Design, Synthesis, in Vitro Antioxidant, Anti-Inflammatory and Antidiabetic Evaluation of New N-Substitutedbenzylidene-5-(4-Formylphenyl)-(3-Hydroxyphenyl)-4,5-Dihydropyrazole-1-Carbothioamide Derivatives

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Abstract

A series of $N$-substitutedbenzylidene-5-(4-formylphenyl)-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide derivatives was designed, synthesized and examined for their therapeutical potential against prooxidant (oxidative stress), inflammation and diabetes. Biological results showed antioxidant activity with IC$_{50}$ value 37.68 mol/L, anti-inflammatory activity with IC$_{50}$ value 26.40 mol/L and antidiabetic activity with IC$_{50}$ value 17.12 mol/L. The results of antioxidant activity showed that compounds $Y_9$ and $Y_{17}$ exhibited excellent antioxidant activity with IC$_{50}$ values 17.43 mol/L and 18.98 mol/L, results of anti-inflammatory activity showed that compounds $Y_2$, $Y_3$ and $Y_7$ exhibited excellent anti-inflammatory activity with IC$_{50}$ values 23.23 mol/L, 22.09 mol/L and 19.05 mol/L respectively and results of antidiabetic activity showed that compounds $Y_1$, $Y_5$ and $Y_6$ exhibited excellent antidiabetic activity with IC$_{50}$ values 17.08 mol/L, 8.36 mol/L and 13.50 mol/L. When compared with ascorbic acid, aspirin and acarbose as standard drug respectively. Heterocyclic compounds have diversity in their structure which makes them broad and economical therapeutic agents. Pyrazole is a five membered ring containing three carbon and two neighboring nitrogen atoms. Pyrazole and its derivatives have various biological as well as clinical potential thus considered for further research. Due to wide range of therapeutical activities pyrazole makes interest among researcher to explore it further for more activities. Pyrazole is present in various biological moieties eg. antimicrobial, antidiabetic, anti-inflammatory, antioxidant, antiviral, anticonvulsant, anticancer, anti-HIV and anti-tuberculosis agents.

Introduction

Antioxidants protects against the oxidative stress and damage produced by ROS (reactive oxygen species). Living organisms have antioxidant defense systems that protects against oxidative damage by removal or repair of damaged molecules [1]. Oxidative stress occurs due to imbalance between the levels of ROS and antioxidants in living system. Free radicals form due to oxidation and high concentration of free radicals leads to precipitate pathological condition. At inflamed site, ROS like superoxide radical anion, hydrogen peroxide and hydroxyl radical are produced by leukocytes, where they synthesis prostaglandins and convert arachidonic acid into proinflammatory intermediates mediated by COX (cyclooxygenase) and LOX (lipoxygenase) [2]. Oxidative stress has been implicated in pathological conditions of various diseases such as inflammation, cancer, dementia and physiological aging. Role of antioxidant as pharmacotherapy has been emerged to minimize the bimolecular damage caused by ROS attack on vital constituents of living organisms.

Persistent increase in blood glucose level leads to Diabetes Mellitus (DM). DM is basically of two types; Type-1 i.e., Insulin dependent and Type-2 i.e., Insulin independent. DM is a syndrome having symptoms like abnormality in lipoprotein, elevated basal metabolic rate and blood glucose level, decrease in the ROS scavenging enzymes leads to increase in oxidative stress which destruct pancreatic beta cells. It has been indicated that increase in blood glucose level cause oxidative stress which may add up in the
pathogenesis of further diabetic complications. Oxidative stress, occurs due to increase in free radical concentration, damages various organs and affecting normal biological functioning [3].

Pain is an unpleasant sensation. Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stage. Non Steroidal Anti-inflammatory Drugs (NSAIDs) are used to treat pain due to inflammation. The main target of NSAIDs is to inhibit COX. There are two isoforms of COX i.e., COX-1 and COX-2 present in almost all the tissues. COX-1 is responsible for prostaglandins production whereas COX-2 is responsible for the increased production of prostaglandins during inflammation [4]. Inhibition of COX-2 should be specific as COX-1 inhibition may leads to alter its housekeeping function [5,6].

Pyrazole is a heterocyclic compound containing five membered ring and has various therapeutical intensity because of its biological and synthetic applications. A number of pyrazole derivatives have been reported for many therapeutical effects such as antimicrobial [7], antidiabetic [8], antioxidant [9], anti-inflammatory [10,11], antituberculosis [12], anticancer [13], analgesics [14], antiepileptic [15], antihypertensive [16], ulcerogenic [17]. Due to its wide range of therapeutic effects it attracts researcher to explore it further for its potential as therapeutic agent in various disease.

\[
\begin{align*}
&\text{Pyrazole moiety} \\
&\text{Chemistry} \\
\end{align*}
\]

Results And Discussion

Chemistry

In the research work, we have synthesized new series of \(N\)-substitutedbenzylidene-5-(4-formylphenyl)-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide analogues using direct condensation of aromatic aldehydes and substituted acetophenone. Synthetic steps of this series have been shown in Scheme-1. The structure of synthesized derivatives was examined by \(^1\text{H-NMR}\), FT-IR, MS and Elemental analysis. In Table 1, physiochemical properties of pyrazole derivatives have been presented. The physiochemical properties included molecular formula, molecular weight, melting points, percentage yield and \(R_f\) value of synthesized analogues.

Antioxidant activity

The antioxidant activity of the newly synthesized analogues was examined by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay using free radical scavenging method (spectrophotometrically). DPPH, on reaction with hydrogen donors, a free radical with maximal absorption at 517 nm is reduced to hydrazine
(corresponding compound) indicating deep violet color of DPPH change to yellow, showing a considerable decrease in absorption. DPPH solution (3 μg/ml) was prepared in methanol and DPPH (in 1:1) solution was used for blank reference. 25 μg/ml, 50 μg/ml, 75 μg/ml, 100 μg/ml of each synthesized analogues and ascorbic acid (standard) was prepared in methanol. Then, equal amount of each concentration and DPPH was taken in a test tube. Afterwards, absorbance was taken at 517 nm by UV spectrophotometer of the solution mixture by stirring it for 5 min and stored at dark place for half an hour at room temperature [18]. The % inhibition was evaluated as follow

\[
\text{% Inhibition} = \frac{A_{\text{Control}} - A_{\text{Sample}}}{A_{\text{Control}}} \times 100
\]

Where,

- \(A_{\text{Control}}\) = absorbance of the control reaction.
- \(A_{\text{Sample}}\) = absorbance of the test compound.

IC\(_{50}\) value was calculated from the graph shown in Figures 3-5 which indicates % inhibition and synthesized compounds. The results of antioxidant activity explained that compounds Y\(_9\) and Y\(_{17}\) having maximum in vitro antioxidant potency with IC\(_{50}\) values 17.43 mol/L and 18.98 mol/L, in comparison with ascorbic acid (standard drug). The presented results are showing in Table 2.

**Antidiabetic activity**

All the synthesized derivatives were investigate for the \(\alpha\)-amylase inhibitory activity by using diastase based on colorimetric method [19]. For preparing enzyme solution, 1 mg diastase (amylase enzyme) was taken in 100 mL of 20 mM phosphate buffer. 25 μg/ml, 50 μg/ml, 75 μg/ml, 100 μg/ml concentration of synthesized compounds was prepared in DMSO. 0.25g potato starch was taken and adding in 50 mL of 20 mM phosphate buffer for potato starch solution by heating 15 min. The colour reagent was prepared by mixing 20 mL of 96 mM 3,5 dinitrosalicylic acid with 5.31 M sodium potassium tartrate in 8 mL of 2 M sodium hydroxide and 12 mL distilled water. After preparation of valuable solutions that needed for activity, 1 mL of synthesized derivatives solution and 1 mL of enzyme solution incubated in 25 °C temp. for 10 min. After that taken 1 mL of this mixture and added 1 mL of potato starch solution in test tube, incubated in 25 °C temp. for 10 min. Then test tubes was closed after adding 1 mL colour reagent and placed at water bath at 85 °C for 15 min. When reaction mixture was cooled diluted with 9 mL of distilled water and taken absorbance at 540 nm in UV spectrophotometer. % inhibition was calculated as follow.
% Inhibition = \frac{A_{Control} - A_{Sample}}{A_{Control}} \times 100 \quad \text{Equation 1}

IC_{50} value was calculated from the graph shown in Figures 6-8 which indicates % inhibition and synthesized compound. The evaluation of antidiabetic activity explain that compounds \(Y_1, Y_5\) and \(Y_6\) exhibited excellent antidiabetic potency with IC_{50} values 17.08 mol/L, 08.36 mol/L and 13.50 mol/L respectively, in comparison with acarbose (standard drug). The presented results are showing in Table 3.

**Anti-inflammatory activity**

All the synthesized derivatives were investigated for the protein albumin denaturation [20,21]. Different concentration of test compounds was prepared (10 \(\mu\)g/ml, 30 \(\mu\)g/ml, 50 \(\mu\)g/ml, 70 \(\mu\)g/ml and 100 \(\mu\)g/ml) in methanol. After preparation of test samples 1 % aqueous solution of bovine albumin serum in 0.05 M tris buffer saline and pH (7.6 at 25 °C) of reaction mixture was adjusted by adding small amount of 1 N HCl. The blank solution was taken is methanol. Then equal amount of test and protein was taken in the test tube and incubated for 20 min. at 37 °C. After incubation the reaction mixture was heated for 20 min. at 57 °C temperature and cooling the reaction mixture, the turbidity was measured at 660 nm in UV spectrophotometer. Percent inhibition of protein denaturation was calculated as follows:

% Inhibition = \frac{A_{Control} - A_{Sample}}{A_{Control}} \times 100 \quad \text{Equation 1}

IC_{50} value was calculated from the graph shown in Figures 9-11 which indicates % inhibition and synthesized compound. The results of anti-inflammatory activity showed that compounds \(Y_2, Y_3\) and \(Y_7\) exhibited excellent anti-inflammatory activity with IC_{50} values 23.23 mol/L, 22.09 mol/L and 19.05 mol/L respectively, in comparison with aspirin (standard drug). The presented results are showing in Table 4.

**SAR (Structure Activity Relationship) studies:**

From the antioxidant, antidiabetic and anti-inflammatory testing evaluation of newly synthesized \(N\)-substitutedbenzylidene-5-(4-formylphenyl)-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide derivatives, the ensuing structure activity relationship showed in fig 12.

1. Presence of electron withdrawing and releasing group (-OH and -Cl, Compounds \(Y_9\) and \(Y_{17}\)) on benzylidene portion enhanced the antioxidant potency of the synthesized compounds.
2. Presence of electron withdrawing and releasing group (-CHO and -OCH_3, Compounds \(Y_1, Y_5\) and \(Y_6\)) on benzylidene portion enhanced the antidiabetic activity and (Compounds \(Y_2, Y_3\) and \(Y_7\)) anti-inflammatory activity of the synthesized compounds.
**Experimental section**

In Scheme-1, synthetic procedure of pyrazole derivatives has been explained. The scheme was drawn via ChemDraw Ultra 8.03. The completion of reaction was examined by TLC (Thin Layer Chromatography) by using silica gel glass plate. Open capillary tube method was used to examine melting point of synthesized analogues. Attenuated total reflection (ATR-IR) spectrophotometer of Bruker FTIR 12060280 (Software: OPUS 7.2.139.1294) was used for evaluating chemical structure of synthesized analogues by recording IR spectra. Bruker Avance III 600 NMR spectrometer was used for $^1$H/$^{13}$CNMR (Nuclear Magnetic Resonance). The spectra was recorded in ppm ($\delta$) with suitable deuterated solvent like DMSO and internal solvent like tetramethyl silane and data have shown s, singlet; d, doublet; t, triplet; m, multiplet (multiplicity), number of proton and carbon values. Mass spectra were recorded by Waters Micromass Q-ToF Micro spectrophotometer. Perkin-Elmer 2400 was used for elemental analysis.

**General procedure for the synthesis of N-substitutedbenzylidene-5-(4-formylphenyl)-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide derivatives ($Y_1$-$Y_{26}$)**

**Step I: Synthesis of 4-(3-(4-hydroxyphenyl)-3-oxoprop-1-enyl)benzaldehyde (intermediate 1)**

An equal quantity of 4-hydroxy acetophenone and terephthaldehyde (0.01 mol) was taken in a 20 mL ethanol and stirred for few minutes until it get mixed. A 10 mL fraction of 40% aqueous solution of KOH was prepared and slowly mixed drop wise in a reaction mixture. The reaction mixture stirred for a day at room temperature. When reaction was completed, the reaction mixture was acidied with diluted HCl and precipitate was formed, collected by filtration. The completion of reaction was monitored by using TLC.

**Step II: Synthesis of 3,5-bis(4-hydroxyphenyl)-4,5-dihydropyrazole-1-caebothioamide (intermediate 2)**

A mixture of intermediate 1 (0.01 mol), thiosemicarbazide (0.01 mol) and KOH (0.0025 mol) in 50 mL ethanol were taken in RBF and refluxed for 72 hours. When reaction was completed, the reaction mixture was acidified with HCl and to yield solid precipitate, filtered, washed out by water, dried and recrystallized with ethanol. By using TLC, reaction completion was examined [22].

**Step III: Synthesis of N-substitutedbenzylidene-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide derivatives**

A mixture of intermediate 2 (0.01 mol), substituted benzaldehyde (0.01 mol) in 50 mL ethanol were taken in RBF and refluxed for some time then 1 mL glacial acetic acid was added drop wise in a reaction mixture and refluxed for 48 hours. When reaction was completed, the resulting mixture was cooled, poured in water to yield solid precipitate, filtered, dried and recrystallized with ethanol. By using TLC, reaction completion was examined.

**Spectral data of synthesized pyrimidine derivatives**
Compound Y₁: 5-(4-Formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3135 (C-H str., benzene), 1438 (C=C str., benzene), 1359 (C=N str., pyrazole moiety), 1088 (N-N str., pyrazole moiety), 1274 (C-N str., carbonyl), 3225 (OH str., aromatic), 1749 (CHO str., aromatic), 1217 (C=S str., aliphatic), 3012 (NH₂ str., aliphatic);

¹H NMR: 6.81-7.76 (s, 8H, Ar-H), 1.95-4.01 (s, 3H, pyrazole), 9.12 (s, 1H, Ar-CHO), 5.02 (s, 1H, Ar-OH), 2.12 (s, 1H, amine); ¹³C-NMR: 40.3, 66.5, 115.2, 118.2, 121.9, 127.6, 129.8, 130.5, 134.8, 135.5, 149.5, 151.9, 168.7, 173.3, 191.5; MS ES + (ToF): m/z 326 [M⁺+1].

Compound Y₂: (E)-N-(4-Formylbenzylidene)-5-(4-formylphenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3153 (C-H str., benzene), 1599 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1090 (N-N str., pyrazole moiety), 1278 (C-N str., carbonyl), 3503 (OH str., aromatic), 1751 (CHO str., aromatic), 1215 (C=S str., aliphatic), 1619 (C=C str., aliphatic), 1028 (-NH- str., aliphatic); ¹H NMR: 6.52-8.24 (s, 8H, Ar-H), 1.81-3.82 (s, 3H, pyrazole), 9.82 (s, 1H, Ar-CHO), 5.12 (s, 1H, Ar-OH), 8.12 (s, 1H, CH (aliphatic)); ¹³C-NMR: 40.5, 66.9, 115.3, 118.3, 121.7, 127.5, 129.2, 130.3, 134.9, 135.6, 149.3, 151.3, 163.4, 168.6, 187.3, 191.3; MS ES + (ToF): m/z 440 [M⁺+1].

Compound Y₃: (E)-N-(3-Formylbenzylidene)-5-(4-formylphenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3146 (C-H str., benzene), 1592 (C=C str., benzene), 1358 (C=N str., pyrazole moiety), 1090 (N-N str., pyrazole moiety), 1274 (C-N str., carbonyl), 3202 (OH str., aromatic), 1746 (CHO str., aromatic), 1228 (C=S str., aliphatic), 1647 (C=C str., aliphatic), 1015 (-NH- str., aliphatic); ¹H NMR: 6.02-8.54 (s, 8H, Ar-H), 2.08-3.42 (s, 3H, pyrazole), 9.72 (s, 1H, Ar-CHO), 5.32 (s, 1H, Ar-OH), 8.02 (s, 1H, CH (aliphatic)); ¹³C-NMR: 40.0, 66.3, 115.0, 118.5, 121.6, 127.9, 129.1, 130.4, 132.1, 134.8, 135.6, 137.0, 149.5, 151.1, 163.5, 168.7, 187.2, 191.5; MS ES + (ToF): m/z 442 [M⁺+1].

Compound Y₄: (E)-N-(4-Hydroxy-3-methoxybenzylidene)-5-(4-formylphenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3144 (C-H str., benzene), 1592 (C=C str., benzene), 1356 (C=N str., pyrazole moiety), 1088 (N-N str., pyrazole moiety), 1275 (C-N str., carbonyl), 3202 (OH str., aromatic), 1716 (CHO str., aromatic), 1218 (C=S str., aliphatic), 1650 (C=C str., aliphatic), 1028 (-NH- str., aliphatic), 2852 (C-OCH₃ str., aromatic); ¹H NMR: 6.02-8.27 (s, 8H, Ar-H), 1.01-3.18 (s, 3H, pyrazole), 9.22 (s, 1H, Ar-CHO), 5.15 (s, 1H, Ar-OH), 8.14 (s, 1H, CH (aliphatic)); ¹³C-NMR: 40.5, 56.5, 66.5, 114.3, 115.5, 117.2, 118.7, 121.8, 122.7, 127.6, 129.8, 130.7, 134.2, 135.8, 149.5, 151.8, 163.3, 168.9, 187.0, 191.4; MS ES + (ToF): m/z 460 [M⁺+1].

Compound Y₅: (E)-N-(3-Methoxybenzylidene)-5-(4-formylphenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3077 (C-H str., benzene), 1600 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1275 (C-N str., carbonyl), 3506 (OH str., aromatic), 1752 (CHO str., aromatic), 1221 (C=S str., aliphatic), 1691 (C=C str., aliphatic), 1029 (-NH- str., aliphatic), 2845 (C-OCH₃ str., aromatic); ¹H NMR: 6.22-8.00 (s, 8H, Ar-H), 1.00-3.21 (s, 3H, pyrazole), 9.54 (s, 1H, Ar-CHO), 5.55 (s,
 Compound Y₆: (E)-N(4-Methoxybenzylidene)-5-(4-formylphenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3085 (C-H str., benzene), 1601 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1276 (C-N str., carbonyl), 3205 (OH str., aromatic), 1793 (CHO str., aromatic), 1219 (C=S str., aliphatic), 1651 (C=C str., aliphatic), 1028 (-NH- str., aliphatic), 2820 (C-OCH₃ str., aromatic); ¹H NMR: 6.24-8.25 (s, 8H, Ar-H), 1.04-3.38 (s, 3H, pyrazole), 9.62 (s, 1H, Ar-CHO), 5.65 (s, 1H, Ar-OH), 8.54 (s, 1H, CH (aliphatic)); ¹³C-NMR: 40.9, 56.2, 66.1, 113.3, 115.5, 116.7, 119.0, 121.5, 127.5, 129.8, 130.0, 134.2, 135.6, 149.3, 151.6, 160.4, 163.6, 187.9, 191.9; MS ES + (ToF): m/z 444 [M⁺+1].

 Compound Y₇: (E)-N(2-Methoxybenzylidene)-5-(4-formylphenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3125 (C-H str., benzene), 1600 (C=C str., benzene), 1358 (C=N str., pyrazole moiety), 1167 (N-N str., pyrazole moiety), 1279 (C-N str., carbonyl), 3511 (OH str., aromatic), 1747 (CHO str., aromatic), 1219 (C=S str., aliphatic), 1652 (C=C str., aliphatic), 1021 (-NH- str., aliphatic), 2836 (C-OCH₃ str., aromatic); ¹H NMR: 6.62-8.71 (s, 8H, Ar-H), 1.61-3.43 (s, 3H, pyrazole), 9.62 (s, 1H, Ar-CHO), 5.45 (s, 1H, Ar-OH), 8.44 (s, 1H, CH (aliphatic)); ¹³C-NMR: 44.5, 55.7, 66.4, 114.7, 115.2, 118.1 121.4, 126.7, 127.0, 129.4, 130.8, 134.7, 135.9, 149.4, 151.2, 163.1, 187.5, 191.0; MS ES + (ToF): m/z 442 [M⁺+1].

 Compound Y₈: (E)-N(3,4-Dimethoxybenzylidene)-5-(4-formylphenyl)-3-(4-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3116 (C-H str., benzene), 1597 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1272 (C-N str., carbonyl), 3204 (OH str., aromatic), 1770 (CHO str., aromatic), 1222 (C=S str., aliphatic), 1645 (C=C str., aliphatic), 1017 (-NH- str., aliphatic), 2800 (C-OCH₃ str., aromatic); ¹H NMR: 6.21-7.99 (s, 8H, Ar-H), 1.51-3.17 (s, 3H, pyrazole), 9.72 (s, 1H, Ar-CHO), 5.55 (s, 1H, Ar-OH), 8.54 (s, 1H, CH (aliphatic)); ¹³C-NMR: 41.0, 65.2, 66.2, 114.4, 115.4, 118.8, 121.9, 122.5, 127.1, 129.6, 130.4, 134.4, 135.7, 149.9, 151.1, 152.2, 168.5, 187.5, 191.4; MS ES + (ToF): m/z 472 [M⁺+1].

 Compound Y₉: (E)-N(4-Hydroxybenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3091 (C-H str., benzene), 1600 (C=C str., benzene), 1358 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1277 (C-N str., carbonyl), 3514 (OH str., aromatic), 1755 (CHO str., aromatic), 1220 (C=S str., aliphatic), 1646 (C=C str., aliphatic), 1028 (-NH- str., aliphatic); ¹H NMR: 6.23-7.99 (s, 8H, Ar-H), 1.81-3.58 (s, 3H, pyrazole), 9.72 (s, 1H, Ar-CHO), 5.18 (s, 1H, Ar-OH), 8.64 (s, 1H, CH (aliphatic)); ¹³C-NMR: 41.0, 65.2, 115.9, 116.2, 119.4, 122.2, 126.4, 127.9, 129.4, 131.1, 134.4, 135.9, 149.4, 152.1, 160.7, 162.6, 167.3, 187.9, 191.6; MS ES + (ToF): m/z 430 [M⁺+1].

 Compound Y₁₀: (E)-N(3-Nitrobenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3137 (C-H str., benzene), 1596 (C=C str., benzene), 1355 (C=N str., pyrazole moiety), 1167 (N-N str., pyrazole moiety), 1280 (C-N str., carbonyl), 3509 (OH str., aromatic), 1735 (CHO str., aromatic), 1219 (C=S str., aliphatic), 1651 (C=C str., aliphatic), 1028 (-NH- str., aliphatic); ¹H NMR: 7.28-8.10 (s, 8H, Ar-H), 1.47-3.25 (s, 3H, pyrazole), 9.62 (s, 1H, Ar-CHO), 5.65 (s, 1H, Ar-OH), 8.54 (s, 1H, CH (aliphatic)); ¹³C-NMR: 41.0, 56.2, 115.9, 116.2, 119.4, 122.2, 126.4, 127.9, 129.4, 131.1, 134.4, 135.9, 149.4, 152.1, 160.7, 162.6, 167.3, 187.9, 191.6; MS ES + (ToF): m/z 430 [M⁺+1].
aromatic), 1215 (C=S str., aliphatic), 1689 (C=C str., aliphatic), 1003 (-NH- str., aliphatic), 1509 (C-NO$_2$ str., aromatic);

$^1$H NMR: 6.72-8.21 (s, 8H, Ar-H), 1.96-3.32 (s, 3H, pyrazole), 9.82 (s, 1H, Ar-CHO), 5.19 (s, 1H, Ar-OH), 8.74 (s, 1H, CH (aliphatic)); $^{13}$C-NMR: 40.9, 66.9, 155.7, 118.3, 121.2, 123.9, 124.4, 127.9, 129.0, 130.9, 134.4, 135.7, 148.2, 149.9, 152.1, 164.0, 168.9, 187.4, 191.2; MS ES + (ToF): m/z 457[M$^+$+1].

Compound Y$_11$: (E)-N-(2-Nitrobenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3121 (C-H str., benzene), 1602 (C=C str., benzene), 1343 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1277 (C-N str., carbonyl), 3520 (OH str., aromatic), 1746 (CHO str., aromatic), 1218 (C=S str., aliphatic), 1651 (C=C str., aliphatic), 1028 (-NH- str., aliphatic), 1574 (C-NO$_2$ str., aromatic)

$^1$H NMR: 6.52-8.25 (s, 8H, Ar-H), 1.97-3.98 (s, 3H, pyrazole), 9.82 (s, 1H, Ar-CHO), 5.13 (s, 1H, Ar-OH), 8.18 (s, 1H, CH (aliphatic)); $^{13}$C-NMR: 40.9, 66.1, 115.3, 118.5, 121.2, 123.9, 124.5, 127.2, 129.5, 130.1, 135.2, 135.8, 148.7, 149.5, 150.6, 151.6, 163.2, 168.3, 187.2, 191.0; MS ES + (ToF): m/z 458 [M$^+$+1].

Compound Y$_12$: (E)-N-(4-Nitrobenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3145 (C-H str., benzene), 1601 (C=C str., benzene), 1342 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1277 (C-N str., carbonyl), 3207 (OH str., aromatic), 1731 (CHO str., aromatic), 1217 (C=S str., aliphatic), 1651 (C=C str., aliphatic), 1029 (-NH- str., aliphatic), 1574 (C-NO$_2$ str., aromatic)

$^1$H NMR: 6.62-8.97 (s, 8H, Ar-H), 2.01-3.90 (s, 3H, pyrazole), 9.20 (s, 1H, Ar-CHO), 5.14 (s, 1H, Ar-OH), 8.19 (s, 1H, CH (aliphatic)); $^{13}$C-NMR: 40.5, 66.9, 115.5, 118.8, 121.0, 123.6, 124.4, 126.3, 127.5, 129.0, 130.7, 132.4, 134.7, 135.3, 148.9, 149.4, 151.8, 163.5, 168.0, 187.0, 190.9; MS ES + (ToF): m/z 459 [M$^+$+1].

Compound Y$_13$: (E)-N-(3-Bromobenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3147 (C-H str., benzene), 1595 (C=C str., benzene), 1356 (C=N str., pyrazole moiety), 1167 (N-N str., pyrazole moiety), 1276 (C-N str., carbonyl), 3206 (OH str., aromatic), 1748 (CHO str., aromatic), 1217 (C=S str., aliphatic), 1650 (C=C str., aliphatic), 1017 (-NH- str., aliphatic), 617 (C-Br str., aromatic)

$^1$H NMR: 6.23-8.21 (s, 8H, Ar-H), 1.05-3.08 (s, 3H, pyrazole), 9.02 (s, 1H, Ar-CHO), 5.16 (s, 1H, Ar-OH), 8.20 (s, 1H, CH (aliphatic)); $^{13}$C-NMR: 40.9, 66.5, 115.5, 118.4, 121.7, 123.7, 127.3, 128.5, 129.2, 130.1, 131.5, 134.6, 135.6, 149.2, 151.2, 163.0, 187.5, 191.9; MS ES + (ToF): m/z 491 [M$^+$+1].

Compound Y$_14$: (E)-N-(4-Bromobenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3152 (C-H str., benzene), 1588 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1167 (N-N str., pyrazole moiety), 1277 (C-N str., carbonyl), 3208 (OH str., aromatic), 1739 (CHO str,
1 H NMR: 6.24-8.22 (s, 8H, Ar-H), 1.06-3.28 (s, 3H, pyrazole), 9.31 (s, 1H, Ar-CHO), 5.17 (s, 1H, Ar-OH), 8.02 (s, 1H, CH (aliphatic)); 13 C-NMR: 40.3, 66.6, 115.8, 118.0, 121.3, 123.8, 127.6, 128.3, 129.8, 130.2, 131.6, 134.5, 135.9, 149.7, 151.8, 163.6, 187.6, 191.8; MS ES + (ToF): m/z 493 [M^+1].

Compound Y_{15}: (E)-N-(2-Chlorobenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3152 (C-H str., benzene), 1591 (C=C str., benzene), 1358 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1278 (C-N str., carbonyl), 3248 (OH str., aromatic), 1747 (CHO str., aromatic), 1218 (C=S str., aliphatic), 1650 (C=C str., aliphatic), 1049 (-NH- str., aliphatic), 718 (C-Cl str., aromatic);

1 H NMR: 6.34-8.32 (s, 8H, Ar-H), 1.07-3.38 (s, 3H, pyrazole), 9.33 (s, 1H, Ar-CHO), 5.18 (s, 1H, Ar-OH), 8.06 (s, 1H, CH (aliphatic)); 13 C-NMR: 41.3, 65.9, 114.3, 117.5,120.9, 127.5, 129.5, 130.4, 132.9, 133.9, 134.5, 135.7, 149.4, 151.8, 163.5, 187.0, 191.3; MS ES + (ToF): m/z 446 [M^+1].

Compound Y_{16}: (E)-N-(3-Chlorobenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3147 (C-H str., benzene), 1599 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1278 (C-N str., carbonyl), 3215 (OH str., aromatic), 1725 (CHO str., aromatic), 1220 (C=S str., aliphatic), 1659 (C=C str., aliphatic), 1012 (-NH- str., aliphatic), 703 (C-Cl str., aromatic);

1 H NMR: 6.34-8.52 (s, 8H, Ar-H), 2.06-3.29 (s, 3H, pyrazole), 9.33 (s, 1H, Ar-CHO), 5.12 (s, 1H, Ar-OH), 8.16 (s, 1H, CH (aliphatic)); 13 C-NMR: 40.3, 66.9, 114.9, 117.9, 120.0, 127.6, 129.3, 130.8, 132.3, 133.5, 134.8, 135.3, 149.1, 151.0, 163.2, 187.9, 191.5; MS ES + (ToF): m/z 445 [M^+1].

Compound Y_{17}: (E)-N-(4-Chlorobenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3147 (C-H str., benzene), 1599 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1278 (C-N str., carbonyl), 3215 (OH str., aromatic), 1725 (CHO str., aromatic), 1220 (C=S str., aliphatic), 1659 (C=C str., aliphatic), 1012 (-NH- str., aliphatic), 709 (C-Cl str., aromatic);

1 H NMR: 6.44-8.24 (s, 8H, Ar-H), 1.26-3.20 (s, 3H, pyrazole), 9.71 (s, 1H, Ar-CHO), 5.37 (s, 1H, Ar-OH), 8.22 (s, 1H, CH (aliphatic)); 13 C-NMR: 41.6, 65.2, 115.3, 118.5, 121.9, 127.9, 129.3, 130.8, 132.0, 133.1, 134.6, 135.4, 149.7, 151.2, 163.9, 187.7, 191.0; MS ES + (ToF): m/z 448 [M^+1].

Compound Y_{18}: (E)-N-(2,4-Dichlorobenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3059 (C-H str., benzene), 1602 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1279 (C-N str., carbonyl), 3203 (OH str., aromatic), 1725
(CHO str., aromatic), 1218 (C=S str., aliphatic), 1656 (C=C str., aliphatic), 1049 (-NH- str., aliphatic), 719 (C-Cl str., aromatic);

\(^{1}H\) NMR: 6.44-7.92 (s, 8H, Ar-H), 2.16-3.28 (s, 3H, pyrazole), 8.99 (s, 1H, Ar-CHO), 5.15 (s, 1H, Ar-OH), 8.52 (s, 1H, CH (aliphatic)); \(^{13}C\) NMR: 40.9, 66.0, 115.4, 118.9, 121.5, 127.3, 129.7, 130.9, 132.1, 133.6, 134.6, 135.7, 149.8, 151.9, 163.9, 187.9, 191.0; MS ES + (ToF): m/z 482 [M\(^{+}\),MS + (ToF): m/z 482 [M\(^{+}\)].

**Compound Y\(_{19}\):** (E)-N-(2-Hydroxy-4-methoxybenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3151 (C-H str., benzene), 1592 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1275 (C-N str., carbonyl), 1502 (OH str., aromatic), 1746 (CHO str., aromatic), 1223 (C=S str., aliphatic), 1650 (C=C str., aliphatic), 1031 (-NH- str., aliphatic), 2854 (OCH\(_3\) str., aromatic);

\(^{1}H\) NMR: 5.99-8.02 (s, 8H, Ar-H), 1.66-3.08 (s, 3H, pyrazole), 9.42 (s, 1H, Ar-CHO), 5.02 (s, 1H, Ar-OH), 8.52 (s, 1H, CH (aliphatic)); \(^{13}C\) NMR: 40.9, 55.3, 66.9, 102.4, 107.2, 110.9, 115.5, 118.4, 121.8, 127.6, 129.5, 130.0, 131.6, 134.7, 135.9, 149.9, 152.0, 163.6, 164.9, 168.6, 187.0, 191.7; MS ES + (ToF): m/z 460 [M\(^{+}\), MS ES + (ToF): m/z 460 [M\(^{+}\)].

**Compound Y\(_{20}\):** (E)-N-(4-(Dimethylamino)benzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3155 (C-H str., benzene), 1588 (C=C str., benzene), 1356 (C=N str., pyrazole moiety), 1167 (N-N str., pyrazole moiety), 1276 (C-N str., carbonyl), 3207 (OH str., aromatic), 1740 (CHO str., aromatic), 1229 (C=S str., aliphatic), 1650 (C=C str., aliphatic), 1031 (-NH- str., aliphatic), 2818 (C-(CH\(_3\))\(_2\)N str., aromatic); \(^{1}H\) NMR: 6.74-8.45 (s, 8H, Ar-H), 1.72-3.42 (s, 3H, pyrazole), 9.26 (s, 1H, Ar-CHO), 5.37 (s, 1H, Ar-OH), 8.42 (s, 1H, CH (aliphatic)); \(^{13}C\) NMR: 40.3, 66.3, 114.5, 115.9, 118.4, 121.8, 127.6, 129.5, 130.0, 131.6, 134.7, 135.9, 149.9, 152.0, 162.2, 163.6, 164.9, 168.6, 187.0, 191.7; MS ES + (ToF): m/z 457 [M\(^{+}\), MS ES + (ToF): m/z 457 [M\(^{+}\)].

**Compound Y\(_{21}\):** (E)-N-(4-(Diethylamino)benzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3139 (C-H str., benzene), 1586 (C=C str., benzene), 1352 (C=N str., pyrazole moiety), 1170 (N-N str., pyrazole moiety), 1274 (C-N str., carbonyl), 3207 (OH str., aromatic), 1721 (CHO str., aromatic), 1245 (C=S str., aliphatic), 1654 (C=C str., aliphatic), 1032 (-NH- str., aliphatic); \(^{1}H\) NMR: 6.92-8.42 (s, 8H, Ar-H), 1.72-3.25 (s, 3H, pyrazole), 9.27 (s, 1H, Ar-CHO), 5.27 (s, 1H, Ar-OH), 8.47 (s, 1H, CH (aliphatic)); \(^{13}C\) NMR: 13.5, 91.2, 40.6, 44.7, 66.6, 114.3, 115.9, 118.4, 121.1, 123.5, 127.3, 129.4, 130.2, 13.4, 135.2, 139.4, 148.5, 151.9, 163.6, 187.0, 191.2; MS ES + (ToF): m/z 483 [M\(^{+}\), MS ES + (ToF): m/z 483 [M\(^{+}\)].

**Compound Y\(_{22}\):** (E)-N-((E)-4-(4-(4-Styrylbenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3058 (C-H str., benzene), 1598 (C=C str., benzene), 1354 (C=N str., pyrazole moiety), 1169 (N-N str., pyrazole moiety), 1278 (C-N str., carbonyl), 3202 (OH str., aromatic), 1763 (CHO str., aromatic), 1169 (C=S str., aliphatic), 1693 (C=C str., aliphatic), 1031 (-NH- str., aliphatic); \(^{1}H\) NMR: 7.24-8.47 (s, 8H, Ar-H), 1.92-3.27 (s, 3H, pyrazole), 9.54 (s, 1H, Ar-CHO), 5.22 (s, 1H, Ar-OH), 8.23 (s,
1H, CH (aliphatic)); $^{13}$C-NMR: 44.3, 66.2, 115.3, 118.2, 119.5, 121.1, 126.3, 127.5, 128.5, 129.6, 130.0, 134.6, 135.9, 140.7, 149.9, 151.0, 163.7, 168.0, 187.7, 191.9; MS ES + (ToF): m/z 516 [M$^+$+1].

**Compound Y$_{23}$**: (E)-N-(3-Methylbenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3153 (C-H str., benzene), 1589 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1277 (C-N str., carbonyl), 3202 (OH str., aromatic), 1721 (CHO str., aromatic), 1237 (C=S str., aliphatic), 1641 (C=C str., aliphatic), 1016 (-NH- str., aliphatic), 3011 (CH$_3$ str., aromatic);

$^1$H NMR: 6.28-8.86 (s, 8H, Ar-H), 1.97-3.25 (s, 3H, pyrazole), 9.24 (s, 1H, Ar-CHO), 5.32 (s, 1H, Ar-OH), 8.13 (s, 1H, CH (aliphatic)); $^{13}$C-NMR: 24.5, 44.0, 65.9, 116.2, 119.9, 121.0, 127.4, 129.8, 129.9, 130.8, 134.5, 135.9, 140.7, 149.5, 151.9, 163.7, 168.2, 187.7, 191.3; MS ES + (ToF): m/z 426 [M$^+$+1].

**Compound Y$_{24}$**: (E)-N-(3,4,5-Trimethoxybenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3154 (C-H str., benzene), 1595 (C=C str., benzene), 1356 (C=N str., pyrazole moiety), 1168 (N-N str., pyrazole moiety), 1269 (C-N str., carbonyl), 3206 (OH str., aromatic), 1722 (CHO str., aromatic), 1238 (C=S str., aliphatic), 1265 (C=C str., aliphatic), 1017 (-NH- str., aliphatic), 2859 (OCH$_3$ str., aromatic);

$^1$H NMR: 6.65-8.87 (s, 8H, Ar-H), 1.98-3.24 (s, 3H, pyrazole), 9.52 (s, 1H, Ar-CHO), 5.66 (s, 1H, Ar-OH), 8.21 (s, 1H, CH (aliphatic)); $^{13}$C-NMR: 40.3, 56.6, 66.3, 106.6, 115.9, 118.5, 121.3, 127.5, 128.9, 129.1, 130.9, 134.2, 135.7, 149.4, 150.3, 151.9, 164.1, 168.3, 187.7, 192.0; MS ES + (ToF): m/z 504 [M$^+$+1].

**Compound Y$_{25}$**: (E)-N-(2,6-Dichlorobenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3128 (C-H str., benzene), 1592 (C=C str., benzene), 1356 (C=N str., pyrazole moiety), 1169 (N-N str., pyrazole moiety), 1274 (C-N str., carbonyl), 3505 (OH str., aromatic), 1739 (CHO str., aromatic), 1216 (C=S str., aliphatic), 1641 (C=C str., aliphatic), 1016 (-NH- str., aliphatic), 709 (C-Cl str., aromatic);

$^1$H NMR: 6.29-8.18 (s, 8H, Ar-H), 1.29-3.27 (s, 3H, pyrazole), 9.28 (s, 1H, Ar-CHO), 5.26 (s, 1H, Ar-OH), 8.04(s, 1H, CH (aliphatic)); $^{13}$C-NMR: 40.1, 66.4, 115.0, 118.2, 121.8, 127.5, 129.7, 130.3, 131.9, 133.9, 134.9, 135.4, 149.3, 151.8, 163.7, 168.9, 187.0, 191.1; MS ES + (ToF): m/z 481 [M$^+$+1].

**Compound Y$_{26}$**: (E)-N-(3-Hydroxybenzylidene)-5-(4-formylphenyl)-3-(3-hydroxyphenyl)-4,5-dihydropyrazole-1-carbothioamide, IR: 3024 (C-H str., benzene), 1602 (C=C str., benzene), 1357 (C=N str., pyrazole moiety), 1167 (N-N str., pyrazole moiety), 1278 (C-N str., carbonyl), 3505 (OH str., aromatic), 1727 (CHO str., aromatic), 1220 (C=S str., aliphatic), 1649 (C=C str., aliphatic), 1031 (-NH-str., aliphatic); $^1$H-NMR: 6.92-8.91 (s, 8H, Ar-H), 1.21-3.77 (s, 3H, pyrazole), 9.87 (s, 1H, Ar-CHO), 5.26 (s, 1H, Ar-OH), 8.22 (s, 1H, CH (aliphatic)); $^{13}$C-NMR: 40.4, 66.4, 115.3, 118.8, 121.9, 127.9, 129.5, 130.5, 134.5, 135.9, 149.5, 151.3, 158.3, 163.2, 168.7, 187.5, 191.9; MS ES + (ToF): m/z 430 [M$^+$+1].
Conclusion

We may summarized that the synthesized compounds $S_9$ and $S_{17}$ displayed appreciable anti-oxidative potential and compounds $S_1$, $S_5$ and $S_6$ was found to be excellent antidiabetic activity due to the presence of e` withdrawing and donating groups (-CHO and –CHO$_3$) on phenyl nucleus. Compounds $S_2$, $S_3$ and $S_7$ was found to be excellent anti-inflammatory activity due to the presence of e` withdrawing and donating groups (-CHO and –CHO$_3$) on phenyl nucleus. These analogues may be extended for its further elaboration to develop a novel therapeutic agent.

Abbreviations

ROS: Reactive oxygen species; COX: Cycloxygenase; LOX: Lipoxygenase
DM: Diabetes Mellitus; NSAIDs: Non-steroidal anti-inflammatory drugs; $R_f$: Retention factor
DPPH: 1,1-diphenyl-2-picrylhydrazyl, HCl: Hydrochloric acid, IR: Infrared EA: Elemental analyzer. MS: Mass spectroscopy, NMR: Nuclear magnetic resonance, Ppm: Parts per million, TLC: Thin layer chromatography.

Declarations

Authors’ contributions.

PKV- designed and finalized the scheme; S S performed review work and wrote the paper. All authors read and approved the final manuscript.

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Competing interests

The author(s) confirms that this article content has no competing interest.

Availability of data and materials

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Tables

Table 1: The physicochemical properties of newly synthesized derivatives (Y1-Y26):
| Compound | M. Formula | M. Wt. | M.pt. (°C) | Rf Value* | % Yield |
|----------|------------|--------|------------|-----------|---------|
| Y₁       | C₁₇H₁₅N₃O₂S | 325.38 | 145-147    | 0.52      | 68.47   |
| Y₂       | C₂₅H₁₉N₃O₃S | 441.50 | 115-118    | 0.31      | 62.44   |
| Y₃       | C₂₅H₁₉N₃O₃S | 441.50 | 122-125    | 0.42      | 56.45   |
| Y₄       | C₂₅H₂₁N₃O₄S | 459.51 | 110-114    | 0.81      | 60.31   |
| Y₅       | C₂₅H₂₁N₃O₃S | 443.51 | 120-125    | 0.26      | 60.09   |
| Y₆       | C₂₅H₂₁N₃O₃S | 443.51 | 98-100     | 0.42      | 70.18   |
| Y₇       | C₂₅H₂₁N₃O₃S | 443.51 | 120-125    | 0.45      | 63.30   |
| Y₈       | C₂₆H₂₃N₃O₄S | 473.54 | 146-150    | 0.18      | 53.33   |
| Y₉       | C₂₄H₁₉N₃O₃S | 429.49 | 110-115    | 0.32      | 64.21   |
| Y₁₀      | C₂₄H₁₈N₄O₄S | 458.48 | 80-85      | 0.46      | 86.88   |
| Y₁₁      | C₂₄H₁₈N₄O₄S | 458.48 | 130-135    | 0.38      | 65.11   |
| Y₁₂      | C₂₄H₁₈N₄O₄S | 458.48 | 150-154    | 0.48      | 76.88   |
| Y₁₃      | C₂₄H₁₈BrN₃O₂S | 492.38 | 97-102     | 0.44      | 27.96   |
| Y₁₄      | C₂₄H₁₈BrN₃O₂S | 492.38 | 140-143    | 0.36      | 78.67   |
| Y₁₅      | C₂₄H₁₈ClN₃O₂S | 447.93 | 160-165    | 0.42      | 51.36   |
| Y₁₆      | C₂₄H₁₈ClN₃O₂S | 447.93 | 105-110    | 0.52      | 74.77   |
| Y₁₇      | C₂₄H₁₈ClN₃O₂S | 447.93 | 160-164    | 0.23      | 61.81   |
| Y₁₈      | C₂₄H₁₇Cl₂N₂O₂S | 483.38 | 148-152    | 0.32      | 48.63   |
| Y₁₉      | C₂₅H₂₁N₃O₄S | 459.51 | 135-140    | 0.28      | 38.80   |
| Y₂₀      | C₂₆H₂₄N₄O₂S | 456.55 | 115-120    | 0.30      | 43.87   |
| Y₂₁      | C₂₈H₂₈N₃O₂S | 484.62 | 120-125    | 0.44      | 54.42   |
| Y₂₂      | C₃₂H₂₅N₃O₃S | 515.62 | 210-215    | 0.46      | 54.43   |
| Y₂₃      | C₂₅H₂₁N₃O₂S | 427.51 | 165-170    | 0.52      | 62.38   |
| Y₂₄      | C₂₇H₂₅N₃O₅S | 503.57 | 145-151    | 0.48      | 39.47   |
|   | Formula       | Molecular Weight | Melting Point | pKa (water) | pKa (DMSO) |
|---|--------------|-----------------|-------------|------------|------------|
| Y<sub>25</sub> | C<sub>24</sub>H<sub>17</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S | 482.38         | 144-149     | 0.40       | 46.41      |
| Y<sub>26</sub> | C<sub>24</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S | 429.49         | 127-132     | 0.34       | 44.31      |

Table 2: *In vitro* antioxidant activity of newly synthesized derivatives (Y<sub>1</sub>-Y<sub>26</sub>)
| Compounds | % Inhibition | IC<sub>50</sub> |
|-----------|--------------|----------------|
|           | 25 µg/ml     | 50 µg/ml | 75 µg/ml | 100 µg/ml |
| Y<sub>1</sub> | 23.81 | 42.40 | 49.40 | 66.42 | 70.87 |
| Y<sub>2</sub> | 35.35 | 59.04 | 87.50 | 90.23 | 39.18 |
| Y<sub>3</sub> | 11.19 | 36.07 | 43.45 | 92.26 | 66.76 |
| Y<sub>4</sub> | 27.38 | 71.42 | 80.53 | 83.80 | 40.40 |
| Y<sub>5</sub> | 34.52 | 40.11 | 57.14 | 67.54 | 62.93 |
| Y<sub>6</sub> | 16.66 | 26.78 | 41.66 | 84.52 | 71.26 |
| Y<sub>7</sub> | 11.90 | 34.52 | 52.14 | 84.52 | 67.05 |
| Y<sub>8</sub> | 21.42 | 32.61 | 56.78 | 83.92 | 64.10 |
| Y<sub>9</sub> | 56.33 | 60.35 | 85.71 | 91.07 | 17.43 |
| Y<sub>10</sub> | 38.33 | 80.35 | 85.71 | 91.07 | 26.03 |
| Y<sub>11</sub> | 46.54 | 63.33 | 85.71 | 90.47 | 27.64 |
| Y<sub>12</sub> | 35.11 | 78.57 | 89.88 | 95.23 | 30.31 |
| Y<sub>13</sub> | 50.00 | 59.28 | 69.04 | 82.73 | 27.21 |
| Y<sub>14</sub> | 47.16 | 62.02 | 82.73 | 85.11 | 26.74 |
| Y<sub>15</sub> | 19.64 | 77.38 | 80.30 | 86.95 | 42.91 |
| Y<sub>16</sub> | 22.61 | 70.95 | 80.35 | 83.35 | 43.85 |
| Y<sub>17</sub> | 45.35 | 77.38 | 83.33 | 88.69 | 18.98 |
| Y<sub>18</sub> | 40.11 | 70.71 | 82.14 | 88.69 | 30.06 |
| Y<sub>19</sub> | 23.81 | 42.40 | 49.40 | 66.42 | 70.87 |
| Y<sub>20</sub> | 33.33 | 56.30 | 87.50 | 88.90 | 41.68 |
| Y<sub>21</sub> | 44.88 | 60.35 | 86.90 | 94.64 | 31.67 |
| Y<sub>22</sub> | 35.95 | 68.57 | 82.73 | 88.69 | 34.99 |
| Y<sub>23</sub> | 45.95 | 62.73 | 83.92 | 89.28 | 28.69 |
|           | 48.80 | 56.90 | 64.28 | 85.11 | 32.92 |
| $Y_{24}$ |  |  |  |  |  |
|---|---|---|---|---|---|
| $Y_{25}$ | 51.90 | 60.47 | 88.69 | 90.47 | 22.78 |
| $Y_{26}$ | 18.45 | 41.66 | 50.59 | 82.14 | 64.73 |
| Ascorbic acid | 36.90 | 62.50 | 83.33 | 95.83 | 37.68 |

Table 3: *In vitro* antidiabetic activity of newly synthesized derivatives ($Y_1$-$Y_{26}$)
| Compounds | % Inhibition | IC<sub>50</sub> |
|-----------|--------------|----------------|
|           | 25 µg/ml     | 50 µg/ml       | 75 µg/ml | 100 µg/ml |
| Y<sub>1</sub> | 46.32 | 68.36 | 69.38 | 71.42 | **17.08** |
| Y<sub>2</sub> | 36.73 | 56.12 | 58.16 | 69.38 | 49.75 |
| Y<sub>3</sub> | 13.26 | 21.42 | 57.14 | 69.38 | 74.41 |
| Y<sub>4</sub> | 38.77 | 46.93 | 60.20 | 68.36 | 53.79 |
| Y<sub>5</sub> | 55.10 | 58.16 | 67.34 | 72.44 | **8.36** |
| Y<sub>6</sub> | 52.04 | 54.08 | 61.22 | 62.24 | **13.50** |
| Y<sub>7</sub> | 43.87 | 46.93 | 60.20 | 68.36 | 48.55 |
| Y<sub>8</sub> | 41.83 | 45.91 | 58.16 | 65.30 | 54.41 |
| Y<sub>9</sub> | 34.69 | 55.10 | 59.18 | 81.63 | 49.36 |
| Y<sub>10</sub> | 44.89 | 60.20 | 67.34 | 69.38 | 30.12 |
| Y<sub>11</sub> | 28.16 | 41.42 | 55.57 | 77.34 | 61.60 |
| Y<sub>12</sub> | 30.40 | 43.46 | 59.70 | 70.50 | 66.59 |
| Y<sub>13</sub> | 28.36 | 30.61 | 58.77 | 82.85 | 62.34 |
| Y<sub>14</sub> | 25.30 | 35.51 | 43.87 | 48.97 | 99.14 |
| Y<sub>15</sub> | 11.22 | 16.32 | 35.71 | 58.16 | 91.16 |
| Y<sub>16</sub> | 22.04 | 42.65 | 55.71 | 76.93 | 63.52 |
| Y<sub>17</sub> | 11.22 | 22.44 | 43.46 | 76.53 | 75.91 |
| Y<sub>18</sub> | 21.22 | 32.44 | 38.77 | 58.16 | 88.97 |
| Y<sub>19</sub> | 14.28 | 25.51 | 33.67 | 72.44 | 81.07 |
| Y<sub>20</sub> | 19.18 | 40.20 | 55.16 | 82.65 | 63.39 |
| Y<sub>21</sub> | 43.26 | 64.28 | 79.59 | 82.65 | 29.88 |
| Y<sub>22</sub> | 40.20 | 68.38 | 70.40 | 88.57 | 33.84 |
| Y<sub>23</sub> | 42.44 | 66.53 | 81.63 | 83.67 | 29.06 |
|          | 53.06 | 55.10 | 75.51 | 94.89 | 28.88 |
|     | Y_{24} | Y_{25} | Y_{26} | Acarbose |
|-----|--------|--------|--------|----------|
|     | 50.20  | 63.26  | 76.53  | 83.67    | 22.04    |
|     | 41.83  | 52.04  | 68.36  | 78.57    | 42.37    |
|     | 50.71  | 50.92  | 63.26  | 69.79    | 17.12    |

Table 4: *In vitro* anti-inflammatory activity of newly synthesized derivatives (Y_{1}-Y_{26})
| Compounds | % Inhibition | IC<sub>50</sub> |
|-----------|--------------|----------------|
|           | 10µg/ml      | 30µg/ml | 50 µg/ml | 70 µg/ml | 100 µg/ml |
| Y<sub>1</sub> | 36.28 | 46.97 | 60.40 | 81.80 | 91.73 | 31.51 |
| Y<sub>2</sub> | 37.09 | 57.98 | 69.64 | 71.80 | 86.64 | **23.23** |
| Y<sub>3</sub> | 37.09 | 58.11 | 68.49 | 74.60 | 81.09 | **22.09** |
| Y<sub>4</sub> | 37.09 | 48.78 | 64.35 | 75.62 | 91.09 | 30.06 |
| Y<sub>5</sub> | 36.59 | 40.02 | 50.66 | 85.87 | 88.09 | 36.65 |
| Y<sub>6</sub> | 28.37 | 51.55 | 64.47 | 75.11 | 85.24 | 34.16 |
| Y<sub>7</sub> | 45.82 | 54.73 | 65.87 | 71.22 | 87.70 | **19.05** |
| Y<sub>8</sub> | 35.69 | 40.15 | 53.07 | 64.99 | 78.16 | 43.21 |
| Y<sub>9</sub> | 36.84 | 49.77 | 61.55 | 72.06 | 81.34 | 31.36 |
| Y<sub>10</sub> | 32.64 | 46.59 | 50.40 | 66.64 | 77.45 | 42.43 |
| Y<sub>11</sub> | 38.75 | 51.80 | 64.47 | 85.80 | 91.81 | 25.60 |
| Y<sub>12</sub> | 37.73 | 40.15 | 53.07 | 63.71 | 81.73 | 41.72 |
| Y<sub>13</sub> | 34.19 | 47.98 | 61.04 | 73.33 | 80.33 | 34.15 |
| Y<sub>14</sub> | 24.55 | 49.77 | 60.15 | 71.55 | 81.80 | 39.58 |
| Y<sub>15</sub> | 27.48 | 48.58 | 64.73 | 76.38 | 87.78 | 35.44 |
| Y<sub>16</sub> | 34.93 | 49.38 | 50.40 | 62.56 | 70.33 | 42.77 |
| Y<sub>17</sub> | 30.61 | 44.68 | 57.98 | 68.47 | 88.72 | 39.32 |
| Y<sub>18</sub> | 20.61 | 46.84 | 59.38 | 76.31 | 88.72 | 40.72 |
| Y<sub>19</sub> | 20.02 | 36.20 | 51.34 | 66.69 | 78.72 | 51.17 |
| Y<sub>20</sub> | 21.17 | 33.33 | 57.15 | 71.73 | 87.96 | 46.54 |
| Y<sub>21</sub> | 23.91 | 41.55 | 51.80 | 73.38 | 85.67 | 44.47 |
| Y<sub>22</sub> | 28.11 | 38.75 | 59.13 | 61.17 | 71.66 | 48.46 |
| Y<sub>23</sub> | 27.86 | 48.11 | 51.85 | 76.44 | 88.47 | 39.34 |
|           | 26.18 | 46.13 | 61.67 | 70.27 | 73.79 | **41.38** |
Figures

Figure 1

Different activities of pyrazole derivatives
Figure 2

Some marketed drugs that contain pyrazole moiety
Figure 3

Standard graph of ascorbic acid

Figure 4

Graph of potent antioxidant compounds Y9 and Y17
Figure 5

Graph of potent antioxidant compounds Y9 and Y17

Figure 6

Standard graph of acarbose
Figure 7

Graph of potent antidiabetic compounds Y1, Y5 and Y6

Figure 8

IC50 values of compounds Y1, Y5 and Y6 compared to acarbose
Figure 9
Standard graph of aspirin

Figure 10
Graph of potent anti-inflammatory compounds Y2, Y3 and Y7
Figure 11

IC50 values of compounds Y2, Y3 and Y7 compared to aspirin

Figure 12

Structural activity relationship studies of synthesized derivatives