

Synthesis and biological evaluation of some new polyfluorinated 4-thiazolidinone and α -aminophosphonic acid derivatives

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Abstract A simple route for the synthesis of new polyfluorinated 4-thiazolidinones and 1,4-bis(4-thiazolidinone)-phenylenes was achieved from one-pot three-component reaction of fluorinated aniline, mono- and dialdehyde and thioglycolic acid followed by fluorination with trifluoroacetamide and 4-fluorobenzaldehyde. Also, some new fluorinated α -aminophosphonates, 1,4-bis(α -aminophosphonate)phenylenes and their corresponding acids were synthesized via one-pot three-component reaction of fluorinated aniline, mono- and dialdehyde and diethyl phosphite followed by fluorination with trifluoroacetic anhydride. All the synthesized compounds were screened for their antifungal activity against *Alternaria alternata* and *Fusarium oxysporium*. Also, their effects on the enzymatic effect of cellobiase produced from *Alternaria alternata* and *Fusarium oxysporium* were estimated. Compounds that have trifluoromethyl groups recorded good inhibition against the fungal strains and also enhanced the enzymatic effect of cellobiase.

Keywords Synthesis · Antifungal · Fluorine · 4-thiazolidinone · α -Aminophosphonic acids and their esters

Introduction

Fluorine occupies a unique place among all elements of the periodic classification because of its high electronegativity and its specific properties. Thus, organofluorine chemistry is of great importance because of this singular nature of the fluorine atom combined with the unique physical and chemical properties that fluorine imparts to compounds that contain it. The strong electronic contribution and negligible steric demands of fluorine present interesting and unusual properties. Indeed, the specific physicochemical properties of fluorinated organic compounds are of huge interest in a wide range of applications [1–5]. Consequently, organofluorine chemistry has been steadily growing and today possesses a distinctive role in highly diverse technological developments (fluoropolymers, pharmaceutical and agrochemical products, materials science, etc.) [6, 7]. Therefore, the development of new methods to introduce fluorine into molecules is of great interest to organic and medicinal chemists.

4-Thiazolidinones are key structures in numerous compounds of therapeutic importance as antimicrobial, plant protection, anticancer and anti-AIDS activities [8–15]. On the other hand, α -aminophosphonate derivatives are structural mimics of α -amino acids, and some of these compounds exhibit very high potency in inhibiting the enzymes that are involved in the metabolism of the corresponding amino acids. These compounds have already been found to act as antibacterial agents, neuroactive compounds, anticancer drugs and pesticides, with some of them already being commercialized [16–22].

Keeping in view the diverse biological activities associated with organofluorine compounds, 4-thiazolidinones and α -aminophosphonates, it was intended to construct novel fluorinated 4-thiazolidinones and α -aminophosphonates

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hoping to achieve additive effects toward their biological activities. As an extension of our research work on the synthesis of bioactive heterocycles [23–27], we wish to report herein the synthesis of some new fluorinated 4-thiazolidinones and α -aminophosphonates and evaluation of their fungicidal properties and enzymatic effect on cellobiase.

Results and discussion

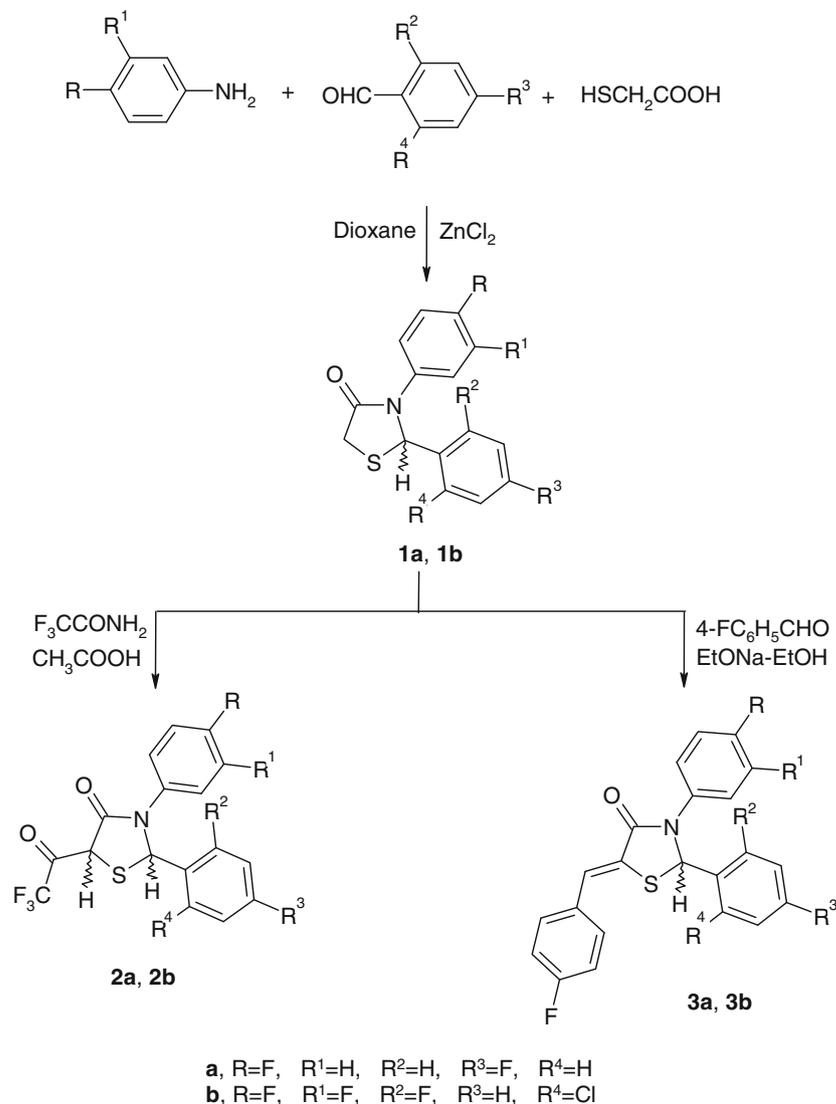
Chemistry

The most convenient method for the synthesis of 2,3-disubstituted-4-thiazolidinones is the one-pot three-component reaction of a primary amine, carbonyl compound and

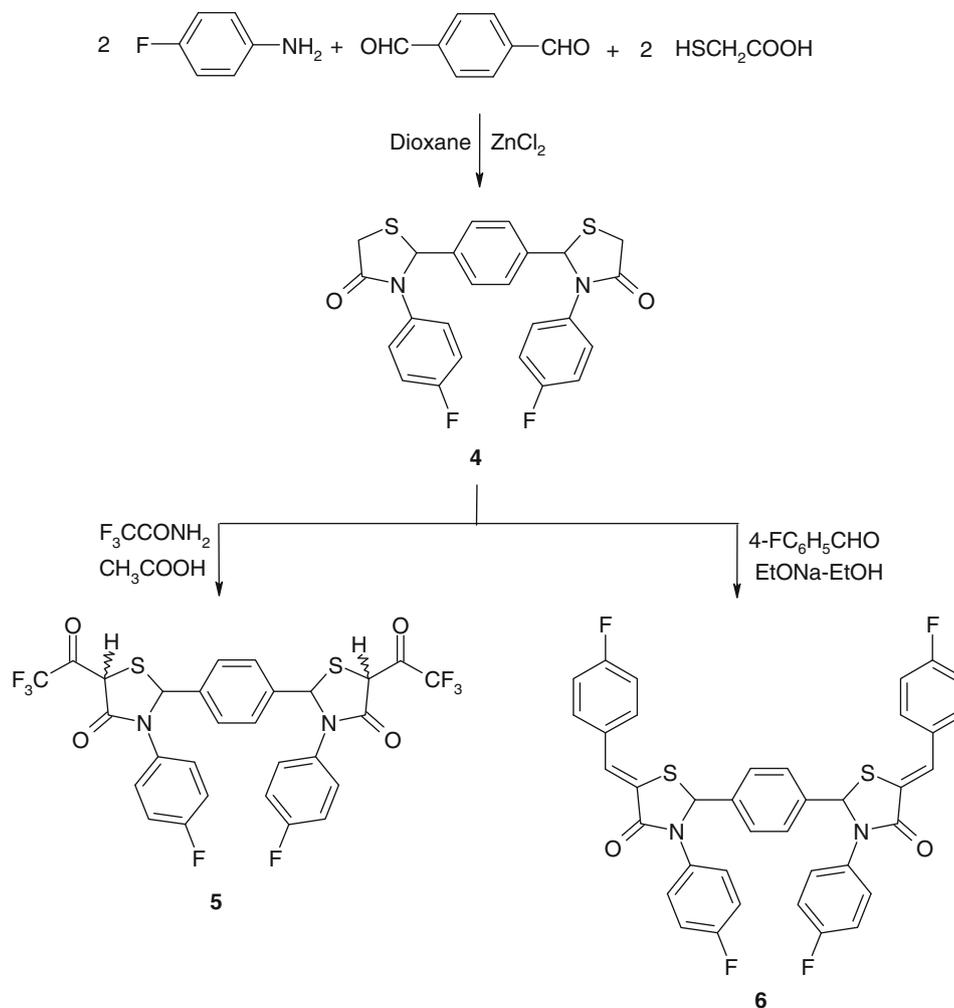
thioglycolic acid. The different reaction conditions, such as long-term heating with a dehydrant, using an acylation agent or microwave-assistant organic synthesis, were described [28, 29]. Based on the above-mentioned approach, we have synthesized 2,3-bis(fluorinated substituted phenyl)thiazolidin-4-one (**1a,b**) from the reaction of fluorinated substituted aniline, fluorinated substituted benzaldehyde and thioglycolic acid in dry dioxane in the presence of anhydrous zinc chloride (Scheme 1).

Compounds **1a,b** contain an active methylene group in position C-5 of the core ring, which opens wide opportunities for their modification, taking into consideration the critical influence of the presence and the nature of the C-5 position moieties on biological activity. The polyfluorinated 4-thiazolidinone derivatives **2a,b** and **3a,b** have been

Scheme 1



Scheme 2

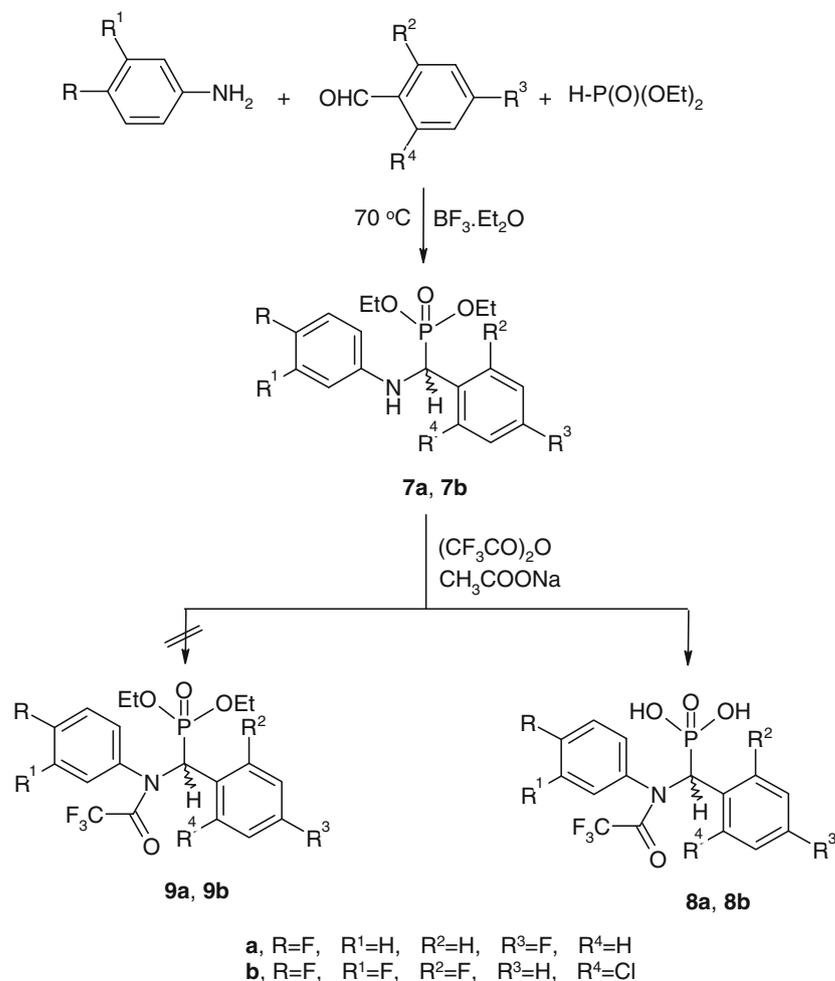


achieved via fluorination of compounds **1a,b** with fluorine reagents such as trifluoroacetamide and 4-fluorobenzaldehyde. Thus, fusion of compounds **1a,b** with trifluoroacetamide in the presence of glacial acetic acid afforded 2,3-bis(fluorinated substituted phenyl)-5-(trifluoroacetyl)thiazolidin-4-ones (**2a,b**), while their condensation with 4-fluorobenzaldehyde in ethanolic sodium ethoxide under Knoevenagel reaction condition gave 5-(4-fluorobenzylidene)-2,3-bis(fluorinated substituted phenyl)thiazolidin-4-ones (**3a,b**) (Scheme 1).

The main aim of this work is the combination of many fluorinated rings together in a single molecular structure hoping to achieve additive biocidal effects toward their antifungal activity, where the fluorine atoms leads to a strong polarization and changes various physical and biological properties of the molecules. Thus, one-pot three-component reaction of 4-fluoroaniline, 1,4-terephthalaldehyde and thioglycolic acid in dry dioxane in the presence of anhydrous zinc chloride as a catalyst under reflux afforded

2,2'-(1,4-phenylene)bis[3-(4-fluorophenyl)thiazolidin-4-one] (**4**) (Scheme 2). Furthermore, the latter *bis*-thiazolidinone **4** reacted with trifluoroacetamide and 4-fluorobenzaldehyde under the same previously described conditions to yield the interesting 2,2'-(1,4-phenylene)bis[3-(4-fluorophenyl)-5-(2,2,2-trifluoroacetyl)thiazolidin-4-one] (**5**) and 2,2'-(1,4-phenylene)bis[5-(4-fluorobenzylidene)-3-(4-fluorophenyl)thiazolidin-4-one] (**6**), respectively (Scheme 2). The structures of the new thiazolidinone derivatives **1–6** were assigned on the basis of their analytical and spectral data. The characteristic C=O bands of the thiazolidinone rings appeared in the region $1,656\text{--}1,696\text{ cm}^{-1}$ in the IR spectra of the thiazolidinones **1–6**, while C=O of the trifluoroacetyl moiety in **2a,b** and **5** appeared at $1,729$, $1,730$ and $1,731\text{ cm}^{-1}$, respectively. Furthermore, the compounds **1a,b** and **4** display doublets at $3.85\text{--}3.95\text{ ppm}$ because of the H_A and H_B systems in their $^1\text{H NMR}$ spectra. In the compounds **2a,b**, **3a,b**, **5** and **6**. These H_A and H_B systems were absent,

Scheme 3

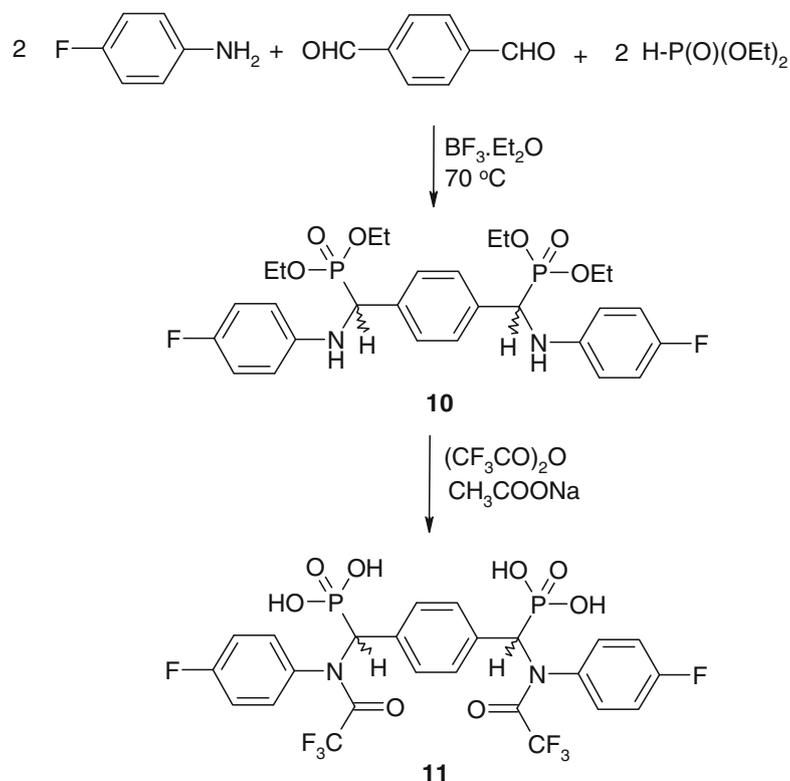


confirming that trifluoroacetylation and condensation reactions had taken place on the 5-CH₂ groups. Regarding compounds **1–6**, their ¹H-NMR spectra showed singlets at 5.92–6.03 ppm because of a proton of 2-CH. Also, the ¹³C-NMR spectra recorded the characteristic C=O bands of the thiazolidinone rings at 170.6–171.4 ppm, while C=O of the trifluoroacetyl moiety in **2a,b** and **5** appeared at 195.0, 193.5 and 195.1 ppm, respectively.

Introduction of the fluorine-containing group in a biomolecule may change the 'normal' route of its interaction with a biological target or the direction of binding. Therefore, such an approach is very popular for the construction of new biologically active molecules. However, in contrast to the rather well-developed α-aminophosphonic acid area, only limited representatives of fluorine containing α-aminophosphonates are currently known [30–38]. Thus, the synthesis of new fluorinated α-aminophosphonates as potential drug candidates is of current interest. One-pot three-component reaction of fluorinated

substituted anilines, fluorinated substituted benzaldehydes and diethyl phosphite in the presence of BF₃·Et₂O as a catalyst at 70 °C under Kabachnik-Fields reaction condition afforded the corresponding diethyl[(fluorinated substituted phenylamino) (fluorinated substituted phenyl)methyl]phosphonates (**7a,b**) in high yield [37, 38] (Scheme 3). The fluorination of the α-aminophosphonates **7a,b** with trifluoroacetic anhydride in the presence of anhydrous sodium acetate gave [2,2,2-trifluoro-N-(fluorinated substituted phenyl)acetamido] [fluorinated substituted phenyl]methyl phosphonic acids (**8a,b**) and not the diesters **9a,b** (Scheme 3). This reaction underwent trifluoroacetylation of the NH group of compounds **7a,b** followed by hydrolysis of the diester because of the presence of the formed trifluoroacetic acid. Similarly, applying the Kabachnik-Fields reaction to 4-fluoroaniline, 1,4-terephthalaldehyde and diethyl phosphite in the presence of BF₃·Et₂O as a catalyst at 70 °C afforded diethyl 1,4-phenylene-bis[N-(4-fluorophenyl)aminomethylphosphonate] (**10**) (Scheme 4). The latter bis-aminophosphonate also

Scheme 4



underwent trifluoroacetylation followed by acid hydrolysis to give the novel interesting 1,4-phenylene-bis[*N*-(2,2,2-trifluoroacetyl)-*N*-(4-fluorophenyl)aminomethylphosphonic acid] (**11**) (Scheme 4). The chemical structures of α -aminophosphonic acid derivatives **7a,b**, **8a,b**, **10** and **11** were confirmed by elemental analysis, IR, ^1H -, ^{13}C - and ^{31}P -NMR spectra. Compounds **7a,b** and **10** exhibited characteristic IR stretching frequencies in the region 3,339–3,100, 1,281–1,238 and 1,013–1,092 cm^{-1} for NH, P=O and P–O–C functions, respectively. The P–CH protons of **7a,b** and **10** resonated as doublets at δ 4.69, 4.12 and 5.06 ppm ($J_{\text{PCH}} = 23.9, 15.6$ and 17.2 Hz), respectively, because of their coupling with phosphorus. The ethyl groups of the diethyl phosphonate moieties resonated as two distinct triplets and quartets at δ 1.19–1.28 and 3.69–4.20 ppm [38]. Also, the P–CH carbon atom shift signals for **7b** and **10** appeared as doublets at δ 44.0 and 43.3 ppm ($J_{\text{PCH}} = 143.8$ and 150 Hz), respectively, in their ^{13}C -NMR spectra, while the phosphorus atoms were resonated in the ^{31}P -NMR spectrum as singlets at δ 22.3 and 20.5 ppm, respectively. Similarly, the spectroscopic data of **8a,b** and **11** were in complete agreement with the proposed structures. The appearance of OH, C=O and P=O was at 3,200–3,365, 1,709–1,731 and 1,220–1,257 cm^{-1} , respectively, in their IR spectra. Also, in their ^1H -NMR spectra, the P–CH protons

appeared as doublets at δ 3.65, 4.00 and 4.61 ($J_{\text{PCH}} = 16.8, 19.2,$ and 19.2 Hz) for **8a,b** and **11**, respectively. Also, the ^{13}C -NMR spectra were supported for the proposed structures, which exhibited the resonances of P–CH and C=O at the region δ 51.5, 50.6, 48.5 and 193, 195, 190.3 ppm, respectively. The ^{31}P -NMR spectra of **8b** and **11** recorded singlets for them at δ 14.4 and 15.3 ppm, respectively. Although the compounds **10** and **11** have two chiral centers, they exist in only one diastereomeric form because of the presence of one peak for each carbon and phosphorus of the P–CH moiety in their NMR spectra [39].

Biological evaluation

In vitro antifungal activity

The newly synthesized compounds were evaluated for their in vitro antifungal activity against two fungal strains, *Alternaria alternate* and *Fusarium oxysporium*, by the poisoned food method [40, 41]. Fluconazole was used as the reference drug, and the results were recorded as the percentage of growth inhibition (Table 1). The results revealed that, in general, all the tested compounds possessed good antifungal activity. On the basis of percentage of growth inhibition against the tested fungal strains, it seems that replacement of the active methylene group in

Table 1 In vitro antifungal activity of the synthesized compounds on some fungi at concentrations of 250, 500 and 100 ppm

Compound	Percent of growth inhibition/%					
	<i>Alternaria alternate</i>			<i>Fusarium oxysporium</i>		
	250 ppm	500 ppm	1,000 ppm	250 ppm	500 ppm	1,000 ppm
1a	76.8	78.1	80.9	76.3	80.2	82.2
1b	77.8	80.2	82.0	77.4	80.8	83.3
2a	88.1	89.0	91.5	84.3	87.0	90.4
2b	88.7	90.3	91.9	85.6	88.1	92.3
3a	80.5	82.3	85.8	74.8	76.3	81.7
3b	80.9	83.4	85.9	76.2	77.6	81.9
4	76.2	77.0	78.9	76.5	78.2	81.8
5	85.4	88.3	90.5	87.3	88.3	90.1
6	78.9	80.3	82.1	74.2	76.7	79.9
7a	80.1	82.8	85.2	80.1	83.3	87.1
7b	82.4	83.4	85.6	80.2	84.1	88.1
8a	80.3	82.1	84.4	79.5	80.5	86.5
8b	81.6	83.5	86.3	79.7	81.3	88.3
10	79.9	80.1	83.5	78.0	80.5	82.1
11	83.2	86.1	89.4	85.3	87.2	88.7
Fluconazole	92.0	94.3	95.8	90.8	92.4	94.3

compounds **1a,b** and **4** with trifluoroacetyl and 4-fluorobenzylidene exhibited a noticeable increase in the antifungal activity. Also, trifluoroacetylation of the NH groups of compounds **7a,b** and **10** and transformation of ethoxy groups into hydroxyl caused improvement the antifungal activity.

The effect of the synthesized compounds on the enzymatic effect on cellobiase

The effect of synthesized compounds on cellobiase activity produced by *Alternaria alternate* and *Fusarium oxysporium* was estimated [42, 43]. The obtained results were recorded in Table 2. Generally, at lower concentration, the enzymatic effect of the tested compounds increased while the higher concentration of the synthesized compounds inhibited that enzymatic effect. Only compounds **2a,b**, **5**, **8b** and **11** exhibited highly enzymatic effects at low concentration because of the hydrophobic character of CF₃ groups that essentially improves the pharmacokinetic profiles of potential drugs.

Conclusions

In this article, some new fluorinated 4-thiazolidinone and α -aminophosphonic acid derivatives were synthesized. All the synthesized compounds were screened for their antifungal activity and the enzymatic effect on cellobiase. Of the tested compounds, **2a,b**, **5** and **11** exhibited good

antifungal activity against the tested fungi and also enhanced the enzymatic effect of cellobiase. However, none of the newly synthesized compounds was found to be superior compared to the used references.

Experimental

Melting points of the products were determined on Stuart SMP3. A Perkins-Elmer model RXI-FT-IR system 55529 was used for recording the IR spectra of the prepared compounds using CDCl₃ and D₂O solvents. ¹H-, ¹³C- and ³¹P-NMR spectra were recorded on a Bruker 600 MHz spectrometer operating at 600, 150 and 242 MHz, respectively. The chemical shifts are reported in ppm with respect to the references and were stated relative to tetramethylsilane (TMS) for ¹H- and ¹³C-NMR and to 85 % phosphoric acid for ³¹P-NMR. Mass spectra were recorded on a gas chromatographic DI analysis Shimadzu instrument Q-2010 Plus at 70 eV. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) and elemental analysis. The biological activities were measured at the Department of Biochemistry, Faculty of Science, King Abdulaziz University.

2,3-Bis(fluorinated substituted phenyl)thiazolidin-4-one (**1a,b**)

A mixture of fluorinated substituted aniline (2.5 mmol) and fluorinated substituted benzaldehyde (2.5 mmol) was

Table 2 The effect of synthesized compounds on cellobiase activity produced by *Alternaria alternate* and *Fusarium oxysporium*

Compound*	<i>Alternaria alternate</i>			<i>Fusarium oxysporium</i>		
	10 $\mu\text{g}/\text{cm}^3$	50 $\mu\text{g}/\text{cm}^3$	100 $\mu\text{g}/\text{cm}^3$	10 $\mu\text{g}/\text{cm}^3$	50 $\mu\text{g}/\text{cm}^3$	100 $\mu\text{g}/\text{cm}^3$
1a	0.32	0.30	0.25	0.31	0.30	0.26
1b	0.33	0.32	0.26	0.33	0.31	0.26
2a	0.35	0.33	0.30	0.33	0.31	0.27
2b	0.36	0.33	0.32	0.34	0.32	0.25
3a	0.29	0.25	0.22	0.26	0.22	0.18
3b	0.31	0.27	0.24	0.26	0.23	0.17
4	0.28	0.26	0.22	0.26	0.24	0.22
5	0.38	0.35	0.31	0.35	0.33	0.30
6	0.30	0.28	0.22	0.28	0.25	0.22
7a	0.31	0.28	0.25	0.30	0.28	0.24
7b	0.32	0.30	0.27	0.32	0.27	0.21
8a	0.34	0.31	0.29	0.28	0.26	0.22
8b	0.36	0.33	0.29	0.30	0.29	0.23
10	0.34	0.32	0.28	0.30	0.27	0.25
11	0.41	0.36	0.32	0.37	0.33	0.31

* DMF as solvent recorded 0.04 $\mu\text{g}/\text{cm}^3$

heated in dry dioxane (15 cm^3) under reflux for 10 min, followed by addition of a solution of thioglycolic acid (3 mmol) in dry dioxane (5 cm^3) and 1.5 g freshly fused zinc chloride. The reaction mixture was heated under reflux for an additional 6 h. The mixture was cooled then neutralized with aqueous NaHCO_3 (10 %, 30 cm^3). The formed solid was filtered off, washed with water three times and crystallized from ethanol to give the pale yellow crystals.

2,3-Bis(4-fluorophenyl)thiazolidin-4-one
(**1a**, $\text{C}_{15}\text{H}_{11}\text{F}_2\text{NOS}$)

Yield 0.45 g (62 %). M.p.: 98–100 °C; IR (CDCl_3): $\bar{\nu} = 1,656$ (C=O), 1,239 (C–F) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): $\delta = 3.88, 3.91$ (dd, 2H, 5- CH_2 , AB system), 6.02 (s, 1H, 2-CH), 6.96–6.99 (m, 4H, Ar–H), 7.02–7.09 (m, 2H, Ar–H), 7.27–7.29 (m, 2H, Ar–H) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 33.4$ (5- CH_2), 65.1 (2-CH), 116.0, 116.3, 127.8, 127.9, 133.0, 134.7, 160.4, 162.0, 171.0 (C=O) ppm; anal. calcd. for $\text{C}_{15}\text{H}_{11}\text{F}_2\text{NOS}$ (291.32): C, 61.84; H, 3.81; N, 4.81; S, 11.01. Found: C, 61.66; H, 3.59; N, 4.71; S, 10.70.

2-(2-Chloro-6-fluorophenyl)-3-(3,4-difluorophenyl)thiazolidin-4-one (**1b**, $\text{C}_{15}\text{H}_9\text{ClF}_3\text{NOS}$)

Yield 0.51 g (60 %). M.p.: 70–72 °C; IR (CDCl_3): $\bar{\nu} = 1,660$ (C=O), 1,203 (C–F) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): $\delta = 3.85, 3.88$ (dd, 2H, 5- CH_2 , AB system), 6.00 (s, 1H, 2-CH), 6.99–7.10 (m, 6H, Ar–H) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 33.5$ (5- CH_2), 58.5 (2-CH), 114.8, 115.6, 117.5, 121.1, 125.6, 127.6, 130.7, 130.9, 133.4, 160.6, 161.0, 162.3, 170.6 (C=O) ppm;

MS (70 eV): $m/z = 344$ (M^+); anal. calcd. for $\text{C}_{15}\text{H}_9\text{ClF}_3\text{NOS}$ (343.75): C, 52.41; H, 2.64; N, 4.07; S, 9.33. Found: C, 52.19; H, 2.53; N, 3.82; S, 9.11.

5-(2,2,2-Trifluoroacetyl)-2,3-bis(fluorinated substituted phenyl)thiazolidin-4-one (**2a,b**)

A mixture of 2,3-bis(fluorinated substituted phenyl)thiazolidin-4-one (**1a,b**) (2.5 mmol) and 0.28 g trifluoroacetamide (2.5 mmol) in the presence of few drops of glacial acetic acid was fused at 120 °C for 1 h. The cooled reaction mixture was poured onto 100 g of crushed ice. The formed solid was filtered off, washed with water three times then crystallized from aqueous ethanol to give the yellowish crystals.

5-(2,2,2-Trifluoroacetyl)-2,3-bis(4-fluorophenyl)thiazolidin-4-one (**2a**, $\text{C}_{17}\text{H}_{10}\text{F}_5\text{NO}_2\text{S}$)

Yield 0.78 g (81 %). M.p.: 122–124 °C; IR (CDCl_3): $\bar{\nu} = 1,729$ (C=O), 1,669 (C=O), 1,222 (C–F) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): $\delta = 4.20$ (s, 1H, 5-CH), 6.03 (s, 1H, 2-CH), 6.95–6.99 (m, 4H, Ar–H), 7.00–7.10 (m, 2H, Ar–H), 7.27–7.30 (m, 2H, Ar–H) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 45.3$ (5-CH), 65.1 (2-CH), 113.9 (CF_3), 116.0, 116.3, 127.8, 127.9, 133.0, 134.7, 160.4, 162.0, 171.0 (C=O), 195.0 (C=O) ppm. MS (70 eV): $m/z = 387$ (M^+); anal. calcd. for $\text{C}_{17}\text{H}_{10}\text{F}_5\text{NO}_2\text{S}$ (387.33): C, 52.72; H, 2.60; N, 3.62; S, 8.28. Found: C, 52.47; H, 2.39; N, 3.36; S, 8.02.

2-(2-Chloro-6-fluorophenyl)-3-(3,4-difluorophenyl)-5-(2,2,2-trifluoroacetyl)thiazolidin-4-one (**2b**, $\text{C}_{17}\text{H}_8\text{ClF}_6\text{NO}_2\text{S}$)

Yield 0.6 g (55 %). M.p.: 101–103 °C; IR (CDCl_3): $\bar{\nu} = 1,730$ (C=O), 1,696 (C=O), 1,220 (C–F) cm^{-1} ; ^1H

NMR (600 MHz, CDCl_3): $\delta = 4.10$ (s, 1H, 5-CH), 6.02 (s, 1H, 2-CH), 6.98–7.10 (m, 6H, Ar-H) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 44.5$ (5-CH), 64.7 (2-CH), 110.0 (CF_3), 114.9, 115.7, 117.5, 121.1, 125.6, 127.6, 130.8, 130.9, 133.4, 160.6, 161.0, 162.3, 170.6 (C=O), 193.5 (C=O) ppm; anal. calcd. for $\text{C}_{17}\text{H}_8\text{ClF}_6\text{NO}_2\text{S}$ (439.75): C, 46.43; H, 1.83; N, 3.19; S, 7.29. Found: C, 46.26; H, 1.54; N, 2.87; S, 7.08.

5-(4-Fluorobenzylidene)-2,3-bis(fluorinated substituted phenyl)thiazolidin-4-one (3a,b)

A mixture of 2,3-bis(fluorinated substituted phenyl)thiazolidin-4-one (**1a,b**) (2.5 mmol) and 0.31 g 4-fluorobenzaldehyde (2.5 mmol) in ethanolic sodium ethoxide (0.2 g Na in 15 cm^3 of ethanol) was heated under reflux for 10 h. The cooled reaction mixture was poured onto ice cold water, then acidified with diluted acetic acid. The formed solid was filtered off and crystallized from ethanol to give the yellowish products.

5-(4-Fluorobenzylidene)-2,3-bis(4-fluorophenyl)thiazolidin-4-one (3a, $\text{C}_{22}\text{H}_{14}\text{F}_3\text{NOS}$)

Yield 0.73 g (74 %). M.p.: 242–244 °C; IR (CDCl_3): $\bar{\nu} = 1,682$ (C=O), 1,221 (C–F) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): $\delta = 5.95$ (s, 1H, 2-CH), 6.90–7.30 (m, 13H, Ar–H and =CH) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 65.1$ (2-CH), 116.0, 116.1, 116.3, 127.8, 127.9, 129.1, 129.2, 133.0, 133.1, 134.7, 162.0, 162.1, 163.7, 171.0 (C=O) ppm; anal. calcd. for $\text{C}_{22}\text{H}_{14}\text{F}_3\text{NOS}$ (397.41): C, 66.49; H, 3.55; N, 3.52; S, 8.07. Found: C, 66.21; H, 3.38; N, 3.34; S, 7.94.

2-(2-Chloro-6-fluorophenyl)-3-(3,4-difluorophenyl)-5-(4-fluorobenzylidene) thiazolidin-4-one (3b, $\text{C}_{22}\text{H}_{12}\text{ClF}_4\text{NOS}$)

Yield 0.84 g (75 %). M.p.: 264–265 °C; IR (CDCl_3): $\bar{\nu} = 1,667$ (C=O), 1,600 (C=C), 1,231 (C–F) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): $\delta = 5.92$ (s, 1H, 2-CH), 6.78–7.23 (m, 11H, Ar–H and =CH) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 58.6$ (2-CH), 115.4, 115.5, 115.6, 117.5, 121.2, 121.3, 124.3, 124.4, 125.5, 125.6, 127.6, 130.7, 130.8, 130.9, 133.3, 133.4, 160.5, 161.0, 162.0, 162.2, 171.40 (C=O) ppm; MS (70 eV): $m/z = 450$ (M^+); anal. calcd. for $\text{C}_{22}\text{H}_{12}\text{ClF}_4\text{NOS}$ (449.84): C, 58.74; H, 2.69; N, 3.11; S, 7.13. Found: C, 58.42; H, 2.42; N, 3.01; S, 6.92.

2,2'-(1,4-Phenylene)bis[3-(4-fluorophenyl)thiazolidin-4-one] (4, $\text{C}_{24}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_2\text{S}_2$)

A mixture of 0.22 g 4-fluoroaniline (2 mmol) and 0.134 g 1,4-terephthalaldehyde (1 mmol) was heated in dry dioxane (15 cm^3) under reflux for 15 min, followed by addition of a solution of thioglycolic acid (3 mmol) in dry dioxane (5 cm^3) and 1.5 g freshly fused zinc chloride. The reaction mixture was heated under reflux for an additional 10 h. The mixture was cooled then neutralized with aqueous NaHCO_3 (10 %, 30 cm^3). The formed solid was filtered off, washed with water three times and crystallized from

tetrahydrofuran to give pale yellow crystals. Yield 0.41 g (88 %). M.p.: 247–249 °C. IR (CDCl_3): $\bar{\nu} = 1,665$ (C=O), 1,227 (C–F); ^1H NMR (600 MHz, CDCl_3): $\delta = 3.89$, 3.95 (dd, 4H, 5- CH_2 , $AA'BB'$ system), 5.95 (s, 2H, 2-CH), 6.90–6.93 (m, 4H, Ar–H), 6.94–6.98 (m, 4H, Ar–H), 7.21–7.22 (m, 4H, Ar–H) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 33.3$ (5- CH_2), 65.2 (2-CH), 116.1, 127.8, 127.9, 132.9, 140.0, 162.0, 170.9 (2 C=O) ppm; MS (70 eV): $m/z = 468$ (M^+); anal. calcd. for $\text{C}_{24}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_2\text{S}_2$ (468.55): C, 61.52; H, 3.87; N, 5.98; S, 13.69. Found: C, 61.32; H, 3.64; N, 5.77; S, 13.48.

2,2'-(1,4-Phenylene)bis[3-(4-fluorophenyl)-5-(2,2,2-trifluoroacetyl) thiazolidin-4-one] (5, $\text{C}_{28}\text{H}_{16}\text{F}_8\text{N}_2\text{O}_4\text{S}_2$)

A mixture of 0.468 g 2,2'-(1,4-phenylene)bis[3-(4-fluorophenyl) thiazolidin-4-one] (**4**) (1 mmol) and 0.226 g trifluoroacetamide (2 mmol) in the presence of a few drops of glacial acetic acid was fused at 250 °C for 2 h. The cooled reaction mixture was poured onto 100 g of crushed ice. The formed solid was filtered off, washed with water three times then crystallized from methanol to give white crystals. Yield 0.48 g (74 %). M.p.: 202–204 °C. IR (CDCl_3): $\bar{\nu} = 1,731$ (C=O), 1,667 (C=O), 1,222 (C–F) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): $\delta = 4.23$ (s, 2H, 5-CH), 5.96 (s, 2H, 2-CH), 6.90–6.99 (m, 8H, Ar–H), 7.21–7.23 (m, 4H, Ar–H) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 48.1$ (5-CH), 65.2 (2-CH), 114.4 (CF_3), 116.2, 127.7, 127.9, 133.0, 140.0, 162.0, 171.0 (C=O), 195.1 (C=O) ppm; anal. calcd. for $\text{C}_{28}\text{H}_{16}\text{F}_8\text{N}_2\text{O}_4\text{S}_2$ (660.57): C, 50.91; H, 2.44; N, 4.24; S, 9.71. Found: C, 50.66; H, 2.24; N, 3.97; S, 9.53.

2,2'-(1,4-Phenylene)bis[5-(4-fluorobenzylidene)-3-(4-fluorophenyl) thiazolidin-4-one] (6, $\text{C}_{38}\text{H}_{24}\text{F}_4\text{N}_2\text{O}_2\text{S}_2$)

A mixture of 0.468 g 2,2'-(1,4-phenylene)bis[3-(4-fluorophenyl) thiazolidin-4-one] (**4**) (1 mmol) and 0.248 g 4-fluorobenzaldehyde (2 mmol) in ethanolic sodium ethoxide (0.2 g Na in 30 cm^3 of ethanol) was heated under reflux for 10 h. The cooled reaction mixture was poured onto ice cold water then acidified with diluted acetic acid. The formed solid was filtered off and crystallized from ethanol to give yellow crystals. Yield 0.53 g (79 %). M.p.: 263–265 °C; IR (CDCl_3): $\bar{\nu} = 1,670$ (C=O), 1,597 (C=C), 1,227 (C–F) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): $\delta = 5.95$ (s, 2H, 2-CH), 6.92–6.97 (m, 8H, Ar–H), 7.10–7.30 (m, 14H, Ar–H and =CH) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 65.1$ (2-CH), 116.1, 116.3, 127.83, 127.9, 128.1, 129.2, 133.0, 133.1, 134.7, 162.0, 163.7, 171.0 (2 C=O) ppm; anal. calcd. for $\text{C}_{38}\text{H}_{24}\text{F}_4\text{N}_2\text{O}_2\text{S}_2$ (680.75): C, 67.05; H, 3.55; N, 4.12; S, 9.42. Found: C, 66.83; H, 3.28; N, 3.94; S, 9.20.

Diethyl [(fluorinated substituted phenylamino)(fluorinated substituted phenyl)methyl]phosphonate (7a,b)

A mixture of fluorinated substituted anilines (1 mmol), fluorinated substituted benzaldehyde (1 mmol) and diethyl

phosphite (1.5 mmol) in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.1 cm^3) was heated under reflux at 70°C for 2 h. The mixture was concentrated to dryness under reduced pressure, and the residue was taken up with ethyl acetate. The organic layer was washed with anhydrous sodium sulfate, and the solvent was removed under vacuum to give the crude product, which was recrystallized from ethanol to give white crystals.

Diethyl [(4-fluorophenylamino)(4-fluorophenyl)methyl]phosphonate (7a, $\text{C}_{17}\text{H}_{20}\text{F}_2\text{NO}_3\text{P}$)

Yield 0.34 g (96 %). M.p.: $80\text{--}82^\circ\text{C}$ (Lit [37]. $80\text{--}81^\circ\text{C}$); IR (CDCl_3): $\bar{\nu} = 3,331$ (NH), 1,273 (P=O), 1,231 (C–F), 1,014 (P–O–C) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): 1.19 (t, 3H, $J = 7.14$ Hz, CH_3), 1.28 (t, 3H, $J = 7.14$ Hz, CH_3), 3.69–4.20 (m, 4H, CH_2), 4.69 (d, 1H, $J = 23.9$ Hz, CH–P), 6.49–6.60 (m, 2H, Ar–H), 6.78–6.86 (m, 2H, Ar–H), 6.99–7.49 (m, 5H, Ar–H and NH) [38]; anal. calcd. for $\text{C}_{17}\text{H}_{20}\text{F}_2\text{NO}_3\text{P}$ (355.32): C, 57.47; H, 5.67; N, 3.94. Found: C, 57.12; H, 5.55; N, 3.71.

Diethyl [(2-chloro-6-fluorophenyl)(3,4-difluorophenylamino)methyl] phosphonate (7b, $\text{C}_{17}\text{H}_{18}\text{ClF}_3\text{NO}_3\text{P}$)

Yield 0.33 g (83 %). M.p.: $90\text{--}92^\circ\text{C}$; IR (CDCl_3): $\bar{\nu} = 3,339$ (NH), 1,281 (P=O), 1,225 (C–F), 1,013 (P–O–C) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): $\delta = 1.25$ (t, 6H, $J = 6$ Hz, CH_3), 3.90 (q, 4H, $J = 6$ Hz, CH_2), 4.12 (d, 1H, $J = 15.6$ Hz, CH–P), 6.78–7.20 (m, 6H, Ar–H), 8.00 (br, 1H, NH) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 13.8$ (CH_3), 44.0 (d, $J = 143.8$ Hz, CH–P), 62.4 (CH_2), 114.9, 115.6, 117.5, 121.1, 125.5, 127.6, 130.7, 130.8, 133.4, 160.6, 161.0, 162.3 ppm; ^{31}P NMR (242 MHz, CDCl_3): $\delta = 22.3$ ppm. MS (70 eV): $m/z = 407$ (M^+); anal. calcd. for $\text{C}_{17}\text{H}_{18}\text{ClF}_3\text{NO}_3\text{P}$ (407.75): C, 50.08; H, 4.45; N, 3.44. Found: C, 49.82; H, 4.18; N, 3.13.

[2,2,2-Trifluoro-N-(aryl)acetamido][aryl]methylphosphonic acid (8a,b)

A mixture of diethyl α -aminophosphonates **7a,b** (1 mmol), 1 g freshly fused sodium acetate and 5 cm^3 of trifluoroacetic anhydride was stirred and heated under reflux for 4 h. The cooled reaction mixture was poured onto 100 g of crushed ice. The formed solid was filtered off, washed with water three times then crystallized from ethyl acetate to give white crystals.

[2,2,2-Trifluoro-N-(4-fluorophenyl)acetamido][4-fluorophenyl]methylphosphonic acid (8a, $\text{C}_{15}\text{H}_{11}\text{F}_5\text{NO}_4\text{P}$)

Yield 0.27 g (69 %). M.p.: $206\text{--}208^\circ\text{C}$; IR (KBr): $\bar{\nu} = 3,365$ (br, OH), 1,729 (C=O), 1,248 (C–F), 1,220 (P=O) cm^{-1} ; ^1H NMR (600 MHz, D_2O): $\delta = 3.56$ (d, 1H, $J = 16.8$ Hz, CH–P), 4.75 (br, 2H, OH), 6.96–6.99 (m, 4H, Ar–H), 7.00–7.08 (m, 2H, Ar–H), 7.26–7.29 (m, 2H, Ar–H) ppm; ^{13}C NMR (150 MHz, D_2O): $\delta = 51.5$ (d, $J = 149$ Hz, CH–P), 113.9 (CF_3), 116.0, 116.3, 127.8, 127.9, 133.1, 134.7,

160.4, 162.0, 193.0 (C=O) ppm; MS (70 eV): $m/z = 395$ (M^+); anal. calcd. For $\text{C}_{15}\text{H}_{11}\text{F}_5\text{NO}_4\text{P}$ (395.23): C, 45.59; H, 2.81; N, 3.54. Found: C, 45.21; H, 2.63; N, 3.37.

{(2-Chloro-6-fluorophenyl)[(3,4-difluorophenyl)(2,2,2-trifluoroacetyl)amino]methyl}phosphonic acid

(8b, $\text{C}_{15}\text{H}_9\text{ClF}_6\text{NO}_4\text{P}$)

Yield 0.32 g (72 %). M.p.: $232\text{--}234^\circ\text{C}$; IR (KBr): $\bar{\nu} = 3,200$ (br, OH), 1,709 (C=O), 1,265 (C–F), 1,257 (P=O) cm^{-1} ; ^1H NMR (600 MHz, D_2O): $\delta = 4.00$ (d, 1H, $J = 19.2$ Hz, CH–P), 6.78–7.19 (m, 6H, Ar–H) ppm; ^{13}C NMR (150 MHz, D_2O): $\delta = 50.6$ (d, $J = 158.7$ Hz, CH–P), 109.1 (CF_3), 114.8, 115.6, 117.5, 121.1, 125.6, 127.6, 130.8, 130.9, 133.2, 160.7, 161.0, 162.5, 195.0 (C=O) ppm; ^{31}P NMR (242 MHz, D_2O): $\delta = 14.4$ ppm; anal. calcd. for $\text{C}_{15}\text{H}_9\text{ClF}_6\text{NO}_4\text{P}$ (447.65): C, 40.25; H, 2.03; N, 3.13. Found: C, 40.03; H, 1.86; N, 2.97.

Diethyl 1,4-phenylenebis[N-(4-fluorophenyl)aminomethyl]phosphonate (10, $\text{C}_{28}\text{H}_{36}\text{F}_2\text{N}_2\text{O}_6\text{P}_2$)

A mixture of 0.22 g 4-fluoroaniline (2 mmol), 0.134 g 1,4-terephthalaldehyde (1 mmol) and diethyl phosphite (4 mmol) in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.15 cm^3) was heated under reflux at 70°C for 2 h. The mixture was concentrated to dryness under reduced pressure, and the residue was taken up with ethyl acetate. The organic layer was washed with anhydrous sodium sulfate, and the solvent was removed under vacuum to give the crude product, which was recrystallized from ethanol to give white crystals. Yield 0.47 g (80 %). M.p.: $158\text{--}159^\circ\text{C}$; IR (CDCl_3): $\bar{\nu} = 3,100$ (NH), 1,238 (C–F), 1,230 (P=O), 1,092 (P–O–C) cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): $\delta = 1.25$ (t, 12H, $J = 7.2$ Hz, CH_3), 3.91–3.96 (m, 8H, CH_2), 5.06 (d, 2H, $J = 17.2$ Hz, CH–P), 6.00 (br, 2H, NH), 6.96–6.99 (m, 8H, Ar–H), 7.00–7.10 (m, 4H, Ar–H) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 13.1$ (CH_3), 43.3 (d, $J = 150$ Hz, CH–P), 62.3 (CH_2), 116.2, 127.7, 127.9, 133.0, 140.0, 162.0 ppm; ^{31}P NMR (242 MHz, CDCl_3): $\delta = 20.5$ ppm; anal. calcd. for $\text{C}_{28}\text{H}_{36}\text{F}_2\text{N}_2\text{O}_6\text{P}_2$ (596.55): C, 56.38; H, 6.08; N, 4.70. Found: C, 56.13; H, 5.83; N, 4.39.

1,4-Phenylenebis[N-(2,2,2-trifluoroacetyl)-N-(4-fluorophenyl)aminomethyl]phosphonic acid]

(11, $\text{C}_{24}\text{H}_{18}\text{F}_8\text{N}_2\text{O}_8\text{P}_2$)

A mixture of 0.596 g diethyl 1,4-phenylenebis[N-(4-fluorophenyl)aminomethyl]phosphonate (**9**) (1 mmol), 2 g freshly fused sodium acetate and 5 cm^3 of trifluoroacetic anhydride was stirred and heated under reflux for 5 h. The cooled reaction mixture was poured onto 100 g of crushed ice. The formed solid was filtered off, washed with water three times then crystallized from ethyl acetate to give white crystals. Yield 0.52 g (77 %). M.p.: $243\text{--}245^\circ\text{C}$; IR (KBr): $\bar{\nu} = 3,357$ (br, OH), 1,731 (C=O), 1,244 (C–F), 1,230 (P=O) cm^{-1} ; ^1H NMR (600 MHz, D_2O): $\delta = 4.61$ (d, 2H, $J = 19.2$ Hz, CH–P),

6.96–6.99 (m, 8H, Ar–H), 7.00–7.10 (m, 4H, Ar–H) ppm; ^{13}C NMR (150 MHz, D_2O): $\delta = 48.5$ (d, $J = 163.5$ Hz, CH–P), 110.2 (2 CF_3), 116.2, 127.8, 127.9, 133.0, 140.0, 160.3, 190.3 (2 C=O) ppm; ^{31}P NMR (242 MHz, D_2O): $\delta = 15.3$ ppm; anal. calcd. for $\text{C}_{24}\text{H}_{18}\text{F}_8\text{N}_2\text{O}_8\text{P}_2$ (676.35): C, 42.62; H, 2.68; N, 4.14. Found: C, 42.38; H, 2.46; N, 3.89.

Biological assay

In vitro antifungal assay

The antifungal activity of newly synthesized compounds was evaluated against the fungal strains *Alternaria alternata* and *Fusarium oxysporium* in three replications by the food poison technique [40, 41]. The molds were grown on to potato-dextrose Agar (PDA) medium at 25 °C for 7 days and used as inocula. Then 100 μM^3 volume of each compound, having three concentrations of 250, 500 and 1,000 ppm, was reconstituted in dry acetone and poured into a sterile petri plate. The poisoned agar plates were incubated at the center with fungal plugs obtained from the actively growing colony and incubated at 25 °C for 7 days. Dry acetone was used as solvent, and fluconazole was used as the reference drug. The experiments were performed in triplicates. The diameter of the fungal colonies was measured and expressed as percent inhibition determined by applying the following formula: percent of growth inhibition % = $(dc - dt)/dc \times 100$ where dc = average diameter of fungal colony in control plates; dt = average diameter of fungal colony in experimental plates.

The effect of the synthesized compounds on the enzymatic effect on cellobiase

The effect of synthesized compounds on cellobiase activity produced by *Alternaria alternata* and *Fusarium oxysporium* was estimated. The procedure for determining cellobiase activity was according to Tolan and Foody [42, 43]. Each compound was dissolved in an appropriate amount of DMF at concentrations of 10, 50 and 100 $\mu\text{g}/\text{cm}^3$, then added separately to the assay mixture consisting of 1 cm^3 of 15 mM cellobiose solution (prepared in 0.05 M citrate buffer pH 4.8) and 1 cm^3 of the diluted enzyme solution at 50 °C for 1 h. The released reducing sugar (glucose) was estimated colorimetrically at 540 nm as an indication for the enzyme activity. The obtained results are recorded in Table 2.

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