

Microvawe assisted synthesis of N-(methyl and methoxy) benzylidene-4-fluoroaniline derivatives and their carbonic anhydrase I and II inhibition properties

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Abstract: In this study, some Schiff base derivatives (**6a-f**) were synthesized using a microwave method. The synthesized compounds were characterized by 1D, 2D NMR and mass spectral data. Their inhibitory effects were studied on carbonic anhydrase isozymes (hCA I and II), purified from human erythrocyte cells by Sepharose-4B-L-tyrosine-sulfanilamide affinity chromatography and the compounds *N*-3-Methylbenzylidene-4-fluoroaniline (**6b**), *N*-4-Methylbenzylidene-4-fluoroaniline (**6c**), *N*-2-Methoxybenzylidene-4-fluoroaniline (**6d**) showed moderate activity on hCAII in the range of IC₅₀ values.

Keywords: Schiff base; carbonic anhydrase; microbial; N-benzylideneaniline. © 2019 ACG Publications. All rights reserved.

1. Introduction

Schiff bases, synthesized by Hugo Schiff for the first time in 1864, are the most common compounds used in organic chemistry. Aldehyde- or ketone-like compounds in which the carbonyl group is replaced by an azomethine (anil or imine) group are called Schiff bases.² Schiff bases are used in diverse applications and fields, including the design of medical compounds, pharmacology and pharmaceuticals, organic chemistry, paints, plastics, the perfume industry, catalysis and materials science, enzymatic reactions, biochemistry, photochromism, measurement of the intensity of radiation, optical computers, the electronics industry, image systems, physicochemistry, and as spectrophotometric reagents used in analytical chemistry.^{3,4}

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In biological systems, Schiff bases have shown antiproliferative⁵, antipyretic⁶, antibacterial⁷, antifungal⁸, antimicrobial^{9,10}, anticonvulsant^{11,12}, anti-HIV^{13,14}, antiinflammatory¹⁵, antitumor¹⁶, antiviral¹⁷, and anticancer^{18,19} activities that are worth examining further.

2. Background

Microwave technology was first used by Gedye in 1986 in organic synthesis.²⁰ Microwave reactions under solvent-free conditions allow for the direct and fast heating of materials with low cost, less pollution, and faster reactions while offering high efficiency and ease of use.^{21,22}

Carbonic anhydrase (CA, EC 4.2.1.1) is a metalloenzyme including Zn^{2+} in the active region, found in all living species, which catalyzes the reversible conversion of carbon dioxide to bicarbonate and H^+ .²³ This reaction plays a critical role in many physiological processes associated with metabolic pathways, including carbon dioxide.²⁴ Therefore, the regulation of enzyme activity has emerged as an approach in the treatment of diseases such as neuropathic pain,²⁵ glaucoma, edema, idiopathic intracranial hypertension,²⁶ cerebral ischemia,²⁷ cancer,²⁸ and epilepsy.²⁹ The synthesis and discovery of new carbonic anhydrase inhibitors are therefore of great importance. Previous studies have reported that some Schiff bases have an effect on carbonic anhydrase enzyme activity.³⁰ For this reason, the effects of synthesized Schiff base derivatives on the activities of CA-I and CA-II enzymes purified from human erythrocytes were investigated. In addition, *in vitro* antibacterial properties of the compounds were also determined.³⁰

We have also recently synthesized, eight different Schiff bases with structure **1** derived from cinnamaldehyde and p-methoxycinnamaldehyde by microwave irradiation and studied their inhibitory activities on hCA-I and hCA-II isoenzymes. We determined most of compounds to have stronger inhibitory effect comparable with acetazolamide, the used reference and mild antibacterial activity.³²

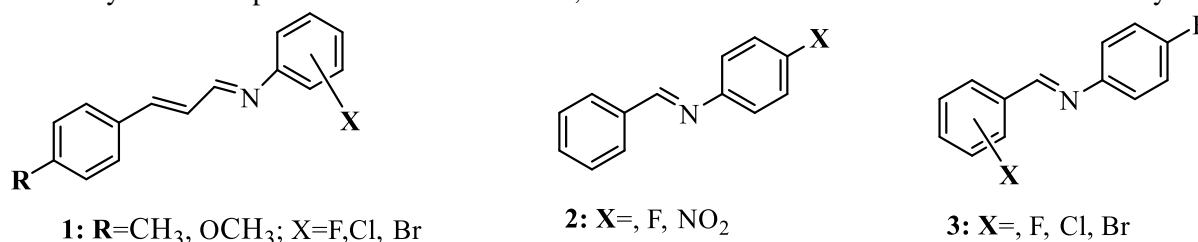


Figure 1. Representative Schiff bases synthesized by our research group in our previous papers

In our previous study, nine N-benzylidene-4-fluoro(nitro)anilines with structures **2** were synthesized and their effects on carbonic anhydrase isoenzymes (hCA-I and hCA-II) were investigated. These study showed that the two compounds have a strong inhibitory effect on the hCA-I and hCA-II isoenzymes.³³ Furthermore, nine Schiff bases derived halogen substituted benzaldehydes and 4-fluoroaniline with structures **3** were synthesized and the data of *in vitro* antibacterial potentials are reported.³⁴

3. Experimental

3.1. Chemical Material and Apparatus

2-Methylbenzaldehyde (**4a**), 3-methylbenzaldehyde (**4b**), 4-methylbenzaldehyde (**4c**), 2-methoxybenzaldehyde (**4d**), 3-methoxybenzaldehyde (**4e**), 4-methoxybenzaldehyde (**4f**), and 4-fluoroaniline (**5**) are commercially available (Merck, Sigma-Aldrich) and were used without further purification. All other chemicals were of analytical grade and obtained from Merck. Reactions were monitored via thin-layer chromatography (TLC). ¹H NMR and ¹³C NMR spectra were recorded on a 400 (100) MHz Varian spectrometer using CDCl₃. Melting points were determined on a capillary melting apparatus (BUCHI 530) and are uncorrected. An MD 20 DB-DG Vestel microwave oven was used (230 V-50 Hz, 1050 W).

3.2. General Synthesis of Schiff Bases **6a-f**

4-Fluoroaniline (**5**) (1 mmol) was added to 2-methylbenzaldehyde (**4a**), 3-methylbenzaldehyde (**4b**), 4-methylbenzaldehyde (**4c**), 2-methoxybenzaldehyde (**4d**), 3-methoxybenzaldehyde (**4e**), or 4-methoxybenzaldehyde (**4f**) (1 mmol), and then the reaction mixture was exposed to microwave radiation at 900 W. The progress of the reaction was monitored by TLC (runner phase: n-hexane and ethyl acetate, 4:1). It was determined that the reactions were completed in 5 minutes for all aromatic aniline derivatives. ^1H NMR and ^{13}C NMR spectra of the residue showed the formation of compounds (**6a-f**) as sole compounds.

(*E/Z*)- *N*-2-Methylbenzylidene-4-fluoroaniline (**6a**): Yield: 92%, yellow solid, m.p. 106-108 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.04, 8.02 (two, s, N=CH, $J = 7.7$ Hz), 7.39 (t, 1xArH, $J = 7.5$ Hz), 7.23 (t, 1xArH, $J = 7.1$ Hz), 6.90-6.74 (m, 4xArH), 6.62 (dd, 2xArH, $J = 8.8, 4.5$ Hz), 2.63 (s, Me). ^{13}C NMR (101 MHz, CDCl_3) δ 173.3, 157.9, 156.0, 141.9, 141.3, 132.9, 131.9, 131.6, 131.1, 128.6, 127.8, 126.5, 125.9, 116.6 (d, $J_{\text{CF}}=8$ Hz), 115.7 (d, $J_{\text{CF}}=22$ Hz), 22.1. HRMS(MH^+) calcd. for $\text{C}_{14}\text{H}_{13}\text{FN}$ (**6a**): m/z : 214.1032; found m/z : 214.1043.

N-3-Methylbenzylidene-4-fluoroaniline (**6b**)³⁵: Yield: 93%, colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, N=CH), 7.72 (s, 1xArH), 7.63 (d, $J = 7.5$ Hz, 1H), 7.34 (t, 1xArH, $J = 7.5$ Hz), 7.27 (d, $J = 7.5$ Hz, 1H), 7.17 (dd, 2xArH, $J = 8.9, 5.0$ Hz), 7.05 (t, 2xArH, $J_{\text{HFC}} = 8.6$ Hz), 2.40 (s, Me) ^{13}C NMR (101 MHz, CDCl_3) δ 161.2 (d, $J = 244$ Hz), 160.4 (CFN), 148.5, 139.0, 136.0, 132.3, 129.2, 128.2, 126.6, 122.2, 115.7, 21.2. HRMS(MH^+) calcd. for $\text{C}_{14}\text{H}_{13}\text{FN}$ (**6b**): m/z : 214.1032; found m/z : 214.1043.

N-4-Methylbenzylidene-4-fluoroaniline (**6c**): Yield: 94%, yellow solid, m.p. 70 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.34 (s, N=CH), 7.75 (d, 2xArH, $J = 8.0$ Hz), 7.23 (d, 2xArH, $J = 7.9$ Hz), 7.15 (dd, 2xArH, $J = 8.8, 5.0$ Hz), 7.03 (t, 2xArH, $^3J_{\text{HF}} = 8.6$ Hz), 2.37 (s, CH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 161.4 (d, $J_{\text{CF}} = 210$ Hz) 160.3 (CH=N), 148.3, 142.1, 133.5, 129.3, 129.0, 122.4, 115.7, 21.6. ^1H and ^{13}C NMR data is agreement with data given in the literature.³⁶ HRMS(MH^+) calcd. for $\text{C}_{14}\text{H}_{13}\text{FN}$ (**6c**): m/z : 214.1032; found 214.1047.

N-2-Methoxybenzylidene-4-fluoroaniline (**6d**)³⁵: Yield: 93%, colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.90 (s, N=CH), 8.12 (d, 1xArH, $J = 8.0$ Hz), 7.43 (t, 1xArH, $J = 7.8$ Hz), 7.20 (dd, 2xArH, $J = 8.7, 5.0$ Hz), 7.04 (dd, 1xArH, $J = 16.2, 7.9$ Hz), 6.94 (d, 1xArH, $J = 8.3$ Hz), 3.88 (s, OCH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 161.1 (d, $J_{\text{CF}} = 274$ Hz), 159.5 (CH=N), 159.3, 156.6, 148.7, 132.8, 127.3, 125.0, 124.8, 122.9, 120.8, 115.9, 111.2, 55.6 (OCH_3). HRMS(MH^+) calcd. for $\text{C}_{14}\text{H}_{13}\text{FNO}$ (**6d**): m/z : 230.0981; found m/z : 230.0994.

N-3-Methoxybenzylidene-4-fluoroaniline (**6e**)³⁷: Yield: 92%, colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.38 (s, N=CH), 7.49 (d, 1xArH, $J = 1.1$ Hz), 7.41-7.32 (m, 2xArH), 7.18 (dd, 2xArH, $J = 8.9, 5.0$ Hz), 7.09-7.01 (m, 3xArH), 3.86 (s, OCH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 161.6 (d, $J_{\text{CF}} = 208$ Hz), 160.6 (CH=N), 148.4, 138.0, 129.7, 122.1, 118.6, 116.2, 112.3, 56.4. HRMS(MH^+) calcd. for $\text{C}_{14}\text{H}_{13}\text{FNO}$ (**6e**): m/z : 230.0981; found m/z : 230.0992.

N-4-Methoxybenzylidene-4-fluoroaniline (**6f**): Yield: 91%, m.p. 74 °C, yellow solid, Lit³⁸. m.p. 70-72 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.35 (s, N=CH), 7.83 (d, 2xArH, $J = 8.7$ Hz), 7.17 (dd, 2xArH, $J = 8.9, 5.0$ Hz), 7.06 (t, 2xArH, $^3J_{\text{HF}} = 8.7$ Hz), 6.98 (d, 2xArH, $J = 8.8$ Hz), 3.86 (s, OCH_3). ^{13}C NMR (101 MHz, CDCl_3) δ 161.1 (d, $J_{\text{CF}}=260$ Hz), 159.5 (CH=N), 148.3, 130.5, 122.9, 114.4, 55.3. HRMS(MH^+) calcd. for $\text{C}_{14}\text{H}_{13}\text{FNO}$ (**6f**): m/z : 230.0981; found m/z : 230.0995.

3.3. Purification of Carbonic Anhydrase and Kinetic Studies

Human erythrocytes were hemolyzed with iced distilled water and centrifuged at 4 °C and 20000 x g for 30 minutes. The obtained supernatant was applied to a Sepharose 4B-L-tyrosine-sulfanilamide

affinity column in accordance with a previously described procedure, and the CA-I and CA-II enzymes were separately eluted.³⁹ The esterase activity of the CA enzyme was used in enzyme activity measurements. The activity measurements were performed spectrophotometrically at 348 nm according to the method described by Verpoorte and colleagues.⁴⁰ In order to investigate the *in vitro* effects of the synthesized substances on enzyme activity, measurements were made for at least five different compound concentrations and saturated substrate concentrations. The concentration amount that caused 50% inhibition (IC₅₀) for each compound was determined by drawing a % activity-compound concentration graph by taking 100% for the control measurement as in previous studies.⁴¹⁻⁴³

3.4. *In vitro* Antibacterial Activity

Studies of antibacterial activities of **6a-f** are given in supporting information of this article.

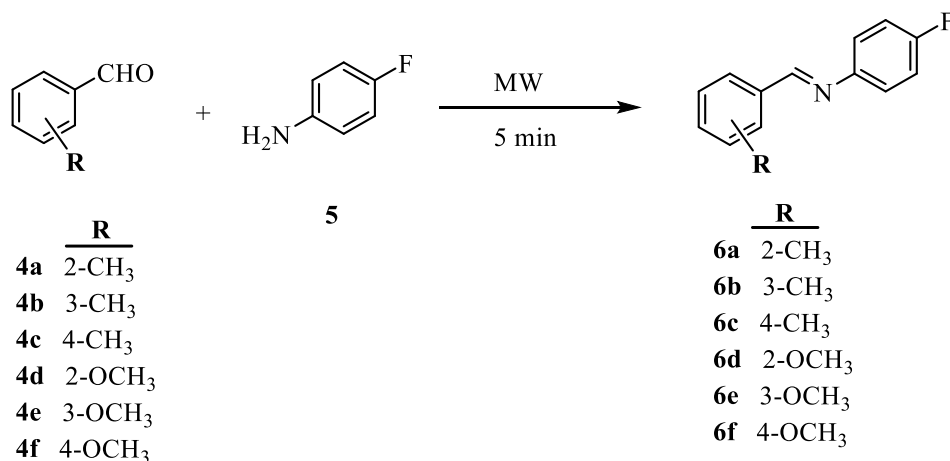
4. Present Study

In vitro antibacterial activities of the synthesized compounds were tested using the agar-well diffusion assay (AWDA) as previously described⁴⁴ at the Antimikrop R & D and Biocidal Analysis Center (Ankara, Turkey). The detail of strains and method are given in supporting information.

In this study, we present facile synthesis of six Schiff bases (**6a-f**) derived from 4-fluoroaniline and methyl or methoxy substituted benzaldehydes and their inhibitory effect on the hCA-I and hCA-II isoenzymes (Scheme 1).

As shown in Scheme 1, the preparation Schiff bases (**6a-f**) were readily and efficiently prepared via microwave irradiation. All ¹H NMR, ¹³C NMR and HRMS data of the prepared compounds were good agreement with the structures.

In their preparation and characterization, the *in vitro* effects of synthesized compounds **6a-f** on CA-I and CA-II activities were investigated. For this purpose, activity measurements were conducted at five different concentrations of the compounds and a saturated substrate concentration. According to the results, an activity % versus compound concentration graph was drawn. IC₅₀ values were calculated with the help of the obtained graph and the results are summarized in Table 1.⁴⁵



Scheme 1. The synthesis route of compounds **6a-f**

Accordingly, all substances showed inhibition effects on both CA-I and CA-II. However, the inhibition effect of all substances was higher for the CA-II enzyme (Table 1, Figures S1 and S2).

On the other hand, among the compounds of interest, **6b** showed the strongest inhibitory effect on both CA-I and CA-II. As is understood from the results, the different groups in the molecular structure and the different positions of the same groups cause these compounds to act differently on the CA-I and CA-II enzyme activities.

It has been reported that CA inhibition can be used in the treatment of diseases such as edema, cancer, infectious diseases, seizures, and glaucoma, and many CA inhibitor classes and inhibition mechanisms have been determined for this purpose.²⁶ In particular, it has been reported that CA-I is involved in brain and retinal edema while CA-II is involved in pathological conditions such as epilepsy, edema, and glaucoma, and inhibition of these enzymes can be a treatment method.⁴² In previous studies, some Schiff base derivatives were synthesized and their inhibitory properties were reported in terms of CA enzyme activity.³⁰ In this study, we have determined the CA inhibitor properties of some new Schiff base derivatives, which can be synthesized by an easy, inexpensive, and quick method. The *in vitro* antibacterial activities of the synthesized compounds were evaluated and none of the compounds showed biological activity against tested microbial strains (see supporting information Table S1).

Table 1. IC₅₀ values of the compounds against hCA-I and hCA-II

| Compounds | hCA-I | | hCA-II | |
|---------------|-----------------------|----------------|-----------------------|----------------|
| | IC ₅₀ (μM) | r ² | IC ₅₀ (μM) | r ² |
| 6a | 1165 | 0.97 | 746.27 | 1 |
| 6b | 7.43 | 0.97 | 3.41 | 0.92 |
| 6c | 27.73 | 0.86 | 8.77 | 0.98 |
| 6d | 16.5 | 0.95 | 5.73 | 0.97 |
| 6e | 43.32 | 0.99 | 21 | 0.94 |
| 6f | 35.92 | 0.99 | 14.44 | 0.96 |
| Acetazolamide | 1.17 | 0.94 | 0.98 | 0.97 |

As a conclusion, Schiff bases have extensive biological applications in the pharmaceutical field. Microwave irradiation provides significant improvement over existing conventional procedures and reveal a novel method that with short reaction times, excellent efficiency and without formation of undesirable side products for the synthesis of Schiff bases **6a-f**. In addition, their effects on CA-I and CA-II enzymes were determined. The results showed that the compound **6b** showed the strongest inhibitory effect on both CA-I and CA-II.

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Supporting Information

Supporting information accompanies this paper at <http://www.acgpubs.org/journal/organic-communications>

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