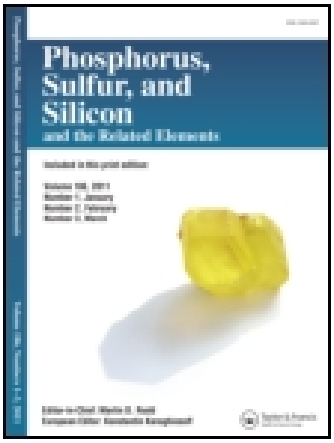

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Synthesis and In-Vitro Antimicrobial Activity of Novel Aminophosphinic Acids Containing Cyclobutane and 1,3-Thiazole

Pelin Koparir [a] , Muhsin Karaarslan [b] , Cahit Orek [c] & Metin Koparir [c]
[a] Department of Chemistry , Forensic Medicine Institute , TR-4400, Malatya, Turkey
[b] Department of Chemistry , Aksaray University , TR-68100, Aksaray, Turkey
[c] Department of Chemistry , Firat University , TR-23119, Elazığ, Turkey
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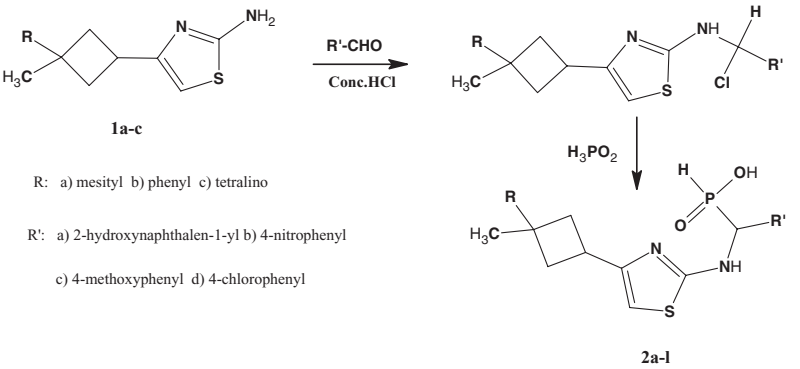
SYNTHESIS AND IN-VITRO ANTIMICROBIAL ACTIVITY OF NOVEL AMINOPHOSPHINIC ACIDS CONTAINING CYCLOBUTANE AND 1,3-THIAZOLE

Pelin Koparir,[1] Muhsin Karaarslan,[2] Cahit Orek,[3] and Metin Koparir[3]

[1]*Department of Chemistry, Forensic Medicine Institute, TR-4400 Malatya, Turkey*
[2]*Department of Chemistry, Aksaray University, TR-68100 Aksaray, Turkey*
[3]*Department of Chemistry, Firat University, TR-23119, Elazığ, Turkey*

GRAPHICAL ABSTRACT



Abstract *The compounds {[4-(3-methyl-3-aryl(mesityl-phenyl-tetralino)cyclobutyl)-1,3-thiazol-2-yl]amino}(aryl)methyl-phosphinic acids* ***2a–l*** *were prepared by condensation of 2-amino-4-(3-aryl(mesityl-phenyl-tetralino)-3-methylcyclobutyl) thiazoles* ***1a–c*** *with various aromatic aldehydes and hypophosphorous acid through a one-pot reaction. The characterizations of these compounds were obtained by elemental analyses, infrared (IR) spectra, and ^{1}H, ^{13}C, and ^{31}P NMR (nuclear magnetic resonance) techniques. The synthesized compounds were tested in vitro against one Gram-positive and two Gram-negative bacterial strains, one mycobacterial strain, and a fungus* Candida albicans*. Compound* ***2f*** *showed significant activity against Staphylococcus aureus, whereas the others had no remarkable activity on this strain. Compound* ***2g*** *was found to be more active than the others against* Mycobacterium fortuitum *at an MIC (minimum inhibitory concentration) value of 32 μg/mL. The antibacterial and antifungal activities of* ***2a–l*** *were also compared with various standard drugs.*

[Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource*: *Biological Activities. Table S1. Figures S1–S6.]*

Keywords Aminophosphinic acids; cyclobutane; thiazole

Received 13 June 2011; accepted 8 July 2011.
Address correspondence to Pelin Koparir, Department of Chemistry, Forensic Medicine Institute, TR-4400, Malatya, Turkey. E-mail: pelin.kutulay@adalet.gov.tr

INTRODUCTION

Phosphinic acids are of growing importance in understanding and modulating biological processes.[1] In recent years, the synthesis of α-substituted phosphoryl derivatives (phosphonic and phosphinic acids) has attracted significant attention due to their biological activities which facilitate their broad application as enzyme inhibitors, antimetabolites, and antibiotics.[2]

Among functionalized phosphinic acids, α-aminoalkylphosphinic derivatives have potential biological activities, such as antibacterial,[2] herbicidal,[3] and fungicidal.[4] 1-aminoalkylphosphinic acids, the phosphinic acid analogues of 1-amino carboxylic acids, are an important class of compounds that exhibit a variety of interesting and useful properties. In addition, the structure of the phosphinic functional group mimics the transition state of peptide bond hydrolysis, and the symmetric nature of the phosphinic acid derivatives is expected to be of benefit in their binding to the homodimer of HIV protease having C_2-axis symmetry.

Proteolytic enzymes, responsible for cleavage of an amide bond in peptide substrates, are involved in a variety of physiological and pathological processes, thus representing a group of the most attractive targets for drug design and development.[5,6] The discovery of highly potent and selective inhibitors of proteases, which are able to discriminate between different members of the same family of proteases, remains a continuous challenge. A phosphinic moiety ($-PO_2^-CH_2-$) is considered to mimic the high-energy tetrahedral transition state of peptide bond hydrolysis, and due to this ability, phospihinate pseudopeptides attract considerable interest, providing a wide range of potent inactivators of proteolitic enzymes, particularly metalloproteases.[7–9]

It is well known that 3-substituted cyclobutane carboxylic acid derivatives exhibit anti-inflamatory and antidepressant activities and liquid crystal properties.[10] Various thiazole derivatives show herbicidal, anti-inflamatory, antimicrobial, or antiparasitic activity.[11] However, the syntheses and physiochemical properties of 1,1,3-trisubstituted cyclobutane, substituted thiazole and its aminophosphinic acid derivatives containing the mesityl, tetralino, or phenyl group have not been reported so far. These compounds, containing cyclobutane, thiazole, and aminophosphinic acid functions in their molecules, seem to be suitable candidates for further chemical modifications and may be pharmacologically active and useful as ligands in coordination chemistry.

In light of the abovementioned observations, we have selected **1a–c** as the starting compounds, which were synthesized according to the literature procedure published previously[12–15] for the synthesis of mainly cyclobutane, thiazole, and aminophosphinic acid derivatives, as shown in Scheme 1.

In light of studies conducted on the synthetic chemistry of phosphinic acids during last 15 years, we have also partly contributed to this progress by developing a new aminophosphinic acid synthesis method. Finally, we have also partly contributed to this progress by obtaining an aminophosphinic acid derivative which involves thiazole and cyclobutane groups.

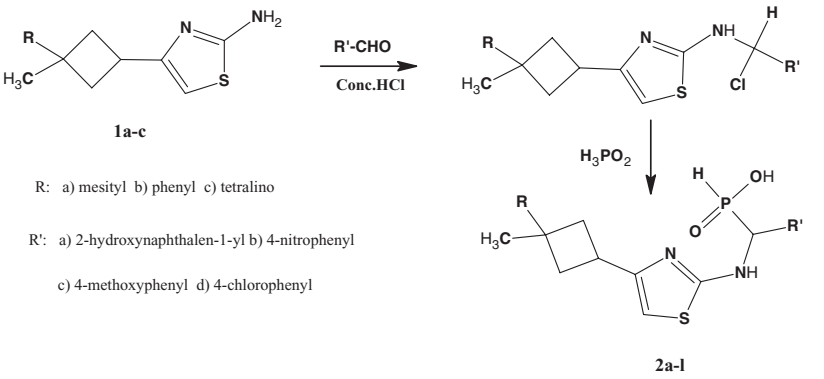
The newly synthesized compounds were evaluated for their in-vitro antimicrobial activities, and the results are presented in Table S1.

RESULTS AND DISCUSSION

Chemistry

The reactions for the synthesis of **2a–l** are shown in Scheme 1. When 2-hydroxy-1-naphthaldehyde, 4-nitrobenzaldehyde, 4-methoxybenzaldehyde, and 4-chlorobenzaldehyde

were added to 2-amino-4-(3-aryl (mesityl-phenyl-tetralino)-3-methylcyclobutyl) thiazoles **1a–c** in the presence of hypophosphorous acid, **2a–l** were obtained.



Compound **2**	R	R'	Compound **2**	R	R'
a	Mesityl	2-hydroxynaphthalen-1-yl	**g**	Phenyl	4-methoxyphenyl
b	Mesityl	4-nitrophenyl	**h**	Phenyl	4-chlorophenyl
c	Mesityl	4-methoxyphenyl	**i**	Tetralino	2-hydroxynaphthalen-1-yl
d	Mesityl	4-chlorophenyl	**j**	Tetralino	4-nitrophenyl
e	Phenyl	2-hydroxynaphthalen-1-yl	**k**	Tetralino	4-methoxyphenyl
f	Phenyl	4-nitrophenyl	**l**	Tetralino	4-chlorophenyl

Scheme 1 Synthesis of the compound (**2a–l**).

The yields of **2b**, **2f**, and **2j** were high. The reason for this could be the lack of conjugation between n-electrons on nitrogen atoms with the aromatic ring in intermediate compounds of **2b**, **2f**, and **2j**. On the other hand, the yields of **2a**, **2c**, **2e**, **2g**, **2i**, and **2k** were very poor because of an effective conjugation they have with the aromatic ring in intermediate compounds of **2a**, **2c**, **2e**, **2g**, **2i**, and **2k**. In addition, lower yields were found in the presence of substituents with higher electron attack power.

In the infrared (IR) spectrum of **2a–l**, the most characteristic absorptions are at 3461–3533 cm^{-1} (OH), 3270–3309 cm^{-1} (NH), 1602–1613 cm^{-1} (C=N), 1249–1258 cm^{-1} (P=O), 980–1099 cm^{-1} (P–O), and 2379–2401 cm^{-1} (P–H). In the ^{1}H NMR spectra, characteristic signals due to the (NH) protons appeared at 5.43–5.49 ppm, signals due to the (PH) protons appeared at 4.99–5.13 ppm, signals due to the (CH–P) protons appeared at 4.76–4.79 ppm, and signals due to the aromatic protons appeared as multiples at 6.73–8.16 ppm. The data for all compounds are given in the Experimental section. Spectra for **2a** (Figures S1–S3) and **2c** (Figures S4–S6) can be found in the Supplemental Materials available online.

Antimicrobial Screening

The synthesized compounds, **2a–l**, were tested for antibacterial, antifungal, and antimycobacterial activities against various strains by the microdilution method.[16–20] For the determination of antibacterial activity, one Gram-positive and two Gram-negative bacterial strains were utilized. Antimycobacterial and antifungal assays of all compounds

were also performed against *Mycobacterium fortuitum* ATCC 6841, a rapidly growing mycobacterium, and the yeast *Candida albicans* ATCC 2091, respectively. The results are summarized in Table S1 (Supplemental Materials online).

EXPERIMENTAL

Melting points were determined on a Thomas Hovver melting point apparatus and uncorrected, but checked by differential scanning calorimeter (DSC). The IR spectra were measured with a Perkin–Emler Spectrum One FTIR spectrophotometer. The ^{1}H, ^{13}C, and ^{31}P spectra were taken on a Bruker AC-300 and a Bruker AC-400 NMR spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 161.9 MHz for ^{31}P NMR. Compounds were dissolved in $CDCl_3$ and DMSO, and chemical shifts were referenced to TMS (^{1}H and ^{13}C NMR) and 85% H_3PO_4 (^{31}P NMR). Elemental analyses were done on a LECO-CHNS-938. Starting chemicals were obtained from Merck or Aldrich.

General Procedure for the Synthesis of 1a–c

The synthesis of **1a–c** [where the aryl group is mesityl **(1a)**, phenyl **(1b)**, or tetralino **(1c)**] was carried out according to the method given in the literature.[12–15]

General Procedure for the Synthesis of 2a–l

In total, 0.05 mol of **1a–c** was dissolved in 0.05 mol of concentrated HCl, and to this solution, 0.05 mol of hypophosporus acid was added. The reaction mixture was put inside a fuming cupboard, and to this, 0.05 mol of aldehyde ($\mathbf{R_1}$) was added.[21–23] The reaction mixture was refluxed for 12 h inside the fuming cupboard. The reaction mixture was evaporated and cooled. Addition of water and methanol to this cooled solution resulted in the formation of a solid product. The solid was filtered, washed thoroughly with water, and recrystallized from the methanol–water mixture.

[(2-Hydroxynaphthalen-1-yl)({4-[3-Methyl-3-(2,4,6-Trimethylphenyl)Cyclobutyl]-1,3-Thiazol-2-yl}Amino)Methyl]Phosphinic Acid (2a)

White solid, yield 49%, m.p. 327–328 °C. IR (KBr, cm^{-1}) υ: 3488 (−OH), 3293 (−NH), 2385 (−P−H), 1609 (−C=N), 1254 (−P=O), 1080 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si, δ, ppm): 13.59 (s, 1H, OH), 8.81 (br, 1H, POH), 7.18–7.65 (m, 6H, Ar−H), 6.73 (s, 2H, aromatics, in mesitylene), 6.01 (s, 1H, =CH−S in thiazole ring), 5.44 (br, 1H, NH), 5.09 (d, 1H, PH), 4.78 (d, 1H, CHP), 3.93 (q, 1H, >CH− in cyclobutane ring), 2.63 (d, 4H, $-CH_2-$ in cyclobutane ring), 2.21 (s, 3H, CH_3), 2.15 (s, 6H, CH_3), 1.54 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 172.0, 167.0, 162.0, 161.4, 159.8, 136.1 131.3, 130.7, 130.2, 130.1, 129.7, 127.4, 127.3, 127.0, 126.9, 126.8, 101.9, 42.3, 40.5, 32.5, 32.2, 31.4, 29.9. ^{31}P NMR (161.9 MHz, $CDCl_3$, δ, ppm): 28.3; Elemental analysis: $C_{28}H_{31}N_2O_3PS$ Calculated: C, 66.38; H, 6.17; N, 5.53. Found: C, 66.40; H, 6.16; N, 5.56.

[({4-[3-Methyl-3-(2,4,6-Trimethylphenyl)Cyclobutyl]-1,3-Thiazol-2-yl}Amino)(4-Nitrophenyl)Methyl]Phosphinic Acid (2b)

Shining white solid, yield 79%, m.p. 357–358 °C. IR (KBr, cm^{-1}) υ: 3479 (−OH), 3299 (−NH), 2389 (−P−H), 1607 (C=N), 1255 (−P=O), 1079 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si, δ, ppm): 8.79 (br, 1H, POH), 7.48–8.16 (m, 4H, Ar−H), 6.73 (s, 2H, aromatics, in mesitylene), 6.00 (s, 1H, =CH−S in thiazole ring), 5.43 (br, 1H, NH), 5.11 (d, 1H, PH), 4.78 (d, 1H, CHP), 3.94 (q, 1H, >CH− in cyclobutane ring), 2.64 (d, 4H, $-CH_2-$ in cyclobutane ring), 2.21 (s, 3H, CH_3), 2.16 (s, 6H, CH_3), 1.55 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 171.9, 166.8, 162.4, 161.2, 157.8, 148.5, 148.0, 139.4, 139.0, 137.6, 133.3, 129.7, 126.9, 124.0, 99.8, 42.2, 31.8, 29.8. ^{31}P NMR (161.9 MHz, $CDCl_3$, δ, ppm): 28.3; Elemental analysis: $C_{24}H_{28}N_3O_4PS$ Calculated: C, 59.37; H, 5.81; N, 8.65. Found: C, 59.47; H, 5.79; N, 8.69.

[(4-Methoxyphenyl)({4-[3-Methyl-3-(2,4,6-Trimethylphenyl) Cyclobutyl]-1,3-Thiazol-2-yl}Amino)Methyl]Phosphinic Acid (2c)

Yellow solid, yield 48%, m.p. 333–334 °C. IR (KBr, cm^{-1}) υ: 3485 (−OH), 3287 (−NH), 2392 (−P−H), 1609 (−C=N), 1254 (−P=O), 1082 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si, δ, ppm): 8.80 (br, 1H, POH), 6.88–7.21 (m, 4H, Ar−H), 6.74 (s, 2H, aromatics, in mesitylene), 5.99 (s, 1H, =CH−S in thiazole ring), 5.45 (br, 1H, NH), 5.10 (d, 1H, PH), 4.76 (d, 1H, CHP), 3.92 (q, 1H, >CH− in cyclobutane ring), 3.79 (s, 3H, OCH_3), 2.63 (d, 4H, $-CH_2-$ in cyclobutane ring), 2.20 (s, 3H, CH_3), 2.15 (s, 6H, CH_3), 1.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 172.0, 166.9, 163.4, 161.2, 157.8, 148.5, 148.0, 139.8, 138.9, 137.6, 133.4, 129.4, 127.1, 127.0, 100.0, 56.0, 42.2, 38.3, 29.1. ^{31}P NMR (161.9 MHz, $CDCl_3$, δ, ppm): 28.3; Elemental analysis: $C_{25}H_{31}N_2O_3PS$ Calculated: C, 63.81; H, 6.64; N, 5.95. Found: C, 63.79; H, 6.63; N, 6.00.

[(4-Chlorophenyl)({4-[3-Methyl-3-(2,4,6-Trimethylphenyl) Cyclobutyl]-1,3-Thiazol-2-yl}Amino)Methyl]Phosphinic Acid (2d)

White solid, yield 60%, m.p. 343–344 °C. IR (KBr, cm^{-1}) υ: 3498 (−OH), 3282 (−NH), 2398 (−P−H), 1611 (−C=N), 1249 (−P=O), 1083 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si, δ, ppm): 8.81 (br, 1H, POH), 7.20–7.31 (m, 4H, Ar−H), 6.73 (s, 2H, aromatics, in mesitylene), 6.03 (s, 1H, =CH−S in thiazole ring), 5.46 (br, 1H, NH), 5.12 (d, 1H, PH), 4.79 (d, 1H, CHP), 3.92 (q, 1H, >CH− in cyclobutane ring), 2.63 (d, 4H, $-CH_2-$ in cyclobutane ring), 2.20 (s, 3H, CH_3), 2.16 (s, 6H, CH_3), 1.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm):171.8, 166.8, 162.4, 161.2, 157.8, 148.5, 148.0, 139.4, 139.1, 133.3, 129.7, 127.1, 126.8, 100.0, 42.2, 31.8, 26.4, 22.4, 29.2. ^{31}P NMR (161.9 MHz, $CDCl_3$, δ, ppm): 28.4; Elemental analysis: $C_{24}H_{28}ClN_2O_2PS$ Calculated: C, 60.69; H, 5.94; N, 5.90. Found: C, 60.71; H, 5.91; N, 5.89.

[(2-Hydroxynaphthalen-1-yl)({[4-(3-Methyl-3-Phenylcyclobutyl)-1,3-Thiazol-2-yl]Amino})Methyl]Phosphinic Acid (2e)

Yellow solid, yield 48%, m.p. 324–225 °C. IR (KBr, cm^{-1}) υ: 3498 (−OH), 3309 (−NH), 2401 (−P−H), 1602 (−C=N), 1258 (−P=O), 980 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si, δ, ppm): 13.64 (s, 1H, OH), 8.61 (br, 1H, POH), 7.16–7.56 (m, 11H,

Ar−H), 6.01 (s, 1H, =CH−S in thiazole ring), 5.49 (br, 1H, NH), 4.99 (d, 1H, PH), 4.77 (d, 1H, CHP), 3.94 (quint, 1H, J = 7 Hz >CH− in cyclobutane ring), 2.61 (d, 4H, J = 9 Hz $-CH_2-$ in cyclobutane ring), 1.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 171.0, 167.0, 161.0, 157.8, 156.9, 148.5, 144.2, 139.2, 133.0, 130.0, 128.7, 127.4, 125.6, 111.3, 100.0, 42.7, 42.4, 36.4, 33.1, 31.1. ^{31}P NMR (161.9 MHz, $CDCl_3$, δ, ppm): 28.6; Elemental analysis: $C_{25}H_{25}N_2O_3PS$ Calculated: C, 64.64; H, 5.42; N, 6.03. Found: C, 64.74; H, 5.41; N, 6.09.

({[4-(3-Methyl-3-Phenylcyclobutyl)-1,3-Thiazol-2-yl]Amino} (4-Nitrophenyl)Methyl]Phosphinic Acid (2f)

Orange solid, yield 84%, m.p. 238–239 °C. IR (KBr, cm^{-1}) υ: 3503 (−OH), 3298 (−NH), 2431 (−P−H), 1612 (−C=N), 1254 (−P=O), 1079 (−P−O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, Me_4Si, δ, ppm): 8.61 (br, 1H, POH), 7.14–8.19 (m, 9H, Ar−H), 5.99 (s, 1H, =CH−S in thiazole ring), 5.51 (br, 1H, NH), 5.01 (d, 1H, PH), 4.78 (d, 1H, CHP), 3.93 (quint, 1H, >CH− in cyclobutane ring), 2.62 (d, 4H, $-CH_2-$ in cyclobutane ring), 1.54 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm):172.0, 167.1, 162.0, 157.8, 148.4, 148.0, 144.2, 139.8, 131.2, 127.8, 125.9, 111.0, 42.4, 36.4, 33.8, 29.9. ^{31}P NMR (161.9 MHz, $CDCl_3$, δ, ppm): 28.6; Elemental analysis: $C_{20}H_{21}N_3O_4PS$ Calculated: C, 55.81; H, 4.92; N, 9.76. Found: C, 55.79; H, 5.00; N, 9.75.

[(4-Methoxyphenyl)({[4-(3-Methyl-3-Phenylcyclobutyl)-1,3-Thiazol-2-yl]Amino})Methyl]Phosphinic Acid (2g)

Light yellow solid, yield 45%, m.p. 271–273 °C. IR (KBr, cm^{-1}) υ: 3461 (−OH), 3281 (−NH), 2379 (−P−H), 1611 (−C=N), 1253 (−P=O), 1082 (−P−O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, Me_4Si, δ, ppm): 8.59 (br, 1H, POH), 7.16–7.39 (m, 9H, Ar−H), 6.04 (s, 1H, =CH−S in thiazole ring), 5.49 (br, 1H, NH), 4.99 (d, 1H, PH), 4.76 (d, 1H, CHP), 3.94 (quint, 1H, >CH− in cyclobutane ring), 3.81 (s, 3H, OCH_3), 2.59 (d, 4H, $-CH_2-$ in cyclobutane ring), 1.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm):172.6, 166.1, 161.8, 157.8, 149.2, 148.4, 144.1, 139.3, 131.2, 127.7, 125.8, 111.4, 100.3, 56.9, 42.4, 36.4, 32.1, 30.0. ^{31}P NMR (161.9 MHz, $CDCl_3$, δ, ppm): 28.4; Elemental analysis: $C_{22}H_{25}N_2O_3PS$ Calculated: C, 61.67; H, 5.88; N, 6.54. Found: C, 61.65; H, 5.90; N, 6.51.

[(4-Chlorophenyl)({[4-(3-Methyl-3-Phenylcyclobutyl)-1,3-Thiazol-2-yl]Amino})Methyl]Phosphinic Acid (2h)

Yellow solid, yield 65%, m.p. 251–252 °C. IR (KBr, cm^{-1}) υ: 3482 (−OH), 3290 (−NH), 2392 (−P−H), 1613 (−C=N), 1254 (−P=O), 1051 (−P−O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, Me_4Si, δ, ppm): 8.58 (br, 1H, POH), 7.14–7.27 (m, 9H, Ar−H), 6.03 (s, 1H, =CH−S in thiazole ring), 5.47 (br, 1H, NH), 5.02 (d, 1H, PH), 4.78 (d, 1H, CHP), 3.93 (quint, 1H, >CH− in cyclobutane ring), 2.62 (d, 4H, $-CH_2-$ in cyclobutane ring), 1.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm):171.9, 167.0, 166.0, 161.1, 157.8, 148.0, 144.1, 139.0, 136.9, 134.0, 132.6, 129.7, 125.9, 110.1, 98.9, 42.4, 36.4, 32.0, 30.0. ^{31}P NMR (161.9 MHz, CDCl3, δ, ppm): 28.5; Elemental analysis: $C_{21}H_{22}ClN_2O_2PS$ Calculated: C, 58.26; H, 5.12; N, 6.47. Found: C, 58.20; H, 5.09; N, 6.48.

[(2-Hydroxynaphthalen-1-yl)({4-[3-Methyl-3-(5,6,7,8-Tetrahydronaphthalen-2-yl)Cyclobutyl]-1,3-Thiazol-2-yl}Amino) Methyl]Phosphinic Acid (2i)

White solid, yield 54%, m.p. 280–281 °C. IR (KBr, cm^{-1}) υ: 3533 (−OH), 3299 (−NH), 2391 (−P−H), 1613 (−C=N), 1255 (−P=O), 1101 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, D_2O + NaOD, δ, ppm): 6.86–7.79 (m, 9H, Ar−H), 5.95 (s, 1H, =CH−S in thiazole ring), 5.13 (d, 1H, PH), 4.79 (d, 1H, CHP), 3.52 (quint, 1H, J = 8.80 Hz >CH− in cyclobutane ring), 2.76–2.81 (m, 4H, the alicyclic protons of tetraline as two broad), 2.34–2.55 (m, 4H, $-CH_2-$ in cyclobutane ring), 1.81–1.84 (m, 4H, the alicyclic protons of tetraline), 1.54 (s, 3H, CH_3). ^{13}C NMR (D_2O + NaOD, δ, ppm): 171.9, 167.0, 161.0, 157.8, 152.0, 138.8, 136.1, 131.0, 130.1, 129.7, 127.5, 127.0, 124.3, 102.2, 42.5, 40.1, 32.6, 31.5, 31.0, 25.3, 25.3, 22.1, ^{31}P NMR (161.9 MHz, D_2O + NaOD, δ, ppm): 28.6; Elemental analysis: $C_{29}H_{31}N_2O_3PS$ Calculated: C, 67.16; H, 6.03; N, 5.40. Found: C, 67.11; H, 5.99; N, 5.39.

[({4-[3-Methyl-3-(5,6,7,8-Tetrahydronaphthalen-2-yl)Cyclobutyl]-1,3-Thiazol-2-yl}Amino)(4-Nitrophenyl)Methyl]Phosphinic Acid (2j)

White solid, yield 70%, m.p. 274–275 °C. IR (KBr, cm^{-1}) υ: 3463 (−OH), 3289 (−NH), 2379 (−P−H), 1605 (−C=N), 1252 (−P=O), 1091 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, D_2O + NaOD, δ, ppm): 6.94–8.13 (m, 7H, Ar−H), 5.98 (s, 1H, =CH−S in thiazole ring), 5.12 (d, 1H, PH), 4.77 (d, 1H, CHP), 3.53 (quint, 1H, J = 8.80 Hz >CH− in cyclobutane ring), 2.78–2.81 (m, 4H, the alicyclic protons of tetraline as two broad), 2.33–2.55 (m, 4H, $-CH_2-$ in cyclobutane ring), 1.82–1.84 (m, 4H, the alicyclic protons of tetraline), 1.53 (s, 3H, CH_3). ^{13}C NMR (D_2O + NaOD, δ, ppm):171.8, 167.0, 157.8, 152.0, 138.8, 136.1, 131.0, 129.7, 128.6, 127.5, 100.0, 40.1, 32.6, 31.5, 31.0, 25.3, 25.2, 22.1. ^{31}P NMR (161.9 MHz, D_2O + NaOD, δ, ppm): 28.3; Elemental analysis: $C_{25}H_{28}N_3O_4PS$ Calculated: C, 60.35; H, 5.67; N, 8.45. Found: C, 60.25; H, 5.47; N, 8.43.

[(4-Methoxyphenyl)({4-[3-Methyl-3-(5,6,7,8-Tetrahydronaphthalen-2-yl)Cyclobutyl]-1,3-Thiazol-2-yl}Amino)Methyl]Phosphinic Acid (2k)

Shining white solid, yield 50%, m.p. 266–267 °C. IR (KBr, cm^{-1}) υ: 3463 (−OH), 3270 (−NH), 2391 (−P−H), 1601 (−C=N), 1250 (−P=O), 1077 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, D_2O + NaOD, δ, ppm): 6.87–7.24 (m, 7H, Ar−H), 5.99 (s, 1H, =CH−S in thiazole ring), 5.13 (d, 1H, PH), 4.78 (d, 1H, CHP), 3.79 (s, 3H, OCH_3), 3.53 (quint, 1H, J = 8.80 Hz >CH− in cyclobutane ring), 2.76–2.80 (m, 4H, the alicyclic protons of tetraline as two broad), 2.34–2.55 (m, 4H, $-CH_2-$ in cyclobutane ring), 1.81–1.84 (m, 4H, the alicyclic protons of tetraline), 1.53 (s, 3H, CH_3). ^{13}C NMR (D_2O + NaOD, δ, ppm):172.5, 166.9, 160.8, 157.8, 157.0, 148.0, 139.3, 138.8, 136.2, 131.4, 130.4, 129.6, 124.5, 99.7, 42.5, 32.6, 31.4, 25.4, 25.1, 22.3. ^{31}P NMR (161.9 MHz, D_2O + NaOD, δ, ppm): 28.3; Elemental analysis: $C_{26}H_{31}N_2O_3PS$ Calculated: C, 64.71; H, 6.47; N, 5.80. Found: C, 64.61; H, 6.37; N, 5.78.

[(4-Chlorophenyl)({4-[3-Methyl-3-(5,6,7,8-Tetrahydronaphthalen-2-yl)Cyclobutyl]-1,3-Thiazol-2-yl}Amino)Methyl]Phosphinic Acid (2l)

White solid, yield 58%, m.p. 249–250 °C. IR (KBr, cm^{-1}) υ: 3465 (−OH), 3278 (−NH), 2399 (−P−H), 1609 (−C=N), 1255 (−P=O), 1099 (−P−O) cm^{-1}. ^{1}H NMR (400 MHz, D_2O + NaOD, δ, ppm): 6.90–7.26 (m, 7H, Ar−H), 6.00 (s, 1H, =CH−S in thiazole ring), 5.12 (d, 1H, PH), 4.76 (d, 1H, CHP), 3.53 (quint, 1H, J = 8.80 Hz >CH− in cyclobutane ring), 2.74–2.81 (m, 4H, the alicyclic protons of tetraline as two broad), 2.33–2.55 (m, 4H, $-CH_2-$ in cyclobutane ring), 1.81–1.85 (m, 4H, the alicyclic protons of tetraline), 1.53 (s, 3H, CH_3). ^{13}C NMR (D_2O + NaOD, δ, ppm):171.0, 165.9, 160.8, 157.8, 157.0, 148.0, 140.2, 139.6, 137.8, 136.2, 131.4, 129.7, 127.0, 103,6 100.1, 42.5, 32.6, 32.4, 31.5, 25.1, 22.2. ^{31}P NMR (161.9 MHz, D_2O + NaOD, δ, ppm): 28.3; Elemental analysis: $C_{25}H_{28}ClN_2O_2PS$ Calculated: C, 61.66; H, 5.80; N, 5.75. Found: C, 61.60; H, 5.79; N, 5.74.

Biological Screening

Compounds **2a–l** were examined for their in-vitro growth inhibitory activity against different bacterial strains (in addition to *M. fortuitum* ATCC 6841, a rapidly growing mycobacterium, and a yeast, *C. albicans* ATCC 2091). The bacterial strains utilized were *Staphylococcus aureus* ATCC 29213 as Gram-positive, and *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 as Gram-negative bacteria. Antibacterial, antifungal, and antimycobacterial assays were all performed by the two-fold serial microdilution technique.[16–20]

Supplementary Data

Figures S1–S6 and Table S1 are available online in Supplemental Materials.

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