



One-pot facile synthesis of novel 1,2,3-triazole-appended α -aminophosphonates

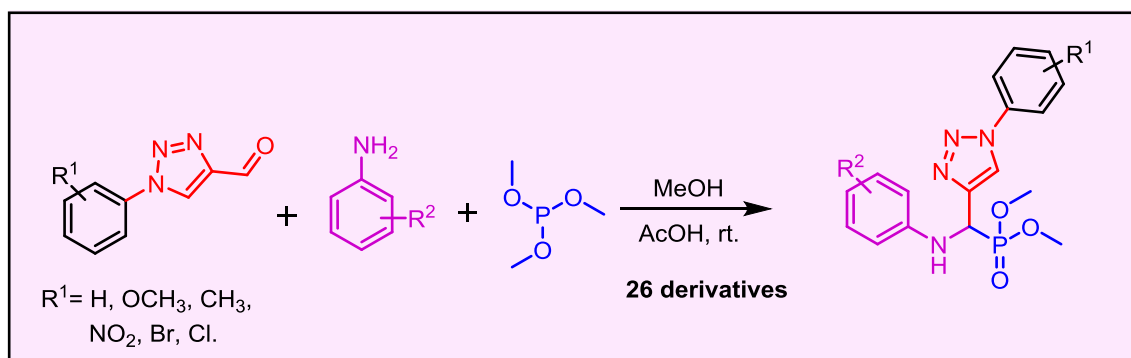
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Abstract

New α -aminophosphonates bearing 1,2,3-triazolyl moiety were easily synthesized by one-pot reaction of 1-aryl-1*H*-1,2,3-triazole-4-carbaldehydes, anilines and trimethyl phosphite in good to excellent yields. All the synthesized compounds were characterized by IR, ¹H NMR and ¹³C NMR analysis. These novel 1,2,3-triazole-incorporated α -aminophosphonates may be potential biological compounds due to the presence of both important moieties, 1,2,3-triazole and aminophosphonates.

Graphical abstract



Keywords 1,2,3-Triazole · α -Aminophosphonate · Multicomponent reaction · C–P bond formation

Introduction

The design and development of new synthetic strategies leading to diversely functionalized structures, which incorporates various active pharmacophores in a single molecular motif, have attracted great attention in synthetic organic chemistry. In particular, heterocyclic compounds hold a

special place among medicinally active products. The development of a simple and efficient synthesis of compounds incorporating heterocyclic ring has given a new dimension to the drug discovery and development.

The term click chemistry which was hosted by Sharpless group is a cycloaddition reaction between alkyne and azide catalyzed by Cu(I), and it selectively gives 1, 4-disubstituted 1,2,3-triazoles [1–6]. The 1,2,3-triazole ring has great importance in medicinal chemistry [7–9]. The 1,2,3-triazole containing drugs, 5-amino-1-(3,5-dichloro-4-(4-chlorobenzoyl)benzyl)-1*H*-1,2,3-triazole-4-carboxamide (CAI), cefatrizine and tazobactam are available in the market (Fig. 1). The 1,2,3-triazole is an bioisostere of amide [10] and also displays various biological activities including α -glucosidases inhibitors [11], anticancer [12],

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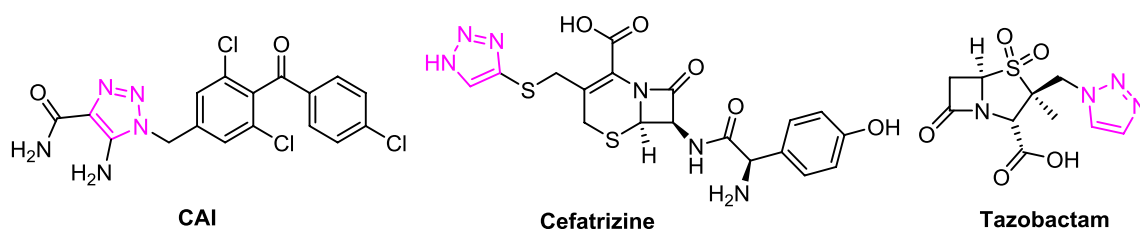


Fig. 1 Structures of 1,2,3-triazole containing drugs

anti-inflammatory, anti-nociceptive [13], antifungal [14], antibacterial [15] and antitubercular activities [16].

Organophosphorous compounds have found a wide range of applications in the agriculture, organic and medicinal chemistry owing to their biological and pharmacological properties as well as synthetic intermediates [17]. The α -aminophosphonates are a well-known privileged structure and have a wide range of applications in medicinal chemistry [18–22] and are structural analogues of amino acids [18, 19]. The α -aminophosphonates possess a wide spectrum of biological activities including antifungal [23], antimicrobial [24], antiviral [25, 26], anticancer [27], anti-inflammatory [28] and antiproliferative activities [29]. The heterocyclic ring containing α -aminophosphonates displays various biological activities [18, 19, 30–33]. Furthermore, there are some reports on the synthesis of β -aminophosphonates, phosphinates [34], α -aminophosphonic acids [35] and the biological activity of aminophosphonic acids [36]. The

representative structures of α -aminophosphonate group appended on heterocyclic skeleton are shown in Fig. 2.

A literature survey reveals that an extensive work was done on the synthesis of α -aminophosphonates using a variety of catalysts such as LiClO_4 [37–39], (LiClO_4 , TsOH) [40], MoO_2Cl_2 [41], GaI_3 [42], $\text{Mg}(\text{ClO}_4)_2$ [43], solvate ionic liquid [44], nano-magnetic sulfated zirconia ($\text{Fe}_3\text{O}_4 @ \text{ZrO}_2/\text{SO}_4^{2-}$) [45], $\text{Yb}(\text{OTf})_3$ [46], HfCl_4 [47], $\text{SiO}_2\text{-ZnBr}_2$ [48], lanthanide triflate [49], ytterbium perfluorooctanoate [50], SmI_2 [51], $\text{TaCl}_5\text{-SiO}_2$ [52], BiCl_3 [53], FeCl_3 [54], $[\text{CpRu}(\text{PPh}_3)_2\text{Cl}]$ [55], camphor sulfonic acid [56] and 1-hexanesulphonic acid sodium salt [57].

In view of the above and continuation of research program on chemistry and biology of 1,2,3-triazole containing compounds [58–66], herein, we would like to report about the synthesis of new 1,2,3-triazole-appended α -aminophosphonates using the molecular hybridization approach.

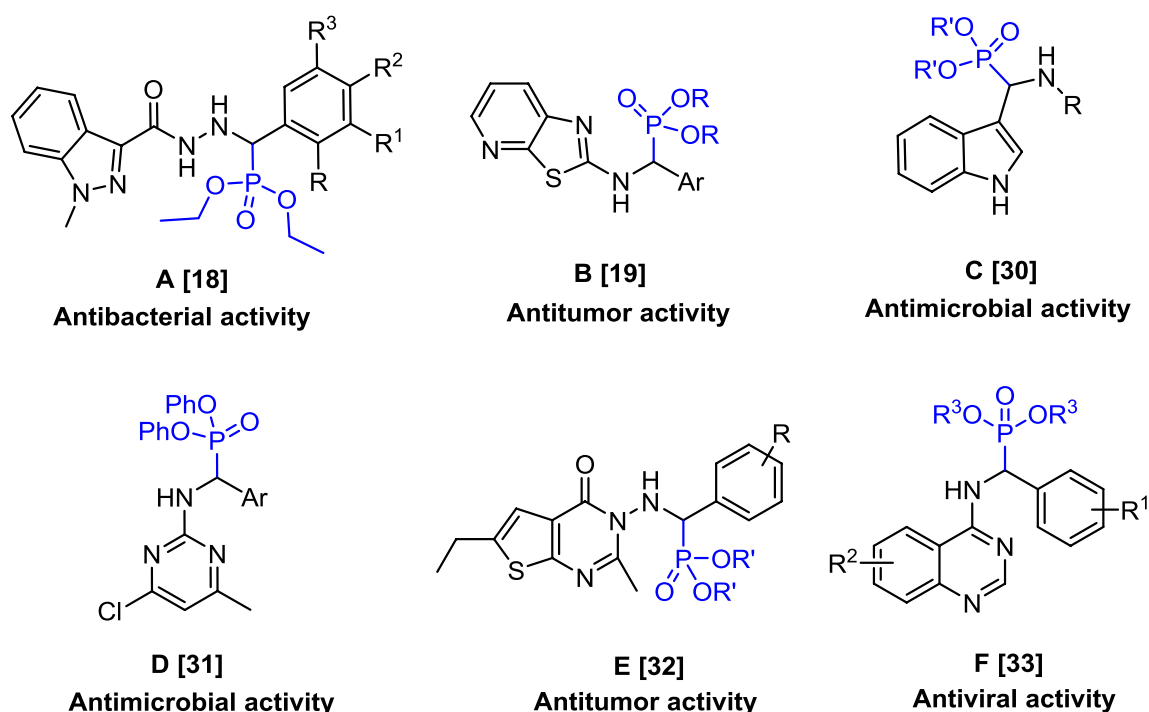


Fig. 2 Representative structures of α -aminophosphonate conjugated with heterocycles

Experimental

All the required reagents were purchased from Sigma-Aldrich, Alfa Aesar, Spectrochem and used without purification. Melting points were obtained on open capillary electrothermal apparatus and are uncorrected. Infrared (IR) spectra were measured using Alpha Bruker FT-IR spectrometer. The compounds were confirmed by NMR on a Bruker Avance 400 and 200 MHz spectrometer. The compounds were solubilized in CDCl_3 and the TMS used as internal standard. The DEPT experiment was used for the assignment of the ^{13}C signals. Multiplicity of the signals is shown as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublet (dd) and coupling constant J are given in Hz. The HRMS spectra were recorded under electrospray ionization ESI HRMS.

General procedure for the preparation of 1,2,3-triazole-appended α -aminophosphonates 14a-z

In a round-bottom flask equipped with a magnetic stirring bar, a mixture of 1-aryl-1*H*-1,2,3-triazole-4-carbaldehydes (0.5 mmol) and anilines (0.5 mmol) in methanol–acetic acid was stirred, once the formation of Schiff's base takes place, trimethyl phosphite (0.5 mmol) was added to the reaction mixture and stirred for 1.5–3 h at room temperature till completion of the reaction. The progress of reaction was monitored by TLC. After completion of the reaction, the resulting mixture was poured on 50 mL ice water to obtain solid, filtered, dried and recrystallized by aqueous ethanol to get α -aminophosphonates.

Dimethyl ((1-phenyl-1*H*-1,2,3-triazol-4-yl) (*p*-tolylamino)methyl)phosphonate (14b)

IR ν_{max} cm^{-1} : 3309, 1611, 1514, 1449, 1236, 1039, 822, 756, 689. ^1H NMR (200 MHz, CDCl_3) δ 8.07 (s, 1H), 7.68 (s, 2H), 7.49–7.45 (m, 3H), 6.98 (d, $J=6$ Hz, 2H), 6.68 (d, $J=6$ Hz, 2H), 5.20 (d, $J=22$ Hz, 1H), 4.62 (s, 1H), 3.87 (d, $J=12$ Hz, 3H), 3.73 (d, $J=12$ Hz, 3H), 2.21 (s, 3H). ^{13}C NMR (50 MHz, CDCl_3) δ 143.5, 143.3, 136.9, 129.9, 129.7, 128.9, 128.6, 120.8, 120.4, 114.3, 54.4 (d, $J=7$ Hz), 53.9 (d, $J=7$ Hz), 48.8 (d, $J=158.5$ Hz), 20.4.

Dimethyl (((2,4-difluorophenyl)amino) (1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)phosphonate (14e)

IR ν_{max} cm^{-1} : 3296, 1599, 1510, 1441, 1248, 1204, 1041, 835, 755. ^1H NMR (200 MHz, CDCl_3) δ 8.12 (s,

1H), 7.73 (d, $J=6$ Hz, 2H), 7.51–7.43 (m, 3H), 6.83 (s, 1H), 6.78–6.75 (m, 2H), 5.16 (dd, $J=22$ and 8 Hz, 1H), 4.70 (s, 1H), 3.89 (d, $J=10$ Hz, 3H), 3.74 (d, $J=10$ Hz, 3H). ^{13}C NMR (50 MHz, CDCl_3) δ 143.9, 136.8, 129.8, 129.0, 120.7, 120.4, 114.3, 111.1, 110.7, 104.4, 103.8, 103.4, 54.5 (d, $J=7$ Hz), 53.9 (d, $J=7.5$ Hz), 48.8 (d, $J=159.5$ Hz).

Dimethyl (((4-methoxyphenyl)amino) (1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)phosphonate (14f)

IR ν_{max} cm^{-1} : 3301, 1592, 1505, 1456, 1229, 1176, 1028, 826, 754, 682. ^1H NMR (400 MHz, CDCl_3) δ 8.07 (s, 1H), 7.69 (d, $J=8$ Hz, 2H), 7.49 (t, $J=8$ Hz, 2H), 7.41 (t, $J=8$ Hz, 1H), 6.74 (m, 4H), 5.14 (dd, $J=24$ and 8 Hz, 1H), 4.49 (t, $J=8$ Hz, 1H), 3.87 (d, $J=12$ Hz, 3H), 3.73 (d, $J=12$ Hz, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 153.3, 144.5, 139.7, 136.8, 129.7, 128.8, 120.7, 120.4, 115.7, 114.8, 55.6, 54.4 (d, $J=7.0$ Hz), 53.8 (d, $J=7.0$ Hz), 49.6 (d, $J=159$ Hz). HRMS, calculated mass for $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_4\text{P}$ ($\text{M}+\text{H}$) $^+$: 389.1379 and found: 389.1386.

Dimethyl (((2,4-difluorophenyl)amino) (1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phosphonate (14g)

IR ν_{max} cm^{-1} : 3283, 1610, 1509, 1459, 1285, 1243, 1023, 957, 750. ^1H NMR (400 MHz, CDCl_3) δ 8.23 (s, 1H), 7.78 (d, $J=4$ Hz, 1H), 7.41 (s, 1H), 7.07 (t, $J=8$ Hz, 2H), 6.83–6.72 (m, 3H), 5.16 (dd, $J=20$ and 8 Hz, 1H), 4.70 (s, 1H), 3.87 (d, $J=12$ Hz, 3H), 3.85 (s, 3H), 3.72 (d, $J=12$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 150.9, 142.3, 130.3, 126.0, 125.3, 124.8, 121.2, 114.6, 112.2, 110.9, 110.7, 103.9, 103.7, 103.5, 55.9, 54.3 (d, $J=7$ Hz), 53.9 (d, $J=7$ Hz), 49.0 (d, $J=159$ Hz).

Dimethyl (((4-chlorophenyl)amino) (1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)phosphonate (14h)

IR ν_{max} cm^{-1} : 3292, 1593, 1532, 1490, 1240, 1174, 1025, 824, 751, 639. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (s, 1H), 7.77 (dd, $J=8$, 4 Hz, 1H), 7.41 (t, $J=8$ Hz, 1H), 7.12 (d, $J=8$ Hz, 2H), 7.09–7.04 (m, 2H), 6.70 (d, $J=12$ Hz, 2H), 5.16 (dd, $J=24$ and 8 Hz, 1H), 4.75 (s, 1H), 3.84 (d, $J=12$ Hz, 3H), 3.82 (s, 3H), 3.71 (d, $J=12$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 151.0, 144.6, 142.4, 130.2, 129.1, 126.2, 125.3, 124.8, 123.8, 121.2, 115.4, 112.3, 55.9, 54.2 (d, $J=7$ Hz), 53.9 (d, $J=7$ Hz), 48.9 (d, $J=159$ Hz).

Dimethyl ((1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)(*p*-tolylamino)methyl)phosphonate (14i)

IR $\nu_{\max}$ cm^{-1} : 3302, 1605, 1508, 1463, 1242, 1174, 1028, 820, 748, 661. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (s, 1H), 7.77 (d, $J=8$ Hz, 1H), 7.39 (t, $J=8$ Hz, 1H), 7.09–7.03 (m, 2H), 6.98 (d, $J=8$ Hz, 2H), 6.69 (d, $J=8$ Hz, 2H), 5.19 (dd, $J=20$ and 8 Hz, 1H), 4.58 (s, 1H), 3.85 (d, $J=8$ Hz, 3H), 3.82 (s, 3H), 3.71 (d, $J=12$ Hz, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 150.9, 143.7, 142.9, 130.1, 129.8, 128.3, 126.2, 125.3, 124.8, 121.2, 114.4, 112.2, 55.9, 54.2 (d, $J=6$ Hz), 53.9 (d, $J=8$ Hz), 49.0 (d, $J=159$ Hz), 20.4.

Dimethyl (((3-bromophenyl)amino) (1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl) phosphonate (14j)

IR $\nu_{\max}$ cm^{-1} : 3289, 1588, 1470, 1231, 1175, 1028, 864, 826, 758, 667. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (s, 1H), 7.75 (d, $J=8$ Hz, 1H), 7.38 (t, $J=8$ Hz, 1H), 7.08–6.97 (m, 3H), 6.90 (s, 1H), 6.84 (d, $J=8$ Hz, 1H), 6.67 (d, $J=8$ Hz, 1H), 5.15 (dd, $J=24$ and 4 Hz, 1H), 4.91 (s, 1H), 3.82 (d, $J=8$ Hz, 3H), 3.79 (s, 3H), 3.69 (d, $J=8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 151.0, 147.5, 142.2, 130.7, 130.3, 126.1, 125.4, 124.9, 123.2, 121.9, 121.3, 116.9, 112.7, 112.3, 56.0, 54.3 (d, $J=7$ Hz), 54.0 (d, $J=7$ Hz), 48.5 (d, $J=159$ Hz).

Dimethyl ((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)(phenylamino)methyl)phosphonate (14m)

IR $\nu_{\max}$ cm^{-1} : 3291, 1599, 1497, 1461, 1215, 1178, 1031, 988, 830, 749, 696. ^1H NMR (400 MHz, CDCl_3) δ 8.06 (s, 1H), 7.56 (d, $J=8$ Hz, 2H), 7.17 (t, $J=8$ Hz, 2H), 6.96 (d, $J=12$ Hz, 2H), 6.79–6.76 (m, 3H), 5.26 (d, $J=24$ Hz, 1H), 4.95 (s, 1H), 3.87 (d, $J=12$ Hz, 3H), 3.83 (s, 3H), 3.74 (d, $J=8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.8, 145.9, 144.2, 130.3, 129.3, 121.9, 120.9, 119.0, 114.7, 114.0, 55.6, 54.3 (d, $J=7$ Hz), 53.9 (d, $J=7$ Hz), 48.4 (d, $J=159$ Hz).

Dimethyl (((4-chlorophenyl)amino) (1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl) phosphonate (14r)

IR $\nu_{\max}$ cm^{-1} : 3297, 1552, 1502, 1328, 1227, 1178, 1047, 1007, 833, 747. ^1H NMR (400 MHz, CDCl_3) δ 8.39 (d, $J=8.0$ Hz, 2H), 8.21 (d, $J=4$ Hz, 1H), 7.94 (d, $J=8.0$ Hz, 2H), 7.12 (d, $J=8$ Hz, 2H), 6.68 (d, $J=8$ Hz, 2H), 5.18 (dd, $J=24$ and 8 Hz, 1H), 4.81 (t, $J=8$ Hz, 1H), 3.89 (d, $J=12$ Hz, 3H), 3.76 (d, $J=12$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 147.4, 145.2, 144.3, 140.9, 129.4, 125.6, 124.3, 121.6, 120.5, 115.3, 54.6 (d, $J=7$ Hz), 54.0 (d, $J=7$ Hz), 48.5 (d, $J=158$ Hz).

Dimethyl ((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl) (*p*-tolylamino)methyl)phosphonate (14s)

IR $\nu_{\max}$ cm^{-1} : 3288, 1602, 1521, 1444, 1334, 1239, 1172, 1014, 843, 797, 745, 676. ^1H NMR (400 MHz, CDCl_3) δ 8.36 (d, $J=8$ Hz, 2H), 8.23 (s, 1H), 7.90 (d, $J=8$ Hz, 2H), 6.97 (d, $J=12$ Hz, 2H), 6.67 (d, $J=8$ Hz, 2H), 5.23 (dd, $J=24$ and 8 Hz, 1H), 4.74 (t, $J=8.0$ Hz, 1H), 3.89 (d, $J=12$ Hz, 3H), 3.77 (d, $J=12$ Hz, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 147.2, 145.7, 143.3, 140.9, 129.9, 128.8, 125.4, 120.7, 120.4, 114.2, 54.5 (d, $J=7$ Hz), 53.9 (d, $J=7$ Hz), 48.6 (d, $J=158$ Hz), 20.4. HRMS, calculated mass for $\text{C}_{18}\text{H}_{21}\text{N}_5\text{O}_5\text{P}$ ($\text{M} + \text{H}^+$): 418.1280 and found: 418.1283.

Dimethyl ((1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl) (4-methoxyphenyl)amino)methyl)phosphonate (14v)

IR $\nu_{\max}$ cm^{-1} : 3328, 1592, 1510, 1234, 1177, 1038, 831, 776, 674. ^1H NMR (400 MHz, CDCl_3) δ 8.09 (s, 1H), 7.74 (s, 1H), 7.59 (d, $J=8$ Hz, 1H), 7.42–7.39 (m, 2H), 6.73 (q, $J=8$ Hz, 4H), 5.14 (dd, $J=24$ and 8 Hz, 1H), 4.53 (s, 1H), 3.88 (d, $J=8$ Hz, 3H), 3.74 (d, $J=12$ Hz, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 153.3, 144.9, 139.7, 139.6, 137.6, 135.5, 130.8, 128.9, 120.6, 118.3, 115.7, 114.8, 55.6, 54.4 (d, $J=7$ Hz), 53.8 (d, $J=7$ Hz), 49.5 (d, $J=159$ Hz).

Dimethyl ((1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl) (4-chlorophenyl)amino)methyl)phosphonate (14w)

IR $\nu_{\max}$ cm^{-1} : 3304, 1592, 1493, 1239, 1035, 829, 776, 646. ^1H NMR (400 MHz, CDCl_3) δ 8.12 (s, 1H), 7.73 (s, 1H), 7.57 (d, $J=8$ Hz, 1H), 7.44–7.40 (m, 2H), 7.10 (d, $J=8$ Hz, 2H), 6.68 (d, $J=8$ Hz, 2H), 5.18 (dd, $J=20$ and 8 Hz, 1H), 4.94 (t, $J=8$ Hz, 1H), 3.87 (d, $J=8$ Hz, 3H), 3.74 (d, $J=12$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 144.4, 144.3, 137.6, 135.6, 130.8, 129.2, 128.9, 123.9, 120.7, 120.6, 118.3, 115.2, 54.4 (d, $J=7.0$ Hz), 53.9 (d, $J=8$ Hz), 48.5 (d, $J=158$ Hz).

Dimethyl ((1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl) (*p*-tolylamino)methyl)phosphonate (14x)

IR $\nu_{\max}$ cm^{-1} : 3323, 1593, 1514, 1490, 1242, 1040, 889, 779, 676. ^1H NMR (400 MHz, CDCl_3) δ 8.08 (s, 1H), 7.74 (s, 1H), 7.58 (d, $J=8$ Hz, 1H), 7.42–7.39 (m, 2H), 6.97 (d, $J=8$ Hz, 2H), 6.67 (d, $J=8$ Hz, 2H), 5.20 (dd, $J=20$ and 8 Hz, 1H), 4.65 (t, $J=8$ Hz, 1H), 3.88 (d, $J=12$ Hz, 3H), 3.74 (d, $J=8$ Hz, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 144.9, 143.4, 143.3, 137.7, 135.5, 130.8, 129.9, 128.9, 128.6, 120.6, 118.3, 114.2, 54.4 (d, $J=7$ Hz), 53.8 (d, $J=7$ Hz), 48.8 (d, $J=158$ Hz), 20.4.

Dimethyl ((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)((4-chlorophenyl)amino)methyl)phosphonate (**14z**)

IR $\nu_{\max}$ cm^{-1} : 3280, 1591, 1489, 1313, 1237, 1036, 818, 740. ^1H NMR (400 MHz, CDCl_3) δ 8.11 (s, 1H), 7.61 (d, $J=8$ Hz, 2H), 7.45 (d, $J=8$ Hz, 2H), 7.10 (d, $J=8$ Hz, 2H), 6.69 (d, $J=8$ Hz, 2H), 5.18 (dd, $J=20$ and 8 Hz, 1H), 5.00 (t, $J=8$ Hz, 1H), 3.87 (d, $J=12$ Hz, 3H), 3.74 (d, $J=12$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 144.5, 144.4, 135.3, 134.8, 129.9, 129.3, 124.0, 121.6, 120.8, 115.3, 54.5 (d, $J=7$ Hz), 54.0 (d, $J=7$ Hz), 48.6 (d, $J=159$ Hz).

Results and discussion

Chemistry

To optimize the best reaction condition for executing a one-pot three component reaction for the preparation of new triazole-appended α -aminophosphonates requires 1,2,3-triazolyl aldehydes as a starting material. The 1-aryl-1*H*-1,2,3-triazole-4-carbaldehydes were prepared from corresponding commercially available anilines. Anilines, sodium nitrite and hydrochloric acid were appropriately combined to form corresponding diazonium salts, which were subsequently converted into aromatic azides by adding the solution of sodium azide. The synthesis of 1,2,3-triazoles involves the 1,3-dipolar cycloaddition (click reaction) between propargyl alcohol and aromatic azides using *t*-butanol: H_2O as solvent, catalyzed by Cu(I) and provided only the 1,4-regioisomers in good yields ranging from 60 to 86%. Triazolyl alcohols were further oxidized to aldehydes using Collins reagent $\text{CrO}_3:2\text{Py}$ in CH_2Cl_2 in 50–65% yields.

The triazolyl aldehydes have many applications in synthetic organic chemistry for the construction of diversely functionalized bioactive molecules (Fig. 3). Boechat et al. reported [67] the hydrazone **1** was derived from triazolyl aldehyde and isonicotinic acid hydrazide and it displays good antitubercular activity. Wang et al. constructed [68] the molecules **2**, **3** and evaluated for their anti-phytopathogenic activity. The molecule **4** has been synthesized and evaluated for their antifungal activity by Dai et al. [69]. The triazolyl nitrone **5** as anti-inflammatory and anticancer agents was also reported [70]. The tuberculosis inhibitory activity was reported [71] for the compound **6** and antifungal activity for **7** [72]. Ismail et al. combined two heterocycles in single molecule **8** and it was evaluated as immune potentiator [73]. The molecule **9** [74] were reported for their α -glycosidases activity and **10** [75] were reported in the literature for their antimicrobial activity.

Recently, we have reported [58, 59] the use of triazolyl aldehydes for the synthesis of triazole-diindolylmethane

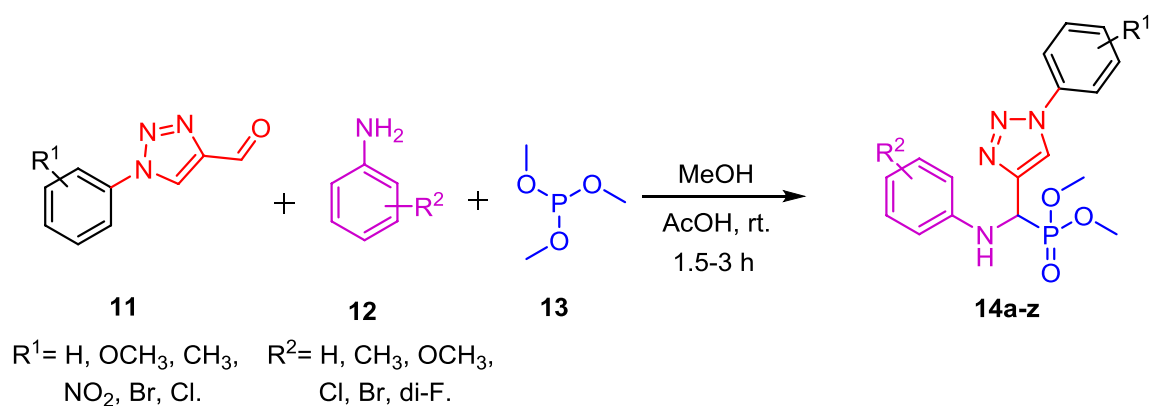
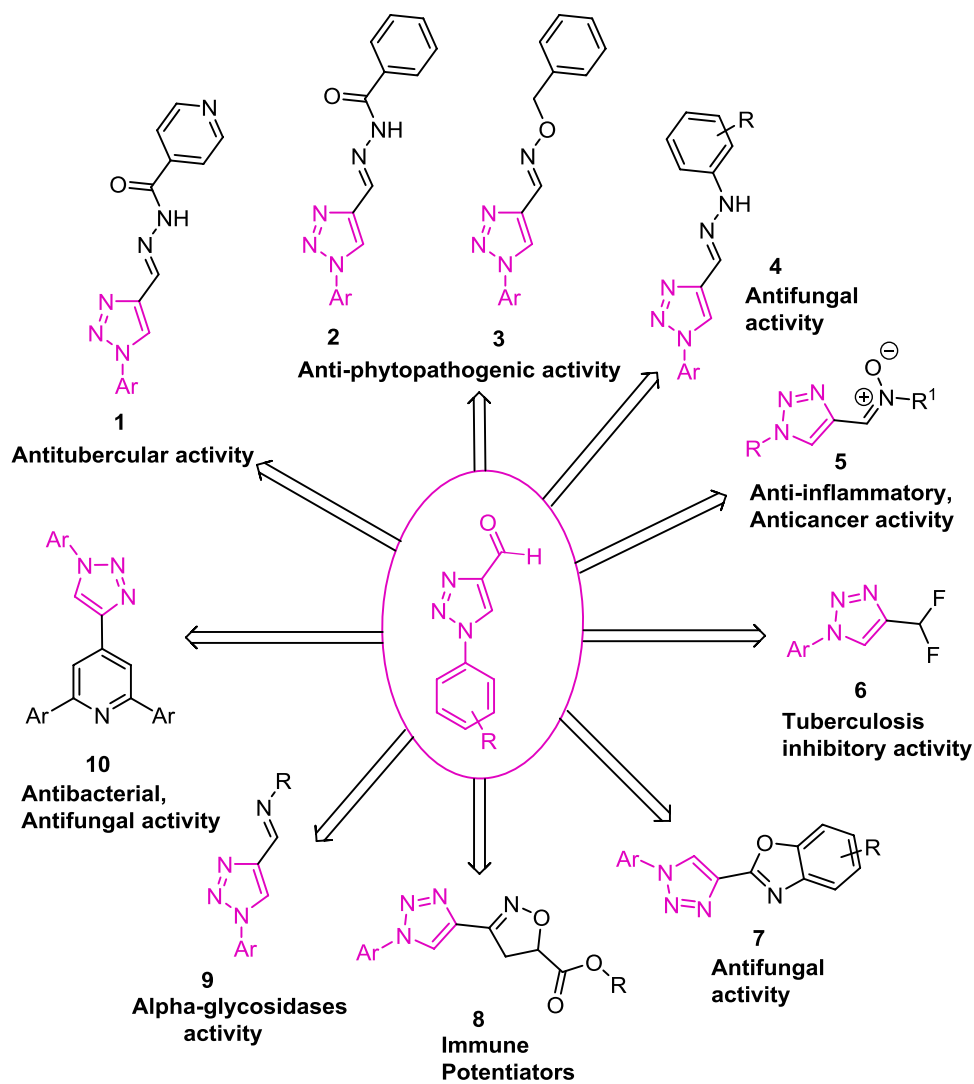
and triazole-biscoumarin conjugates as antitubercular agents. Keeping in mind all the above, we have planned to synthesize a novel 1,2,3-triazole-appended α -aminophosphonates via MCR approach. The acid-catalyzed one-pot multicomponent reaction between aldehyde, amine and trialkyl phosphite forms α -aminophosphonates. The first step involved in this reaction is the formation of an imine intermediate followed by an addition of the trialkyl phosphite across the $\text{C}=\text{N}$ double bond and finally the $\text{C}-\text{P}$ and $\text{C}-\text{N}$ bond formation takes place. The most important application of the synthesis of α -aminophosphonate involves the formation of the $\text{C}-\text{P}$ and $\text{C}-\text{N}$ bond. Recently, Maghsoodlou et al. reported [76] the synthesis of α -aminophosphonates using acetic acid as a medium as well as a catalyst. In our present study, we have synthesized new 1,2,3-triazole-appended α -aminophosphonates **14a–z** using one-pot three component reaction between 1-aryl-1*H*-1,2,3-triazole-4-carbaldehydes **11**, anilines **12** to form Schiff's base and then trimethyl phosphite was added in methanol–acetic acid at room temperature in excellent yields (Scheme 1). In this study, we have reduced the concentration of acetic acid and added methanol as a co-solvent.

The structures of the newly synthesized 1,2,3-triazole-appended α -aminophosphonates has been confirmed by physical data and spectral analysis. In the ^1H NMR spectrum of compound **14b**, the doublet signal was observed for chiral proton at δ 5.20 ppm. Singlet signal at δ 4.62 ppm was observed for NH proton. The two doublet signals observed at δ 3.73 and 3.87 ppm for two methoxy groups were attached to phosphorus. The singlet signal at δ 8.07 ppm was observed for triazolyl proton. In the ^{13}C NMR spectrum of **14b**, the peaks were observed at δ 53.9, 54.4 ppm due to the two methoxy groups attached to phosphorus and a peak at 48.8 ppm due to methine carbon. The structures, yields and melting points for all the newly synthesized 1,2,3-triazole-appended α -aminophosphonates are given in Fig. 4.

Conclusion

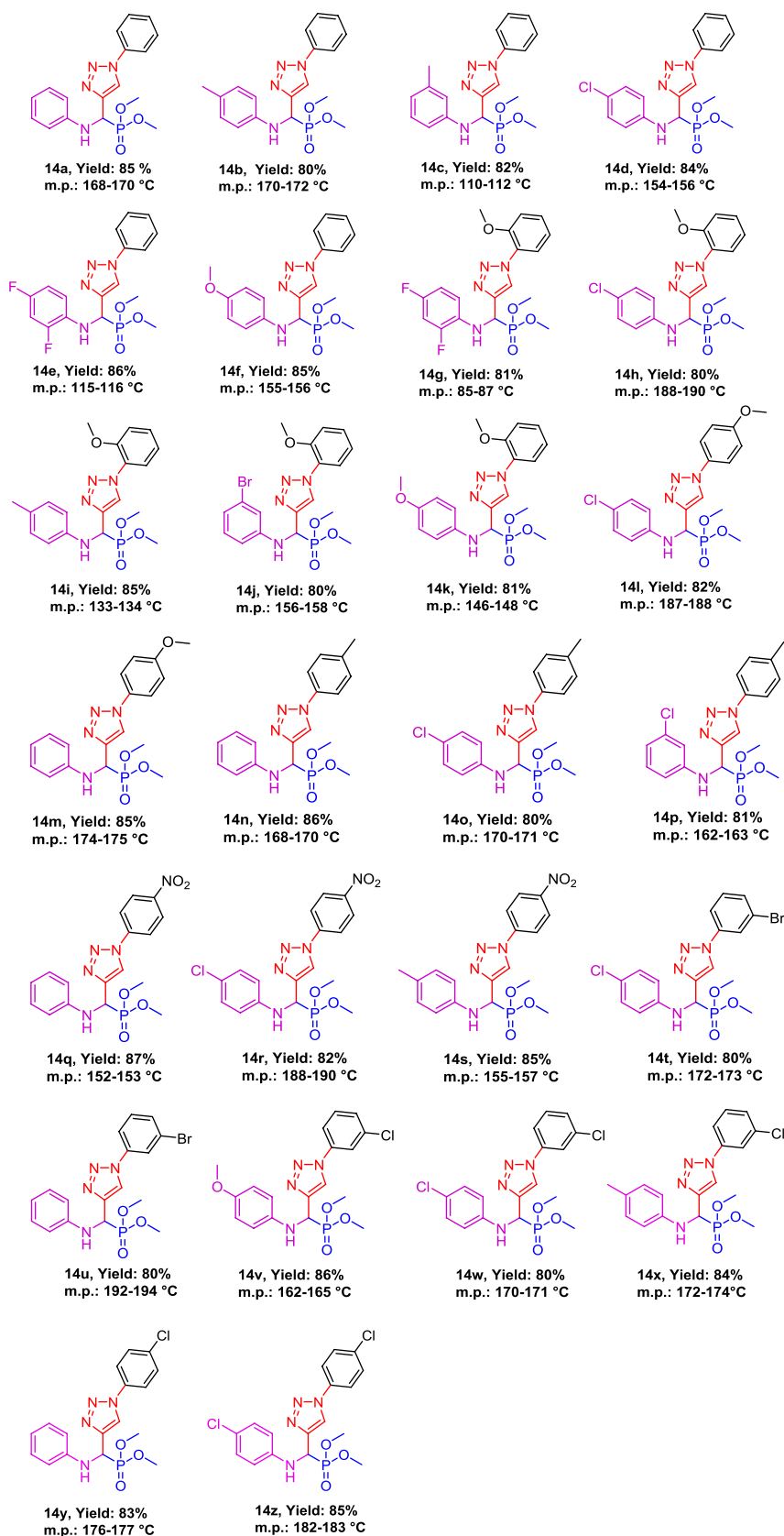
In summary, we have demonstrated a library of novel 1,2,3-triazole-incorporated α -aminophosphonates from the corresponding triazolyl aldehydes, anilines and trimethyl phosphite in excellent yields for the first time. The synthesized molecules having two pharmacophoric units, likely 1,2,3-triazole and α -aminophosphonates may display better biological activities.

Fig. 3 Applications of 1,2,3-triazolyl aldehydes for the synthesis of bioactive molecules



Scheme 1 Synthesis of 1,2,3-triazole-appended α -aminophosphonate hybrids

Fig. 4 The structures, yield and melting points for 1,2,3-triazole-appended α -aminophosphonate derivatives



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References

- H.C. Kolb, M.G. Finn, K.B. Sharpless, *Angew. Chem. Int. Ed.* **40**, 2004 (2001)
- P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **113**, 4905 (2013)
- F. Amblard, J.H. Cho, R.F. Schinazi, *Chem. Rev.* **109**, 4207 (2009)
- V.K. Tiwari, B.B. Mishra, K.B. Mishra, N. Mishra, A.S. Singh, X. Chen, *Chem. Rev.* **116**, 3086 (2016)
- K. Kacprzak, I. Skiera, M. Piasecka, Z. Paryzek, *Chem. Rev.* **116**, 5689 (2016)
- S.G. Agalave, S.R. Maujan, V.S. Pore, *Chem. Asian J.* **6**, 2696 (2011)
- G.C. Tron, T. Pirali, R.A. Billington, P.L. Canonico, G. Sorba, A.A. Genazzani, *Med. Res. Rev.* **28**, 278 (2008)
- D. Dheer, V. Singh, R. Shankar, *Bioorg. Chem.* **71**, 30 (2017)
- H.C. Kolb, K.B. Sharpless, *Drug Discovery Today* **8**, 1128 (2003)
- I. Mohammed, I.R. Kummetha, G. Singh, N. Sharova, G. Lichinchi, J. Dang, M. Stevenson, T.M. Rana, *J. Med. Chem.* **59**, 7677 (2016)
- S.B. Ferreira, A.C.R. Sodero, M.F.C. Cardoso, E.S. Lima, C.R. Kaiser, F.P. Silva Jr., V.F. Ferreira, *J. Med. Chem.* **53**, 2364 (2010)
- M. Allam, A.K.D. Bhavani, A. Mudiraj, N. Ranjan, M. Thippana, P.P. Babu, *Eur. J. Med. Chem.* **156**, 43 (2018)
- S. Shafi, M.M. Alam, N. Mulakayala, C. Mulakayala, G. Vanaja, A.M. Kalle, R. Pallu, M.S. Alam, *Eur. J. Med. Chem.* **49**, 324 (2012)
- S.N. Darandale, N.A. Mulla, D.N. Pansare, J.N. Sangshetti, D.B. Shinde, *Eur. J. Med. Chem.* **65**, 527 (2013)
- F. Bi, S. Ji, H. Venter, J. Liu, S.J. Semple, S. Ma, *Bioorg. Med. Chem. Lett.* **28**, 884 (2018)
- K.D. Thomas, A.V. Adhikari, I.H. Chowdhury, E. Sumesh, N.K. Pal, *Eur. J. Med. Chem.* **46**, 2503 (2011)
- M. Ordóñez, J.L. Viveros-Ceballos, C. Cativiela, F.J. Sayago, *Tetrahedron* **71**, 1745 (2015)
- N.A. Shafakat Ali, S. Zakir, M. Patel, M. Farooqui, *Eur. J. Med. Chem.* **50**, 39 (2012)
- L. Gu, C. Jin, *Org. Biomol. Chem.* **10**, 7098 (2012)
- A. Mucha, P. Kafarski, L. Berlicki, *J. Med. Chem.* **54**, 5955 (2011)
- S.A.R. Mulla, M.Y. Pathan, S.S. Chavan, S.P. Gamble, D. Sarkar, *RSC Adv.* **4**, 7666 (2014)
- F. Bahrami, F. Panahi, F. Daneshgar, R. Yousefi, M.B. Shahsavani, A. Khalafi-Nezhad, *RSC Adv.* **6**, 5915 (2016)
- M.H. Shaikh, D.D. Subhedar, F.A.K. Khan, J.N. Sangshetti, B.B. Shingate, *Res. Chem. Intermed.* **42**, 5115 (2016)
- A.H. Kategaonkar, S.S. Sonar, S.B. Sapkal, V.U. Gawali, B.B. Shingate, M.S. Shingare, *Phosphorus, sulfur silicon. Relat. Elem.* **185**, 2113 (2010)
- Y. Xu, K. Yan, B. Song, G. Xu, S. Yang, W. Xue, D. Hu, P. Lu, G. Ouyang, L. Jin, Z. Chen, *Molecules* **11**, 666 (2006)
- A. Ouahrouch, M. Taourirte, D. Schols, R. Snoeck, G. Andrei, J.W. Engels, H.B. Lazrek, *Arch. Pharm. Chem. Life Sci.* **349**, 30 (2016)
- M.M. Azaam, E.R. Kenawy, A.S. Badr, A.A. El-din, M.A. Khamis, El-Magd, *J. Saudi Chem. Soc.* **22**, 34 (2018)
- R. Damiche, S. Chafaa, *J. Mol. Struct.* **1130**, 1009 (2017)
- S.A. Dake, D.S. Raut, K.R. Kharat, R.S. Mhaske, S.U. Deshmukh, R.P. Pawar, *Bioorg. Med. Chem. Lett.* **21**, 2527 (2011)
- M.V.N. Reddy, B.S. Kumar, A. Balakrishna, C.S. Reddy, S.K. Nayak, C.D. Reddy, *Arkivoc* (xv), 246 (2007)
- M.F. Abdel-Megeed, B.E. Badr, M.M. Azaam, G.A. El-Hiti, *Arch. Pharm. Chem. Life Sci.* **345**, 784 (2012)
- Y.C. Guo, J. Li, J.L. Ma, Z.R. Yu, H.W. Wang, W.J. Zhu, X.C. Liao, Y.F. Zhao, *Chin. Chem. Lett.* **26**, 755 (2015)
- H. Luo, D. Hu, J. Wu, M. He, L. Jin, S. Yang, B. Song, *Int. J. Mol. Sci.* **13**, 6730 (2012)
- F. Palacios, C. Alonso, J.M. de los Santos, *Chem. Rev.* **105**, 899 (2005)
- M. Ordóñez, H. Rojas-Cabrera, C. Cativiela, *Tetrahedron* **65**, 17 (2009)
- P. Kafarski, B. Lejczak, *Phosphorus, sulfur silicon. Relat. Elem.* **63**, 193 (1991)
- N. Azizi, M.R. Saidi, *Eur. J. Org. Chem.* 4630 (2003)
- N. Azizi, M.R. Saidi, *Tetrahedron* **59**, 5329 (2003)
- M.R. Saidi, N. Azizi, *Synlett* 1347 (2002)
- N. Azizi, F. Rajabi, M.R. Saidi, *Tetrahedron Lett.* **45**, 9233 (2004)
- R.G. de Noronha, C.C. Romao, A.C. Fernandes, *Catal. Commun.* **12**, 337 (2011)
- P. Sun, Z. Hu, Z. Huang, *Synth. Commun.* **34**, 4293 (2004)
- S. Bhagat, A.K. Chakraborti, *J. Org. Chem.* **72**, 1263 (2007)
- D.J. Eyckens, L.C. Henderson, *RSC Adv.* **7**, 27900 (2017)
- H. Ghafari, A. Rashidizadeh, H.R.E. Zand, *RSC Adv.* **6**, 16046 (2016)
- Y. Heo, D.H. Cho, M.K. Mishra, D.O. Jang, *Tetrahedron Lett.* **53**, 3897 (2012)
- X.C. Li, S.S. Gong, D.Y. Zeng, Y.H. You, Q. Sun, *Tetrahedron Lett.* **57**, 1782 (2016)
- M.R. Sivala, S.R. Devineni, M. Golla, V. Medarametla, G.K. Pothuru, N.R. Chamarthi, *J. Chem. Sci.* **128**, 1303 (2016)
- S.G. Lee, J.H. Park, J. Kang, J.K. Lee, *Chem. Commun.* 1698 (2001)
- J. Tang, L. Wang, W. Wang, L. Zhang, S. Wu, D. Mao, *J. Fluor. Chem.* **132**, 102 (2011)
- F. Xu, Y. Luo, M. Deng, Q. Shen, *Eur. J. Org. Chem.* 4728 (2003)
- S. Chandrasekhar, S.J. Prakash, V. Jagadeshwar, C. Narsihmulu, *Tetrahedron Lett.* **42**, 5561 (2001)
- Z.P. Zhan, J.P. Li, *Synth. Commun.* **35**, 2501 (2005)
- Z. Rezaei, H. Firouzabadi, N. Iranpoor, A. Ghaderi, M.R. Jafari, A.A. Jafari, H.R. Zare, *Eur. J. Med. Chem.* **44**, 4266 (2009)
- I.R. Cabrita, S.C.A. Sousa, P.R. Florindo, A.C. Fernandes, *Tetrahedron* **74**, 1817 (2018)
- P.V. Shinde, A.H. Kategaonkar, B.B. Shingate, M.S. Shingare, *Tetrahedron Lett.* **52**, 2889 (2011)
- K.S. Niraldar, B.B. Shingate, M.S. Shingare, *Ultrason. Sonochem.* **17**, 760 (2010)
- A.B. Danne, A.S. Choudhari, S. Chakraborty, D. Sarkar, V.M. Khedkar, B.B. Shingate, *Med. Chem. Commun.* **9**, 1114 (2018)
- A.B. Danne, A.S. Choudhari, D. Sarkar, J.N. Sangshetti, V.M. Khedkar, B.B. Shingate, *Res. Chem. Intermed.* **44**, 6283 (2018)
- M.H. Shaikh, D.D. Subhedar, L. Nawale, D. Sarkar, F.A.K. Khan, J. Sangshetti, B.B. Shingate, *Mini Rev. Med. Chem.* (2018). <https://doi.org/10.2174/1389557518666180718124858>
- M.H. Shaikh, D.D. Subhedar, F.A.K. Khan, J.N. Sangshetti, L. Nawale, M. Arkile, D. Sarkar, B.B. Shingate, *J. Heterocyclic Chem.* **54**, 413 (2017)
- M.H. Shaikh, D.D. Subhedar, M. Arkile, V.M. Khedkar, N. Jadhav, D. Sarkar, B.B. Shingate, *Bioorg. Med. Chem. Lett.* **26**, 561 (2016)
- M.H. Shaikh, D.D. Subhedar, F.A.K. Khan, J.N. Sangshetti, B.B. Shingate, *Chin. Chem. Lett.* **27**, 295 (2016)

64. M.H. Shaikh, D.D. Subhedar, V.M. Khedkar, P.C. Jha, F.A.K. Khan, J.N. Sangshetti, B.B. Shingate, *Chin. Chem. Lett.* **27**, 1058 (2016)
65. M.H. Shaikh, D.D. Subhedar, B.B. Shingate, F.A.K. Khan, J.N. Sangshetti, V.M. Khedkar, L. Nawale, D. Sarkar, G.R. Navale, S.S. Shinde, *Med. Chem. Res.* **25**, 790 (2016)
66. M.H. Shaikh, D.D. Subhedar, L. Nawale, D. Sarkar, F.A.K. Khan, J.N. Sangshetti, B.B. Shingate, *Med. Chem. Commun.* **6**, 1104 (2015)
67. N. Boechat, V.F. Ferreira, S.B. Ferreira, M.L.G. Ferreira, F.C. Silva, M.M. Bastos, M.S. Costa, M.C.S. Lourenco, A.C. Pinto, A.U. Krettli, A.C. Aguiar, B.M. Teixeira, N.V. Silva, P.R.C. Martins, F.A.F.M. Bezerra, A.L.S. Camilo, G.P. Silva, C.C.P. Costa, *J. Med. Chem.* **54**, 5988 (2011)
68. X. Wang, Z.C. Dai, Y.F. Chen, L.L. Cao, W. Yan, S.K. Li, J.X. Wang, Z.G. Zhang, Y.H. Ye, *Eur. J. Med. Chem.* **126**, 171 (2017)
69. Z.C. Dai, Y.F. Chen, M. Zhang, S.K. Li, T.T. Yang, L. Shen, J.X. Wang, S.S. Qian, H.L. Zhu, Y.H. Ye, *Org. Biomol. Chem.* **13**, 477 (2015)
70. P.S. Rao, C. Kurumurthy, B. Veeraswamy, G.S. Kumar, Y. Poornachandra, C.G. Kumar, S.B. Vasamsetti, S. Kotamraju, B. Narsaiah, *Eur. J. Med. Chem.* **80**, 184 (2014)
71. M.S. Costa, N. Boechat, E.A. Rangel, F.C. Silva, A.M.T. de Souza, C.R. Rodrigues, H.C. Castro, I.N. Junior, M.C.S. Lourenco, S.M.S.V. Wardell, V.F. Ferreira, *Bioorg. Med. Chem.* **14**, 8644 (2006)
72. Y.Q. Jiang, S.H. Jia, X.Y. Li, Y.M. Sun, W. Li, W.W. Zhang, G.Q. Xu, *J. Chin. Chem. Soc.* **64**, 1197 (2017)
73. T. Ismail, S. Shafi, I. Hyder, T. Sidiq, A. Khajuria, S.M. Alam, M.S.K. Halmuthur, *Arch. Pharm. Chem. Life Sci.* **348**, 796 (2015)
74. D. Gonzaga, M.R. Senger, F.C. Silva, V.F. Ferreira, F.P. Silva Jr., *Eur. J. Med. Chem.* **74**, 461 (2014)
75. N.J.P. Subhashini, Ch.B. Reddy, P.A. Kumar, B. Lingaiah, *Russ. J. Gen. Chem.* **86**, 2845 (2016)
76. M. Rostamizadeh, M.T. Maghsoodlou, N. Hazeri, S.M. Habibi-khorassani, L. Keishams, Phosphorus, sulfur silicon. *Relat. Elem.* **186**, 334 (2011)