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Schiff bases and their amines: Synthesis and discovery of carbonic anhydrase and acetylcholinesterase enzymes inhibitors

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Abstract

Three series of symmetrical Schiff bases were synthesized from 1,2-diaminoethane, 1,3-diaminopropane and 1,4-diaminobutane and substituted benzaldehydes, and reduced by sodium borohydride to the corresponding benzylic diamines **4–6**. All of the compounds obtained were characterized using elemental analysis, FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The enzyme inhibitory properties of these compounds were tested and the influence of the alkane chain length and the substituents on the phenyl group on the enzyme inhibition activity were examined. The novel Schiff bases and their amine derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**) were effective inhibitors of the cytosolic carbonic anhydrase I and II isoforms (hCA I and II), and acetylcholinesterase (AChE) with K_i values in the range of 159.43 ± 30.03 to 563.73 ± 115.30 nM for hCA I, 104.88 ± 18.44 to 524.32 ± 95.03 nM for hCA II, and 3.95 ± 0.74 to 30.83 ± 6.81 nM for AChE.

KEYWORDS
1,2-diaminoethane, 1,3-diaminopropane, acetylcholinesterase, carbonic anhydrase, enzyme inhibition, Schiff bases

1 | INTRODUCTION

Schiff bases are known as imines or azomethines compounds containing carbon–nitrogen double bond.[1] They are prepared by the condensation between primary amine and active carbonyl compounds.[2] Schiff bases are an important class which are widely used and investigated organic compounds due to their unique properties and numerous applications in many fields including analytical, biological, and inorganic chemistry.[3–9] Schiff bases form stable complexes with most of transition metals owing to their strong coordinative ability. The catalytic and biological properties of Schiff bases and their metal complexes have been extensively studied.[10–15] They have been shown to exhibit a broad range of biological activities such as antibacterial, antifungal, antimalarial, anti-inflammatory, and antiviral activities.[16–24] Schiff bases are also used in synthesis of amines. The reduction of Schiff bases using borohydride reagents or transition metal hydrogenation catalysts is the most efficient and convenient method for the synthesis of substituted amines which are extremely important pharmacophores in numerous biologically active compounds.[25]

Human carbonic anhydrase (hCA) enzymes include a class of sixteen isoenzymes which their action is to catalyze the reversible hydration of carbon dioxide (CO_2), which generates a proton (H^+) and bicarbonate anion (HCO_3^-).[26–30] This simple biological act is central to regulating pH mechanism in the extra- and intracellular space in disparate organs and tissues. CAs are metalloenzymes available in all three of life's phylogenetic domains (Eukarya, Archaea, and Bacteria) and different isoenzymes present in most organisms evaluated so

far.[31,32] CA inhibitors (CAIs) utilized in the clinical agents are essentially diuretics and factors for glaucoma-relevant intraocular hypertension, as showed by the drugs in Figure 1.[33–35] CAIs are clinically used for decades for the treatment of diverse diseases such as epilepsy, intracranial hypertension, obesity, glaucoma, and as diuretics. Recently, they started to be utilized for the therapy of hypoxic tumors, being also evaluated as important drugs for arthritis, cerebral ischemia, and neuropathic pain.[36,37]

Agglomeration of β-amyloid, the cholinergic system malfunctioning and biometal dyshomeostasis are significant hypothetical determinants that give rise to Alzheimer's disease (AD).[38–40] Scientists have been working on Tau-hypothesis, cholinergic hypothesis, amyloid cascade hypothesis, etc. Hence, most marketed drugs (Figure 2)[41] are based on cholinergic hypothesis that tries to decrease acetylcholine (ACh) levels in pre-synaptic regions.[42,43] Acetylcholinesterase inhibitors (AChEIs) are used for the symptomatic therapy of mild-to-moderate AD. These compounds inhibit AChE, an enzyme answerable for the breakdown of ACh, a neurotransmitter associated with memory function.[44]

In this study, three series of symmetrical Schiff bases **1–3** were prepared using 1,2-diaminoethane, 1,3-diaminopropane and 1,4-diaminobutane and substituted benzaldehydes. The reaction of the Schiff bases with sodium borohydride afforded the corresponding benzylic diamines **4–6**. Carbonic anhydrase and acetylcholinesterase inhibitory properties of novel Schiff bases and their amines derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**) were investigated.

2 | RESULTS AND DISCUSSION

2.1 | Synthesis of Schiff bases and *N,N′*-dialkylalkanediamines

As shown in Scheme 1, three series of symmetrical Schiff bases were easily prepared in good yields (80–97%) via condensation of 1,2-diaminoethane, 1,3-diaminopropane, and 1,4-diaminobutane with two molar equivalents of the substituted benzaldehydes in ethanol at reflux temperature. The obtained Schiff bases **1–3** were reduced by treatment with sodium borohydride in methanol at room temperature to corresponding benzylic diamines **4–6** in 60–83% yields. All the compounds are soluble in the common polar solvents such as ethanol and dichloromethane. The Schiff bases and diamines were characterized by ^{1}H and ^{13}C NMR spectroscopy, FTIR and elemental analysis, which support the proposed structures. In the ^{1}H NMR spectra of **1–3**, characteristic imino protons (N=C*H*) of Schiff bases appear at the range 8.12–8.23 ppm as sharp singlets. The ^{13}C NMR spectra of the Schiff bases further supported the assigned structures. The ^{13}C NMR shift of N=CH carbon atoms in **1–3** appear at the range 160.0–162.1 ppm as singlet signal. In the IR spectra of the Schiff bases, the characteristic C=N stretching frequencies were observed between 1491 and 1590 cm^{-1}. The formation of *N,N′*-dialkylalkanediamines **4–6** was confirmed by the presence of N—*H* proton resonance

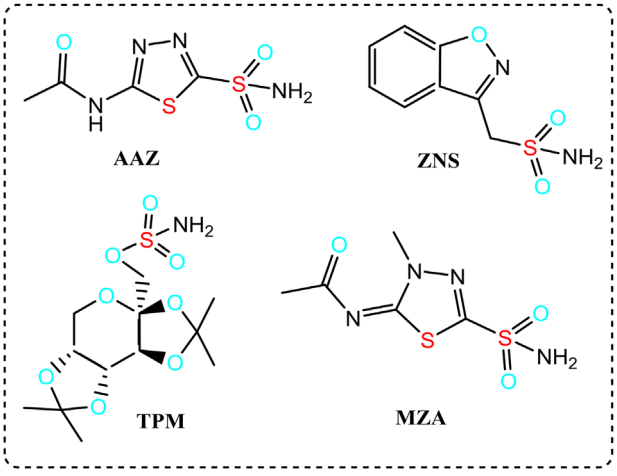


FIGURE 1 Clinically used CA inhibitors with antiepileptic activity. AAZ: acetazolamide, ZNS: zonisamide, TPM: topiramate, MZA: methazolamide

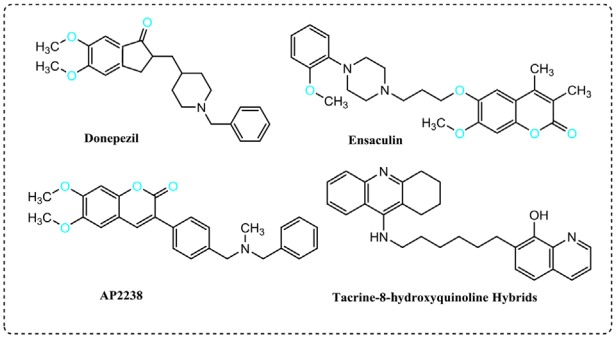
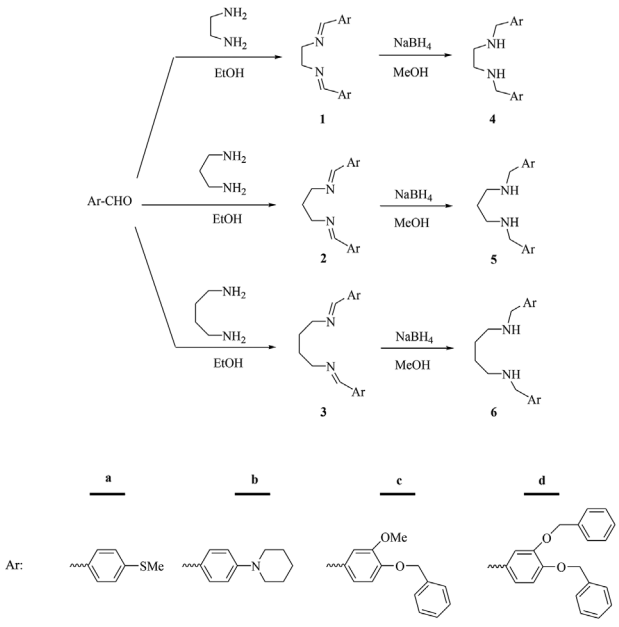


FIGURE 2 Examples of known AChE inhibitors: donepezil as indanone derivative, ensaculin and AP2238 as coumarin derivatives



SCHEME 1 Synthesis of Schiff bases and *N,N′*-dialkylalkanediamines

in the ^{1}H NMR spectra and by the absence of the Schiff base N═C*H* proton resonance in the ^{1}H NMR spectra and N═CH carbon resonance in the ^{13}C NMR spectra. The ^{1}H NMR spectra of **4–6** exhibit a broad singlet at the range 1.36–2.00 ppm for N—*H* protons. The benzylic protons exhibited a singlet at the range 3.66–4.74 ppm. The benzylic carbon resonance of these *N*,*N*′-dialkylalkanediamines appeared at the range 53.4–56.6 ppm as singlet signal in the ^{13}C NMR spectra. The elemental analysis data of the Schiff bases and *N*,*N*′-dialkylalkanediamines agree closely with the theoretical requirements of their structures.

2.2 | Biochemical results

hCA enzymes are significant not only for pH maintenance, also for bone resorption, signal transduction, renal acidification, calcification, gastric acid formation, adaptation to cellular stress, gluconeogenesis, metabolism, biosynthesis, and other processes.[45] Presently, there are over 21 clinically utilized CA inhibitor compounds, but all define little to no isoenzyme specificity. Accordingly, there is a requirement to extend CA inhibitor compounds that are isoform selective, for example, the targeted inhibition of CA IX as an anticancer chemotherapy.[46] The design of CA isoform specific inhibitor compounds is challenging due to high sequence similarity and the structural homology within the active sites of the CA isoenzymes.[47] Hence, there are particular structural discrepancies that have been used for selective inhibitor compound development. CA IX isoform has a larger active site hole that shows amino acid discrepancies in comparison to other CA isoenzymes.[48] For instance, phenylalanine in CA II and also residue 131 is a valine in CA IX, which permits bulkier inhibitor compounds to bind CA IX.[49] Additionally, many of the CA isoforms are valuable aims for many pharmacological applications such as diuretics, antiglaucoma drugs, antiobesity, antitumor, anticonvulsant, agents/diagnostic tools.[50] For example, hCA I inhibitor are used in cerebral edema and retinal. hCA IV, II, XIV, and XII inhibitors are utilized as antiglaucoma agents, in the management of edema, as diuretics, antiepileptic drugs, and also for the therapy of altitude sickness.[51] In this study, we obtained the effects of novel Schiff bases and their amines derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**) against hCA I, hCA II, and AChE enzymes. We report the inhibition effects of these derivatives on the activity of hCA I and hCA II isoenzymes and AChE enzyme under *in vitro* conditions. The following results are presented in Table 1.

Abnormal levels of CA I isoenzyme in the blood are used as a marker for hemolytic anemia.[52] The slow cytosolic isoform hCA I was inhibited by the investigated novel Schiff bases and their amines derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**), with K_i values ranging between 159.43 ± 30.03 and 563.73 ± 115.30 nM. Furthermore, 1,2-bis(4-benzyloxy-3-methoxybenzylamino)ethane, **4c**, demonstrated the most powerful hCA I isoenzyme inhibition properties with a K_i value of 159.43 ± 30.03 nM. The standard and clinically used drug acetazolamide (AZA) demonstrated a K_i value of 620.83 ± 149.27 nM (Table 1 and Figure 3). Thus, the investigated compounds showed better inhibitory profiles compared to AZA, a clinically used CA inhibitor.

Additionally, CA II is often associated with several diseases such as glaucoma, osteoporosis, and renal tubular acidosis.[53] hCA II was also efficiently inhibited by the novel Schiff bases and their amines derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**) investigated here. These compounds appeared to strongly inhibit hCA II with K_i values ranging from 104.88 ± 18.44 to 524.32 ± 95.03 nM. These values are better than those of the clinically used drugs AZA (K_i of 603.18 ± 78.44 nM). All the novel derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**) demonstrated marked inhibition against hCA II, but the compounds of 1,2-bis(4-methylthiobenzylamino)ethane, **4a**, and 1,2-bis(4-benzyloxy-3-methoxybenzylamino)ethane, **4c**, showed excellent inhibitions profile against cytosolic hCA II with K_i values of 129.73 ± 18.47 and 104.88 ± 18.44 nM, respectively (Table 1 and Figure 3).

The inhibitory effects of the newly synthesized Schiff bases and their amines derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**) on AChE are shown in Table 1. The AChE inhibition profiles of the compounds evaluated here were quite interesting. Overall, the novel Schiff bases and their amines derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**) had excellent inhibitory activity with K_i values ranging from 3.95 ± 0.74 to 30.83 ± 6.81 nM. Furthermore, tacrine, used as a standard AChE inhibitor in this study, demonstrated K_i value of 67.25 ± 16.08 nM toward AChE. The compounds of 1,3-bis(4-methylthiobenzylamino)propane, **5a**, 1,3-bis(4-(1-piperidinyl)-benzylamino)propane, **5b**, 1,3-bis(4-benzyloxy-3-methoxybenzylamino)-propane, **5c**, showed excellent inhibitions profile against AChE with K_i values of 3.95 ± 0.74, 5.77 ± 1.04, and 7.84 ± 2.76 nM, respectively (Table 1 and Figure 3).

Recently, drug development and research are based on the cholinergic hypothesis which offers that the elective loss of cholinergic neuron cells results in a deficiency of ACh in special places of the brain that mediate memory functions and learning. Based on this supposition the cholinergic ratiocination will improve the recognition in AD.[54,55] Nowadays available therapy for patients suffering from AD involve approved AChEIs such as donepezil, galantamine, and rivastigmine which avoid the hydrolysis of ACh therewith enhancing its concentrations.[56] Hence, clinical effect and efficiency is limited as accessible AChEIs can only ameliorate AD symptoms and, therefore, the search for novel molecules remains an emerging demand for the therapy of AD. On the other hand, the design of multi-targeted drugs that can simultaneously act on ACh and other molecular targets involved in the development of the disease offer an interesting approach to manage AD.[57]

3 | CONCLUSION

Three series of symmetrical Schiff bases and amines were successfully synthesized in good yields and characterized by elemental analysis and spectroscopic methods. These compounds were investigated for their hCA I and II isoforms, and AChE inhibition

TABLE 1 The inhibition values of novel Schiff bases and their amines derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**) against human carbonic anhydrase isoenzymes I and II (hCA I and II), and AChE enzyme

	IC_{50} (nM)						K_i (nM)		
Compounds	hCA I	r^2	hCA II	r^2	AChE	r^2	hCA I	hCA II	AChE
1a	301.23	0.9722	263.44	0.9902	28.36	0.9911	324.74 ± 28.33	281.33 ± 98.03	22.47 ± 1.73
1b	261.28	0.9902	235.37	0.9721	19.76	0.9692	257.88 ± 70.12	230.41 ± 91.44	15.33 ± 3.54
1c	248.82	0.9788	203.77	0.9732	30.18	0.9787	269.03 ± 38.01	227.47 ± 58.52	25.81 ± 7.31
1d	281.33	0.9889	235.82	0.9947	34.03	0.9880	302.12 ± 54.44	254.93 ± 83.99	28.18 ± 10.05
2a	182.83	0.9683	158.46	0.9476	14.76	0.9630	172.83 ± 50.05	166.82 ± 47.82	9.14 ± 2.01
2b	201.47	0.9847	179.03	0.9770	20.22	0.9881	190.02 ± 14.04	173.66 ± 40.11	13.08 ± 0.88
2c	208.02	0.9903	168.38	0.9868	21.38	0.9689	234.18 ± 25.55	149.81 ± 27.48	16.83 ± 3.73
2d	194.18	0.9937	143.28	0.9772	21.01	0.9722	201.30 ± 60.84	146.17 ± 36.92	15.87 ± 4.88
3b	402.17	0.9625	348.11	0.9954	19.77	0.9699	378.94 ± 100.51	327.15 ± 118.0	14.63 ± 2.66
3c	438.32	0.9528	401.33	0.9722	18.67	0.9907	398.58 ± 93.03	385.72 ± 91.23	10.11 ± 3.83
3d	462.10	0.9707	398.76	0.9890	20.74	0.9627	449.73 ± 98.11	359.14 ± 103.4	11.08 ± 0.96
4a	199.02	0.9829	148.91	0.9937	40.17	0.9744	218.04 ± 24.82	129.73 ± 18.47	28.95 ± 5.87
4b	171.48	0.9902	139.09	0.9799	37.43	0.9307	203.49 ± 59.44	154.83 ± 59.22	30.83 ± 6.81
4c	170.27	0.9477	124.77	0.9550	36.10	0.9633	159.43 ± 30.03	104.88 ± 18.44	29.77 ± 8.93
5a	291.56	0.9921	238.67	0.9930	9.03	0.9754	290.73 ± 88.32	258.47 ± 37.94	3.95 ± 0.74
5b	267.83	0.9683	219.49	0.9744	8.04	0.9840	301.55 ± 92.05	245.18 ± 60.34	5.77 ± 1.04
5c	250.02	0.9883	213.79	0.9810	10.85	0.9927	231.66 ± 58.32	209.47 ± 27.93	7.84 ± 2.76
6a	504.23	0.9773	494.38	0.9308	24.83	0.9888	482.48 ± 103.94	451.03 ± 154.2	16.07 ± 6.41
6c	538.27	0.9880	478.36	0.9638	29.49	0.9728	563.73 ± 115.30	524.32 ± 95.03	20.37 ± 9.04
6d	494.37	0.9955	422.85	0.9901	29.01	0.9825	488.18 ± 77.03	518.23 ± 118.0	23.55 ± 7.74
AZA[a]	604.33	0.9743	532.48	0.9699	–	–	620.83 ± 149.27	603.18 ± 78.44	–
TAC[b]	–	–	–	–	103.11	0.9921	–	–	67.25 ± 16.08

[a]Acetazolamide (AZA) was used as a standard inhibitor for both carbonic anhydrase I and II isoenzymes.
[b]Tacrine (TAC) was used as a standard inhibitor for AChE enzyme.

properties. These molecules showed nanomolar inhibition against these enzymes. Inhibition of AChE and hCA I and II isoforms can have a significant role in discovery and drug design as well as in toxicology and medicine. Additionally, these molecules are drug candidates as anticholinergic, antidiabetic, and antiepileptic applications. Compounds **4c**, **4a**, and **5a** were good inhibitors for hCA I and II and AChE enzymes, respectively.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All reactions for the preparation of the Schiff bases and amines were carried out under air. Chemicals were obtained from Sigma–Aldrich and Fluka. ^{1}H and ^{13}C NMR spectra were recorded with a Varian AS 400 Merkur spectrometer operating at 400 MHz (^{1}H), 100 MHz (^{13}C) in $CDCl_3$ with tetramethylsilane as an internal reference. Coupling constants (*J* values) are given in hertz. NMR multiplicities are abbreviated as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, quint = quintet, and m = multiplet signal. FT-IR spectra were recorded as KBr pellets in the range 400–4000 cm^{-1} on Perkin Elmer Spectrum 100. Melting points were measured in open capillary tubes with an Electrothermal-9200 melting point apparatus. Elemental analyses were performed by LECO CHNS-932 elemental analyzer.

The NMR spectra of the investigated compounds are provided as Supporting Information. Their InChI codes and some biological activity data are also provided as Supporting Information.

4.1.2 | General procedure for the preparation of Schiff bases 1–3

Diaminoalkane (5 mmol) was added dropwise to a solution of the aromatic aldehyde (10 mmol) in ethanol (30 mL) over a period of 2 min. The reaction mixture was stirred at reflux for 3 h, then volatiles were removed in vacuum to dryness. The crude product was crystallized from dichloromethane or ethanol/diethyl ether.

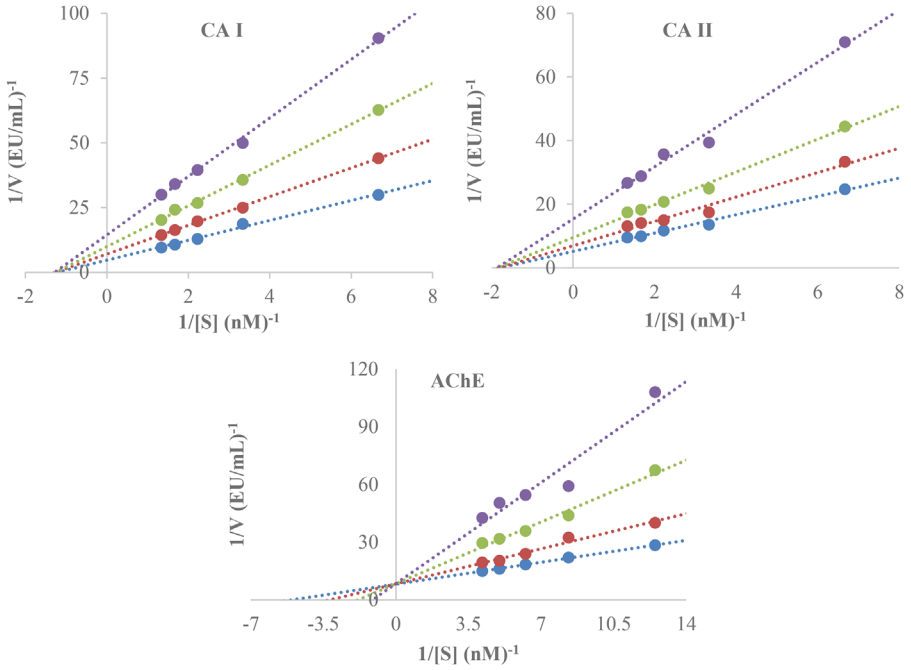


FIGURE 3 Determination of Lineweaver–Burk graphs for excellent inhibitors of hCA I and hCA II isoenzymes, and AChE enzyme

1,2-Bis(4-methylthiobenzylideneamino)ethane 1a

Yield: 1.54 g, 94%; m.p.: 110–111°C, IR, υ: 1590 cm^{-1} (C═N). ^1H NMR ($CDCl_3$) δ: 2.49 (s, 6H, SCH_3), 3.94 (s, 4H, NCH_2CH_2N), 7.22 and 7.59 (d, 8H, *J* = 8 Hz, Ar-*H*), 8.20 (s, 2H, N═C*H*). ^{13}C NMR ($CDCl_3$) δ: 15.2 (SCH_3), 61.6 (NCH_2CH_2N), 125.7, 128.3, 132.8, 141.9 (Ar-*C*), 162.0 (N═CH). Anal. calcd. for $C_{18}H_{20}N_2S_2$: C, 65.85; H, 6.09; N, 8.54. Found: C, 65.88; H, 6.11; N, 8.50.

1,2-Bis(4-(1-piperidinyl)benzylideneamino)ethane 1b

Yield: 1.84 g, 92%; m.p.: 216–218°C, IR, υ: 1605 cm^{-1} (CN). ^1H NMR ($CDCl_3$) δ: 1.58–1.62 (m, 4H, $N(CH_2CH_2)_2CH_2$), 1.65–1.70 (m, 8H, $N(CH_2CH_2)_2CH_2$), 3.24 (t, 8H, *J* = 4 Hz, $N(CH_2CH_2)_2CH_2$), 3.87 (s, 4H, NCH_2CH_2N), 6.87 and 7.56 (d, 8H, *J* = 8 Hz, Ar-*H*), 8.15 (s, 2H, NC*H*). ^{13}C NMR ($CDCl_3$) δ: 24.3 ($N(CH_2CH_2)_2CH_2$), 25.6 ($N(CH_2CH_2)_2CH_2$), 49.4 ($N(CH_2CH_2)_2CH_2$), 61.9 (NCH_2CH_2N), 114.9, 126.4, 129.3, 153.3 (Ar-*C*), 162.1 (N═CH). Anal. calcd. for $C_{26}H_{34}N_4$: C, 77.61; H, 8.46; N, 13.93. Found: C, 77.65; H, 8.48; N, 13.90.

1,2-Bis(4-benzyloxy-3-methoxybenzylideneamino)ethane 1c

Yield: 2.39 g, 94%; m.p.: 151–152°C, IR, υ: 1508 cm^{-1} (C═N). ^1H NMR ($CDCl_3$) δ: 3.91 (s, 10H, NCH_2CH_2N, OCH_3), 5.17 (s, 4H, OCH_2Ar), 6.86–7.43 (m, 16H, Ar-*H*), 8.16 (s, 2H, NC*H*). ^{13}C NMR ($CDCl_3$) δ: 56.0 (OCH_3), 61.6 (NCH_2CH_2N), 70.8 (OCH_2Ar), 109.2, 112.9, 122.9, 127.2, 127.9, 128.6, 129.8, 136.7, 149.9, 150.4 (Ar-*C*), 162.1 (NCH). Anal. calcd. for $C_{32}H_{32}N_2O_4$: C, 75.59; H, 6.30; N, 5.51. Found: C, 75.64; H, 6.32; N, 5.49.

1,2-Bis(3,4-dibenzyloxybenzylideneamino)ethane 1d

Yield: 3.2 g, 97%; m.p.: 150–151°C, IR, υ: 1511 cm^{-1} (CN). ^1H NMR ($CDCl_3$) δ: 3.90 (s, 4H, NCH_2CH_2N), 5.16 (s, 8H, OCH_2Ar), 6.88–7.46 (m, 26H, Ar-*H*), 8.12 (s, 2H, N═C*H*). ^{13}C NMR ($CDCl_3$) δ: 61.6 (NCH_2CH_2N), 70.9 and 71.1 (OCH_2Ar), 112.4, 113.9, 123.1, 127.1, 127.4, 127.8, 127.9, 128.4, 128.5, 130.0, 136.9, 137.1, 149.2, 151.1 (Ar-*C*), 162.0 (N═CH). Anal. calcd. for $C_{44}H_{40}N_2O_4$: C, 80.00; H, 6.06; N, 4.24. Found: C, 80.06; H, 6.08; N, 4.22.

1,3-Bis(4-methylthiobenzylideneamino)propane 2a

Yield: 1.52 g, 89%; m.p.: 65–66°C, IR, υ: 1641 cm^{-1} (C═N). ^1H NMR ($CDCl_3$) δ: 2.50 (s, 6H, SCH_3), 2.10 (quint, 2H, *J* = 8 Hz, $NCH_2CH_2CH_2N$), 3.69 (t, 4H, *J* = 4 Hz, $NCH_2CH_2CH_2N$), 7.25 and 7.63 (d, 8H, *J* = 8 Hz, Ar-*H*), 8.23 (s, 2H, N═C*H*). ^{13}C NMR ($CDCl_3$) δ: 15.2 (SCH_3), 32.0 ($NCH_2CH_2CH_2N$), 59.2 ($NCH_2CH_2CH_2N$), 125.8, 128.3, 133.0, 141.8 (Ar-*C*), 160.6 (NCH). Anal. calcd. for $C_{19}H_{22}N_2S_2$: C, 66.67; H, 6.43; N, 8.19. Found: C, 66.71; H, 6.40; N, 8.22.

1,3-Bis(4-(1-piperidinyl)benzylideneamino)propane 2b

Yield: 1.79 g, 86%; m.p.: 112–113°C, IR, υ: 1605 cm^{-1} (C═N). ^1H NMR ($CDCl_3$) δ: 1.60 (quint, 4H, *J* = 4 Hz, $N(CH_2CH_2)_2CH_2$), 1.69 (quint, 8H, *J* = 4 Hz, $N(CH_2CH_2)_2CH_2$), 3.26 (t, 8H, *J* = 4 Hz, $N(CH_2CH_2)_2CH_2$), 2.07 (quint, 2H, *J* = 8 Hz, $NCH_2CH_2CH_2N$), 3.64 (t, 4H, *J* = 8 Hz, $NCH_2CH_2CH_2N$), 6.90 and 7.59 (d, 8H, *J* = 8 Hz, Ar-*H*), 8.15 (s, 2H, N═C*H*). ^{13}C NMR ($CDCl_3$) δ: 32.3 ($NCH_2CH_2CH_2N$), 59.2 ($NCH_2CH_2CH_2N$), 24.3 ($N(CH_2CH_2)_2CH_2$), 25.5 ($N(CH_2CH_2)_2CH_2$), 49.5 ($N(CH_2CH_2)_2CH_2$), 115.0, 126.6, 129.2, 153.3 (Ar-*C*), 160.9 (NCH). Anal. calcd. for $C_{27}H_{36}N_4$: C, 77.88; H, 8.65; N, 13.46. Found: C, 77.92; H, 8.61; N, 13.44.

1,3-Bis(4-benzyloxy-3-methoxybenzylideneamino)propane 2c

Yield: 2.09 g, 80%; m.p.: 81–82°C, IR, υ: 1509 cm^{-1} (C═N). ^1H NMR ($CDCl_3$) δ: 3.94 (s, 6H, OCH_3), 2.09 (quint, 2H, *J* = 8 Hz,

NCH$_2$C*H*$_2$CH$_2$N), 3.68 (t, 4H, *J* = 4 Hz, NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N), 5.19 (s, 4H, OC*H*$_2$Ar), 6.87–7.44 (m, 16H, Ar-*H*), 8.18 (s, 2H, N=C*H*). ^{13}C NMR (CDCl$_3$) δ: 56.0 (OCH$_3$), 32.1 (NCH$_2$CH$_2$CH$_2$N), 59.2 (NCH$_2$CH$_2$CH$_2$N), 70.8 (OCH$_2$Ar), 109.1, 112.9, 122.7, 127.2, 127.9, 128.6, 129.9, 136.7, 149.9, 150.37 (Ar-*C*), 160.7 (NCH). Anal. calcd. for $C_{33}H_{34}N_2O_4$: C, 75.86; H, 6.51; N, 5.36. Found: C, 75.90; H, 6.53; N, 5.38.

1,3-Bis(3,4-dibenzyloxybenzylideneamino)propane 2d

Yield: 3.17 g, 94%; m.p.: 104–105°C, IR, υ: 1514 cm^{-1} (CN). ^{1}H NMR (CDCl$_3$) δ: 2.08 (quint, 2H, *J* = 8 Hz, NCH$_2$C*H*$_2$CH$_2$N), 3.66 (t, 4H, *J* = 8 Hz, NC*H*$_2$CH$_2$C*H*$_2$N), 5.18 and 5.19 (s, 8H, OC*H*$_2$Ar), 6.92–7.49 (m, 26H, Ar-*H*), 8.15 (s, 2H, NC*H*). ^{13}C NMR (CDCl$_3$) δ: 32.1 (NCH$_2$CH$_2$CH$_2$N), 59.1 (NCH$_2$CH$_2$CH$_2$N), 71.0 and 71.1 (OCH$_2$Ar), 112.3, 114.0, 123.0, 127.1, 127.3, 127.8, 128.4, 128.5, 130.1, 136.9, 137.1, 149.2, 151.0 (Ar-*C*), 160.6 (NCH). Anal. calcd. for $C_{45}H_{42}N_2O_4$: C, 80.12; H, 6.23; N, 4.15. Found: C, 80.17; H, 6.25; N, 4.13.

1,4-Bis(4-methylthiobenzylideneamino)butane 3a

This compound was not characterized.

1,4-Bis(4-(1-piperidinyl)benzylideneamino)butane 3b

Yield: 1.76 g, 82%; m.p.: 166–168°C, IR, υ: 1602 cm^{-1} (C=N). ^{1}H NMR (CDCl$_3$) δ: 1.73 (quint, 4H, *J* = 4 Hz, NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N), 3.59 (t, 4H, *J* = 4 Hz, NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N), 1.61 (quint, 4H, *J* = 4 Hz, N(CH$_2$CH$_2$)$_2$C*H*$_2$), 1.68 (quint, 8H, *J* = 4 Hz, N(CH$_2$C*H*$_2$)$_2$CH$_2$), 3.25 (t, 8H, *J* = 4 Hz, N(C*H*$_2$CH$_2$)$_2$CH$_2$), 6.89 and 7.58 (d, 8H, *J* = 8 Hz, Ar-*H*), 8.14 (s, 2H, N=C*H*). ^{13}C NMR (CDCl$_3$) δ: 28.9 (NCH$_2$CH$_2$CH$_2$CH$_2$N), 61.5 (NCH$_2$CH$_2$CH$_2$CH$_2$N), 24.3 (N(CH$_2$CH$_2$)$_2$CH$_2$), 25.5 (N(CH$_2$CH$_2$)$_2$CH$_2$), 49.5 (N(CH$_2$CH$_2$)$_2$CH$_2$), 115.0, 126.6, 129.2, 153.3 (Ar-*C*), 160.6 (NCH). Anal. calcd. for $C_{28}H_{38}N_4$: C, 78.14; H, 8.84; N, 13.02. Found: C, 78.19; H, 8.82; N, 13.10.

1,4-Bis(4-benzyloxy-3-methoxybenzylideneamino)butane 3c

Yield: 2.41 g, 90%; m.p.: 124–126°C, IR, υ: 1513 cm^{-1} (CN). ^{1}H NMR (CDCl$_3$) δ: 3.94 (s, 6H, OC*H*$_3$), 1.72–1.79 (m, 4H, NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N), 3.61–3.64 (m, 4H, NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N), 5.19 (s, 4H, OC*H*$_2$Ar), 6.86–7.44 (m, 16H, Ar-*H*), 8.16 (s, 2H, N=C*H*). ^{13}C NMR (CDCl$_3$) δ: 56.0 (OCH$_3$), 28.8 (NCH$_2$CH$_2$CH$_2$CH$_2$N), 61.4 (NCH$_2$CH$_2$CH$_2$CH$_2$N), 70.8 (OCH$_2$Ar), 109.1, 112.9, 122.7, 127.2, 127.9, 128.5, 129.6, 136.7, 149.9, 150.3 (Ar-*C*), 160.4 (NCH). Anal. calcd. for $C_{34}H_{36}N_2O_4$: C, 76.12; H, 6.72; N, 5.22. Found: C, 76.16; H, 6.70; N, 5.25.

1,4-Bis(3,4-dibenzyloxybenzylideneamino)butane 3d

Yield: 2.96 g, 86%; m.p.: 132–134°C, IR, υ: 1507 cm^{-1} (C=N). ^{1}H NMR (CDCl$_3$) δ: 1.73–1.76 (m, 4H, NCH$_2$C*H*$_2$C*H*$_2$CH$_2$N), 3.60–3.63 (m, 4H, NC*H*$_2$CH$_2$CH$_2$C*H*$_2$N), 5.18 and 5.19 (s, 8H, OC*H*$_2$Ar), 6.91–7.49 (m, 26H, Ar-*H*), 8.14 (s, 2H, N=C*H*). ^{13}C NMR (CDCl$_3$) δ: 28.8 (NCH$_2$CH$_2$CH$_2$CH$_2$N), 61.4 (NCH$_2$CH$_2$CH$_2$CH$_2$N), 71.0 and 71.1 (OCH$_2$Ar), 112.4, 114.0, 123.0, 127.1, 127.4, 127.8, 128.4, 128.5, 130.1, 136.9, 137.0, 149.2, 151.0 (Ar-*C*), 160.3 (NCH). Anal. calcd. for $C_{46}H_{44}N_2O_4$: C, 80.23; H, 6.40; N, 4.07. Found: C, 80.28; H, 6.43; N, 4.03.

4.1.3 | General procedure for the preparation of *N,N′*-dialkylalkanediamines 4–6

Sodium borohydride (15 mmol) was added portionwise to a solution of diimine (10 mmol) in methanol (30 mL) at room temperature over a period of 30 min. The reaction mixture was stirred for 12 h and then heated under reflux for 1 h. Upon cooling to room temperature, the mixture was treated with 1 N HCl, and organic phase was extracted with dichloromethane (3 × 30 mL). After drying over MgSO$_4$ and evaporation, the crude product was crystallized from toluene/*n*-hexane.

1,2-Bis(4-methylthiobenzylamino)ethane 4a

Yield: 1.99 g, 60%; m.p.: 43–44°C, IR, υ: 1491 cm^{-1} (C=N). ^{1}H NMR (CDCl$_3$) δ: 1.66 (bs, 2H, N-*H*), 2.47 (s, 6H, SC*H*$_3$), 2.73 (s, 4H, NC*H*$_2$C*H*$_2$N), 3.72 (s, 4H, NC*H*$_2$Ar), 7.22 (s, 8H, Ar-*H*). ^{13}C NMR (CDCl$_3$) δ: 16.2 (SCH$_3$), 48.7 (NCH$_2$CH$_2$N), 53.4 (NCH$_2$Ar), 126.9, 128.7, 136.7, 137.5 (Ar-*C*). Anal. calcd. for $C_{18}H_{24}N_2S_2$: C, 65.06; H, 7.23; N, 8.43. Found: C, 65.11; H, 7.21; N, 8.47.

1,2-Bis(4-(1-piperidinyl)benzylamino)ethane 4b

Yield: 2.51 g, 62%; m.p.: 87–89°C, IR, υ: 1510 cm^{-1} (CN). ^{1}H NMR (CDCl$_3$) δ: 1.53–1.59 (m, 4H, N(CH$_2$CH$_2$)$_2$C*H*$_2$), 1.67–1.73 (m, 10H, N(CH$_2$C*H*$_2$)$_2$CH$_2$, N-*H*), 3.12 (t, 8H, *J* = 4 Hz, N(C*H*$_2$CH$_2$)$_2$CH$_2$), 2.73 (s, 4H, NC*H*$_2$C*H*$_2$N), 3.67 (s, 4H, NC*H*$_2$Ar), 6.88 and 7.17 (d, 8H, *J* = 8 Hz, Ar-*H*). ^{13}C NMR (CDCl$_3$) δ: 24.3 (N(CH$_2$CH$_2$)$_2$CH$_2$), 25.9 (N-(CH$_2$CH$_2$)$_2$CH$_2$), 50.3 (N(CH$_2$CH$_2$)$_2$CH$_2$), 48.7 (NCH$_2$CH$_2$N), 53.4 (NCH$_2$Ar), 116.5, 128.9, 131.1, 151.3 (Ar-*C*). Anal. calcd. for $C_{26}H_{38}N_4$: C, 76.84; H, 9.36; N, 13.79. Found: C, 76.87; H, 9.38; N, 13.76.

1,2-Bis(4-benzyloxy-3-methoxybenzylamino)ethane 4c

Yield: 3.28 g, 64%; m.p.: 158–160°C, IR, υ: 1514 cm^{-1} (CN). ^{1}H NMR (CDCl$_3$) δ: 2.00 (bs, 2H, N-*H*), 3.93 (s, 6H, OC*H*$_3$), 3.67 (s, 4H, NC*H*$_2$C*H*$_2$N), 4.74 (s, 4H, NC*H*$_2$Ar), 5.13 (s, 4H, OC*H*$_2$Ar), 6.77–7.42 (m, 16H, Ar-*H*). ^{13}C NMR (CDCl$_3$) δ: 52.2 (OCH$_3$), 47.3 (NCH$_2$CH$_2$N), 56.6 (NCH$_2$Ar), 71.0 (OCH$_2$Ar), 112.7, 113.9, 121.4, 125.4, 127.3, 127.9, 128.5, 128.6, 136.8, 148.8, 150.4 (Ar-*C*). Anal. calcd. for $C_{32}H_{36}N_2O_4$: C, 75.00; H, 7.03; N, 5.47. Found: C, 75.04; H, 7.01; N, 5.49.

1,3-Bis(4-methylthiobenzylamino)propane 5a

Yield: 2.14 g, 62%; m.p.: 92–94°C, IR, υ: 1511 cm^{-1} (C=N). ^{1}H NMR (CDCl$_3$) δ: 2.47 (s, 6H, SC*H*$_3$), 1.67–1.74 (m, 4H, NCH$_2$C*H*$_2$CH$_2$N, N-*H*), 2.67–2.70 (m, 4H, NC*H*$_2$CH$_2$C*H*$_2$N), 3.73 (s, 4H, NC*H*$_2$Ar), 7.21 (s, 8H, Ar-*H*). ^{13}C NMR (CDCl$_3$) δ: 16.1 (SCH$_3$), 29.9 (NCH$_2$CH$_2$CH$_2$N), 47.9 (NCH$_2$CH$_2$CH$_2$N), 53.4 (NCH$_2$Ar), 126.8, 128.6, 136.7, 137.3 (Ar-*C*). Anal. calcd. for $C_{19}H_{26}N_2S_2$: C, 65.90; H, 7.51; N, 8.09. Found: C, 65.95; H, 7.53; N, 8.12.

1,3-Bis(4-(1-piperidinyl)benzylamino)propane 5b

Yield: 2.90 g, 69%; m.p.: 60–61°C, IR, υ: 1509 cm^{-1} (C=N). ^{1}H NMR (CDCl$_3$) δ: 1.53–1.59 (m, 6H, N(CH$_2$CH$_2$)$_2$C*H*$_2$, N-*H*), 1.68–1.73 (m, 10H, N(CH$_2$C*H*$_2$)$_2$CH$_2$, NCH$_2$C*H*$_2$CH$_2$N), 3.12 (t, 8H, *J* = 4 Hz,

N(CH_2CH_2)$_2CH_2$), 2.67 (t, 4H, *J* = 4 Hz, NCH_2CH_2CH_2N), 3.68 (s, 4H, NCH_2Ar), 6.88 and 7.17 (d, 8H, *J* = 8 Hz, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ: 29.9 (NCH_2CH_2CH_2N), 47.8 (NCH_2CH_2CH_2N), 24.3 (N(CH_2CH_2)$_2CH_2$), 25.9 (N(CH_2CH_2)$_2CH_2$), 50.8 (N(CH_2CH_2)$_2CH_2$), 53.5 (NCH_2Ar), 116.5, 128.8, 131.1, 151.3 (Ar-*C*). Anal. calcd. for $C_{27}H_{40}N_4$: C, 77.14; H, 9.52; N, 13.33. Found: C, 77.17; H, 9.55; N, 13.36.

1,3-Bis(4-benzyloxy-3-methoxybenzylamino)propane 5c

Yield: 3.78 g, 72%; m.p.: 66–68°C, IR, υ: 1512 cm^{-1} (CN). ^{1}H NMR ($CDCl_3$) δ: 1.69–1.79 (m, 4H, NCH_2CH_2CH_2N, N-*H*), 2.70 (t, 4H, *J* = 4 Hz, NCH_2CH_2CH_2N), 3.86 (s, 6H, OCH_3), 3.70 (s, 4H, NCH_2Ar), 5.13 (s, 4H, OCH_2Ar), 6.73–7.44 (m, 16H, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ: 56.0 (OCH_3), 29.9 (NCH_2CH_2CH_2N), 48.0 (NCH_2CH_2CH_2N), 53.8 (NCH_2Ar), 71.1 (OCH_2Ar), 111.9, 114.0, 120.1, 127.2, 127.7, 128.5, 133.5, 137.3, 147.1, 149.7 (Ar-*C*). Anal. calcd. for $C_{33}H_{38}N_2O_4$: C, 75.29; H, 7.22; N, 5.32. Found: C, 75.33; H, 7.20; N, 5.34.

1,4-Bis(4-methylthiobenzylamino)butane 6a

Yield: 2.56 g, 71%; m.p.: 71–73°C, IR, υ: 1509 cm^{-1} (CN). ^{1}H NMR ($CDCl_3$) δ: 1.36 (bs, 2H, N-*H*), 2.47 (s, 6H, SCH_3), 1.52–1.55 (m, 4H, NCH_2CH_2CH_2CH_2N), 2.60 (t, 4H, *J* = 4 Hz, NCH_2CH_2CH_2CH_2N), 3.73 (s, 4H, NCH_2Ar), 7.22 (s, 8H, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ: 16.1 (SCH_3), 27.8 (NCH_2CH_2CH_2CH_2N), 49.2 (NCH_2CH_2CH_2CH_2N), 53.5 (NCH_2Ar), 126.9, 128.6, 136.6, 137.5 (Ar-*C*). Anal. calcd. for $C_{20}H_{28}N_2S_2$: C, 66.67; H, 7.78; N, 7.78. Found: C, 66.71; H, 7.76; N, 7.81.

1,4-Bis(4-benzyloxy-3-methoxybenzylamino)butane 6c

Yield: 4.37 g, 81%; m.p.: 97–98°C, IR, υ: 1510 cm^{-1} (C═N). ^{1}H NMR ($CDCl_3$) δ: 3.88 (s, 6H, OCH_3), 1.53–1.56 (m, 6H, NCH_2CH_2CH_2CH_2N, N-*H*), 2.63 (t, 4H, *J* = 4 Hz, NCH_2CH_2CH_2CH_2N), 3.70 (s, 4H, NCH_2Ar), 5.13 (s, 4H, OCH_2Ar), 6.74–7.44 (m, 16H, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ: 56.0 (OCH_3), 27.9 (NCH_2CH_2CH_2CH_2N), 49.3 (NCH_2CH_2CH_2CH_2N), 53.8 (NCH_2Ar), 71.1 (OCH_2Ar), 111.9, 114.0, 120.1, 127.2, 127.7, 128.5, 133.8, 137.3, 147.1, 149.7 (Ar-*C*). Anal. calcd. for $C_{34}H_{40}N_2O_4$: C, 75.56; H, 7.41; N, 5.19. Found: C, 75.60; H, 7.44; N, 5.16.

1,4-Bis(3,4-dibenzyloxybenzylamino)butane 6d

Yield: 5.74 g, 83%; m.p.: 69–70°C, IR, υ: 1519 cm^{-1} (C═N). ^{1}H NMR ($CDCl_3$) δ: 1.47–1.54 (m, 6H, NCH_2CH_2CH_2CH_2N, N-*H*), 2.57 (t, 4H, *J* = 4 Hz, NCH_2CH_2CH_2CH_2N), 3.66 (s, 4H, NCH_2Ar), 5.13 and 5.15 (s, 8H, OCH_2Ar), 6.78–7.45 (m, 26H, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ: 27.8 (NCH_2CH_2CH_2CH_2N), 49.2 (NCH_2CH_2CH_2CH_2N), 53.6 (NCH_2Ar), 71.2 and 71.4 (OCH_2Ar), 115.1, 121.0, 127.3, 127.7, 128.4, 134.0, 137.3, 137.4, 147.9, 149.0 (Ar-*C*). Anal. calcd. for $C_{46}H_{48}N_2O_4$: C, 79.77; H, 6.94; N, 4.05. Found: C, 79.73; H, 6.90; N, 4.09.

4.2 | Biochemical studies

4.2.1 | Carbonic anhydrase I and II isoenzymes purification and inhibition studies

The purification of CA I and II from human red blood cells was previously explained[58–60] with a simple one-step procedure by a Sepharose-4B-L-tyrosine-sulphanilamide affinity chromatoghraphy. The protein quantity in the column effluents were evaluated spectrophotometrically at 280 nm as previously described.[61,62] For purity of both isoenzymes sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) was applied.[63] CA isoenzymes activities were obtained in conforming with the procedure of Verpoorte et al.[64] as explained previously.[65] The enhance in absorbance of the reaction medium was spectrophotometrically obtained at 348 nm. We utilized the esterase activity procedure for ascertaining the inhibition agents by the Lineweaver–Burk procedure. [66] CA activity (%) versus inhibitory concentration and 1/*V* versus 1/[S] graphs were drawn. The quantity of protein was determined at 595 nm according to Bradford's procedure.[67] Bovine serum albumin was used as standard protein as given previously in details.[68] For the designation of the inhibition efficacy of each novel Schiff bases and their amines derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**), on both hCA isoenzymes, an activity (%)-[Schiff bases and their amines derivatives] graph was drawn. The IC_{50} values were obtained from activity (%) versus compounds plots. For the calculation of K_i values, three different novel Schiff bases and their amines derivatives concentrations were used.[69]

4.2.2 | AChE activity determination

The inhibitory effects of novel Schiff bases and their amines derivatives (**1a–d**, **2a–d**, **3b–d**, **4a–c**, **5a–c**, **6a**, **6c**, **6d**) on AChE activitiy were measured conforming to the spectrophotometric procedure of Ellman et al.[70] Acetylthiocholine iodide (AChI) was utilized as substrate for the enzymatic reaction. 5,5′-Dithiobis(2-nitrobenzoic acid) (DTNB) was utilized for the measurement of the AChE activitiy.[71] Briefly, 100 µL of Tris/HCl buffer (1 M, pH 8.0), 780 µL of sample solution dissolved in deionized water at different concentrations, and 20 µL of AChE solution were mixed and incubated for 5 min at 25°C. Then, 50 µL of DTNB (0.5 mM) was added.[72] Then reaction was initiated by the addition of 50 µL of AChI. The hydrolysis of these substrates was monitored spectrophotometrically by formation of the yellow 5-thio-2-nitrobenzoate anion as the result of the reaction of DTNB with thiocholine, released by enzymatic hydrolysis of AChI, with an absorption maximum at a wavelength of 412 nm.[73–75] For the calculation of K_i values, three different novel Schiff bases and their amines derivatives concentrations were used. Finally, the Lineweaver–Burk curves were drawn.[66]

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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