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Synthesis of Benzimidazole derivatives containing Schiff base exhibiting antiurease activities

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Abstract

In this study some novel Schiff bases derivatives of benzimidazole containing thiophene ring were designed and synthesized by using various aldehydes. Seven different aromatic aldehydes with various side groups were used for synthesized. ^{1}H-NMR, ^{13}C-NMR spectra and LC-MS were used to identify all of the compounds. All synthesized compounds anti urease activities were calculated according to phenol-hypochlorite method by Weatherburn. The results indicated that all compounds have anti urease activity between 12.70±0.11 µg/mL and 14.00±0.08 µg/mL IC_{50} values. Especially the compound N'-[(1E)-2-furylmethylene]-2-[5,6-dimethyl-2-(2-thienylmethyl)-1*H*-benzimidazol-1-yl]acetohydrazide (5g) has very close IC_{50} value (12.70±0.11 µg/mL) to thiourea (12.60±0.10 µg/mL) that is the standard inhibitor. 5g bearing furan ring at the N-3 position on the benzimidazole nucleus has the smallest volume of side group than others.

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1. Introduction

Enzyme inhibition studies, which are important areas of pharmaceutical research, have already led to the discovery of wide variety of drugs useful in a number of diseases. Urease inhibitors are important to control the damaging effects of ureolytic bacterial infections in humans such as urinary stone formation, peptic ulcer and hepatic coma. Also, urease inhibitors have been regarded as targets for new antiulcer drugs [1,2]. Urease inhibitors have received special attention over the past few years because of their potential uses besides of using medicine. Controlling hydrolysis of urea in soil is crucial situation. Urease inhibitors protect soil from pH elevation [3]. These inhibitors, which are generally divided into two classes, substrate structural analogs like hydroxamic acid and those which affect the mechanism of the reaction like phosphoramidat, lansoprazole, omeprazole, thiol-compounds, quinines and Schiff base derivatives are reported as potent urease inhibitors [4]. In our recent studies we have investigated Schiff base derivatives, which were most active inhibitors of Jack bean urease [5,6].

Benzimidazoles are significant heterocyclic compounds because of their structurally similarity to purine and its derivatives, proteins inside the bacterial cell wall and it is the basic part of the structure of vitamin B_{12}. [7] Also, benzimidazoles have a wide range of biological activities including antioxidant [8], anticancer, antimicrobial [9], antihistaminic, antiinflammatory [10], enzyme inhibitions [11,12] and they have an important role in the field of medicine. A condensation reaction between aldehydes or ketones with primary amines in alcoholic conditions form Schiff bases. Aromatic-based Schiff bases have many advantages and show more potential in biological applications as a result of the free electron delocalization with the ring structure. They are very significant class of organic compounds that show interest in industrial sectors with many biological and pharmaceutical applications [13]. The heterocyclic compounds such as imidazole and benzimidazole and also thiophene ring have most predominant heteroatoms which are mainly nitrogen, oxygen, and sulfur (N, O, S). Also, they are important class of pharmacophores and they are well known as drugs [14,15].

The present study covers the synthesis of novel benzimidazoles containing thiophene ring linked with Schiff base and their evaluation as urease inhibitors.

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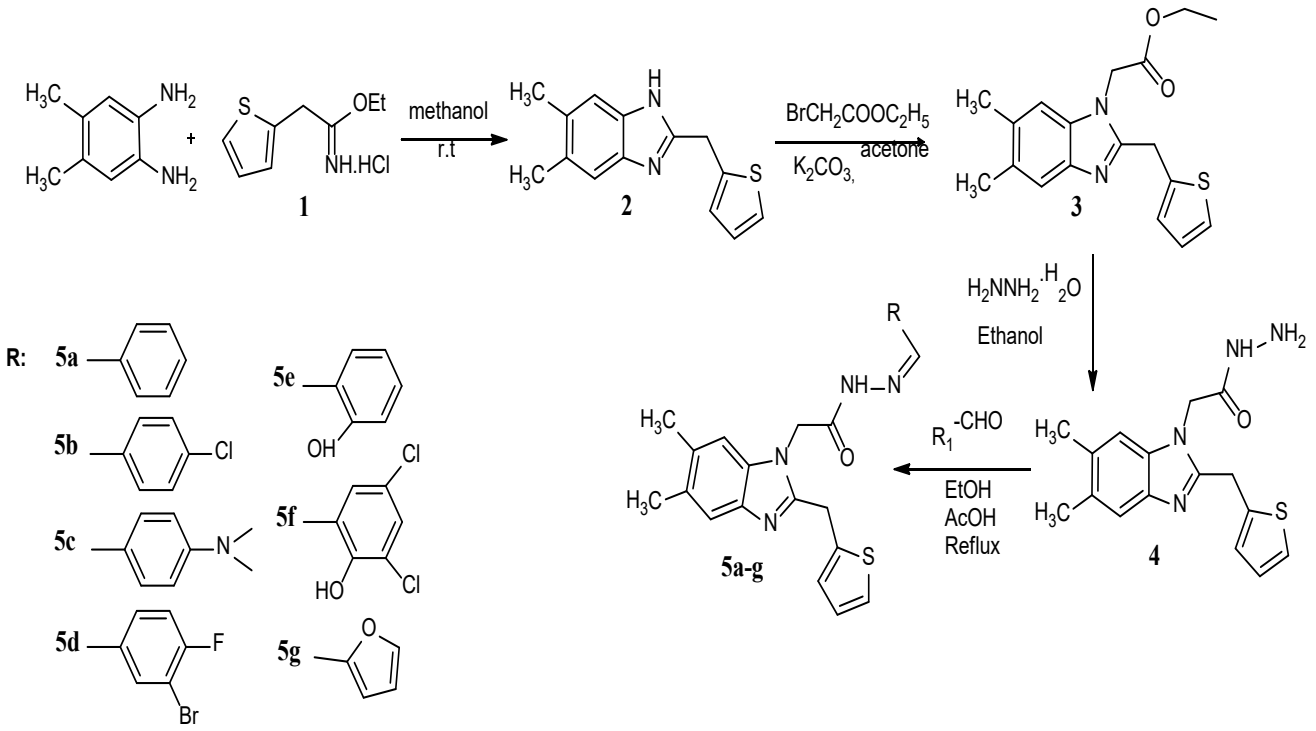
2. Results and Discussion

2.1. Chemistry

I have synthesized seven new Schiff bases based of benzimidazole. Synthesis scheme of all target compounds is shown in Scheme 1. Firstly, iminoester hydrochloride (**1**) was prepared according to the procedure [16]. Compound 1 was added to the solution of 4,5-dimethyl-1,2-phenylenediamine in methanol and refluxed. The starting benzimidazole (2) was reacted with ethyl bromoacetate in acetone with K_2CO_3 to synthesize ethyl[5,6-dimethyl-2-(thiophen-2ylmethyl)-1*H*-benzimidazol-1-yl]acetate (3).



Scheme 1. The synthetic way of the target compounds

Ethyl [5,6-dimethyl-2-(thiophen-2-ylmethyl)-1*H*-benzimidazol-1-yl]acetate (3) reacted with hydrazine hydrate in pure ethanol gave benzimidazole derivative of hydrazide compound 4. After this stage, hydrazide (4) was treated with seven different aromatic aldehydes catalysed with AcOH in ethanol to synthesize Schiff bases (5a-g). The structures of all these compounds were identified by Infirared (IR), Proton and Carbon Nuclear Magnetic Resonance data and Mass spectra. All data of compounds are compatible with each other. IR spectra gave NH bands from benzimidazoles of these compounds between 3187 and 3407 cm^{-1} ,C=O band between 1656 and 1706 cm^{1} and C=N band between 1521 and 1600 cm^{-1}. Proton NMR spectra of Schiff bases (5a-f) gave the correct signals with proposed structures. NH signals are appeared at about 11.43-11.86 ppm with different cis/trans conformer ratios. NCH_2 signals are between 5.14 and 5.44 ppm. There are two -CH_3 signals in spectrum from benzimidazole ring. C═N signals of benzimidazoles are at about 152.64 ppm in carbon NMR spectra for all compounds. The imine carbon atoms from Schiff bases (**5a-g**) are resonated at 149.11 (for **5a**), 150.32 (for **5b**), 149.06 (for **5c**), 152.79 ppm (for **5d**) ,151.26 (for **5f**), 149.41 (for **5g**) in the ^{13}C-NMR spectrum.

2.2. Urease inhibitory assay

Urease inhibition studies of new compounds were calculated according to Phenol-hypochlorite method by Weatherburn (1967) [17]. All of the compounds and thiourea were dissolved in DMSO and screened at 20 µg/mL final concentration. Schiff bases showed inhibitor activity at low final concentrations. Thiourea was used as positive control. In this study lower IC_{50} values of compounds display higher enzyme inhibitory effectiveness.

Table 1: The new Schiff Bases Chemical Structures and IC_{50} values

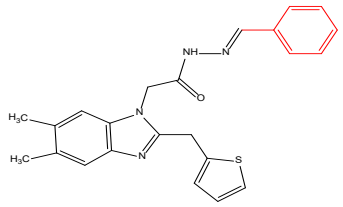
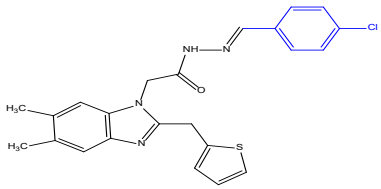
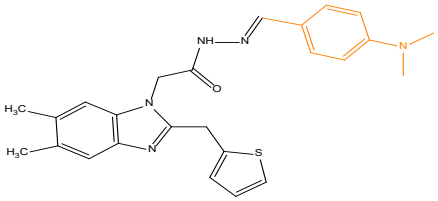
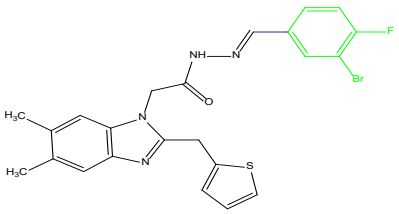
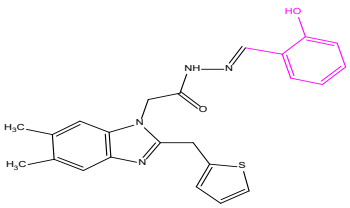
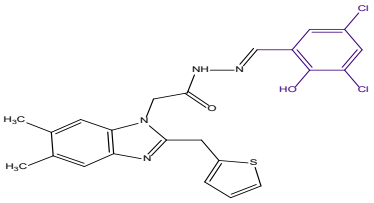
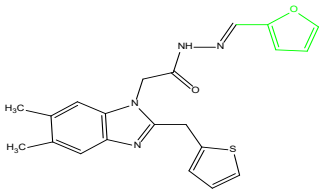
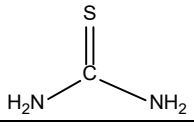
Compounds	Chemical Structure	IC_{50} (µg/mL)
5a		12.79±0.10 µg/mL
5b		12.80±0.08 µg/mL
5c		13.50±0.12 µg/mL
5d		14.00±0.08 µg/mL
5e		13.12±0.09 µg/mL
5f		13.60±0.06 µg/mL
5g		12.70±0.11 µg/mL
Thiourea		12.60±0.10 µg/mL

Table 1 shows IC_{50} values of compounds and the standard at 20 µg/mL final concentrations. All Schiff bases have anti urease activity between 12.70±0.11 and 14.00±0.08 µg/mL values. **5g** has the best inhibition activity with IC_{50}: 12.70±0.11 µg/mL. **5g** bearing furan ring at the N-3 position on the benzimidazole nucleus. The results show that antiurease activity decreases with increased volume of side groups.

3. Experimental

3.1. Synthesis of compound 2

0.2 g (0.010 mol) iminoester hydrocloride (1) was added to the solution of 0.13 g 4,5-dimethly1,2-phenylenediamine (1 mmol) in 40 ml dry methanol. The mixture was stirred about an hour and then refluxed at about 2h. When the reaction completed controlled by TLC, the balloon was cooled until room temperature. Water was added to the mixture to precipitate the product. White compound was filtrated and recrystallized from ethanol.

3.1.1. 5,6-Dimethyl -2- (thiophen-2-ylmethyl) -1*H*-benzimidazole (2)

Yield 83%, mp: 147-149°C , IR (ν_{max}, cm^{-1}): 3250 (NH), 1500 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6): 1.17 (t, J= 6.8 Hz, 3H, CH_3), 4.40 (s, 2H, CH_2), 6.80–7.45 (m, 5H, ArH) and 12.08 (s, 1H, NH).^{13}C-NMR (100 MHz, DMSO-d_6): 20.36 (CH_3), 29.77 (CH_2), 125.32, 126.62, 126.40, 127.32, 130.07, 140.17 (Ar–C) and 152.11 (C=N). LC-MS, m/z: 242.98 $[M+H]^+$.

3.2. Synthesis of compound 3

2.42 g compound **1** (0.010 mol) in 10 mL of acetone and 3.45 g K_2CO_3 (0.025 mol) was stirred at room temperature for 1h in a balloon. Ethyl bromoacetate (0.011 mol) was added into the mixture and stirred at room temperature for further 8h. The mixture was poured into water and the white solid was filtered off and recrystallized from a solution of ethanol:water (1:3).

3.2.1. **Ethyl [5,6-dimethyl-2-(thiophen-2-ylmethyl)-1*H*-benzimidazol-1-yl]acetate (3):** Yield 90%, mp: 114-116 °C, IR (ν_{max}, cm^{-1}): 1738 (C=O), 1515 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6): 1.12 (t, 3H, J= 7.2 Hz, CH_3), 4.02 (m, 2H, OCH_2), 4.41 (s, 2H, CH_2), 5.08 (s, 2H, NCH_2), 6.92 (t, J= 7.2 Hz, 3H, ArH), 7.19 (s, 1H, ArH), 7.35 (d, J=7.2 Hz 1H, ArH). ^{13}C-NMR (100 MHz, DMSO-d_6): 14.38 (CH_3), 20.27 (CH_3), 20.51 (CH_3), 28.03 (CH_2), 44.92 (NCH_2), 61.55 (OCH_2), ArC [110.65, 119.30, 125.69, 126.65, 130.31, 131.07, 134.60, 139.15, 140.99], 152.39 (C=N) and 168.24 (C=O). LC-MS, m/z: 328.94 $[M+H]^+$.

3.3. Synthesis of compound 4

To a solution of compound **2** (3.28 g, 0.010 mol) in 10 mL of ethanol, hydrazine monohydrate (0.035 mol) was added and the mixture was stirred for 4h. The reaction was scanned by TLC (ethanol:ethyl acetate, 3:1). The mixture was filtered off, dried and recrystallized.

3.3.1. 2-[5,6-Dimethyl-2-(thiophen-2-ylmethyl)-1*H*-benzimidazol-1-yl]acetohydrazide (4)

Yield 85%, mp: 237-239 °C. IR (ν_{max}, cm^{-1}): 3379-3165 ($NH-NH_2$), 1663 (C=O), 1518 (CN). ^{1}H-NMR (400 MHz, DMSO-d_6): 9.45 (s, 1H, NH), 7.86 (m, 2H, ArH), 7.17 (s, 1H, ArH), 6.94 (m, 3H, ArH), 4.72 (s, 2H, NCH_2), 4.42 (s, 2H, NH_2), 4.02 (s, 2H, CH_2). ^{13}C-NMR (100 MHz, DMSO-d_6): 20.29, 20.57 (CH_3), 28.15 (CH_2), 44.86 (NCH_2), ArC [110.59, 119.27, 125.55, 126.61, 127.18, 130.13, 134.52, 139.34, 141.08], 152.71 (C=N), 166.41 (C=O), 170.59 (C-S). LC-MS, m/z: 314.94 $[M+H]^+$.

3.4. Synthesis of compounds 5a–g.

About ten mmol of aromatic aldehyde was added to the solution of compound **3** (3.14 g, 10 mmol) in 15 mL dry ethanol and containing 0.5 mL of glacial acetic acid. The mixture was then refluxed for 5h and the reaction was viewed by TLC. Then, the mixture was cooled to room temperature, and a white solid was precipitated. The product was filtrated, washed with water, and recrystallized from ethanol to obtain pure compounds **5a–g**.

3.4.1. 2-[5,6-Dimethyl-2-(2-thienylmethyl)-1*H*-benzimidazol-1-yl]-*N*'-[(1*E*)-phenylmethylene] acetohydrazide (5a)

Yield: 90%, mp: 217–219°C. IR (ν_{max}, cm^{-1}): 3187 (NH), 1700 (C═O), 1521(C═N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.10 (3H,t, J=8.0 Hz, CH_3), 4.46 (2H, s, CH_2), 5.44 (2H, s, NCH_2), 6.94 (1H, s, ArH), 7.27 (1H, s, ArH), 7.36–7.52 (3H, m, ArH), 7.79 (2H, d, *J*=8.0 Hz, ArH), 8.31 (1H, s, CH), 11.85 (1H, s, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 20.28, 20.44 (CH_3), 27.83 (CH_2), 44.88 (NCH_2), ArC:[111.12, 118.51, 125.79, 126.87, 127.21, 129.13, 129.20, 129.33, 133.41, 134.92, 138.64, 143.29, 146.67], 149.11 (C=N, Schiff base), 152.64 (C=N, benzimidazole), 168.34 (C=O). LC-MS, m/z: 242.98 $[M+H]^+$. LC-MS, m/z: 403.05 $[M+H]^+$. Cal: 402.51 $[M^+]$.

3.4.2. *N*'-[(1*E*)-(4-chlorophenyl)methylene]-2-[5,6-dimethyl-2-(2-thienylmethyl)-1*H*-benzimidazol-1-yl]acetohydrazide (5b)

Yield: 90%, mp: 114–116°C. IR (ν_{max}, cm^{-1}): 3207 (NH), 1697 (C═O), 1608 (C═N). ^{1}H-NMR (400 MHz, DMSO-d_6): 1.12 (3H, t, J= 8.2 Hz, CH_3), 4.48 (2H, s, CH_2), 5.44 (2H, s, NCH_2,), 6.92-7.27 (3H ,m, ArH), 7.37 (1H, s, ArH), 7.52 (1H, d, *J*=8.0 Hz, ArH), 7.71 (2H, d, *J*=8.0 Hz, ArH), 7.78 (1H, d, *J*=8.0 Hz, ArH), 8.32 (1H, s, CH), 11.85 (1H, s, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 20.28, 20.43 (CH_3), 27.82 (CH_2), 44.87 (NCH_2), ArC: [111.10, 118.49, 125.79, 126.87, 127.21, 129.13, 129.32, 130.85, 131.50, 134.40, 134.92, 135.08, 138.86, 143.31, 146.68], 150.32 (C=N, Schiff base), 152.63 (C=N, benzimidazole), 168.32 (C=O). LC-MS, m/z: 437.00 $[M+H]^+$. Cal: 436.96 $[M^+]$.

3.4.3. *N*'-{(1*E*)-[4-(dimethylamino) phenyl] methylene } -2-[5,6-dimethyl -2-(2-thienylmethyl) -1*H*- benzimidazol-1-yl]acetohydrazide (5c)

Yield: 92%, mp: 199-200 °C. IR (ν_{max}, cm^{-1}): 3190 (NH), 3024 (ArCH), 1656 (C═O), 1597 (C═N) cm^{-1} . ^{1} H-NMR (400 MHz, DMSO-d_6): 1.18 (3H, t, J= 8 Hz, CH_3), 4.44 (2H, s, CH_2) and 5.31 (2H, s, NCH_2), 6.70 (2H, t, J = 8 Hz, ArH), 6.92 (1H, s, ArH), 7.19 (1H, s, ArH), 7.25 (1H, s, ArH), 7.34 (1H, s, ArH), 7.49-7.52 (2H, m, ArH), 7.93 (1H, s, CH), 11.43 (1H, s, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 20.25, 20.41, 20.48 (CH_3), 40.19 (N–CH_3), 44.65 (CH_2) and 45.28 (NCH_2), ArC: [110.91, 112.16, 118.76, 121.61, 125.70, 126.74, 127.27, 128.79, 129.02, 130.70, 131.37, 134.34, 134.68, 138.96, 140.25, 145.74], 149.06 (C═N, Schiff base), 152.05 (C═N, benzimidazole), 167.70 (C═O). LC-MS, m/z: 446.10 $[M+H]^+$. Cal: 445.58 $[M^+]$.

3.4.4. *N*'- [(1*E*) - (3-bromo - 4- fluorophenyl) methylene] -2- [5,6-dimethyl -2- (2-thienylmethyl) -1*H*- benzimidazol -1 -yl]acetohydrazide (5d)

Yield: 93%, mp: 258–260 °C. IR (ν_{max}, cm^{-1}): 3407 (NH), 3094 (ArCH), 1707 (C═O), 1609, 1540 (C═N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm: 1.05 (3H, s, CH_3), 4.40 (2H, s, CH_2), 5.42 (2H, s, NCH_2), 6.93 (s, 2H, ArH), 7.20–7.45 (3H, m, Ar–H), 7.79 (1H, s, Ar–H), 8.01 (1H, s, N═CH), 8.14 (1H, s, ArH), 11.81 (1H, s, NH). ^{13}C-NMR (100 MHz, DMSO-d_6), : 20.29, 28.18 (CH_3), 44.68 (CH_2), 45.75 (NCH_2), ArC: [109.37, 110.79, 117.48, 119.18, 125.55, 126.60, 127.10, 129.06, 129.98, 130.75, 131.87, 132.82, 135.03, 139.32, 141.11, 141.86], 152.79 (C═N, Schiff base), 158.18 (Benzimidazole, C═N), 160.66 (C-F, d, J_{CF} = 247 Hz), 168.76 (C═O). LC-MS, m/z: 500.00 $[M+H]^+$. Cal M^+: 499.40 $[M^+]$.

3.4.5. *N*'-[(1*E*)-(2-hydroxyphenyl)methylene]-2-[5,6-dimethyl-2-(2-thienylmethyl)-1*H*-benzimidazol-1-yl]acetohydrazide (5e):

Yield: 89%, mp: 200–202 °C. IR (ν_{max}, cm^{-1}): 3397 (NH), 1698 (C═O), 1606, 1548 (C═N) cm^{-1}. ^{1} H-NMR (400 MHz, DMSO-d_6): 1.20 (3H, t, J=7.2 Hz, CH_3), 4.34 (2H, s, CH_2), 5.14 (2H, s, NCH_2), 6.91 (s, 2H, ArH), 7.20–7.34 (3H, m, Ar–H), 7.75 (1H, s, Ar–H), 8.36 (1H, s, N═CH), 8.56 (1H, s, ArH), 10.23 (1H, s, OH), 11.71 (1H, s, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 21.29, 30.18 (CH_3), 44.62 (CH_2), 45.75 (NCH_2), ArC:[110.62, 119.36, 122.05, 124.40, 126.66, 127.68, 128.07, 128.76, 129.16, 130.32, 130.75, 131.04, 134.66, 135.02, 139.30, 141.07], 147.19, 151.26 (C═N, Schiff base), 152.72 (Benzimidazole, C═N), 164.01, 168.50 (C═O). LC-MS, m/z: 418.94 $[M+H]^+$. Cal: 418.51 $[M]^+$.

3.4.6. *N*'-[(1*E*) - (3,5-dichloro-2-hydroxyphenyl) methylene]-2-[5,6-dimethyl-2-(2-thienylmethyl)-1*H*-benzimidazol-1-yl]acetohydrazide (5f)

Yield: 95%, mp: 278–280 °C. IR (ν_{max}, cm^{-1}): 3076 (NH), 1706 (C═O), 1479 (C═N) cm^{-1}. ^{1} H-NMR (400 MHz, DMSO-d_6): 1.12 (3H, t, J=8.0 Hz, CH_3), 4.44 (2H, s, CH_2), 5.44 (2H, s, NCH_2), 6.90-6.98 (m, 2H, ArH), 7.35 (1H, d, J=8.0 Hz, ArH), 7.23 (1H, d, J=8.0 Hz, ArH), 7.79 (1H, s, Ar–H), 8.29 (1H, s, N═CH), 8.39 (1H, s, ArH), 10.33 (1H, s, OH), 11.86 (1H, s, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 20.29, 28.18 (CH_3), 44.68 (CH_2), 45.75 (NCH_2), ArC: [110.62, 119.34, 123.05, 124.40, 125.54, 126.68, 127.07, 128.76, 130.00, 130.32, 130.75, 131.04, 134.66, 135.02, 139.30, 141.07], 147.19, 151.26 (C═N, Schiff base), 152.72 (Benzimidazole, C═N), 164.01, 168.50 (C═O). LC-MS, m/z: 486.98 $[M+H]^+$. 487.40 $[M]^+$.

3.4.7. *N*'-[(1*E*) -2-furylmethylene] -2- [5,6-dimethyl -2- (2-thienylmethyl) - 1*H* – benzimidazol -1- yl] acetohydrazide (5g)

Yield: 82%, mp: 208–210 °C. IR (ν_{max}, cm^{-1}): 3087 (NH), 1702 (C═O), 1509 (C═N) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 1.04, (3H, s, CH_3), 4.40 (2H, s, CH_2), 5.28 (2H, s, NCH_2), 6.61-6.93 (m, 3H, ArH), 7.19, (1H, s, ArH), 7.34 (1H, s, ArH), 7.92 (2H, t, ArH), 8.11(1H, s, ArH), 11.66 (1H, s, NH). ^{13}C-NMR (100 MHz, DMSO-d_6): 19.00, 20.27 (CH_3), 44.56 (CH_2), 56.47 (NCH_2), ArC:[110.62, 112.64, 114.37, 119.15, 125.56, 126.57, 127.12, 130.05, 130.86, 134.67, 134.93, 137.79, 139.33, 141.05, 145.59], 149.41 (C═N, Schiff base), 152.79 (Benzimidazole, C═N), 163.57, 168.26 (C═O). LC-MS, m/z: 392.97 $[M+H]^+$. Cal: 392.47 $[M]^+$.

3.5. Antiurease activity assay

Urease enzyme inhibition studies were performed according to the method developed by Weatherburn (1967) in the literature [17]. Phenol-hypochlorite method based on enzyme substrat interaction resulting ammonium ion. Reaction mixtures including 400 µL of buffer at pH 8.2 (100 mM urea, 0.01 M K_2HPO_4, 1 mM EDTA and 0.01 M LiCl), 200 µL of Jack Bean Urease and 100 µL of the test compound solution in DMSO were incubated at room temperature for 15 min. 650 µL phenol reagent (1% w/v phenol and 0.005% w/v sodium nitroprusside) and 650 µL alkali reagent (0.5% w/v sodium hydroxide and 0.1% v/v NaOCl) were added to each tube and the increasing absorbance at 625 nm with blue-navy colour was measured after 50 min, using a UV/vis spectrophotometer. Jack bean urease was used as model enzyme. Thiourea was used as positive control. Different concentrations of inhibitory compounds were used and IC_{50} values were calculated.

The percentage inhibition was calculated using the following equation 100 −(ODtest well/ODcontrol)×100.

4. Conclusions

I designed and synthesized new Schiff bases containing thiophene ring and derivatives of benzimidazoles. I used seven different aromatic aldehydes with several side groups. Schiff bases synthesized with high efficiency and their chemical structures were confirmed by spectral methods. Their urease inhibition activities were evaluated using Phenol-hypochlorite method by Weatherburn and compared to the standard inhibitor thiourea. Results indicate that all synthesized Schiff bases have antiurease activity and especially compound N'-[(1E)-2-furylmethylene]-2-[5,6-dimethyl-2-(2-thienylmethyl)-1*H*-benzimidazol-1-yl]acetohydrazide has the best IC_{50} value that is bearing furan ring at the N-3 position on the benzimidazole nucleus, which has the smallest volume of side group than others.

Conflicts of interest

The authors state that did not have conflict of interests

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