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SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL SCREENING OF SOME NOVEL THIAZOLIDIN-4-ONE AND α-AMINOPHOSPHONATE DERIVATIVES

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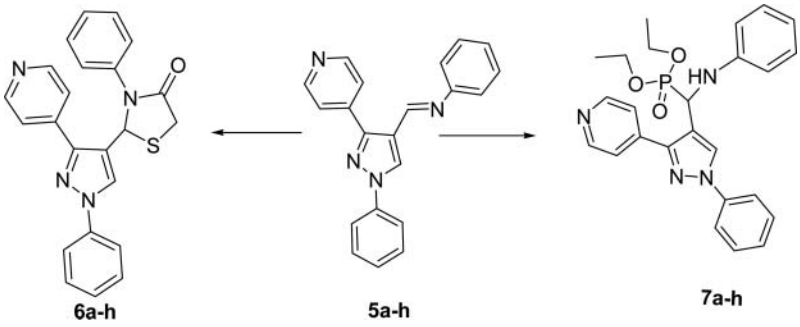
GRAPHICAL ABSTRACT



Abstract *Synthesis of some new functionalized thiazolidin-4-ones and α-amino phosphonate derivatives has been reported. The imines were synthesized from the reaction of various substituted anilines with 1-phenyl-3-(pyridine-4-yl)-1H-pyrazole-4-carbaldehyde in ethanol at reflux condition. The corresponding thiazolidin-4-ones and α-aminophosphonates were prepared by reaction of imines with mercaptoacetic acid and triethyl phosphite, respectively. The structures of the newly synthesized compounds were confirmed by IR, ^1H NMR, and mass spectral data and were evaluated for their antimicrobial activities.*

Keywords 1-Phenyl-3-(pyridine-4-yl)-1*H*-pyrazole-4-carbaldehyde; imines; thiazolidin-4-ones; α-aminophosphonates

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INTRODUCTION

Thiazolidin-4-one scaffold has been gaining prominence due to the fact that its derivatives have been known to possess a wide spectrum of properties such as antibacterial,[1,2] antifungal,[3,4] anticonvulsant,[5,6] cox-1 inhibitor,[7] antituberculosis,[8–10] antihistamic,[11] anticancer,[12] and anti-HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI)[13–15] activities. α-aminophosphonates have been the focus of attention in recent years because of their structural analogy to the corresponding α-amino acids as well as heterocyclic phosphonates[16] and ω-aminophosphonates.[17] They act as peptide mimics,[18] antibiotics, herbicides,[19] pharmacological agents,[20] and enzyme inhibitors.[21] In addition, α-aminophosphonates have broad application due to their antifungal[22] and antibacterial activities.[23]

In our continuous program in the search of new potent and biologically active heterocycles, we planned to synthesize some new series of various substituted thiazolidin-4-ones and α-aminophosphonates and evaluated their antibacterial activity against the standard drug Streptomycin.

RESULTS AND DISCUSSION

1-(Pyridine-4-yl) ethanone **1** reacted with phenyl hydrazine in ethanol to produce (*E*)-2-phenyl-1-(1-(pyridine-4-yl)ethylidene)hydrazine[24] **2**. Vilsmeier–Hack reaction on compound **2** gives 1-phenyl-3-(pyridine-4-yl)-1*H*-pyrazole-4-carbaldehyde **3**. Compound **3** on reaction with the different substituted anilines in ethanol in the presence of catalytic amount of acetic acid afforded corresponding imine derivatives **5a–h**. The structures were assigned for 5a–h based on elemental and spectral analyses. For example, the IR spectrum of the isolated product **5a** showed absorption at 1630 cm^{-1} (C═N) and 1525 cm^{-1} (C═N pyridine). The ^{1}H NMR spectrum of **5a** reveled a singlet at δ 2.56 and δ 9.13 attributed to methyl protons and −CH═N proton, respectively. A multiplet in the region δ 7.68 corresponds to aromatic protons and pyrazole proton. Elemental analysis and mass spectral data agree with the proposed structures for **5a–h**. The imine derivatives **5a–h** were allowed to condense with mercapto acetic acid in dry dioxane and triethyl phosphite in ethanol under acidic catalyst, thiazolidin-4-ones **6a–h**, and α-aminophosphonates **7a–h** were obtained in good yield. Mechanistically, a role of HCl for the formation of α-aminophosphonates has been proposed to protonate the imines that ultimately enhances the electrophilicity of imines carbon. Then, subsequently, the lone pair of phosphorus of triethyl phosphite as a phosphorus nucleophile attacks imines carbon to give phosphonium intermediate; finally, the hydrolysis of phosphonium intermediate yields α-aminophosphonates and EtOH.[25,26]

The IR spectrum of **6a** showed bands at 1700 and 1628 cm^{-1} due to N−C═O and C═N groups, respectively. The ^{1}H NMR spectrum of **6a** showed a singlet at δ 3.92 and δ 6.37 due to $-CH_2$ and −CH protons of thiazolidin-4-one ring. The IR spectrum of **7a** showed absorption bands at 1230 and 1045 cm^{-1} due to P═O and P−O−C_2H_5 groups, respectively. The ^{1}HNMR spectrum of **7a** revealed a doublet of doublet at δ 4.79 and multiplet at δ 3.33 that were attributed to −CH-P═O and CH_2 proton of α-aminophosphonates. Elemental analysis and mass spectral data agree with the proposed structures **6a–h** and **7a–h**.

All the newly synthesized thiazolidin-4-ones and α-aminophosphonates were screened for their antibacterial activities against Gram-positive *Bacillus subtilis* (ATCC No. 6633), *Staphylococcus aureus* (ATCC No. 25923), and Gram-negative *Salmonella typhimurium* (ATCC No. 23564), *Pseudomonas aeruginosa* (ATCC No. 27853) bacteria.

Table 1 Physical data of synthesized compounds 5a–h, 6a–h, and 7a–h

Entry	R_1	R_2	R_3	Yield (%)	mp (°C)
5a	CH_3	H	H	75	140–142
5b	H	H	CH_3	69	210–212
5c	Cl	H	H	72	172–174
5d	H	H	Cl	65	189–191
5e	H	H	OCH_3	58	198–201
5f	H	H	F	73	245–247
5g	H	F	F	81	195–197
5h	F	F	F	64	233–235
6a	CH_3	H	H	67	295–297
6b	H	H	CH_3	73	275–277
6c	Cl	H	H	67	300–3002
6d	H	H	Cl	65	202–204
6e	H	H	OCH_3	76	289–291
6f	H	H	F	64	276–278
6g	H	F	F	71	174–176
6h	F	F	F	69	189–181
7a	CH_3	H	H	58	305–307
7b	H	H	CH_3	63	193–195
7c	Cl	H	H	78	286–288
7d	H	H	Cl	83	207–209
7e	H	H	OCH_3	64	215–217
7f	H	H	F	73	276–278
7g	H	F	F	67	209–211
7h	F	F	F	66	291–293

The compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1 mg/mL. Antibacterial activity of DMSO against the test organisms was investigated and was found to be nil. Molten nutrient agar (15 cm^3) kept at 45 °C was then poured into the Petri dishes and allowed to solidify. A total of 10-mL diameter holes were then punched carefully using a sterile cork borer and completely filled with the test solutions. The plates were incubated for 24 h at 37 °C. After 24 h, the inhibition zone that appeared around the holes in each plate was measured. Antibacterial activity was determined by measuring the diameter of inhibition zone and examining the minimum inhibitory concentration (MIC). Activity of each compound was compared with streptomycin as standards. The observed data of antibacterial activity of compounds and the standard drug are given in Table S1. The compounds **6d**, **6g**, **7g**, and **7h** show excellent antibacterial activity against Gram-positive bacterial strains. Likewise, compounds **6g**, **6h**, and **7e** showed excellent activity against Gram-negative bacterial strains.

EXPERIMENTAL

Melting points were determined in an open capillary in liquid paraffin bath and were uncorrected. The progress of reaction was monitored by thin layer chromatography (TLC) using silica gel (Merck). IR spectra were recorded on a SHIMADZU–FT-IR spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on BRUKER ADVANCE–II 400 NMR spectrometer in DMSO-d_6/$CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ ppm. Mass spectra were recorded on a

Table S1 The MIC of tested compounds 6a–h and 7a–h in μg/mL

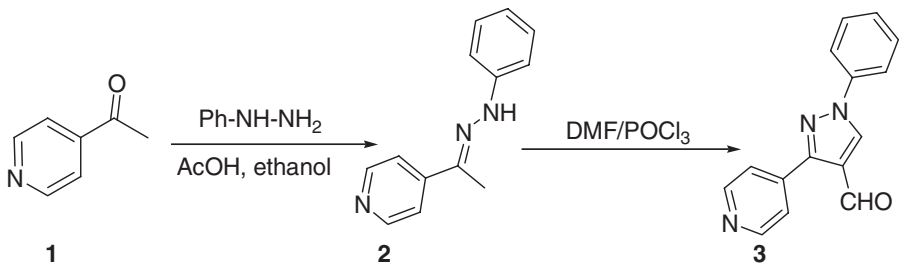
Tested compounds	*B. subtilis* ZI[a] (MIC)[b]	*S. aureus* ZI[a] (MIC)[b]	*S. typhi* ZI[a] (MIC)[b]	*P. aeroginosa* ZI[a] (MIC)[b]
6a	15 (15)	16 (15)	12 (15)	10 (15)
6b	16 (15)	21 (15)	15 (15)	16 (15)
6c	18 (15)	20 (15)	13 (15)	15 (15)
6d	17 (10)	22 (10)	13 (15)	17 (15)
6g	19 (10)	23 (10)	16 (15)	19 (10)
6h	14 (15)	20 (15)	19 (10)	18 (10)
7a	15 (15)	19 (15)	7 (15)	10 (15)
7b	13 (15)	15 (15)	5 (15)	7 (15)
7c	13 (15)	14 (15)	9 (15)	11 (15)
7d	14 (15)	16 (15)	8 (10)	7 (15)
7e	17 (15)	19 (15)	18 (10)	16 (15)
7g	18 (10)	16 (15)	17 (15)	15 (15)
7h	19 (10)	18 (15)	14 (15)	13 (15)
Streptomycin	22 (10)	24 (10)	20 (10)	19 (10)

[a]Zone of inhibition. [b]MIC in μg/mL.

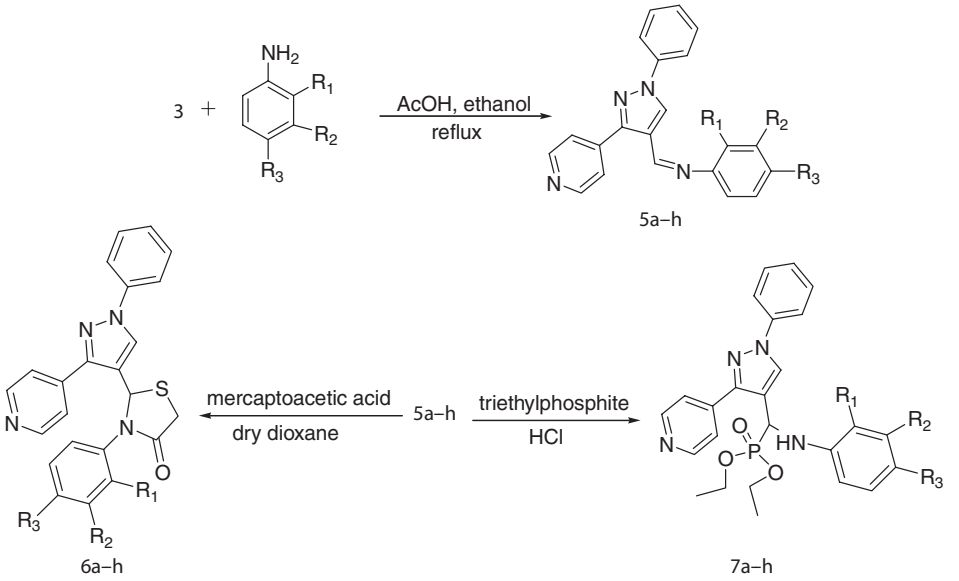
PEP-SCIUX-APIQ pulsar (electron preionization) mass spectrometer. Elemental analyses were performed on Perkin-Elmer EAL-240 elemental analyzer.

General Procedure for the Synthesis of 1-phenyl-3-(pyridine-4-yl)-1*H*-pyrazole-4-carbaldehyde 3

A solution of 1-(Pyridine-4-yl) ethanone **1** (1 mmol) and phenyl hydrazine (1 mmol) in absolute ethanol (25 mL) containing catalytic amount of sulfuric acid (0.1 mL) was stirred at room temperature for 10 min. The yellow colored solid thus obtained was filtered, washed with cold ethanol, and dried under vacuum to get the compound **2**. To a stirred solution of dimethylformamide (DMF) (1 mmol), phosphorus oxychloride (6 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature for 30 min. Then, the (*E*)-2-phenyl-1-(1-(pyridine-4-yl)ethylidene)hydrazine **2** (2 mmol) was added at 0 °C and the reaction mixture was stirred overnight at room temperature. The resultant contents were poured onto crushed ice; solid product was separated by filtration and washed with cold sodium bicarbonate solution (10%) followed by water and crystallized from ethanol.



Scheme 1



Scheme 2

Spectral and Analytical Data of Compound 3

3: ^{1}H NMR (DMSO-d_6), δ ppm = 10.2 (s, 1H, −CHO), 8.75 (d, 2H, J = 4.65 Hz, C-2 and C-6 pyridine ring protons), 8.49 (s, 1H, pyrazole proton), 7.38 (m, 7H, Ar-H); IR (KBr discs cm^{-1}), 2765 (−CHO), 1735 (−C=O), 1520 (−C=N, pyridine); ES-MS, *m/z*: 249. Anal. calcd. for $C_{15}H_{11}N_3O$ (249.27): C, 72.28%; H, 4.45%, N, 16.86%. Found: C, 72.25%; H, 4.37%, N, 16.97%.

General Procedure for the Synthesis of 5a–h

An equimolar mixture of 1-phenyl-3-(pyridine-4-yl)-1*H*-pyrazole-4-carbaldehyde **3** (4 mmol) and different substituted anilines **4a–h** (4 mmol) in ethanol (10 mL) containing catalytic amount of glacial acetic acid (0.5 mL) was refluxed for 3–5 h. The progress of reaction was monitored by TLC (solvent system—hexane:ethyl acetate, 9:1). After completion of reaction, the excess of solvent was evaporated under vacuum. The separated solid was filtered off, washed well with water followed with cold ethanol, and crystallized from ethanol.

Spectral and Analytical Data of Compounds 5a–h

5a: ^{1}H NMR (DMSO-d_6), δ ppm = 9.13 (s, 1H, −CH=N), 8.73 (d, 2H, C-2 and C-6 pyridine ring protons), 8.21 (d, 2H, Ar-H), 7.65 (2H, d, J = 5.5 Hz, Ar-H), 7.68 (6H, m, Ar-H and pyrazole protons), 7.03 (d, 2H, J = 8.59 Hz, Ar-H), 2.56 (s, 3H,−CH_3); IR (KBr discs, cm^{-1}), 1627 (C=N), 1523 (C=N, pyridine); ES-MS, *m/z*: 339.20. Anal. calcd. for $C_{22}H_{18}N_4$ (338.41): C, 78.08%; H, 5.36%, N, 16.56%. Found: C, 78.15%; H, 5.27%, N, 16.59%.

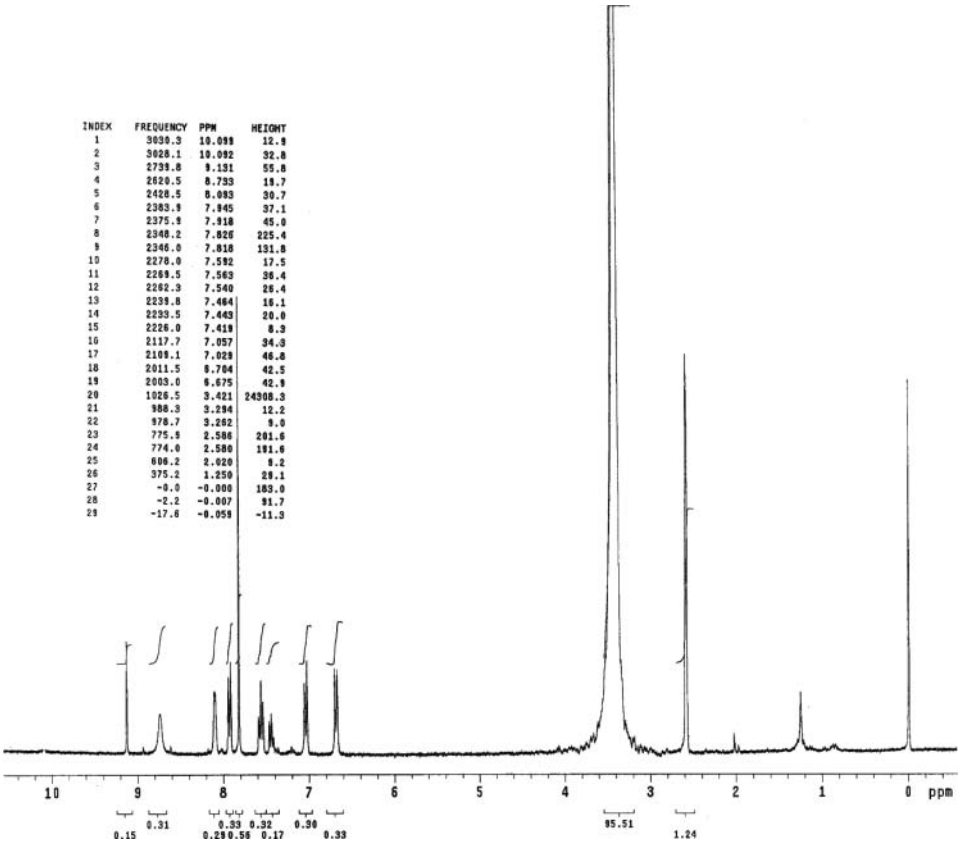


Figure S1 ^{1}H NMR spectrum of 5a.

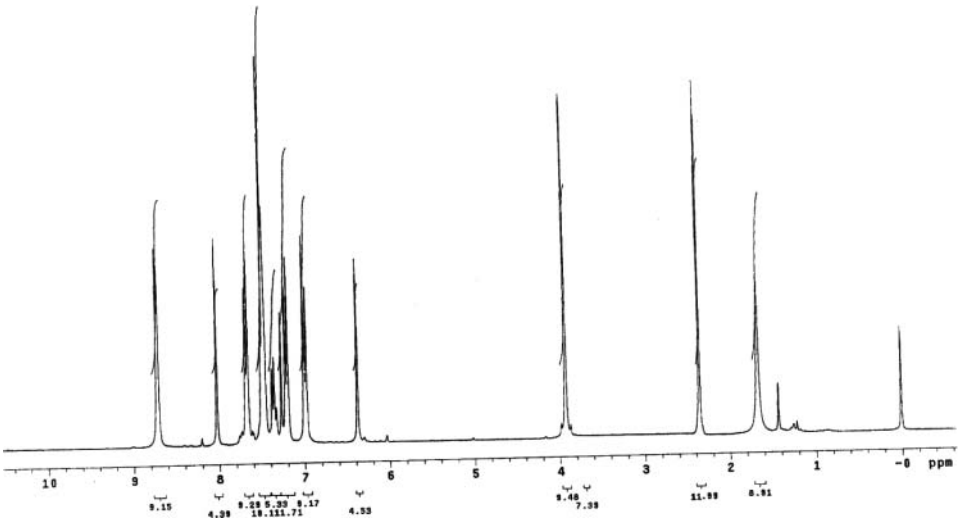


Figure S2 ^{1}H NMR spectrum of 6a.

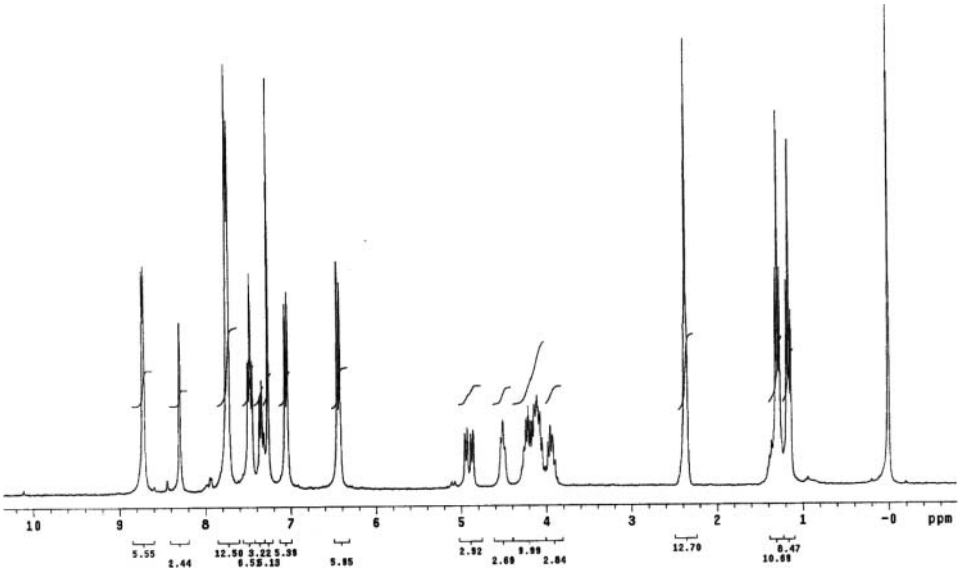


Figure S3 ^{1}H NMR spectrum of 7a.

5b: ^{1}H NMR (DMSO-d_6), δ ppm = 8.94 (s, 1H, −CH=N), 8.79 (d, 2H, C-2 and C-6 pyridine ring protons), 7.98 (2H, d, J = 5 Hz, Ar-H), 7.88 (d, 2H, J = 8.5 Hz, Ar-H), 7.35 (m, 6H, Ar-H and pyrazole protons), 7.11 (d, 2H, J = 7.69 Hz, Ar-H), 2.37 (s, 3H,−CH_3); IR (KBr discs, cm^{-1}), 1637 (C=N), 1595 (C=N, pyridine); ES-MS, *m/z*: 339.28. Anal. calcd. for $C_{22}H_{18}N_4$ (338.41): C, 78.08%; H, 5.36%; N, 16.56%. Found: C; 78.24%; H, 5.32%; N, 16.50%.

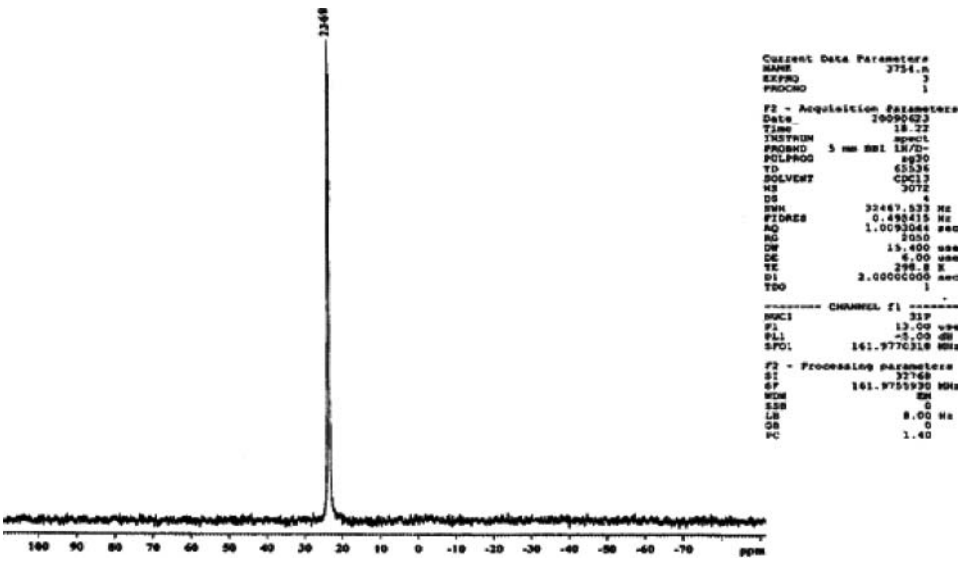


Figure S4 ^{31}H NMR spectrum of 7a.

5c: ^{1}H NMR (DMSO-d_6), δ ppm = 8.89 (s, 1H, −CH=N), 8.76 (d, 2H, C-2 and C-6 pyridine protons), 7.73 (d, 2H, J = 5.5 Hz, Ar-H), 7.15 (m, 10H, Ar-H and pyrazole protons); IR (KBr discs, cm^{-1}), 1632 (C=N), 1576 (C=N, pyridine); ES-MS, *m/z:* 359.70. Anal. calcd. for $C_{21}H_{15}ClN_4$ (358.82): C, 70.29%; H, 4.21%; N, 15.61%. Found: C, 70.24%; H, 4.32%; N, 15.56%.

5d: ^{1}H NMR (DMSO-d_6), δ ppm = 8.85, (s, 1H, −CH=N), 8.69 (d, 2H, C-2 and C-6 pyridine protons), 7.85 (d, 2H, J = 8 Hz, Ar-H), 7.52 (d, 2H, J = 5 Hz, Ar-H), 7.38 (m, 6H, Ar-H and pyrazole protons), 7.23 (d, 2H, J = 8.5 Hz); IR (KBr discs cm^{-1}), 1625 (C=N), 1568 (C=N, pyridine); ES-MS, *m/z*: 359.45. Anal. calcd. for $C_{21}H_{15}ClN_4$ (358.82): C, 70.29%; H, 4.21%; N, 15.61%. Found: C, 70.32%; H, 4.38%; N, 15.63%.

5e: ^{1}H NMR ($CDCl_3$), δ ppm = 8.78 (s, 1H, −CH=N), 8.67 (d, 2H, C-2 and C-6 pyridine protons), 7.79 (d, 2H, J = 5 38 Hz, Ar-H), 7.65 (d, 2H, J = 8.5 Hz, Ar-H), 7.45 (m, 6H, Ar-H and pyrazole protons), 7.15 (d, 2H, J = 7.8 Hz, Ar-H), 3.59 (s, 3H, OCH_3); IR (KBr discs cm^{-1}), 1634 (C=N), 1580 (C=N, pyridine); ES-MS, *m/z*: 354. Anal. calcd. for $C_{22}H_{18}N_4O$ (354.15): C, 74.56%; H, 5.12%; N, 15.81%. Found: C, 74.72%; H, 5.18%; N, 15.63%.

5f: ^{1}H NMR (DMSO-d_6), δ ppm = 8.77 (s, 1H, −CH=N), 8.76 (d, 2H, C-2 and C-6 pyridine protons), 7.81 (d, 2H, J = 5.5 Hz, Ar-H), 7.73 (d, 2H, J = 8. Hz, Ar-H), 7.22 (d, 2H, J = 7.74 Hz, Ar-H), 7.23 (m, 6H, Ar-H and pyrazole protons); IR (KBr discs cm^{-1}), 1655 (C=N), 1576 (C=N, pyridine); ES-MS, *m/z*: 342. Anal. calcd. for $C_{21}H_{15}FN_4$ (342.51): C, 73.67%; H, 4.42%; N, 16.36%. Found: C, 73.52%; H, 4.45%; N, 16.53%.

5g: ^{1}H NMR ($CDCl_3$), δ ppm = 8.92 (s, 1H, CH=N−), 8.73 (d, 2H, C-2 and C-6 pyridine protons), 7.89 (2H, d, J = 5 Hz, Ar-H), 7.13 (m, 9H, Ar-H and pyrazole proton); IR (KBr discs cm^{-1}), 1628 (C=N), 1555 (C=N, pyridine); ES-MS, *m/z*: 360.50. Anal. calcd. for $C_{21}H_{14}F_2N_4$ (360.12): C, 69.99%; H, 3.92%; N, 15.55%. Found: C, 70.12%; H, 3.98%; N, 15.38%.

5h: ^{1}H NMR ($CDCl_3$), δ ppm = 8.85 (d, 2H, C-2 and C-6 pyridine protons), 8.68 (s, 1H, CH=N−), 7.76 (2H, d, J = 5.37 Hz, Ar-H), 7.17 (8H, m, Ar-H and pyrazole proton); IR (KBr discs cm^{-1}), 1636 (C=N), 1558 (C=N, pyridine); ES-MS, *m/z*: 378. Anal. calcd. for $C_{21}H_{13}F_3N_4$ (378.11): C, 66.66%; H, 3.46%; N, 14.81%. Found: C, 66.52%; H, 3.68%; N, 14.93%.

General Procedure for the Synthesis of 6a–h

A solution of compounds **5a–h** (1.5 mmol) and mercaptoacetic acid (3 mmol) in dry dioxane (5) was refluxed for 6–7 h. The progress of the reaction was monitored on TLC using hexane:ethyl acetate (8:2) as the solvent system. After completion of reaction, the solvent was evaporated under vacuum and residue was washed with 4 N Na_2CO_3 solution followed with water. The separated solid was filtered off, washed with water till carbonate free, and then with ether, and crystallized from ethanol.

Spectral and Analytical Data of Compounds 6a–h

6a: ^{1}H NMR ($CDCl_3$), δ ppm = 8.70 (d, 2H, C-2 and C-6 pyridine ring protons, J = 4.50 Hz), 8.02 (s, 1H, pyrazoyl proton), 7.65 (d, 2H, J = 7.9 Hz, Ar-H), 7.28 (7H, m, Ar-H), 6.96 (d, 2H, J = 8 Hz, Ar-H), 6.37 (s, 1H, −CH proton of thiazolidinone ring), 3.92 (s, 2H, -S-CH_2-CO-proton), 2.28 (s, 3H, −CH_3); IR (KBr discs, cm^{-1}), 3050 (C−H,

Ar), 1700 (N—C=O), 1628 (C=N); ES-MS, *m/z*: 413.41. Anal. calcd. for $C_{24}H_{20}N_4OS$ (412.51): C, 69.88%; H, 4.89%; N, 13.58%; S, 7.77%. Found: C, 69.77%; H, 4.93%; N, 13.52%; S,7.84%.

6b: ^{1}H NMR ($CDCl_3$), δ ppm = 8.76 (d, 2H, C-2 and C-6 pyridine ring protons, J = 4.8 Hz), 8.11 (s, 1H, pyrazoyl proton), 7.59 (d, 2H, J = 8.2 Hz, Ar-H), 7.18 (d, 2H, J = 8.5 Hz), 7.32 (m, 5H, Ar-H), 6.82 (d, 2H, J = 8.3 Hz, Ar-H), 6.39 (s, 1H, —CH proton of thiazolidinone ring), 3.73 (s, 2H, -S-CH_2-CO- proton), 2.38 (s, 3H, —CH_3); IR (KBr discs, cm^{-1}), 3088 (C—H, Ar), 1720 (N—C=O), 1602 (C=N); ES-MS, *m/z*: 413.61. Anal. calcd. for $C_{24}H_{20}N_4OS$ (412.51): C, 69.88%; H, 4.89%; N, 13.58%; S, 7.77%. Found: C, 69.77%; H, 4.93%; N, 13.52%; S, 7.84%.

6c: ^{1}H NMR ($CDCl_3$), δ ppm = 8.70 (d, 2H, C-2 and C-6 pyridine ring protons, J = 4.93 Hz), 8.11 (s, 1H, pyrazoyl proton), 7.71 (d, 2H, J = 8.38 Hz, Ar-H), 7.22 (m, 9H, Ar-H), 6.34 (s, 1H, —CH proton of thiazolidinone ring), 3.70 (s, 2H, -S-CH_2-CO-proton); IR (KBr discs, cm^{-1}), 3150 (C—H, Ar), 1705 (N—C=O), 1639 (C=N); ES-MS, *m/z*: 433.30. Anal. calcd. for $C_{23}H_{17}ClN_4OS$ (432.93): C, 63.81%; H, 3.96%; N, 12.94%; S, 7.41%. Found: C, 63.78%; H, 3.98%; N, 13.05%; S, 7.54%.

6d: ^{1}H NMR ($CDCl_3$), δ ppm = 8.73 (d, 2H, C-2 and C-6 pyridine ring protons, J = 4.53 Hz), 8.05 (s, 1H, pyrazoyl proton), 7.67 (d, 2H, J = 7.9 Hz, Ar-H), 7.32 (m, 5H, Ar-H), 7.23 (d, 2H, J = 8.4 Hz), 6.97 (d, 2H, J = 8.5 Hz, Ar-H), 6.37 (s, 1H, —CH proton of hiazolidinone ring), 3.74 (s, 2H, -S-CH_2-CO- proton); IR (KBr discs, cm^{-1}), 3059 (C—H, Ar), 1715 (N—C=O), 1655 (C=N); ES-MS, *m/z*: 433.20. Anal. calcd. for $C_{23}H_{17}ClN_4OS$ (432.93): C, 63.81%; H, 3.96%; N, 12.94%; S, 7.41%. Found: C, 63.78%; H, 3.98%; N, 13.05%; S, 7.54%.

6e: ^{1}H NMR ($CDCl_3$), δ ppm = 8.73 (d, 2H, C-2 and C-6 pyridine ring protons, J = 4.77 Hz), 8.07 (s, 1H pyrazoyl proton), 7.59 (d, 2H, J = 8.2 Hz, Ar-H), 7.30 (m, 5H, Ar-H), 7.18 (d, 2H, J = 8.5 Hz), 6.72 (d, 2H, J = 8.3 Hz, Ar-H), 6.41 (s, 1H, —CH proton of thiazolidinone ring), 3.98 (s, 2H, -S-CH_2-CO-proton), 3.34 (s, 3H, -OCH_3); IR (KBr discs, cm^{-1}), 3115 (C—H, Ar), 1725 (N—C=O), 1623 (C=N); ES-MS, *m/z*: 429.10. Anal. calcd. for $C_{24}H_{20}N_4O_2S$ (428.51): C, 67.27%; H, 4.70%; N, 13.07%; S, 7.48%. Found: C, 67.19%; H, 4.72%; N, 12.98%; S, 7.56%.

6f: ^{1}H NMR ($CDCl_3$), δ ppm = 8.78 (d, 2H, C-2 and C-6 pyridine ring proton, J = 4.48 Hz), 8.14 (s, 1H pyrazoyl proton), 7.63 (d, 2H, J = 8.5 Hz, Ar-H), 7.25 (d, 2H, J = 8.3 Hz), 7.41(m, 5H, Ar-H), 6.78 (d, 2H, J = 8.4 Hz, Ar-H), 6.40 (s, 1H, —CH proton of thiazolidinone ring), 4.05 (s, 2H, -S-CH_2-CO- proton); IR (KBr discs, cm^{-1}), 3063 (C—H, Ar-H), 1696 (N—C=O), 1627 (C=N); ES-MS, *m/z*: 417.30. Anal. calcd. for $C_{23}H_{17}FN_4O_3S$ (416.47): C, 66.33%; H, 4.11%; N, 13.45%; S, 7.70%. Found: C, 66.28%; H, 4.23%; N, 13.36%; S, 7.88%.

6g: ^{1}H NMR ($CDCl_3$), δ ppm = 8.78 (d, 2H, C-2 and C-6 pyridine ring proton, J = 4.68 Hz), 8.17 (s, 1H pyrazoyl proton), 7.73 (d, 2H, J = 8.5, Ar-H), 7.35 (m, 6H, Ar-H), 7.19 (d, 2H, J = 8.2, Ar-H), 6.35 (s, 1H, —CH proton of thiazolidinone ring), 3.97 (s, 2H, -S-CH_2-CO- proton); IR (KBr discs, cm^{-1}), 3070 (C—H, Ar), 1696 (N—C=O), 1637 (C=N); ES-MS, *m/z*: 437.60. Anal. calcd. for $C_{23}H_{16}F_2N_4OS$ (434.46): C, 66.58%; H, 3.71%; N, 12.90%; S, 7.12%. Found: C, 66.45%; H, 3.66%; N, 13.05%; S, 7.45%.

6h: ^{1}H NMR (DMSO-δ_6), δ ppm = 8.68 (d, 2H, C-2 and C-6 pyridine ring proton, J = 4.20 Hz), 8.10 (s, 1H, pyrazoyl proton), 7.65 (d, 2H, J = 8.2, Ar-H), 7.23 (m, 7H, Ar-H), 6.44 (s, 1H, —CH proton of thiazolidinone ring), 3.92 (s, -S-CH_2-CO- proton); IR (KBr discs, cm^{-1}), 3055 (C—H, Ar), 1700 (N—C=O), 1608 (C=N); ES-MS, *m/z*: 453.30. Anal.

calcd. for $C_{23}H_{15}F_3N_4OS$ (452.09): C, 61.06%; H, 3.34%; N, 12.38%; S, 7.09%. Found: C, 61.02%; H, 3.47%; N, 12.57%; S, 7.21%.

General Procedure for the Synthesis of 7a–h

A solution of compounds **5a–h** (1.5 mmol) and triethyl phosphite (3 mmol) in ethanol containing conc. HCl (0.5 mL) was stirred at room temperature for 10–15 min. After completion of the reaction (checked by TLC), the reaction mixture was poured onto crushed ice and neutralized with 1:1 ammonia. The separated solid was filtered off, washed with water, and crystallized from ethanol.

Spectral and Analytical Data of Compounds 7a–h

7a: ^{1}H NMR ($CDCl_3$), δ ppm = 8.86 (d, 2H, C-2 and C-6 pyridine ring protons), 8.45 (s, 1H, pyrazoyl proton), 7.75 (m, 7H, Ar-H), 7.14 (d, 2H, J = 8.3 Hz, Ar-H), 6.57 (d, 2H, J = 8 Hz, Ar-H), 4.79 (dd, ^2JPH = 20.6 Hz, 8.3 Hz −CH− proton), 4.33 (m, 4H), 3.49 (t, 1H, J = 7.59 Hz, 1H, NH), 2.40 (s, 3H, CH_3), 1.31 (t, 3H, J = 7.3 Hz), 1.22 (t, 3H, J = 6.9 Hz); ^{31}P NMR ($CDCl_3$), δ ppm = 23.68; IR (KBr discs, cm^{-1}), 3155 (N-H), 2940 (C−H alkane), 1230 (P=O), 1045 (P-O-Et), ES-MS, *m/z*: 477. Anal. calcd. for $C_{26}H_{29}N_4O_3P$ (476.51): C, 65.53%; H, 6.13%; N, 11.76%. Found: C, 65.43%; H, 6.15%; N, 11.73%.

7b: ^{1}H NMR ($CDCl_3$), δ ppm = 8.91 (d, 2H, C-2 and C-6 pyridine ring protons), 8.43 (s, 1H, pyrazoyl proton), 7.87 (d, 2H, J = 6.36 Hz, Ar-H), 7.26 (m, 7H, Ar-H), 6.48 (d, 2H, J = 6.2 Hz, Ar-H), 4.68 (dd, 1H, ^2JPH = 20.9 Hz, 8.5 Hz), 4.21 (m, 4H), 3.49 (t, 1H, J = 7.09 Hz, NH), 2.25 (s, 3H, CH_3), 1.42 (t, 3H, J = 7.1 Hz), 1.29 (t, 3H, J = 6.7 Hz); ^{31}P NMR ($CDCl_3$), δ ppm = 25.82; IR (KBr discs, cm^{-1}), 3206 (N-H), 2940 (C−H alkane), 1230 (P=O), 1105 (P-O-Et), ES-MS, *m/z*: 477.30. Anal. calcd. for $C_{26}H_{29}N_4O_3P$ (476.51): C, 65.53%; H, 6.13%; N, 11.76%. Found: C, 65.43%; H, 6.15%; N, 11.73%.

7c: ^{1}H NMR ($CDCl_3$), δ ppm = 8.89 (d, 2H, C-2 and C-6 pyridine ring protons), 8.51 (s, 1H, pyrazoyl proton), 7.78 (d, 2H, J = 6.4 Hz, Ar-H), 7.39 (m, 9H, Ar-H), 4.86 (dd, 1H, ^2JPH = 19.9 Hz, 8.1 Hz), 4.52 (t, 1H, J = 7.25 Hz, NH), 4.24 (m, 4H), 1.46 (t, 3H, J = 7.3 Hz), 1.32 (t, 3H, J = 6.8 Hz); ^{31}P NMR ($CDCl_3$), δ ppm = 23.82; IR (KBr discs, cm^{-1}), 3208 (N-H), 2940 (C−H alkane), 1238 (P=O), 1056 (P-O-Et), ES-MS, *m/z*: 497. Anal. calcd. for $C_{25}H_{26}ClN_4O_3P$ (496.93): C, 60.43%; H, 5.27%; N, 11.27%. Found: C, 60.35%; H, 5.30%; N, 11.25%.

7d: ^{1}H NMR ($CDCl_3$), δ ppm = 8.80 (d, 2H, C-2 and C-6 pyridine ring protons), 8.58 (s, 1H, pyrazoyl proton), 7.78 (d, 2H, J = 6 Hz, Ar-H), 7.31 (m, 5H, Ar-H), 7.09 (d, 2H, J = 8.5 Hz, Ar-H), 6.53 (d, 2H, J = 6.3 Hz, Ar-H), 4.92 (dd, 1H, ^2JPH = 18.8 Hz, 8.3 Hz),4.43 (t, 1H, NH, J = 7.19 Hz), 4.28 (m, 4H), 1.52 (t, 3H, J = 7.1 Hz), 1.27 (t, 3H, J = 6.7 Hz); ^{31}P NMR (DMSO-d_6), δ ppm = 27.82; IR (KBr discs, cm^{-1}), 3208 (N-H), 2965 (C−H alkane), 1235 (P=O), 1123 (P-O-Et), ES-MS, *m/z*: 497.10. Anal. calcd. for $C_{26}H_{29}ClN_4O_3P$ (496.93): C, 60.43%; H, 5.27%; N, 11.27%. Found: C, 60.35%; H, 5.30%; N, 11.25%.

7e: ^{1}H NMR ($CDCl_3$), δ ppm = 8.84 (d, 2H, C-2 and C-6 pyridine ring protons), 8.47 (s, 1H, pyrazoyl proton), 7. 81 (d, 2H, J = 6.3 Hz, Ar-H), 7.35 (m, 5H, Ar-H), 7.05 (d, 2H, J = 8.79 Hz, Ar-H), 6.42 (d, 2H, J = 6 Hz, Ar-H), 4.88 (dd, 1H, ^2JPH = 19.2 Hz, 8.5 Hz), 4.47 (t, 1H, NH, J = 7.4 Hz), 4.25 (m, 4H), 3.31 (s, 3H, -OCH_3), 1.55 (t, 3H, J = 7.4 Hz), 1.30 (t, 3H, J = 6.8 Hz); ^{31}P NMR ($CDCl_3$), δ ppm = 22.78;IR (KBr discs, cm^{-1}), 3238 (N-H), 2930 (C−H alkane), 1244 (P=O), 1113 (P-O-Et); ES-MS, *m/z*: 492. Anal.

calcd. for $C_{26}H_{29}N_4O_4P$ (492.51): C, 63.41%; H, 5.93%; N, 11.38%. Found: C, 63.38%; H, 5.89%; N, 11.37%.

7f: ^{1}H NMR ($CDCl_3$), δ ppm = 8.78 (d, 2H, C-2 and C-6 pyridine ring protons), 8.54 (s, 1H, pyrazoyl proton), 7.87 (d, 2H, J = 6.69 Hz, Ar-H), 7.24 (m, 5H, Ar-H), 7.15 (d, 2H, J = 8.3 Hz, Ar-H), 6.57 (d, 2H, J = 8.4 Hz, Ar-H), 4.94 (dd, 1H, ^2JPH = 19.3 Hz, 7.1 Hz), 4.55 (t, 1H, J = 7.3 Hz, NH), 4.32 (m, 4H), 1.46 (t, 3H, J = 7.1 Hz), 1.28 (t, 3H, J = 6.7 Hz); ^{31}P NMR ($CDCl_3$), δ ppm = 26.81;IR (KBr discs, cm^{-1}), 3208 (N-H), 2946 (C—H alkane), 1235 (P═O), 1123 (P-O-Et); ES-MS, *m/z*: 481. Anal. calcd. for $C_{25}H_{26}FN_4O_3P$ (480.47): C, 62.49%; H, 5.45%; N, 11.66%. Found: C, 62.39%; H, 5.46%; N, 11.65%.

7g: ^{1}H NMR ($CDCl_3$), δ ppm = 8.75 (d, 2H, C-2 and C-6 pyridine ring protons), 8.57 (s, 1H, pyrazoyl proton), 7.81 (d, 2H, J = 6.69 Hz, Ar-H), 7.45 (m, 6H, Ar-H), 6.48 (d, 2H, J = 6.2 Hz, Ar-H), 4.98 (dd, 1H, ^2JPH = 18.9 Hz, 7.6 Hz), 4.61 (s, 1H, J = 7.24 Hz, NH), 4.29 (m, 4H), 1.52 (t, 3H, J = 7.3 Hz), 1.31 (t, 3H, J = 6.7 Hz); ^{31}P NMR ($CDCl_3$), δ ppm = 24.10; IR (KBr discs, cm^{-1}), 3208 (N-H), 2966 (C—H alkane), 1246 (P═O), 1123 (P-O-Et); ES-MS, *m/z*: 499. Anal. calcd. for $C_{25}H_{25}F_2N_4O_3P$ (498.46): C, 60.24%; H, 5.06%; N, 11.24%. Found: C, 60.16%; H, 5.08%; N, 11.22%.

7h: ^{1}H NMR ($CDCl_3$), δ ppm = 8.79 (d, 2H, C-2 and C-6 pyridine ring protons), 8.45 (s, 1H, pyrazoyl proton), 7.45 (m, 7H, Ar-H), 6.51 (d, 2H, J = 6 Hz, Ar-H), 5.03 (dd, 1H, ^2JPH = 19.8 Hz, 8.5 Hz), 4.56 (s, 1H, 7.4 Hz, NH), 4.34 (m, 4H), 1.45 (t, 3H, J = 7.1 Hz), 1.29 (t, 3H, J = 6.5 Hz); ^{31}P NMR ($CDCl_3$), δ ppm = 23.88; IR (KBr discs, cm^{-1}), 3250 (N-H), 2950 C—H alkane), 1256 (P═O), 1134 (P-O-Et); ES-MS, *m/z*: 517.40. Anal. calcd. for $C_{25}H_{24}F_3N_4O_3P$ (516.45): C, 58.14%; H, 4.68%; N, 10.85%. Found: C, 58.07%; H, 4.65%; N, 10.01%.

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