folia medica

Folia Medica 64(3):478-487
DOI: 10.3897/folmed.64.e62476

Original Article

Microwave-Assisted Synthesis of Bioactive Tetrahydropyrimidine Derivatives as Antidiabetic Agents

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Received: 26 Dec 2020 ♦ **Accepted:** 19 Feb 2021 ♦ **Published:** 30 June 2022

Citation: Vachhani M, Lalpara J, Hadiyal S, Dubal G. Microwave-assisted synthesis of bioactive tetrahydropyrimidine derivatives as antidiabetic agents. Folia Med (Plovdiv) 2022;64(3):478-487. doi: 10.3897/folmed.64.e62476.

Abstract

Introduction: In drug discovery, pyrimidine analogues show good biological response and many drug moieties have pyrimidine core.

Aim: On the basis of prior review, we synthesized a series of N-(substituted phenyl)-1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide parade a 1,3,4-oxadiazole core which were evaluated for in vitro antidiabetic screening.

Materials and methods: The tetrahydropyrimidine derivatives have been synthesized by microwave irradiation method. It was carried out by Biginelli condensation of 1,3,4-oxadiazole based aldehyde, substituted acetoacetanilide and N,N'-dimethyl urea. All synthesized compounds were evaluated for antidiabetic screening.

Results: By the results derived from antidiabetic activity, compounds **4a**, **4e**, **4g**, and **4i** show good inhibition compared to others because of electron withdrawing and hydroxyl groups. All results are compared with standard drug acarbose.

Conclusions: In conclusion, a series of 1,3,4-oxadizole bearing tetrahydropyrimidine has been synthesized and evaluated for in vitro antidiabetic screening. The derivatives **4a**, **4e**, **4g**, and **4i** exhibited promising antidiabetic activity.

Keywords

1,3,4-oxadiazole, antidiabetic activity, microwave irradiation, tetrahydropyrimidine

INTRODUCTION

Heterocyclic moieties have been broadly employed in the synthesis of pharmacologically active entities.[1,2] Specifically, pyrimidine and fused pyrimidine-based entities play a key role in the field of drug discovery. Currently, much consideration has been paid to pyrimidine derivatives due to their biological activity and therapeutical potential.[3] Tetrahydropyrimidine (THPM) derivatives shows a wide range of biological activities such as anticancer[4], antimicrobial[5], anti-inflammatory[6], antimalarial[7], and antidiabetic[8] activities. Pyrimidine-2-thione moiety inhibits the motility of the mitotic kinesin Eg5.[9] *N,N'*-diacylated tetrahydropyrimidine-2(1*H*)-thione analogues show antiproliferative activity.[10] Different substitution-based pyrimidine derivatives have diverse biological response. Synthesis of pyrimidine derivatives, Biginelli condensation[11,12] is an efficient, simple, and atom-economical method for the condensation of aldehyde, β-ketoester, and urea derivatives under acidic condition. There are many available strategies for Biginelli condensation such as perchloric acid doped silica, which is successfully used as an efficient mild catalyst (SiO_2/

$HClO_4$),[13] Bronsted acid ionic liquid 1-methylimidazolium hydrogen sulfate with chlorotrimethylsilane[14], using Bronsted base (*t*-BuOK)[15], recyclable bioglycerol-based sulfonic acid functionalized carbon catalyst[16], using greener synthetic aspect catalysed by $ZrOCl_2$ in media[17], NBS catalysed in water by ultrasound assisted[18], catalysed by Zeolite[19], and mesoporous nano catalyst (Fe_3O_4 SBA-15)[20]. Considering that some of these methods agonize from low yield, costly catalyst we concentrated our efforts on the cost-effective synthesis of tetrahydropyrimidine derivatives using easily available reagents without any catalyst.

AIM

We developed a series of 1,3,4-oxadiazole bearing tetrahydropyrimidine derivatives. Both the moieties pyrimidine and 1,3,4-oxadiazole parade wide range of biological response **(Fig. 1)**. All synthesized compounds were evaluated for their antidiabetic activity.

MATERIALS AND METHODS

General

All chemicals, solvents, and media were purchased from Sigma Aldrich, combi-block, enamine, Himedia, SRL. All purchased chemicals were used without further purification, reactions were continuously monitored by thin layer chromatography (TLC) on silica gel-(G60 F254, Merck) of 0.5 mm thickness, visualizing with ultraviolet light (254 and 365 nm), or with iodine vapour or aq $KMnO_4$. Melting points were determined using a Buchi B-540 capillary apparatus. NMR spectra were recorded on a Bruker Advance 400 MHz spectrometer (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR) respectively in solvents like $CDCl_3$, DMSO and chemical shifts were referenced to the solvent residual signals with respect to tetramethylsilane. Standard abbreviations are used to represent signals multiplicities for ^{1}H NMR spectrum s - singlet, d - doublet, t - triplet, q - quartet, m - multiplate. The reaction temperature was monitored by ruby thermometer. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in EI (70eV) model using direct inlet probe technique and m/z were reported in atomic units per elementary charge.

Chemistry

Procedure for synthesis of 2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (Int-1)

To mixture of 4-nitrobenzohydrazide (10 mmol) and chloroacetic acid (10 mmol) in $POCl_3$ (5 ml) solvent and reflux at 80-90°C for 4-5 hours. Reaction progress was continuously monitored by TLC using hexane: ethyl acetate (7:3) as mobile phase. After completion of reaction, product precipitated in crushed ice water. The reaction mass was filtered using Whatman filter paper and dried under vacuum dryer. White amorphous solid was obtained **(Int-1)**.

Procedure for synthesis of 4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) benzaldehyde (1)

To mixture of 2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (Int-1) (1 mmol) and 4-hydroxybenzaldehyde (1 mmol) in acetonitrile (5 ml) solvent and heated at reflux condition for 5 hours. K_2CO_3 (10 mol%) was added as a catalyst in reaction mixture. Reaction progress was continuously monitored by TLC using hexane:ethyl acetate (7:3) as mobile phase. After completion of reaction, the product precipitated in crushed ice water. The reaction mass was filtered using Whatman filter paper and dried under vacuum dryer. Brown solid was obtained **(1)**.

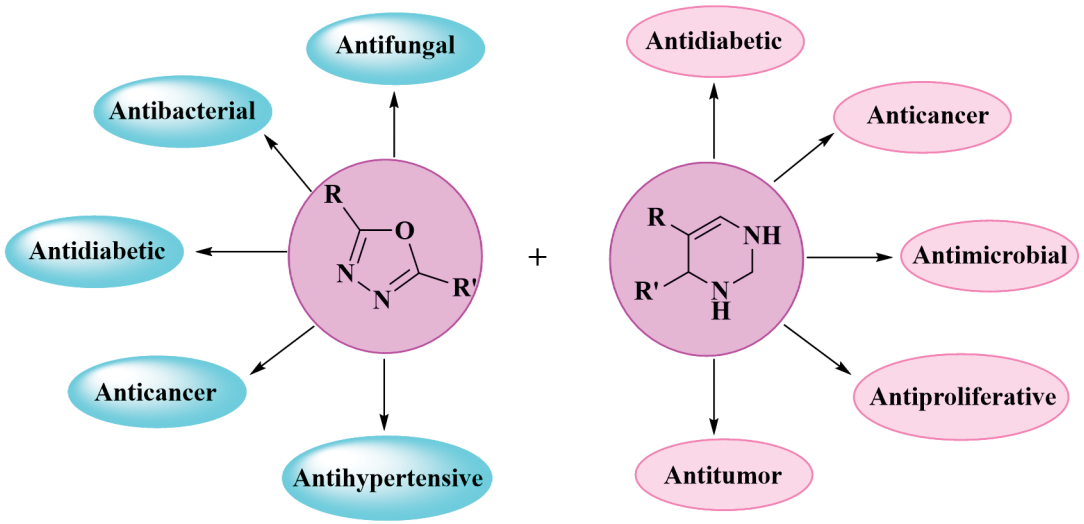

Figure 1. Diverse biological response of two different pharmacophore.

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General conventional heating method for synthesis of N-(substituted phenyl)-1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4a-j)

To mixture of 4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) benzaldehyde (1) (1 mmol), N,N'-Dimethylurea (1 mmol) (3) and substituted acetoacetanilide (1 mmol) (2a-j) in ethanol solvent for 20-24 hours at reflux condition. Reaction progress was continuously monitored by TLC using hexane:ethyl acetate (7:3) as mobile phase. After completion of reaction, product fallout in crushed ice water. The reaction mass was filtered using Whatman filter paper and dried under vacuum to get crude material which was purified by column chromatography using 30% ethyl acetate/n-hexane as a mobile phase to get pure compounds **(4a-j)**.

General microwave assisted procedure for synthesis of N-(substituted phenyl)-1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4a-j)

To mixture of 4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) benzaldehyde (1) (1 mmol), N,N'-Dimethylurea (1 mmol) (3) and substituted acetoacetanilide (1 mmol) (2a-j) in ethanol solvent under microwave irradiation condition for 22-24 min. Reaction progress was continuously monitored by TLC using hexane:ethyl acetate (7:3) as mobile phase. After completion of reaction, product fallout in crushed ice water. The reaction mass was filtered using Whatman filter paper and dried under vacuum to get crude material which was purified by column chromatography using 30% ethyl acetate/n-hexane as a mobile phase to get pure compounds **(4a-j)**.

All compounds **(4a-j)** synthesized by the above mentioned method and structure of compounds were confirmed by various spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

1,3,6-trimethyl-N-(4-nitrophenyl)-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4a)

Yield: 92%, colour: light yellowish powder, m.p. (°C): 250–254. IR (KBr, ν_{max}, cm^{-1}): (-N-H amidic), 3045 (=C-H aromatic), 2912 & 2894 (-C-H aliphatic), 1697 (-CONH amidic ketone), 1642 & 1592 (C=C aromatic), 1542 (-NO_2 asymmetric), 1341 (-NO_2 symmetric), 1307 (-C-O-C asymmetric), 1175 (-C-N), 1042 (-C-O-C symmetric), 874 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δppm: 12.11 (s, 1H, -NH), 8.46-8.53 (m, 1H, aromatic), 8.37-8.48 (m, 1H, Phenyl), 8.15-8.26 (m, 4H, aromatic), 7.94-8.06 (m, 1H, aromatic), 7.75 (d, *J*=6.2 Hz, 2H, aromatic), 7.15-7.23 (m, 2H, aromatic), 6.61 (d, *J*=5.9 Hz, 1H, aromatic), 4.79 (d, *J*=3.5, 2H, -CH_2), 4.17 (s, 1H, Chiral -CH), 3.40 (s, 3H, -CH_3) 3.07 (s, 6H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 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, 28.34, 30.21, 13.99. Mass m/z: 599. Elemental Analysis: $C_{29}H_{25}N_7O_7$; Calculated: C, 58.10; H, 4.20; N, 16.35; Found: C, 58.06; H, 4.15; N, 16.32.

N-(4-bromophenyl)-1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4b)

Yield: 86%, colour: dark brown colour powder, m.p. (°C): 250–254. IR (KBr, ν_{max}, cm^{-1}): 3365 (N-H amidic), 3081 (=C-H aromatic), 2947 & 2900 (-C-H aliphatic), 1685 (-CONH amidic ketone), 1641 & 1598 (C=C aromatic), 1524 (-NO_2 asymmetric), 1352 (NO_2 symmetric), 1305 (=C-O-C asymmetric), 1175 (C-N), 1072 (=C-O-C symmetric), 833 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δppm: 12.10 (s, 1H, -NH), 8.40-8.52 (m, 1H, aromatic), 8.34-8.41 (m, 4H, aromatic), 8.08-8.23 (m, 1H, aromatic), 7.89-7.93 (m, 1H, aromatic), 7.68 (d, *J*=6.1 Hz, 2H, aromatic), 7.13 (m, 2H, aromatic), 6.54 (d, *J*=5.5 Hz, 1H, aromatic), 4.77 (d, *J*=3.5, 2H, -CH_2), 4.10 (s, 1H, Chiral -CH), 3.01 (s, 3H, -CH_3), 3.15 (s, 3H, -CH_3), 2.98 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 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, 28.34, 30.21, 13.99. Mass m/z: 620. Elemental Analysis: $C_{29}H_{25}BrN_6O_6$. Calculated: C, 54.99; H, 3.98; N, 13.27; Found: C, 54.94; H, 3.92; N, 13.23.

1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-2-oxo-N-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4c)

Yield: 86%, colour: dark brown color powder, m.p. (°C): 250–254. IR (KBr, ν_{max}, cm^{-1}): 3365 (-N-H amidic), 3081 (=C-H aromatic), 2947 & 2900 (-C-H aliphatic), 1685 (-CONH amidic ketone), 1641 & 1598 (C=C aromatic), 1524 (-NO_2 asymmetric), 1352 (NO_2 symmetric), 1305 (=C-O-C asymmetric), 1175 (C-N), 1072 (=C-O-C symmetric), 833 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δppm: 12.02 (s, 1H, -NH), 8.35-8.46 (m, 1H, aromatic), 8.23-8.39 (m, 4H, aromatic), 7.80-7.84 (m, 2H, aromatic), 7.59 (d, *J*=6.1 Hz, 2H, aromatic), 7.05-7.12 (m, 2H, aromatic), 6.48 (d, *J*=5.5 Hz, 1H, aromatic), 4.64 (d, *J*=3.5, 2H, -CH_2), 4.02 (s, 1H, Chiral -CH), 3.15 (s, 3H, -CH_3), 3.05 (s, 3H, -CH_3), 2.98 (s, 3H, -CH_3) 2.19 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 165.24, 163.38, 160.17, 158.42, 155.68, 148.48, 147.99, 139.14, 137.88, 135.55, 129.12, 128.11, 128.40, 127.31, 126.87, 123.92, 115.19, 112.10, 70.23, 66.05, 28.34, 30.21, 20.14, 13.99. Mass m/z: 568. Elemental Analysis: $C_{30}H_{28}N_6O_6$. Calculated: C, 63.37; H, 4.96; N, 14.78; Found: C, 63.34; H, 4.92; N, 14.71.

N-(4-chlorophenyl)-1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) phenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide (4d)

Yield: 89%, colour: 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 (-C-H aliphatic), 1668 (-CONH amidic), 1613 & 1589 (C=C aromatic), 1512 (NO_2 asymmetric), 1325 (NO_2 symmetric), 1305 (-C-O-C asymmetric), 1175 (C-N), 1072 (-C-O-C symmetric), 830 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δppm: 12.04 (s, 1H, -NH), 8.44 (m, 1H, aromatic), 8.31-8.43 (m, 1H, aromatic), 8.10-8.23 (m, 4H, aromatic), 7.89-7.99 (m, 1H, aromatic), 7.72 (d, *J*=6.2 Hz, 2H, aromatic), 7.11-7.25 (m, 2H, aromatic), 6.55 (d, *J*=5.4 Hz, 1H, aromatic), 4.76 (d, *J*=2.98, 2H, -CH_2), 4.13 (s, 1H, Chiral -CH), 3.20 (s, 3H, -CH_3), 3.15 (s, 3H, -CH_3), 2.98 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 166.04, 16.31, 160.17, 158.45, 155.53, 148.72, 147.89, 139.27, 137.76, 135.55, 129.12, 128.11, 128.40, 127.31, 126.87, 123.92, 115.19, 112.10, 70.23, 66.05, 28.34, 30.21, 13.99. Mass m/z: 576. Elemental Analysis: $C_{27}H_{21}ClN_6O_6$; Calculated: C, 59.14; H, 4.28; N, 14.27; Found: C, 59.11; H, 4.25; N, 14.21.

N-(4-fluorophenyl)-1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)phenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide (4e)

Yield: 87%, colour: violet crystal, m.p. (C): 179–182. IR (KBr, ν_{max}, cm^{-1}): 3370 (N-H cyclic), (-N-H amidic), 3090 (=C-H aromatic), 2962 & 2900 (-C-H aliphatic), 1686 (-CONH amidic), 1639 & 1585 (C=C aromatic), 1531 (-NO_2 asymmetric), 1342 (-NO_2 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) δppm: 12.02 (s, 1H, -NH), 8.41 (m, 1H, aromatic), 8.32 (m, 1H, aromatic), 8.07-8.19 (m, 4H, aromatic), 7.90-8.02 (m, 1H, aromatic), 7.69 (d, *J*=5.9 Hz, 2H, aromatic), 7.11-7.24 (m, 2H, aromatic), 6.57 (d, *J*=5.7 Hz, 1H, Phenyl), 4.71 (d, *J*=3.3, 2H, -CH_2), 4.10 (s, 1H, Chiral -CH), 3.20 (s, 3H, -CH_3), 3.01 (s, 3H, -CH_3), 2.94 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 165.12, 163.27, 160.20, 158.76, 155.11, 148.49, 147.73, 139.42, 137.56, 135.48, 129.81, 128.43, 128.37, 127.67, 126.77, 123.89, 115.28, 112.11, 70.45, 66.33, 28.37, 30.12, 13.86. Mass m/z: 572. Elemental Analysis: $C_{29}H_{25}FN_6O_6$; Calculated: C, 60.84; H, 4.40; N, 14.68; Found: C, 60.79; H, 4.37; N, 14.65.

N-(2-chlorophenyl)-1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) phenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide (4f)

Yield: 89%, colour: 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 (-C-H aliphatic), 1668 (-CONH amidic), 1613 & 1589 (C=C aromatic), 1512 (NO_2 asymmetric), 1325 (NO_2 symmetric), 1305 (-C-O-C asymmetric), 1175 (C-N), 1072 (-C-O-C symmetric), 695 (o-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δppm: 12.03 (s, 1H, -NH), 8.54-8.62 (m, 1H, aromatic), 8.35-8.48 (m, 1H, aromatic), 8.05-8.22 (m, 4H, aromatic), 7.85-7.92 (m, 1H, aromatic), 7.78 (d, *J*=6.3 Hz, 2H, aromatic), 7.11-7.23 (m, 2H, aromatic), 6.61 (d, *J*=5.4 Hz, 1H, aromatic), 4.78 (d, *J*=3.0, 2H, -CH_2), 4.10 (s, 1H, Chiral -CH), 3.17 (s, 3H, -CH_3), 3.12 (s, 3H, -CH_3), 2.94 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 166.04, 16.31, 160.17, 158.45, 155.53, 148.72, 147.89, 139.27, 137.76, 135.55, 129.12, 128.11, 128.40, 127.31, 126.87, 123.92, 115.19, 112.10, 70.23, 66.05, 28.34, 30.21, 13.99. Mass m/z: 576. Elemental Analysis: $C_{27}H_{21}ClN_6O_6$; Calculated: C, 59.14; H, 4.28; N, 14.27; Found: C, 59.10 s; H, 4.25; N, 14.21.

N-(4-hydroxyphenyl)-1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) phenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxamide (4g)

Yield: 83%, colour: brown colour powder, m.p. (°C):235–238. IR (KBr, ν_{max}, cm^{-1}): 3368 (-OH, aromatic), 3256 (N-H amidic), 3078 (=C-H aromatic), 2962 & 2900 (-C-H aliphatic), 1685 (-CONH amidic), 1641 & 1598 (C=C aromatic), 1524 (NO_2 asymmetric), 1352 (NO_2 symmetric), 1305 (-C-O-C asymmetric), 1175 (C-N), 1072 (-C-O-C symmetric), 842 (p-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δppm: 12.00 (s, 1H, -NH), 8.36-8.48 (m, 1H, aromatic), 8.31-8.42 (m, 1H, aromatic), 8.09-8.22 (m, 4H, aromatic), 7.85-7.92 (m, 1H, aromatic), 7.64 (d, *J*=5.9 Hz, 2H, aromatic), 7.11-7.26 (m, 2H, aromatic), 6.53 (d, *J*=5.8 Hz, 1H, aromatic), 5.02 (s, 1H, -OH) 4.76 (d, *J*=3.1, 2H, -CH_2), 4.15 (s, 1H, Chiral -CH), 3.12 (s, 3H, -CH3), 2.15 (s, 3H, -CH_3). 2.94 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 165.45, 163.99, 160.74, 158.26, 155.49, 148.72, 147.89, 139.27, 137.76, 135.55, 129.12, 128.11, 128.40, 127.31, 126.87, 123.92, 115.19, 112.10, 70.23, 66.05, 28.34, 30.21, 13.99. Mass m/z: 570. Elemental Analysis: $C_{29}H_{26}N6O_7$; Calculated: C, 61.05; H, 4.59; N, 14.73; Found: C, 61.01; H, 4.53; N, 14.70.

1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-2-oxo-N-(o-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4h)

Yield: 89%, colour: 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 (-C-H aliphatic), 1668 (-CONH amidic), 1613 & 1589 (C=C aromatic), 1512 (NO_2 asymmetric), 1325 (NO_2 symmetric), 1305 (-C-O-C asymmetric), 1175 (C-N), 1072 (-C-O-C symmetric), 695 (o-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δppm: 12.03 (s, 1H, -NH), 8.54-8.62 (m, 1H, aromatic), 8.35-8.48 (m, 1H, aromatic), 8.05-8.22 (m, 4H, aromatic), 7.85-7.92 (m, 1H, aromatic), 7.78 (d, *J*=6.3 Hz, 2H, aromatic), 7.11-7.23 (m, 2H, aromatic), 6.61 (d, *J*=5.4 Hz, 1H, aromatic), 4.78 (d, *J*=3.0, 2H, -CH_2), 4.10 (s, 1H, Chiral -CH), 3.17 (s, 3H, -CH_3), 3.12 (s, 3H, -CH_3), 2.94 (s, 3H,

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-CH_3), 2.19 (s, 3H, -CH^3). ^{13}C NMR (101 MHz, DMSO) δppm: 165.24, 163.38, 160.17, 158.42, 155.68, 148.48, 147.99, 139.14, 137.88, 135.55, 130.54, 129.12, 128.11, 128.40, 127.31, 126.87, 123.92, 115.19, 112.10, 70.23, 66.05, 28.34, 30.21, 20.14, 13.99. Mass m/z: 568. Elemental Analysis: $C_{30}H_{28}N_6O_6$. Calculated: C, 63.37; H, 4.96; N, 14.78; Found: C, 63.34; H, 4.92; N, 14.71.

1,3,6-trimethyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-2-oxo-N-(m-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4i)

Yield: 82%, colour: dark brown colour powder, m.p. (°C): 195–198. IR (KBr, ν_{max}, cm^{-1}): 3261 (-N-H amidic), 3075 (=C-H aromatic), 2962 & 2900 (-C-H aliphatic), 1685 (-CONH amidic), 1641 & 1598 (-C=C aromatic), 1524 (-NO_2 asymmetric), 1352 (NO_2 symmetric), 1305 (-C-O-C asymmetric), 1175 (C-N), 1072 (-C-O-C symmetric), 675 & 710 (m-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δppm: 12.04 (s, 1H, -NH), 8.40-8.51 (m, 1H, Phenyl), 8.32-8.48 (m, 1H, aromatic), 8.05-8.21 (m, 4H, aromatic), 7.88-7.98 (m, 1H, aromatic), 7.71 (d, *J*=6.0 Hz, 2H, aromatic), 7.00-7.13 (m, 2H, aromatic), 6.54 (d, *J*=5.2 Hz, 1H, aromatic), 4.70 (d, *J*=3.1, 2H, -CH2), 4.06 (s, 1H, Chiral -CH), 3.12 (s, 3H, -CH3) 2.94 (s, 3H, -CH_3). 2.15 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 165.24, 163.38, 160.17, 158.42, 155.68, 148.48, 147.99, 139.14, 137.88, 135.55, 130.99, 131.53, 129.12, 128.11, 128.40, 127.31, 126.87, 123.92, 115.19, 112.10, 70.23, 66.05, 28.34, 30.21, 20.14, 13.99. Mass m/z: 576. Elemental Analysis: $C_{30}H_{28}N_6O_6$; Calculated: C, 56.20; H, 3.67; N, 14.57; Found: C, 56.14; H, 3.63; N, 14.54.

1,3,6-trimethyl-N-(3-nitrophenyl)-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy) phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4j)

Yield: 82%, colour: dark brown colour powder, m.p. (°C): 195–198. IR (KBr, ν_{max}, cm^{-1}): 3261 (-N-H amidic), 3075 (=C-H aromatic), 2962 & 2900 (-C-H aliphatic), 1685 (-CONH amidic), 1641 & 1598 (-C=C aromatic), 1524 (-NO_2 asymmetric), 1352 (NO_2 symmetric), 1305 (-C-O-C asymmetric), 1175 (C-N), 1072 (-C-O-C symmetric), 675 & 710 (m-disubstituted aromatic), ^{1}H NMR (400 MHz, DMSO) δppm: 12.04 (s, 1H, -NH), 8.40 (m, 1H, Phenyl), 8.32 (m, 1H, aromatic), 8.05 (m, 4H, aromatic), 7.88 (m, 1H, aromatic), 7.71 (d, *J*=6.0 Hz, 2H, aromatic), 7.00 (m, 2H, aromatic), 6.54 (d, *J*=5.2 Hz, 1H, aromatic), 4.70 (d, *J*=3.1, 2H, -CH2), 4.06 (s, 1H, Chiral -CH), 3.12 (s, 3H, -CH3) 2.94 (s, 3H, -CH_3). 2.15 (s, 3H, -CH_3). ^{13}C NMR (101 MHz, DMSO) δppm: 165.41, 163.99, 162.34, 158.38, 155.89, 149.79, 148.78, 140.14, 139.88, 136.57, 129.12, 129.01, 128.80, 127.33, 126.36, 123.42, 115.19, 112.83, 70.13, 66.95, 28.37, 30.93, 13.85. Mass m/z: 599. Elemental Analysis: $C_{29}H_{25}N_7O_8$; Calculated: C, 58.10; H, 4.20; N, 16.35; Found: C, 58.06; H, 4.15; N, 16.32.

Alpha amylase inhibition assay

In vitro antidiabetic activity of synthesized compounds (**4a-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 50–125 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 minutes at 30°C. Thereafter, 200 µL of starch solution (1% in water (w/v)) was added to each tube and incubated for 3 minutes. 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 minutes 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 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 µg/mL–50 µg/mL) and the reaction was performed similarly to the reaction with dissolved compounds as mentioned above. The α-amylase inhibitory activity was expressed as percentage inhibition and was calculated using the equation given below. The % of a-amylase inhibition graph was plotted against the IC50 value. Triplicates have been done for each sample.[21]

% of α amylase inhibition =
$100 \times Abs_{100\%\ control} - Abs_{sample} / Abs_{100\%\ control}$

RESULTS AND DISCUSSION

Chemistry

In the present study, we synthesized bioactive tetrahydropyrimidine analogues parade 1,3,4-oxadiazole pharmacophore. Synthesis of 1,3,4-oxadiazole based aldehyde **(Fig. 2)** which is used in preparation of tetrahydropyrimidine by Biginelli condensation. Furthermore, synthesized aldehyde, N, N-dimethyl urea and acetoacetanilide derivatives were condensed by Biginelli condensation to obtained final adducts **(Fig. 3)**. Final reaction was carried out by conventional heating method as well as microwave irradiation method. Reaction optimized on the compound **4a (Table 1)** with the help of different polar protic and aprotic solvents, diverse catalyst such as HCl and triphenyl phosphene by both conventional and microwave methods. On the basis of optimization, we found that microwave irradiation method was more convenient compared to the con-

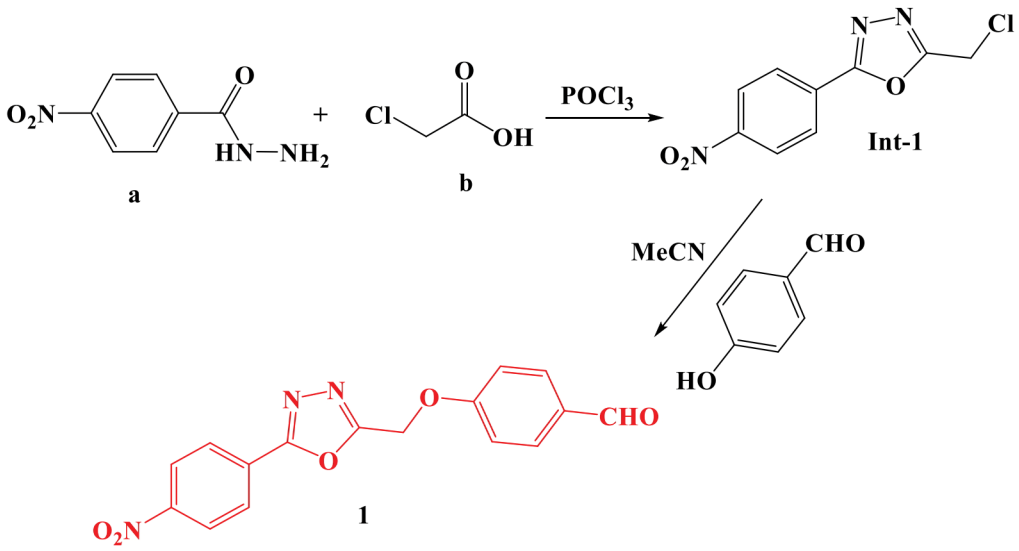
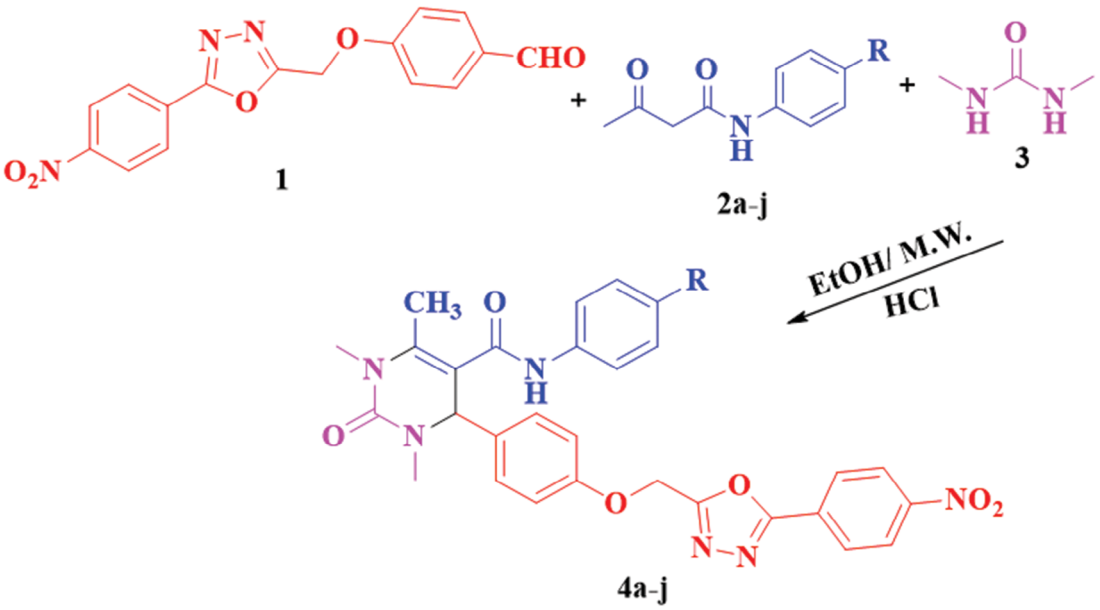


Figure 2. Synthetic route for 1,3,4-oxadiazole bearing aldehyde.



Where R=

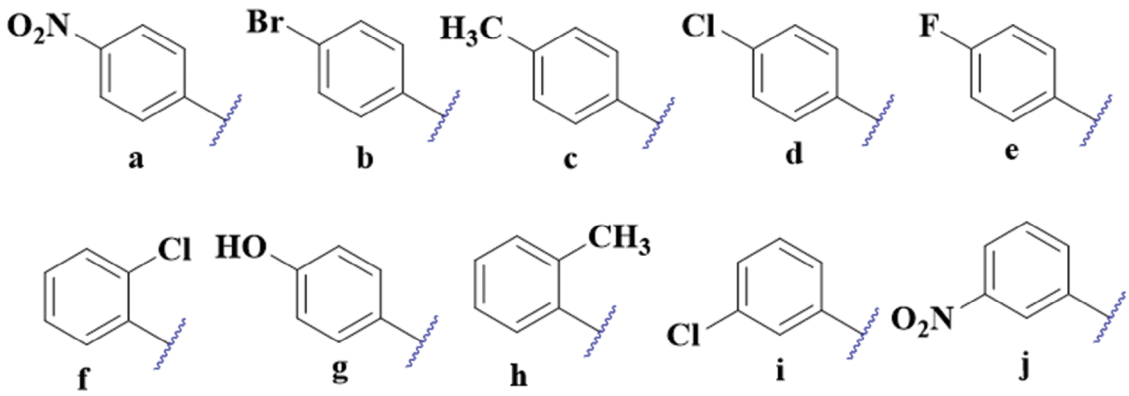


Figure 3. Microwave assisted one pot Biginelli synthesis of 1,3,4-oxadiazole bearing THPMs.

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Table 1. Optimization reaction conditions and comparison for synthesized compound **4a**

Entry	Solvent	Catalyst	Conventional Heating[a]			Microwave assisted[b]		
			Temp (°C)	Time (hr)	Yield (%)[c]	Temp (°C)	Time (min)	Yield (%)[c]
1	MeOH	HCl	reflux	21	12	reflux	20	22
2	MeCN	HCl	reflux	22	trace	reflux	22	16
3	THF	HCl	reflux	22	trace	reflux	20	11
4	DMF	-	100	20	24	100	19	39
5	**EtOH**	**HCl**	reflux	**20**	**59**	**reflux**	**20**	**92**
6	MeOH	PPh_3	reflux	21	19	reflux	20	32
7	EtOH	PPh_3	reflux	20	53	reflux	20	23

[a] Reaction carried out by conventional heating method; [b] Reaction carried out by microwave irradiation; [c] Isolated yield of product. Bold values indicate final optimal condition for the reaction

ventional heating method because of its less time consuming and gave higher yielded product.

Biology

All synthesized compounds were evaluated for in vitro antidiabetic activity by alpha amylase inhibition strategy. Some of the compounds show good inhibition as compared with the standard drug acarbose. Compounds **4a** (IC_{50}=82.23), **4e** (IC_{50}=82.31), **4g** (IC_{50}=78.13), and **4i** (IC_{50}=83.41) show good inhibition and the rest of all compounds shows good to moderate inhibition. All details are presented in **Table 2**. Comparisons of IC_{50} value of each compounds are shown in **Fig. 4**.

CONCLUSIONS

In this study, a series of 1,3,4-oxadiazole bearing tetrahydropyrimidine derivatives was synthesized by microwave irradiation method. All synthesized compounds were evaluated for in vitro antidiabetic screening. Derivatives **4a** (IC_{50}=82.23), **4e** (IC_{50}=82.31), **4g** (IC_{50}=78.13), and **4i** (IC_{50}=83.41) show excellent inhibition and the rest of the compounds show medium to moderate inhibition. All data are compared with the standard drug acarbose. In summary, new tetrahydropyrimidine derivatives may be used for their therapeutic potential and can serve as new therapies for diseases.

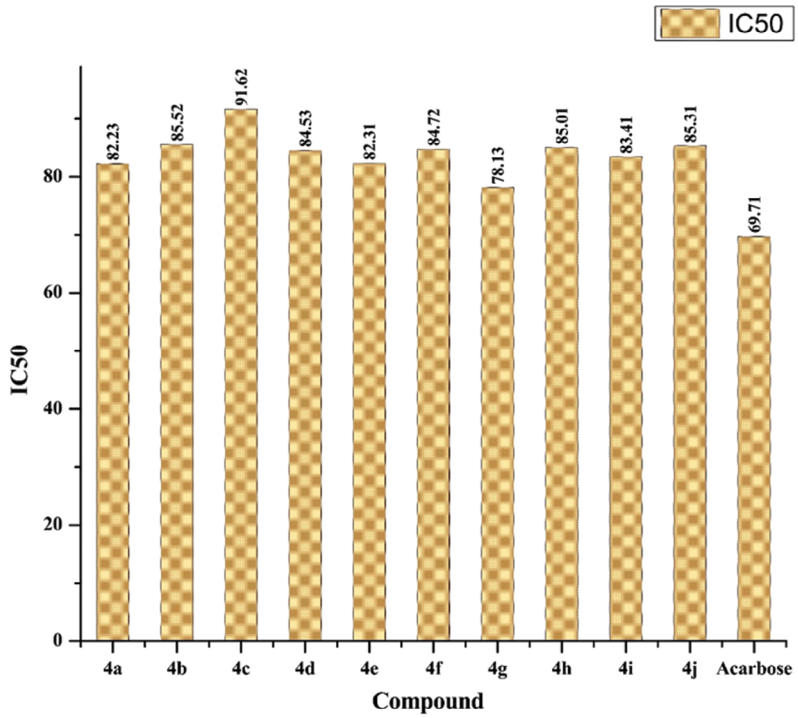

Figure 4. Comparisons of IC_{50} value of each compounds.

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

Entry	Compound	Concentration (μg/mL)	% Inhibition[a]	IC_{50}
1	4a	50	36.04±1.29	82.23
		75	45.76±1.41	
		100	60.39±2.45	
		125	78.91±3.41	
2	4b	50	35.84±3.07	85.52
		75	43.73±2.52	
		100	58.61±4.32	
		125	76.35±2.19	
3	4c	50	32.40±2.63	91.62
		75	41.62±0.13	
		100	54.25±2.81	
		125	70.27±2.60	
4	4d	50	35.62±0.72	84.53
		75	44.04±1.08	
		100	59.57±1.32	
		125	76.64±2.73	
5	4e	50	34.35±1.34	82.31
		75	46.20±1.75	
		100	59.14±2.42	
		125	78.48±1.26	
6	4f	50	33.71±1.84	84.72
		75	44.46±0.52	
		100	58.63±1.75	
		125	75.93±2.05	
7	4g	50	36.88±1.34	78.13
		75	48.53±0.34	
		100	59.88±1.13	
		125	78.10±1.46	
8	4h	50	31.31±1.23	85.01
		75	45.74±1.04	
		100	56.30±0.82	
		125	74.42±1.75	
9	4i	50	31.00±1.19	83.41
		75	46.75±1.82	
		100	56.23±2.07	
		125	72.40±1.36	
10	4j	50	35.76±1.56	85.31
		75	44.62±0.71	
		100	57.73±0.93	
		125	77.81±1.87	
11	Acarbose	50	39.50±0.29	69.71
		75	52.76±0.60	
		100	68.36±0.16	
		125	84.51±0.84	

[a] Inhibition ± standard deviation

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Acknowledgements

The authors have no support to report.

Authors are thankful to the School of Science, Department of Chemistry, RK University, Rajkot for providing all the facilities for completion of this work, and the National Facility for Drug Discovery (NFDD), Rajkot for providing spectral data.

Funding

The authors have no funding to report.

Competing Interests

The authors have declared that no competing interests exist.

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Микроволновой синтез биоактивных производных тетрагидропиримидина в качестве антидиабетических агентов

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Дата получения: 26 декабря 2020 ♦ **Дата приемки:** 19 февраля 2021 ♦ **Дата публикации:** 30 июня 2022

Образец цитирования: Vachhani M, Lalpara J, Hadiyal S, Dubal G. Microwave-assisted synthesis of bioactive tetrahydropyrimidine derivatives as antidiabetic agents. Folia Med (Plovdiv) 2022;64(3):478-487. doi: 10.3897/folmed.64.e62476.

Резюме

Введение: При открытии лекарств аналоги пиримидина демонстрируют хороший биологический отклик, и многие части лекарств имеют пиримидиновое ядро.

Цель: На основании предыдущего обзора синтезирован ряд N-(замещённый фенил) -1,3,6-триметил-4-(4-((5-(4-нитрофенил)-1,3,4-оксадиазол-2-ил)метокси)фенил)-2-оксо-1,2,3,4-тетрагидропиримидин-5-карбоксамид парада 1,3,4-оксадиазольного ядра, которые оценивали с помощью антидиабетического скрининга *in vitro*.

Материалы и методы: Производные тетрагидропиримидина синтезированы методом микроволнового облучения. Его осуществляли конденсацией Биджинелли 1,3,4-оксадиазола на основе альдегида, замещённого ацетоацетанилида и N,N'-диметилмочевины. Все синтезированные соединения были оценены с помощью антидиабетического скрининга.

Результаты: Согласно результатам, полученным в отношении противодиабетической активности, соединения **4a**, **4e**, **4g** и **4i** демонстрируют хорошее ингибирование по сравнению с другими из-за электроноакцепторных и гидроксильных групп. Все результаты сравнивают со стандартным препаратом акарбозой.

Заключение: В заключение, ряд 1,3,4-оксадизола, содержащего тетрагидропиримидин, был синтезирован и оценен на предмет антидиабетической активности *in vitro*. Производные **4a**, **4e**, **4g** и **4i** проявляли многообещающую противодиабетическую активность.

Ключевые слова

1,3,4-оксадиазол, антидиабетическая активность, СВЧ-облучение, тетрагидропиримидин