Res Chem Intermed
DOI 10.1007/s11164-015-2348-z

$[Et_3NH][HSO_4]$-catalyzed one-pot, solvent-free synthesis and biological evaluation of α-amino phosphonates

Mubarak H. Shaikh[1] · Dnyaneshwar D. Subhedar[1] · Firoz A. Kalam Khan[2] · Jaiprakash N. Sangshetti[2] · Bapurao B. Shingate[1]

Received: 25 August 2015 / Accepted: 30 October 2015

Abstract A series of dimethyl (phenyl(phenylamino)methyl)phosphonates and novel dimethyl ((phenylamino)(2-(prop-2-yn-1-yloxy)phenyl)methyl)phosphonates as potential antifungal agents were synthesized via one-pot, three-component condensation of aldehydes, amines and trimethyl phosphite in solvent-free conditions using $[Et_3NH][HSO_4]$ as an efficient, eco-friendly and reusable catalyst. Compared to other methods, this new method consistently has advantages, including excellent yields, a short reaction time, mild reaction conditions and catalyst reusability. The newly synthesized propargylated ether containing α-amino phosphonates were evaluated for antifungal and antioxidant activity and were also analyzed for absorption, distribution, metabolism and excretion (ADME) properties.

Electronic supplementary material The online version of this article (doi:10.1007/s11164-015-2348-z) contains supplementary material which is available to authorized users.

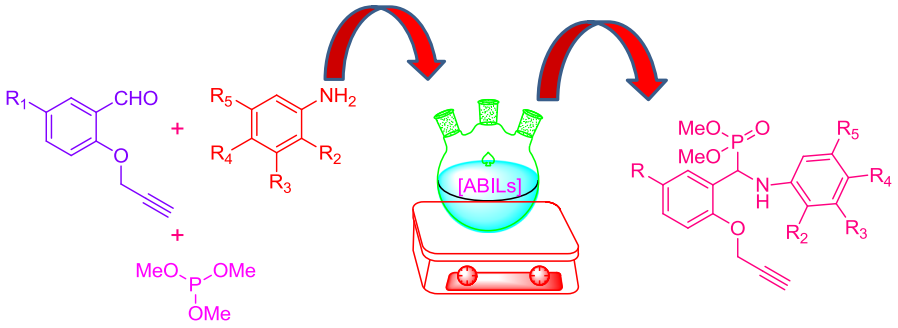
✉ Bapurao B. Shingate
bapushingate@gmail.com

[1] Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431 004, India

[2] Department of Pharmaceutical Chemistry, Y. B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Aurangabad 431 001, India

Published online: 20 November 2015

Graphical Abstract



Keywords Ionic liquid · α-Aminophosphonate · Antifungal · Antioxidant · ADME prediction

Introduction

Multi-component reactions have been developed as efficient and influential tools in modern synthetic organic chemistry, facilitating the facile creation of several new bonds in one-pot reactions. These days, greener (eco-friendly) reaction media are gaining greater importance in safe organic transformations. Ionic liquids, referred to as 'designer solvents' due to their physical and chemical properties, can be adjusted by a careful choice of cations and anions. Ionic liquids have become a promising alternative media for various chemical processes due to their good solvating capability, non-inflammability, negligible vapor pressure, ease of recyclability, controlled miscibility and high thermal stability [1, 2]. In particular, acidic Bronsted ionic liquids (ABILs) are of special importance, because they simultaneously possess proton acidity and the characteristic properties of ionic liquids [3]. ABILs offer environmentally friendly catalyst properties due to the combination of the advantages of liquid acids and solid acids, such as uniform acid sites, stability in water and air, easy separation and reusability. Ionic liquids have been proved to be very excellent catalysts, as well as solvents, for many organic transformations [4].

Phosphonic acids and phosphonates are of immense interest in synthetic organic chemistry due to their widespread biological activities [5, 6]. They are employed in the synthetic operations leading to carbon–carbon bond formation [7], and as transition state analogues in production of antibody catalysts for a wide variety of reactions [8]. α-Aminophosphonates are an important class of compounds in pharmaceutical chemistry. In recent years, considerable interest has been focused on the synthesis of α-aminophosphonates, because they are considered to be structural analogues of the corresponding α-amino acids and transition-state mimics of peptide hydrolysis. The utilities of α-aminophosphonates as antibiotics and pharmacologic agents [9], enzymes inhibitors [10], peptide mimics [11] and haptens of catalytic antibodies [12] are well documented.

Numerous syntheses of α-aminophosphonates have been carried out under various solvents using different types of catalysts: $In(OTf)_3/MgSO_4$ [13], GaI_3 [14], $BiCl_3$ [15], $Cu(OTf)_2$ [16], $SbCl_3/Al_2O_3$ [17], $InCl_3$ [18] and $ZrCl_4$ [19] are well documented. The synthesis of α-aminophosphonates has also been carried out in the presence of ionic liquids [20–25], Lewis acid–surfactant-combined catalysts [26] even in the absence of a solvent and catalyst [27], Lewis acids like $ZnCl_2$ [28], BF_3Et_2O [29], CdI_2/Benzene [30] and CdI_2/microwave [31]. Under solvent-free conditions using trifluoroacetic acid (TFA) [32], TsCl [33], $LiClO_4$ [34], $Mg(ClO_4)_2$ [35], metal triflate [36], $Na_2CaP_2O_7$ [37] and $ZrOCl_2{\cdot}8H_2O$ or $ZrO(ClO_4)_2{\cdot}6H_2O$ [38] as catalysts for the preparation of α-aminophosphonates are also reported. However, most of these procedures are sluggish, require long reaction times, use strong acidic conditions, give unsatisfactory yields and also suffer from the formation of many side products.

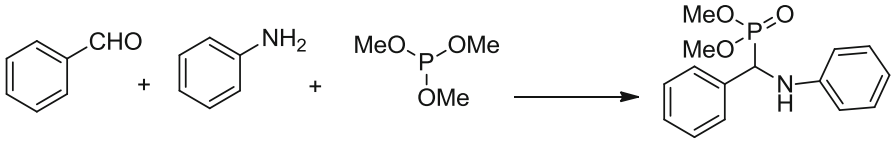
Consequently, there is still a need to develop a more efficient, simple, mild and high-yield protocol for the synthesis of α-aminophosphonates. In this regards, ABILs [Et_3NH][HSO_4] would be a good candidate as it is prepared via a simple and atom-economical, acid-base neutralization reaction from a cheap amine and acid [39].

Results and discussion

Considering the significance of α-aminophosphonates and in continuation of our earlier work on solvent-free reactions using catalyst\s such as camphor sulfonic acid [40], 1-hexanesulphonic acid sodium salt [41] and alum [42] for the synthesis of α-aminophosphonates, herein, we would like to report a new method for the synthesis of α-aminophosphonates via a one-pot, multi-component reaction using ABILs [Et_3NH][HSO_4] under solvent-free conditions.

In search of an efficient catalyst and the best experimental reaction conditions, the reaction of benzaldehyde **1**, aniline **2** and trimethyl phosphite **3** at room temperature was considered as a standard model reaction (Scheme 1).

Initially, the reaction was carried out in the absence of the catalyst; the product formed in a trace amount (Table 1, entry 1). To determine the appropriate concentration of the catalyst [Et_3NH][HSO_4], we investigated the model reaction at different concentrations of [Et_3NH][HSO_4], such as 5, 10, 15, 20 and 25 mol%. The α-aminophosphonates formed in 70, 82, 89, 95 and 95 % yields, respectively (Table 1, entries 2–6).



Scheme 1 Standard model reaction

Table 1 Effect of catalyst concentration

Entry	$[Et_3NH][HSO_4]$ mol%	Time (min)	Yield (%)[a]
1	–	60	Trace
2	5	60	70
3	10	45	82
4	15	15	89
5	20	10	95
6	25	10	95

Reaction conditions Aldehyde (1.25 mmol), aniline (1.25 mmol), trimethyl phosphite (1.25 mmol), solvent-free at room temperature

[a] Isolated yield

The increase in concentration of catalyst from 20 to 25 mol% does not increase the yield of product. This indicates that 20 mol% of $[Et_3NH][HSO_4]$ is sufficient for the reaction by considering the product yield.

In the next step, we also compared the reported methods [20, 21, 43] using various ionic liquids for the synthesis of α-aminophosphonates (Table 2, entries 1–8). In comparison with the above methods, $[Et_3NH][HSO_4]$ provided better results in terms of high yield and a solvent-free protocol, and the reaction was carried out at room temperature (Table 2, entry, 8).

To evaluate the effect of solvents, dichloromethane, tetrahydrofuran, 1,4-dioxane, toluene, acetonitrile and ethanol were used for the model reaction. It was observed that the use of solvents retards the reaction rate and affords the desired product in lower yields than that for neat conditions (Table 3).

The recyclability of the ionic liquid $[Et_3NH][HSO_4]$ was also studied and the results are summarized in Table 4. After the completion of the reaction, the reaction mixture was quenched with ice crystals and extracted with ethyl acetate. The residual ionic liquid was washed with diethyl ether, dried under vacuum at 60 °C and reused for subsequent reactions. The recovered ionic liquid could be used for five times without obvious loss of catalytic activity (Table 4, entries 1–5).

With these optimized reaction conditions for the model reaction, i.e. 20 mol% $[Et_3NH][HSO_4]$ catalyst, room temperature and solvent-free conditions, we

Table 2 Comparison of ionic liquids used for the synthesis of α-aminophosphonate

Entry	Ionic liquid	Catalyst	Condition	Time	Yield (%)[a]	References
1	$[bmim]PF_6$	–	RT	8 h	82	[20]
2	$[bmim]BF_4$	–	RT	5 h	90	[20]
3	[bmim]OTf	$Yb(OTf)_3$	MW	2 min	55	[21]
4	$[bmim]SbF_6$	$Yb(OTf)_3$	MW	2 min	72	[21]
5	$[bmim]PF_6$	$Yb(OTf)_3$	MW	2 min	86	[21]
6	$[bmim]BF_4$	$Yb(OTf)_3$	MW	2 min	99	[21]
7	$[bnmim][HSO_4]$ (50 mol%)	–	RT	1–3 h	96	[23]
	$[bmim]PF_6$	$Sc(OTf)_3$	RT	27 h	80	[43]
8	$[Et_3NH][HSO_4]$	–	RT	10 min	95	Present work

[a] Isolated yield

Table 3 Screening of solvents

Entry	Solvent	Yield[a] (%)
1	Dichloromethane	42
2	Tetrahydrofuran	45
3	1,4-Dioxane	48
4	Toluene	54
5	Acetonitrile	56
6	Ethanol	60
7	IL[b]	95

Reaction conditions Aldehyde (1.25 mmol), aniline (1.25 mmol), trimethyl phosphite (1.25 mmol), [Et_3NH][HSO_4] at room temperature for 20 min

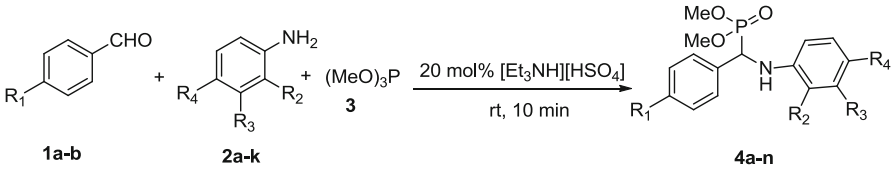
[a] Isolated yield

[b] 20 mol% [Et_3NH][HSO_4]

Table 4 Reusability of catalyst for model reaction

Entry	Run	Time[a] (min)	Yield[b]
1	1	10	95
2	2	10	95
3	3	10	92
4	4	10	90
5	5	10	90

[a] Reaction progress monitored by thin layer chromatography (TLC); [b] Isolated yield



1a, R_1= H
1b, R_1= OMe

2a, R_2= H, R_3= H, R_4= H
2b, R_2= H, R_3= H, R_4= Br
2c, R_2= H, R_3= NO_2, R_4= H
2d, R_2= Me, R_3= H, R_4= H
2e, R_2= H, R_3= H, R_4= NO_2
2f, R_2= H, R_3=Br, R_4= H
2g, R_2= Br, R_3= H, R_4= H
2h, R_2= H, R_3= H, R_4= F
2i, R_2= H, R_3= H, R_4= Me
2j, R_2= H, R_3= Me, R_4= H
2k, R_2= H, R_3= H, R_4= OMe

Scheme 2 Synthesis of α-amino phosphonates **4a–n**

synthesized a series of α-aminophosphonates (**4a–n**) by reacting benzaldehyde/anisaldehyde (**1a** and **1b**), anilines (**2a–k**) (with electron-donating and withdrawing groups) and trimethyl phosphite (**3**) in excellent yields (Scheme 2). The physical data of the synthesized α-aminophosphonates are in good agreement with the literature reports (Table 5).

The compounds having terminal alkynes are useful intermediates for a 1,3-dipolar cycloaddition reaction, i.e. click reaction [55–57], and also display various

Table 5 Synthesis of derivatives of dimethyl (phenyl(phenylamino)methyl)phosphonate **4a–n**

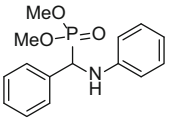
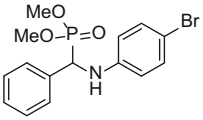
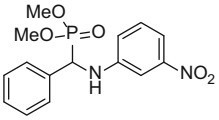
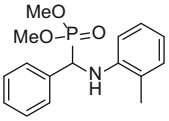
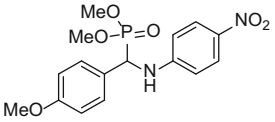
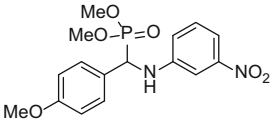
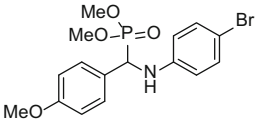
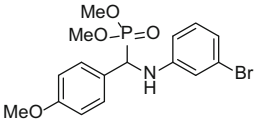
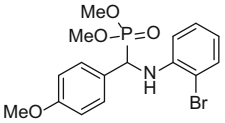
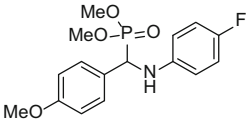
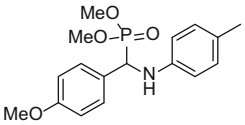
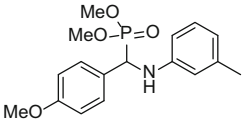
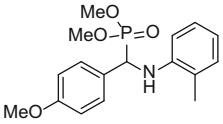
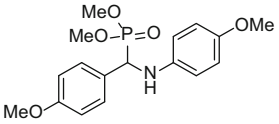
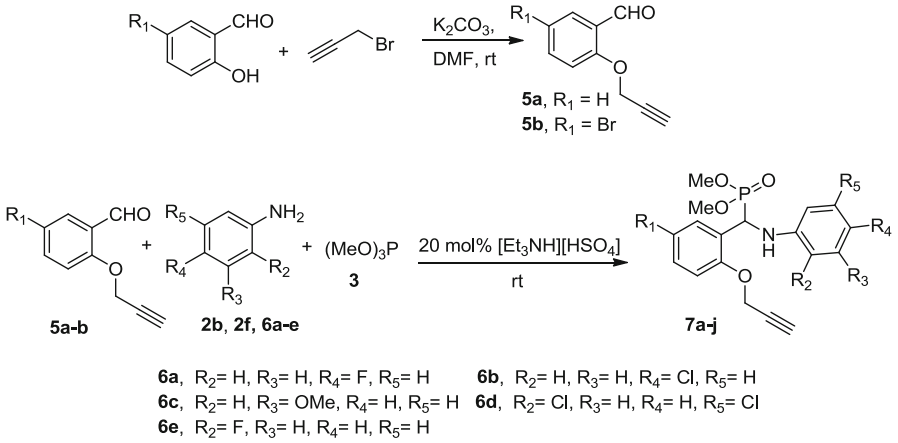
Compound	Structure	Yield (%)	Melting point (found; °C)	Melting point (reported; °C)
4a		95	85–86	86 [44, 45]
4b		93	60–61	60 [46]
4c		92	129–130	130 [46]
4d		93	48–49	48 [46]
4e		95	112–113	112 [47, 48]
4f		92	148–149	148 [47, 48]
4g		93	105–106	105 [49]
4h		93	98–99	98 [50]
4i		90	51–52	52 [50]
4j		94	52–53	52 [51, 52]

Table 5 continued

Compound	Structure	Yield (%)	Melting point (found; °C)	Melting point (reported; °C)
4k		94	95–96	96 [44, 45]
4l		92	86–87	86 [50]
4m		91	65–66	66 [53]
4n		95	118–119	120 [54]

Reaction conditions Aldehyde (1.25 mmol), aniline (1.25 mmol), trimethyl phosphite (1.25 mmol), [Et_3NH][HSO_4] at room temperature for 10 min

biological activities [58]. For the applicability of the above-developed methodology for the synthesis of α-amino phosphonates, herein, we utilized the same for the synthesis of new propargylated ether containing α-amino phosphonates. The propargylated ether group containing aldehydes **5a–b** were synthesized from the corresponding salicylaldehydes using propargyl bromide in the presence of K_2CO_3 in good yields. The one-pot, solvent-free, multi-component reaction of aldehydes **5a–b** with various anilines (**2b**, **2f**, **6a–e**) and trimethyl phosphate **3** in the presence of 20 mol% [Et_3N][HSO_4] at room temperature afforded the corresponding propargylated ether containing new α-amino phosphonates (**7a–j**) in excellent yields (Scheme 3). The formation of α-aminophosphonate derivatives **7a–j** has been confirmed by physical data and spectroscopic methods such as proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 (^{13}C) NMR. In the starting material compound **5a**, the proton of alkyne C–H was observed at δ 2.57 ppm, and the singlet at δ 4.79 ppm for methylene protons attached to the oxygen heteroatom and singlet for aldehyde proton were observed at δ 9.91 ppm. According to the ^{1}H NMR spectrum of representative compound **7b**, the singlet observed at δ 2.47 ppm was for the proton of alkyne C–H, and the singlet at δ 4.77 ppm was for the methylene proton attached to the oxygen heteroatom. Similarly, a doublet was observed at δ 3.37 and 3.75 ppm for methoxy protons. In addition to this, a doublet observed at δ 5.29 ppm was assigned to the proton present on the methine carbon attached to phosphorous and nitrogen heteroatoms, and a signal for an aldehydic proton was not



Scheme 3 Synthesis of new propargylated ether containing α-amino phosphonates

observed, thus confirming the formation of α-amino phosphonates. Furthermore, all the aromatic protons appeared at expected chemical shifts and integral values. The synthesis of α-aminophosphonates was further confirmed by ^{13}C NMR spectral data, in which the carbon signals of $-OCH_3$ groups were resonated at δ 46.1 and 49.2 ppm, respectively. The signals at δ 53.8 ppm indicate the presence of methylene carbon attached to the oxygen heteroatom, and δ 56.1 ppm indicates the methine carbon attached to the nitrogen and phosphorous heteroatoms. In addition to this, the signal observed at δ 75.8 and 78.3 ppm indicates the presence of alkyne carbon, while all other carbons gave peaks at expected values. The physical data, yield and time required to complete the reactions are given in spectroscopic data. The proposed structures were confirmed by ^{1}H NMR and ^{13}C NMR (supporting information).

Plausible mechanism

The two-step reaction mechanism is similar to that reported in the literature using an acid catalyst. The first step involves the activation of a carbonyl group via protonation by acidic ionic liquid $[Et_3N][HSO_4]$ and then a nucleophilic attack of aromatic amine produces imine after removal of water (Fig. 1). In the second step, the nucleophilic attack of trimethyl phosphite on imine gives a phosphonium intermediate, which, followed by the attack of water, gave the α-amino phosphonate, methanol and regeneration of $[Et_3NH][HSO_4]$.

Antifungal activity

All the synthesized, new propargylated ethers containing α-amino phosphonate derivatives **7a–j** showed good to excellent antifungal activity against the five fungal strains (Table 6). Compound **7d** having *bromo-* at the R_1 position and *fluoro-* at the R_4 position and compound **7h** having *bromo-* at the R_1position, *chloro-* at R_2 and R_5

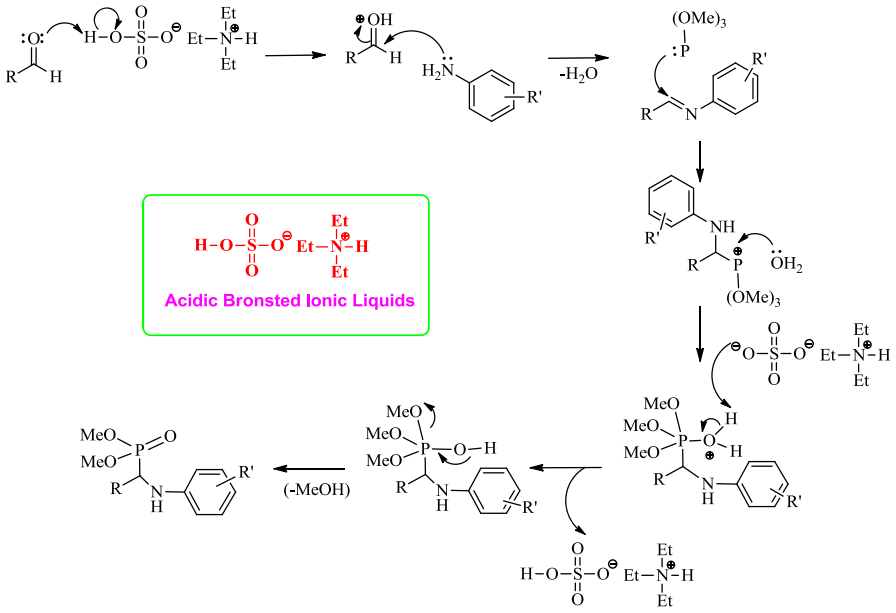


Fig. 1 Plausible mechanism for the formation of α-amino phosphonates

positions of the phenyl ring has been found to be a good inhibitor of *C. albicans* with a minimum inhibitory concentration (MIC) value of 25 μg/mL were equipotent to the standard drug miconazole and less potent as compared to fluconazole. Compounds **7c** (*chloro-* group at R_4) and **7j** (*bromo-* group at R_1 and R_3) with MIC values of 25 μg/mL showed equivalent potency for fungal strain *A. niger* as compared to the standard drug miconazole.

Antioxidant activity

According to the 1,1-diphenyl-1-picrylhydrazyl (DPPH) assay, compounds **7d** having *bromo-* at the R_1 position and *fluoro-* at the R_4 position, **7e** having *bromo-* at the R_1 and R_4 positions, **7f** having *bromo-* at the R_1 position and *chloro-* at the R_4 position, **7g** having *bromo-* at the R_1 position and *methoxy-* at the R_3 position, and **7i** having *bromo-* at the R_1 position and *fluoro-* at the R_2 position exhibited better radical scavenging activity than the synthetic commercial antioxidant butylated hydroxytoluene (BHT), with half maximal inhibitory concentration (IC_{50}) values of 12.74, 15.76, 14.30, 12.90 and 14.23 μg/mL, respectively (Table 6). Similarly, compounds **7d** having *bromo-* at the R_1 position and *fluoro-* at the R_4 position, and **7g** having *bromo-* at the R_1 position and *methoxy-* at the R_3 position shows excellent antioxidant activity compared to the standard antioxidant drug ascorbic acid with IC_{50} values of 12.74 and 12.90 μg/mL, respectively.

Table 6 In vitro antifungal and antioxidant evaluation of new propargylated ether containing α-aminophosphonates

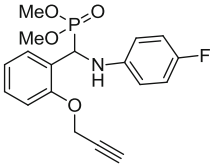
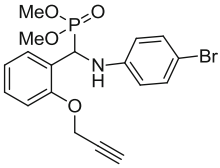
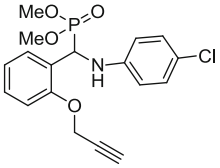
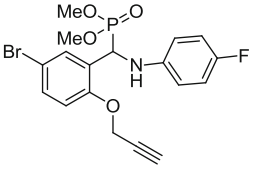
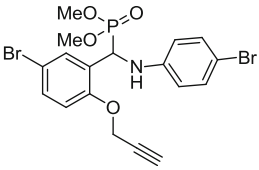
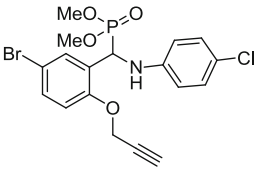
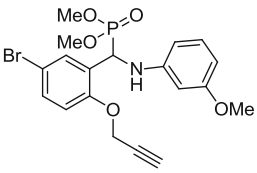
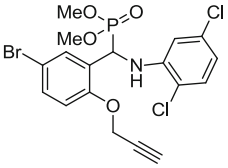
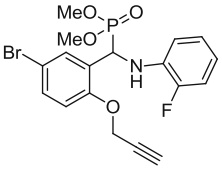
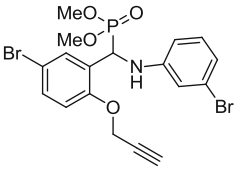
Entry	Structure	Antifungal activity					Antioxidant activity IC_{50} (μg/mL) DPPH scavenging activity
		MIC Values in μg/mL					
		CA	*FO*	*AF*	*AN*	*CN*	
7a		100	150	100	50	*	22.11
7b		150	125	150	150	*	18.24
7c		100	75	75	25	50	19.14
7d		25	50	50	100	50	12.74
7e		50	125	100	125	100	15.76
7f		100	150	125	50	150	14.30
7g		50	50	125	125	150	12.90

Table 6 continued

Entry	Structure	Antifungal activity					Antioxidant activity IC_{50} (μg/mL) DPPH scavenging activity
		MIC Values in μg/mL					
		CA	*FO*	*AF*	*AN*	*CN*	
7h		25	50	50	*	*	16.80
7i		75	100	*	*	150	14.23
7j		150	100	100	25	*	16.83
MA	–	25	25	12.5	25	25	NT
FA	–	6.25	6.25	6.25	12.5	6.25	NT
BHT	–	–	–	–	–	–	16.47
AA	–	–	–	–	–	–	12.69

CA Candida albicans, *FO Fusarium oxysporum*, *AF Aspergillus flavus*, *AN Aspergillus niger, CN Cryptococcus neoformans, MA* Miconazole, *FA* Fluconazole, *BHT Butylated Hydroxy Toluene, AA* Acsorbic acid

* and – No activity was observed up to 200 μg/mL

In silico ADME prediction

A computational study was performed for prediction of ADME properties and it was observed that the compounds exhibited a good % absorption (% ABS) ranging from 86.21 to 89.40 % (Table 7). Furthermore, none of the synthesized compounds violated Lipinski's rule of five. Therefore, a molecule likely to be developed as an orally active drug candidate should show no more than one violation of the following four criteria: miLog *P* (octanol–water partition coefficient) $\leq$5, molecular weight $\leq$500, number of hydrogen bond acceptors $\leq$10 and number of hydrogen bond donors $\leq$5 [59]. The larger the value of the drug likeness model score, the higher is also probability that the particular molecule will be active. Therefore, compound **7c** was found to be most active of the synthesized compounds. All the tested compounds followed the criteria for an orally active drug and, therefore, these compounds may have a good potential for eventual development as oral agents.

Table 7 Pharmacokinetic parameters important for good oral bioavailability

Entry	% ABS	TPSA (A^2)	*n*-ROTB	MV	MW	miLog *P*	*n*-ON	*n*-OHNH	Lipinski violation	Drug-likeness model score
Rule	–	–	–	–	<500	≤5	<10	<5	≤1	–
7a	89.40	56.80	8	317.10	363.32	2.99	5	1	0	0.30
7b	89.40	56.80	8	330.05	424.23	3.64	5	1	0	0.12
7c	89.40	56.80	8	325.70	379.78	3.50	5	1	0	0.48
7d	89.40	56.80	8	334.98	442.22	3.77	5	1	0	−0.40
7e	89.40	56.80	8	347.94	503.13	4.42	5	1	1	−0.37
7f	89.40	56.80	8	343.59	458.68	4.29	5	1	0	−0.25
7g	86.21	66.03	9	355.60	454.26	3.64	6	1	0	−0.48
7h	89.40	56.80	8	357.12	493.12	4.90	5	1	0	−0.03
7i	89.40	56.80	8	334.98	442.22	3.73	5	1	0	−0.25
7j	89.40	56.80	8	347.94	503.13	4.40	5	1	1	−0.41

ABS absorption; *TPSA* topological polar surface area; *n-ROTB* number of rotatable bonds; *MV* molecular volume; *MW* molecular weight; *lmiLog P* logarithm of partition coefficient; *n-ON* number of hydrogen bond acceptors; *n-OHNH* number of hydrogen bonds donors.

Conclusion

In summary, we have developed an efficient, greener and expeditious synthetic protocol for α-amino phosphonates as antifungal and antioxidant agents. This technique overcomes some of the problems associated with excessive or wasteful heating. Remarkable advantages of this synthetic strategy over others are: (1) reaction performs at ambient room temperature, (2) reduced reaction time, (3) non-toxic and economically viable catalyst, (4) omission of solvent and (5) simplified work-up procedure. This is the first report on the use of $[Et_3NH][HSO_4]$ catalyst for the syntheses of α-amino phosphonates.

Experimental

All the solvents and reagents were purchased from commercial suppliers Spectrochem Pvt. Ltd., Sigma Aldrich and Rankem India Ltd., and were used without further purification. The progress of each reaction was monitored by ascending TLC using TLC aluminum sheets, pre-coated silica gel F_{254} (Merck, Germany) and by locating the spots using ultraviolet (UV) light as the visualizing agent or iodine vapors. Melting points were taken in an open capillary method and are uncorrected. ^{1}H NMR spectra were recorded [deuterated chloroform ($CDCl_3$)] on a Bruker Avance 200 NMR spectrometer. ^{13}C NMR spectra were recorded ($CDCl_3$) on a Bruker Avance 50 NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. The splitting pattern abbreviations are designed as singlet (s); doublet (d); double doublet (dd); bs (broad singlet), triplet (t); quartet (q) and multiplet (m).

Synthesis of [Et_3NH][HSO_4]

Sulfuric acid (1.96 g, 0.02 mol) 98 % solution in water was dropped into triethylamine (2.02 g, 0.02 mol) with stirring at 60 °C for 1 h. After the addition, the reaction mixture was stirred for another 1 h at 70 °C. The water molecule was removed by heating the residue at 80–90 °C under a high vacuum until the weight of the residue remained constant.

*General procedure for the one-pot synthesis of dimethyl (phenyl(phenylamino)methyl)phosphonates (**4a–n**) and dimethyl ((phenylamino)(2-(prop-2-yn-1-yloxy)phenyl)methyl)phosphonate (**7a–j**)*

A mixture of aldehyde (1.25 mmol), aniline (1.25 mmol), trimethyl phosphite (1.25 mmol) and [Et_3NH][HSO_4] (20 mol%) was magnetically stirred at room temperature for 10 min. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (2 × 25 mL). The organic extracts were washed with brine (2 × 25 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the corresponding crude compounds. The obtained crude compounds were recrystallized using ethanol.

Spectral data

*2-(prop-2-yn-1-yloxy)benzaldehyde (**5a**)* Compound **5a**, as an off-white solid, was obtained via alkylation of salicylaldehyde with propargyl bromide using K_2CO_3 as a base in 2 h with a 95 % yield. Melting point (Mp.) 48–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.57 (s, 1H, alkyne C–H), 4.79 (s, 2H, –OCH_2), 7.10 (d, 2H, Ar–H, $J = 8$ Hz), 7.87 (d, 2H, Ar–H, $J = 8$ Hz), and 9.91 (s, 1H, CHO).

*Dimethyl (((4-fluorophenyl)amino)(2-(prop-2-yn-1-yloxy)phenyl)methyl)phosphonate (**7a**)* Compound **7a**, as an off-white solid, was obtained via one-pot, three-component condensation between 2-(prop-2-yn-1-yloxy)benzaldehyde (**5a**), 4-fluoroaniline (**6a**) and trimethylphosphite (**3**) using 20 mol% of catalyst [Et_3-NH][HSO_4] in 10 min with a 95 % yield. Mp. 124–125 °C. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.47 (s, 1H), 3.38 (d, 3H, $J = 6$ Hz), 3.76 (d, 3H, $J = 6$ Hz), 4.76 (s, 2H), 5.28 (d, 1H, $J = 12$ Hz), 6.50 (d, 2H, $J = 2$ Hz), 6.69–6.73 (m, 2H), 6.91–6.95 (m, 2H), 7.18 (s, 1H) and 7.41 (d, 1H, $J = 4$ Hz).

*Dimethyl (((4-bromophenyl)amino)(2-(prop-2-yn-1-yloxy)phenyl)methyl)phosphonate (**7b**)* Compound **7b** as an off-white solid was obtained via one-pot, three-component condensation between 2-(prop-2-yn-1-yloxy)benzaldehyde (**5a**), 4-bromoaniline (**2b**) and trimethylphosphite (**3**) using 20 mol% of catalyst [Et_3-NH][HSO_4] in 10 min with a 95 % yield. Mp. 110 °C. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.47 (s, 1H), 3.37 (d, 3H, $J = 4$ Hz), 3.75 (d, 3H, $J = 4$ Hz), 4.77

(s, 2H), 5.29 (d, 1H, $J = 10$ Hz), 6.43 (d, 2H, $J = 4$ Hz), 6.89–6.95 (m, 2H), 7.09 (d, 2H, $J = 4$ Hz), 7.18–7.21 (*t*, 1H) and 7.40 (d, 1H, $J = 2$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 46.1, 49.2, 53.8, 56.1, 75.8, 78.3, 112, 114.9, 122.1, 123, 124.3, 128.4, 129, 144.4, 144.7 and 155.1.

*Dimethyl (((4-chlorophenyl)amino)(2-(prop-2-yn-1-yloxy)phenyl)methyl)phosphonate (**7c**)* Compound **7c** as an off-white solid was obtained via one-pot, three-component condensation between 2-(prop-2-yn-1-yloxy)benzaldehyde (**5a**), 4-chloroaniline (**6b**) and trimethylphosphite (**3**) using 20 mol% of catalyst $[Et_3NH][HSO_4]$ in 10 min with a 95 % yield. Mp. 110 °C. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.47 (s, 1H), 3.37 (d, 3H, $J = 4$ Hz), 3.75 (d, 3H, $J = 4$ Hz), 4.77 (s, 2H), 5.29 (d, 1H, $J = 10$ Hz), 6.48 (d, 2H, $J = 2$ Hz), 6.89–6.96 (m, 4H), 7.17–7.20 (*t*, 1H) and 7.40 (d, 1H, $J = 4$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 46.6, 49.7, 53.9, 56.1, 75.7, 78.4, 112, 114.6, 114.7, 115.4, 115.8, 122, 124.5, 128.4, 128.5, 129.1 and 155.

*Dimethyl ((5-bromo-2-(prop-2-yn-1-yloxy)phenyl)((4-fluorophenyl)amino)methyl)phosphonate (**7d**)* Compound **7d** as an off-white solid was obtained via one-pot, three-component condensation between 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (**5b**), 4-fluoroaniline (**6a**) and trimethylphosphite (**3**) using 20 mol% of catalyst $[Et_3NH][HSO_4]$ in 10 min with a 95 % yield. Mp. 118 °C. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.57–2.60 (m, 1H), 3.58 (d, 3H, $J = 10$ Hz), 3.84 (d, 3H, $J = 10$ Hz), 4.87 (d, 2H, $J = 2$ Hz), 5.20–5.51 (m, 2H), 6.50 (d, 1H, $J = 2$ Hz), 6.59–6.69 (m, 1H), 6.95 (d, 1H, $J = 8$ Hz), 7.15 (d, 1H, $J = 8$ Hz), 7.36–7.42 (m, 1H) and 7.54–7.56 (*t*, 1H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 46.6, 49.7, 53.9, 56.4, 76.2, 77.8, 113.8, 113.9, 114.5, 114.6, 115.5, 115.9, 127.2, 131.2, 131.9, 154 and 158.8.

*Dimethyl ((5-bromo-2-(prop-2-yn-1-yloxy)phenyl)((4-bromophenyl)amino)methyl)phosphonate (**7e**)* Compound **7e** as an off-white solid was obtained via one-pot, three-component condensation between 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (**5b**), 4-bromoaniline (**2b**) and trimethylphosphite (**3**) using 20 mol% of catalyst $[Et_3NH][HSO_4]$ in 10 min with a 95 % yield. Mp. 136 °C.

*Dimethyl ((5-bromo-2-(prop-2-yn-1-yloxy)phenyl)((4-chlorophenyl)amino)methyl)phosphonate (**7f**)* Compound **7f** as an off-white solid was obtained via one-pot, three-component condensation between 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (**5b**), 4-chloroaniline (**6b**) and trimethylphosphite (**3**) using 20 mol% of catalyst $[Et_3NH][HSO_4]$ in 10 min with a 95 % yield. Mp. 140 °C. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.49 (s, 1H), 3.46 (d, 3H, $J = 4$ Hz), 3.76 (d, 3H, $J = 6$ Hz), 4.76 (s, 2H), 5.21 (d, 1H, $J = 12$ Hz), 6.46 (d, 2H, $J = 2$ Hz), 6.84 (d, 1H, $J = 4$ Hz), 6.98 (d, 2H, $J = 2$ Hz), 7.29 (d, 1H, $J = 4$ Hz) and 7.50 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 46.1, 49.2, 54, 56.3, 76.2, 77.8, 113.8, 114.8, 123.3, 127.1, 129.1, 131.1, 131.2, 131.9, 144.1, 144.4 and 154.

*Dimethyl((5-bromo-2-(prop-2-yn-1-yloxy)phenyl)((3-methoxyphenyl)amino)methyl) phosphonate (**7g**)* Compound **7g** as an off-white solid was obtained via one-pot, three-component condensation between 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (**5b**), 3-methoxyaniline (**6c**) and trimethylphosphite (**3**) using 20 mol% of catalyst [Et_3NH][HSO_4] in 20 min with a 95 % yield. Mp. 102 °C.

*Dimethyl ((5-bromo-2-(prop-2-yn-1-yloxy)phenyl)((2,5-dichlorophenyl)amino)-methyl) phosphonate (**7h**)* Compound **7h** as an off-white solid was obtained via one-pot, three-component condensation between 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (**5b**), 2,5-dichloroaniline (**6d**) and trimethylphosphite (**3**) using 20 mol% of catalyst [Et_3NH][HSO_4] in 30 min with a 95 % yield. Mp. 142 °C.

*Dimethyl ((5-bromo-2-(prop-2-yn-1-yloxy)phenyl)((2-fluorophenyl)amino)methyl) phosphonate (**7i**)* Compound **7i** as an off-white solid was obtained via one-pot, three-component condensation between 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (**5b**), 2-fluoroaniline (**6e**) and trimethylphosphite (**3**) using 20 mol% of catalyst [Et_3NH][HSO_4] in 30 min with a 95 % yield. Mp. 92–93 °C.

*Dimethyl((5-bromo-2-(prop-2-yn-1-yloxy)phenyl)((3-bromophenyl)amino)methyl) phosphonate (**7j**)* Compound **7j** as an off-white solid was obtained via one-pot, three-component condensation between 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (**5b**), 3-bromoaniline (**2f**) and trimethylphosphite (**3**) using 20 mol% of catalyst [Et_3NH][HSO_4] in 20 min with a 95 % yield. Mp. 158 °C. ^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.53–2.60 (m, 1H), 3.54 (d, 3H, $J = 10$ Hz), 3.83 (d, 3H, $J = 12$ Hz), 4.83 (s, 2H), 5.26 (d, 1H, $J = 22$ Hz), 6.50–6.57 (m, 2H), 6.77–6.93 (m, 3H), 7.33–7.39 (m, 1H) and 7.57–7.68 (m, 1H).

Experimental protocol for biological activity

Antifungal activity

The antifungal activity was evaluated against five human pathogenic fungal strains, such as *Candida albicans* (NCIM 3471), *Fusarium oxysporum* (NCIM 1332), *Aspergillus flavus* (NCIM 539), *Aspergillus niger* (NCIM 1196), *Cryptococcus neoformans* (NCIM 576), which are often encountered clinically and were compared with standard drug miconazole. MIC values were determined using the standard agar method [60].

DPPH radical scavenging antioxidant activity

The hydrogen atom or electron donation ability of the some compounds were measured from the bleaching of the purple-colored methanol solution of DPPH [61]. The spectrophotometric assay uses the stable radical DPPH as a reagent. 1 mL of various concentrations of the test compounds (5, 10, 25, 50 and 100 μg/mL) in methanol was added to 4 mL of 0.004 % (w/v) methanol solution of DPPH. The

reaction mixture was incubated at 37 °C. The scavenging activity on DPPH was determined by measuring the absorbance at 517 nm after 30 min. All tests were performed in triplicate and the mean values were entered. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation: % of scavenging = $[(A_{control} - A_{sample})/(A_{sample} \times 100)]$, where $A_{control}$ is the absorbance of the control (DPPH radical without the test sample) and A_{sample} is the absorbance of the test sample (DPPH radical with the test sample). The control contains all reagents except the test samples.

In silico ADME prediction

The success of a drug is determined not only by good efficacy but also by an acceptable ADME profile. In the present study, we calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB) and Lipinski's rule of five [62] using a Molinspiration online property calculation toolkit [63]. Absorption (% ABS) was calculated by: % ABS = 109 − (0.345 × TPSA) [64]. Drug-likeness model score (a collective property of physical–chemical properties, pharmacokinetics and pharmacodynamics of a compound represented by a numerical value) was computed by Mol Soft software [65].

Acknowledgments The authors, M.H.S. and D.D.S., are very grateful for the award of senior research fellowship bestowed by the Council of Scientific and Industrial Research (CSIR), New Delhi. The authors are also thankful to the head of the Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, for providing laboratory facilities.

References

1. Z. Lei, C. Dai, B. Chen, Chem. Rev. **114**, 1289 (2014)
2. M.V. Fedorov, A.A. Kornyshev, Chem. Rev. **114**, 2978 (2014)
3. X.X. Han, H. Du, C.T. Hung, L.L. Liu, P.H. Wu, D.H. Ren, S.J. Huang, S.B. Liu, Green Chem. **17**, 499 (2015)
4. Z.N. Siddiqui, K. Khan, ACS Sustain. Chem. Eng. **2**, 1187 (2014). **(reference cited their in)**
5. L.D. Quin, G.S. Quin, *A Guide to Organophosphorus Chemistry* (Wiley, New York, 2000)
6. D.E.C. Corbridge, *Phosphorus Chemistry, Biochemistry and Technology* (Elsevier, Amsterdam, 2000)
7. R. Engel, Chem. Rev. **77**, 349 (1977)
8. R.A. Lerner, S.J. Benkovic, P.G. Schultz, Science **252**, 659 (1991)
9. M.R. Saidi, N. Azizi, Synlett **8**, 1347 (2002)
10. M. Sienczyk, J. Oleksyszyn, Curr. Med. Chem. **16**, 1673 (2009)
11. K. Panigrahi, M.J. Eggen, J.H. Maeng, Q. Shen, D.B. Berkowitz, Chem. Biol. **16**, 928 (2009)
12. R. Hirschmann, A.B. Smith, C.M. Taylor, P.A. Benkovic, S.D. Taylor, K.M. Yager, P.A. Sprengler, S. Venkovic, J. Sci. **265**, 234 (1994)
13. R. Ghosh, S. Maiti, A. Chakraborty, D. Maiti, J. Mol. Cat. Chem. **53**, 210 (2004)
14. P.P. Sun, Z.X. Hu, Z.H. Huang, Synth. Commun. **34**, 4293 (2004)
15. Z.P. Zhan, J.P. Li, Synth. Commun. **35**, 2501 (2005)
16. A.S. Paraskar, A. Sudalai, Arkivoc **X**, 183 (2006)

17. K.S. Ambica, S.C. Taneja, M.S. Hundal, K.K. Kapoor, Tetrahedron Lett. **49**, 2208 (2008)
18. B.C. Ranu, A. Hajra, U. Jana, Org. Lett. **1**, 1141 (1999)
19. J.S. Yadav, B.V.S. Reddy, S. Raj, K.B. Reddy, A.R. Prasad, Synthesis **15**, 2277 (2001)
20. J.S. Yadav, B.V.S. Reddy, P. Sreedhar, Green Chem. **4**, 436 (2002)
21. S. Lee, J.K. Lee, C.E. Song, D.C. Kim, Bull. Korean Chem. Soc. **23**, 667 (2002)
22. Z. Zhou, Y. Pei, L. Wu, Org. Chem. Int. (2012). doi:10.1155/2012/375656
23. S.A. Sadaphal, S.S. Sonar, A.H. Kategaonkar, M.S. Shingare, Bull. Korean Chem. Soc. **30**, 1054 (2009)
24. S. Lee, J.H. Park, J. Kang, J.K. Lee, Chem. Commun. 1698 (2001)
25. 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)
26. K. Manabe, S. Kobayashi, Chem. Commun. 669 (2000)
27. S. Chandrasekhar, C. Narsihmulu, S.S. Sultana, B. Saritha, S.J. Prakash, Synlett **4**, 505 (2003)
28. J. Zou, Pol. J. Chem. **55**, 643 (1981)
29. S. Laschat, H. Kunz, Synthesis 90 (1992)
30. M.M. Kabachnik, T.N. Ternovskaya, E.V. Zobnina, I.P. Beletskaya, Russ. J. Org. Chem. **38**, 480 (2002)
31. M.M. Kabachnik, E.V. Zobnina, I.P. Beletskaya, Russ. J. Org. Chem. **41**, 505 (2005)
32. T. Akiyama, M. Sanada, K. Fuchibe, Synlett **10**, 1463 (2003)
33. B. Kaboudin, E. Jafari, Synlett **12**, 1837 (2008)
34. N. Azizi, F. Rajabi, M.R. Saidi, Tetrahedron Lett. **45**, 9233 (2004)
35. S. Bhagat, A.K. Chakraborti, J. Org. Chem. **72**, 1263 (2007)
36. H. Firouzabadi, N. Iranpoor, S. Sobhani, Synthesis **16**, 2692 (2004)
37. A. Elmakssoudi, M. Zahouily, A. Mezdar, A. Rayadh, S. Sebti, Comptes Rendus Chim. **8**, 1954 (2005)
38. S. Bhagat, A.K. Chakraborti, J. Org. Chem. **73**, 6029 (2008)
39. J. Weng, C. Wang, H. Li, Y. Wang, Green Chem. **8**, 96 (2006)
40. P.V. Shinde, A.H. Kategaonkar, B.B. Shingate, M.S. Shingare, Tetrahedron Lett. **52**, 2889 (2011)
41. K.S. Niralwad, B.B. Shingate, M.S. Shingare, Ultra. Sonochem. **17**, 760 (2010)
42. S.S. Sonar, S.A. Sadaphal, N.V. Shitole, N.R. Jogdand, B.B. Shingate, M.S. Shingare, Bull. Korean Chem. Soc. **30**, 1711 (2009)
43. S. Lee, J.H. Park, J. Kang, J.K. Lee, Chem. Commun. 1698 (2001)
44. C. Qian, T. Huang, J. Org. Chem. **63**, 4125 (1998)
45. X.J. Mu, M.Y. Lei, J.P. Zou, W. Zhang, Tetrahedron Lett. **47**, 1125 (2006)
46. B. Karmakar, S. Paul, J. Banerji, Arkivoc **ii**, 161 (2011)
47. R. Ghosh, S. Maiti, A. Chakraborty, D.J. Maiti, Mol. Catal. A: Chem. **210**, 53 (2004)
48. M. Xia, Y.D. Lu, Ultra. Sonochem. **14**, 235 (2007)
49. B.C. Ranu, A. Hajra, Green Chem. **4**, 551 (2002)
50. M.H. Sarvari, Tetrahedron **64**, 5459 (2008)
51. R.K. Reddy, A. Vijender, P. Krishnaiah, G. Venkataramana, V.L. Reddy, Venkateswarlu. Synth. Commun. **34**, 1677 (2004)
52. X.Y. Lv, J.M. Zhang, C.H. Xing, W.Q. Du, S.Z. Zhu, Synth. Commun. **37**, 743 (2007)
53. M. Zahouily, A. Elmakssoudi, A. Mezdar, A. Rayadh, S. Sebti, Catal. Commun. **8**, 225 (2007)
54. S. Chandrasekhar, S.J. Prakash, V. Jagadeswar, C. Narsihmulu, Tetrahedron Lett. **42**, 5561 (2001)
55. H.C. Kolb, M.G. Finn, K.B. Sharpless, Angew. Chem. Int. Ed. **40**, 2004 (2001)
56. V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, Angew. Chem. Int. Ed. **41**, 2596 (2002)
57. C.W. Tornoe, C. Christensen, M. Meldal, J. Org. Chem. **67**, 3057 (2002)
58. C. Arkona, J. Rademann, Angew. Chem. Int. Ed. **52**, 8210 (2013)
59. P. Ertl, B. Rohde, P. Selzer, J. Med. Chem. **43**, 3714 (2000)
60. D. Greenwood, R.C.B. Slack, J.F. Peutherer, *Medical Microbiology*, 14th edn. (ELBS, London, 1992)
61. M. Burits, F. Bucar, Phytother. Res. **14**, 323 (2000)
62. C.A. Lipinski, L. Lombardo, B.W. Dominy, P.J. Feeney, Adv. Drug Deliv. Rev. **46**, 3 (2001)
63. Molinspiration Chemoinformatics Brastislava, Slovak Republic. http://www.molinspiration.com/cgi-bin/properties (2014)
64. Y. Zhao, M.H. Abraham, J. Lee, A. Hersey, N.C. Luscombe, G. Beck, B. Sherborne, I. Cooper, Pharm. Res. **19**, 1446 (2002)
65. Drug-likeness and molecular property prediction, available from: http://www.molsoft.com/mprop/