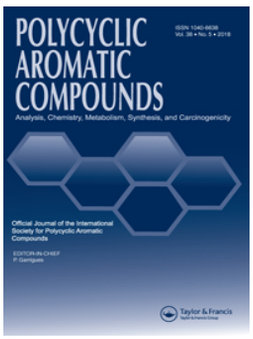

Polycyclic Aromatic Compounds

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Design and Rapid Microwave Irradiated One-Pot Synthesis of Tetrahydropyrimidine Derivatives and Their Screening *In Vitro* Antidiabetic Activity

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ABSTRACT

A rapid and efficient method has been developed for one-pot synthesis of some newly designed tetrahydropyrimidine derivatives with aid of 1,3,4-oxadiazole containing aldehyde, substituted acetoacetanilide and thiourea/guanidine in the occurrence of microwave irradiation. The significant yield of products, atom economy, less time consuming, and catalyst-free synthesis were considered preferences of microwave irradiation. All synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectrometry techniques. All synthesized compounds were evaluated bioassay for *in vitro* antidiabetic screening *viz* α-amylase inhibition strategy and checked their potency against standard reference drug acarbose.

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Biginelli; polycyclic aldehyde; tetrahydropyrimidine; antidiabetic; microwave irradiation

Introduction

Heterocycle-based compounds play vital role in drug design, biological response, and pharmaceutical process. Several drug molecules contain heterocyclic moiety as a core part. Among all the heterocycles, pyrimidine-based heterocycles are generally fascinating in biological applications. Synthesis of pyrimidine by Biginelli reaction[1] which is multicomponent reactions (MCRs), and there are broadly used in synthesis of heterocycle-based moiety because of their advances such as one-pot synthesis, rapid access, greener approach, efficient. Pyrimidine-based heterocycle possesses many biological responses such as anticancer,[2,3] antimalarial,[4] anti-HIV,[5] and antidiabetic[6] (Figure 1). Several methods have been reported for pyrimidine synthesis.[7] Among them some of the syntheses of pyrimidine are in the presence of Lewis base catalyzed and solvent-free conditions using diverse catalysts like Me_3SiCl, CAN, $SmCl_3$, Mannich type synthesis of dihydropyrimidines. Along these ways, 3,4-dihydropyrimidin-2(1H)-ones as a unique class of heterocyclic compounds get more scientist consideration in restorative and synthetic organic chemistry inferable from their helpful pharmacological properties.[8]

One other heterocycle 1,3,4 oxadiazole also own a wide variety of biological response and huge application in the field of pharmaceutical science.[9] Oxadiazole possess such responses like antitumor,[10] anticonvulsant,[11] anticancer,[12] antimicrobial,[13] and antifungal[14] (Figure 2). Numerous methods are there for synthesis of 1,3,4-oxadiazole.[15] Out of them, some of the methods to synthesis of oxadiazole *viz*. cyclization of diacylhydrazines which prepared from the reaction of several acid hydrazide and diverse acid with reagents such as phosphorus pentoxide, phosphorus oxychloride, silica sulfuric acid, thionyl chloride have been utilized.[16–18] In the event that we utilized two heterocyclic moieties and made one new compound, there had a higher biological

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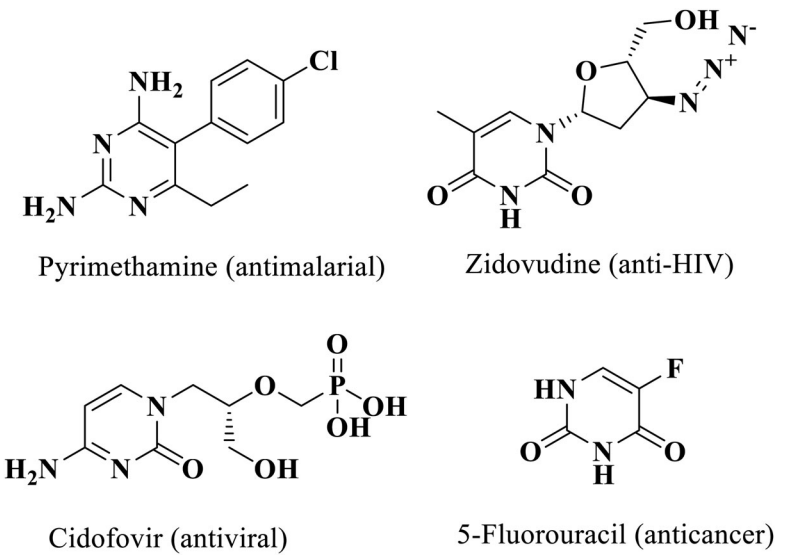


Figure 1. Some drug molecule containing pyrimidine pharmacophore.

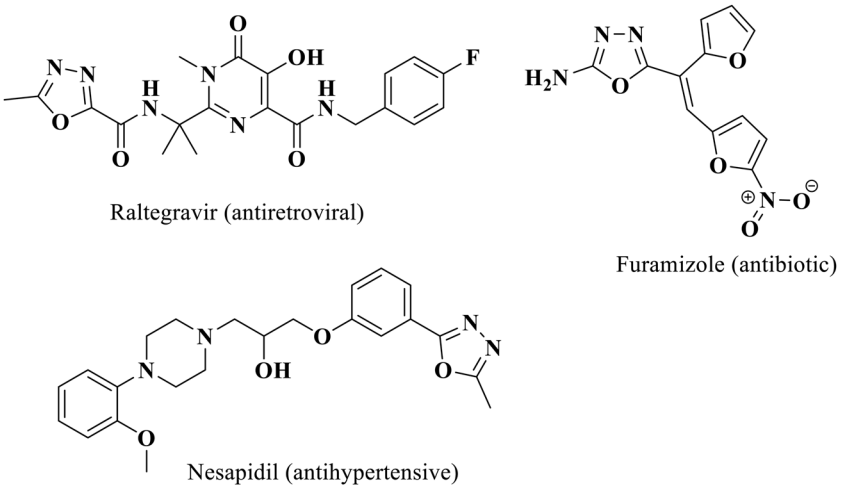


Figure 2. Some marketed drug containing oxadiazole moiety.

response. The use of microwave irradiation in organic synthesis for conveying reaction at exceptionally accelerated rates is an emergent method.[19–23]

Currently, we have synthesized 1,3,4-oxadiazole-based tetrahydropyrimidine (THPM) derivatives and evaluated for *in vitro* antidiabetic screening against alpha amylase inhibition, used acarbose as reference drug.

Experimental

Experimental section

All chemicals were purchased from Merck; all purchased chemicals were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on silica gel-G plates (G60 F254 (Merck)) of 0.5 mm thickness, visualizing with ultraviolet light (254 and 365 nm), or

with iodine vapor or aq. $KMnO_4$. Melting points were determined using a Buchi B-540 capillary apparatus. IR data were recorded on a Shimadzu FT-IR-8400 instrument using the DRS (diffusive reflectance system) method and are reported in cm^{-1} (KBr). NMR spectra were recorded on a Bruker Advance 400 MHz spectrometer (400 MHz for ^1H NMR and 101 MHz for ^{13}C NMR), respectively, in deuterated solvents like DMSO-d_6 and $CDCl_3$. Chemical shifts are referenced to the solvent residual signals with respect to tetramethylsilane. Elemental analysis was carried out on Euro EA 3000 elemental analyzer, and the results are in agreement with the structures assigned. The control of reaction temperature was monitored by a ruby thermometer. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in EI (70 eV) model using the direct inlet probe technique, and m/z is reported in atomic units per elementary charge. Microwave experiments were carried out in an Anton-Paar Monowave 300 Microwave synthesizer using borosilicate glass G10 vial sealed with PTFE-coated silicone septum. The control of all the reaction temperature was monitored by a ruby thermometer.

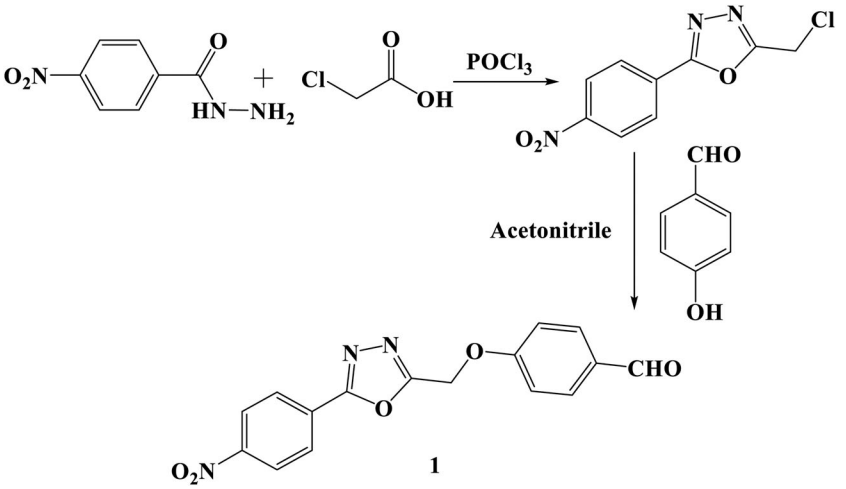
Alpha amylase inhibition assay

In vitro antidiabetic activity of synthesized compounds (**4a–j, 5a–j**) has been screened against alpha amylase (from Malt EC No. 232-588-1), using acarbose as a standard reference drug. The α-amylase inhibition assay was performed using the 3,5-dinitrosalicylic acid (DNSA) method. All the compounds were dissolved in 10% DMSO and were further dissolved in buffer at pH 6.9 to give concentrations ranging from 50 to 125 µg/mL. A volume of 200 µL of α-amylase solution (2 units/mL) was mixed with 200 µL of the dissolved compounds and was incubated for 10 min at 30 °C. Thereafter 200 µL of starch solution (1% in water (w/v)) was added to each tube and incubated for 3 min. The reaction was terminated by the addition of 200 µL DNSA reagent (12 g of sodium potassium tartrate tetra hydrate in 8.0 mL of 2 M NaOH and 20 mL of 96 mM of 3,5-dinitrosalicylic acid solution) and was boiled for 10 min in a water bath at 85–90 °C. The mixture was cooled to ambient temperature and was diluted with 5 mL of distilled water, and the absorbance was measured at 540 nm using a UV-Visible spectrometer. The blank with 100% enzyme activity was prepared by replacing the dissolved compounds with 200 µL of buffer. A blank reaction was similarly prepared using the dissolved compounds at each concentration in the absence of enzyme solution. A positive control was prepared using acarbose (150–50 µg/mL), and the reaction was performed similar to the reaction with dissolved compounds as mentioned above. The α-amylase inhibitory activity was expressed as percent inhibition and was calculated using the equation given below. The % of α-amylase inhibition graph was plotted against the IC50 value. Triplicates have been done for each sample.[24]

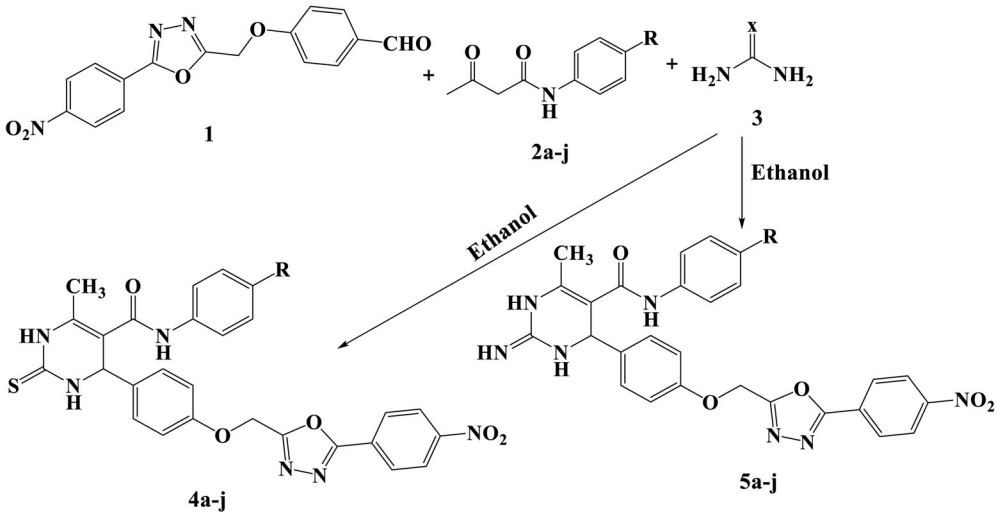
$$\%\ \text{of}\ \alpha\ \text{amylase inhibition} = 100 \times \mathrm{Abs}_{100\%\ \text{control}} - \mathrm{Abs}_{\text{sample}}/\mathrm{Abs}_{100\%\ \text{control}}$$

General process for synthesis of polycyclic aromatic aldehyde containing 1,3,4-oxadiazole ring (1)

Stir a solution of 4-nitrobenzohydrazide (2 mmol), monochloroacetic acid (2 mmol), and phosphorus oxychloride (5 ml) under reflux condition for 5 h to obtain 1,3,4-oxadiazole derivatives. Reaction progress was continuously monitored by TLC. After completion of the reaction, a product fallout in crushed ice water. Further, 1,3,4-oxadiazole derivative (1 mmol) reacts with 4-hydroxybenzaldehyde (1 mmol) in MeCN solvent, also added K_2CO_3 as a catalyst, then reaction mixture will reflux for 5 h to get 1,3,4-oxadiazole containing polycyclic aromatic aldehyde (**1**) (Scheme 1). The progress of reaction was continuously monitored by TLC. After completion of reaction, the reaction mixture was poured in ice cold water and dried to obtained light brown powder.



Scheme 1. Synthesis of polycyclic aromatic aldehyde containing 1,3,4-oxadiazole moiety.
Where X = S, NH.



Where X= S, NH

Scheme 2. Microwave assisted one-pot synthesis of 1,3,4-oxadiazole-based THPMs.

General process for synthesis of THPM derivatives containing oxadiazole moiety (4a–j, 5a–j)

Now, move toward the main reaction scheme of THPM. First of all, Biginelli condensation of 1,3,4-oxadiazole contain aldehyde (1 mmol) (**1**), β-dicarbonyl (1 mmol) (**2**) (substituted acetoacetanilide), and urea derivatives thiourea/Guanidine (1.2 mmol) (**3**) in ethanol solvent and catalytic amount of acidic media under microwave irradiation (200 W) for 25 min to get product as 1,3,4-oxadiazole-based THPM derivatives (**4a–j, 5a–j**). The progress of reaction was continuously monitored by TLC. Crude product material was purified by column chromatography using 30% ethyl acetate/*n*-hexane as a mobile phase to get pure compounds.

The spectral data of synthesized product

(4a) 6-methyl-*N*-(4-nitrophenyl)-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) phenyl)-2-thioxo-1,2,3,4-THPM-5-carboxamide

Yield: 92%, color: light yellowish powder, m.p. (°C): 250–254. IR (KBr, ν_{max}, cm^{-1}): 3385 ($_{N\text{-}H}$ cyclic), 3254 ($_{N\text{-}H}$ amidic), 3045 ($_{=C\text{-}H}$ aromatic), 2912 & 2894 ($\nu_{C\text{-}H}$ aliphatic), 1697 (CONH amidic ketone), 1602 ($_{c=s}$ thioamide), 1642 & 1592 ($_{C=C}$ aromatic), 1542 ($_{NO2}$ asymmetric), 1341 ($_{NO2}$ symmetric), 1307 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1042 ($_{=C\text{-}O\text{-}C}$ symmetric), 874 (*p*-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ: 12.11 (s, 1H, -NH), 10.85 (s, 1H, -NH), 10.47 (s, 1H, -NH), 8.46 (m, 1H, Phenyl), 8.37 (m, 1H, Phenyl), 8.15 (m, 4H, Phenyl), 7.94 (m, 1H, Phenyl), 7.75 (d, $J = 6.2$ Hz, 2H, Phenyl), 7.15 (m, 2H, Phenyl), 6.61 (d, $J = 5.9$ Hz, 1H, Phenyl), 4.79 (d, $J = 3.5$, 2H, $-CH_2$), 4.17 (s, 1H, Chiral -CH), 3.40 (s, 3H, $-CH_3$). ^{13}C NMR (101 MHz, DMSO) δ 166.81, 163.99, 161.32, 159.38, 155.68, 149.38, 148.62, 139.14, 137.88, 135.55, 129.12, 129.01, 128.80, 127.33, 126.37, 123.72, 115.19, 112.33, 70.23, 66.05, 13.99. Mass *m*/*z*: 587. Elemental Analysis: $C_{27}H_{21}N_7O_7S$; Calculated: C, 55.19; H, 3.60; N, 16.69; Found: C, 55.14; H, 3.58; N, 16.67.

(4b) 6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-2-thioxo-*N*-(*p*-tolyl)-1,2,3,4-THPM-5-carboxamide

Yield: 89%, Color: Light gray powder, m.p. (°C): 240–242. IR (KBr, ν_{max}, cm^{-1}): 3371 ($_{N\text{-}H}$ cyclic), 3263 ($_{N\text{-}H}$ amidic), 3090 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($_{C\text{-}H}$ aliphatic), 1685 (CONH amidic), 1611 ($_{c=s}$ thioamide), 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 841 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ 11.99 (s, 1H, -NH), 10.83 (s, 1H, -NH), 10.43 (s, 1H, -NH), 8.42 (m, 1H, Phenyl), 8.31 (m, 1H, Phenyl), 8.03 (m, 4H, Phenyl), 7.97 (m, 1H, Phenyl), 7.69 (d, $J = 6.0$ Hz, 2H, Phenyl), 7.09 (m, 2H, Phenyl), 6.58 (d, $J = 5.1$ Hz, 1H, Phenyl), 4.74 (d, $J = 3.3$, 2H, $-CH_2$), 4.08 (s, 1H, Chiral -CH), 3.38 (s, 3H, $-CH_3$), 3.04 (s, 3H, $-CH_3$). ^{13}C NMR (101 MHz, DMSO) δ 167.32, 163.04, 161.55, 158.34, 153.52, 149.15, 147.42, 140.14, 136.88, 133.447, 129.99, 129.00, 128.42, 127.13, 126.35, 123.85, 114.26, 110.31, 70.54, 65.09, 22.36, 15.05. Mass, *m*/*z*: 556. Elemental Analysis: $C_{28}H_{24}N_6O_5S$; Calculated: C, 60.42; H, 4.35; N, 15.10; Found: C, 60.42; H, 4.35; N, 15.10.

(4c) 6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-2-thioxo-*N*-(*o*-tolyl)-1,2,3,4-THPM-5-carboxamide

Yield: 86%, Color: Light gray powder, m.p. (°C): 192–195. IR (KBr, ν_{max}, cm^{-1}): 3345 ($_{N\text{-}H}$ cyclic), 3254 ($_{N\text{-}H}$ amidic), 3075 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic), 1605 ($_{c=s}$ thioamide), 1625 & 1584 ($_{C=C}$ aromatic), 1518 ($_{NO2}$ asymmetric), 1336 ($_{NO2}$ symmetric), 1310 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1146 ($_{C\text{-}N}$), 1021 ($_{=C\text{-}O\text{-}C}$ symmetric), 678 & 726 (o-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ 11.95 (s, 1H, -NH), 10.71 (s, 1H, -NH), 10.14 (s, 1H, -NH), 8.34 (m, 1H, Phenyl), 8.26 (m, 1H, Phenyl), 8.07 (m, 4H, Phenyl), 7.76 (m, 1H, Phenyl), 7.64 (d, $J = 5.7$ Hz, 2H, Phenyl), 7.11 (m, 2H, Phenyl), 6.52 (d, $J = 5.5$ Hz, 1H, Phenyl), 4.60 (d, $J = 2.9$, 2H, $-CH_2$), 4.09 (s, 1H, -Chiral CH), 3.35 (s, 3H, $-CH_3$), 3.01 (s, 3H, $-CH_3$). ^{13}C NMR (101 MHz, DMSO) δ 166.85, 163.99, 161.32, 159.38, 155.68, 149.38, 148.62, 139.14, 137.88, 135.55, 129.12, 129.00, 130.84, 128.80, 127.33, 126.37, 125.31, 123.72, 115.19, 112.33, 69.42, 66.05, 21.36, 13.99. Mass *m*/*z*: 556. Elemental Analysis: $C_{28}H_{24}N_6O_5S$; Calculated: C, 60.42; H, 4.35; N, 15.10; Found: C, 60.39; H, 4.31; N, 15.04.

(4d) *N*-(2-chlorophenyl)-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)-2-thioxo-1,2,3,4-THPM-5-carboxamide

Yield: 85%, Color: off white powder, m.p. (°C): 195–198. IR (KBr, ν_{max}, cm^{-1}): 3392 ($_{N-H}$ cyclic), 3245 ($_{N-H}$ amidic), 3100 ($_{=C-H}$ aromatic), 2994 & 2903 (ν_{C-H} aliphatic), 1683 (CONH amidic), 1610 ($_{c=s}$ thioamide), 1644 & 1578 ($_{C=C}$ aromatic), 1521 ($_{NO2}$ asymmetric), 1350 ($_{NO2}$ symmetric), 1313 ($_{=C-O-C}$ asymmetric), 1156 ($_{C-N}$), 1027 ($_{=C-O-C}$ symmetric), 698 (o-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ 12.05 (s, 1H, -NH), 10.80 (s, 1H, -NH), 10.38 (s, 1H, -NH), 8.41 (m, 1H, Phenyl), 8.25 (m, 1H, Phenyl), 8.01 (m, 4H, Phenyl), 7.82 (m, 1H, Phenyl), 7.68 (d, $J = 6.0$ Hz, 2H, Phenyl), 7.03 (m, 2H, Phenyl), 6.53 (d, $J = 5.3$ Hz, 1H, Phenyl), 4.71 (d, $J = 3.4$, 2H, $-CH_2$), 4.09 (s, 1H, Chiral -CH), 3.12 (s, 3H, $-CH_3$). Mass *m*/*z*: 576. Elemental Analysis: $C_{27}H_{21}ClN_6O_5S$; Calculated: C, 56.20; H, 3.67; N, 14.57; Found %: C, 56.14; H, 3.65; N, 14.53.

(4e) *N*-(4-chlorophenyl)-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)-2-thioxo-1,2,3,4-THPM-5-carboxamide

Yield: 89%, Color: off white powder, m.p. (°C): 212–214. IR (KBr, ν_{max}, cm^{-1}): 3379 ($_{N-H}$ cyclic), 3245 ($_{N-H}$ amidic), 3098 ($_{=C-H}$ aromatic), 2957 & 2893 (ν_{C-H} aliphatic), 1668 (CONH amidic), 1604 ($_{c=s}$ thioamide), 1613 & 1589 ($_{C=C}$ aromatic), 1512 ($_{NO2}$ asymmetric), 1325 ($_{NO2}$ symmetric), 1305 ($_{=C-O-C}$ asymmetric), 1175 ($_{C-N}$), 1072 ($_{=C-O-C}$ symmetric), 830 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ 12.04 (s, 1H, -NH), 10.82 (s, 1H, -NH), 10.40 (s, 1H, -NH), 8.44 (m, 1H, Phenyl), 8.31 (m, 1H, Phenyl), 8.10 (m, 4H, Phenyl), 7.89 (m, 1H, Phenyl), 7.72 (d, $J = 6.2$ Hz, 2H, Phenyl), 7.11 (m, 2H, Phenyl), 6.55 (d, $J = 5.4$ Hz, 1H, Phenyl), 4.76 (d, $J = 2.98$, 2H, $-CH_2$), 4.13 (s, 1H, Chiral -CH), 3.20 (s, 3H, $-CH_3$). Mass *m*/*z*: 576. Elemental Analysis: $C_{27}H_{21}ClN_6O_5S$; Calculated: C, 56.20; H, 3.67; N, 14.57; Found: C, 56.16; H, 3.61; N, 14.52.

(4f) *N*-(4-fluorophenyl)-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)-2-thioxo-1,2,3,4-THPM-5-carboxamide

Yield: 87%, Color: violet crystal, m.p. (°C): 179–182. IR (KBr, ν_{max}, cm^{-1}): 3370 ($_{N-H}$ cyclic), 3247 ($_{N-H}$ amidic), 3090 ($_{=C-H}$ aromatic), 2962 & 2900 (ν_{C-H} aliphatic), 1686 (CONH amidic), 1611 ($_{c=s}$ thioamide), 1639 & 1585 ($_{C=C}$ aromatic), 1531 ($_{NO2}$ asymmetric), 1342 ($_{NO2}$ symmetric), 1308 ($_{=C-O-C}$ asymmetric), 1142 ($_{C-N}$), 1068 ($_{=C-O-C}$ symmetric), 856 ($_{C-H}$ p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ 12.02 (s, 1H, -NH), 10.81 (s, 1H, -NH), 10.44 (s, 1H, -NH), 8.41 (m, 1H, Phenyl), 8.32 (m, 1H, Phenyl), 8.07 (m, 4H, Phenyl), 7.90 (m, 1H, Phenyl), 7.69 (d, $J = 5.9$ Hz, 2H, Phenyl), 7.11 (m, 2H, Phenyl), 6.57 (d, $J = 5.7$ Hz, 1H, Phenyl), 4.71 (d, $J = 3.3$, 2H, $-CH_2$), 4.10 (s, 1H, Chiral -CH), 3.01 (s, 3H, $-CH_3$). Mass *m*/*z*: 560. Elemental Analysis: $C_{27}H_{21}FN_6O_5S$; Calculated: C, 57.85; H, 3.78; N, 14.99; Found: C, 57.79; H, 3.72; N, 14.96.

(4g) *N*-(4-hydroxyphenyl)-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) phenyl)-2-thioxo-1,2,3,4-THPM-5-carboxamide

Yield: 83%, Color: Brown color powder, m.p. (°C):235–238. IR (KBr, ν_{max}, cm^{-1}): 3345 ($_{N-H}$ cyclic), 3256 ($_{N-H}$ amidic), 3078 ($_{=C-H}$ aromatic), 2962 & 2900 (ν_{C-H} aliphatic), 1685 (CONH amidic), 1607 ($_{c=s}$ thioamide), 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C-O-C}$ asymmetric), 1175 ($_{C-N}$), 1072 ($_{=C-O-C}$ symmetric), 842 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ 12.00 (s, 1H, -NH), 10.82 (s, 1H, -NH), 10.37 (s, 1H, -NH), 8.36 (m, 1H, Phenyl), 8.31 (m, 1H, Phenyl), 8.09 (m, 4H, Phenyl), 7.85 (m, 1H, Phenyl), 7.64 (d, $J = 5.9$ Hz, 2H, Phenyl), 7.11 (m, 2H, Phenyl), 6.53 (d, $J = 5.8$ Hz, 1H, Phenyl), 5.02 (s, 1H, -OH) 4.76 (d, $J = 3.1$, 2H, $-CH_2$), 4.15 (s, 1H, Chiral -CH), 3.12 (s, 3H, $-CH_3$). Mass *m*/*z*:

558. Elemental Analysis: $C_{27}H_{22}N_6O_6S$; Calculated: C, 58.06; H, 3.97; N, 15.05; Found: C, 58.01; H, 3.93; N, 15.00.

(4h) *N*-(4-bromophenyl)-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)-2-thioxo-1,2,3,4-THPM-5-carboxamide

Yield: 86%, Color: Dark brown color powder, m.p. (°C):250–254. IR (KBr, ν_{max}, cm^{-1}): 3398 ($_{OH,}$ aromatic) 3365 ($_{N\text{-}H}$ cyclic), 3267 ($_{N\text{-}H}$ amidic), 3081 ($_{=C\text{-}H}$ aromatic), 2947 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic ketone), 1614 ($_{c=s}$ thioamide), 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 833 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ 12.10 (s, 1H, -NH), 10.81 (s, 1H, -NH), 10.44 (s, 1H, -NH), 8.40 (m, 1H, Phenyl), 8.34 (m, 4H, Phenyl), 8.08 (m, 4H, Phenyl), 7.89 (m, 1H, Phenyl), 7.68 (d, $J = 6.1$ Hz, 2H, Phenyl), 7.13 (m, 2H, Phenyl), 6.54 (d, $J = 5.5$ Hz, 1H, Phenyl), 4.77 (d, $J = 3.5$, 2H, -CH_2), 4.10 (s, 1H, Chiral -CH), 3.01 (s, 3H, -CH_3). Mass *m*/*z*: 620. Elemental Analysis: $C2_7H_{21}BrN_6O_5S$; Calculated: C, 52.18; H, 3.41; N, 13.52; Found: C, 52.12; H, 3.39; N, 13.49.

(4i) *N*-(3-chlorophenyl)-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)-2-thioxo-1,2,3,4-THPM-5-carboxamide

Yield: 82%, Color: Dark brown color powder, m.p. (°C): 195–198. IR (KBr, ν_{max}, cm^{-1}): 3372 ($_{N\text{-}H}$ cyclic), 3261 ($_{N\text{-}H}$ amidic), 3075 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic), 1609 ($_{c=s}$ thioamide), 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 675 & 710 (m-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ 12.04 (s, 1H, -NH), 10.78 (s, 1H, -NH), 10.39 (s, 1H, -NH), 8.40 (m, 1H, Phenyl), 8.32 (m, 1H, Phenyl), 8.05 (m, 4H, Phenyl), 7.88 (m, 1H, Phenyl), 7.71 (d, $J = 6.0$ Hz, 2H, Phenyl), 7.00 (m, 2H, Phenyl), 6.54 (d, $J = 5.2$ Hz, 1H, Phenyl), 4.70 (d, $J = 3.1$, 2H, -CH_2), 4.06 (s, 1H, Chiral -CH), 3.12 (s, 3H, -CH_3). Mass *m*/*z*: 576. Elemental Analysis: $C_{27}H_{22}ClN_7O_5$; Calculated: C, 56.20; H, 3.67; N, 14.57; Found: C, 56.14; H, 3.63; N, 14.54.

(4j) 6-methyl-*N*-(3-nitrophenyl)-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)-2-thioxo-1,2,3,4-THPM-5-carboxamide

Yield: 90%, Color: Yellow color powder, m.p. (°C): 237–239. IR (KBr, ν_{max}, cm^{-1}): 3401 ($_{N\text{-}H}$ cyclic), 3305 ($_{N\text{-}H}$ amidic), 3090 ($_{=C\text{-}H}$ aromatic), 2942 & 2893 ($\nu_{C\text{-}H}$ aliphatic), 1680 (CONH amidic ketone), 1611 ($_{c=s}$ thioamide), 1644 & 1594 ($_{C=C}$ aromatic), 1543 ($_{NO2}$ asymmetric), 1351 ($_{NO2}$ symmetric), 1302 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1176 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 678 & 724 (m-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ 12.10 (s, 1H, -NH), 10.83 (s, 1H, -NH), 10.46 (s, 1H, -NH), 8.46 (m, 1H, Phenyl), 8.31 (m, 1H, Phenyl), 8.19 (m, 4H, Phenyl), 7.98 (m, 1H, Phenyl), 7.74 (d, $J = 5.7$ Hz, 2H, Phenyl), 7.13 (m, 2H, Phenyl), 6.63 (d, $J = 5.0$ Hz, 1H, Phenyl), 4.80 (d, $J = 2.8$, 2H, -CH_2), 4.14 (s, 1H, Chiral -CH), 3.11 (s, 3H, -CH_3). Mass *m*/*z*: 587. Elemental Analysis: $C_{27}H_{22}N_8O_7$; Calculated: C, 55.19; H, 3.60; N, 16.69; Found: C, 55.17; H, 3.57; N, 16.64.

(5a) 2-imino-6-methyl-*N*-(4-nitrophenyl)-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl)-1,2,3,4-THPM-5-carboxamide

Yield: 91%, Color: Yellow color powder, m.p. (°C): 252–254. IR (KBr, ν_{max}, cm^{-1}): 3363 ($_{N\text{-}H}$ cyclic), 3255 ($_{N\text{-}H}$ amidic), 3086 ($_{=C\text{-}H}$ aromatic), 2955 & 2916 ($\nu_{C\text{-}H}$ aliphatic), 1697 (CONH amidic ketone) 1651 & 1604 ($_{C=C}$ aromatic), 1519 ($_{NO2}$ asymmetric), 1350 ($_{NO2}$ symmetric), 1303 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1180 ($_{C\text{-}N}$), 1064 ($_{=C\text{-}O\text{-}C}$ symmetric), 848 (*p*-disubstituted aromatic), ^{1}H NMR

Table 1. Comparisons and yield optimization of conventional heating and microwave assisted synthesis of compound **4a**.

			Conventional heating[a]			Microwave assisted[b]		
Entry	Solvent	Catalyst	Temp (°C)	Time (hr)	Yield (%)[c]	Temp (°C)	Time (min.)	Yield (%)[c]
1	MeOH	–	70	22	10	90	25	20
2	Acetonitrile	–	80	22	Trace	90	25	15
3	THF	–	70	24	Trace	90	25	10
4	DMF	–	110	21	20	90	25	39
5	**EtOH**	**HCl**	**80**	**22**	**56**	**90**	**25**	**92**
6	MeOH	PPh3	70	24	15	90	25	30
7	EtOH	–	70	24	49	90	25	25

[a]Reaction condition polycyclic aromatic aldehyde (1 mmol), substituted acetoacetanilide (1 mmol), and thiourea/guanidine (1.2 mmol) using EtOH solvent by conventional heating method.
[b]The Biginelli condensation by microwave irradiation (200 W).
[c] Isolated yield of product.
Bold character signifies final optimal condition of reaction.

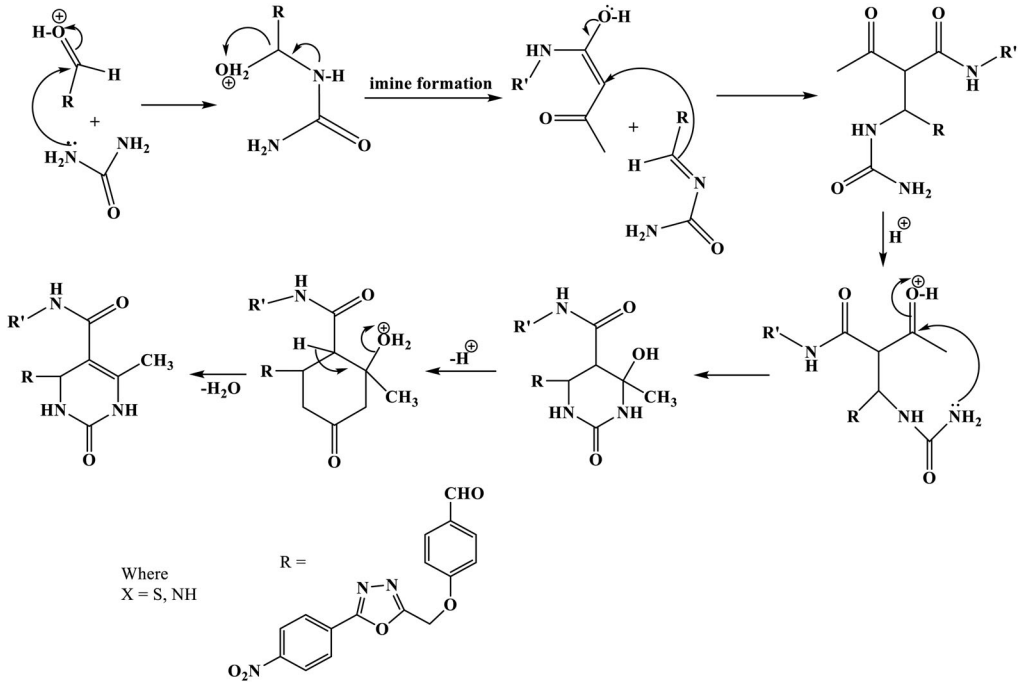


Figure 3. Plausible reaction mechanism.

(400 MHz, DMSO) δ 12.11 (s, 1H, -NH), 10.84 (s, 1H, -NH), 10.47 (s, 1H, -NH), 8.46 (s, 1H, -NH), 8.37 (s, 3H, Phenyl), 8.23–8.08 (m, 3H, Phenyl), 8.04–7.91 (m, 1H, Phenyl), 7.74 (d, $J = 6.2$ Hz, 1H, Phenyl), 7.07 (d, $J = 5.9$ Hz, 3H, Phenyl), 6.67 (d, $J = 5.8$ Hz, 1H, Phenyl), 4.83 (d, $J = 3.2$, 2H, $-CH_2$), 4.18 (s, 1H, Chiral -CH), 3.38 (s, 3H, $-CH_3$), ^{13}C NMR (101 MHz, DMSO) δ 166.85, 163.99, 161.32, 159.38, 155.68, 149.38, 148.62, 139.14, 137.88, 135.55, 129.12, 128.80, 127.33, 126.37, 123.72, 123.59, 115.19, 112.33, 66.05, 31.05, 15.48, Mass *m/z*: 570. Elemental Analysis: $C_{27}H_{22}N_8O_7$; Calculated: C, 56.84; H, 3.89; N, 19.64; Found: C, 56.79; H, 3.82; N, 19.61.

(5b) 2-imino-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-*N*-(*p*-tolyl)-1,2,3,4-THPM-5-carboxamide

Yield: 87%, Color: Blackish white color powder, m.p. (°C): 235–238. IR (KBr, ν_{max}, cm^{-1}): 3371 ($_{N-H}$ cyclic), 3263 ($_{N-H}$ amidic), 3090 ($_{=C-H}$ aromatic), 2962 & 2900 ($_{C-H}$ aliphatic), 1685 (CONH

amidic) 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 841 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ: 12.08 (s, 1H, -NH), 10.75 (s, 1H, -NH), 10.34 (s, 1H, -NH), 8.32 (s, 1H, -NH), 8.37 (s, 3H, Phenyl), 8.23–8.08 (m, 3H, Phenyl), 8.1–7.91 (m, 1H, Phenyl), 7.71 (d, $J = 5.8$ Hz, 1H, Phenyl), 7.04 (d, $J = 5.4$ Hz, 3H, Phenyl), 6.62 (d, $J = 5.1$ Hz, 1H, Phenyl), 4.83 (d, $J = 3.7$ Hz, 2H, -CH_2), 4.09 (s, 1H, Chiral -CH), 3.32 (s, 3H, -CH_3), 3.18 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δ: 164.85, 163.94, 161.12, 158.27, 155.68, 148.99, 148.59, 138.46, 136.65, 134.55, 129.12, 128.80, 127.33, 126.37, 123.72, 123.59, 115.19, 112.33, 66.05, 30.21, 20.99, 18.48, Mass *m/z*: 539. Elemental Analysis: $C_{28}H_{25}N_7O_5$; Calculated: C, 62.33; H, 4.67; N, 18.17; Found: C, 62.30; H, 4.62; N, 18.14.

(5c) 2-imino-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-*N*-(*o*-tolyl)-1,2,3,4-THPM-5-carboxamide

Yield: 85%, Color: Blackish white color powder, m.p. (°C): 201–203. IR (KBr, ν_{max}, cm^{-1}): 3371 ($_{N\text{-}H}$ cyclic), 3263 ($_{N\text{-}H}$ amidic), 3090 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic) 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 694 & 704 (o-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ: 12.12 (s, 1H, -NH), 10.71 (s, 1H, -NH), 10.50 (s, 1H, -NH), 8.45 (s, 1H, -NH), 8.34 (s, 3H, Phenyl), 8.22–8.09 (m, 3H, Phenyl), 7.94–7.85 (m, 1H, Phenyl), 7.70 (d, $J = 6.0$ Hz, 1H, Phenyl), 7.04 (d, $J = 5.8$ Hz, 3H, Phenyl), 6.71 (d, $J = 5.5$ Hz, 1H, Phneyl), 4.86 (s,

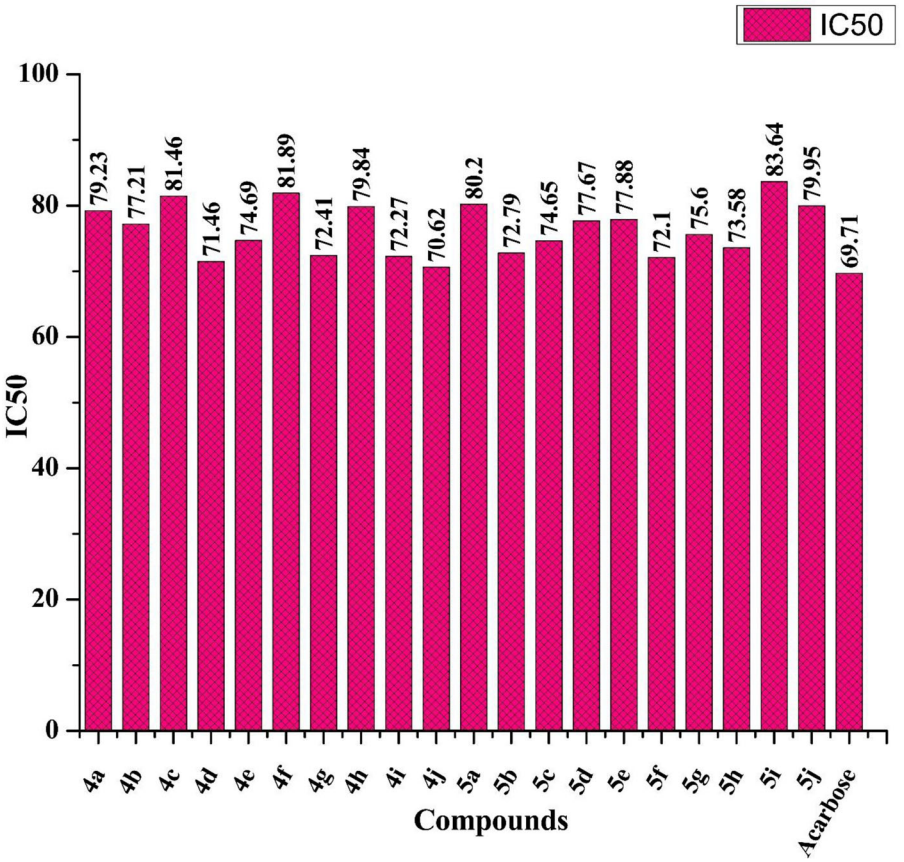


Figure 4. Comparison IC50 value for synthesized compounds and acarbose.

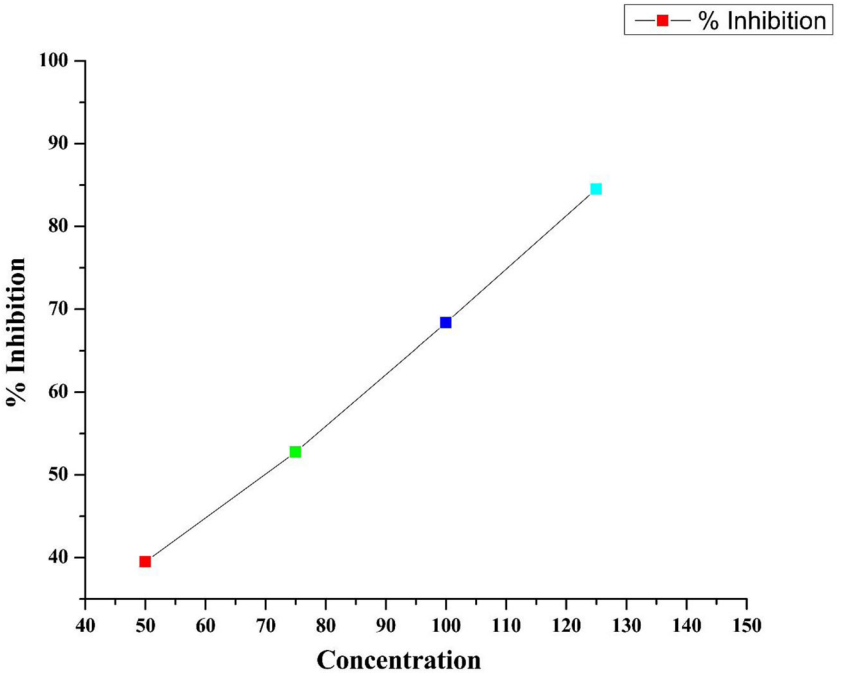


Figure 5. Activity of acarbose (Concentration [μg/mL] → % Inhibition).

2H, -CH_2), 4.22 (s, 1H, Chiral -CH), 3.42 (s, 3H, -CH_3), 3.20 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δ: 168.85, 166.99, 163.32, 160.34, 156.68, 150.40, 149.40, 139.14, 138.46, 137.88, 136.62, 129.51, 128.83, 127.56, 126.45, 122.72, 123.59, 120.36, 116.19, 113.33, 58.60, 32.40, 21.36, 15.48, Mass *m/z*: 539. Elemental Analysis: $C_{28}H_{25}N_7O_5$; Calculated: C, 62.33; H, 4.67; N, 18.17; Found: C, 62.28; H, 4.60; N, 18.14.

(5d) *N*-(2-chlorophenyl)-2-imino-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl)-1,2,3,4-THPM-5-carboxamide

Yield: 83%, Color: Off white color powder, m.p. (°C): 201–204. IR (KBr, ν_{max}, cm^{-1}): 3371 ($_{N\text{-}H}$ cyclic), 3263 ($_{N\text{-}H}$ amidic), 3090 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic) 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 694 (o-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ: 12.10 (s, 1H, -NH), 10.84 (s, 1H, -NH), 10.47 (s, 1H, -NH), 8.46 (s, 1H, -NH), 8.37 (s, 3H, -NH), 8.21–8.04 (m, 3H, Phenyl), 8.00–7.94 (m, 1H, Phenyl), 7.74 (d, $J = 6.2$ Hz, 1H, Phenyl), 7.07 (d, $J = 5.8$ Hz, 3H, Phenyl), 6.67 (d, $J = 5.7$ Hz, 1H, Phenyl), 4.83 (d, $J = 3.2$ Hz, 2H, -CH_2), 4.18 (s, 1H, Chiral -CH), 3.33 (s, 3H, -CH_3). Mass, *m/z*: 559. Elemental Analysis: $C_{27}H_{22}ClN_7O_5$; Calculated: C, 57.91; H, 3.96; Cl, 6.33; N, 17.51; Found: C, 57.88; H, 3.92; N, 17.48.

(5e) *N*-(4-chlorophenyl)-2-imino-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl)-1,2,3,4-THPM-5-carboxamide

Yield: 87%, Color: Off white color powder, m.p. (°C): 209–211. IR (KBr, ν_{max}, cm^{-1}): 3371 ($_{N\text{-}H}$ cyclic), 3263 ($_{N\text{-}H}$ amidic), 3090 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic) 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 830 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ: 12.01 (s, 1H, -NH), 10.82 (s, 1H, -NH), 10.47 (s, 1H, -NH), 8.35 (s, 1H,

Table 2. α-Amylase inhibitory effects of synthesized compounds and acarbose.

Entry	Compound	Concentration (μg/mL)	OD	% Inhibition[a]	IC50
1	4a	50	0.138	37.04 ± 1.30	79.23
		75	0.114	47.79 ± 2.41	
		100	0.0845	61.33 ± 3.69	
		125	0.0414	80.93 ± 4.30	
2	4b	50	0.136	37.90 ± 3.27	77.21
		75	0.112	48.83 ± 2.39	
		100	0.0818	62.44 ± 5.45	
		125	0.0421	80.67 ± 2.39	
3	4c	50	0.145	33.49 ± 2.75	81.46
		75	0.117	46.65 ± 0.09	
		100	0.0892	59.18 ± 2.61	
		125	0.0456	79.09 ± 2.53	
4	4d	50	0.137	37.51 ± 0.65	71.46
		75	0.105	52.01 ± 1.20	
		100	0.0865	60.50 ± 1.24	
		125	0.0392	82.02 ± 1.97	
5	4e	50	0.144	34.38 ± 1.22	74.69
		75	0.109	50.22 ± 1.92	
		100	0.0895	59.11 ± 3.42	
		125	0.0408	81.35 ± 0.63	
6	4f	50	0.149	31.78 ± 1.62	81.89
		75	0.118	46.06 ± 0.43	
		100	0.0870	60.27 ± 0.77	
		125	0.0457	78.99 ± 2.67	
7	4g	50	0.139	36.28 ± 1.36	72.41
		75	0.106	51.55 ± 0.37	
		100	0.0813	62.88 ± 1.11	
		125	0.0413	81.10 ± 1.59	
8	4h	50	0.150	31.51 ± 1.11	79.84
		75	0.114	47.76 ± 1.62	
		100	0.0891	59.31 ± 0.64	
		125	0.0449	79.55 ± 0.77	
9	4i	50	0.144	34.00 ± 1.01	72.27
		75	0.105	51.95 ± 1.31	
		100	0.0866	60.46 ± 1.17	
		125	0.0405	81.44 ± 1.08	
10	4j	50	0.136	37.76 ± 1.50	70.62
		75	0.103	52.62 ± 0.75	
		100	0.0860	60.73 ± 0.90	
		125	0.0398	81.81 ± 0.90	
11	5a	50	0.153	30.05 ± 0.63	80.20
		75	0.115	47.20 ± 2.45	
		100	0.0863	60.67 ± 0.98	
		125	0.0481	78.07 ± 0.37	
12	5b	50	0.137	37.22 ± 0.18	72.79
		75	0.107	51.23 ± 0.34	
		100	0.0883	59.65 ± 2.03	
		125	0.0408	81.35 ± 0.63	
13	5c	50	0.150	31.34 ± 0.88	74.65
		75	0.109	50.28 ± 1.04	
		100	0.0874	60.11 ± 1.26	
		125	0.0476	78.23 ± 1.43	
14	5d	50	0.139	36.49 ± 0.32	77.67
		75	0.112	48.78 ± 0.27	
		100	0.0864	60.57 ± 0.51	
		125	0.0408	81.35 ± 0.63	
15	5e	50	0.141	35.71 ± 0.06	77.88
		75	0.112	48.73 ± 2.22	
		100	0.0877	59.99 ± 0.57	
		125	0.0432	80.27 ± 1.44	
16	5f	50	0.135	38.29 ± 0.11	72.10
		75	0.106	51.54 ± 0.29	
		100	0.0859	60.79 ± 0.93	

(*continued*)

Table 2. Continued.

Entry	Compound	Concentration (μg/mL)	OD	% Inhibition[a]	IC50
		125	0.0418	80.91 ± 0.92	
17	5g	50	0.143	34.49 ± 0.20	75.60
		75	0.110	49.77 ± 1.63	
		100	0.0894	59.22 ± 0.51	
		125	0.0453	79.36 ± 0.42	
18	5h	50	0.135	38.16 ± 0.48	73.58
		75	0.108	50.75 ± 0.94	
		100	0.0851	61.16 ± 0.76	
		125	0.0406	81.47 ± 0.36	
19	5i	50	0.144	34.23 ± 0.90	83.64
		75	0.116	47.11 ± 0.09	
		100	0.0975	55.52 ± 1.51	
		125	0.0520	76.27 ± 1.18	
20	5j	50	0.144	34.00 ± 1.01	79.95
		75	0.114	48.01 ± 0.54	
		100	0.0919	58.06 ± 0.87	
		125	0.0491	77.57 ± 0.25	
21	Acarbose	50	0.132	39.50 ± 0.29	69.71
		75	0.103	52.76 ± 0.60	
		100	0.0693	68.36 ± 0.16	
		125	0.0340	84.51 ± 0.84	

[a]Inhibition ± standard deviation.

-NH), 8.40 (s, 3H, Phenyl), 8.22–8.08 (m, 3H, Phenyl), 8.03–7.90 (m, 1H, Phenyl), 7.74 (d, $J = 6.2$ Hz, 1H, Phenyl), 7.07 (d, $J = 5.7$ Hz, 3H, Phenyl), 6.67 (d, $J = 5.8$ Hz, 1H, Phenyl), 4.83 (d, $J = 3.0$ Hz, 2H, -CH_2), 4.18 (s, 1H, Chiral -CH), 3.38 (s, 3H, -CH_3). Mass *m*/*z*: 559. Elemental Analysis: $C_{27}H_{22}ClN_7O_5$; Calculated: C, 57.91; H, 3.96; N, 17.51; Found: C, 57.87; H, 3.90; N, 17.45.

(5f) *N*-(4-fluorophenyl)-2-imino-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl)-1,2,3,4-THPM-5-carboxamide

Yield: 86%, Color: Violet crystal, m.p. (°C): 189–192. IR (KBr, ν_{max}, cm^{-1}): 3371 ($_{N\text{-}H}$ cyclic), 3263 ($_{N\text{-}H}$ amidic), 3090 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic) 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 838 ($_{C\text{-}H}$ p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ: 12.15 (s, 1H, -NH), 10.84 (s, 1H, -NH), 10.50 (s, 1H, -NH), 8.48 (s, 1H, -NH), 8.39 (s, 3H, Phenyl), 8.25–8.11 (m, 3H, Phenyl), 8.05–7.94 (m, 1H, Phenyl), 7.79 (d, $J = 6.5$ Hz, 1H, Phenyl), 7.08 (d, $J = 5.9$ Hz, 3H, Phenyl), 6.70 (d, $J = 5.8$ Hz, 1H, Phenyl), 4.88 (d, $J = 3.4$ Hz, 2H, -CH_2), 4.23 (s, 1H, Chiral -CH), 3.46 (s, 3H, -CH_3). Mass *m*/*z*: 543. Elemental Analysis: $C_{27}H_{22}FN_7O_5$; Calculated: C, 59.67; H, 4.08; N, 18.04; Found: C, 59.62; H, 4.03; N, 18.01.

(5g) *N*-(4-hydroxyphenyl)-2-imino-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1,2,3,4-THPM-5-carboxamide

Yield: 84%, Color: Brown powder, m.p. (°C): 227–230. IR (KBr, ν_{max}, cm^{-1}): 3371 ($_{N\text{-}H}$ cyclic), 3263 ($_{N\text{-}H}$ amidic), 3090 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic) 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 842 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ: 12.11 (s, 1H, -NH), 10.84 (s, 1H,-NH), 10.47 (s, 1H, -NH), 8.45 (s, 1H, -NH), 8.37 (s, 3H, Phenyl), 8.24–8.09 (m, 3H, Phenyl), 8.02–7.91 (m, 1H, Phenyl), 7.18 (d, $J = 6.2$ Hz, 1H, Phenyl), 7.07 (d, $J = 6.0$ Hz, 3H, Phenyl), 6.67 (d, $J = 5.4$ Hz, 1H, Phenyl), 5.64 (s, 1H, -OH) 4.83

(d, $J = 3.4$ Hz, 2H, -CH_2), 4.20 (s, 1H, Chiral -CH), 3.38 (s, 3H, -CH_3). Mass *m*/*z*: 541. Elemental Analysis: $C_{27}H_{23}N_7O_6$; Calculated: C, 59.89; H, 4.28; N, 18.11; Found: C, 59.83; H, 4.24; N, 18.06.

(5h) *N*-(4-bromophenyl)-2-imino-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl)-1,2,3,4-THPM-5-carboxamide

Yield: 84%, Color: Dark brown powder, m.p. (°C): 248–250. IR (KBr, ν_{max}, cm^{-1}): 3401 ($_{OH,}$ aromatic) 3371 ($_{N\text{-}H}$ cyclic), 3263 ($_{N\text{-}H}$ amidic), 3090 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic ketone) 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 833 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ: 12.20 (s, 1H, -NH), 10.92 (s, 1H, -NH), 10.55 (s, 1H, -NH), 8.58 (s, 1H, -NH, Phenyl), 8.42 (s, 3H, Phenyl), 8.33–8.16 (m, 3H, Phenyl), 8.14–7.98 (m, 1H, Phenyl), 7.81 (d, $J = 6.0$ Hz, 1H, Phenyl), 7.07 (d, $J = 5.7$ Hz, 3H, Phenyl), 6.67 (d, $J = 5.3$ Hz, 1H, Phenyl), 4.83 (d, $J = 3.1$ Hz, 2H, -CH_2), 4.23 (s, 1H, Chiral -CH), 3.38 (s, 3H, -CH_3). Mass *m*/*z*: 603. Elemental Analysis: $C_{27}H_{22}BrN_7O_5$; Calculated: C, 53.65; H, 3.67; N, 16.22; Found: C, 53.60; H, 3.64; N, 16.19.

(5i) *N*-(3-chlorophenyl)-2-imino-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl)-1,2,3,4-THPM-5-carboxamide

Yield: 83%, Color: Dark brown powder, m.p. (°C): 199–201. IR (KBr, ν_{max}, cm^{-1}): 3371 ($_{N\text{-}H}$ cyclic), 3263 ($_{N\text{-}H}$ amidic), 3090 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic) 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 675 & 710 (m-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ: 12.01 (s, 1H, -NH), 10.78 (s, 1H, -NH), 10.39 (s, 1H, -NH), 8.34 (s, 1H, -NH), 8.29 (s, 3H, Phenyl), 8.23–8.07 (m, 3H, Phenyl), 8.04–7.91 (m, 1H, Phenyl), 7.74 (d, $J = 6.5$ Hz, 1H, Phenyl), 7.07 (d, $J = 5.9$ Hz, 3H, Phenyl), 6.67 (d, $J = 6.0$ Hz, 1H, Phenyl), 4.83 (d, $J = 3.6$ Hz, 2H, -CH_2), 4.18 (s, 1H, Chiral -CH), 3.38 (s, 3H, -CH_3). Mass *m*/*z*: 559. Elemental Analysis: $C_{27}H_{22}ClN_7O_5$; Calculated: C, 57.91; H, 3.96; N, 17.51; Found: C, 57.85; H, 3.92; N, 17.47.

(5j) 2-imino-6-methyl-*N*-(3-nitrophenyl)-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl)-1,2,3,4-THPM-5-carboxamide

Yield: 83%, Color: Yellow powder, m.p. (°C): 234–237. IR (KBr, ν_{max}, cm^{-1}): 3371 ($_{N\text{-}H}$ cyclic), 3263 ($_{N\text{-}H}$ amidic), 3090 ($_{=C\text{-}H}$ aromatic), 2962 & 2900 ($\nu_{C\text{-}H}$ aliphatic), 1685 (CONH amidic ketone) 1641 & 1598 ($_{C=C}$ aromatic), 1524 ($_{NO2}$ asymmetric), 1352 ($_{NO2}$ symmetric), 1305 ($_{=C\text{-}O\text{-}C}$ asymmetric), 1175 ($_{C\text{-}N}$), 1072 ($_{=C\text{-}O\text{-}C}$ symmetric), 680 & 725 (m-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δ 12.10 (s, 1H, -NH), 10.85 (s, 1H, -NH), 10.50 (s, 1H, -NH), 8.46 (s, 1H, -NH), 8.37 (s, 3H, Phenyl), 8.23–8.06 (m, 3H, Phenyl), 8.01–7.94 (m, 1H, Phenyl), 7.74 (d, $J = 6.2$ Hz, 1H, Phenyl), 7.07 (d, $J = 5.9$ Hz, 3H, Phenyl), 6.67 (d, $J = 5.8$ Hz, 1H, Phenyl), 4.89 (d, $J = 3.4$ Hz, 2H, -CH_2), 4.24 (s, 1H, Chiral -CH), 3.34 (s, 3H, -CH_3). Mass *m*/*z*: 570. Elemental Analysis: $C_{27}H_{22}N_8O_7$; Calculated: C, 56.84; H, 3.89; N, 19.64; Found: C, 56.79; H, 3.83; N, 19.60.

Result and discussion

Chemistry

In summary, we wish to report herein novel bioactive series of THPMs derivative. A simple, efficient, and rapid microwave irradiation technique has been developed for the synthesis of Biginelli condensation of 1,3,4-oxadiazole containing pyrimidine derivatives. Here, we were synthesized THPMs by the conventional heating method as well as the microwave irradiation technique

(200 W) analyses the investigations of both. However, we saw under microwave irradiation response rate amazingly increment with contrast with conventional heating. So as to verify that the reaction was proceeded out in the presence of microwave irradiation that got higher yield and rapider reaction time compared to the convention heating method. The outcomes were summed up in Table 1 (Entry 1–7). The plausible reaction mechanism is indicated in Figure 3. In this study, we saw that the utilization of microwave irradiation has decreased the time of reaction from 24 h to 25 min with higher amount of yield between 80% and 92% (Scheme 2).

Biology

Performing α-amylase inhibition assay of synthesized compounds and acarbose used as standard drug with different concentrations ranging 50–125 μg/mL. The result shows α-amylase activity of synthesized compounds from moderate to good. Apart from this, IC50 values are 71.46 μg/mL (**4d**), 72.41 μg/mL (**4 g**), **4i** (72.27 μg/mL), **4j** (70.62 μg/mL), **5b** (72.79 μg/mL), and **5f** (72.10), which is nearer to 69.71 μg/mL that is acarbose (Table 2) (Figures 4 and 5).

Conclusion

In conclusion, we describe rapid and efficient one-pot synthesis of 1,3,4-oxadiazole containing THPMs derivatives. This process involved 1,3,4-oxadiazole containing aldehyde, diverse urea derivatives alike thiourea/guanidine with substituted acetoacetanilide, which was performed by the conventional heating method as well as the microwave irradiation. Microwave-assisted reaction extremely simplified the reaction process with less time consuming, and the desired product has been gotten in modest to excellent yields holding operationally effective. The synthesized compounds were confirmed by spectroscopic techniques such as ^{1}H, ^{13}C, IR, and mass spectrometry. We were screening *in vitro* antidiabetic activity of synthesized products; many of them were like **4d**, **4 g**, **4i**, **4j**, **5b**, and **5f** and have shown very good potency compared to standard reference drug acarbose.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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