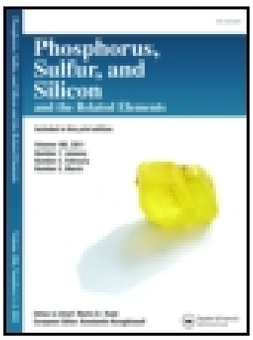

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Benzothiazolederivatives as potent biological agents

MICROWAVE ASSISTED NEAT SYNTHESIS OF α-AMINOPHOSPHONATE/PHOSPHINATE DERIVATIVES OF 2-(2-AMINOPHENYL)BENZOTHIAZOLE AS POTENT ANTIMICROBIAL AND ANTIOXIDANT AGENTS

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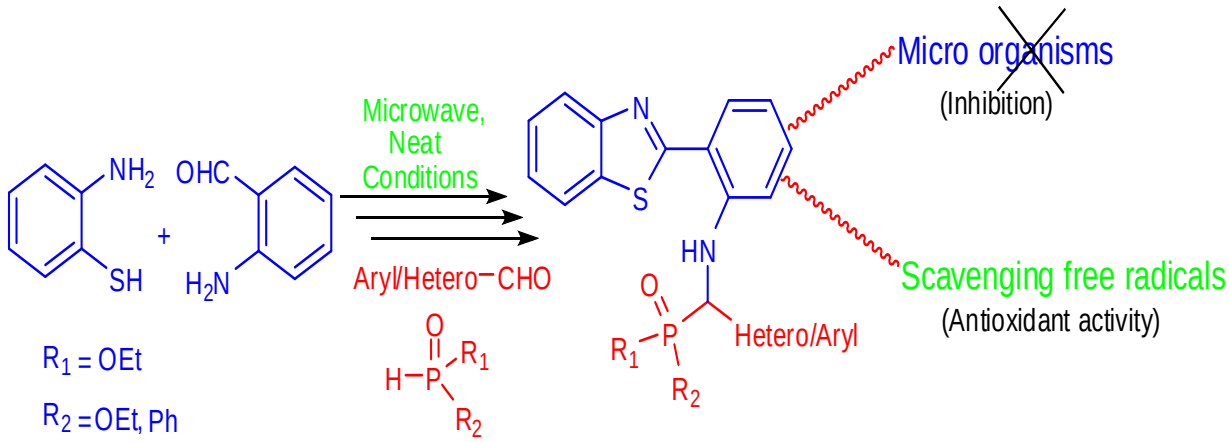
Abstract

A series diethyl/ethylphenyl(2-(benzo[*d*]thiazol-2-yl)phenylamino)phosphonates and phosphinates were synthesized under microwaveirradiation and neat conditions *via* Kabachnik-Fields reaction in high yields (80-93%). The compounds were screened for antimicrobial and antioxidant properties.A few compounds showedeffective antibacterialand antifungal agents at MIC value 12.5 μg/mL as compared with the standard at MIC value 6.25 μg/mL.



Keywords

2-(2-Aminophenyl benzothiazole, Neat conditions, Microwave irradiation, Kabachnik-Field reaction, Antimicrobial and Antioxidant activity.

INTRODUCTION

Organic chemists now focus to develop new transformations that are not only efficient, selective and high yielding but are also environmentally benign. Microwave assisted organic syntheses have gained enormous attention of the chemists due to their advantages such as shorter reaction times, cleaner products, operational simplicity, higher yields and being a potential alternative to accomplish the effective synthesis of heterocyclic bioactive compounds.[1]Meanwhile, neat reactions or green chemical approaches have attained great advantages in chemical processes by reducing environmental pollution.[2]

Heterocycles are versatile building blocks indesign and discovery of new physiological/pharmacologically active compounds. The benzothiazole scaffold represents an important moiety found in numerous drugs and agrochemicals.[3]Benzothiazole derivatives have a wide range of biological applications such as anticancer,[4] antimalarial,[5]antiviral,[6] anti-inflammatory,[7] antidiabetic,[8] antihelmintic,[9] antimicrobial,[10] antioxidant,[11] and Alzheimer's disease.[12]Benzothiazole also exhibits industrial applications such as vulcanization,[13] dyes, nonlinear optics (NLO)[14] and radioactive amyloid imaging agents.

On the other hand, α-aminophosphonates show broad and biologically diverse applications due to their structural resemblance of the naturally occurring α-amino acids.[15] Thus, α-aminophosphonates occupy a distinctive position in the design and discovery of new drug moieties for the treatment of various ailments. Their use as herbicides, antitumor agents, enzyme inhibitors, haptens of catalytic antibodies, inhibitors of UDP-galactopyranose mutase, inhibitors of serine hydrolases and pharmacogenic agents.[16-23]

Based on the wide variety of biological applications of benzothiazoles and *α*-aminophosphonates, herein, we report the synthesis of hybrid compounds containing these two pharmacophoric units in a single entity by usingsimple, neat, and catalyst-free, more convenient and eco-friendly approach under microwave condition. Further, these compounds were screenedfor anti-bacterial,anti-fungal activity and also forfree radicals scavenging.

RESULTS AND DISCUSSION

In continuation of our research in the development of new biologically active *α*-aminophosphonates and their biological applications,[17, 23, 24] *α*-aminophosphonate and phosphinate derivatives of 2-(2-aminophenyl)benzothiazole were synthesized in solvent-free conditions, under microwave irradiation *via* Kabachnik-Fields reaction. [25-27]Westarted the synthesis by cyclo-condensation of 2-aminothiophenol (**3**) with 2-aminobenzaldehyde (**4**) in the presence of glacial acetic acid under microwave irradiation to obtain,[28]2-(2-aminophenyl)benzothiazole as depicted in **Scheme 1**.

To synthesize an*α*-aminophosphonate library of benzothiazoles, we reinvestigated the reaction conditions by selecting 2-(2-aminophenyl)benzothiazole (**5**), 2,4-dichlorobenzaldehyde (**7a**) and diethyl phosphite (**8**) as model substrates under microwave conditions **Scheme 2**. Initially the model reaction was carried out without catalyst and solvent at 490 W **(Table S1, Entry 1)**. The reaction was completed in 10 min with high yield (90%). The progress of the reaction was also tested in different solvents and solvent-free with different Lewis acid catalysts such as $AlCl_3$, $FeCl_3$, CuI, $ZnCl_2$, $ZnBr_2$ $BiCl_3$, $NbCl_5$ and ZnO**(Table S1, Entry 2-15)**. As

previously reported advantages of silica supported catalysts, they were used to get high yields (87, 90 and 92%).[24]No significant difference in the yield was observed when the reaction was carried out with catalyst as well as undersolvent-free conditions (90%) **Table S1**.

The model reaction was optimized by screening at 700, 560, 455, 420 and 350 Watts to find out the effect of microwave power on the reaction. A microwave power 455 W was found to be optimal(**Figure 1**). The generality of the reaction conditions was tested with different aromatic and heterocyclic aldehydes **6a-f**, diethyl phosphite (**7**) and ethyl phenylphosphinate (**8**) as depicted in **Scheme 3**.

Spectroscopy

The structure of the novel title compounds **9-20** was confirmed by FT-IR, ^{1}H, ^{13}C carbon, ^{31}P NMR, mass spectra and elemental analysis. The ^{1}H NMR spectroscopicsignals observed δ 1.36-1.08 (triplet/multiplet) and δ 4.32-3.81 (multiplet) confirms the presence of the O-CH_2-CH_3 phosphate functionality. The signals at δ 5.48-4.88 ppm (doublet/doublet of doublet) correspond to P-CH. NH appeared as singlet/multiplet at δ 10.43-10.08 ppm.[29] In the^{13}C NMR spectra, the chemical shift at δ 16.7-16.2 (doublet,J = 6.4-5.4 Hz), δ 56.4-52.0 (doublet, J = 155.5-134.0 Hz), and 64.2-62.3 ppm (doublet,J = 7.5-6.2 Hz), corresponds to the O-CH_2-$\underline{C}H_3$, P-$\underline{C}$H and O-$\underline{C}H_2$grouos, respectively. In the^{31}P NMR spectra, the signals at δ 20.9-19.6 and 36.4-35.2ppm are due tothe phosphorus atom of phosphonates **9-14** and phosphinates **15-20**, respectively.[24] The FT-IR spectra showed absorption bands at 3300-3109 cm^{-1} for NH str, 1230-1205 cm^{-1} for P=O str, and 1029-1005 cm^{-1} for P-O str of the α-aminophosphonates and phosphinates. The structures of the compounds were further supported by molecular ion peaks in the mass spectra, and elemental analytical data.

Biological activity

Antimicrobial activity

The α-aminophosphonates and phosphinates were screened for their *in vitro* antibacterial activity against four bacterial stains, *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichiacoli*by use of the agar well diffusion method.[30]Minimum inhibitory concentrations (MIC) weredetermined by themicrotiter dilution assay.[31]All title compounds showed promising activity against the bacterial pathogens at 100 µg/mL concentration and most of the compounds exhibited an increased inhibition activity compared with the staring compound 2-(2-aminophenyl)benzothiazole (**3**) (**Table S 2**). Compounds **18**, **19** and **20** showed the highest inhibition activity with lowest MIC values 12.5 µg/mLagainst all bacterial stains. The reason might be the presence of the heterocyclic moiety. Compound **11>16>12>13** showed moderate inhibition activity against *Bacillus subtilis*, **16>13>12>11** showedbetter activity against *Staphylococcus aureus.* Similarly,**11>13>16**showed moderate activity against *Pseudomonas aeruginosa* and **13>11**showedreasonable activity against *Escherichiacoli*.

The new compounds **9-20** were screened for *in vitro* antifungal activity against four fungal pathogens *Candida albicans, Candida non-albicans, Aspergillus niger* and *Penicillium chrysogenum*by use of the disc diffusion method[32]and the microtiter dilution assay for MIC.[31] Among the compounds,**20>19>18** exhibited good inhibition activity at 100 µg/mL and with lowest MIC values 12.5 µg/mL against fungal pathogens. Moderate inhibition activity of compounds was observed in the order **11>13>14>9** against*Candida albicans*, **11>16>13** against *Candida non-albicans,***11>13>14** against *Aspergillus niger* and **11>13>14>12** against *Penicillium chrysogenum* as shown in **Table S 2 (Supplemental Materials)**.

Antioxidant activity

The antioxidant activity of the synthesized compounds was evaluated by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical assay[33] (**Table S 3**) and hydrogen peroxide scavenging activity[34](**Table S 4**) at four concentrations (25, 50, 75 and 100 μg/mL). IC_{50} values were also calculated from these methods. It was notified from the antioxidant data that compounds **20>18>19** showed good radical scavenging activity, probably due to the presence of the heterocyclic ring in the phosphinates, involved rapid abstraction of free radicals. Compounds, **20**(IC_{50}, 32.09, 51.42 μg/mL) and **18**(IC_{50}, 41.11, 61.94 μg/mL) exhibited an IC_{50} value closer to the standard antioxidant, ascorbic acid (IC_{50}, 26.5, 41.76 μg/mL) as shown in **Figure 2**.

A noteworthy enhancement of the antimicrobial and antioxidant activities was observed for all compounds substituted with heterocyclic ring in ethyl phenyl [2-(benzo[*d*]thiazol-2-yl)phenylamino]methylphosphinates **18** and **20** when compared with diethyl [2-(benzo[*d*]thiazol-2-yl)phenylamino]methylphosphonates **12** and **13**.

CONCLUSION

Keeping in mind the hazardous impact on human kind, catalyst and solvent-free conditions have been exploited to synthesize diethyl and ethyl phenyl [2-(benzo[d]thiazol-2-yl)phenylamino] substituted methylphosphonates/phosphinates **9-20** in high yields under microwave irradiation in short reaction time. The product compounds were screened for their antibacterial, antifungal and antioxidant activities. The biological assay results revealed that the compounds possessing a heterocyclic ring substitution showed an increased inhibition activity at lower concentration than the substituted aromatic compounds. Among the heterocyclic

compounds, **18**, **19** and **20** showed the highest activity which drew our interest to further evaluating these potent compounds *in vivo*.

EXPERIMENTAL

General methods

All solvents and chemicals were purchased from Merck and Sigma Aldrich, respectively and were used without further purification. Melting points were determined in open capillary tube on a Guna melting pointing apparatus and are uncorrected. Microwave irradiation was carried outby use of aCATA-4R microwave oven. IR spectra were recorded on a Bruker ALPHA interferometer instrument. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker 500 MHz instrument. $CDCl_3$ and TMS were used as solvents and internal reference for ^{1}H and ^{13}C NMR. Chemical shifts δ and coupling constants J were expressed in ppm and Hz, respectively. MS were recorded on ESI-MS in positive mode.Elemental analysis were carried out in FLASH EA Thermo Finnigan 1112 instrument. The Supplemental Materials contains sample ^{1}H, ^{13}C, ^{31}P NMR and mass spectra for 11 (Figures S 1 -- S 4)

2-(2-Aminophenyl)benzothiazole (**5**):[28]A mixture of 2-aminothiophenol **3** (750 mg, 6 mmol), 2-aminobenzaldehyde **4** (720 mg, 6 mmol) and 2 mL of glacial acetic acid were taken in a 100 mL flat bottomed flask.The reaction mixture was irradiated with microwave radiation at 490 W. The progress of the reaction was monitored at 1 min intervalsby use of TLC (hexane/EtOAc 7:3). After completion, the reaction mixture was washed with water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuum to get a yellowish green solid. To obtain pure **5**, column chromatography was performed (hexane/EtOAc 4:1).

Diethyl [2-(benzo[*d*]thiazol-2-yl)phenylamino]-(2,4-dichlorophenyl)methane-phosphonate (9): **5** (220 mg, 1 mmol), 2,4-dichlorobenzaldehyde **6a** (170 mg, 1 mmol) and diethyl phosphite **7** (1.5 mmol) were taken in a flat bottomed flask. The mixture was microwave irradiated at 455 W under neat conditions. The progress of the reaction was monitored by TLC (hexane/EtOAc 2:3) in 1 min intervals. After completion of the reaction, the reaction mixture was washed with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and extracted with EtOAc. The solvents were removed under reduced pressure. Pure**9** was obtained by column chromatography (hexane/EtOAc 3:1) as pale yellow solid, m. p.: 83-85°C. IR (ν_{max}, cm^{-1}): 3226 (NH), 1249 (P=O), 1016 (P-O-C). ^{1}H NMR (400 MHz) δ: 10.43 (1H, s, NH), 8.12 (1H, d, J = 8.0 Hz, Ar-H), 7.90 (1H, d, J = 8.0 Hz, Ar-H), 7.75 (1H, d, J = 8.0 Hz, Ar-H), 7.61-7.59 (1H, m, Ar-H), 7.51-7.47 (1H, m, Ar-H), 7.42-7.38 (2H, m, Ar-H), 7.25-7.17 (2H, m, Ar-H), 6.75 (1H, t, J = 7.8 Hz, Ar-H), 6.56 (1H, d, J = 8.4 Hz, Ar-H), 5.53 (1H, dd, J = 8.0, 16.4 Hz, P-CH), 4.29-3.91 (4H, m, OCH_2), 1.31-1.17 (6H, m, OCH_2CH_3). ^{13}C NMR (100 MHz) δ: 169.0 (C_7), 153.3 (C_1), 145.5 (C_{13}), 145.3 (C_{17}), 134.7 (C_6), 134.6 (C_{20}), 134.2 (C_{22}), 133.1 (C_{21}), 132.1 (C_2), 130.5 (C_5), 129.1 (C_{18}), 127.8 (C_{11}), 126.2 (C_{19}), 125.2 (C_9), 122.6 (C_3), 121.1 (C_4), 117.0 (C_8), 116.2 (C_{10}), 112.1 (C_{12}), 64.0 (C_{15}, d, J = 6.7 Hz, OCH_2), 63.4 (C_{15}, d, J = 7.1 Hz, OCH_2), 52.0 (C_{14}, d, J = 154 Hz, P-C), 16.6 (C_{16}, d, J = 5.4 Hz, OCH_2CH_3), 16.3 (C_{16}, d, J = 5.4 Hz, $O\text{-}CH_2CH_3$). ^{31}P NMR (161 MHz) δ: 19.8. EI-MS *m/z*: 521 $(M)^+$, 523 $(M+2)^+$, 525 $(M+4)^+$. Calcd. for $C_{24}H_{23}Cl_2N_2O_3PS$: C, 55.29; H, 4.45; N, 5.37; Found: C, 55.20; H, 4.34; N, 5.29.

The same procedure was employed for the synthesis of **10**-**20**.

Ethyl [2-(benzo[d]thiazol-2-yl)phenylamino](2,4-dichlorophenyl)methyl(phenyl)-phosphinate (15)was obtained as white solid, m. p.: 116-118°C. IR (ν_{max}, cm^{-1}): 3210 (NH), 1217 (P=O), 1024 (P-O-C). ^{1}H NMR (500 MHz) δ: 10.33 (1H, s, NH), 8.21 (1H, d, J = 8.0 Hz, Ar-H), 8.08 (1H, d, J = 8.0 Hz, Ar-H), 7.83-7.35 (6H, m, Ar-H), 7.33-7.06 (6H, m, Ar-H), 6.64-6.57 (1H, m, Ar-H), 6.43 (1H, d, J = 8.5 Hz, Ar-H), 5.44 (1H, dd, J = 7.5, 9.5 Hz, PCH), 4.22-3.81 (2H, m, OCH_2), 1.30-1.08 (3H, m, OCH_2CH_3). ^{13}C NMR (125 MHz) δ: 168.7 (C_7), 153.4 (C_1), 145.5 (C_{13}), 137.4 (C_{23}), 134.8 (C_{20}), 134.1 (C_{26}), 133.1 (C_6), 132.7 (C_{28}), 132.5 ($C_{18, 22}$), 132.2 (C_{24}), 131.9 (C_{25}), 130.5 (C_{27}), 130.4 (C_{17}), 128.5 ($C_{19, 21}$), 127.8 (C_{11}), 126.3 (C_2), 125.1 (C_9), 122.9 (C_4), 122.6 (C_3), 121.5 (C_5), 116.8 (C_8), 116.3 (C_{10}), 112.1 (C_{12}), 62.4 (C_{15},d, J = 6.8 Hz, P-O-CH_2), 54.7 (C_{14}, d, J = 134.0 Hz, P-C), 16.6 (C_{16}, d, J = 5.7 Hz, P-O-CH_2CH_3). ^{31}P NMR (202 MHz) δ: 35.7. EI-MS m/z: 553 $(M)^+$, 555 $(M+2)^+$, 557 $(M+4)^+$. Calcd. for $C_{28}H_{23}Cl_2N_2O_3PS$: C, 60.77; H, 4.19; N, 5.06; Found: C, 60.70; H, 4.12; N, 4.97.

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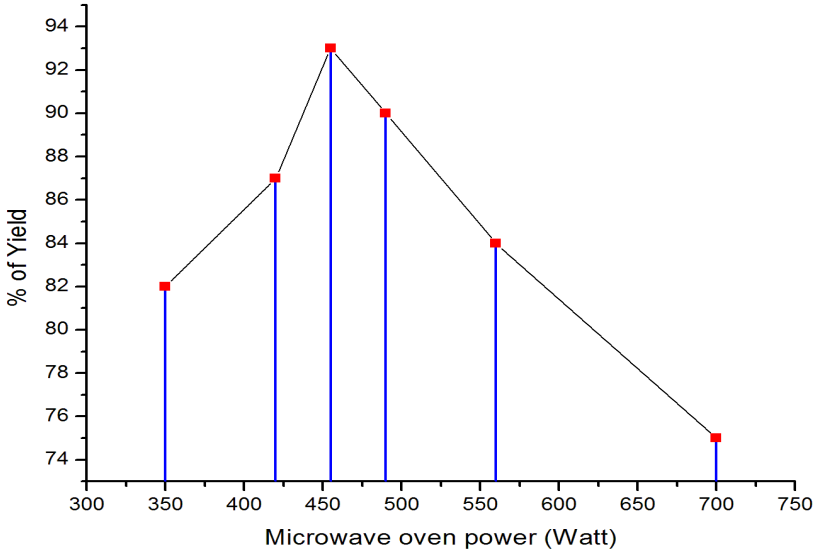


Figure 1. Effect of microwave oven power (Watt) on the yield of the compound **9**.

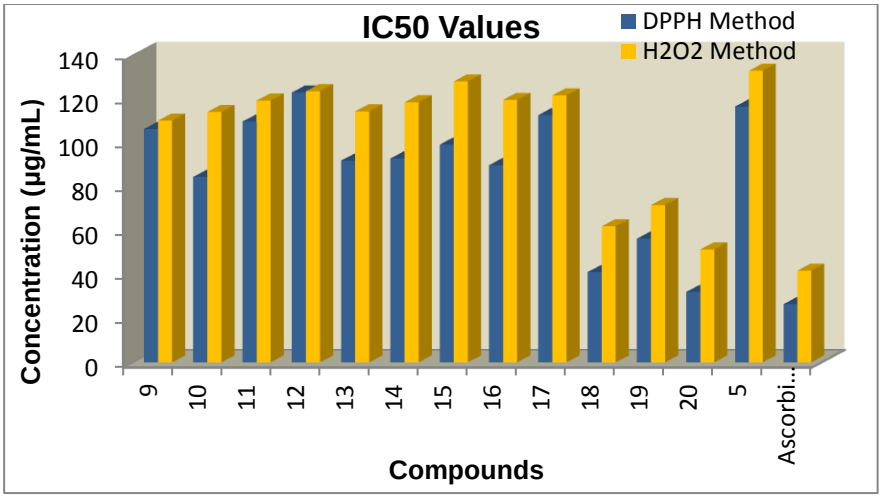
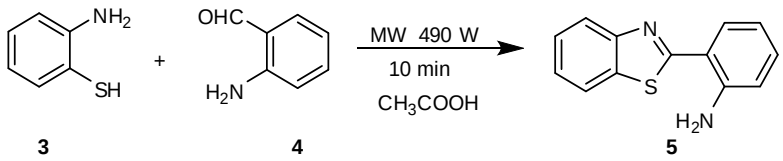
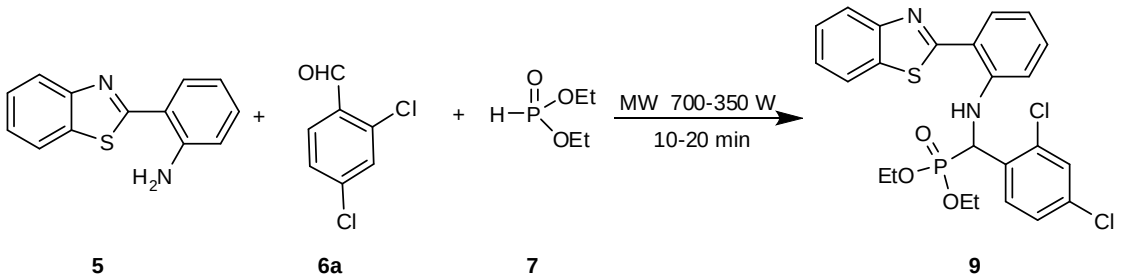


Figure 2. Half inhibitor concentration values of the title compounds **9-20**.



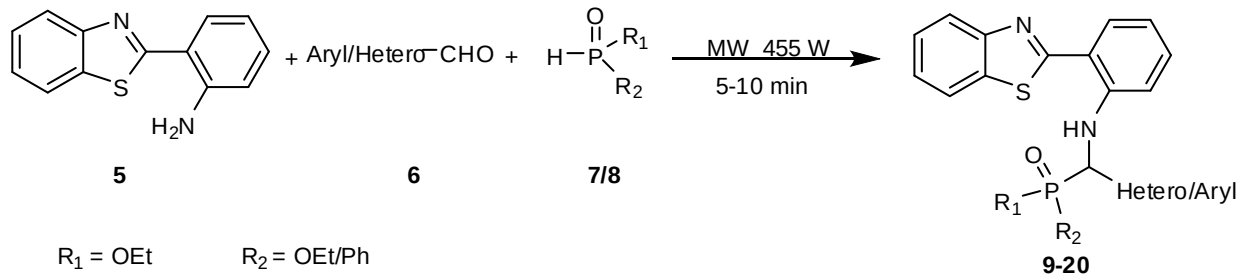
3 4 5

Scheme 1. Synthesis of 2-(2-aminophenyl)benzothiazole **(5)**.



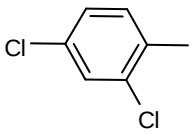
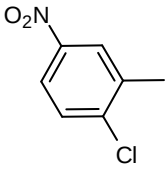
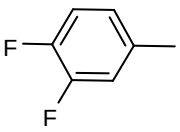
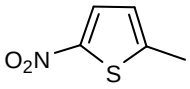
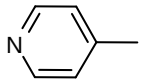
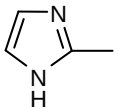
5 **6a** **7** **9**

Scheme 2. Model reaction for the synthesis of diethyl(2(benzo[*d*]thiazol-2-yl)phenylamino)(2,4-dichlorophenyl)methylphosphonate **(9)**.



5 **6** **7/8** **9-20**

R_1 = OEt R_2 = OEt/Ph

Compd.	6a	6b	6c	6d	6e	6f
Aryl/Hetero						

Scheme 3. Schematic representation of the synthesized compounds of α-aminophosphonates **(9-20)**.