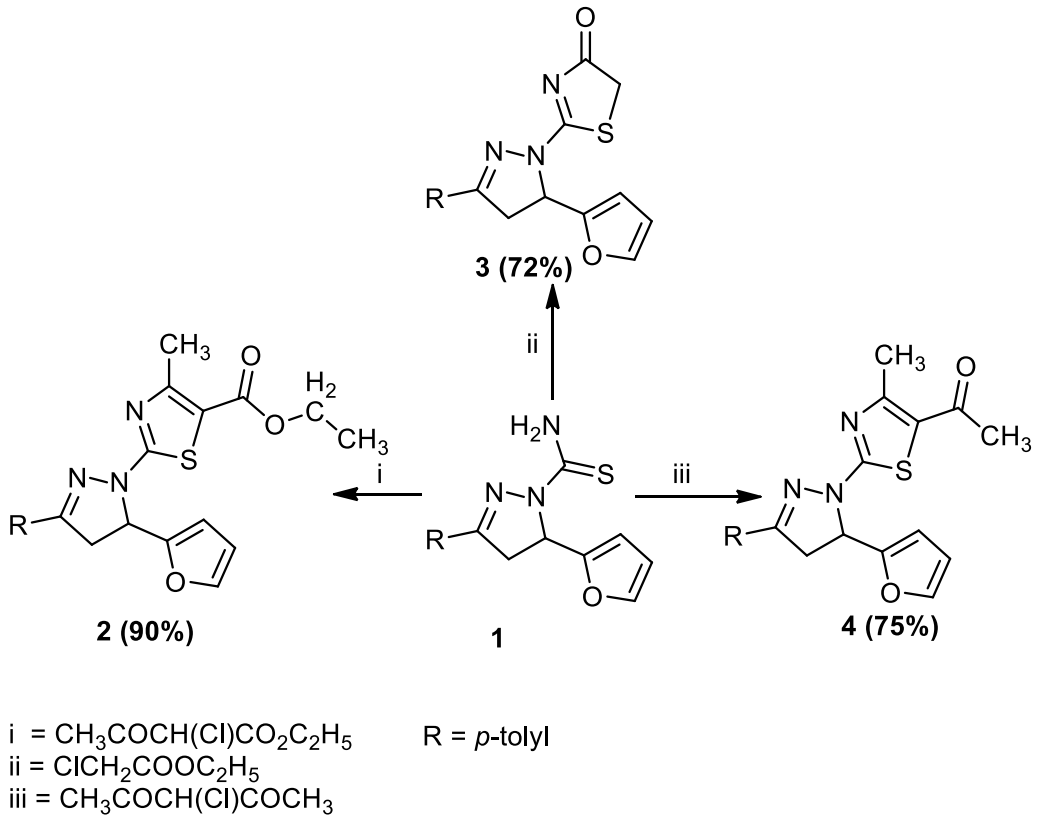
Results and discussion

The reaction of 5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**1**) with ethyl 2-chloro-3-oxobutanoate, ethyl 2-chloroacetate or 3-chloropentane-2,4-dione in ethanol containing an amount of triethylamine afforded ethyl 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carboxylate (**2**), 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one (**3**) and 1-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)ethan-1-one (**4**), respectively (Scheme 1).

The structures of the compounds (**2–4**) were clarified by elemental analyses, FTIR, MS, NMR spectra and chemical transformation. Compound (**2**) reacted with hydrazine hydrate to afford 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbohydrazide (**5**) (Scheme 2). The structure of compound (**5**) was elucidated by elemental analyses, spectral data, and chemical transformations. Compound (**5**) reacted with nitrous acid, potassium thiocyanate, 3-(2-arylhydrazono)pentane-2,4-dione (**8a** and **8b**) or ethyl 2-(2-arylhydrazono)-3-oxobutanoate (**9a** and **9b**) to afford the following: 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl azide (**6**), 2-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl)hydrazine-1-carbothioamide (**7**), (3,5-dimethyl-4-(phenyldiazenyl)-1*H*-pyrazol-1-yl)(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)methanone (**10a**), (3,5-dimethyl-4-(*p*-tolyldiazenyl)-1*H*-pyrazol-1-yl)(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)methanone (**10b**), 2-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl)-5-methyl-4-(2-phenylhydrazono)-2,4-dihydro-3*H*-pyrazol-3-one (**11a**) and 2-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl)-5-methyl-4-(2-(*p*-tolyl)hydrazono)-2,4-dihydro-3*H*-pyrazol-3-one (**11b**), respectively (Scheme 2). The structures of compounds (**6**, **7**, **10a** and **10b**) and (**11a** and **11b**) were confirmed by elemental analyses, spectral data and chemical transformations whenever possible.

Treatment of 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl azide (**6**) with aniline, 4-toluidine or anthranilic acid in boiling dioxane gave1-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)-3-phenylurea (**12a**), 1-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)-3-(*p*-tolyl)urea (**12b**) and 3-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)quinazoline-2,4(1*H*,3*H*)-dione (**13**), respectively. Also, compound (**6**) reacted with 2-naphthol in boiling benzene to afford naphthalen-2-yl(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carboxylate (**14**) (Scheme 3). The structures of compounds (**12–14**) were confirmed by elemental analyses, spectral data and an alternative synthetic route. Thus, compound (**6**) reacted with methyl anthranilate in dioxane to afford a product identical in all aspects (mp, mixed mp and spectra) to compound (**13**).

Next, treatment of 2-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl)hydrazine-1-carbothioamide (**7**) with sodium hydroxide yielded 5-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)-1,3,4-oxadiazole-2-thiol (**15**). The latter reacted with the appropriate hydrazonoyl halides (**16a–d**) in refluxing chloroform in the presence of triethylamine to give *N*′-(5-substituted-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbohydrazide (**20a–d**). The mechanism outlined in Scheme 4 seemed to be the most plausible pathway for the formation of (**20**) from the reaction of (**15**) or (**15a**) with (**16**) by two



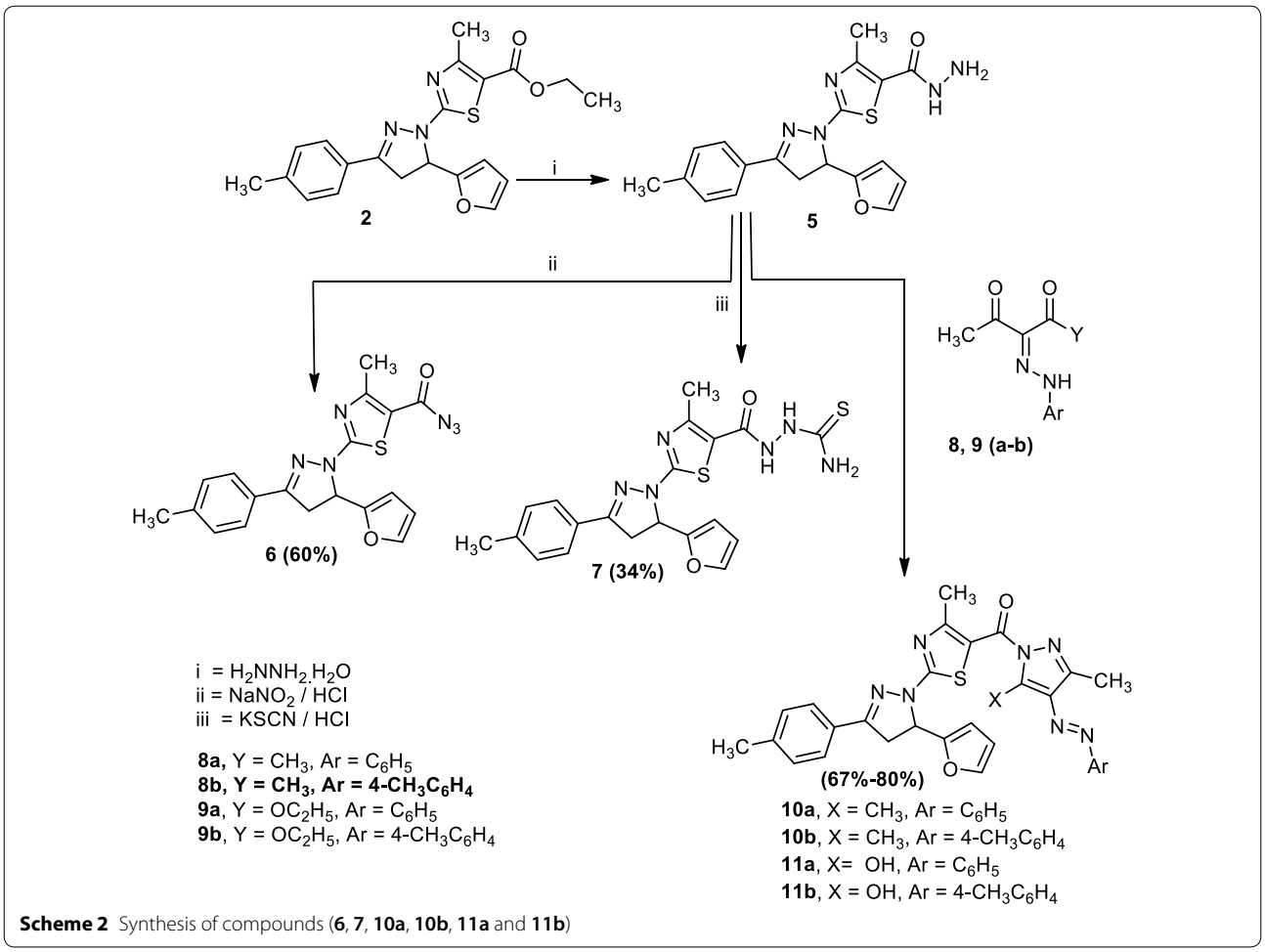
Scheme 1 Synthesis of compounds (**2**–**4**)

possible pathways. The first pathway was via 1,3-addition of the thiol tautomer (**15**) to the nitrilimine (**19a**–**d**) (which produced in situ from the reaction of hydrazonoyl halide [16a–d] with triethylamine) to give the thiohydrazonate ester (**17**) that underwent nucleophilic cyclization to yield *spiro* compound (**18**). The latter underwent ring opening and cyclization to yield (**20**). The second pathway was via 1,3-cycloaddition of nitrilimine (**19**) to the C=S double bond of (**15a**) to give (**18**) directly (Scheme 4). Attempts to isolate the thiohydrazonate ester (**17**) or the intermediate (**18**) did not succeed, even under mild conditions, as these two compounds readily underwent in situ cyclization to give the final isolable product (**20**), as shown in Scheme 4.

Treatment of 2-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl) hydrazine-1-carbothioamide (**7**) with the appropriate hydrazonoyl halides (**16b**) and (**16c**) in ethanolic triethylamine afforded 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-*N*'-(4-methyl-5-(phenyldiazenyl)-thiazol-2-yl)thiazole-5-carbohydrazide (**21a**) and 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-*N*'-(4-phenyl-5-(phenyldiazenyl) thiazol-2-yl)thiazole-5-carbohydrazide (**21b**), respectively (Scheme 5). The structures of compounds (**21a** and **21b**) were confirmed by elemental analyses and spectral data.

On the other hand, the treatment of compound (**5**) with maleic anhydride and phthalic anhydride afforded 1-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl)-1,2-dihydropyridazine-3,6-dione (**22**) and 2-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-dione (**23**), respectively (Scheme 6). The structures of compounds (**22**) and (**23**) were elucidated by elemental analyses and spectral data (*cf.* Experimental).

Finally, treatment of 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one (**3**) with arylidenemalononitriles (**24a**–**c**) in boiling ethanol containing a catalytic amount of piperidine afforded 5-amino-2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-7-aryl-7*H*-pyrano[2,3-*d*]thiazole-6-carbonitrile (**25a**–**c**). The structures of compounds (**25a**–**c**) were elucidated by elemental analyses, spectral data and a synthetic route. Thus, the infrared (IR) spectrum of compound (**25a**) showed bands at 3388 and 3175 cm^{-1},



Scheme 2 Synthesis of compounds (**6**, **7**, **10a**, **10b**, **11a** and **11b**)

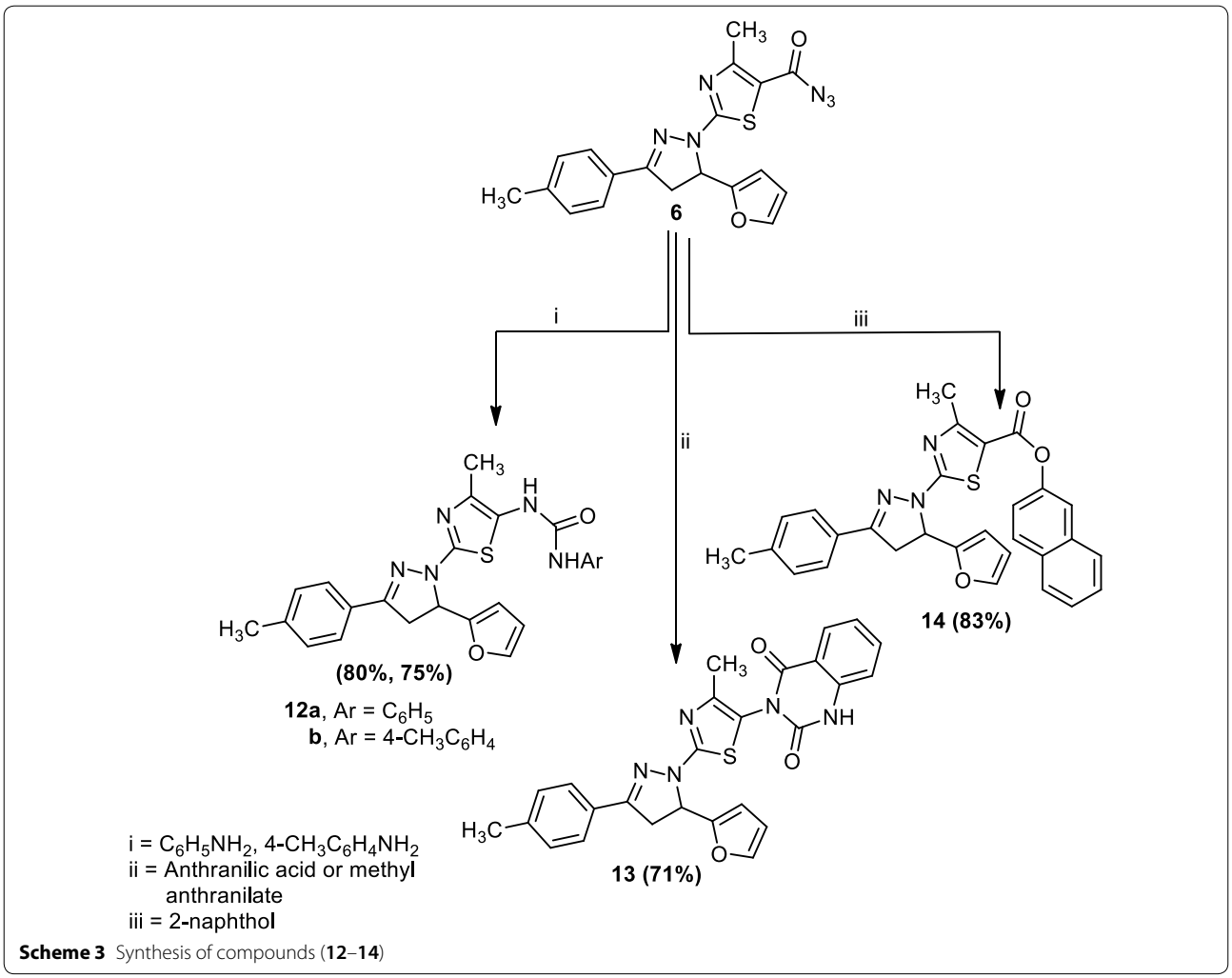
which corresponded to the NH_2 group. Furthermore, a mixture of malononitrile, an appropriate aldehyde and 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one (**3**) in ethanol containing a few drops of piperidine as a catalyst was heated under reflux to afford products identical in all aspects (mp, mixed mp and spectra) with (**25a**–**c**), respectively (Scheme 7).

Antimicrobial activity

For their in vitro antibacterial activity against *Streptococcus pneumonia* and *Bacillus subtilis* and *Pseudomonas aeruginosa* and *Escherichia coli*, twenty-one of the newly synthesized target compounds were assessed. They were also assessed against a representative panel of fungal strains for their in vitro antifungal activity (i.e., *Aspergillus fumigatus* and *Candida albicans*). Ampicillin and gentamicin for in vitro antibacterial activity were used as reference drugs; While Amphotericin B was used for in vitro antifungal activity as a reference drug. Examinations were conducted at Al-Azhar University's Regional Center for Mycology and Biotechnology (Nasr City, Cairo, Egypt). Microbes were obtained from the Microbiological Resource Center, Faculty of Agriculture, Ain Shams University, Cairo, Egypt.

Table 1 summarizes the test results for antimicrobial effects

- *Streptococcus pneumonia, Bacillus subtilis, Pseudomonas aeruginosa* and *Escherichia coli* were resistant to compounds (**10a** and **11b**).
- *Aspergillus fumigatus* was susceptible to compounds (**11a**), (**20a**), (**20b**), (**20d**), and (**22**).
- *Aspergillas fumigates* and *Candida albicans* were resistant to compound (**25b**).
- *Candida albicans* was moderate of all compounds in the table compared to amphotericin B.
- *Streptococcus pneumonia, Pseudomonas aeruginosa* and *Escherichia coli* were moderate of all compounds in the table compared to ampicillin and gentamicin.



Scheme 3 Synthesis of compounds (**12**–**14**)

According to these results, we can suggest the following structure activity relationships:

A. In the thiazoles (**3**), (**4**), and (**14**)

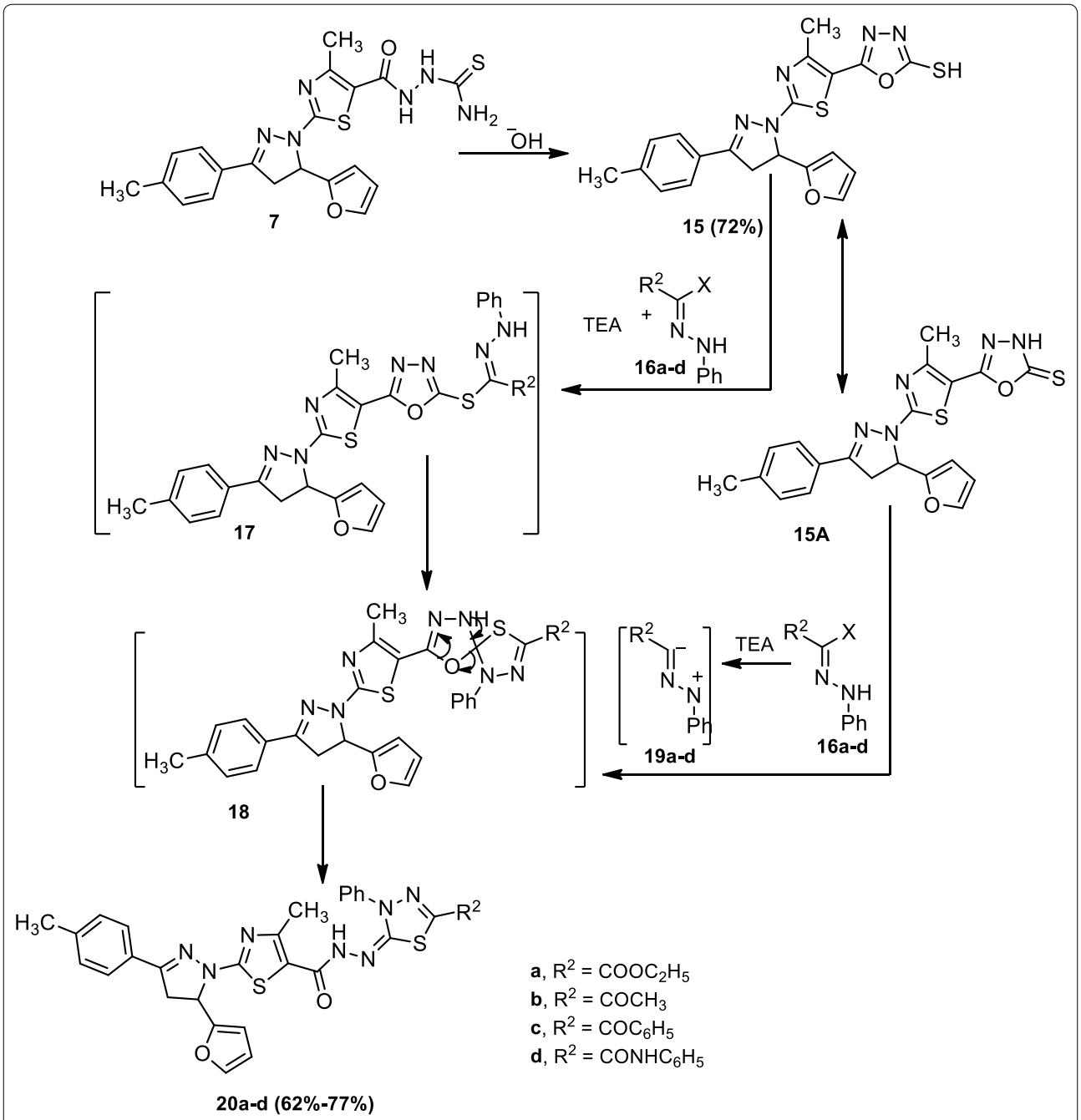
(1) Attachment of $C_{10}H_7OCO$ group in (**14**) at position 5 in the thiazole ring is very important for antimicrobial activity and increases the activity towards Gram-negative bact.
(2) Attachment of H or CH_3CO group at position 5 in the thiazole ring showed a moderate antimicrobial activity for all microorganisms in Table 1.

B. In the thiazolyluera (**12a**) and (**12b**)

(1) Attachment of PhNHCONH or 4-$CH_3C_6H_4$NHCONH group in (**12a**) or (**12b**) at position 5 in the thiazole ring showed a moderate antimicrobial activity for all microorganisms in Table 1.

C. In the thiazolylpyrazoles **10**, **11**(**a**–**b**)

(1) Attachment of methyl and –N=NPh groups in (**10a**) and attachment of OH and –N=NPh groups in (**11b**) at positions 3, 4 respectively, in the moiety of the pyrazole ring had no activity against all the tested Gram-positive and Gram-negative bact. but had moderate activity against test fungi.
(2) Attachment of OH and –N=NPh groups in (**11a**) at position 3 and position 4 in the moiety of the pyrazole ring displayed potent effect against all the tested Gram-positive, Gram-negative bact. and fungi.
(3) Attachment of CH_3 and 4–$CH_3C_6H_4$N=N groups in (**10b**) at position 3 and position 4 in



Scheme 4 Synthesis of compounds (**15**) and (**20a**–**d**)

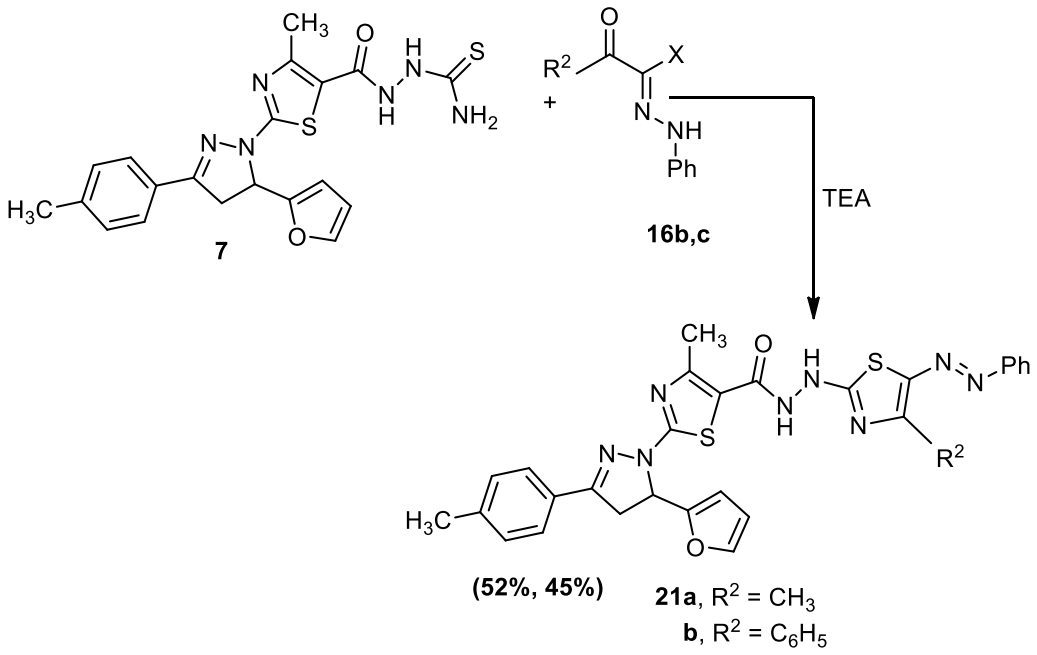
the moiety of the pyrazole ring displayed potent effect against Gram-negative bact., a moderate activity against Gram-positive bact. and fungi.

D. In the thiazolylquinazolinedione (**13**)

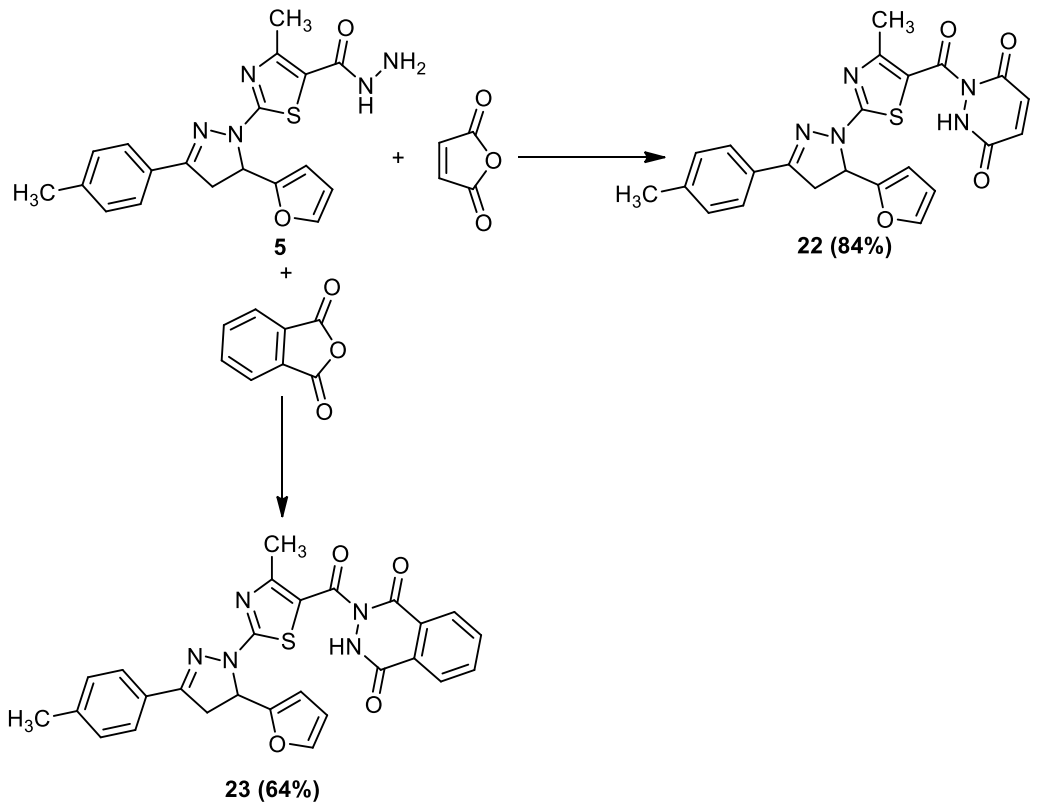
(1) Attachment of quinazoline-2,4(1*H*,3*H*)-dione ring at position 5 in the thiazole ring showed a moderate antimicrobial activity for all microorganisms in Table 1.

E. In the thiazolyloxadiazole (**15**)

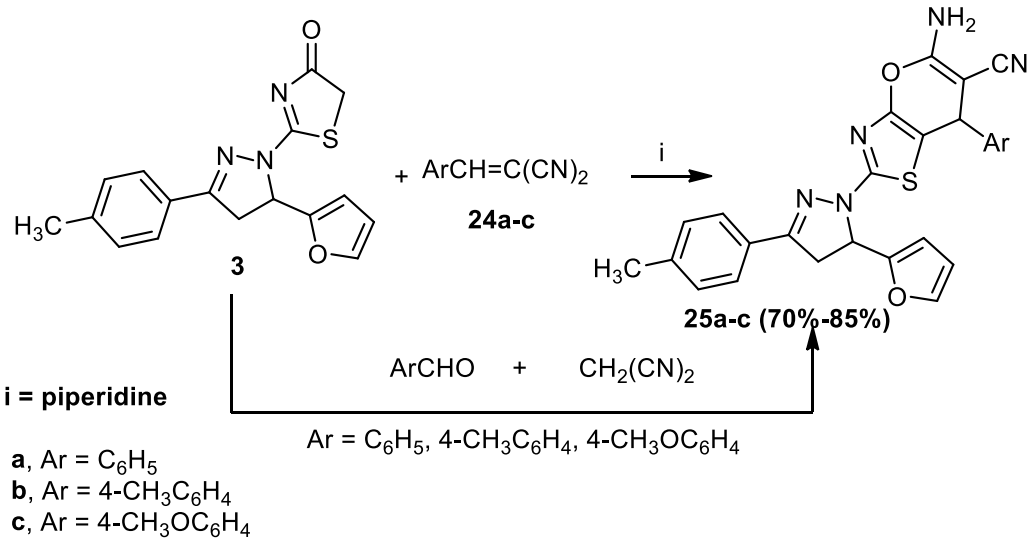
(1) Attachment of 1,3,4-oxadiazole-2-thiole ring at position 5 in the thiazole ring showed a moderate antimicrobial activity for all microorganisms in Table 1.



Scheme 5 Synthesis of compounds (**21a** and **21b**)



Scheme 6 Synthesis of compounds (**22**) and (**23**)



Scheme 7 Synthesis of compounds (**25a**–**c**)

Table 1 Mean zone of inhibition beyond well diameter (6 mm) produced on a range of clinically pathogenic microorganisms using a 5 mg/mL concentration of tested samples

Compound no.	Microorganisms					
	Fungi		Gram-Positive Bacteria		Gram-Negative Bacteria	
	AF	*CA*	*SP*	*BS*	*PA*	*EC*
3	16.2	12.5	16.8	14.6	12.1	12.8
4	15.7	13.2	10.5	13.6	12.6	11.2
10a	12.6	11.2	0	0	0	0
10b	17.3	16.9	17.3	18.3	18.3	22.6
11a	21.2	19.6	23.8	23.8	17.3	19.9
11b	15.7	13.3	0	0	0	0
12a	18.9	15.4	15.7	14.1	10.8	11.1
12b	16.7	18.1	16.7	21.1	10.7	9.9
13	19.1	16.9	13.6	14.7	12.1	10.4
14	15.7	14.1	17.2	14.9	15.2	17.2
15	16.4	12.7	19.9	18.4	11.6	10.9
20a	20.8	16.8	13.1	10.8	13.4	12.3
20b	26.8	15.3	11.2	12.7	9.8	11.3
20c	15.9	17.1	18.7	15.4	11.7	10.3
20d	20.6	15.8	18.9	12.7	11.3	9.9
21a	17.7	18.2	19.2	15.4	10.2	8.8
21b	19.1	18.9	17.3	17.7	0	9.9
22	23.8	32.4	13.2	13.3	0	10.2
23	18.8	15.6	17.9	13.3	11.4	10.7
25a	18.4	16.3	12.6	13.2	10.1	10.9
25b	0	0	12.7	14	9.7	8.3
Amphotericin B	23.7	25.4	–	–	–	–
Ampicillin	–	–	23.8	32.4	–	–
Gentamicin	–	–	–	–	17.3	19.9

F. In the thiazolylthiadiazole carbohydrazide (**20a**–**d**)

(1) Attachment of $C_2H_5CO_2$ group in (**20a**) at position 2 in the moiety of the 1,3,4-thiadiazole ring displayed potent effect against *Af* fungus, moderate activity against Gram-positive bact., Gram-negative bact., and *CA* fungus.
(2) Attachment of CH_3CO group in (**20b**) at position 5 in the moiety of the 1,3,4-thiadiazole ring displayed potent effect against *Af* fungus, moderate activity against Gram-positive bact., Gram-negative bact., and *CA* fungus.
(3) Attachment of C_6H_5CO group in (**20c**) at position 5 in the moiety of the 1,3,4-thiadiazole ring displayed a moderate antimicrobial activity for all microorganisms in Table 1.
(4) Attachment of C_6H_5CONH group in (**20d**) at position 2 in the moiety of the 1,3,4-thiadiazole ring displayed potent effect against *Af* fungus, moderate activity against Gram-positive bact., Gram-negative bact., and *CA* fungus.

G. In the thiazolylthiazole carbohydrazide (**21a**, **b**)

(1) Attachment of CH_3– group in (**21a**) at position 4 in the moiety of the thiazole ring displayed a moderate antimicrobial activity for all microorganisms in Table 1.
(2) Attachment of C_6H_5– group in (**21b**) at position 4 in the moiety of the thiazole ring displayed a moderate antimicrobial activity for all microorganisms in Table 1 except *PA* which has no activity.

H. In the thiazolylpyridazine-3,6-dione (**22**)
Attachment of carbonyl-1,2-dihydropyridazine-3,6-dione group at position 5 in the thiazole ring displayed potent effect against fungi and a moderate activity against Gram-positive bact., and Gram-negative bact. except *PA* which has no activity.

I. In the thiazolylphthalazine-1,4-dione (**23**)
Attachment of carbonyl-2,3-dihydrophthalazine-1,4-dione group at position 5 in the thiazole ring showed a moderate antimicrobial activity for all microorganisms in Table 1.

J. In the thiazolylpyrano[2,3-*d*]thiazole-6-carbonitrile (**25a**, **b**)

(1) Attachment of C_6H_5- group in (**25a**) at position 7 in the moiety of the pyrano[2,3-*d*]thiazole-6-carbonitrile ring displayed a moderate antimicrobial activity for all microorganisms in Table 1.
(2) Attachment of 4–$CH_3C_6H_4$ group in (**25b**) at position 7 in the moiety of the pyrano[2,3-*d*] thiazole-6-carbonitrile ring displayed a moderate activity against Gram-positive bact., and Gram-negative bact. and has no activity on fungi.

Conclusions

Hydrazonoyl halides were used as precursors to synthesize a new series of novel functionalized 1,3,4-thiadiazoles, 1,3-thiazoles and pyrazoline-containing moieties. Antibacterial and antifungal activities of these compounds were assessed in vitro. *Streptococcus pneumonia*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli* were resistant to compounds (**10a**), (**11b**) on the basis of the screening results. *Aspergillus fumigatus* was susceptible to compounds (**11a**), (**20a**), (**20b**), (**20d**), and (**22**). *Candida albicans* compared to amphotericin B was moderate for all compounds. Compared to ampicillin and gentamycin, *Streptococcus pneumonia*, *Pseudomonas aeruginosa* and *Escherichia coli* were moderate for all compounds.

Experimental

General information

An electrothermal device (Bibby Sci. Lim. Stone, Staffordshire, UK) has been used to determine all melting points and they are uncorrected. A FT—IR 8201 PC spectrophotometer (Shimadzu, Tokyo, Japan) was used to determine the IR spectra. On Varian Mercury VX-300 NMR spectrometer (Varian, Inc., Karlsruhe, Germany) operating at 300 MHz (^{1}H NMR), the ^{1}H-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solutions. The chemical shifts are expressed in δ ppm units using TMS as an internal reference. On a Shimadzu GC–MS QP1000 EX instrument (Tokyo, Japan) mass spectra were recorded. Elemental analyses were performed at the University of Cairo's Microanalytical Center. As previously reported, hydrazonoyl halides [46–49] and 5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide [39] Additional file 1: Figure S1 were prepared. In the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt, antimicrobial screening was conducted.

Compounds (2–4)

General procedure

A mixture of compound (**1**) (2.85 g, 5 mmol), and the appropriate halogenated reagents (ethyl 2-chloro-3-oxobutanoate, ethyl 2-chloroacetate, or 3-chloropentane-2,4-dione) (10 mmol) in ethanol (20 mL) containing a catalytic amount of triethylamine was refluxed for 2 h.

The reaction mixture was left to cool to room temperature. The formed solid was filtered off, dried, and recrystallized from an appropriate solvent to obtain the corresponding compounds (**2**–**4**), respectively.

*Compound (***2***). Additional file 2: Figure S2* Yellow solid from ethanol, yield (3.56 g, 90%), mp: 124–125 °C; IR (KBr, cm^{-1}): 3115 (=C–H aromatic), 3068 (=C–H), 2976 (–C–H), 1697 (C=O); ^{1}H NMR: δ: 1.23 (t, 3H, *J* = 7.5 Hz, –OCH$_2$<u>CH$_3$</u>), 2.36 (s, 3H, 4–C<u>H$_3$</u>-thiazole), 2.50 (s, 3H, 4–C<u>H$_3$</u>C$_6$H$_4$), 3.40 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.80 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 4.15 (q, 2H, *J* = 7.5 Hz, –O<u>CH$_2$</u>CH$_3$), 5.56 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.40–7.72 (m, 7H, ArH's + furyl-H's); ^{13}C-NMR (DMSO-*d*6) δ:14.2 (CH_3), 17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 60.3 (OCH_2), 61.8 (CH), 94.5, 110.6, 117.0, 125.7, 129.2, 130.0, 140.7, 149.8, 150.9, 152.5, 163.6. MS (*m/z*): 396 (M+ 1, 2), 395 (M+, 10), 347 (6), 255 (10), 228 (28), 169 (100), 168 (66), 167 (40), 84 (12), 77 (38), 30 (26); *Anal.*Calcd. for $C_{21}H_{21}N_3O_3S$ (395.47): C, 63.78; H, 5.35; N, 10.63; S, 8.11; found: C, 63.75; H, 5.36; N, 10.65; S, 8.11.

*Compound (***3***). Additional file 3: Figure S3* Pale yellow solid from dioxane, yield (2.34 g, 72%), mp: 244–245 °C; IR (KBr, cm^{-1}): 3143 (=C–H aromatic), 3039 (=C–H), 2991 (–C–H), 1697 (C=O); ^{1}H NMR: δ: 2.44 (s, 3H, 4-<u>CH$_3$</u>C$_6$H$_4$), 3.61 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.92 (s, 2H, thiazole-H), 3.95 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.85 (q, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.42–7.76 (m, 7H, ArH's + furyl-H's); ^{13}C-NMR (DMSO-*d*6) δ: 21.4 (CH_3), 35.8 (CH_3),38.8 (CH_2), 61.8 (CH), 94.4, 106.5, 125.7, 129.2, 130.0, 140.7, 142.1, 150.8, 154.1, 173.5, 187.6. MS (*m/z*): 327 (M+ 2, 1), 326 (M+ 1, 10), 325 (M+, 50), 308 (47), 293 (100), 275 (51), 101 (35), 77 (41), 69 (68), 59 (48), 44 (36), 30 (41); *Anal.* Calcd. for $C_{17}H_{15}N_3O_2S$ (325.38): C, 62.75; H, 4.65; N, 12.91; S, 9.85; found: C, 62.71; H, 4.67; N, 12.92; S, 9.86.

*Compound (***4***). Additional file 4: Figure S4* Yellow solid from glacial acetic acid, yield (2.74 g, 75%), mp: 176–177 °C; IR (KBr, cm^{-1}): 3134 (=C–H aromatic), 3026 (=C–H), 2966 (–C–H), 1751 (C=O); ^{1}H NMR: δ:2.36 (s, 3H, 4-<u>CH$_3$</u>C$_6$H$_4$), 2.46 (s, 3H, 4-<u>CH$_3$</u>-thiazole), 2.50 (s, 3H, CO–CH$_3$), 3.50 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.85 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.79 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.40 (m, 2H, furyl-H), 7.29–7.72 (m, 5H, ArH's + 1furyl-H); ^{13}C-NMR (DMSO-*d*6) δ:17.0 (CH_3), 21.3 (CH_3), 28.6 (CH_3), 35.7 (CH_2), 61.7 (CH), 94.5, 110.6, 113.5, 125.8, 129.2, 130.0, 140.8, 142.2, 149.9, 151.1, 153.5, 153.9, 191.2. MS (*m/z*): 367 (M+ 2, 2), 366 (M+ 1, 9), 365 (M+, 38), 264 (16), 263 (14), 224 (10), 223 (11), 205 (8), 142 (25), 114 (100), 44 (16); *Anal.* Calcd. for $C_{20}H_{19}N_3O_2S$ (365.45): C, 65.73; H, 5.24; N, 11.50; S, 8.77; found: C, 65.71; H, 5.25; N, 11.50; S, 8.76.

*Compound (***5***). Additional file 5: Figure S5* A mixture of ethyl 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carboxylate (**2**) (3.95 g, 10 mmol), and hydrazine hydrate (20 mL) was heated under reflux for 12 h. The reaction mixture was left to cool to room temperature. The formed precipitate was filtered off, washed with ethanol, and recrystallized from glacial acetic acid to obtain compound (**5**) as a white solid yield (1.52 g, 40%), mp: 204–207 °C; IR (KBr, cm^{-1}): 3400 (N–H), 3028 (=C–H), 2924 (–C–H), 1590 (C=O); ^{1}H NMR: δ: 2.31 (s, 3H, 4-<u>CH$_3$</u>C$_6$H$_4$), 2.36 (s, 3H, 4-<u>CH$_3$</u>-thiazole), 3.47 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.64 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.71 (s, 1H, N–H), 5.59 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.29–7.64 (m, 9H, ArH's + 2N–H + furyl-H's); ^{13}C-NMR (DMSO-*d*6) δ:17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.5, 107.8, 110.6, 1253.7, 129.2, 130.0, 140.7, 142.2, 145.5, 149.9, 151.1, 154.0, 185.8. MS (*m/z*): 383 (M+ 2, 3), 382 (M+ 1, 22), 381 (M+, 100), 200 (54), 183 (13), 115 (14), 152 (22), 104 (19), 103 (40), 91 (19), 43 (87); *Anal.* Calcd. for $C_{19}H_{19}N_5O_2S$ (381.45): C, 59.82; H, 5.02; N, 18.36; S, 8.41; found: C, 59.79; H, 5.03; N, 18.37; S, 8.42.

*Compound (***6***). Additional file 6: Figure S6* Sodium nitrite (0.69 g, 10 mmol) was dissolved in the least amount of water, and then added dropwise, to a suspension of 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbohydrazide (**5**) (3.8 g, 10 mmol) in 37% HCl (10 mmol) at 0–5 °C. The formed precipitate was filtered off, washed with water, and recrystallized from ethanol to obtain compound (**6**) as a brownish yellow solid, yield (2.35 g, 60%), mp: 138–140 °C; IR (KBr, cm^{-1}): 3032 (=C–H), 2921 (–C–H), 2126 (-N_3), 1664 (C=O); ^{1}H NMR: δ:2.35 (s, 3H, 4-<u>CH$_3$</u>C$_6$H$_4$), 2.50 (s, 3H, 4-<u>CH$_3$</u>-thiazole), 3.40 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.83 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.60 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.36–8.60 (m, 7H, ArH's and furyl protons); ^{13}C-NMR (DMSO-*d*6) δ:17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.5, 107.8, 110.6, 112.9, 125.7, 129.3, 130.0, 140.7, 142.4, 146.2, 148.9, 151.1, 154.0, 166.4. MS (*m/z*): 393 (M+ 1, 4), 392 (M+, 14), 206 (19), 205 (100), 190 (13), 161 (17), 127 (9), 103 (11), 86 (11); *Anal.* Calcd. for $C_{19}H_{16}N_6O_2S$ (392.43): C, 58.15; H, 4.11; N, 21.42; S, 8.17; found: C, 58.17; H, 4.10; N, 21.42; S, 8.16.

*Compound (***7***). Additional file 7: Figure S7* Amixture of 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-

1-yl)-4-methylthiazole-5-carbohydrazide (5) (3.81 g, 10 mmol), ammonium thiocyanate (5 g, 6.5 mmol) and hydrochloric acid (50 mL, 37% 150 mL of H_2O) was heated under reflux for 1 h.The resulting oily residue was solidified, collected, and recrystallized from glacial acetic acid to obtain a white solid, yield (1.49 g, 34%), mp: 230–232 °C; IR (KBr, cm^{-1}): 3268 (N–H), 3150 (=C–H aromatic), 3037 (=C–H), 2966 (–C–H), 1666 (–C=O); ^{1}H NMR: δ:2.36 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.42 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.48 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.88 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.76 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.39-7.69 (m, 9H, ArH's, furyl-H's and 2 N–H), 9.23 (s, 1H, N–H), 9.58 (s, 1H, N-H); ^{13}C-NMR (DMSO-*d*6) δ:17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.5, 108.8, 110.6, 125.7, 129.2, 130.0, 140.7, 142.2, 145.2, 149.8, 151.0, 154.1, 157.8, 181.2. MS (*m/z*): 440 (M+, 2), 438 (9), 425 (14), 382 (18), 319 (22), 318 (100), 290 (33), 205 (11), 169 (10), 151 (19), 128 (14); *Anal.* Calcd. for $C_{20}H_{20}N_6O_2S_2$ (440.54): C, 54.53; H, 4.58; N, 19.08; S, 14.56; found: C, 54.55; H, 4.57; N, 19.08; S, 14.55.

Compounds (10a, b) and (11a, b), General procedure

A mixture of 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbohydrazide (**5**) (3.81 g, 10 mmol), and the appropriate amount of 3-(2-arylhydrazono)pentane-2,4-dione or ethyl 3-oxo-2-(2-arylhydrazono)butanoate (10 mmol) in acetic acid (20 mL) was heated under reflux for 2 h. The reaction mixture was left to cool to room temperature. The formed solid was filtered off, dried, and recrystallized from an appropriate solvent to obtain the corresponding compounds (**10a**, **10b**, **11a**, and **11d**), respectively.

*Compound (***10a***). Additional file 8: Figure S8* Yellow solid from glacial acetic acid, yield (3.90 g, 71%), mp: 234–235 °C; IR (KBr, cm^{-1}): 3432 (N-H), 3112 (=C–H aromatic), 2965 (–C–H), 1699 (C=O); ^{1}H NMR: δ:2.42 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.62 (s, 3H, pyrazole–C$\underline{H_3}$), 2.74 (s, 3H, pyrazole–C$\underline{H_3}$), 3.02 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.62 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.69 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.85 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.32 (q, 1H, Furyl-H), 6.45 (d, 1H, Furyl-H), 7.25–7.86 (m, 10H, ArH's, 1Furyl-H); ^{13}C-NMR (DMSO-*d*6) δ:11.4 (CH_3), 12.28 (CH_3), 17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 109.6, 110.6, 121.7, 125.7, 129.2, 130.0, 130.2, 136.0, 138.7, 148.6, 150.9, 151.4, 152.4, 153.9, 160.2. MS (*m/z*): 549 (M+, 4), 515 (19), 431 (10), 430 (57), 304 (14), 132 (16), 128 (59), 127 (45), 89 (10), 88 (15), 62 (20), 61 (22), 43 (100); *Anal.* Calcd. for $C_{30}H_{27}N_7O_2S$ (549.65): C, 65.56; H, 4.95; N, 17.84; S, 5.83; found: C, 65.59; H, 4.94; N, 17.85; S, 5.80.

*Compound (***10b***). Additional file 9: Figure S9* Yellow solid from glacial acetic acid, yield (4.17 g, 74%), mp: 225–226 °C; IR (KBr, cm^{-1}): 3107 (=C–H aromatic), 3025 (=C–H), 2972 (–C–H), 1670 (C=O); ^{1}H NMR: δ: 2.42 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.43 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.6 (s, 3H, pyrazole–C$\underline{H_3}$), 2.74 (s, 3H, pyrazole–C$\underline{H_3}$), 3.01 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.63 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.70 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.80 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.32–7.77 (m, 11H, ArH's, furyl-H's); ^{13}C-NMR (DMSO-*d*6) δ:11.4 (CH_3), 12.28 (CH_3), 17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 109.6, 110.6, 119.2, 125.8, 129.3, 129.7, 130.0, 130.1, 138.7, 139.1. 140.8, 141.7, 142.5, 149.3, 149.9, 150.9, 151.3, 153.9, 160.2. MS (*m/z*): 565 (M+2, 2), 564 (M+1, 15), 563 (M+, 59), 522 (24), 450 (16), 432 (34), 431 (100), 327 (23), 326 (88), 296 (12), 91 (12); *Anal.* Calcd. for $C_{31}H_{29}N_7O_2S$ (563.67): C, 66.05; H, 5.19; N, 17.39; S, 5.69; found: C, 66.07; H, 5.18; N, 17.39; S, 5.68.

Compound (11a). Additional file 10: Figure S10 Orange solid from dioxane, yield (3.69 g, 67%), mp: 279–280 °C; IR (KBr, cm^{-1}): 3431 (O–H), 3141 (=C–H aromatic), 3067 (=C–H aromatic), 2918 (–C–H), 1701 (C=O); ^{1}H NMR: δ: 2.40 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.41 (s, 3H, 4-$\underline{CH_3}$-thiazole), 2.70 (s, 3H, pyrazole–C$\underline{H_3}$), 3.62 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.71 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.90 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.31–7.73 (m, 12H, ArH's, furyl-H's), 13.58 (s, 1H, O–H); ^{13}C-NMR (DMSO-*d*6) δ:11.4 (CH_3), 12.28 (CH_3), 17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 109.6, 110.6, 119.2, 125.7. 127.3, 129.7, 130.1, 130.2. 138.7, 139.2, 140.7141.7, 142.3, 149.2, 149.9, 151.0, 151.4, 154.1, 160.3. MS (*m/z*): 551 (M+, 1), 501 (10), 398 (11), 236 (25), 235 (100), 155 (10), 91 (11), 18 (22); *Anal.* Calcd. for $C_{29}H_{25}N_7O_3S$ (551.62): C, 63.14; H, 4.57; N, 17.77; S, 5.81; found: C, 63.17; H, 4.56; N, 17.76; S, 5.80.

*Compound (***11b***). Additional file 11: Figure S11* Orange solid from dioxane, yield (4.52 g, 80%), mp. 289–290 °C; IR (KBr, cm^{-1}): 3437 (OH), 3143(=C–H aromatic), 3064 (=C–H aromatic), 2918 (–C–H), 1699 (C=O); ^{1}H NMR: δ: 2.87 (s, 6H, 4-$\underline{CH_3}C_6H_4$), 2.94 (s, 3H, pyrazole–C$\underline{H_3}$), 2.96 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.57 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.62 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline), 5.96 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.31–8.02 (m, 11H, ArH's, furyl-H's), 13.62 (s, 1H, N–H); ^{13}C-NMR (DMSO-*d*6) δ: 11.0 (CH_3), 17.0 (CH_3), 20.8 (CH_3), 21.49 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 109.6, 110.6, 119.2, 125.7, 127.3, 129.7, 130.1, 130.2, 138.7, 139.2, 140.7, 141.7, 142.3, 149.2, 149.9, 151.0, 151.4, 154.1, 160.3. MS (*m/z*): 567 (M+ 2, 11), 566 (M+

1, 46), 565 (M+ , 100), 425 (12), 385 (15), 215 (5), 179 (5), 105 (6), 95 (6), 91 (6), 55 (10), 43 (16); *Anal.* Calcd. for $C_{30}H_{27}N_7O_3S$ (565.65): C, 63.70; H, 4.81; N, 17.33; S, 5.67; found: C, 63.73; H, 4.80; N, 17.30; S, 5.67.

Compounds (12a and 12b), and (13), general procedure

A mixture of 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl azide (**6**) (2.2 g, 5 mmol) and the appropriate amount of aromatic amines (aniline, 4-methylaniline), anthranilic acid or methyl anthranilate (5 mmol) in dioxane (20 mL), was heated under reflux for 3 h. The reaction mixture was left to cool to room temperature. The formed solid formed was filtered off, dried, and recrystallized from an appropriate solvent to obtain the corresponding compounds (**12a**), and (**12b**), and (**13**), respectively.

*Compound (***12a***). Additional file 12: Figure S12* White solid from dioxane, yield (1.83 g, 80%), mp: 226–229 °C; IR (KBr, cm^{-1}): 3308 (N–H), 3104 (=C–H aromatic), 3031 (=C–H), 2918 (–C–H), 1637 (CON–H); ^{1}H NMR: δ: 2.06 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.35 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.45 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.77 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.58 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.39 (s, 2H, N–H), 6.94–8.72 (m, 12H, ArH's + furyl-H's); ^{13}C-NMR (DMSO-*d*6) δ:13.6 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 109.6, 110.6, 116.2, 125.7, 129.2, 129.7, 130.1, 134.2, 134.7, 140.7, 142.3, 148.9, 150.3, 153.9, 157.6, 160.3. MS (*m/z*): 459 (M+2, 1), 458 (M+1, 9), 257 (M+, 70), 443 (80), 278 (85), 261 (23), 260 (12), 247 (10), 181 (25), 78 (17), 79 (14), 77 (28), 75 (19), 51 (15), 43 (38), 42 (21), 41 (20), 30 (61), 28 (100); *Anal.* Calcd. for $C_{25}H_{23}N_5O_2S$ (457.55): C, 65.63; H, 5.07; N, 15.31; S, 7.01; found: C, 65.61; H, 5.08; N, 15.32; S, 7.02.

*Compound (***12b***). Additional file 13: Figure S13* Pale yellow solid from dioxane, yield (1.62 g, 75%), mp: 191–192 °C; IR (KBr, cm^{-1}): 3308 (N–H), 3104 (=C–H aromatic), 3031 (=C–H), 2918 (–C–H), 1637 (CONH); ^{1}H NMR: δ:2.06 (s, 6H, $2CH_3C_6H_4$), 2.35 (s, 3H, 4–CH_3-thiazole), 3.45 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.77 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.58 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.39 (s, 2H, N–H), 6.94–8.72 (m, 11H, ArH's + furyl-H's); ^{13}C-NMR (DMSO-*d*6) δ:13.6 (CH_3), 20.8 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 109.6, 110.6, 112.1, 125.7, 129.1, 129.2, 130.0, 134.1, 140.7, 142.4, 148.5. 150.9, 154.0, 157.6, 160.4; *Anal.* Calcd. for $C_{26}H_{25}N_5O_2S$ (471.58): C, 66.22; H, 5.34; N, 14.85; S, 6.80; found: C, 66.11; H, 545; N, 14.98; S, 6.69.

*Compound (***13***). Additional file 14: Figure S14* White solid from glacial acetic acid, yield (1.71 g, 71%), mp: 260–263 °C; IR (KBr, cm^{-1}): 3286 (N–H), 3157 (=C–H aromatic), 2955 (–C–H), 1735 (–C=O), 1657 (CON–H); ^{1}H NMR: δ: 2.34 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.35 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.44 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.84 (dd 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.76 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.44 (m, 2H, furyl-H's), 7.20–7.95 (m, 9H, ArH's + 1Furyl-H), 11.58 (s, 1H, N–H); ^{13}C-NMR (DMSO-*d*6) δ:13.7 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 110.6, 114.6, 115.2, 117.3, 123.0, 125.7, 127.9, 129.3, 130.0, 139.8, 140.7, 142.4, 150.9, 152.1, 153.9, 156.7, 159.4, 160.8. MS (*m/z*): 483 (M+, 2%), 470 (22), 469 (85), 426 (30), 396 (23), 426 (27), 364 (18), 363 (88), 341 (27), 337 (28), 309 (40), 299 (19), 283 (34), 280 (16), 267 (65), 219 (14), 186 (37), 181 (17), 180 (34), 173 (15), 171 (93), 151 (28), 129 (24), 126 (33), 115 (32), 113 (45), 111 (30), 97 (34), 87 (24), 85 (59), 82 (25), 81 (18), 69 (35), 68 (46), 59 (3), 57 (17), 55 (24), 45 (37), 44 (32), 43 (92), 41 (38); *Anal.* Calcd. for $C_{26}H_{21}N_5O_3S$ (483.54): C, 64.58; H, 4.38; N, 14.48; S, 6.63; found: C, 64.54; H, 4.39; N, 14.49; S, 6.65.

*Compound (***14***). Additional file 15: Figure S15* Amixture of 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl azide (**6**) (2.2 g, 5 mmol), and 2-naphthol (0.72 g, 5 mmol), in dry benzene (20 mL) was refluxed for 3 h. The reaction mixture was left to cool at room temperature. The formed solid was filtered off, dried, and recrystallized from glacial acetic acid to obtain compound (**14**) as a brown solid, yield (2.11 g, 83%), mp: 219–222 °C; IR (KBr, cm^{-1}): 3286 (N–H), 3157 (=C–H aromatic), 2955 (–C–H), 1735 (–C=O), ^{1}H NMR: δ: 2.14 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.35 (s, 3H, 4–CH_3-thiazole), 3.37 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.81 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.61 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.40–8.13 (m, 14H, ArH's, furyl-H's), 8.95 (s, 1H, N-H); ^{13}C-NMR (DMSO-*d*6) δ:17.7 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 110.6, 116.9, 117.3, 118.9, 125.7, 126.4, 127.6, 127.8, 129.2, 129.3, 134.1, 14.7, 172.4, 149.8, 151.0, 151.6, 152.9, 155.0, 160.1. MS (*m/z*): 508 (M+, 2), 307 (100), 201 (14), 172 (13), 171 (26), 156 (26), 132 (32), 128 (19), 106 (21), 105 (29), 104 (27); *Anal.* Calcd. for $C_{29}H_{24}N_4O_3S$ (508.59): C, 68.49; H, 4.76; N, 11.02; S, 6.30; found: C, 68.48; H, 4.75; N, 11.00; S, 6.32.

*Compound (***15***). Additional file 16: Figure S16* 2-(5-(Furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbohydrazide (3.81 g, 10 mmol) was suspended in ethanol, and then carbon disulfide (10 mL) was added, dropwise, to the suspension at 5–10 °C. The mixture was heated for 10 h under

reflux in the presence of potassium hydroxide (0.56 g, 10 mmol). The solution was cooled and acidified to pH 5–6 using HCl solution, and the formed solid was collected and recrystallized to obtain a yellow solid from dioxane, yield (3.05 g, 72%), mp: 267–270 °C; IR (KBr, cm^{-1}): 3110 (S–H), 2920 (–C–H); ^{1}H NMR: δ: 2.36 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.41 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.50 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.92 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.80 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.41–7.72 (m, 7H, ArH's + furyl-H's), 14.55 (s, 1H, S–H); ^{13}C-NMR (DMSO-*d*6) δ:17.5 (CH_3), 21.5 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 110.6, 125.7, 129.3, 130.1, 140.7, 140.9, 142.4, 149.8, 150.9, 152.7, 152.9, 169.2. MS (*m/z*): 424 (M+ 1, 4), 423 (M+, 5), 392 (20), 230 (8), 216 (12), 192 (13), 190 (15), 189 (100); *Anal.* Calcd. for $C_{20}H_{17}N_5O_2S_2$ (423.51): C, 56.72; H, 4.05; N, 16.54; S, 15.14; found: C, 56.74; H, 4.04; N, 16.55; S, 15.12.

Compounds (20a–d), General procedure

Equal molar quantities of 5-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)-1,3,4-oxadiazole-2-thiol (**15**) (2.11 g, 5 mmol), and the appropriate hydrazonoyl halides (**16a–d**) (5 mmol) in ethanol (20 mL) containing a catalytic amount of triethylamine were heated under reflux for 2 h. The reaction mixture was left to cool to room temperature. The formed solid was filtered off, dried, and recrystallized from an appropriate solvent to obtain the corresponding compounds (**20a–d**), respectively.

*Compound (***20a***). Additional file 17: Figure S17* Yellow solid from glacial acetic acid, yield (2.36 g, 77%), mp: 206–209 °C; IR (KBr, cm^{-1}): 3438 (N–H), 3153; 3037 (=C–H), 2973; 2925 (–C–H), 1703 (–C=O); ^{1}H NMR: δ: 1.31 (t, 3H, –OCH$_2\underline{CH_3}$), 2.37 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.42 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.47(dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.83 (dd 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.83 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 4.33 (q, 2H, –O$\underline{CH_2}CH_3$), 6.41 (m, 2H, furyl-H's), 7.30–7.90 (m, 10H, ArH's, 1Furyl-H), 10.54 (s, 1H, N–H); ^{13}C-NMR (DMSO-*d*6) δ:13.9 (CH_3), 17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 62.6, 94.6, 107.9, 110.6, 123.1, 125.7, 130.1, 129.2, 129.3, 138.8, 140.7, 142.4, 146.6, 147.9, 149.9, 151.1, 154.0, 154.2, 131.3, 161.4. MS (*m/z*): 613 (M+, 9), 609 (11), 409 (10), 406 (13), 390 (22), 360 (12), 239 (14), 168 (13), 152 (59), 151 (100), 135 (29), 129 (11), 106 (17), 85 (30), 73 (30), 71 (50), 69 (25), 55 (38), 43 (82), 29 (17); *Anal.* Calcd. for $C_{30}H_{27}N_7O_4S_2$ (613.71): C, 58.71; H, 4.43; N, 15.98; S, 10.45; found: C, 58.73; H, 4.41; N, 15.99; S, 10.44.

*Compound (***20b***). Additional file 18: Figure S18* Yellow solid from glacial acetic acid, yield (1.89 g, 65%), mp: 258–261 °C; IR (KBr, cm^{-1}): 3430 (N–H), 3160; 3109 (=C–H), 2925 (–C–H), 1679 (–C=O); ^{1}H NMR: δ: 2.37 (s, 3H, CO–CH_3), 2.43 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.50 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.40 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.83 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.74 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.41 (m, 2H, furyl-H's), 7.30–7.97 (m, 10H, ArH's, 1Furyl-H), 10.52 (s, 1H, N–H); ^{13}C-NMR (DMSO-*d*6) δ:17.7 (CH_3), 21.4 (CH_3), 24.8 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 107.9, 110.6, 116.9, 123.1, 125.7, 129.1, 129.2, 130.0, 140.7, 142.4, 146.6, 149.8, 150.2. 150.9, 152.9, 154.4, 161.3, 191. MS (*m/z*): 583 (M+, 9), 515 (19), 430 (56), 304 (13), 132 (15), 128 (59), 127 (45), 61 (22), 43 (100); *Anal.* Calcd. for $C_{29}H_{25}N_7O_3S_2$ (583.68): C, 59.67; H, 4.32; N, 16.80; S, 10.99; found: C, 59.66; H, 4.33; N, 16.81; S, 10.98.

*Compound (***20c***). Additional file 19: Figure S19* Red solid from dioxane, yield (2.00 g, 62%) mp: 255–256 °C; IR (KBr, cm^{-1}): 3245 (N–H), 3130 (=C–H), 2963 (–C–H), 1617 (–C=O); ^{1}H NMR: δ: 2.37 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.45 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.47 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.84 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.75 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.41 (m, 2H, furyl-H's), 7.31–8.23 (m, 15H, ArH's, 1Furyl-H), 10.57 (s, 1H, N–H); ^{13}C-NMR (DMSO-*d*6) δ:17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 107.9, 110.6, 123.1, 125.7, 128.3, 140.7, 142.4, 146.4, 149.9, 150.4, 153.9, 154.2, 155.9, 161.3. MS (*m/z*): 645 (M+, 1), 498 (11), 339 (11), 281 (17), 243 (51), 242 (11), 256 (12), 239 (15), 153 (15), 152 (60), 151 (100), 135 (29), 106 (17), 85 (31), 83 (62), 171 (32), 73 (35), 71 (76), 60 (100), 43 (51); *Anal.* Calcd. for $C_{34}H_{27}N_7O_3S_2$ (645.75): C, 63.24; H, 4.21; N, 15.18; S, 9.93; found: C, 63.27; H, 4.20; N, 15.16; S, 9.93.

*Compound (***20d***). Additional file 20: Figure S20* Yellow solid from dioxane, yield (2.34 g, 71%), mp: 244-247 °C; IR (KBr, cm^{-1}): 3245 (N–H), 3130 (=C–H), 2963 (–C–H), 1667 (–C=O); ^{1}H NMR δ: 2.37 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.45 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.47 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.83 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.75 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.40 (m, 2H, furyl-H's), 7.14–8.13 (m, 15H, ArH's + 1Furyl-H), 10.55 (s, 1H, N–H), 107.9 (s, 1H, N–H); ^{13}C-NMR (DMSO-*d*6) δ:17.1 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 110.6, 121.1, 125.7, 128.5, 129.1, 130.7, 137.1, 138.8, 140.7, 142.4, 146.4, 147.9, 149.8, 151., 153.9, 161.3. MS (*m/z*): 660 (M+, 10), 382 (13), 359 (10), 341 (66), 340 (18), 284 (23), 268 (19), 267 (100), 185 (20), 129 (35), 116 (25), 112 (25), 109 (15), 98 (80), 84 (37), 83 (41), 55 (50), 43 (63); *Anal.* Calcd. for

$C_{34}H_{28}N_8O_3S_2$ (660.77): C, 61.80; H, 4.27; N, 16.96; S, 9.71; found: C, 61.84; H, 4.25; N, 16.95; S, 9.70.

Compounds (21a) and (21b), general procedure

A mixture of 2-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl) hydrazinecarbothioamide (**7**) (2.20 g, 5 mmol), and the appropriate hydrazonoyl halides (**16b** and **16c**) (5 mmol), in ethanol (20 mL) containing a catalytic amount of triethylamine was heated under reflux for 2 h. The reaction mixture was left to cool to room temperature. The formed solid was filtered off, dried, and recrystallized from glacial acetic acid to obtain compounds (**21a**), and (**21b**), respectively.

*Compound (***21a***). Additional file 21: Figure S21* Red solid from glacial acetic acid, yield (1.51 g, 52%), mp: 239–240 °C; IR (KBr, cm^{-1}): 3432 (N–H), 3034 (=C–H), 2922 (–C–H), 1625 (C=O); ^{1}H NMR: δ: 2.37 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.49 (s, 3H, 4-$\underline{CH_3}$-thiazole), 2.49 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.43 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.85 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.75 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.41–7.72 (m, 13H, ArH's + 1 N–H, furyl-H's), 10.51 (s, 1H, N–H); ^{13}C-NMR (DMSO-*d*6) δ:13.4 (CH_3),17.1 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 49.5, 108.8, 110.6, 122.3, 129.3, 125.6, 140.4, 142.4, 146.4, 145.2, 149.8, 150.0., 152.4, 153.9, 157.8, 171.6. MS (*m/z*): 582 (M + 1, 3), 581 (M+, 65), 301 (13), 300 (33), 299 (100), 298 (12), 288 (12), 287 (16), 28 6(78), 285 (11), 239 (19), 227 (25), 225 (15), 211 (18), 44 (31), 18 (17); *Anal.* Calcd. for $C_{29}H_{26}N_8O_2S_2$ (582.70): C, 59.78; H, 4.50; N, 19.23; S, 11.01; found: C, 59.80; H, 4.49; N, 19.21; S, 11.00.

*Compound (***21b***). Additional file 22: Figure S22* Red solid from glacial acetic acid, yield (1.45 g, 45%), mp: 227–230 °C; IR (KBr, cm^{-1}): 3434 (N–H), 3022 (=C–H), 2918 (–C–H), 1631 (CON–H); ^{1}H NMR: δ: 2.37 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.49 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.50 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.87 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.79 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.41–8.26 (m, 18H, ArH's, 1 N-H, furyl-H's), 10.73 (s, 1H, N-H); ^{13}C-NMR (DMSO-*d*6) δ:17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 108.6, 110.6, 122.3, 125.7, 129.0, 129.1, 129.9, 134.5, 138.9, 140.7, 142.4, 145.3, 147.4, 149.8, 151. 0, 152.4, 157.7, 170.3. MS (*m/z*): 644 (M+, 8), 614 (11), 607 (9), 308 (10), 281 (17), 243 (51), 242 (63), 210 (13), 170 (13), 156 (25), 73 (35), 71 (76), 60 (100), 55 (18), 43 (51), 41 (26); *Anal.* Calcd. for $C_{34}H_{28}N_8O_2S_2$ (644.77): C, 63.33; H, 4.38; N, 17.38; S, 9.95; found: C, 63.36; H, 4.37; N, 17.37; S, 9.94.

Compounds (22) and (23), general procedure

A mixture of 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbohydrazide (**5**) (1.95 g, 5 mmol), and the appropriate maleic anhydride or phthalic anhydride (5 mmol) was heated under reflux in glacial acetic acid for 2 h. The reaction mixture was left to cool to room temperature. The formed solid was filtered off, dried, and recrystallized from acetic acid to obtain compounds (**22**) and (**23**), respectively.

*Compound (***22***). Additional file 23: Figure S23* Yellow solid, yield (1.93 g, 84%), mp: 230–233 °C; IR (KBr, cm^{-1}): 3398; 3229 (N-H), 2951 (–C–H), 1715 (–C=O); ^{1}H NMR: δ: 2.36 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.41 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.50 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.91 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.77 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.26–7.70 (m, 10H, Ar–H, furyl-H's, pyridazine-H); ^{13}C-NMR (DMSO-*d*6) δ:17.0 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.6 (CH), 94.6, 110.2, 110.6, 125.2, 125.7, 129.5, 140.7, 142.4, 149.4, 149.8, 151., 157.1, 158.8, 167.1. MS (*m/z*): 461 (M+, 9), 402 (20), 384 (100), 369 (41), 351 (29), 247 (20), 144 (14), 230 (11), 159 (18), 149 (16), 145 (18), 135 (25), 133 (17) 122 (17), 121 (22), 105 (21), 95 (38), 91 (18), 67 (18), 57 (22), 55 (31), 43 (40); *Anal.* Calcd. for $C_{23}H_{19}N_5O_4S$ (461.49): C, 59.86; H, 4.15; N, 15.18; S, 6.95; found: C, 59.89; H, 4.14; N, 15.17; S, 6.94.

*Compound (***23***). Additional file 24: Figure S24* White solid, yield (1.63 g, 64%), mp: 152–154 °C; IR (KBr, cm^{-1}): 3436 (N–H), 2923 (–C–H), 1735 (–C=O); ^{1}H NMR: δ: 2.41 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.58 (s, 3H, 4-$\underline{CH_3}$-thiazole), 3.65 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.71 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.80 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.32 (q, 1H, Furyl-H), 6.40 (d, 1H, furyl-H), 7.24–7.94 (m, 10H, ArH's, 1Furyl-H, N–H); ^{13}C-NMR (DMSO-*d*6) δ:17.1 (CH_3), 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 94.6, 106, 110.6, 125.7, 129.2, 132.7, 140.7, 142.4, 149.5, 149.8, 150.9., 153.8, 155.8, 163.8. MS (*m/z*): 511 (M+, 31), 453 (26), 452 (53), 437 (13), 263 (17), 262 (69), 250 (20), 249 (51), 248 (22), 203 (36), 202 (21), 191 (25), 189 (100) 188 (21), 187 (28), 175 (31), 136 (25), 135(25), 119 (26), 107 (27), 105 (21), 95 (29), 93 (26), 81 (34), 69 (34); *Anal.* Calcd. for $C_{27}H_{21}N_5O_4S$ (511.55): C, 63.39; H, 4.14; N, 13.69; S, 6.27; found: C, 63.41; H, 4.14; N, 13.68; S, 6.26.

Compounds (25a–c), general methods

Method A A mixture of 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-5(4*H*)-one (**2**) (1.6 g, 5 mmol), and the appropriate arylidenemalononitrile (**24a–c**) in ethanol (20 mL) containing a catalytic amount

of piperdine was heated under reflux for 2 h. The reaction mixture was left to cool to room temperature. The formed solid was filtered off, dried, and recrystallized from dioxane to yield compounds (**25a**–**c**), respectively.

Method B A mixture of compound (**2**) (1.6 g, 5 mmol) and the corresponding amount of benzaldehyde, 4-methylbenzaldehyde or 4-methoxybenzaldehyde (5 mmol), malononitrile (0.33 g, 5 mmol), and piperdine (0.42 g, 5 mmol) in ethanol (20 mL) was heated for 2 h under reflux. The formed solid was filtered off, dried, and recrystallized from dioxane to obtain products that were identical in all respects (mp, mixed mp, and IR spectra) to the product obtained using Method A.

*Compound (***25a***). Additional file 25: Figure S25* White solid from dioxane, yield (2.03 g, 85%), mp: 250–252 °C; IR (KBr, cm^{-1}): 3388; 3262 (N–H), 3158 (–C=H), 2925 (–C–H), 2100 (–CN); ^{1}H NMR: δ: 2.35 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 4.20 (s, 1H, pyran-H), 3.28 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.70 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.96 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.28 (d, 1H, Furyl-H), 6.37 (q, 1H, Furyl-H), 7.26–7.79 (m, 10H, ArH's, 1furyl-H), 7.97 (s, 2H, -NH_2); ^{13}C-NMR (DMSO-*d*6) *δ*: 21.4 (CH_3), 35.7 (CH_2), 61.8 (CH), 66.4, 83.9, 94.6, 110.6, 118.9, 125.7, 128.3, 129.2, 130.1, 140.7, 141.4, 142.4, 150.9, 153.8., 153.9, 159.5. MS (*m/z*): 479 (M+, 9), 435 (16), 268 (21), 252 (10), 239 (16), 201 (13), 199 (11), 182 (14), 162 (23), 156 (11), 155 (12), 146 (20), 108 (23), 107 (18), 91 (100), 86 (96), 79 (23), 72 (27), 55 (12); *Anal.* Calcd. for $C_{27}H_{21}N_5O_2S$ (479.55): C, 67.62; H, 4.41; N, 14.60; S, 6.69; found: C, 67.65; H, 4.40; N, 14.60; S, 6.67.

*Compound (***25b***). Additional file 26: Figure S26* Yellow solid from dioxane, yield (1.90 g, 77%), mp: 196–197 °C; IR (KBr, cm^{-1}): 3436 (N–H), 3035 (–C=H), 2929 (–C–H), 2150 (–CN); ^{1}H NMR: δ: 2.36 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 2.39 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 3.30 (s, 1H, pyran-H), 3.63 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.97 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 5.97 (dd 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.44 (q, 1H, furyl-H), 6.54 (d, 1H, furyl-H), 7.33–7.82 (m, 11H, ArH's, 1furyl-H, -NH_2); ^{13}C-NMR (DMSO-*d*6) δ:20.9 (CH_3), 21.1 (CH_3), 34.1 (CH_2), 33.7, 38.2, 61.8 (CH), 93.5, 107.9, 109.6, 128.3, 129.9, 130.2, 131.4, 125.3, 140.7, 142.8, 143.6, 148.7, 154.4, 154.8, 157.6., 159.1. MS (*m/z*): 493 (M+, 10), 492 (34), 449 (26), 377 (10), 343 (17), 333 (28), 302 (15), 297 (12), 272 (11), 270 (28), 230 (40), 229 (22), 228 (100), 200 (14), 156 (50), 104 (15), 43 (26); *Anal.* Calcd. for $C_{28}H_{23}N_5O_2S$ (493.58): C, 68.13; H, 4.70; N, 14.19; S, 6.50; found: C, 68.16; H, 4.71; N, 14.16; S, 6.49.

*Compound (***25c***). Additional file 27: Figure S27* Yellow solid from dioxane, yield (1.78 g, 70%), mp: 228–231 °C; IR (KBr, cm^{-1}): 3436 (N–H), 3035 (–C=H), 2929 (–C–H), 2150 (–CN); ^{1}H NMR: δ: 2.39 (s, 3H, 4-$\underline{CH_3}C_6H_4$), 3.62 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 3.83 (s, 3H, –OCH_3), 4.01 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 4.70 (s, 1H, pyran-H), 5.96 (dd, 1H, *J* = 13.6 Hz, 16.2 Hz, pyrazoline-H), 6.44–7.81 (m, 13H, ArH's, furyl-H's, -NH_2); ^{13}C-NMR (DMSO-*d*6) δ: 21.9 (CH_3), 33.7 (CH_2), 34.1, 38.2, 55.2, 128.3, 128.9, 131.3. 135.2, 140.1, 142.4, 154.9, 156.1., 157.2, 159.1. MS (*m/z*): 511 (M+2, 3), 510 (M+2, 13), 509 (M+, 36), 407 (22), 334 (12), 256 (13), 242 (15), 233 (27), 228 (11), 156 (12), 153 (10), 105 (100), 77 (22); *Anal. Calcd.* for $C_{28}H_{23}N_5O_3S$ (509.58): C, 66.00; H, 4.55; N, 13.74; S, 6.29; found: C, 66.02; H, 4.53; N, 13.73; S, 6.30.

Antimicrobial activity assay

The chemical compounds being investigated were tested against a panel of Gram-positive and Gram-negative bacterial pathogens and fungi individually. Antimicrobial tests were performed using the agar well-diffusion method [50–52]. After cooling and solidifying the media, In the solidified agar, wells (6 mm in diameter) were made, the microbial inoculum was then spread evenly using a sterile cotton swab on a sterile Petri dish containing a medium of nutrient agar (NA) or Sabouraud Dextrose Agar (SDA) media for bacteria and fungi, respectively. By dissolving 1 mg of the compound in 1 mL of dimethylsulfoxide (DMSO) a 100-µL of aliquot of the tested compound solution was prepared. The inoculated plates were then incubated for bacteria and yeast for 24 h at 37 °C and fungi for 48 h at 28 °C. In order to dissolve the tested compound, the negative controls were prepared using DMSO. Amphotericin B (1 mg/mL), Ampicillin (1 mg/mL) and Gentamicin (1 mg/mL) have been used as bacterial and fungal standards, respectively. Antimicrobial activity was evaluated after incubation by measuring the inhibition zone against the microorganisms tested. Antimicrobial activity has been expressed in millimeters (mm) as inhibition diameter zones.

Additional files

Additional file 1: Figure S1. ^{1}H NMR, Mass and IR spectra of compound (**1**).

Additional file 2: Figure S2. ^{1}H NMR, Mass and IR spectra of compound (**2**).

Additional file 3: Figure S3. ^{1}H NMR, Mass and IR spectra of compound (**3**).

Additional file 4: Figure S4. ^{1}H NMR, Mass and IR spectra of compound (**4**).

Additional file 5: Figure S5. ^{1}H NMR, Mass and IR spectra of compound (**5**).

Additional file 6: Figure S6. ^{1}H NMR, Mass and IR spectra of compound (**6**).

Additional file 7: Figure S7. ^{1}H NMR, Mass and IR spectra of compound (**7**).

Additional file 8: Figure S8. ^{1}H NMR, Mass, and IR spectra of compound (**10a**).

Additional file 9: Figure S9. ^{1}H NMR, Mass and IR spectra of compound (**10b**).

Additional file 10: Figure S10. ^{1}H NMR, Mass and IR spectra of compound (**11a**).

Additional file 11: Figure S11. ^{1}H NMR, Mass, and IR spectra of compound (**11b**).

Additional file 12: Figure S12. ^{1}H NMR, Mass and IR spectra of compound (**12a**).

Additional file 13: Figure S13. ^{1}H NMR, Mass and IR spectra of compound (**12b**).

Additional file 14: Figure S14. ^{1}H NMR and Mass spectra of compound (**13**).

Additional file 15: Figure S15. ^{1}H NMR and Mass spectra of compound (**14**).

Additional file 16: Figure S16. ^{1}H NMR, Mass and IR spectra of compound (**15**).

Additional file 17: Figure S17. ^{1}H NMR and IR spectra of compound (**20a**).

Additional file 18: Figure S18. ^{1}H NMR and IR spectra of compound (**20b**).

Additional file 19: Figure S19. ^{1}H NMR and Mass spectra of compound (**20c**).

Additional file 20: Figure S20. ^{1}H NMR spectra of compound (**20d**).

Additional file 21: Figure S21. ^{1}H NMR and Mass spectra of compound (**21a**).

Additional file 22: Figure S22. ^{1}H NMR, Mass and IR spectra of compound (**21b**).

Additional file 23: Figure S23. ^{1}H NMR, Mass and IR spectra of compound (**22**).

Additional file 24: Figure S24. ^{1}H NMR, Mass and IR spectra of compound (**23**).

Additional file 25: Figure S25. ^{1}H NMR, Mass and IR spectra of compound (**25a**).

Additional file 26: Figure S26. ^{1}H NMR and Mass spectra of compound (**25b**).

Additional file 27: Figure S27. ^{1}H NMR and Mass spectra of compound (**25c**).

Abbreviations

NA: nutrient agar; SDA: sabouraud dextrose agar; mp: melting point; Mw: molecular weight; *AF*: *Aspergillus fumigatus*; *CA*: *Candida albicans*; *SP*: *Streptococcus pneumoniae*; *BS*: *Bacillis subtillis*; *PA*: *Pseudomonas aeruginosa*; *EC*: Escherichia coli.

Authors' contributions

AOA, IEES, YHZ, AMH, MAH, and MMM designed the research, performed the research, analyzed the data, wrote the paper. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and analyzed during the current study available from the corresponding author on reasonable request. And the samples are available from the authors.

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