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# Urease and acetylcholinesterase enzyme inhibitor novel phthalonitrile azo compounds

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Based on the relationship between *Helicobacter pylori* and Alzehimer's disease, new azo phthalonitrile compounds containing different amino pyridines have been synthesized. These compounds can inhibit both Urease and Acetylcholinesterase, which are the most important enzymes in the treatment of *Helicobacter pylori* and Alzehimer's disease, respectively. All compounds have shown better inhibition than standards in the presence of both enzymes. Especialy, azo phthalonitrile compound **4** is more active than other compounds and standards, showed a significant inhibition performance and efficient $IC_{50}$ values to Urease (20.47±0.14 µM) and Acetylcholinesterase (4.73±0.07 µM) enzymes. Interestingly, the inhibitory effect of the newly synthesized compounds against to Urease and Acetylcholinesterase is same ranking.

**Keywords**: Phthalonitrile, Azo dyes, Urease, Acetylcholinesterase, Enzyme inhibition

*Helicobacter pylori* (*H. pylori*) is a gram-negative bacterium first isolated in 1982 by Warren and Marshall [24, 32]. *H. pylori* lives in the human gastric mucosa and causes the epithelium cells to die by the creation of cytotoxins. The gastric lumen has an acidic pH. H. pylori can live here for only few minutes and should reach the mucus layer as soon as possible [4]. The mucus layer, which consists of sulfated polysaccharides, allows the diffusion of protons from the stomach acid and protects the mucosal cells from acid by acting as a buffer. Bacteria reach this layer, thanks to its rapid movement and Urease enzyme. Bicarbonate and urea are released from gastric epithelial cells. By breaking down the urea and obtaining ammonia with its Urease enzyme, the bacterium creates the pH at which it can colonize and live in this ammonia cloud [33]. Urease is an enzyme that catalyzes the hydrolysis of urea to ammonia and carbon dioxide and contains a nickel atom in its structure.

The main etiological factor for stomach cancer is *H. Pylori* [23]. However epidemiological studies have shown that H. pylori infection is also associated with non-gastric diseases like Alzehimer's disease [3, 8, 21, 28]. Alzheimer's disease generaly is characterised by progressive loss of cognitive ability primarily memory loss, leading to dementia. The main clinical treatment of this disease contains the maintenance of adequate levels of Acetylcholine (ACh) at neurotransmission sites. Thus, the inhibition of Acetylcholinesterase (AChE) prevents the hydrolysis of ACh thereby maintaining normal memory function.

Based on these knowledges, new chemical compounds that inhibit both of enzymes can be important to prevent *H. pylori* and Alzehimer's disease. Although there are a few reports about both Urease and Acetylcholinesterase inhibition, none of the report contain our new conceptual approach [5, 10,25]. The present work was designed to obtain new inhibitor candidates for both Urease and Acetylcholinesterase enzymes.

Aminopyridines that very important chemical compounds have been reported for variety of biological activities and most of their in clinical uses in neurological disorders [29, 31]. It is known that many azo and phthalonitrile compounds inhibit various clinically important metabolic enzymes like Urease and Acetylcholinesterase [15-17, 20]. Therefore, in this work we have designed the new phthalonitrile azo compounds containing amino pyridine derivatives that can inhibit both Urease and Acetylcholinesterase enzymes.

## Expemimental Details

4-Nitro–1,2-dicyanobenzene, 4,5-dichloro-1,2-dicyanobenzene, 3-(4-Hydroxyphenlyazo) pyridine **(I)** and 4-(4-Hydroxyphenlyazo)pyridine **(II)** were prepared according to literature procedures [6, 26, 35-36]. FT-IR spectra were recorded by Perkin-Elmer

Spectrum 100 Infrared Spectrometer. $^{1}$H NMR and $^{13}$C NMR studies were performed by Agilent 400 FT-NMR. Mass spectra were performed by Thermo Scientific TSQ Quantum Access Max.

**Synthesis procedure**

**Synthesis of 4-(4-[pyridin-3-lydiazenyl]phenoxy) phthalonitrile (1)**

3-(4-Hydroxyphenlyazo) pyridine (**I**) (1 g, 5.02 mmol) and 4-Nitro–1,2-dicyanobenzene (0.86 g, 5.02 mmol) were dissolved in dry dimethylformamide (DMF, 50 mL). After stirring for 30 min, finely ground anhydrous $K_2CO_3$ (15 g, 10.86 mmol) was added to reaction mixture and was stirred at 60°C for 72 h, and then poured into ice water (500 mL). The raw product was filtered off and washed with water until the filtrate became neutral. Pure compound **1** was obtained by column chromatography (silica gel, MeOH : $CHCl_3$, 5:200). Yield: 1.29 g, 79%; m. p. 179-180 °C. FTIR$\nu_{max}$/cm$^{-1}$ 3071, 3047, 2232 (C≡N), 1586 (C=C), 1563, 1485, 1420, 1305, 1284, 1251, 1213, 847, 811, 700. $^{1}$H NMR (DMSO-$d_6$) δ, ppm: 9.11-9.10 (1H, d.d, ArH), 8.74-8.73 (1H, d.d, ArH), 8.19-8.18 (1H, d.d, ArH), 8.16-8.14 (1H, d, ArH), 8.04-8.02 (1H, d, ArH), 7.96-7.95 (1H, d, ArH), 7.64-7.60 (1H, q.d, ArH). 7.58-7.55 (1H, d.d, ArH), 7.40-7.38 (1H, d.d, ArH). $^{13}$C NMR (DMSO-$d_6$) δ, ppm: 160.41, 157.60, 152.62, 149.53, 147.75, 146.74, 136.88, 127.36, 125.66, 125.08, 124.23, 123.78, 121.12, 117.34, 116.26, 115.76, 109.70. MS: m/z 325,87 [$M^+$].

**Synthesis of 4-Chloro-5-(4-[pyridin-3-yldiazenyl] phenoxy)phthalonitrile (2) and 4,5 bis(4-[pyridin-3-yldiazenyl]phenoxy)phthalonitrile (3)**

3-(4-Hydroxyphenlyazo) pyridine (**I**) (1 g, 5.02 mmol) and 4,5-dichloro-1,2-dicyanobenzene (0.49 g, 2.51 mmol) were dissolved in dry dimethylformamide (DMF, 50 mL). After stirring for 30 min, finely ground anhydrous $K_2CO_3$ (2.5g, 18.86 mmol) was added to reaction mixture and was stirred at 60°C for 72 h, and then poured into ice water (500 mL). The raw product was filtered off and washed with water until the filtrate became neutral. Pure compounds **2** (first fraction) and **3** (second fraction) were obtained by column chromatography (silica gel, MeOH : $CHCl_3$, 5:200).

**4-Chloro-5-(4-[pyridin-3-yldiazenyl]phenoxy) phthalonitrile (2)**

Yield: 0.10 g, 5%; m. p. 158-159°C. FTIR $\nu_{max}$/cm$^{-1}$ 3095, 3020, 2235 (C≡N), 1578 (C=C), 1554, 1485, 1418, 1380, 1273, 1205, 1143, 1010, 854, 816, 697. $^{1}$H NMR (DMSO-$d_6$) δ, ppm: 9.11-9.10 (1H, d, ArH), 8.75-8.73 (1H, d.d, ArH), 8.61 (1H, s, ArH), 8.19-8.16 (1H, d.q, ArH), 8.03-8.01 (1H, d, ArH), 8.02 (1H, s, ArH), 7.64-7.61 (1H, q, ArH), 7.38-7.36 (1H, d, ArH). $^{13}$C NMR (DMSO-$d_6$) δ, ppm: 157.78, 155.82, 152.59, 149.44, 147.76, 146.70, 136.88, 130.66, 127.40, 125.66, 125.49, 125.10, 120.07, 115.99, 115.32, 115.30, 111.64. MS: m/z 359,99 [$M^+$].

**4,5 bis(4-[pyridin-3-yldiazenyl]phenoxy)phthalonitrile (3)**

Yield: 0.25 g, 19%; m. p. 200-201 °C. FTIR$\nu_{max}$/cm$^{-1}$ 3039, 2233 (C≡N), 1583, 1576 (C=C), 1488, 1413, 1396, 1300, 1200, 1146, 1078, 848, 814, 698. $^{1}$H NMR (DMSO-$d_6$) δ, ppm: 9.07-9.07 (2H, d, ArH), 8.72-8.70 (2H, d.d, ArH), 8.17 (2H, s, ArH), 8.15-8.12 (2H, d.q, ArH), 7.96-7.94 (4H, d, ArH), 7.61-7.58 (2H, q, ArH), 7.30-7.28 (4H, d, ArH). $^{13}$C NMR (DMSO-$d_6$) δ, ppm: 158.46, 152.50, 150.66, 149.00, 147.73, 146.67, 127.55, 127.31, 125.46, 125.04, 119.19, 115.64, 112.62. MS: m/z 522,69 [$M^+$].

**Synthesis of 4-(4-[pyridin-4-lydiazenyl]phenoxy) phthalonitrile (4)**

4-(4-Hydroxyphenlyazo) pyridine (**II**) (1 g, 5.02 mmol) and 4-Nitro–1,2-dicyanobenzene (0.87 g, 5.02 mmol) were dissolved in dry dimethylformamide (DMF, 50 mL). After stirring for 30 min, finely ground anhydrous $K_2CO_3$ (1.5 g, 10.86 mmol) was added to reaction mixture and was stirred at 60°C for 72 h, and then poured into ice water (500 mL). The raw product was filtered off and washed with water until the filtrate became neutral. Pure compound **4** was obtained by column chromatography (silica gel, MeOH : $CHCl_3$, 5:200). Yield: 0.98 g, 60%; m. p. 217-218 °C. FTIR$\nu_{max}$/cm$^{-1}$ 3099, 3056, 2971, 2232 (C≡N), 1586 (C=C), 1563, 1482, 1408 (N=N), 1279, 1244, 1208, 868, 852, 832. $^{1}$H NMR (DMSO-$d_6$) δ, ppm: 8.83-8.80 (2H, m, ArH), 8.17-8.14 (1H, d.d, ArH), 8.06-8.03 (2H, d.d, ArH), 7.98-7.96 (1H, t, ArH), 7.74-7.72 (2H, m, ArH), 7.60-7.56 (1H, d.t, ArH), 7.41-7.38 (2H, d.d, ArH). $^{13}$C NMR (DMSO-$d_6$) δ, ppm: 160.22, 158.26, 156.94, 151.99, 149.32, 136.90, 126.09, 124.39, 123.98, 121.07, 117.36, 116.33, 116.25, 115.75, 109.86. MS: m/z 325,78 [$M^+$].

**Synthesis of 4-chloro-5-(4-[pyridin-4-yldiazenyl] phenoxy)phthalonitrile (5) and 4,5 bis(4-[pyridin-4-yldiazenyl]phenoxy)phthalonitrile (6)**

4-(4-Hydroxyphenlyazo) pyridine (**II**) (1 g, 5.02 mmol) and 4,5-dichloro-1,2-dicyanobenzene

(0.40 g, 2.51 mmol) were dissolved in dry dimethylformamide (DMF, 50 mL). After stirring for 30 min, finely ground anhydrous $K_2CO_3$ (2.5g, 18.86 mmol) was added to reaction mixture and was stirred at 60°C for 72 h, and then poured into ice water (500 mL). The raw product was filtered off and washed with water until the filtrate became neutral. Pure compounds **5** (first fraction) and **6** (second fraction) were obtained by column chromatography (silica gel, MeOH : $CHCl_3$, 5:200).

**4-Chloro-5-(4-[pyridin-4-yldiazenyl]phenoxy) phthalonitrile (5)**

Yield: 0.14 g, 7%; m. p. 213-214°C. FTIR$\nu_{max}$/cm$^{-1}$ 3097, 3053, 2997, 2960, 2238 (C≡N), 1579 (C=C), 1550, 1487, 1406 (N=N), 1378, 1305, 1269, 1212, 1152, 1009, 848, 832, 783. $^1$H NMR (DMSO-$d_6$) δ, ppm: 8.83-8.81 (2H, d.d, ArH), 8.62 (1H, s, ArH), 8.06-8.03 (2H, d.d, ArH), 8.05 (1H, s, ArH), 7.74-7.73 (2H, d.d, ArH), 7.39-7.36 (2H, d.d, ArH). $^{13}$C NMR (DMSO-$d_6$) δ, ppm: 158.42, 156.95, 155.63, 152.00, 149.24, 136.91, 130.81, 126.09, 125.78, 120.00, 116.33, 116.02, 115.32, 115.30, 111.83. MS: m/z 359,74 [$M^+$].

**4,5 bis(4-[pyridin-4-yldiazenyl] phenoxy)phthalonitrile (6)**

Yield: 0.11 g, 8%; m. p. 243-244°C. FTIR$\nu_{max}$/cm$^{-1}$ 3047, 2232 (C≡N), 1582 (C=C), 1545, 1490, 1416 (N=N), 1396, 1301, 1203, 1144, 844, 827, 792. $^1$H NMR (DMSO-$d_6$) δ, ppm: 8.80-8.78 (4H, d.d, ArH), 8.20 (2H, s, ArH), 7.99-7.95 (4H, d.d, ArH), 7.71-7.69 (4H, d.d, ArH), 7.32-7.28 (4H, d.d, ArH). $^{13}$C NMR (DMSO-$d_6$) δ, ppm: 159.05, 156.92, 151.95, 150.54, 148.83, 127.79, 125.89. 119.17, 116.29, 115.62, 112.78. MS: m/z 522,72 [$M^+$].

***In-vitro* Urease inhibition studies**

*Jack bean* urease inhibitory activity and kinetic studies steps of the newly synthesized phthalonitrile azo compounds and acetohydroxamic acid were examined as per the literature[34]. Decreasing absorbance of solutions having different concentrations of synthesized compounds and standard at 625 nm was measured by using a UV-visible spectrophotometer (1601UV-Shimadzu, Australia). Acetohydroxamic acid (Sigma-Aldrich) was used as the standard inhibitor. The Urease inhibition percentage was calculated as follows:

$$Urease\ inhibition\ (\%) = [(Acontrol - Acompound)\ /\ Acontrol]\ x100$$

***In-vitro* Acetylcholinesterase inhibition studies**

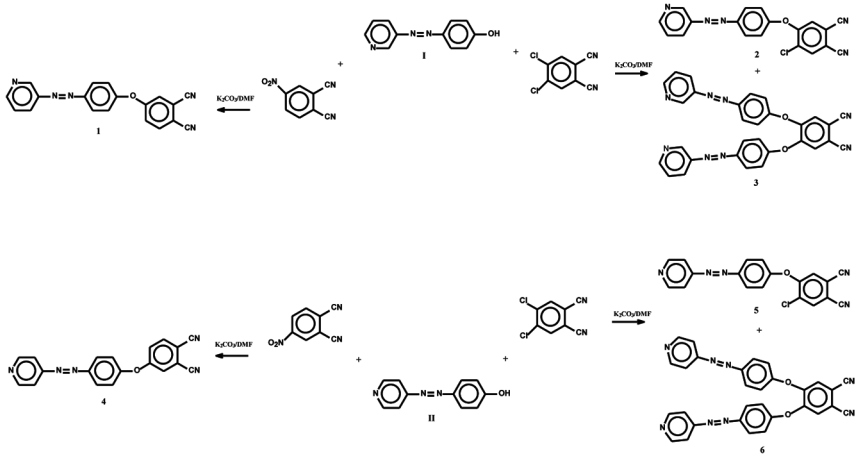
All the synthesized compounds were evaluated to Acetylcholinesterase (AChE) inhibition activity according to the reported protocol[9]. Donepezil was used as a standard inhibitor and assayed at the same reaction conditions. The $IC_{50}$ value was determined as the concentration of compound that give 50% inhibition of maximal activity.

$$AChE\ inhibition\ (\%) = [(Acontrol - Acompound)\ /\ Acontrol]\ x100$$

**Results and Discussion**

**Synthesis and characterization**

Earlier 4-Nitro–1,2-dicyanobenzene and 4,5-dichloro-1,2-dicyanobenzene compounds have been used to synthesize substituted phthalonitrile derivatives through base catalysed nucleophilic aromatic displacement [1-2, 7, 19, 22, 35-36]. The synthetic route of new phthalonitrile azo compounds can be seen in Scheme 1. Generally, substituted



Scheme 1 — Synthetic route of new phthalonitrile azo compounds

phthalonitrile compounds are preferred in order to synthesize pure phthalocyanine dyes and pigment [11-14, 18, 27, 30]. But we have not synthesized phthalocyanines from the newly obtained phthalonitrile compounds.

Compounds **1** and **4** were synthesized by treating 3-(4-hydroxyphenlyazo) pyridine **(I)** and 4-(4-hydroxyphenlyazo)pyridine **(II)** with 4-nitro–1,2-dicyanobenzene, respectively, in DMF at 60°C, using $K_2CO_3$ as the base for the nucleophilic substitution [1,2,7,19,22,35,36]. The formation of compounds **1** and **4** were similar and clearly evident from the appearance of the CN bands at 2232 $cm^{-1}$ in their FTIR spectra.

$^1H$ NMR spectra of compounds **1** and **4** were similar as these compounds are structural isomers of each other. However, $^1H$ NMR spectrum of compound **1** has more spin- spin interaction and splitting because of less symmetrically 3-amino pyridine moiety at structure. In the $^1H$ NMR spectra, while pyridine protons of compound **1** appear as three doublet-doublets at 9.11-9.10, 8.74-8.73, 8.19-8.18 ppm and a quarted-doublet at 7.64-7.60 ppm, pyridine protons of compound **4** appear as two multiplets at 8.83-8.80 and 7.74-7.72 ppm. $^{13}C$ NMR spectra of compounds **1** and **4** gave similar signals for nitrile carbon atoms at 116.26, 115.76 ppm and 116.25, 115.75 ppm, respectively. High resolution MS spectra (ESI) of compounds (**1** and **4**) provided a definitive proof for their characterization. Ionization took place in the methanol solution. Molecular ion peaks of compounds **1** and **4** were detected as expected same values. MS measurements clearly confirmed that the molecular masses of compounds **1** and **4** are same (m/z =325.78 $M^+$).

Compounds **2** and **3** were synthesized by treating 3-(4-hydroxyphenlyazo) pyridine **(I)** with 4,5-dichloro-1,2-dicyanobenzene in DMF at 60°C, using $K_2CO_3$ as the base for the nucleophilic substitution[1,2,7,19,22,35,36]. Compounds **2** and **3** were purified from raw material by coloum chromatography technique. First and second fractions have been determined as compound **2** and **3** by using spectroscopic methods, respectively. In the FTIR spectra of compounds **2** and **3**, CN bands were observed very similarly each other at 2235 and 2233 $cm^{-1}$, respectively. In the $^1H$ NMR spectra, pyridine protons of compound **2** appear at 9.11-9.10, 8.75-8.73, 8.19-8.18 and 7.64-7.60 ppm, pyridine protons of compound **3** appear at 9.07-9.07, 8.72-8.70, 8.15-8.12 and 7.61-7.58 ppm. While the phthalonitrile part aromatic protons of compound **2** were observed as two singlets at 8.61 and 8.02 ppm, phthalonitrile group protons of compound **3** was observed as a singlet at 8.17 ppm. $^{13}C$ NMR spectra of compounds **2** gave two signals for nitrile carbon atoms at 115.32, 115.30 ppm, but compound 3 gave just one signal at 115.64 ppm due to more symmetrically disubstituted structure. Molecular ion peaks of compounds **2** and **3** were detected as expected and ionization took place in the methanol solution. The mass spectra support the proposed formula for these compounds that the molecular masses of compounds **2** (m/z =359.99 $M^+$), **3** (m/z =522.69 $M^+$).

Compounds **5** and **6** were synthesized by treating 4-(4-hydroxyphenlyazo) pyridine **(I)** with 4,5-dichloro-1,2-dicyanobenzene in DMF at 60°C, using $K_2CO_3$ as the base for the nucleophilic substitution [1,2,7,19,22,35,36]. Compounds **5** and **6** were purified from raw material by column chromatography technique. First and second fractions have been determined as compound **5** and **6** by using spectroscopic methods, respectively.

The FTIR spectra of compounds **5** and **6** clearly indicate CN bands at 2238 and 2232 $cm^{-1}$, respectively. Compounds **5** and **6** are more symmetrical than the other studied compounds due to 4-amino pyridine moiety at structures. Because of that, in the $^1H$ NMR spectra, pyridine protons of compound **5** appear as two doublet-doublets at 8.83-8.81 and 7.74-7.73 ppm, pyridine protons of compound **6** appear as two doublet-doublets at 8.80-78 and 7.71-7.69 ppm. While the phthalonitrile part aromatic protons of compound **5** were observed as two singlets at 8.62 and 8.05 ppm, phthalonitrile group protons of compound **6** was observed as a singlet at 8.20 ppm. $^{13}C$ NMR spectra of compounds **5** gave two signals for nitrile carbon atoms at 116.02, 115.30 ppm, but compound **6** gave just one signal at 115.62 ppm due to more symmetrically disubstituted structure. Molecular ion peaks of compounds **5** and **6** were detected as expected and ionization took place in the methanol solution. The mass spectra support the proposed formula for these compounds that the molecular masses of compounds **5** (m/z =359.74 $M^+$), **6** (m/z =522.72 $M^+$).

**Inhibition of Urease enzyme**

All of the newly synthesized phthalonitrile azo compounds have been examined in terms of Urease inhibition potentials. Percentage relative activities

Table 1 — IC50 values of compounds against Urease and AChE enzymes

| Compounds | Urease inhibition $IC_{50}$ (μM) | AChE inhibition $IC_{50}$ (μM) |
|---|---|---|
| 1 | 29.32±0.19 | 11.86±0.09 |
| 2 | 42.29±0.11 | 31.49±0.22 |
| 3 | 46.69±0.17 | 33.42±0.23 |
| 4 | 20.47±0.14 | 4.73±0.07 |
| 5 | 35.72±0.13 | 24.32±0.17 |
| 6 | 34.20±0.19 | 17.76±0.11 |
| Acetohydroxamic acid | 273.74±1.90 | ---- |
| Donepezil chloride | --- | 39.84±0.29 |

versus inhibitor concentrations were separately plotted for each organic molecule and $IC_{50}$ values were determined to Jack bean Urease enzyme. Lower $IC_{50}$ values show higher inhibition. Urease inhibitor activity of the all compounds and Acetohydroxamic acid can be seen in Table 1. The assays were done in triplicate. Acetohydroxamic acid and donepezil chloride were used as standard inhibitors. Particularly, the compound **4** ($IC_{50}$ 20.47±0.14) had the highest inhibitory effect among the examined compounds against to Urease enzyme. All the phthalonitrile azo compounds and the standard can be ranked to the least active from the highest active according to against the Urease enzyme to the following: **4** > **1** > **6** > **5** > **2** > **3** > Acetohydroxamic acid (Table 1).

## Inhibition of Acetylcholinesterase (AChE) enzyme

The inhibitory effect of the all pthalonitrile azo compounds against the AchE enzyme can be ranked to the least active from the highest active to the following: **4** > **1** > **6** > **5** > **2** > **3** > Donepezil Chloride (Table 1). $IC_{50}$ values ranging from 4.73±0.07 μM (compound 4, Table 1) to 33.42±0.23 μM (compound 3, Table 1).

According to results, inhibitory activities of the all azo compounds were significantly higher than that of standard compounds against to both the clinically important metabolic enzymes. Particularly, phthalonitrile azo compound **4** is more active than other compounds and standards and shows a significant inhibition to Urease and AChE enzymes. Generally, phthalonitrile azo compounds **4**, **5** and **6** that containing 4-pyridiyl moieties were more active than the compounds **1**, **2** and **3** that containing 3-pyridiyl moieties.

## Conclusion

The newly synthesized azo phthalonitrile compounds were screened for their inhibitory properties against to Urease and Acetylcholinesterase two clinically important metabolic enzymes. All the synthesized compounds showed higher inhibition performance than standard in the presence of both enzymes. Based on this approach, new and effective compounds can be synthesized and investigated for the both *Helicobacter pylori* and Alzheimer's disease treatments.

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