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Novel sulfonamide-phosphonate conjugates as carbonic anhydrase isozymes inhibitors

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Abstract

The three-components one-pot Kabachnik-Fields reaction of sulfapyridine, diethyl phosphite, and aldehyde under thermal catalysis reaction condition in the presence of bismuth (III) triflate as a catalyst afford the corresponding sulfonamide-phosphonates (3a–3p) in good to excellent yields (78%–91%). The structures of the new synthesized compounds were elucidated and confirmed by variable spectroscopic studies. Single crystal X-ray studies for 3a, 3d, and 3i verified the proposed structure. The newly developed sulfonamide-phosphonates were evaluated for their inhibitory properties against four isoforms of human carbonic anhydrase (hCA I, II, IX, and XII). The results demonstrated that they exhibited greater potency in inhibiting hCA XII compared to hCA I, II, and IX, with K_i ranging from 5.1 to 51.1 nM. Compounds 3l and 3p displayed the highest potency, exhibiting selectivity ratios of I/XII >298.7 and 8.5, and II/XII ratios of 678.1 and 142.1, respectively. Molecular docking studies were conducted to explore their binding patterns within the binding pocket of CA XII. The results revealed that the sulfonamide NH group coordinated with the Zn^{2+} ion, and hydrogen bond interactions were observed with residue Thr200. Additionally, hydrophobic interactions were identified between the benzenesulfonamide phenyl ring and Leu198. Compounds 3p and 3l exhibited an additional hydrogen bonding interaction with other amino acid residues. These supplementary interactions may contribute to the enhanced potency and selectivity of these compounds toward the CA XII isoform.

KEYWORDS

anticancer, carbonic anhydrase inhibitor, one-pot reaction, sulfapyridine, α -aminophosphonate

1 | INTRODUCTION

Carbonic anhydrases (CAs, EC 4.2.1.1) facilitate the conversion of CO_2 into bicarbonate and a proton, along with other hydrolytic reactions. To date, researchers have identified eight genetic families of CAs: α -, β -, γ -, δ -, ζ -, η -, θ , and ι -CAs (Supuran, 2008). Among humans, 15 distinct isoforms of α -CA have been discovered and characterized. Out of these, 12 isoforms exhibit catalytic activity,

while the remaining three are inactive, being nominated as CA-related proteins (Alterio et al., 2012).

Human carbonic anhydrase (hCAs) play vital roles in numerous physiological and pathological processes, including gas exchange, the transportation of CO_2 and HCO_3^- across membranes and tissues, biosynthetic reactions, acid–base regulation, calcification, and tumor-igenesis/metastasis (Ewies et al., 2022; Guler et al., 2016). In particular, isoforms hCA IX and XII are implicated in the pH regulation

machinery of tumor cells, making their inhibition an effective antitumor strategy. It is worth noting that hCA IX expression is closely associated with cancer and poor prognosis in many tumors, whereas hCA XII is present in various normal tissues and organs such as the endometrium, colon, kidney, and eye, except some types of tumors (Nocentini & Supuran, 2018).

Isoforms CA IX and XII are highly expressed in various hypoxic cancers, including colorectal, renal, breast, and non-small cell lung cancer. This overexpression is a result of the activation of the hypoxia-inducible factor transcription factor signaling pathways (Neri & Supuran, 2011). The primary function of CA IX and XII in these cancers is to regulate cellular pH and protect tumor cells from acidosis caused by hypoxia, thereby promoting increased cell division (Pastorekova & Gillies, 2019).

As a result, inhibitors targeting CA IX and XII have been validated as effective anticancer agents, particularly for the treatment of hypoxic cancers. One specific compound, SLC-0111, is currently undergoing Phase Ib/II clinical trials for the treatment of advanced metastatic solid tumors (Supuran, 2017). The most commonly studied and clinically used class of hCA inhibitors possesses a chemical structure that incorporates a primary sulfonamide or its bioisosteres (Supuran, 2008). This preference is mainly due to the deprotonated form of these inhibitors, which can form a strong coordinative bond with the zinc ion in the enzyme, leading to the formation of a highly stable enzyme-inhibitor complex (Supuran, 2012).

The sulfonamide moiety is present in many of clinically approved CA inhibitors, of which acetazolamide (AAZ) (DrugBank, 2023a), methazolamide (DrugBank, 2023b), ethoxzolamide (DrugBank, 2023c), dorzolamide (DrugBank, 2023d), brinzolamide (DrugBank, 2023e), and pazopanib (DrugBank, 2023f) (Figure 1). Therefore, sulfonamide is considered as a promising pharmacophore for the

design of new CA inhibitors (Alp et al., 2012; Angeli et al., 2022; Carta et al., 2012; Hamad et al., 2020; Krymov et al., 2022; Sağlık et al., 2019; Yamali et al., 2020). Insertion of the electron-rich phosphoryl residue in the heterocyclic system could boost the physicochemical properties and so improve the bioavailability of the targeted agents (Modranka et al., 2021). Moreover, the phosphonate moiety was found in the several potent CA inhibitors (Nocentini et al., 2019; Winum et al., 2005). In addition to the reported interaction of isozymes I, II, IV, V, and IX with organic phosphates and phosphonates (Winum et al., 2005).

The Kabachnik-Fields reaction, also known as the Phospha-Mannich condensation, is an alternative method utilized for the synthesis of α -aminophosphonates. This process involves the condensation of dialkyl phosphite, oxo compounds (aldehydes or ketones), and 1st or 2nd amines in the presence of catalyzed basic or acidic reaction conditions (Bekheit & Kamel, 2017; Sabry et al., 2022). Because of their outstanding selectivity, stability in the reaction media, and recyclability, all of these properties making them ideal catalyses for Kabachnik-Fields condensation reaction (Ewies et al., 2019; Ladziata, 2014; Prakash et al., 2012). Additionally, metal triflates demonstrate water tolerance, this is particularly advantageous since water generated during the reaction can potentially deactivate or decompose the catalyst (Wu et al., 2022).

The focus of the present study is to develop a novel series of sulfonamide-phosphonate derivatives as CA inhibitors (Figure 2). The synthesis of target compounds involved the one-pot Kabachnik-Fields reaction, where sulfapyridine, diethyl phosphite (DEP), and aldehyde were condensed together. To assess the inhibitory activity of the newly synthesized agents, they were evaluated both in vitro and in silico against four hCA isoforms: hCA I, II, IX, and XII.

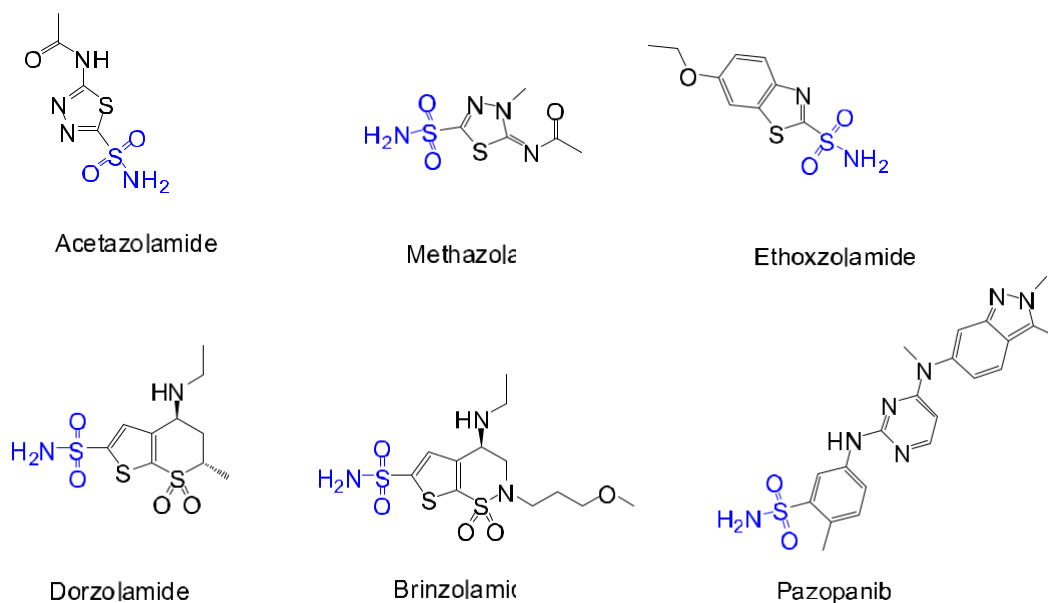


FIGURE 1 Structure of some approved CA inhibitors. CA, carbonic anhydrases.

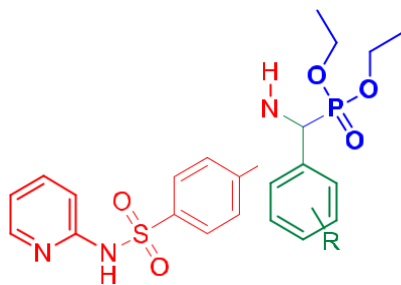


FIGURE 2 Structure of the target sulfonamide-phosphonates.

2 | EXPERIMENTAL SECTION

2.1 | Chemistry

The determination of melting points was conducted using an open capillary tube on an electrothermal melting point apparatus, and the values reported are unadjusted. Infrared spectra (KBr) were obtained using a Shimadzu FT-IR 8400S spectrophotometer. Reactions were monitored through thin layer chromatography on 0.2 mm silica gel F254 plates (Merck) with various solvents used for elution. The chemical structures of the synthesized compounds were characterized by nuclear magnetic resonance spectra (^1H -NMR, ^{13}C -NMR) recorded on a JEOL NMR spectrometer (500 and 125 MHz for ^1H and ^{13}C , respectively), while ^{31}P -NMR spectra were obtained on a Bruker NMR spectrometer (121.4 MHz). Chemical shifts are expressed in parts per million (ppm) using the deuterated solvent peak as an internal reference (the spectral illustrations are presented in Supporting Information S1: Figures 1–75). The purity of all newly synthesized samples was confirmed through microchemical analysis (C/H/N) performed at the Microanalysis Laboratory, Cairo University.

2.1.1 | General procedure for the synthesis of α -aminophosphonates 3a–3p and Schiff-base 4

$\text{Bi}(\text{OTf})_3$ (0.1 mmol) was added to a magnetically stirred mixture of carbonyl compound 2a–q (2.5 mmol), sulfapyridine (0.62 g, 2.5 mmol), and DEP (0.38, 2.5 mmol) in 15 mL THF and heated for the appropriate time (1.5–6 h). The final product was precipitated, filtrated on hot. The separated compound was dissolved in ethyl acetate (50 mL), and washed with water (3×50 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, concentrated to produce the corresponding sulfonamide-phosphonate products 3a–3p or the Schiff-base 4 (in case of using 4-dimethylaminobenzaldehyde as aldehyde).

Diethyl (phenyl((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino)methyl)phosphonate (3a) was obtained as pale-yellow microcrystals, mp 242–244°C and yield 88% (1.04 g). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ (ppm): 0.98 (t, 3H, J = 6.6 Hz, H_3CCOP), 1.08 (t, 3H, J = 7.1 Hz, H_3CCOP), 3.64–3.69 (m, 1H, HC-OP), 3.81–3.85 (m, 1H, HC-OP), 3.93–3.99 (m, 2H, $\text{H}_2\text{C-OP}$), 5.11 (dd, 1H, J = 9.55 & 24.8 Hz, HC-P), 6.84 (d, 3H, J = 8.5 Hz, H-Ar), 7.02 (d, 1H, J = 8.6 Hz, H-Ar), 7.21–7.25 (m, 2H, H-Ar + NH-CP

exchangeable), 7.28 (t, 2H, J = 7.6 Hz, H-Ar), 7.47–7.50 (m, 4H, H-Ar), 7.58 (t, 1H, J = 7 Hz, H-Ar), 8.01 (d, 1H, J = 3.8 Hz, H-Ar), 11.07 (s [br], 1H, NH) ppm; ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$) δ (ppm): 152.8, 151.4, 151.3, 146.4, 139.4, 136.6, 128.8, 128.7, 128.6, 128.1, 117.4, 112.9, 112.8 (C-Ar), 63.1, 63.0, 62.96, 62.90 (2OCH_2), 53.9 (d, $^1J_{\text{PC}}$ = 152.2 Hz, C-P), 16.77, 16.74, 16.55, 16.52 (2OC-CH_3); ^{31}P NMR (121 MHz, $\text{DMSO}-d_6$) δ (ppm): 20.6; Anal. calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_3\text{O}_5\text{PS}$ (475.50): C, 55.57; H, 5.51; N, 8.84. Found: C, 55.64; H, 5.59; N, 8.97.

Diethyl (((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino)(p-tolyl)methyl)phosphonate (3b) was obtained as pale-yellow microcrystals, mp 240–241°C and yield 84% (1.02 g). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ (ppm): 1.00 (t, 3H, J = 7.1 Hz, H_3CCOP), 1.08 (t, 3H, J = 7.1 Hz, H_3CCOP), 2.21 (s, 3H, H_3C), 3.65–3.70 (m, 1H, HC-OP), 3.82–3.86 (m, 1H, HC-OP),

3.93–3.98 (m, 2H, $\text{H}_2\text{C-OP}$), 5.05 (dd, 1H, J = 9.5 & 23.8 Hz, HC-P), 6.82 (d, 3H, J = 8.6 Hz, H-Ar), 7.02 (d, 1H, J = 8.6 Hz, H-Ar), 7.08 (d, 2H, J = 7.6 Hz, H-Ar), 7.16–7.20 (m, 1H, NH-CP exchangeable), 7.35 (d, 2H, J = 6.7 Hz, H-Ar), 7.48 (d, 2H, J = 8.5 Hz, H-Ar), 7.58 (t, 1H, J = 6.6 Hz, H-Ar), 8.01 (d, 1H, J = 3.8 Hz, H-Ar), 11.05 (s [br], 1H, NH-sulfonamide exchangeable); ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$) δ (ppm): 152.8, 151.4, 151.3, 146.4, 139.3, 137.3, 133.5, 129.2, 128.8, 128.7, 128.6, 128.1, 117.4, 112.9, 112.8, (C-Ar), 63.0, 62.9, 62.88, 62.83 (2OCH_2), 53.7 (d, $^1J_{\text{PC}}$ = 152.2 Hz, C-P), 21.2 (CH_3), 16.78, 16.74, 16.59, 16.55 (2OC-CH_3); ^{31}P NMR (121 MHz, $\text{DMSO}-d_6$) δ (ppm): 20.6; IR (KBr): 3278 (NH), 1340 (SO_2 , asy), 1227 (P=O), 1152 (SO_2 , sym), 1023 (P-O-C) cm^{-1} ; Anal. calcd. for $\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}_5\text{PS}$ (489.53): C, 56.43; H, 5.77; N, 8.58. Found: C, 56.49; H, 5.81; N, 8.64.

Diethyl (4-methoxyphenyl)(4-(N-(pyridin-2-yl)sulfamoyl)phenylamino)methylphosphonate (3c) was obtained as pale-yellow microcrystals, mp 237–239°C and yield 81% (1.02 g). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ (ppm): ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ (ppm): 0.99 (t, 3H, J = 7.1 Hz, H_3CCOP), 1.08 (t, 3H, J = 7.1 Hz, H_3CCOP), 3.67–3.72 (m, 4H, HC-OP + OCH_3), 3.79–3.83 (m, 1H, HC-OP), 3.94–3.97 (m, 2H, $\text{H}_2\text{C-OP}$), 5.04 (dd, 1H, J = 9.4 & 23.8 Hz, HC-P), 6.08 (s, 2H, H-Ar), 6.80–6.85 (m, 5H, H-Ar), 7.018 (d, 1H, J = 8.5 Hz, H-Ar), 7.15 (s, 1H, NH-CP), 7.38 (d, 2H, J = 9.5 Hz, H-Ar), 7.47 (d, 1H, J = 8.6 Hz, H-Ar), 8.01 (d, 1H, J = 3.8 Hz, H-Ar), 11.11 (s [br], 1H, NH exchangeable); ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$) δ (ppm): 156.8, 152.2, 151.4, 139.5, 136.3, 131.5, 130.7, 128.3, 128.4, 121.1, 117.2, 112.9, 112.7 (C-Ar), 63.0, 62.91, 62.87, 62.24 (2OCH_2), 55.5 (OCH_3), 53.5 (d, $^1J_{\text{PC}}$ = 152.2 Hz, C-P), 16.77, 16.73, 16.65, 16.61 (2OC-CH_3); Anal. calcd. for $\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}_6\text{PS}$ (505.52): C, 54.65; H, 5.58; N, 8.31. Found: C, 54.74; H, 5.71; N, 8.44.

Diethyl (3-methoxyphenyl)(4-(N-(pyridin-2-yl)sulfamoyl)phenylamino)methylphosphonate (3d) was obtained as pale-yellow microcrystals, mp 238–240°C and yield 85% (1.07 g). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ (ppm): 0.99 (t, 3H, J = 7.1 Hz, H_3CCOP), 1.08 (t, 3H, J = 7.1 Hz, H_3CCOP), 3.68–3.71 (m, 4H, HC-OP + OCH_3), 3.82–3.87 (m, 1H, HC-OP), 3.94–3.99 (m, 2H, $\text{H}_2\text{C-OP}$), 5.09 (dd, 1H, J = 9.5 & 23.8 Hz, HC-P), 6.78–6.85 (m, 4H, H-Ar), 7.01–7.08 (m, 3H, H-Ar), 7.18–7.25 (m, 2H, H-Ar + NH-CP exchangeable), 7.50 (d, 2H, J = 9.5 Hz, H-Ar), 7.57–7.60 (m, 1H, H-Ar), 8.01 (d, 1H, J = 3.8 Hz, H-Ar), 11.11 (s [br], 1H, NH exchangeable); ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$) δ (ppm): 159.6, 152.8, 151.4, 151.3, 146.3, 139.4, 138.2, 129.6, 128.8, 128.1, 121.1, 117.4, 114.8, 113.3, 112.9, 112.8, (C-Ar), 63.08, 63.02, 62.92, 62.91 (2POCH_2),

55.5 (OCH₃), 53.8 (d, ¹J_{PC} = 152.2 Hz, C-P), 16.78, 16.74, 16.58, 16.54 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO-d₆) δ (ppm): 21.7; IR (KBr): 3281 (NH), 1337 (SO₂, asy), 1229 (P=O), 1151 (SO₂, sym), 1012 (2P-O-C) cm⁻¹; Anal. calcd. for C₂₃H₂₈N₃O₆PS (505.52): C, 54.65; H, 5.58; N, 8.31. Found: C, 54.74; H, 5.71; N, 8.44.

Diethyl ((4-hydroxyphenyl)((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino) methyl) phosphonate (3e) was obtained as pale-yellow microcrystals, mp 228–230°C and yield 78% (0.95 g). ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 0.99 (t, 3H, J = 6.6 Hz, H₃CCOP), 1.07 (t, 3H, J = 7.1 Hz, H₃CCOP), 3.62–3.67 (m, 1H, HC-OP), 3.79–3.84 (m, 1H, HC-OP), 3.92–3.95 (m, 2H, H₂C-OP), 4.94 (dd, 1H, J = 9.5 & 23.8 Hz, HC-P), 6.67 (d, 2H, J = 8.5 Hz, H-Ar), 6.81 (d, 3H, J = 9.5 Hz, H-Ar), 7.03 (d, 1H, J = 8.5 Hz, H-Ar), 7.08 (s [br], 1H, NH-exchangeable), 7.27 (d, 2H, J = 7.6 Hz, H-Ar), 7.49 (d, 2H, J = 8.6 Hz, H-Ar), 7.59 (t, 1H, J = 6.6 Hz, H-Ar), 8.01 (d, 1H, J = 4.7 Hz, H-Ar), 9.36 (s [br], 1H, OH-exchangeable), 11.00 (sbr, 1H, NH-exchangeable); ¹³C NMR (125.7 MHz, DMSO-d₆) δ (ppm): 157.4, 152.8, 151.4, 151.3, 146.6, 139.4, 129.96, 129.92, 128.8, 127.9, 126.4, 117.4, 115.4, 112.9, 112.7 (C-Ar), 62.88, 62.83 (2POCH₂), 53.3 (d, ¹J_{PC} = 153.4 Hz, C-P), 16.78, 16.74, 16.60, 16.56 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO-d₆) δ (ppm): 20.6; IR (KBr): 3271 (NH), 2983 (OH, intra), 1357 (SO₂, asy), 1224 (P=O), 1128 (SO₂, sym), 1005 (2P-O-C) cm⁻¹; Anal. calcd. for C₂₂H₂₆N₃O₆PS (491.50): C, 53.76; H, 5.33; N, 8.55. Found: C, 53.87; H, 5.39; N, 8.68.

Diethyl ((4-fluorophenyl)((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino) methyl) phosphonate (3f) was obtained as pale-yellow microcrystals, mp 248–250°C and yield 82% (1.01 g). ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 0.99 (t, 3H, J = 7.1 Hz, H₃CCOP), 1.08 (t, 3H, H₃CCOP), 3.67–3.72 (m, 1H, HC-OP), 3.82–3.87 (m, 1H, HC-OP), 3.92–3.99 (m, 2H, H₂C-OP), 5.17 (dd, 1H, J = 9.5 & 23.8 Hz, HC-P), 6.81–6.85 (m, 3H, H-Ar), 7.01 (d, 1H, J = 8.6 Hz, H-Ar), 7.13 (t, 2H, J = 9.5 Hz, H-Ar), 7.22–7.26 (m, 1H, NH-CP exchangeable), 7.49–7.53 (m, 4H, H-Ar), 7.59 (t, 1H, J = 8.5 Hz, H-Ar), 8.01 (d, 1H, J = 3.8 Hz, H-Ar), 11.07 (s, 1H, NH exchangeable); ¹³C NMR (125.7 MHz, DMSO-d₆) δ (ppm): 163.1, 161.1, 152.8, 151.3, 151.2, 146.4, 139.4, 132.9, 130.7, 128.8, 128.3, 117.4, 115.5, 115.3, 112.9, 112.8 (C-Ar), 63.1, 63.0, 62.9, 62.8 (2OCH₂), 53.2 (d, ¹J_{PC} = 152.2 Hz, C-P), 16.75, 16.72, 16.57, 16.53 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO-d₆) δ (ppm): 21.7; IR (KBr): 3418, 3283(2NH), 1339 (SO₂, asy), 1229 (P=O), 1153 (SO₂, sym), 1017 (2P-O-C) cm⁻¹; Anal. calcd. for C₂₂H₂₅FN₃O₅PS (493.49): C, 53.55; H, 5.11; N, 8.52. Found: C, 53.69; H, 5.23; N, 8.59.

Diethyl ((4-chlorophenyl)((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino)methyl)phosphonate (3g) was obtained as pale-yellow microcrystals, mp 253–255°C and yield 82% (1.04 g). ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 1.01 (t, 3H, J = 6.6 Hz, H₃CCOP), 1.08 (t, 3H, J = 7 Hz, H₃CCOP), 3.70–3.75 (m, 1H, HC-OP), 3.84–3.89 (m, 1H, HC-OP), 3.94–3.99 (m, 2H, H₂C-OP), 5.18 (dd, 1H, J = 9.5 & 23.8 Hz, HC-P), 6.82 (d, 3H, J = 8.6 Hz, H-Ar), 7.02 (d, 1H, J = 8.6 Hz, H-Ar), 7.24 (s, 1H, NH), 7.36 (d, 2H, J = 8.6 Hz, H-Ar), 7.49 (m, 4H, J = 8.6 Hz, H-Ar), 7.59 (t, 1H, J = 7.6 Hz, H-Ar), 8.01 (s, 1H, H-Ar), 11.08 (sbr, 1H, NH); Anal. calcd. for C₂₂H₂₅ClN₃O₅PS (509.94): C, 51.82; H, 4.94; N, 8.24. Found: C, 51.94; H, 5.12; N, 8.57.

Diethyl ((2-chlorophenyl)((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino)methyl) phosphonate (3h) was obtained as pale-yellow microcrystals, mp 252–254°C and yield 79% (1 g). ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 0.95 (t, 3H, J = 7.1 Hz, H₃CCOP), 1.13 (t, 3H, J = 7.1 Hz, H₃CCOP), 3.62–3.67 (m, 1H, HC-OP),

3.78–3.88 (m, 1H, HC-OP), 4.01–4.06 (m, 2H, H₂C-OP), 5.21 (dd, 1H, J = 9.5 & 23.8 Hz, HC-P), 6.71 (d, 2H, J = 8.6 Hz, H-Ar), 6.81 (t, 1H, J = 6.7 Hz, H-Ar), 7.01 (d, 1H, J = 8.6 Hz, H-Ar), 7.25–7.31 (m, 2H, H-Ar), 7.42–7.45 (m, 2H, H-Ar + NH-CP exchangeable), 7.53 (d, 2H, J = 9.5 Hz, H-Ar), 7.57–7.62 (m, 2H, H-Ar), 8.00 (d, 1H, J = 4.7 Hz, H-Ar), 11.16 (s, 1H, NH exchangeable); ¹³C NMR (125.7 MHz, DMSO-d₆) δ (ppm): 162.8, 152.9, 150.8, 150.7, 146.1, 139.5, 134.3, 133.8, 133.7, 130.1, 129.7, 129.0, 127.9, 117.2, 113.0, 112.5, (C-Ar), 63.47, 63.43, 63.24, 63.19 (2OCH₂), 50.9 (d, ¹J_{PC} = 155.8 Hz, C-P), 16.78, 16.74, 16.46, 16.42 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO-d₆) δ (ppm): 20.7; IR (KBr): 3413, 3280 (2NH), 1397 (SO₂, asy), 1229 (P=O), 1132 (SO₂, sym), 1025 (P-O-C) cm⁻¹; Anal. calcd. for C₂₂H₂₅ClN₃O₅PS (509.94): C, 51.82; H, 4.94; N, 8.24. Found: C, 51.93; H, 6.08; N, 8.34.

Diethyl ((4-bromophenyl)((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino)methyl) phosphonate (3i) was obtained as pale-yellow microcrystals, mp 245–247°C and yield 91% (1.23 g). ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 1.01 (t, 3H, J = 7.1 Hz, H₃CCOP), 1.08 (t, 3H, J = 7.1 Hz, H₃CCOP), 3.69–3.77 (m, 1H, HC-OP), 3.84–3.88 (m, 1H, HC-OP), 3.97–4.01 (m, 2H, H₂C-OP), 5.17 (dd, 1H, J = 9.5 & 24.8 Hz, HC-P), 6.83 (d, 3H, J = 9.5 Hz, H-Ar), 7.02 (d, 1H, J = 8.6 Hz, H-Ar), 7.26 (m, 1H, NH-CP exchangeable), 7.42–7.44 (m, 2H, H-Ar), 7.49–7.51 (m, 4H, H-Ar), 7.57–7.61 (m, 1H, H-Ar), 8.01 (d, 1H, J = 4.8 Hz, H-Ar), 11.10 (s [br], 1H, NH-exchangeable); ¹³C NMR (125.7 MHz, DMSO-d₆) δ (ppm): 152.8, 151.2, 151.1, 139.4, 136.3, 131.5, 130.9, 128.8, 128.4, 121.4, 117.2, 112.9, 112.8 (C-Ar), 63.25, 63.20, 63.0, 62.9 (2OCH₂), 53.3 (d, ¹J_{PC} = 152.2 Hz, C-P), 16.77, 16.74, 16.6, 16.5 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO-d₆) δ (ppm): 21; IR (KBr): 3279 (NH), 1337 (SO₂, asy), 1231 (P=O), 1152 (SO₂, sym), 1018 (2P-O-C) cm⁻¹; Anal. calcd. for C₂₂H₂₅BrN₃O₅PS (544.40): C, 47.66; H, 4.55; N, 7.58. Found: C, 47.75; H, 4.69; N, 7.67.

Diethyl ((4-cyanophenyl)((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino)methyl) phosphonate (3j) was obtained as pale-yellow microcrystals, mp 240–242°C and yield 88% (1.1 g). ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 1.01 (t, 3H, J = 7.2 Hz, H₃CCOP), 1.09 (t, 3H, J = 7.1 Hz, H₃CCOP), 3.73–3.78 (m, 1H, HC-OP), 3.86–3.91 (m, 1H, HC-OP), 3.96–4.01 (m, 2H, H₂C-OP), 5.34 (dd, 1H, J = 9.5 & 25.75 Hz, HC-P), 6.83 (d, 3H, J = 8.5 Hz, H-Ar), 7.02 (d, 1H, J = 8.6 Hz, H-Ar), 7.31 (m, 1H, NH-CP exchangeable), 7.50 (d, 2H, J = 8.6 Hz, H-Ar), 7.57–7.61 (m, 1H, H-Ar), 7.67 (d, 2H, J = 8.6 Hz, H-Ar), 7.78 (d, 2H, J = 8.6 Hz, H-Ar), 8.00 (d, 1H, J = 3.8 Hz, H-Ar), 11.08 (s [br], 1H, NH-exchangeable); ¹³C NMR (125.7 MHz, DMSO-d₆) δ (ppm): 152.8, 151.1, 151.0, 142.8, 139.4, 132.5, 129.6, 128.8, 119.2, 117.2, 113.0, 112.9, 110.9 (C-Ar), 63.4, 63.3, 63.1, 63.07 (2POCH₂), 53.8 (d, ¹J_{PC} = 151 Hz, C-P), 16.74, 16.71, 16.56, 16.53 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO-d₆) δ (ppm): 20.7; IR (KBr): 3276 (NH), 2227 (CN), 1337 (SO₂, asy), 1232 (P=O), 1154 (SO₂, sym), 1025 (2P-O-C) cm⁻¹;

Anal. calcd. for C₂₃H₂₅N₄O₅PS (500.51): C, 55.19; H, 5.03; N, 11.19.
Found: C, 55.25; H, 5.09; N, 11.26.

Diethyl (4-nitrophenyl)((4-(N-(pyridin-2-yl)sulfamoyl)phenylamino)methyl)phosphonate (3k) was obtained as pale-green microcrystals, mp 245–247°C and yield 80% (1.04 g). ¹H NMR (500 MHz, DMSO- d₆) δ (ppm): 1.03 (t, 3H, J = 7.1 Hz, H₃CCOP), 1.09 (t, 3H, J = 7.1 Hz, H₃CCOP), 3.75–3.80 (m, 1H, HC-OP), 3.88–3.93 (m, 1H, HC-OP), 3.98–4.05 (m, 2H, H₂C-OP), 5.44 (dd, 1H, J = 9.5 & 25.7 Hz, HC-P), 6.80–6.86 (m, 3H, H-Ar), 7.01 (d, 1H, J = 7.6 Hz, H-Ar), 7.41–7.44 (m, 1H, NH-CP exchangeable), 7.50 (d, 2H, J = 9.5 Hz, H-Ar), 7.59 (t, 1H, J = 6.7 Hz, H-Ar), 7.74 (d, 2H, J = 6.6 Hz, H-Ar), 8.00 (d, 1H, J = 3.8 Hz, H-Ar), 8.18 (d, 2H, J = 8.6 Hz, H-Ar), 11.15 (s [br], 1H, NH-CP); ¹³C NMR (125.7 MHz, DMSO- d₆) δ (ppm): 152.9, 151.0, 150.9, 147.5, 146.3, 145.0, 139.5, 129.9, 128.8, 128.7, 123.7, 117.3, 117.2, 112.9 (C-Ar), 63.5, 63.4, 63.2, 63.1 (2OCH₂), 53.6 (d, ¹J_{PC} = 151 Hz, C-P), 16.76, 16.73, 16.59, 16.55 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO- d₆) δ (ppm): 20.6; IR (KBr): 3414, 3271 (NH), 1335 (SO₂, asy), 1234 (P=O), 1152 (SO₂, sym), 1009 (2P-O-C) cm⁻¹; Anal. calcd. for C₂₂H₂₅N₄O₇PS (520.50): C, 50.77; H, 4.84; N, 10.76. Found: C, 50.84; H, 4.91; N, 10.89.

Diethyl ((2,5-dimethoxyphenyl)((4-(N-(pyridin-2-yl)sulfamoyl)phenylamino)methyl)phosphonate (3l) was obtained as pale-yellow microcrystals, mp 244–246°C and yield 86% (1.15 g). ¹H NMR (500 MHz, DMSO- d₆) δ (ppm): 0.95 (t, 3H, J = 7.1 Hz, H₃CCOP), 1.10 (t, 3H, J = 7.1 Hz, H₃CCOP), 3.61–3.65 (m, 4H, HC-OP + OCH₃), 3.79–3.83 (m, 4H, HC-OP + OCH₃), 3.97–4.01 (m, 2H, H₂C-OP), 5.20 (dd, 1H, J = 9.5 & 23.8 Hz, HC-P), 6.69 (d, 2H, J = 8.5 Hz, H-Ar), 6.77–6.83 (m, 2H, H-Ar), 6.91 (d, 1H, J = 8.5 Hz, H-Ar), 7.01 (d, 1H, J = 8.6 Hz, H-Ar), 7.06 (s, 1H, H-Ar), 7.20–7.23 (m, 1H, NH-CP-exchangeable), 7.52 (d, 2H, J = 8.5 Hz, H-Ar), 7.52 (t, 1H, J = 7.6 Hz, H-Ar), 8.01 (d, 1H, J = 4.8 Hz, H-Ar), 11.10 (sbr, 1H, NH-exchangeable); ¹³C NMR (125.7 MHz, DMSO- d₆) δ (ppm): 153.7, 152.9, 151.4, 151.2, 151.1, 146.3, 139.4, 129.0, 128.4, 125.7, 117.3, 115.4, 113.9, 113.0, 112.5, 112.3, (C-Ar), 63.0, 62.9 (2POCH₂), 56.9, 55.9 (2OCH₃), 47.0 (d, ¹J_{PC} = 155.8 Hz, C-P), 16.78, 16.74, 16.5, 16.4 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO- d₆) δ (ppm): 21.7; IR (KBr): 3437, 3288 (2NH), 1388 (SO₂, asy), 1227 (P=O), 1139 (SO₂, sym), 1017 (P-O-C) cm⁻¹; Anal. calcd. for C₂₄H₃₀N₃O₇PS (535.55): C, 53.83; H, 5.65; N, 7.85. Found: C, 53.90; H, 5.76; N, 7.93.

Diethyl ((4-hydroxy-3-methoxyphenyl)((4-(N-(pyridin-2-yl)sulfamoyl)phenyl) amino) methyl)phosphonate (3m) was obtained as pale-yellow microcrystals, mp 242–244°C and yield 85% (1.10 g). ¹H NMR (500 MHz, DMSO- d₆) δ (ppm): 0.99 (t, 3H, H₃CCOP), 1.07 (t, 3H, H₃CCOP), 3.63–3.69 (m, 4H, HC-OP + OCH₃), 3.79–3.84 (m, 1H, HC-OP), 3.92–3.97 (m, 2H, H₂C-OP), 4.93 (dd, 1H, J = 9.5 & 22.8 Hz, HC-P), 6.65 (d, 1H, J = 7.6 Hz, H-Ar), 6.81–6.87 (m, 4H, H-Ar), 7.01 (d, 1H, J = 8.6 Hz, H-Ar), 7.07 (s, 1H, H-Ar), 7.10 (s [br], 1H, NH-CP exchangeable), 7.48 (d, 2H, J = 8.5 Hz, H-Ar), 7.59 (t, 1H, J = 7.6 Hz, H-Ar), 8.01 (d, 1H, J = 4.8 Hz, H-Ar), 8.93 (s, 1H, OH exchangeable), 10.9 (s [br], 1H, NH exchangeable); ¹³C NMR (125.7 MHz, DMSO- d₆) δ (ppm): 152.8, 151.5, 151.4, 147.8, 146.6, 139.3, 128.8, 127.9, 127.1, 121.5, 121.4, 117.4, 115.6, 113.3, 112.9, 112.7 (C-Ar), 62.86, 62.81 (2OCH₂), 56.27 (OCH₃), 53.6 (d, ¹J_{PC} = 152.6 Hz, C-P), 16.79, 16.75, 16.6, 16.5 (2OC-CH₃); ³¹P

NMR (121 MHz, DMSO- d₆) δ (ppm): 21.7; IR (KBr): 3267 (NH), 2935 (OH, intra), 1392 (SO₂, asy), 1249 (P=O), 1136 (SO₂, sym), 1032 (2P-O-C) cm⁻¹; Anal. calcd. for C₂₃H₂₈N₃O₇PS (521.52): C, 52.97; H, 5.41; N, 8.06. Found: C, 53.08; H, 5.50; N, 8.12.

Diethyl (naphthalen-1-yl)((4-(N-(pyridin-2-yl)sulfamoyl)phenyl) amino)methyl) phosphonate (3n) was obtained as pale-yellow microcrystals, mp 227–230°C and yield 85% (1.10 g). ¹H NMR (500 MHz, DMSO- d₆) δ (ppm): 0.70 (t, 3H, J = 7.1 Hz, H₃CCOP), 1.10 (t, 3H, J = 6.6 Hz, H₃CCOP), 3.36–3.41 (m, 1H, HC-OP), 3.69–3.72 (m, 1H, HC-OP), 3.97–4.03 (m, 2H, H₂C-OP), 5.81 (dd, 1H, J = 8.5 & 23.8 Hz, HC-P), 6.78–6.82 (m, 3H, H-Ar), 6.99 (d, 1H, J = 8.6 Hz, H-Ar), 7.43–7.58 (m, 7H, H-Ar +NH-exchangeable), 7.76 (d, 1H, J = 4.7 Hz, H-Ar), 7.82 (d, 1H, J = 8.5 Hz, H-Ar), 7.90 (d, 1H, J = 8.5 Hz, H-Ar), 7.98 (d, 1H, J = 3.8 Hz, H-Ar), 8.41 (d, 1H, J = 8.6 Hz, H-Ar), 11.05 (s [br], 1H, NH-exchangeable); ¹³C NMR (125.7 MHz, DMSO- d₆) δ (ppm): 152.8, 151.2, 151.1, 139.4, 133.7, 132.8, 131.7, 129.1, 128.8, 128.3, 126.7, 126.5, 126.2, 125.7, 124.3, 117.1, 112.9, 112.7 (C-Ar), 63.2, 63.1, 62.9, 62.8 (2OCH₂), 50.3 (d, ¹J_{PC} = 155.8 Hz, C-P), 16.8, 16.7, 16.27, 16.23 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO- d₆)

δ (ppm): 22; IR (KBr): 3473, 3270 (NH), 1392 (SO₂, asy), 1293 (P=O), 1139 (SO₂, sym), 1015 (P-O-C) cm⁻¹; Anal. calcd. for C₂₆H₂₈N₃O₅PS (525.56): C, 59.42; H, 5.37; N, 8.00. Found: C, 59.50; H, 5.46; N, 8.14.

Diethyl (((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino)(thiophen-2-yl)methyl)phosphonate (3o) was obtained as pale-yellow microcrystals, mp 219–220°C and yield 81% (0.97 g). ¹H NMR (500 MHz, DMSO- d₆) δ (ppm): 1.06 (m, 6H, 2H₃CCOP), 3.79–3.83 (m, 1H, HC-OP), 3.97–4.01 (m, 3H, H₂C-OP + HC-OP), 5.20 (dd, 1H, J = 9.5 & 23.8 Hz, HC-P), 6.84 (t, 1H, H-Ar), 6.89 (t, 2H, J = 9.5 Hz, H-Ar), 6.94 (t, 1H, J = 4.7 Hz, H-Ar), 7.01 (d, 1H, J = 8.5 Hz, H-Ar), 7.12 (s[br], 1H, NH-CP-exchangeable), 7.17 (s, 1H, H-Ar), 7.39 (d, 1H, J = 4.7 Hz, H-Ar), 7.51 (d, 2H, J = 8.5 Hz, H-Ar), 7.57–7.60 (m, 1H, H-Ar), 8.02 (d, 1H, H-Ar), 11.09 (sbr, 1H, NH-exchangeable); ¹³C NMR (125.7 MHz, DMSO- d₆) δ (ppm): 152.7, 151.2, 151.1, 139.6, 139.4, 128.8, 127.4, 127.2, 126.3, 112.8, (C-Ar), 63.3, 63.2, 63.1, 63.0 (2POCH₂), 49.9 (d, ¹J_{PC} = 158.3 Hz, C-P), 16.76, 16.73, 16.6, 16.5 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO- d₆) δ (ppm): 21.7; IR (KBr): 3270 (NH), 1331 (SO₂, asy), 1225 (P=O), 1139 (SO₂, sym), 1005 (2P-O-C) cm⁻¹; Anal. calcd. for C₂₀H₂₄N₃O₅PS₂ (481.52): C, 49.89; H, 5.02; N, 8.73. Found: C, 49.95; H, 5.15; N, 8.80.

Diethyl ((3-ferrocenyl)((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino) methyl)phosphonate (3p) was obtained as pale-yellow microcrystals, mp 254–258°C and yield 78% (0.89 g). ¹H NMR (500 MHz, DMSO- d₆) δ (ppm): 0.90 (t, 3H, J = 7.1 Hz, H₃CCOP), 1.01 (t, 3H, J = 7.1 Hz, H₃CCOP), 3.73–3.76 (m, 2H, HC-OP + CH-ferrocenyl), 3.79–3.84 (m, 2H, HC-OP + CH-ferrocenyl), 3.87–3.90 (m, 5H, H₂C-OP + 3CH-ferrocenyl), 4.11 (d, 2H, J = 8.6 Hz, 1CH-ferrocenyl), 4.31 (s, 1H, CH-ferrocenyl), 4.46 (s, 1H, CH-ferrocenyl), 4.80 (dd, 1H, J = 10 & 17.8 Hz, HC-P), 6.78–6.86 (m, 2H, H-Ar), 6.96 (d, 2H, J = 8.6 Hz, H-Ar), 7.03 (d, 1H, J = 8.5 Hz, H-Ar), 7.54–7.61 (m, 3H, 2H-Ar + NH), 7.98 (d, 1H, J = 4.7 Hz, H-Ar), 11.09 (s [br], 1H, NH); ¹³C NMR (125.7 MHz, DMSO- d₆) δ (ppm): 152.8, 151.8, 139.2, 129.2, 117.5, 112.9, 112.0 (C-Ar), 85.7, 85.6, 69.4, 68.9, 68.0, 67.6, 66.9 (C-ferrocenyl), 62.78, 62.72, 62.57, 62.51 (2OCH₂), 50.0 (d, ¹J_{PC} = 155.8 Hz, C-P), 16.7, 16.6 (2OC-CH₃); ³¹P NMR (121 MHz, DMSO- d₆) δ

(ppm) 21.03: IR (KBr): 3297 (NH), 1329 (SO₂, asy), 1237 (P = O), 1150 (SO₂, sym), 1010 (P-O-C) cm⁻¹.

4-((4-(dimethylamino)benzylidene)amino)-N-(pyridin-2-yl) benzenesulfonamide (4) was obtained as yellow microcrystals, mp 242–244°C and yield 74% (0.7 g). ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.97 (s, 6H, (H₃C)₂N), 6.74 (d, 2H, J = 6.7 Hz, H-Ar), 6.84 (s, 1H, H-Ar), 7.13 (d, 1H, J = 8.6 Hz, H-Ar), 7.23 (d, 2H, J = 6.6 Hz, H-Ar), 7.65–7.71 (m, 3H, H-Ar), 7.82 (d, 2H, J = 6.6 Hz, H-Ar), 7.99 (s, 1H, H-Ar), 8.35 (s, 1H, CH=N), 11.77 (s [br], 1H, HN); ¹³C NMR (125.7 MHz, DMSO): δ = 162.3 (CH=N), 156.2, 153.6, 153.3, 140.5, 138.1, 131.2, 128.4, 123.8, 121.6, 116.3, 114.1, 111.9, (C-Ar), 40.2 ((CH₃)₂N); Anal. calcd. for C₂₀H₂₀N₄O₂S (380.47): C, 63.14; H, 5.30; N, 14.73. Found: C, 63.35; H, 5.53; N, 14.91.

2.2 | CA inhibition

All the details are described in the Supporting Information file.

2.3 | Molecular docking

Molecular Operating Environment software (MOE 2022.02.) was used for the Molecular docking. All the details of the docking protocol are fully described in the Supporting Information file.

2.4 | X-ray diffraction and biological studies

All the details are described in the Supporting Information file.

3 | RESULTS AND DISCUSSION 3.1 |

Chemistry

The one-pot three-component reaction comprising sulfapyridine (1), benzaldehyde (2a), and DEP was selected as a model example to identify the ideal reaction conditions. The reaction was studied using various types of metal trifluoromethanesulfonates M(OTf)_n as catalysts (Table 1). The isolated yields of sulfonamide-phosphonates (3a) is reported each time. It was found that using Bi(OTf)₃ is the optimum catalysis reaction conditions (entry 6) (Scheme 1).

After determining the optimal reaction conditions, the condensation reaction of sulfapyridine (1), DEP, and various substituted benzaldehydes 2b–2m, possessing electron-donating or electron-withdrawing groups, was carried out. The desired sulfonamide-phosphonate derivatives 3b–3m were obtained in good to excellent yields (78%–91%) yields, as shown in Scheme 2.

Chemical structures of the sulfonamide-phosphonate derivatives (3) were elucidated from their spectroscopic data. The ¹³C-NMR spectrum of 3a–3m shows the chiral carbon atom (N-CH-P) as doublet at δ_c ≈ 52–53 ppm, with a coupling constant of ¹J_{PC}.

C ≈ 152–155 Hz. Compound 3f, as an example, exhibit the two CH₃[−] phosphonate groups (H₃C-CH₂OP) as two triplets at 0.99 and 1.08 ppm, while the two CH₂[−] phosphonate groups behave differently where one CH₂ group appeared as a multiplet at δ = 3.92–3.99 (2H, H₂C-OP), while the other CH₂ group appears as two multiples due to their distinct environments, at 3.67–3.72 (m, 1H, HC-OP) and 3.82–3.87 (m, 1H, HC-OP) ppm. The P-C-H proton appeared as a dd at δ = 5.17 ppm (J_{H-H} = 9.5 and 23.8 Hz). Furthermore, 2D NMR techniques (¹H-¹H Cosy and HSQC) revealed a correlation between the neighboring OCH₂-phosphonate groups, providing additional evidence for the structural confirmation of the synthesized agents (Supporting Information S1: Figures 25 and 26). ¹³C-NMR showed a signal at 53.2 ppm as doublet with ¹J_{PC} = 152.2 Hz due to the direct attached carbon to phosphorus atom (C-P). ³¹P-NMR showed a signal at 21.7 ppm due to the phosphonate-phosphorus atom. The structure of 3a, 3d, and 3i were confirmed by single crystal diffraction studies (Figures 3–5).

Different aldehydes rather than substituted benzaldehyde such as 1-naphthaldehyde, thiophene-2-carbaldehyde, and ferrocenecarboxaldehyde were used to expand the applicability of Bi(OTf)₃ to afford the expected sulfonamide-phosphonates 3n–3p (Scheme 3).

It is worth mentioning that, when 4-dimethylaminobenzaldehyde was used, the correspond Schiff-base 4 instead of the expected α-aminophosphonate was formed, that may be due to the formation of insoluble Schiff-base adduct in the reaction medium prevent its further reaction with diethyl phosphate under the applied reaction conditions (Scheme 4). The chemical identities of the Schiff-base 4 were confirmed by its spectroscopic data. In ¹H-NMR spectra, it displayed a single peak at δ_H = 8.35 ppm due to imine proton, whereas the presence of the imine carbon was confirmed by the signal at δ_c = 162.3 ppm in ¹³C-NMR spectra.

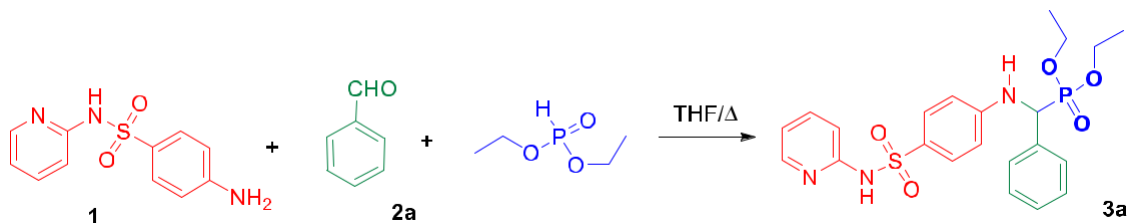
3.2 | Crystal structures

The crystal structure of 3a is monoclinic, P2₁/c (Supporting Information S2: Table 1) and the molecule is shown in Figure 3. It

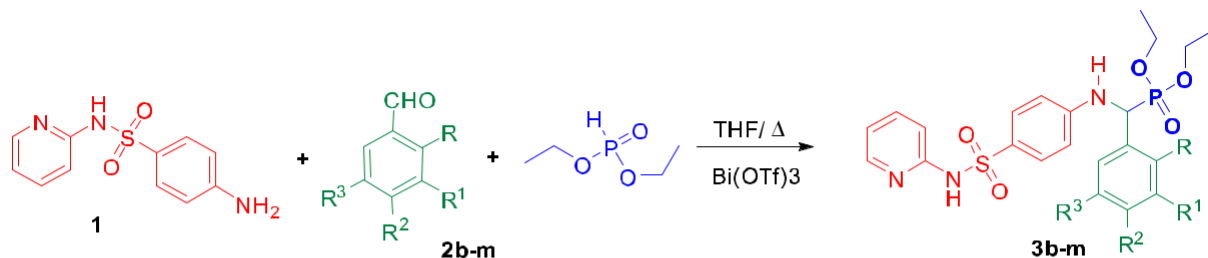
TABLE 1 Synthesis of diethyl (phenyl((4-(N-(pyridin-2-yl)sulfamoyl)phenyl)amino)methyl) phosphonate (3a) under different catalytic reaction conditions.

Entry	Catalyst	Reaction conditions	Time ^a	Isolated yield
1	AgOTf	r.t.	Overnight	-----
2	AgOTf	Reflux	4.5 h	30%
3	Cu(OTf) ₂	Reflux	3 h	40%
4	Mg(OTf) ₂	Reflux	5 h	70%
5	Fe(OTf) ₂	Reflux	8 h	76%
6	Bi(OTf) ₃	Reflux	1.5 h	88%

^aTime required for the precipitation of the product on hot.



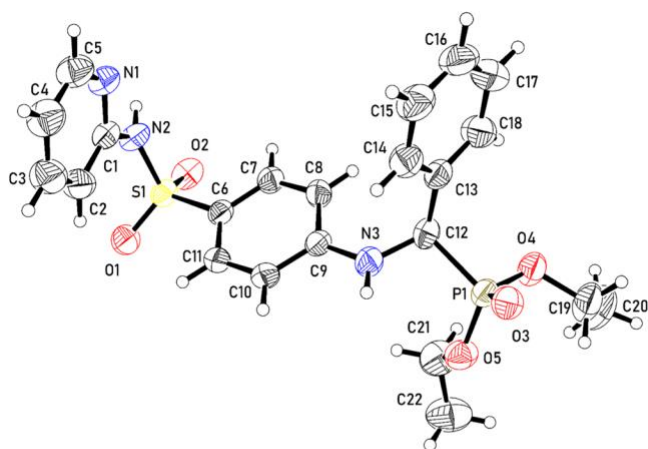
S C H E M E 1 Synthesis of sulfonamide-phosphonate 3a.



2, 3b; $R^2 = \text{Me}$, $R = R^1 = R^3 = \text{H}$
 2, 3c; $R^2 = \text{OMe}$, $R = R^1 = R^3 = \text{H}$
 2, 3d; $R^1 = \text{OMe}$, $R = R^2 = R^3 = \text{H}$
 2, 3e; $R^2 = \text{OH}$, $R = R^1 = R^3 = \text{H}$
 2, 3f; $R^2 = \text{F}$, $R = R^1 = R^3 = \text{H}$
 2, 3g; $R^2 = \text{Cl}$, $R = R^1 = R^3 = \text{H}$

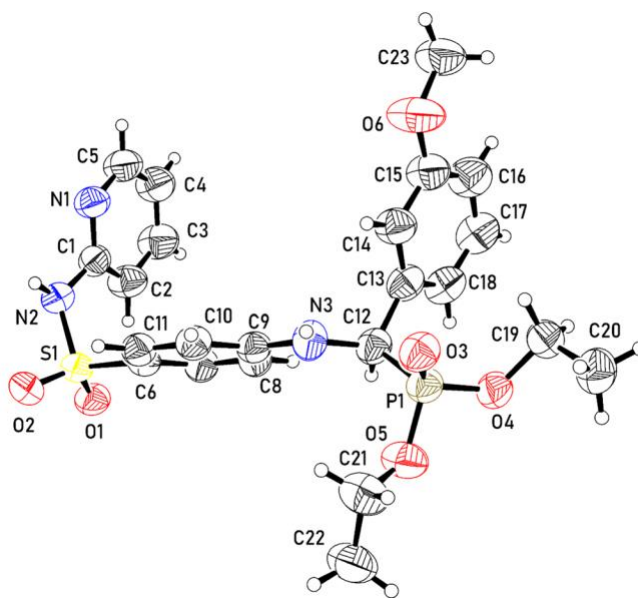
2, 3h; $R = \text{Cl}$, $R^1 = R^2 = R^3 = \text{H}$
 2, 3i; $R^2 = \text{Br}$, $R = R^1 = R^3 = \text{H}$
 2, 3j; $R^2 = \text{CN}$, $R = R^1 = R^3 = \text{H}$
 2, 3k; $R^2 = \text{NO}_2$, $R = R^1 = R^3 = \text{H}$
 2, 3l; $R, R^3 = \text{OMe}$, $R^1 = R^2 = \text{H}$
 2, 3m; $R^2 = \text{OH}$, $R^1 = \text{OMe}$, $R = R^3 = \text{H}$

S C H E M E 2 Synthesis of the sulfonamide-phosphonates 3b–3m.



F I G U R E 3 Ortep representation of a molecule of 3a showing the major component of the disorder with 50% probability atomic displacement ellipsoids.

consists of pyridinamine (A, C1–C5, N1, N2), aniline, (B, C6–C11, N3), and phenyl (C, C13–C18) moieties as well as sulfonyl (O1, O2, S2) and diethylphosphonate (C19–C22, O3–O5, P1) groups. The planes of the pyridinamine and phenyl rings are twisted from that of the aniline group by angles in the 80–90° range (Table 2). For the diethylphosphonate group, torsion angles C20–C19–O4–P1 and C22–C21–O5–P1 are 134.9(8)° and 150.0(5)°, respectively for the major disorder component.



F I G U R E 4 Ortep representation of the molecule of the major disorder component of 3d showing 50% probability atomic displacement ellipsoids.

In the crystal of 3a, pairs of N–H...O hydrogen bonding interactions between aniline and sulfonyl groups of neighboring molecules (Table 2) to form $R_2^2(10)$ rings in graph set notation. In addition, pairs of pyridinamine groups are involved in N–H...N

interactions to form $R_2^2(8)$ rings. Contacts of $\pi\cdots\pi$ type with centroid...centroid separation of 4.14 Å as well as edge-to-face interactions with H...centroid distance of 3.48 Å are also observed.

The crystal structure of 3d is monoclinic, $P2_1/n$ (Supporting Information S2: Table 1). The molecule of 3d (Figure 4) consists of pyridinamine (A, C1–C5, N1, N2), aniline (B, C6–C11, N3), and methoxybenzene (C, C13–C18, C23, O6) moieties as well as sulfonyl (O1, O2, S2) and diethylphosphonate (C19–C22, O3–O5, P1) groups. In the molecule, the planes of the pyridinamine and phenyl rings are twisted from the plane of the aniline group by about 70–75° (Table 2). Torsion angles C20–C19–O4–P1 and C22–C21–O5–P1 in the diethylphosphonate group are 102.6(6)° and 175.1(8)°, respectively for the major disorder component. Identical to the crystal structure of 3a, pairs of N–H...O hydrogen bonds between aniline and sulfonyl groups of neighboring molecules in 3d form $R_2^2(10)$ rings (Table 2). Pairs of pyridinamine groups are also involved in N–H...N contacts to form $R_2^2(8)$ rings.

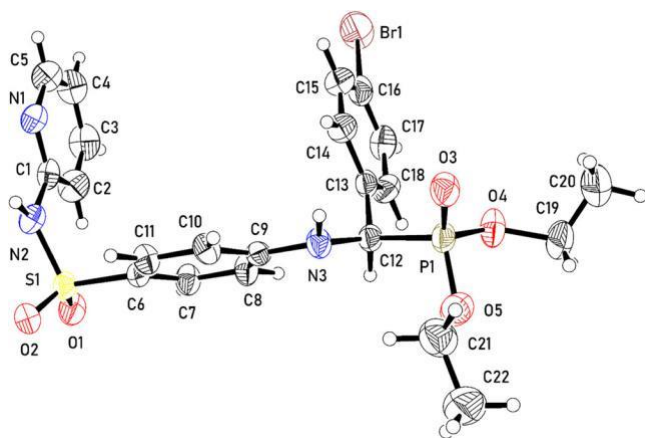


FIGURE 5 Ortep representation of the molecule of 3i showing 50% probability atomic displacement ellipsoids for the major disorder component.

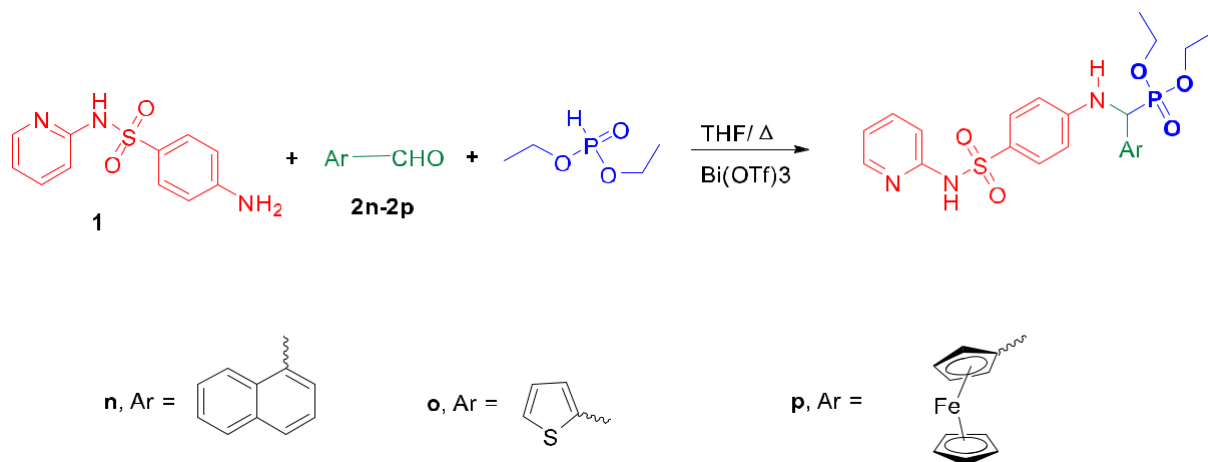
The crystal structure of 3i is triclinic, $P\bar{1}$ (Supporting Information S2: Table 1). The molecule of 3i consists of pyridinamine (A, C1–C5, N1, N2), aniline (B, C6–C11, N3), and bromobenzene (C, C13–C18) groups in addition to sulfonyl (O1, O2, S2) and diethylphosphonate (C19–C22, O3–O5, P1) groups (Figure 5). The planes of the pyridinamine and phenyl rings are twisted from the plane through the aniline group by about 80–85° in the molecule (Table 2). For the diethylphosphonate group, torsion angles C20–C19–O4–P1 and C22–C21–O5–P1 are 105.9(8)° and 173.0(3)°, respectively for the major disorder component. In a similar manner to the crystal structures of 3a and 3d, pairs of N–H...O bonds between aniline and sulfonyl groups in the structure of 3i form $R_2^2(10)$ rings (Table 2). $R_2^2(8)$ rings are also formed between pyridinamine groups through N–H...N interactions. The aniline rings are involved in $\pi\cdots\pi$ interactions with centroid...centroid separation of 4.23 Å.

3.3 | CA inhibition

The inhibitory activity of compounds 3a–3p was assessed against cytosolic hCA I and II, as well as membrane-bound hCA IX and XII isoforms. The evaluation was conducted using a stopped flow carbon dioxide hydration assay, with AAZ as the reference compound (Khalifah & Edsall, 1972). The results of the inhibitory activity of these compounds are summarized in Table 3.

3.4 | Structure–activity relationship study

The biological evaluation of the synthesized compounds revealed that they exhibit higher potency in inhibiting hCA XII compared to hCA I, II, and IX isoforms. Most of the compounds displayed weak inhibition against the ubiquitous hCA I, with inhibition constants (K_i s) ranging from 641.5 to more than 100,000 nM. However, compound 3p, which contains the ferrocenyl moiety, exhibited moderate inhibition of hCA I with a K_i constant of 38.1 nM.



SCHEME 3 Synthesis of the sulfonamide-phosphonates 3n–3p.

SCHEME 4 Formation of the unexpected Schiff-base 4.

TABLE 2 Selected molecular and crystal geometry.

Twist angles (°)		A/B	B/C
3a		83.25 (6)	87.68 (6)
3d		75.54 (10)	70.14 (10)
3i		85.42 (10)	83.59 (9)
Hydrogen bond geometry		D...A (Å)	D-H...A (°)
3a	N(2)-H(2A)...N(1) ^{#1}	2.923 (3)	149.2
	N(3)-H(3A)...O(3) ^{#2}	2.860 (6)	166.5
	N(3)-H(3A)...O(3A) ^{#2}	2.920 (7)	160.2
3d	N(2)-H(2A)...N(1) ^{#3}	2.970 (4)	172 (4)
	N(3)-H(3A)...O(3) ^{#4}	2.994 (4)	138.1
3i	N(2)-H(2A)...N(1) ^{#5}	2.984 (4)	172 (4)
	N(3)-H(3A)...O(3) ^{#6}	2.959 (4)	167 (3)

Note: #1 -x + 2, -y + 2, -z + 1, #2 -x + 1, -y + 2, -z, #3 -x, -y, -z + 1, #4 -x + 1, -y + 1, -z + 1, #5 -x, -y + 1, -z + 2, #6 -x + 1, -y + 1, -z + 1.

The other ubiquitous and physiologically relevant isoform, hCA II, is moderately inhibited by most of the studied compounds (K_i 58.3–783.6 nM), except for compounds 3h, 3k which showed weak inhibition with $K_i > 100,000$ and compound 3l with K_i 7121 nM. Compounds 3e and 3j, bearing p-hydroxyphenyl and p-cyanophenyl groups, showed the highest potency against hCA II with K_i 60 and 58.3 nM, respectively.

Against hCA IX, most of the compounds showed weak inhibition with K_i ranging from 163.3 to more than 100,000 nM. while against hCA XII, K_i reaches one-digit nanomolar values with compound 3p bearing the ferrocenyl moiety ($K_i = 5.1$ nM), which acts as the most potent hCA inhibitor in this study as compared to AAZ ($K_i = 5.7$ nM). Compound 3l bearing 2,5-dimethoxyphenylgroup showed good potency against hCA XII with a K_i 10.5 nM. In particular, most of the synthesized compounds showed the highest potency against hCA XII with K_i ranging from 5.1 to 51.1 nM. Five compounds (3d, e, m, n, & o) showed very weak hCA XII inhibition with K_i more than 100,000 nM. The unsubstituted derivative 3a shows the worst hCA XII inhibition though remaining very potent inhibitor (K_i 51.1 nM).

TABLE 3 The inhibition constants K_i (nM) for human CA isoforms I, II, IX, and XII in response to 3a, 3b, 3d–3f, 3h–3p, and AAZ by a stopped flow CO_2 hydrase assay.

Compound	Inhibition constants K_i (nM) ^a			
	hCA I	hCA II	hCA IX	hCA XII
3a	8328.5	181	163.2	51.1
3b	4643	445.4	>100,000	34.6
3d	>100,000	77.1	>100,000	>100,000
3e	>100,000	60	1784.3	>100,000
3f	898.7	783.6	>100,000	25.5
3h	>100,000	>100,000	>100,000	20
3i	7192.6	188.6	>100,000	28
3j	>100,000	58.3	2571.1	46
3k	>100,000	>100,000	>100,000	29.1
3l	3136.4	7121	>100,000	10.5
3m	>100,000	704.3	>100,000	>100,000
3n	>100,000	313.3	>100,000	>100,000
3o	641.5	272.4	2269	>100,000
3p	38.1	724.7	212.6	5.1
AAZ	250	12.1	25.7	5.7

Abbreviations: AAZ, acetazolamide; hCA, human carbonic anhydrase.

^aMean from three different assays, by a stopped flow technique.

Substitution with a halogen increases the potency as in compounds 3f, h, l with K_i 25.5, 20, 28 nM, respectively. Also, adding an electron withdrawing nitro group in the para position as in compound 3k had a positive effect on the potency against hCA XII with K_i 29.1 nM.

The selectivity index (SI) data reported in Table 4 show that nearly all the compounds that showed high potency against hCA XII, are selective for this tumor-associated isoform over hCA I (SI in the range 7.5 to >5000) and over hCA II (SI in the range 1.3 to >5000). In detail, the two most potent compounds 3l and 3p exhibit a I/XII selectivity >298.7 and 8.5, respectively, whereas both compounds are 678.1- and 142.1-fold II/XII selective CAIs, respectively. Interestingly, compounds with moderate but still high potency, bearing electron withdrawing groups (chloro and nitro groups), 3h

T A B L E 4 Selectivity index (SI) of compounds 3a, 3b, 3d–3f, 3h–3p, and AAZ for hCA IX and XII over hCA I and II calculated as ratio

Compound	SI (K _{I off-target CA} / K _{I target CA})			
	I/IX	II/IX	I/XII	II/XII
3a	51.0	1.1	163.0	3.5
3b	<0.05	<0.004	134.2	12.9
3d	1	<0.001	1	<0.001
3e	>56.0	0.03	1	<0.001
3f	<0.01	<0.01	35.2	30.7
3h	1	1	>5000	>5000
3i	<0.1	<0.002	256.9	6.7
3j	>38.9	0.02	2173.9	1.3
3k	1	1	>3436.4	>3436.4
3l	<0.03	<0.1	<298.7	678.2
3m	1	<0.01	1	<0.01
3n	1	<0.003	1	<0.003
3o	0.3	0.1	0.006	<0.003
3p	0.2	3.4	7.5	142.1
AAZ	51.0	1.1	163	3.5

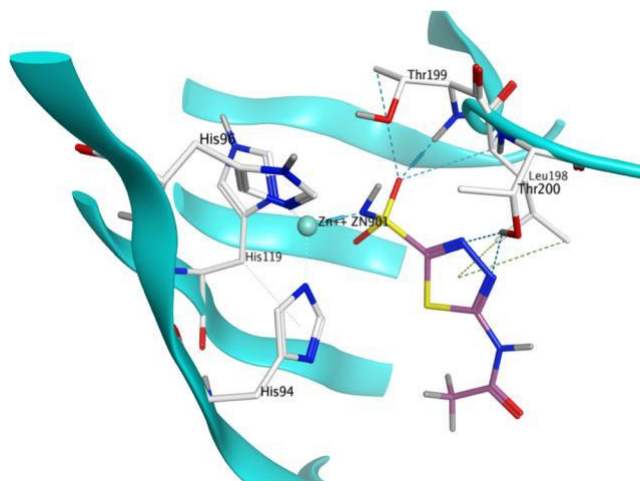
Abbreviations: AAZ, acetazolamide; hCA, human carbonic anhydrase.

and 3k, showed the highest SI >5000 and >3436.4, respectively, as they are nearly inactive against the three other isoforms, while compounds 3f and 3i bearing fluoro and bromo groups on the phenyl ring showed moderate SI (35.2 and 256.9 over hCA I—30.7 and 6.7 over hCA II). These latter six compounds could represent interesting candidates for further antitumor investigations.

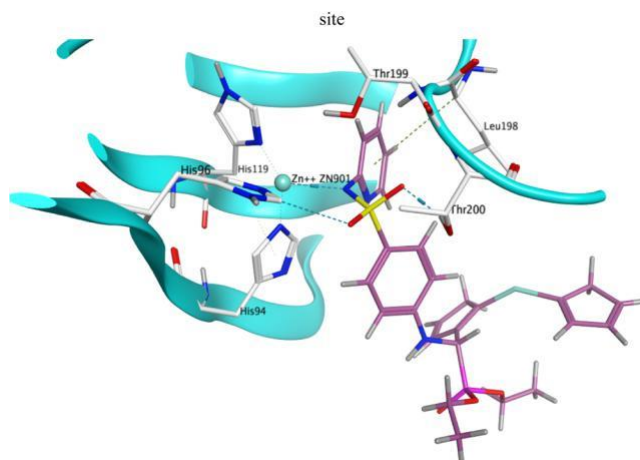
3.5 | Molecular docking study

The catalytic active site of CA is cone-shaped and divided into hydrophobic and hydrophilic subpockets, with a zinc ion located at the base. The zinc ion is coordinated by three histidine residues (His94, His96, and His119) and a solvent molecule. This zinc ion plays a crucial role in promoting bicarbonate formation by binding to a hydroxide ion and subsequently reacting with carbon dioxide. Therefore, it is important for inhibitors to contain a zinc binding group that can coordinate with the zinc ion, although non-zinc coordinating inhibitors have also been reported (Bozdog et al., 2014; Supuran, 2012, 2016).

To investigate the binding patterns of the new sulfapyridine derivatives in the binding pocket of CA XII and understand their structure–activity relationship, molecular docking was performed. The docking protocol was validated by redocking the cocrystallized ligand (AAZ) in the active site of CA II (PDB ID: 1JD0) (Whittington et al., 2001). The self-docking of AAZ reproduced the same binding



F I G U R E 6 3D representation of acetazolamide showing its interaction with the CA XII active site. CA, carbonic anhydrases.



F I G U R E 7 3D representation of compound 3p showing its interaction with the CA XII active site. CA, carbonic anhydrases.

pattern as observed in the crystal structure between the cocrystallized ligand with Zn²⁺, and Thr199 and Thr200 residues, Figure 6, indicating the reliability of the docking settings. This was also confirmed by a small RMSD of 1.0605 Å.

In the docking results of the sulfapyridine derivatives, the sulfonamide NH group coordinated with the zinc ion and formed hydrogen bond interactions with the key amino acid Thr200. Additionally, hydrophobic interactions were observed between the benzenesulfonamide phenyl ring and Leu198. Compound 3p exhibited an additional hydrogen bond interaction between the amine group of the side chain of Lys67 and the oxygen of its terminal phosphate group (Figure 7). Similarly, compound 3l interacted with the side chain amine groups of both Asn62 and Lys67 through hydrogen bonds involving the oxygen of the phosphate group - (Figure 8). These additional interactions may contribute to the potency and selectivity of these compounds toward the CA XII

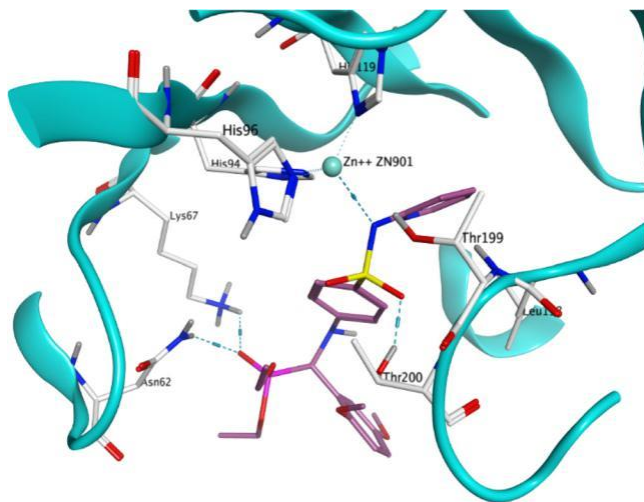


FIGURE 8 3D representation of compound 3l showing its interaction with the CA XII active. CA, carbonic anhydrases.

TABLE 5 Docking energy scores (S) in kcal/mol for the compounds 3a–3p and AAZ in CA XII active site.

Compound	Energy score (S) kcal/mol	Compound	Energy score (S) kcal/mol
3a	–11.6103	3j	–10.9052
3b	–11.7732	3k	–10.7025
3c	–11.8862	3l	–12.4314
3d	–11.2781	3m	–12.8270
3e	–12.1545	3n	–12.1330
3f	–12.2411	3o	–11.9161
3g	–11.8792	3p	–12.2550
3h	–11.0006	AAZ	–7.9858
3i	–10.4795		

Abbreviation: AAZ, acetazolamide.

isoform (for further information, see Supporting Information S2: - Figures 76–89).

The docking scores of all the compounds (3a–3p) and AAZ are presented in Table 5. The most active compounds, 3p and 3l, with K_i values of 5.1 and 10.5 nM, respectively, exhibited the most negative docking scores of –12.2550 and –12.4314 kcal/mol, respectively.

4 | CONCLUSION

In conclusion, a novel series of hybrids sulfonamide-phosphonate 3a–3p was designated and synthesized using the Kabachnik-Fields reaction. Bismuth (III) triflate was found to be the optimal catalyst applied (78%–91% yields). The chemical structures of the synthesized

agents were elucidated through spectroscopic analysis (IR, ^1H , ^{13}C , ^{31}P NMR, ^1H , ^1H -Cosy, and HSQC). X-ray diffraction studies evidenced the chemical structure of the sulfonamide-phosphonates. Evaluation of these sulfonamide-phosphonate hybrids against hCA isoforms I, II, IX, and XII revealed their pronounced inhibitory effects, particularly against hCA XII. The compounds displayed inhibitory concentrations ranging from 5.1 to 51.1 nM, with compounds 3l and 3p demonstrating the highest potency and selectivity toward CA XII.

Molecular docking studies provided insights into the binding patterns of the sulfapyridine derivatives within the CA XII binding pocket. The sulfonamide NH moiety coordinated with the Zn^{2+} ion, and hydrogen bond interactions were observed with Thr200. Hydrophobic interactions between the benzenesulfonamide phenyl ring and Leu198 were also identified. Moreover, compounds 3p and 3l exhibited additional hydrogen bonding interactions with other amino acids, which likely contribute to their enhanced potency and selectivity toward CA XII. Overall, this study presents a promising series of sulfonamide-phosphonate hybrids as potential inhibitors of hCA XII, with implications for the development of targeted therapies for relevant diseases. Further exploration of the structure–activity relationship and optimization of these agents may lead to the development of more potent and selective inhibitors with therapeutic applications.

CONFLICT OF INTEREST STATEMENT The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the Supporting Information Material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.