Indian Journal of Chemistry
Vol. 61, January 2022, pp. 60-68

Synthesis, spectral characterization and anti-diabetic activity evaluation of phosphoramidate derivatives

D Ravikumar[a], Ch Subramanyam[a], Ch Venkataramaiah[b], W Rajendra[b] & K Prasada Rao*[a]

[a] Department of Chemistry, Bapatla Engineering College, Bapatla 522 101, India

[b] Division of Molecular Biology, Department of Zoology, Sri Venkateswara University, Tirupati 517 502, India

Received 22 December 2019; accepted (revised) 6 December 2021

E-mail: prasad17467@gmail.com

In the present work, a series of new phosphoramidate derivatives have been conveniently synthesized by using 4-chlorobenzene-sulfonyl chloride as preliminary material *via* substituted sulfonamides as intermediates with high yields in a short period by conventional and microwave irradiation techniques. All the synthesized compound have been characterized by spectral and elemental analyses. An *in silico* molecular docking study has been performed to find potent anti-diabetic drugs. *In vitro* anti-diabetic activity of the title compounds have also been screened by standard α-amylase inhibition assay. Some of the tested compounds have been proven to possess promising activity when compared with reference drug.

Keywords: Phosphoramidates, 4-chlorobenzene sulfonyl chloride, molecular docking studies, anti-diabetic activity

Type 2 diabetes mellitus (T2DM) is a metabolic disorder caused primarily through insulin resistance and obesity. It is currently renowned as a major health problem worldwide and affects adults of working age in developing countries as per the global status report[1]. Conventional cure methods consist of numerous oral hypoglycemic agents. However, none of these agents sustain glucose levels forever and mostly without toxicity. Hence, researchers are looking forward to better options in novel drug development for T2DM. Dutta reported that[2]. Virtual screening tools such as QSAR data and docking models have been useful in drug discovery at many levels.

Phosphoramidates (PRs) are the major class of organophosphorus compounds containing P-N functionality and are structural analogs to phosphates reported in Gold Book[3]. Recent reports by Manfredini *et al*.[4,5] have shown that PRs exhibit a broad range of biological activities and could be used as prodrug moieties to improve the therapeutic potential of the parent drug. Zemlicka *et al*.[6] reported that the PRs in which the phosphate group is bonded with acyclic/cyclic/aryl amines or amino acid residues could develop lipophilicity and as a result, enriches their bioavailability and biological potency. Drugs possessing PR moiety can be used to treat cancer (Cyclophosphamide) (a), hepatitis C virus (sofosbuvir) (b), Alzheimer's disease; ascardioprotective (phosphocreatine) (c), antibacterial, anti-HIV, antigene agents were reported in literature[7-10]. In the literature[11–13] it is reported that PR moiety plays a key role in many structurally varied bioactive natural products, such as agrocin 84 (d), phosmidosine (e), and GS-6620 (f) (Figure 1). Due to the immense efficacy and possible applications of PRs in diverse fields of chemistry predominantly in pharmacy, fabulous curiosity has been paid for the synthesis of these compounds.

Recent investigations demonstrated the use of organophosphorus compounds in diabetic treatment. Pettersen *et al*. reported[14] that several patents have been filed and granted on various P containing compounds as potential anti-diabetic agents. These results encouraged the author to synthesize some new organophosphorus compounds with potent anti-diabetic activity.

On the other hand, microwave-assisted organic synthesis has been given away to provide several advantages than the standard heating techniques such as clean reactions, improved reaction yields and shortened reaction times, easy workup and/or solvent-free reaction conditions as reported in literature[15-20].

Based on previous reports and present need of developments on the synthesis of phosphoramidates and in an extension of our research to develop new anti-diabetic agents, we focused on the synthesis of some new phosphoramidates.

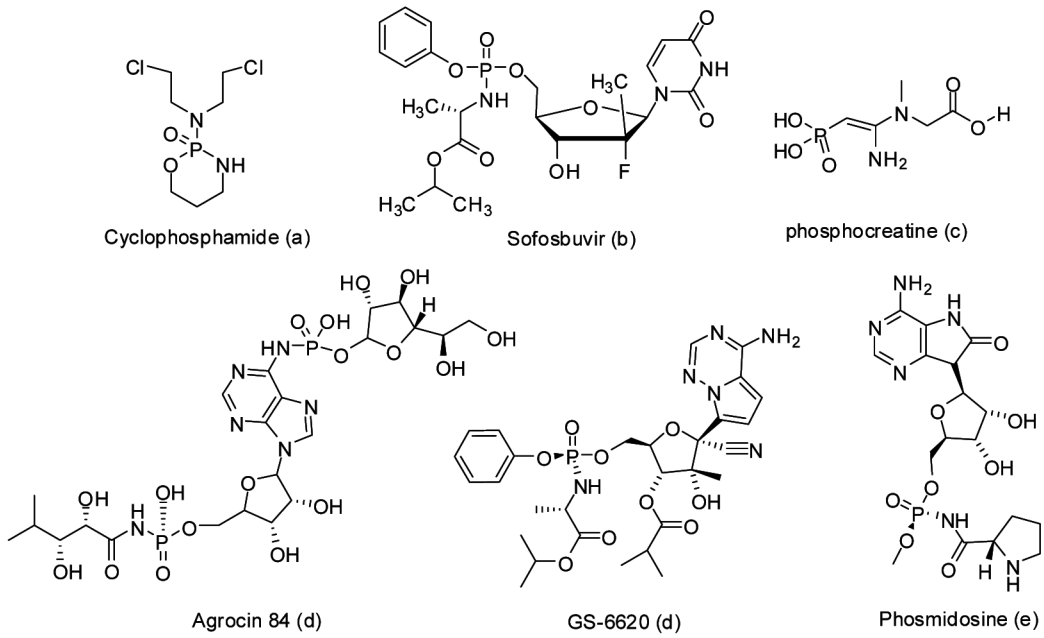


Figure 1 — Some drugs containing P-N functionality

Experimental Section

Materials and characterization techniques

The chemicals were purchased from Sd. Fine Chem. Ltd., India and a few of them were purified using standard procedures. The purity of the compounds was checked by TLC on Al sheet of silica gel. The reaction was carried out on magnetic agitator cum hot plate for conventional technique. Hot sale mini microwave oven digestion reactor was used for MW irradiation experiments. *J* (coupling constants) and δ (chemical shift) values were reported in Hz and ppm, respectively. Bruker AMX spectrometer was used to record ^{31}P (161.9 MHz), ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra. The symbols 's' for singlet, 'd' for doublet, 't' for triplet and 'm' for multiplet were used to represent peaks in NMR spectra. L.C. MS were recorded on Shimadzu 2010A. T. F. Flash 1112 apparatus was used for CHN analysis. Bruker IFS 55 (Equinox) FTIR spectrometer in KBr was used to record IR spectra.

Synthesis of sulfonamides (3a-j) reported in the literature[21,22]

The reaction of equimolar amounts of various amines **2a-j** (0.02 mol) with 4-chlorobenzene-sulfonyl chloride **1** (0.02 mol) in THF at reflux temperature for 4 h to yield the respective sulfonamides **3a-j**.

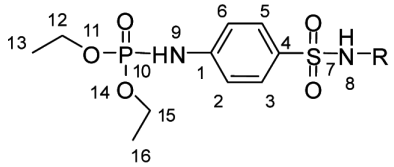


Figure 2 — The general structure of title compounds **5a-j**

Synthesis of phosphoramidate derivatives, 5a-j by conventional heating and microwave irradiation methods

In the conventional method, the sulfonamide **3a** (0.01 mol) was reacted with diethylphosporamidate **4** (0.01 mol) in THF using triethylamine at reflux temperature for 3-5 h to yield the corresponding phosphoramidates **5a-j**. The remaining compounds **5b-j** were also obtained by a similar protocol as discussed above. The yield was found in the range of 65-76%. While in microwave irradiation method, the sulfonamide **3a** (0.01 mol) was mixed with diethylphosporamidate **4** (0.01 mol) in a flask and were microwave radiated at 420 W at ambient temperature for about 9-17 min to obtain respective phosphoramidates **5a-j** (Figure 2). TLC (ethyl acetate: n-hexane, 1:4) was used for verifying the development of the process. Once the reaction was completed, the mixture was frozen to RT. The pure compound **5a** was obtained by column chromatography through ethylacetate: n-hexane (4:1)

as eluent. The remaining compounds **5b-j** were also obtained by a similar protocol as discussed above. The yield was found in the range of 85-95%.

Characterization of title compounds (7a-e and 8a-e)

Diethyl 4-(*N*-thiazol-2-ylsulfamoyl)phenylphosphoramidate, 5a: Yield: 85%; semi solid. ^{1}H NMR (DMSO-d_6): δ_H 12.45 (s, 1H, SO_2NH), 7.58 (d, 2H, Ar-H), 7.34 (d, 1H, Thiazole, -N=C-H), 6.86 (d, 2H, Ar-H), 6.67 (d, 1H, -S-C-*H*), 6.03 (s, 1H, P(O)N*H*), 4.45 (m, 4H, O-CH_2CH$_3$), 1.16 (t, J = 7.6 Hz, 6H, O-CH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ_C 145.7 (C-1), 130.0 (C-3, C-5), 129.7 (C-4), 116.6 (C-2, C-6), 62.1 (C-12, C-15), 16.0 (C-13, C-16), 71.7 (C-17), 137.0 (C-19), 112.1 (C-20); ^{31}P NMR (DMSO-d_6): δ_P 20.4; IR (KBr): 3469, 3331 (NH), 1344, 1161 (SO_2), 1211 (P=O), 1006 cm^{-1} (P-O-C_{alip}); LCMS: *m/z* (%) 392 (M+H$^+$,100). Calcd for $C_{13}H_{18}N_3O_5PS_2$: C, 39.89; H, 4.64; N, 10.74. Found: C, 39.95; H, 4.57; N, 10.83%.

Diethyl 4-(*N*-(4-aminophenyl)sulfamoyl) phenylphosphoramidate, 5b: Yield: 88%; semi solid. ^{1}H NMR (DMSO-d_6): δ_H 9.65 (s, 1H, SO_2NH), 7.58 (d, 2H, Ar-H), 6.86 (d, 2H, Ar-H), 6.45 (d, 4H, Ar-H), 6.03 (s, 1H, P(O)N*H*), 5.13 (s, 2H, -NH$_2$), 4.45 (m, 4H, O-CH_2CH$_3$), 1.16 (t, J = 7.6 Hz, 6H, O-CH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ_C 145.7 (C-1), 130.0 (C-3, C-5), 129.7 (C-4), 116.6 (C-2, C-6), 62.1 (C-12, C-15), 16.0 (C-13, C-16), 127.7 (C-17), 117.1 (C-18, C-19, C-21, C-22), 138.4 (C-20); ^{31}P NMR (DMSO-d_6): δ_P 18.1; IR (KBr): 3445, 3324 (NH), 1336, 1155 (SO_2), 1207(P=O), 1006 cm^{-1} (P-O-C_{alip}); LCMS: *m/z* (%) 400 (M+H$^+$,100). Calcd for $C_{16}H_{22}N_3O_5PS$: C, 48.11; H, 5.55; N, 10.52. Found: C, 48.17; H, 5.48; N, 10.59%.

Diethyl 4-(N-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl) sulfa moyl) phenylphosphoramidate, 5c: Yield: 90%; semi solid. ^{1}H NMR (DMSO-d_6): δ_H 12.45 (s, 1H, SO_2NH), 7.58 (d, 2H, Ar-H), 6.86 (d, 2H, Ar-H), 6.03 (s, 1H, P(O)N*H*), 4.45 (m, 4H, O-CH_2CH$_3$), 3.87 (s, 1H, =CH), 3.24 (s, 3H, -NCH$_3$), 2.95 (s, 3H, -NCH$_3$), 1.16 (t, J = 7.6 Hz, 6H, O-CH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ_C 145.7 (C-1), 130.0 (C-3, C-5), 129.7 (C-4), 116.6 (C-2, C-6), 62.1 (C-12, C-15), 16.0 (C-13, C-16), 163.2 (C-17), 162.3 (C-19), 75.5 (C-18), 151.4 (C-20), 29.0 (C-22), 28.3 (C-23); ^{31}P NMR (DMSO-d_6): δ_P 20.8; IR (KBr): 3460, 3327 (NH), 1340, 1158 (SO_2), 1213 (P=O), 1006 cm^{-1} (P-O-C_{alip}); LCMS: *m/z* (%) 447 (M+H$^+$,100). Calcd for $C_{16}H_{23}N_4O_7PS$: C, 43.05; H, 5.19; N, 12.55. Found: C, 43.11; H, 5.13; N, 12.62%.

Diethyl 4-(*N*-pyridin-3-ylsulfamoyl)phenylphosphoramidate, 5d: Yield: 92%; semi solid. ^{1}H NMR (DMSO-d_6): δ_H 12.45 (s, 1H, SO_2NH), 8.12 (d, 1H, Py-H), 8.07 (s, 1H, Py-H), 7.58 (d, 2H, Ar-H), 7.19 (d, 1H, Py-H), 7.14 (d, 1H, Py-H), 6.86 (d, 2H, Ar-H), 6.03 (s, 1H, P(O)N*H*), 4.45 (m, 4H, O-CH_2CH$_3$), 1.16 (t, J = 7.6 Hz, 6H, O-CH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ_C 145.7 (C-1), 130.0 (C-3, C-5), 129.7 (C-4), 116.6 (C-2, C-6), 62.1 (C-12, C-15), 16.0 (C-13, C-16), 145.1 (C-17), 137.1 (C-18), 138.8 (C-20), 124.7 (C-21), 122.8 (C-18); ^{31}P NMR (DMSO-d_6): δ_P 19.2; IR (KBr): 3460, 3330 (NH), 1341, 1145 (SO_2), 1216 (P=O), 1006 cm^{-1} (P-O-C_{alip}); LCMS: *m/z* (%) 386 (M+H$^+$,100). Calcd for $C_{15}H_{20}N_3O_5PS$: C, 46.75; H, 5.23; N, 10.90. Found: C, 46.82; H, 5.18; N, 10.97%.

Diethyl 4-(*N*-(3-nitrophenyl)sulfamoyl)phenylphosphoramidate, 5e: Yield: 87%; semi solid. ^{1}H NMR (DMSO-d_6): δ_H 12.45 (s, 1H, SO_2NH), 7.87 (s, 1H, Ar-H), 7.63 (d, 1H, Ar-H), 7.58 (d, 2H, Ar-H), 7.36 (t, 1H, Ar-H), 6.88 (d, 1H, Ar-H), 6.86 (d, 2H, Ar-H), 6.03 (s, 1H, P(O)N*H*), 4.45 (m, 4H, O-CH_2CH$_3$), 1.16 (t, J = 7.6 Hz, 6H, O-CH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ_C 145.7 (C-1), 130.0 (C-3, C-5), 129.7 (C-4), 116.6 (C-2, C-6), 62.1 (C-12, C-15), 16.0 (C-13, C-16), 138.6 (C-17), 113.1 (C-18), 148.7 (C-19), 113.9 (C-20), 130.4 (C-21), 125.5 (C-22); ^{31}P NMR (DMSO-d_6): δ_P 20.7; IR (KBr): 3462, 3337 (NH), 1348, 1165 (SO_2), 1219 (P=O), 1006 cm^{-1} (P-O-C_{alip}); LCMS: *m/z* (%) 430 (M+H$^+$,100). Calcd for $C_{16}H_{20}N_3O_7PS$: C, 44.76; H, 4.69; N, 9.79. Found: C, 44.82; H, 4.63; N, 9.85;%.

Diethyl 4-(*N*-(2-nitrophenyl) sulfamoyl) phenylphosphoramidate, 5f: Yield: 94%; semi solid. ^{1}H NMR (DMSO-d_6): δ_H 9.45 (s, 1H, SO_2NH), 7.58 (d, 2H, Ar-H), 7.98 (d, 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.45 (t, 1H, Ar-H), 6.86 (d, 2H, Ar-H), 6.81 (d, 1H, Ar-H), 6.03 (s, 1H, P(O)N*H*), 4.45 (m, 4H, O-CH_2CH$_3$), 1.16 (t, J = 7.6 Hz, 6H, O-CH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ_C 145.7 (C-1), 130.0 (C-3, C-5), 129.7 (C-4), 116.6 (C-2, C-6), 62.1 (C-12, C-15), 16.0 (C-13, C-16), 134.1 (C-17), 137.1 (C-18), 125.9 (C-19), 119.6 (C-20), 135.6 (C-21), 119.8 (C-22); ^{31}P NMR (DMSO-d_6): δ_P 21.8; IR (KBr): 3465, 3334

(NH), 1346, 1159 (SO_2), 1219 (P=O), 1006 cm^{-1} (P-O-C_{alip}); LCMS: *m/z* (%) 430 ($M+H^+$,100). Calcd for $C_{16}H_{20}N_3O_7PS$: C, 44.76; H, 4.69; N, 9.79. Found: C, 44.82; H, 4.63; N, 9.85;%.

Diethyl 4-(*N*-(6-aminopyridin-2-yl)sulfamoyl) phen ylphosphoramidate, 5g: Yield: 95%; semi solid. ^{1}H NMR (DMSO-d_6): δ_H 11.23 (s, 1H, SO_2NH), 7.58 (d, 2H, Ar-H), 6.86 (d, 2H, Ar-H), 7.16 (t, 1H, Ar-H), 6.06 (d, 2H, Ar-H), 6.43 (s, 2H, -NH_2), 6.03 (s, 1H, P(O)N*H*), 4.45 (m, 4H, O-CH_2CH$_3$), 1.16 (t, *J* = 7.6 Hz, 6H, O-CH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ_C 145.7 (C-1), 130.0 (C-3, C-5), 129.7 (C-4), 116.6 (C-2, C-6), 62.1 (C-12, C-15), 16.0 (C-13, C-16), 152.0 (C-17), 153.4 (C-19), 94.5 (C-20), 139.1 (C-21), 99.3 (C-22); ^{31}P NMR (DMSO-d_6): δ_P 18.6; IR (KBr): 3445, 3323 (NH), 1335, 1163 (SO_2), 1213 (P=O), 1006 cm^{-1} (P-O-C_{alip}); LCMS: *m/z* (%) 401 ($M+H^+$,100). Calcd for $C_{15}H_{21}N_4O_5PS$: C, 45.00; H, 5.29; N, 13.99. Found: C, 45.06; H, 5.35; N, 13.93%.

Diethyl 4-(*N*-thiomorpholinosulfamoyl) phenylp hosphoramidate, 5h: Yield: 91%; semi solid. ^{1}H NMR (DMSO-d_6): δ_H 10.35 (s, 1H, SO_2NH), 7.58 (d, 2H, Ar-H), 6.86 (d, 2H, Ar-H), 6.03 (s, 1H, P(O)N*H*), 4.45 (m, 4H, O-CH_2CH$_3$), 2.86 (m, 4H, N-CH$_2$), 2.46 (m, 4H, S-CH$_2$), 1.16 (t, *J* = 7.6 Hz, 6H, O-CH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ_C 145.7 (C-1), 130.0 (C-3, C-5), 129.7 (C-4), 116.6 (C-2, C-6), 62.1 (C-12, C-15), 16.0 (C-13, C-16), 58.6 (C-18, C-22), 25.4 (C-18, C-22); ^{31}P NMR (DMSO-d_6): δ_P 17.8; IR (KBr): 3436, 3315 (NH), 1326, 1148 (SO_2), 1210 (P=O), 1006 cm^{-1} (P-O-C_{alip}); LCMS: *m/z* (%) 410 ($M+H^+$,100). Calcd for $C_{14}H_{24}N_3O_5PS_2$: C, 41.07; H, 5.91; N, 1 0.26. Found: C, 41.13; H, 5.86; N, 10.32%.

Diethyl4-(*N*-(4-methylpiperazin-1-yl)sulfamoyl) phenylphosphoramidate, 5i: Yield: 94%; semi solid. ^{1}H NMR (DMSO-d_6): δ_H 10.35 (s, 1H, SO_2NH), 7.58 (d, 2H, Ar-H), 6.86 (d, 2H, Ar-H), 6.03 (s, 1H, P(O)N*H*), 4.45 (m, 4H, O-CH_2CH$_3$), 2.76 (m, 4H, N-CH$_2$), 2.34 (m, 4H, S-CH$_2$), 2.12 (s, 3H, N-CH$_3$), 1.16 (t, *J* = 7.6 Hz, 6H, O-CH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ_C 145.7 (C-1), 130.0 (C-3, C-5), 129.7 (C-4), 116.6 (C-2, C-6), 62.1 (C-12, C-15), 16.0 (C-13, C-16), 56.0 (C-18, C-22), 52.2 (C-18, C-22), 45.5 (C-23); ^{31}P NMR (DMSO-d_6): δ_P 17.3; IR (KBr): 3426, 3322 (NH), 1329, 1160 (SO_2), 1211 (P=O), 1006 cm^{-1} (P-O-C_{alip}); LCMS: *m/z* (%) 407 ($M+H^+$,100). Calcd for $C_{15}H_{27}N_4O_5PS$: C, 44.33; H, 6.70; N, 13.78. Found: C, 44.39; H, 6.64; N, 13.84%.

Diethyl 4-(*N*-benzo[d]thiazol-2-ylsulfamoyl) phenyl phosphoramidate, 5j: Yield: 89%; semi solid. ^{1}H NMR (DMSO-d_6): δ_H 12.45 (s, 1H, SO_2NH), 8.05 (d, 1H, Ar-H), 7.96 (d, 1H, Ar-H), 7.58 (d, 2H, Ar-H), 7.45 (m, 2H, Ar-H), 6.86 (d, 2H, Ar-H), 6.03 (s, 1H, P(O)N*H*), 4.45 (m, 4H, O-CH_2CH$_3$), 1.16 (t, *J* = 7.6 Hz, 6H, O-CH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ_C 145.7 (C-1), 130.0 (C-3, C-5), 129.7 (C-4), 116.6 (C-2, C-6), 62.1 (C-12, C-15), 16.0 (C-13, C-16), 174.5 (C-17), 130.8 (C-19), 153.2 (C-20), 121.8 (C-22), 124.5 (C-23), 125.3 (C-24), 118.3 (C-25); ^{31}P NMR (DMSO-d_6): δ_P 19.5; IR (KBr): 3455, 3326 (NH), 1337, 1158 (SO_2), 1215 (P=O), 1006 cm^{-1} (P-O-C_{alip}); LCMS: *m/z* (%) 442 ($M+H^+$,100). Calcd for $C_{17}H_{20}N_3O_5PS_2$: C, 46.25; H, 4.57; N, 9.52. Found: C, 46.32; H, 4.52; N, 9.58%.

Molecular docking studies

The structure of PPAR Gamma (PDB: 5YCP) and the reference drug, Rosiglitazone (Pub Chem ID 77999) was downloaded from the RCSB protein Data Bank and Pub Chem Database. The structures of enzyme (5YCP), and the reference drug were shown in Figure 3 (A and B). The chemical structure of title compounds was prepared using Chem Bio Draw; the energy minimization was carried out using Argus lab and converted into Pdbqt file format. Molecular docking studies were carried against PPAR Gamma protein with compounds **5a-j**, and the reference drug Rosiglitazone, using the docking module implemented in Pyrx 2010.12. The grid dimensions were predicted as ° X: 28.27, Y: 27.13, Z: 28.51 respectively. The docking was carried out with the default parameters i.e., placement: triangle matcher, recording 1: London dG, refinement: force field and a maximum of 10 conformations of each compound were allowed to be saved in a separate database file in a .mdb format. The binding energy and binding interactions of the protein–ligand complexes was determined using PyMol viewer tool (www.pymol.org)is reported in literature[23-25].

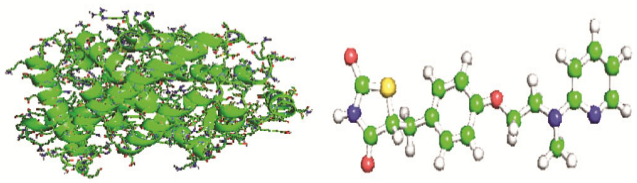


Figure 3 — PDB Structures of target protein (A) and standard drug (B)

α-Amylase inhibitory activity

The α-amylase inhibitory activity had been executed employing standard procedure according to Nickavar and Amin, 2011 which turned into at first proposed by Patil*et al*., 2013 with slight modifications[26,27]. The solution of compounds was organized in DMSO to provide the diverse concentrations (50, 100, 150 and 200 µg/mL). 500 µg/mL *α*-amylase solutions prepared in 0.02M sodium phosphate buffer (pH 6.9) was brought to one-of-a-kind concentrations of the compounds and incubated for 15 min at 25ºC. After 10 min, 500 µg/mL of one% starch solution in 0.02M of sodium phosphate buffer changed into delivered to every tube. The aggregate becomes further incubated at 25ºC for 10 min. Then the response combination becomes terminated via adding 0.5 mL of DNS reagent (12.0 g of sodium potassium tartrate tetrahydrate in eight mL of 2 M NaOH and ninety six mM 3,5-dinitrosalicylic acid solution) and the contents have been heated in a boiling water bathtub for five min. The absorption of the resulting reaction aggregate changed into measured at 540 nm. Acarbose changed into used as tremendous control/standard. Anti-diabetic activity of the compounds was determined by the inhibition of α-amylase. The percentage of inhibition was calculated by the equation:

$$\% \text{ inhibition} = [(AC-AS) / AC] \times 100$$

Where AC and AS is the absorbance of the control and sample respectively.

Results and Discussion

Chemistry

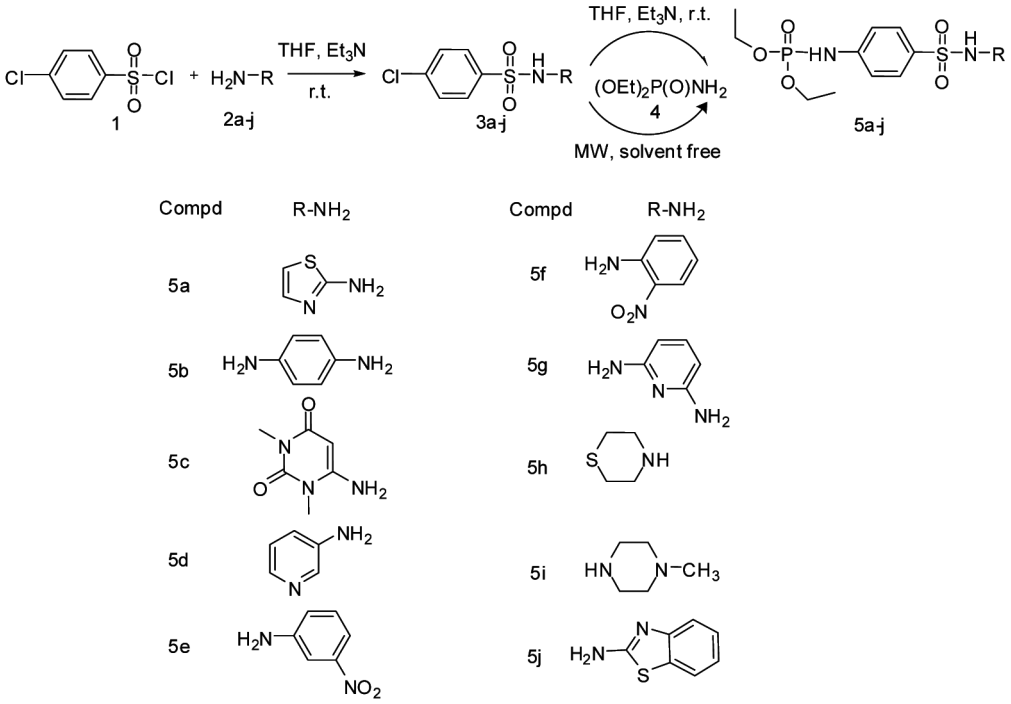
A series of new phosphoramidate derivatives were conveniently synthesized by using 4-chlorobenzene-sulfonyl chloride as starting material via substituted benzene sulfonamides as intermediates with high yields in a short time using conventional and microwave irradiation techniques. Initially, the conventional heating technique was utilized to synthesize the target compounds. We got moderate to good yields of the products in the range of 65-74%. Keeping in mind the importance of MW irradiation in organic synthesis and in an attempt to achieve better yields of the product, we used MW irradiation technique to synthesize target compounds. We analyzed the effect of microwave energy on the version reaction at 420 W. The yield of the products was enhanced and the time of reaction was decreased drastically after using MW conditions. The consequences of the entire synthesis were summarized in Table I. Scheme I represents the synthetic protocol of this process.

The chemical structures of all the title compounds **5a-j** were characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR, mass spectral data and elemental analyses and their data are presented in the experimental section. IR absorptions in the regions 3469-3315 and 1219-1207 cm^{-1} are assigned to NH and P=O stretching vibrations respectively for compounds, reported by Subramanyam *et al*.[28] The ^{1}H NMR spectra gave signals due to Ar-H in the range of δ 8.05-6.06 ppm. The proton signals in the range of 12.45-9.45 and at 6.03 ppm are due to SO_2-NH and P-NH respectively.

Table I — Comparison of microwave irradiation effect on the synthesis of phosphoramidates **5a-j**

Compd	Without MW irradiation [a]		With MW irradiation [b]	
	Time (h)	Yield [c] (%)	Time (min)	Yield [c] (%)
5a	4	65	20	85
5b	5	76	35	88
5c	4.5	70	30	90
5d	4	74	28	92
5e	4	69	26	87
5f	5	73	32	94
5g	4.5	74	35	95
5h	3.5	71	30	91
5i	3	72	18	94
5j	4	70	25	89

[a] Reaction of various substituted benzene sulfonamides **3a-j** and diethylphosphoramidate **4** in THF using triethylamine at RT; [b] Reaction of various substituted benzene sulfonamides **3a-j** and diethylphosphoramidate **4** without solvent under MW irradiation at optimum temperature; [c] Isolated yield



Scheme I — Synthesis of phosphoramidates **5a-j**

Table II — Bonding characterization of synthesized compounds **5a-j** and Rosiglitazone, (Reference drug) against PPAR Gamma protein

Compd	Binding energy (Kcal mol^{-1})	Binding interaction	Bond Length(Å)	Bond Angle (°)	Bond Type
Rtz.	−7.4	Ser 289 CB ….HN	2.4	109.1	H- don
5a	−7.6	Leu 330 CA …HN	2.7	88.7	H- don
5b	−6.9	Gly 258 CB ….HN	2.3	144.8	H- don
5c	−7.8	Ser 342 CZ ….OC	2.7	110.6	H- acc
		Gly 258 CA ….OC	3.2	131.4	H- acc
5d	−6.5	Leu 255 CB ….HN	2.7	94.7	H- don
5e	−8.5	Ser 289 CZ ….HN	2.4	138.4	H- acc
		Gly 343 CB ….ON	2.2	102.5	H- acc
5f	−7.6	Ser 342 CB ….ON	2.4	117.3	H- acc
5g	−6.7	Cys 285 CB ….HN	2.4	116.8	H- don
		Ser 289 CZ ….HN	2.4	145.8	H- don
5h	−6.3	Mer 364 CB ….HN	2.8	121.6	H- don
5i	−6.6	Ile 281 CZ ….HN	2.3	117.6	H- don
5j	−7.5	Ser 289 CA ….HN	2.4	109.1	H- don

The methylene and methyl protons of P-O-CH_2CH_3 resonated as multiplet and triplet respectively at δ 4.45 and δ 1.16.^{13}C NMR chemical shift for methylene and methyl carbons were observed at 62.1 ppm and 16.0 ppm respectively. ^{31}P NMR signals were observed in the region 21.8-17.3 ppm for **5a-j**, reported by Subramanyam *et al*.[29] In their mass spectra, $M^{+\cdot}$ ions were observed in the expected *m/z* values. The representative spectra of compound **5a** are given in supplementary Figures S1-S6 (Supplementary Information).

Biology

Molecular docking analysis was carried out for compounds **5a-j** with a selective pharmacological target such as PPAR Gamma which is a suitable target for anti-diabetic activity. The docking results of title compounds showed that all the majority of the compounds have shown higher binding modes than the control drug Rosiglitazone. The binding affinities and energy profiles of compounds **5a-j** along with reference drug, towards the active site of the enzyme, PPAR Gamma are summarized in Table II. The

present investigation demonstrates that the synthesized compounds will be the promising next-generation anti-diabetic drugs, which can be effectively used in the treatment of manifestation of diabetic complications. The 3D bonding images of best lead compounds were shown in Figure 4. Out of all the title compounds, **5a** (−7.6), **5c** (−7.8), **5e** (−8.5), **5f** (−7.6) and **5j** (−7.5K.Cal/mol) exhibited hydrophobic interactions with selected target protein. The present investigation demonstrates that the synthesized compounds will be the promising next-generation anti-diabetic drugs, which can be effectively used in the treatment of manifestation of diabetic complications.

Molecular docking results motivated us to screen the title compounds for their *in vitro* anti-diabetic activity by α-amylase inhibition activity method at four concentrations 50, 100, 150 and 200 µg/mL. The screening results (Table III) of **5a-j** showed that most of the derivatives exhibit good α-amylase inhibition activity when compared with the standard drug, Acarbose. Especially the compound **5e** bearing 3-

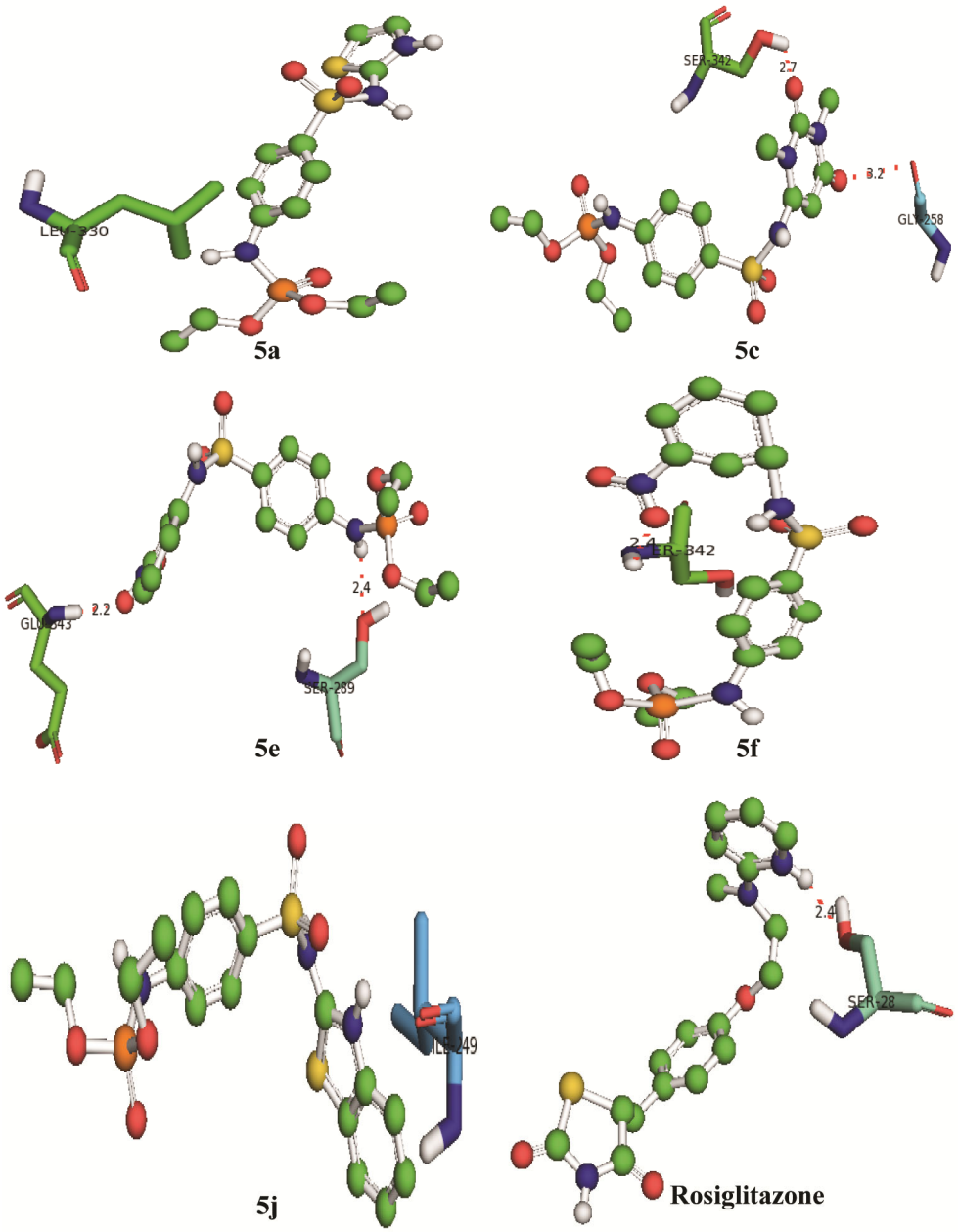


Figure 4 — Bonding interactions of the title lead compounds and standard with PPAR Gamma

Table III — Anti-diabetic activity of phosphoramidates (*α*-amylase inhibition activity)

Compd	% inhibition			
	50 µg/mL	100 µg/mL	150 µg/mL	200 µg/mL
5a	40.7	55.3	67.2	76.9
5b	32.4	43.3	59.9	68.7
5c	41.8	56.7	66.9	77.9
5d	21.2	38.0	48.6	57.1
5e	42.5	58.2	68.4	78.1
5f	22.4	33.4	42.2	55.3
5g	38.4	53.6	62.2	70.3
5h	15.0	23.1	37.0	42.1
5i	7.3	13.5	27.6	35.2
5j	38.8	47.5	59.2	71.3
Acarbose	47.8	61.2	75.2	85.9

nitrophenyl moiety (42.5-78.1 µg/mL); **5c** bearing with 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl motif (41.8-77.9 µg/mL); **5a** incorporated with N-thiazol-2-yl motif (40.7-76.9 µg/mL) and **5j** bearing with N-benzothiazol-2-yl moiety (38.8-71.3 µg/mL) exhibited good inhibition when compared with the standard drug, Acarbose.

Conclusion

The present study reports the successful synthesis of phosphoramidates in high yield in a short time. *In silico* molecular docking, a study was performed for the ligands against human PPAR γ protein for their anti-diabetic activity. The study showed that **5a** (thiazole moiety), **5c** (1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl moiety), **5e** (3-nitrophenyl moiety), **5f** (2-nitrophenyl moiety) and **5j** (N-benzothiazolyl moiety) exhibited higher binding energies with the target gene, PPARγ than the reference drug, Rosiglitazone (-7.4) which demonstrate that the synthesized compounds will become the promising next-generation anti-diabetic agents. *In vitro* anti-diabetic activity was performed by α-amylase inhibition activity method. The screening results of **5a-j** showed that most of the derivatives exhibit good *α*-amylase inhibition activity when compared with the standard drug, Acarbose. Especially the compound **5e** bearing 3-nitrophenyl moiety; **5c** bearing with 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl motif; **5a** incorporated with N-thiazol-2-yl motif and **5j** bearing with N-benzothiazol-2-yl moiety exhibited good inhibition when compared with the standard drug, Acarbose.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/58776.

Acknowledgments

Authors express their thanks to Dr. C. Naga Raju, Department of Chemistry, S. V. University, Tirupati for his constant support, Lila Impex Pharmaceuticals, Vijayawada and University of Hyderabad (Central University) for providing spectral data.

References

1 'Global status report on non-communicable diseases in 2014', World Health Organization, Geneva (2015).
2 Dutta S, *Drugs*, 9 (2015) 10.
3 *Compendium of Chemical Terminology*, 2nd edn (IUPAC the "Gold Book") (1997) Online corrected version (2006) "phosphoramides". DOI:10.1351/goldbook.A00484.
4 (a) Manfredini S, Baraldi P G, Durini E, Vertuani S, Balzarini J, De Clercq E, Karlsson A, Buzzoni V & Thelander L, *J Med Chem*, 42 (1999) 3243; (b) Yang K W, Brandt J J, Chatwood L L & Crowder M W, *Bioorg Med Chem Lett*, 10 (2000) 1085.
5 (a) McGuigan C & Swords B, *J Chem Soc Perkin Trans 1*, 51 (1992); (b) Egron D, Imbach J L, Gosselin G, Aubertin A M & Perigaud C, *J Med Chem*, 46 (2003) 4564; (c) Meyers C L F & Borch R F, *J Med Chem*, 43 (2000) 4319; (d) Chang S L, Griesgraber G W, Southern P J & Wagner C R, *J Med Chem*, 44 (2001) 223.
6 (a) Zemlicka J, *Biochim Biophys Acta*, 1587 (2002) 276; (b) Cahard D, McGuigan C & Balzarini J, *Mini Rev Med Chem*, 4 (2004) 371.
7 Patocka J, *Chemick'elisty*, 92 (1998) 1016.
8 Adams L A, Cox R J, Gibson J S, Mayo-Martin M B, Walter M & Whittingham W, *Chem Commun*, 18 (2002) 2004.
9 McGuigan C, Pathirana R N, Balzarini J & De Clercq E, *J Med Chem*, 36(8) (1993) 1048.
10 Letsinger R L, Singman C N, Histand G & Salunkhe M, *J Am ChemSoc*, 110 (1988) 4470.
11 Roberts W & Tate M, *Nature*, 265 (1977) 379.
12 Gao X, Tang Z, Lu M, Liu H, Jiang Y, Zhao Y & Cai Z, *Chem Commun*, 48 (2012) 10198.
13 Cho A, Zhang L, Xu J, Lee R, Butler T, Metobo S, Aktoudianakis V, Lew W, Ye H, Clarke M, Doerffler E, Byun D, Wang T, Babusis D, Carey A C, German P, Sauer D, Zhong W, Rossi S, Fenaux M, Mc Hutchison J G, Perry J, Feng J, Ray A S & Kim C U, *J Med Chem*, 57 (2014) 1812.
14 Pettersen E F, Goddard T D & Huang C C, *J Comput Chem*, 25 (2004) 1605.
15 Lidstrcom P & Tierney J P, *Microwave Assisted Organic Synthesis* (Blackwell Publishing, Oxford) (2005).
16 Larhed M & Olofsson K, 'Microwave Methods in Organic Synthesis', in *Topics in Current Chemistry*, Series Volume 266 (Springer, Berlin) (2006).
17 Dallinger D & Kappe C, *Chem Rev*, 107 (2007) 2563.

18 Kappe C O, Dallinger D & Murphree S, *Practical Microwave Synthesis for Organic Chemists*: *Strategies*, *Instruments*, *and Protocols* (Wiley-VCH, Weinheim) (2009).
19 Ravi Kumar D, Subramanyam Ch, Mohan S, Chandra Sekhar D & Prasada Rao K, *Materials Today Proceedings*, 5 (2018) 25832.
20 Sujatha B, Mohan S, Subramanyam Ch & Prasada Rao K, *Phosphorus*, *Sulfur*, *Silicon Relat Elem*,192, 3 (2017) 267.
21 Subramanyam Ch, Nayab Rasool Sk, Janakiramudu D B, Rasheed S, Uday Sankar A & Naga Raju C, *Phosphorus*, *Sulfur*, *Silicon Relat Elem*, 192(7) (2017) 845.
22 (a) https://dtp.cancer.gov/dtpstandard/servlet/dwindex?searchtype=NSC&output form at=html&searchlist=204519; (b) National Centre for Biotechnology Information, Pub Chem Database, CID=4651464, https://pubchem.ncbi.nlm.nih.gov /compound/N-4-Aminophenyl-4 chlorobenzenesulfonamide.
23 Morris G M, Huey R, Lindstrom W, Sanner M F, Belew R K, Goodsell D S & Olson A J, *J Comput Chem*, 30 (2009) 2785.
24 TerHaar E, Coll J T, Austen D A, Hsiao H M, Swenson L & Jain J, *Nat Struct Biol*, 8 (2001) 593.
25 Pettersen E F, Goddard T D & Huang C C, *J Comput Chem*, 25 (2004) 1605.
26 Nickavar B & Amin *G*, *Iranian J Pharm Res*, 10 (2011) 849.
27 Patil V S, Nandre K P, Ghosh S, Rao V J, Chopade B A, Sridhar B & Bhosale S V, *Eur J Med Chem*, 59 (2013) 304.
28 Subramanyam Ch, Venkata Ramana K, Rasheed S, Adam S & Naga Raju C, *Phosphorus*, *Sulfur*, *Silicon Relat Elem*, 188 (2013) 1228.
29 Subramanyam Ch, Taslimbhasha S K, Madhava G, Adam S K, Srinivasa Murthy S D & Naga Raju C, *Phosphorus*, *Sulfur*, *Silicon Relat Elem*, 192(3) (2017) 267.