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Synthesis and In Vitro Antimicrobial Activity of New α -Aminophosphonates via Tetrazolo [1,5-a] Quinoline Derivatives

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SYNTHESIS AND IN VITRO ANTIMICROBIAL ACTIVITY OF NEW α -AMINOPHOSPHONATES VIA TETRAZOLO [1,5-a] QUINOLINE DERIVATIVES

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A series of diethyl (4-fluorophenylamino) (substituted tetrazolo[1,5-a]quinolin-4-yl)methyl phosphonate derivatives has been synthesized for the first time from tetrazolo [1,5-a] quinoline derivatives. Elemental analysis, IR, ¹H NMR, ¹³C NMR, and mass spectral data elucidated the structures of the all newly synthesized compounds. In vitro antimicrobial activities of synthesized compounds have been investigated against Gram-positive Bacillus subtilis, Gram-negative Escherichia coli, and two fungi Candida albicans and Aspergillus niger in comparison with standard drugs. Significantly, microbiological behavior of these newly synthesized derivatives possesses significant antibacterial and antifungal activity.

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Keywords α -Aminophosphonate; antibacterial; antifungal; tetrazolo [1,5-a] quinoline

INTRODUCTION

The phosphonate (PO_3^{2-}) moiety is a common structural fragment present in a wide range of biologically active compounds. Such versatile biological activities^{1–8} as enzyme inhibitory, antifungal, antioxidants, and herbicidal of α -aminophosphonates have given the α -aminophosphonate moiety the status of a novel pharmacophore in the context of drug design. Despite structural and electronic differences between phosphonate and carboxylic functionalities (in terms of size, shape, acidity, and geometry), the phosphonate functionality is regarded as a bioisostere of the carboxylic acids.^{9,10} Many of them can serve as haptens

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in catalytic enzymes antibody generation and as transition state analogue inhibitors of different proteolytic enzymes that exhibit a wide spectrum of biological properties, including antimicrobial, antitumor, antihypertensive, and antibacterial activities.^{11–16} It is well known that inclusion of fluorine atoms and fluorine-containing substituents into molecules of organic substances results in profound changes of chemical and physicochemical properties, and consequently, the biological activity of these substances. α -Aminophosphonates are chief substrates in the synthesis of phosphonopeptides.¹⁷

Quinolines and their derivatives are important constituents of pharmacologically active synthetic compounds. The quinoline nucleus can also be frequently recognized in the structure of numerous, naturally occurring alkaloids. They have been associated with a broad spectrum of biological activities.^{18, 19} The fusion of quinoline to the tetrazole ring is known to increase the biological activity. The tetrazole group, which is considered to be analogous to the carboxylic group as a pharmacore, possesses a wide range of biological activities. Several substituted tetrazoles have been shown to possess anticonvulsant,²⁰ anti-inflammatory,²¹ CNS dispersant,²² antimicrobial,²³ anti-AIDS,²⁴ and antifertility agents.^{25, 26}

By considering all the above aspects, for the first time we have synthesized the title compounds to develop our ongoing research work.^{27–30}

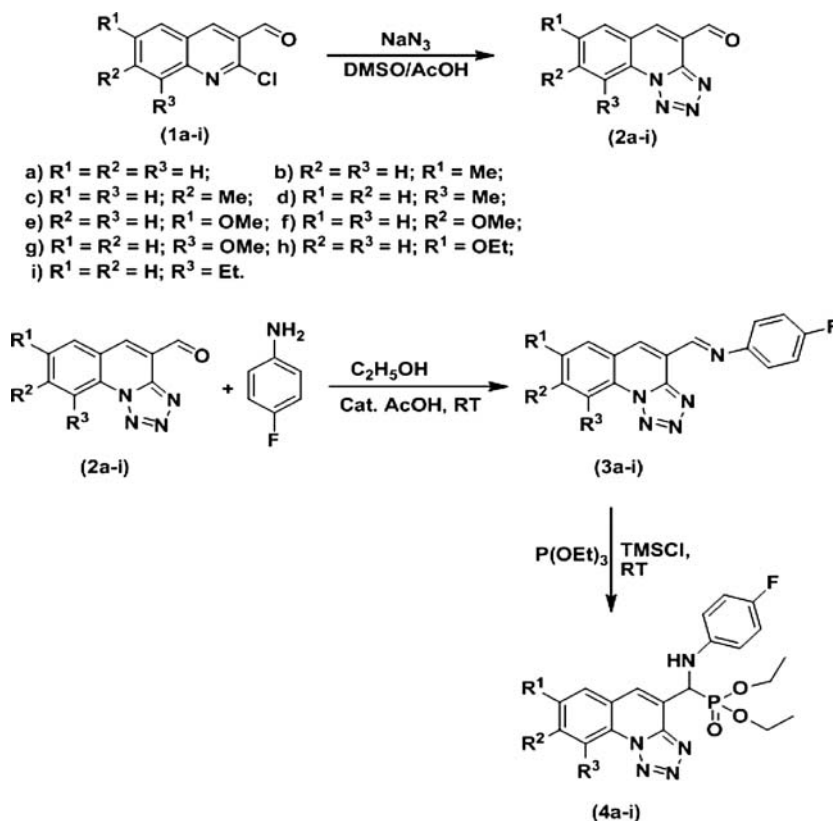
RESULTS AND DISCUSSION

Chemistry

The key intermediate tetrazolo [1,5-a] quinoline-4 carbaldehyde derivatives (**2a–i**) were prepared by the reaction of 2-chloroquinoline-3-carbaldehyde derivatives (**1a–i**) with sodium azide in a DMSO/AcOH mixture.^{31, 32} Furthermore, we have synthesized imines (**3a–i**) by the reaction of tetrazolo [1,5-a] quinoline derivatives (**2a–i**) and 4-fluoroaniline in ethanol at room temperature using a catalytic amount of acetic acid in excellent yields (68–94%). The synthesized imines (**3a–i**), which were further treated with triethyl phosphite in the presence of TMSCl at room temperature, afforded the compounds (**4a–i**), which are outlined in Scheme 1. The time period required for this protocol is less than the previously reported methods on tetrazolo [1,5-a] quinoline moiety.²⁸

Structural Determination

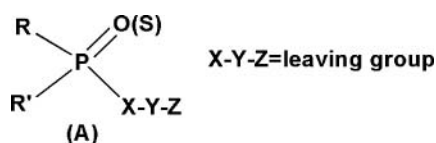
Structures of the compounds (**3a–i**) and (**4a–i**) were elucidated on the basis of the FT-IR, ¹H NMR, ¹³C NMR, and mass spectroscopic analysis. Assignment of selected characteristic IR band positions provide significant indication for the formation of diethyl (4-fluorophenylamino) (substituted tetrazolo[1,5-a]quinolin-4-yl)methylphosphonate derivatives. All the compounds (**4a–i**) showed intense bands in the region of 1607–1670 cm^{–1} corresponding to ν (C=N) stretching, 1221–1251 cm^{–1} of the ν (P=O) stretching and 1021–1067 cm^{–1} of ν (P–O–C) stretching, which confirms the formation of desired compounds (**4a–i**). All the compounds showed an additional sharp band in the region of 3251–3334 cm^{–1} assigned ν (NH) stretch. Further evidence for the formation of desired compounds was confirmed from ¹H NMR and ¹³C NMR spectra, which proved to be a diagnostic tool for the positional elucidation of the proton and carbon, respectively. Assignments of the signals are based on the chemical shift and intensity pattern. The proton at (CH=N) position of compounds (**3a–i**) was observed in the region of 9.12–9.27 ppm. The



Scheme 1 Synthesis of the compounds (4a-i).

aromatic protons of compounds (4a-i) are in the region of 6.57–8.71 ppm. A doublet due to (CH-P) proton in all final compounds was observed in the range of 5.35–5.62 ppm. The aromatic carbons of compounds (4a-i) are in the region of 114.5–159.0 ppm. The carbon (CH-P) position showed a peak around the 52.0–53.0 ppm region. The mass spectrum of compound 4a showed a molecular ion peak ($m+1$) at 430.3, compound 4b at 444.3 ($m+1$), compound 4e at 460.3 ($m+1$), 4h at 474.3 ($m+1$), and compound 4i at 458.3 ($m+1$).

Antimicrobial Screening



Schrader³³ proposed that organophosphorus compounds containing the general structure (A) may have significant biological activity. All organophosphorus compounds are inherently good phosphorylating agents of enzymes by virtue of the group P-XYZ in the general structure (A). Slight variation in structure can have very dramatic effects

on the efficiency of organophosphorus compounds in bi-activity. These chemically and biologically variable parameters, which are hard to estimate, are involved in deciding the structure–activity relationships of these compounds. (See the Supplemental Materials, available online, for complete details.)

In conclusion, a series of new α -aminophosphonate derivatives was synthesized and evaluated for antimicrobial activity. All the synthesized compounds showed good to moderate antibacterial and antifungal activity. The importance of such work lies in the possibility that the new compounds might be more efficacious drugs against bacteria and fungi, which could be helpful in designing more potent antibacterial and antifungal agents for therapeutic use.

EXPERIMENTAL

All chemicals and solvents were purchased from Merck, Spectrochem, and S. D. Fine-chem (India). Melting points were determined in open capillaries on Kumar's melting point apparatus (India) and are uncorrected. IR spectra were recorded on a Jasco FT-IR 4100 (Japan) using KBr discs. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRK-300 and NMR Spectrometer AC200. Mass spectra were recorded on Single-Quadrupole Mass Detector 3100 (Waters). Elemental analyses were performed on a CHNS analyzer Flash 1112 (Thermo Finnigan). The progress of the reactions was monitored by TLC on Merck silica plates. Results are presented as chemical shift δ in ppm, multiplicity, J values in Hertz (Hz), number of protons, and the proton's position. Multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), and m (multiplet). Solvents were commercially available materials of reagent grade.

4-Fluoro-N-((tetrazolo[1,5-a]quinolin-4-yl)methylene)benzenamine (3a)

To a stirred solution of tetrazolo [1, 5-a] quinoline-4 carbaldehyde (5 mmol) in absolute ethanol (10 mL), 4-fluoroaniline (6 mmol) was added with 4 to 5 drops of acetic acid. The progress of the reaction was monitored by TLC (hexane:ethyl acetate solvent system). After the completion of the reaction (15 min), 20 mL of water was added, and the solid obtained was filtered, washed with water, and dried in an oven at 50°C for 5 h. Yield 94%, mp $180\text{--}182^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3 , Me_4Si , δ ppm): 7.16 (t, 2H, $J = 8$ Hz, Ar–H), 7.40 (t, 2H, $J = 7.6$ Hz, Ar–H), 7.79 (t, 1H, $J = 8$ Hz, Ar–H), 7.97 (t, 1H, $J = 8$ Hz, Ar–H), 8.18 (d, 1H, $J = 7.6$ Hz, Ar–H), 8.73 (d, 1H, $J = 8$ Hz, Ar–H), 8.80 (s, 1H, Ar–H), 9.25 (s, 1H, $\text{CH}=\text{N}$). ^{13}C NMR (75 MHz, CDCl_3 , δ ppm): 116.0, 116.3, 116.9, 121.34, 122.9, 123.0, 123.7, 128.4, 130.3, 130.6, 131.1, 132.3, 146.6, 146.9, 151.8 (Ar–C), 160.4 ($\text{C}=\text{N}$). MS: m/z 292 ($m+1$). Elemental analysis: $\text{C}_{16}\text{H}_{10}\text{FN}_5$ Calcd.: C: 65.97%; H: 3.46%; N: 24.04%. Found: C: 65.80%, H: 3.54%, N: 24.17%.

4-Fluoro-N-((7-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)benzenamine (3b)

Yield 85%, mp $234\text{--}236^\circ\text{C}$. ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 2.56 (s, 3H, Ar– CH_3), 7.06 (d, 2H, $J = 8$ Hz, Ar–H), 7.19 (d, 2H, $J = 8$ Hz, Ar–H), 7.70 (d, 1H, $J = 8$ Hz, Ar–H), 7.82 (s, 1H, Ar–H), 8.55 (d, 1H, $J = 10$ Hz, Ar–H), 8.65 (s, 1H, Ar–H), 9.18 (s, 1H, $\text{CH}=\text{N}$). MS: m/z 306.1 ($m+1$). Elemental analysis: $\text{C}_{17}\text{H}_{12}\text{FN}_5$ Calcd.: C: 66.88%; H: 3.96%; N: 22.94%. Found: C: 66.72%, H: 3.78%, N: 22.76%.

4-Fluoro-N-((8-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)benzenamine (3c)

Yield 92%, mp 230–232°C. ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 2.47 (s, 3H, Ar-CH₃), 7.15 (d, 2H, J = 8 Hz, Ar-H), 7.24 (d, 2H, J = 8 Hz, Ar-H), 7.81 (d, 1H, J = 8 Hz, Ar-H), 7.90 (s, 1H, Ar-H), 8.57 (d, 1H, J = 10 Hz, Ar-H), 8.65 (s, 1H, Ar-H), 9.12 (s, 1H, CH=N). MS: m/z 306.1 ($m+1$). Elemental analysis: $\text{C}_{17}\text{H}_{12}\text{FN}_5$ Calcd.: C: 66.88%; H: 3.96%; N: 22.94%. Found: C: 66.81%, H: 3.73%, N: 22.67%.

4-Fluoro-N-((9-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)benzenamine (3d)

Yield 76%, mp 186–188°C. ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 2.38 (s, 3H, Ar-CH₃), 7.03 (d, 2H, J = 8 Hz, Ar-H), 7.21 (d, 2H, J = 8 Hz, Ar-H), 7.84 (d, 1H, J = 8 Hz, Ar-H), 7.93 (s, 1H, Ar-H), 8.63 (d, 1H, J = 10 Hz, Ar-H), 8.79 (s, 1H, Ar-H), 9.23 (s, 1H, CH=N). MS: m/z 306.1 ($m+1$). Elemental analysis: $\text{C}_{17}\text{H}_{12}\text{FN}_5$ Calcd.: C: 66.88%; H: 3.96%; N: 22.94%. Found: C: 66.93%, H: 3.81%, N: 22.69%.

4-Fluoro-N-((7-methoxytetrazolo[1,5-a]quinolin-4-yl)methylene)benzenamine (3e)

Yield 82%, mp 240–242°C. ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 4.01 (s, 3H, Ar-CH₃), 7.16 (d, 2H, J = 8 Hz, Ar-H), 7.49 (d, 2H, J = 8 Hz, Ar-H), 8.56–8.76 (m, 4H, Ar-H), 9.27 (s, 1H, CH=N). MS: m/z 322.1 ($m+1$). Elemental analysis: $\text{C}_{17}\text{H}_{12}\text{FN}_5\text{O}$ Calcd.: C: 63.55%; H: 3.76%; N: 21.80%. Found: C: 63.71%, H: 3.83%, N: 21.61%.

4-Fluoro-N-((8-methoxytetrazolo[1,5-a]quinolin-4-yl)methylene)benzenamine (3f)

Yield 68%, mp 218–220°C. ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 4.12 (s, 3H, Ar-CH₃), 7.05 (d, 2H, J = 8 Hz, Ar-H), 7.97 (d, 2H, J = 8 Hz, Ar-H), 8.78–8.97 (m, 4H, Ar-H), 9.26 (s, 1H, CH=N). MS: m/z 322.1 ($m+1$). Elemental analysis: $\text{C}_{17}\text{H}_{12}\text{FN}_5\text{O}$ Calcd.: C: 63.55%; H: 3.76%; N: 21.80%. Found: C: 63.67%, H: 3.64%, N: 21.73%.

4-Fluoro-N-((9-methoxytetrazolo[1,5-a]quinolin-4-yl)methylene)benzenamine (3g)

Yield 82%, mp 238–240°C. ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 4.04 (s, 3H, Ar-CH₃), 7.13 (d, 2H, J = 8 Hz, Ar-H), 7.76 (d, 2H, J = 8 Hz, Ar-H), 8.68–8.77 (m, 4H, Ar-H), 9.27 (s, 1H, CH=N). MS: m/z 322.1 ($m+1$). Elemental analysis: $\text{C}_{17}\text{H}_{12}\text{FN}_5\text{O}$ Calcd.: C: 63.55%; H: 3.76%; N: 21.80%. Found: C: 63.64%, H: 3.59%, N: 21.81%.

N-((7-Ethoxytetrazolo[1,5-a]quinolin-4-yl)methylene)-4-fluorobenzenamine (3h)

Yield 94%, mp 176–178°C. ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 1.51 (t, 3H, J = 6 Hz, CH₂-CH₃), 4.17 (q, 2H, J = 6 Hz, CH₂-CH₃), 7.17 (d, 2H, J = 8 Hz, Ar-H), 7.48 (d, 2H, J = 8 Hz, Ar-H), 7.94 (d, 2H, J = 6 Hz, Ar-H), 8.64 (s, 1H, Ar-H), 8.92 (s, 1H,

Ar-H), 9.20 (s, 1H, CH = N). MS: m/z 336.1 ($m+1$). Elemental analysis: $C_{18}H_{14}FN_5O$ Calcd.: C: 64.47%; H: 4.21%; N: 20.88%. Found: C: 64.53%, H: 4.06%, N: 20.93%.

4-Fluoro-N-((9-methyltetrazolo[1,5-a]quinolin-4-yl)methylene)benzenamine (3i)

Yield 89%, mp 102–104°C. 1H NMR (200 MHz, $CDCl_3$, Me_4Si , δ ppm): 1.36 (t, 3H, $J = 8$ Hz, CH_2-CH_3), 2.89 (q, 2H, $J = 8$ Hz, CH_2-CH_3), 7.14 (d, 2H, $J = 8$ Hz, Ar-H), 7.21 (d, 2H, $J = 8$ Hz, Ar-H), 7.72 (d, 1H, $J = 8$ Hz, Ar-H), 7.81 (s, 1H, Ar-H), 8.58 (d, 1H, $J = 10$ Hz, Ar-H), 8.67 (s, 1H, Ar-H), 9.24 (s, 1H, CH=N). MS: m/z 320.1 ($m+1$). Elemental analysis: $C_{18}H_{14}FN_5$ Calcd.: C: 67.70%; H: 4.42%; N: 21.93%. Found: C: 67.64%, H: 4.54%, N: 21.78%.

Diethyl(4-fluorophenylamino)(tetrazolo[1,5-a]quinolin-4-yl)methylphosphonate (4a)

A mixture of 4-fluoro-N-((tetrazolo[1,5-a]quinolin-4-yl)methylene)benzenamine (**3a**, 4 mmol), triethylphosphite (10 mmol), and $TMSCl$ (10 mmol) was stirred magnetically at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (5 min), the reaction mixture was poured onto crushed ice. The solid obtained was extracted with chloroform (2×50 mL), washed with water (2×10 mL) and brine (2×20 mL), and the separated organic layer was dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure. The obtained crude product was purified by column chromatography on silica gel by hexane:ethyl acetate (8:2) as an eluent. Yield 95%, mp 162–164°C. IR (KBr, ν_{max}/cm^{-1}): 3286 (N-H), 1612 (C=N), 1230 (P=O), 1051 (P-O-C). 1H NMR (200 MHz, $CDCl_3$, Me_4Si , δ ppm): 1.06 (t, 3H, $J = 6$ and 8 Hz, CH_3), 1.38 (t, 3H, $J = 6$ and 8 Hz, CH_3), 2.79 (brs, 1H, NH), 4.01 (m, 2H, OCH_2), 4.32 (m, 2H, OCH_2), 5.62 (d, 1H, $J = 26$ Hz, CHP), 6.66 (d, 2H, $J = 6$ Hz, Ar-H), 6.80 (t, 2H, $J = 8$ Hz, Ar-H), 7.69 (d, 1H, $J = 8$ Hz, Ar-H), 7.87 (m, 2H, Ar-H), 8.09 (s, 1H, Ar-H), 8.71 (d, 1H, $J = 8$ Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 16.0 (CH_3), 16.4 (CH_3), 52.7 (CH-P), 63.5 (OCH_2), 64.2 (OCH_2), 114.9, 115.7, 116.0, 116.7, 122.8, 123.9, 128.0, 129.0, 130.1, 131.1, 141.5, 141.7, 147.1, 155.0, 158.1 (Ar-C). MS: m/z 430.3 ($m+1$). Elemental analysis: $C_{20}H_{21}FN_5O_3P$ Calcd.: C: 55.94%; H: 4.93%; N: 16.31%. Found: C: 56.20%, H: 5.12%, N: 16.24%.

Diethyl(4-fluorophenylamino)(7-methyltetrazolo[1,5-a]quinolin-4-yl)methylphosphonate (4b)

Yield 86%, mp 158–160°C. IR (KBr, ν_{max}/cm^{-1}): 3316 (N-H), 1623 (C=N), 1221 (P=O), 1025 (P-O-C). 1H NMR (200 MHz, $CDCl_3$, Me_4Si , δ ppm): 1.04 (t, 3H, $J = 6$ and 8 Hz, CH_3), 1.37 (t, 3H, $J = 6$ and 8 Hz, CH_3), 2.54 (s, 3H, Ar- CH_3), 3.73 (brs, 1H, NH), 3.85–4.0 (m, 2H, OCH_2), 4.04–4.35 (m, 2H, OCH_2), 5.60 (d, 1H, $J = 26$ Hz, CHP), 6.65 (d, 2H, $J = 4$ Hz, Ar-H), 6.77 (t, 2H, $J = 8$ Hz, Ar-H), 7.65 (d, 2H, $J = 8$ Hz, Ar-H), 8.03 (s, 1H, Ar-H), 8.54 (d, 1H, $J = 8$ Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 16.1 (CH_3), 16.4 (CH_3), 21.3 (CH_3), 52.7 (CH-P), 63.5 (OCH_2), 64.3 (OCH_2), 115.0, 115.7, 116.0, 116.5, 122.6, 124.0, 128.3, 128.6, 131.0, 132.5, 138.4, 141.7, 147.0,

155.0, 158.2 (Ar-C). MS: m/z 444.3 ($m+1$). Elemental analysis: $C_{21}H_{23}FN_5O_3P$ Calcd.: C: 56.88%; H: 5.23%; N: 15.79%. Found: C: 56.96%, H: 5.32%, N: 15.90%.

Diethyl(4-fluorophenylamino)(8-methyltetrazolo[1,5-a]quinolin-4-yl)methylphosphonate (4c)

Yield 87%, mp 152–154°C. IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3327 (N-H), 1612 (C=N), 1228 (P=O), 1043 (P-O-C). ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 1.21 (t, 3H, J = 6 and 8 Hz, CH_3), 1.45 (t, 3H, J = 6 and 8 Hz, CH_3), 2.38 (s, 3H, Ar- CH_3), 3.62 (brs, 1H, NH), 3.88–4.11 (m, 2H, OCH_2), 4.27–4.43 (m, 2H, OCH_2), 5.48 (d, 1H, J = 26 Hz, CHP), 6.74 (d, 2H, J = 4 Hz, Ar-H), 6.86 (t, 2H, J = 8 Hz, Ar-H), 7.68 (d, 2H, J = 8 Hz, Ar-H), 8.21 (s, 1H, Ar-H), 8.47 (d, 1H, J = 8 Hz, Ar-H). MS: m/z 444.3 ($m+1$). Elemental analysis: $C_{21}H_{23}FN_5O_3P$ Calcd.: C: 56.88%; H: 5.23%; N: 15.79%. Found: C: 56.74%, H: 5.34%, N: 15.86%.

Diethyl(4-fluorophenylamino)(9-methyltetrazolo[1,5-a]quinolin-4-yl)methylphosphonate (4d)

Yield 78%, mp 208–210°C. IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3334 (N-H), 1626 (C=N), 1225 (P=O), 1036 (P-O-C). ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 1.13 (t, 3H, J = 6 and 8 Hz, CH_3), 1.38 (t, 3H, J = 6 and 8 Hz, CH_3), 2.47 (s, 3H, Ar- CH_3), 3.74 (brs, 1H, NH), 3.87–4.10 (m, 2H, OCH_2), 4.34–4.47 (m, 2H, OCH_2), 5.54 (d, 1H, J = 26 Hz, CHP), 6.78 (d, 2H, J = 4 Hz, Ar-H), 6.89 (t, 2H, J = 8 Hz, Ar-H), 7.71 (d, 2H, J = 8 Hz, Ar-H), 8.20 (s, 1H, Ar-H), 8.46 (d, 1H, J = 8 Hz, Ar-H). MS: m/z 444.3 ($m+1$). Elemental analysis: $C_{21}H_{23}FN_5O_3P$ Calcd.: C: 56.88%; H: 5.23%; N: 15.79%. Found: C: 56.73%, H: 5.31%, N: 15.90%.

Diethyl(4-fluorophenylamino)(7-methoxytetrazolo[1,5-a]quinolin-4-yl)methylphosphonate (4e)

Yield 91%, mp 172–174°C. IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3288 (N-H), 1650 (C=N), 1251 (P=O), 1021 (P-O-C). ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 1.04 (t, 3H, J = 6 and 8 Hz, CH_3), 1.37 (t, 3H, J = 6 and 8 Hz, CH_3), 3.91 (s, 3H, OCH_3), 3.93–4.07 (m, 3H, OCH_2 and NH), 4.28–4.35 (m, 2H, OCH_2), 5.60 (d, 1H, J = 26 Hz, CHP), 6.63 (dd, 2H, J = 4, 6 Hz, Ar-H), 6.77 (t, 2H, J = 8 Hz, Ar-H), 7.25 (d, 1H, J = 8 Hz, Ar-H), 7.40 (dd, 1H, J = 2, 6 Hz, Ar-H), 8.02 (d, 1H, J = 0.4 Hz, Ar-H), 8.56 (d, 1H, J = 10 Hz, Ar-H). ^{13}C NMR (75 MHz, CDCl_3 , δ ppm): 16.0 (CH_3), 16.4 (CH_3), 52.7 (CH-P), 55.8 (OCH_3), 63.6 (OCH_2), 64.2 (OCH_2), 109.5, 114.8, 115.7, 116.0, 118.1, 120.7, 123.1, 124.7, 125.3, 130.7, 141.6, 146.5, 155.0, 158.2, 159.0 (Ar-C). MS: m/z 460.3 ($m+1$). Elemental analysis: $C_{21}H_{23}FN_5O_4P$ Calcd.: C: 54.90%; H: 5.05%; N: 15.24%. Found: C: 54.96%, H: 5.20%, N: 15.30%.

Diethyl(4-fluorophenylamino)(8-methoxytetrazolo[1,5-a]quinolin-4-yl)methylphosphonate (4f)

Yield 84%, mp 160–162°C. IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3267 (N-H), 1670 (C=N), 1243 (P=O), 1067 (P-O-C). ^1H NMR (200 MHz, CDCl_3 , Me_4Si , δ ppm): 1.04 (t, 3H, J = 6 and 8 Hz, CH_3), 1.41 (t, 3H, J = 6 and 8 Hz, CH_3), 3.86 (s, 3H, OCH_3), 3.91–4.11 (m, 3H,

OCH₂ and NH), 4.21–4.38 (m, 2H, OCH₂), 5.58 (d, 1H, *J* = 26 Hz, CHP), 6.65 (dd, 2H, *J* = 4, 6 Hz, Ar–H), 6.84 (t, 2H, *J* = 8 Hz, Ar–H), 7.23 (d, 1H, *J* = 8 Hz, Ar–H), 7.38 (dd, 1H, *J* = 2, 6 Hz, Ar–H), 8.14 (d, 1H, *J* = 0.4 Hz, Ar–H), 8.61 (d, 1H, *J* = 10 Hz, Ar–H). MS: *m/z* 460.3 (*m*+1). Elemental analysis: C₂₁H₂₃FN₅O₄P Calcd.: C: 54.90%; H: 5.05%; N: 15.24%. Found: C: 54.78%, H: 5.16%, N: 15.10%.

Diethyl(4-fluorophenylamino)(9-methoxytetrazolo[1,5-a]quinolin-4-yl)methylphosphonate (4g)

Yield 78%, mp 176–178°C. IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3251 (N–H), 1668 (C=N), 1241 (P=O), 1060 (P–O–C). ¹H NMR (200 MHz, CDCl₃, Me₄Si, δ ppm): 1.07 (t, 3H, *J* = 6 and 8 Hz, CH₃), 1.37 (t, 3H, *J* = 6 and 8 Hz, CH₃), 3.78 (s, 3H, OCH₃), 3.86–4.10 (m, 3H, OCH₂ and NH), 4.22–4.37 (m, 2H, OCH₂), 5.62 (d, 1H, *J* = 26 Hz, CHP), 6.58 (dd, 2H, *J* = 4, 6 Hz, Ar–H), 6.81 (t, 2H, *J* = 8 Hz, Ar–H), 7.16 (d, 1H, *J* = 8 Hz, Ar–H), 7.35 (dd, 1H, *J* = 2, 6 Hz, Ar–H), 8.17 (d, 1H, *J* = 0.4 Hz, Ar–H), 8.68 (d, 1H, *J* = 10 Hz, Ar–H). MS: *m/z* 460.3 (*m*+1). Elemental analysis: C₂₁H₂₃FN₅O₄P Calcd.: C: 54.90%; H: 5.05%; N: 15.24%. Found: C: 54.81%, H: 5.18%, N: 15.34%.

Diethyl(7-ethoxytetrazolo[1,5-a]quinolin-4-yl)(4-fluorophenylamino)methylphosphonate (4h)

Yield 84%, mp 134–136°C. IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3301 (N–H), 1628 (C=N), 1233 (P=O), 1043 (P–O–C). ¹H NMR (200 MHz, CDCl₃, Me₄Si, δ ppm): 1.08 (t, 3H, *J* = 6 and 8 Hz, CH₃), 1.36–1.50 (m, 6H, 2 × CH₃), 3.61–4.04 (m, 4H, 2 × OCH₂), 4.25–4.32 (m, 2H, OCH₂), 4.73 (brs, 1H, NH), 5.35 (d, 1H, *J* = 26 Hz, CHP), 6.57 (dd, 2H, *J* = 6 and 8 Hz, Ar–H), 6.82 (d, 2H, *J* = 8 Hz, Ar–H), 6.95 (s, 1H, Ar–H), 7.30 (d, 1H, *J* = 8 Hz, Ar–H), 7.94 (d, 1H, *J* = 10 Hz, Ar–H), 8.30 (s, 1H, Ar–H). ¹³C NMR (75 MHz, CDCl₃, δ ppm): 14.5 (CH₃), 16.0 (CH₃), 16.4 (CH₃), 51.3 (CH–P), 53.3 (OCH₂), 63.6 (OCH₂), 64.0 (OCH₂), 105.6, 114.6, 115.6, 115.9, 123.9, 128.3, 128.7, 129.4, 136.3, 141.7, 143.0, 147.3, 154.8, 157.5, 157.9 (Ar–C). MS: *m/z* 474.3 (*m*+1). Elemental analysis: C₂₂H₂₅FN₅O₄P Calcd.: C: 55.81%; H: 5.32%; N: 14.79%. Found: C: 55.95%, H: 5.45%, N: 14.85%.

Diethyl(9-ethyltetrazolo[1,5-a]quinolin-4-yl)(4-fluorophenylamino)methylphosphonate (4i)

Yield 88%, mp 124–126°C. IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 3306 (N–H), 1607 (C=N), 1225 (P=O), 1052 (P–O–C). ¹H NMR (200 MHz, CDCl₃, Me₄Si, δ ppm): 1.05 (t, 3H, *J* = 6 and 8 Hz, CH₃), 1.34–1.45 (m, 6H, 2 × CH₃), 3.26 (q, 2H, *J* = 8 Hz, Ar–CH₂), 3.68–4.19 (m, 3H, OCH₂ and NH), 4.24–4.31 (m, 2H, OCH₂), 5.39 (d, 1H, *J* = 24 Hz, CHP), 6.61 (dd, 2H, *J* = 4, 8 Hz, Ar–H), 6.82 (t, 2H, *J* = 8 Hz, Ar–H), 7.46 (d, 1H, *J* = 8 Hz, Ar–H), 7.51–7.75 (m, 2H, Ar–H), 8.33 (d, 1H, *J* = 4 Hz, Ar–H). ¹³C NMR (75 MHz, CDCl₃, δ ppm): 14.7 (CH₃), 16.0 (CH₃), 16.4 (CH₃), 24.1 (Ar–CH₂), 51.3 (CH–P), 63.5 (OCH₂), 64.2 (OCH₂), 114.5, 114.9, 115.8, 125.6, 127.3, 128.2, 129.0, 132.6, 137.8, 141.8, 142.2, 145.7, 149.0, 149.1, 154.8 (Ar–C). MS: *m/z* 458.3 (*m*+1). Elemental analysis: C₂₂H₂₅FN₅O₃P Calcd.: C: 57.76%; H: 5.51%; N: 15.31%. Found: C: 57.95%, H: 5.45%, N: 15.60%.

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