Synthesis of Sulfanoquinoxaline-2,3-Dione Hydrazones Derivatives as a Selective Inhibitor for Acetylcholinesterase and Butyryl Cholinesterase

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Some Sulfanoquinoxaline-2,3-diones hydrazone derivatives (1-8) were synthesized from the reactions of 2,3-dioxoquinoxaline-6-sulfonohydrazine with seven substituted benzaldehydes and acetophenone. All the synthesized compounds were biologically evaluated against cholinesterase’s (acetylcholinesterase and butyryl cholinesterase). Compounds 1-8 were found to be a good selective inhibitor for acetylcholinesterase and butyryl cholinesterase. Among the series, compounds 3 (IC50 = 75 ± 10 µg/mL) and 5 (IC50 = 80 ± 10 µg/mL) were found to be the most active inhibitors against acetylcholinesterase, while compounds 6 (IC50 = 110 ± 10 µg/mL), 8 (IC50 = 130 ± 10 µg/mL) and 7 (IC50 = 150 ± 10 µg/mL), were found to be most active inhibitor against butyryl cholinesterase. The IC50 values for all the synthesized compounds were lower than standard, eserine (IC50 = 70 ± 20 µg/mL). Their considerable acetylcholinesterase and butyryl cholinesterase inhibitory activities make them a good candidate for the development of selective acetylcholinesterase and butyryl cholinesterase inhibitors.

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1. INTRODUCTION

Heterocycles containing quinoxaline derivatives have gained considerable attention from researchers in recent years. Quinoxaline and its numerous derivatives have been widely reported because of their biological activity, specifically as antimicrobial [1-6], antibacterial [7-9], anti-cancer [10], anti-inflammatory [12,13] and antiviral [14-16], antimalaria [17] agents. Alzheimer's disease (AD) is a common form of dementia in which severe loss of cholinergic cells occurs, which subsequently leads to low levels of the neurotransmitter Acetylcholinesterase (AChE) in the brain, while activity of butyryl cholinesterase (BChE) does not change or even elevate in advanced AD, which suggests a key involvement of BChE in AChE hydrolysis during AD symptoms. Such neurological changes in the nervous system may contribute to various cognitive and behavioral symptoms that appear during AD. Therefore, inhibiting the activity of BChE may be an effective way to control AD associated disorders.

2. MATERIALS AND METHODS

2.1 General

Melting points were determined with open capillary tube on a Gallenkamp (variable heater) melting point apparatus and were uncorrected. Infrared spectra were recorded as KBr pellets on a Buck Spectrometer. The 1H and 13C NMR was run on a Bruker 600 MHz spectrometer (δ in ppm relative to Me4Si). The purity of the compounds was routinely checked by TLC on silica gel G plates using n-hexane/ethyl acetate (1:1, v/v) solvent system and the developed plates were visualized by UV light. All reagents used were obtained from Sigma–Aldrich Chemical Ltd, except Glacial acetic acid, ethanol, oxalic acid and vanillin which were obtained from BDH Chemical Limited.

2.2 Synthesis of Quinoxaline-2,3-(1H,4H)-Dione-6-Sulfonyl Hydrazide 1

Hydrazine hydrate (10 mL 0.460 mmol) in absolute methanol (100 mL) was added quinoxaline-6-sulfonylchloride (15 g, 0.55 mol) portion wise with constant stirring. The reaction mixture obtained was refluxed at 80 °C for 4 hours. The solution was cooled and poured into crushed ice to give 1. Melting point >330 oC. IR Spectra (KBr) 3347 cm⁻¹ (N-H), 3139 cm⁻¹ (N-H), 3050 cm⁻¹ (N-H), 3039 cm⁻¹ (N-H), 1669 cm⁻¹ (C=O), 1595 cm⁻¹ (C=N), 1391 (SO2), 1159 cm⁻¹ (SO2). 1H NMR (DMSO-d6) 3.37 (br s, 1H, NH, D2O exchangeable), 4.12 (br s, 1H, NH, D2O exchangeable), 12.12 (br s, 1H, NH, D2O exchangeable). 8.37 (br s, 1H, NH, D2O exchangeable), 7.60 (d, 1H, ArH), 7.49-7.50 (dd, 1H, ArH), 7.92 (d, 1H, ArH). 13C NMR (DMSO-d6) 154.86 (C=O), 131.98 (Aromatic), 128.95 (Aromatic), 128.45 (Aromatic), 129.07 (Aromatic), 129.52 (Aromatic), 129.07 (Aromatic), 132.53 (Aromatic), 132.66 (Aromatic), 130.00 (Aromatic).

2.3 Synthesis of N-(E)-(phenylideneamino)-6-(quinoxaline-2,3-(1H,4H)-dione) Sulfonamide 1-6

A mixture of Quinoxaline-6-sulfonylhydrazine 1 (39 mmol), the required benzaldehydes (39 mmol) and glacial acetic acid (25 mL) was refluxed at 120°C for 3 hours. The resulting mixture was cooled and poured into crushed ice with continuous stirring. The solid obtained was filtered and washed with cold water, dried and recrystallized from DMF/water to afford the desired product.

N-(E)-(3-Chlorobenzylideneamino)-6-(Quinoxaline-2,3-(1H,4H)-Dione)Sulfonamide 1

A yellow solid, m.p 239-240oC, lit. 241-243 °C [18]. IR Spectra (KBr): 3238 cm⁻¹ (N-H), 3215 cm⁻¹ (N-H), 3042 cm⁻¹ (CH aromatic), 1692 cm⁻¹ (C=O), 1603 cm⁻¹ (C=N), 1371 (vmaxSO2), 1163 cm⁻¹ (SO2). 1H NMR (DMSO-d6) 12.12 (br s, 2H, NH, D2O exchangeable), 11.61 (br s, 1H, NH, D2O exchangeable), 7.89 (s, 1H, ArH), 7.66 (d, 1H, ArH), 7.24 (d, 1H, ArH), 7.44 (m, 2H, ArH), 7.56 (m, 2H, ArH), 8.72 (s, 1H, N=CH). 13C NMR (DMSO-d6): 160.58 (C=O), 155.18 (C=O), 154.92 (C=N), 145.79, 134.54 (Aromatic), 132.53 (Aromatic), 132.66 (Aromatic), 130.00 (Aromatic), 129.52 (Aromatic), 129.07 (Aromatic), 128.45 (Aromatic), 127.84 (Aromatic), 125.85 (Aromatic), 121.97 (Aromatic), 115.42 (Aromatic), 114.20 (Aromatic).
N-(E)-(3-nitrobenzylideneamino)-6-(quinoxaline-2,3-(1H,4H)-dione)Sulfonamide 2

A yellow solid, m.p 249-251°C, lit.250°C [18]. IR Spectra (KBr): 3247 cm⁻¹ (N-H), 3239 cm⁻¹ (N-H), 3077 cm⁻¹ (CH aromatic), 1680 cm⁻¹ (C=O), 1599 cm⁻¹ (C=N), 1341 cm⁻¹ (vmaxSO₂), 1151 cm⁻¹ (SO₂). ¹H NMR (DMSO-d₆): 12.20 (br s, 1H, NH, D₂O exchangeable), 12.13 (br s, 1H, NH, D₂O exchangeable), 12.00 (br s, 1H, NH, D₂O exchangeable), 8.27 (d, 1H, ArH), 8.15 (dd, 2H, ArH), 7.58 (dd, 1H, ArH), 7.26-7.28 (d, 1H, ArH), 7.66 (m, 1H, ArH), 6.76(m, 1H, ArH) , 8.97 (s, 1H, N=CH). ¹³C NMR (DMSO-d₆): 158.65 (C=O), 155.19 (C=O), 154.91 (C=N), 148.85 (Aromatic), 147.85 (Aromatic), 133.91 (Aromatic), 133.75 (Aromatic), 13214 (Aromatic), 129.63 (Aromatic), 129.41 (Aromatic), 127.94 (Aromatic), 127.79 (Aromatic), 125.93 (Aromatic), 124.76 (Aromatic), 124.65 (Aromatic), 115.55 (Aromatic), 114.20 (Aromatic).

N-(E)-(4-methoxybenzylideneamino)-6-(quinoxaline-2,3-(1H,4H)-dione)Sulfonamide 3

A yellow solid, m.p 260-262 °C, lit. 262-263 °C [18]. IR Spectra (KBr) 3486 cm⁻¹ (N-H), 3212 cm⁻¹ (N-H), 3062 cm⁻¹ (CH aromatic), 1684 cm⁻¹ (C=O), 1586 cm⁻¹ (C=N), 1387 cm⁻¹ (C-O), 1310 (SO₂), 1155 cm⁻¹ (SO₂). ¹H NMR (DMSO-d₆): 12.16 (br s, 2H, NH, D₂O exchangeable), 11.50(br s, 1H, NH, D₂O exchangeable), 7.80 (d, 1H, ArH), 7.58 (dd, 1H, ArH), 7.17 (d, 1H, ArH), 7.12 (m, 1H, ArH), 7.27 (dd, 1H, ArH), 7.32 (t, 1H, ArH), 6.96-6.98(m, 1H, ArH) 7.68 (s, 1H, N=CH), 3.78 (s, 3H, -OCH₃). ¹³C NMR (DMSO-d₆): 159.39 (C=O), 155.20 (C=O), 154.95 (C=N), 146.97 (Aromatic), 134.97 (Aromatic), 132.66 (Aromatic), 130.30 (Aromatic), 129.87 (Aromatic), 129.50 (Aromatic), 125.81 (Aromatic), 125.58 (Aromatic), 122.41 (Aromatic), 122.02 (Aromatic), 119.36 (Aromatic), 115.85 (Aromatic), 115.42 (Aromatic), 114.31 (Aromatic), 112.87 (Aromatic), 111.61 (Aromatic), 55.10 (CH₃).

N-(E)-(4-hydroxybenzylideneamino)-6-(quinoxaline-2,3-(1H,4H)-dione)Sulfonamide 3

A yellow solid, m.p 240-242 °C, lit. 239-241 °C [18]. IR Spectra (KBr): 3668 cm⁻¹ (N-H), 3459 cm⁻¹ (N-H), 3050 cm⁻¹ (CH aromatic), 1684 cm⁻¹ (C=O), 1599 cm⁻¹ (C-N), 1395 cm⁻¹ (C-O), 1322 (SO₂), 1151 cm⁻¹ (SO₂). ¹H NMR (DMSO-d₆): 12.18 (br s, 1H, NH, D₂O exchangeable), 12.13 (br s, 1H, NH, D₂O exchangeable), 7.77 (d, 1H, ArH), 7.67 (d, 1H, ArH), 7.24 (dd, 1H, ArH), 7.52 (d, 2H, ArH), 6.94 (d, 2H, ArH), 8.64 (s, 1H, N=CH), 3.75 (s, 3H, -OCH₃). ¹³C NMR (DMSO-d₆): 158.65 (C=O), 155.19 (C=O), 154.91 (C=N), 148.85 (Aromatic), 147.85 (Aromatic), 133.91 (Aromatic), 133.75 (Aromatic), 13214 (Aromatic), 129.63 (Aromatic), 129.41 (Aromatic), 127.94 (Aromatic), 127.79 (Aromatic), 125.93 (Aromatic), 124.76 (Aromatic), 124.65 (Aromatic), 115.55 (Aromatic), 114.20 (Aromatic).

2.4 Synthesis of N-(E)-(1-(4-dimethylamino)phenyl)methylideneamino)-6-(quinoxaline-2,3-(1H,4H)-dione)Sulfonamide 5

Melting point 288-290 °C lit 286-288 °C [18] IR Spectra (KBr) 3193 cm⁻¹ (N-H), 3135 cm⁻¹ (N-H), 3035 cm⁻¹ (CH aromatic), 1676 cm⁻¹ (C=O), 1584 cm⁻¹ (C=N), 1318 (SO₂), 1159 cm⁻¹ (SO₂). ¹H NMR (DMSO-d₆): 12.13 (br s, 1H, NH, D₂O exchangeable), 11.92 (br s, 1H, NH, D₂O exchangeable), 10.04 (br s, 1H, NH, D₂O exchangeable), 7.76 (s, 1H, ArH), 7.74 (d, 2H, ArH), 7.55 (ddd, 1H, ArH), 7.38-7.44 (dd, 2H, ArH), 7.23-7.32 (ddd, 1H, ArH), 8.61 (s, 1H, N=CH), 2.50 (s, 6H, CH₃). ¹³C NMR (DMSO-d₆): 155.18 (C=O), 154.92 (C=O), 137.27 (Aromatic), 132.79 (Aromatic), 132.05 (Aromatic), 129.72 (Aromatic), 129.40 (Aromatic), 129.02 (Aromatic), 128.40 (Aromatic), 128.34 (Aromatic), 126.24 (Aromatic), 126.01 (Aromatic), 125.66 (Aromatic), 125.58 (Aromatic), 122.40 (Aromatic), 14.67 (CH₃), 14.27 (CH₃).

2.5 Synthesis of N-(E)-(1-(4-methoxy-3-hydroxy-(phenyl)methylideneamino)-6-(quinoxaline-2,3-(1H,4H)-dione)Sulfonamide 6

Melting point 230-231 °C lit 233 °C (decomposed) [18] IR Spectra (KBr) 3363 cm⁻¹ (OH), 3239 cm⁻¹ (N-H), 3054 cm⁻¹ (CH aromatic), 1680 cm⁻¹ (C=O), 1588 cm⁻¹ (C=N), 1391 cm⁻¹ (C-O), 1333 (SO₂), 1156 cm⁻¹ (SO₂). ¹H NMR (DMSO-d₆): 12.10 (br s, 2H, NH, D₂O exchangeable), 11.20 (br s, 1H, NH, D₂O exchangeable), 9.50 (s, 1H, ArH), 7.56-7.57 (dd, 1H, ArH), 7.66 (d, 1H, ArH), 6.98 (dd, 1H, ArH), 7.24-7.26 (d, 1H, ArH), 7.10 (d, 1H, ArH), 7.77 (s, 1H, N=CH), 3.78 (s, 6H, OCH₃). ¹³C NMR (DMSO-d₆): 154.89 (C=O), 148.79
(C=N), 147.73 (C-O), 132.72 (Aromatic), 129.32
(Aromatic), 125.68 (Aromatic), 124.96
(Aromatic), 121.99 (Aromatic), 121.08
(Aromatic), 115.35 (Aromatic), 115.29
(Aromatic), 114.31 (Aromatic), 109.50
(Aromatic), 55.47 (CH3).

2.6 Synthesis of N-(E)-(7-chloro-2-oxoindole-3-ylideneamino)-6-(quinoxaline-2,3-(1H,4H)-dione) Sulfonamide 7

Melting point 268-270 °C lit 273-274 °C [18]. IR Spectra (KBr) 3347 cm⁻¹ (N-H), 3014 cm⁻¹ (N-H), 1680 cm⁻¹ (C=O), 1595 cm⁻¹ (C=N), 1383 cm⁻¹ (C-O), 1322 (SO₂), 1163 cm⁻¹ (SO₂). ¹H NMR (DMSO-d₆) 12.21 (br s, 1H, NH, D₂O exchangeable), 12.17 (br s, 1H, NH, D₂O exchangeable), 10.73 (br s, 1H, NH, D₂O exchangeable), 7.72 (d, 1H, ArH), 7.87 (d, 1H, ArH), 7.63-7.65 (dd, 1H, ArH), 6.85-6.86 (d, 1H, ArH), 7.27-7.29 (d, 1H, ArH), 7.37 (t, 1H, ArH), 7.06 (t, 1H, ArH). ¹³C NMR (DMSO-d₆) 171.93 (C=O), 163.61 (C=O), 155.16 (C=O), 154.86 (C=N), 143.84 (Aromatic),141.84 (Aromatic), 133.07 (Aromatic), 131.58 (Aromatic), 129.86 (Aromatic), 126.58 (Aromatic), 125.67 (Aromatic), 122.75 (Aromatic), 121.60 (Aromatic), 115.36 (Aromatic), 115.12 (Aromatic), 115.02 (Aromatic), 110.50 (Aromatic).

2.7 Synthesis of N-(E)-((1-phenylethylideneamino)-6-(quinoxaline-2,3-(1H,4H)-dione) Sulfonamide 8

Melting point 288-290 °C lit 290-292 °C [18]. IR Spectra (KBr) 3347 cm⁻¹ (N-H), 3139 cm⁻¹ (N-H), 3039 cm⁻¹ (CH aromatic), 2927 cm⁻¹ (CH aliphatic) 1676 cm⁻¹ (C=O), 1595 cm⁻¹ (C=N), 1314 (SO₂), 1167 cm⁻¹ (SO₂). ¹H NMR (DMSO-d₆) 12.17 (br s, 2H, NH, D₂O exchangeable), 8.36 (br s, 1H, NH, D₂O exchangeable), 8.35 (s, 1H, ArH), 7.91 (m, 1H, ArH), 7.25 (d, 1H, ArH), 7.60 (d, 1H, ArH), 7.46 (m, 3H, ArH), 2.50 (s, 3H, CH₃). ¹³C NMR (DMSO-d₆) 158.56 (C=O), 155.12 (C=O) 154.88 (C=N), 151.13, 148.17 (Aromatic), 143.28 (Aromatic), 132.89 (Aromatic), 129.23 (Aromatic), 128.09 (Aromatic), 125.65 (Aromatic), 124.58 (Aromatic), 121.96 (Aromatic), 120.51 (Aromatic), 115.23 (Aromatic), 114.31 (Aromatic), 111.93 (Aromatic) 111.84 (Aromatic), 20.95 (CH₃).

2.8 In vitro Acetylcholinesterase and Butyrylcholinesterase Inhibitory Assays

The anti-cholinesterase (acetylcholinesterase and butyrylcholinesterase) inhibiting activities of the synthesized compounds were determined by using modified method of Ellman et al. (1961)[19] as described by Obuotur (2004)[20]. The synthesized compounds were prepared in a stock solution of DMSO in buffer and was used for the cholinesterase inhibition assay, while Eserine prepared in buffer was used as the reference compound (positive control).

Procedure: To triplicate test tube was added 240 µL of buffer (50 mM Tris-HCl, pH 8.0) and 20 µL of varying concentration of the test compounds (10, 5, 2.5 and 1.25 mg/mL), 20 µL of the enzyme preparation, the reaction mixture was then incubated for 30 mins at 37 °C, after which 20 µL of 10 mM 5,5'-dithiobis (2-nitrobenzoic acid), was added.

The reaction was then initiated by the addition of 20µL of 25 mM ATChI (1.042 mM final concentration). The rate of hydrolysis of ATChI was then determined spectrophotometrically by measuring the change in the absorbance per minute (ΔA/min) due to the formation of the yellow 5-thio-2-nitrobenzoate anion at 412 nm over a period of 4 min at 30s interval. A solution of buffer was used as negative control. The percentage inhibition (%) of the synthesized compounds were determined by using the formula:

\[ I (%) = \left( \frac{V_0 - Vi}{V_0} \right) \times 100 \]

Where: I (%) = Percentage inhibition
Vi = enzyme activity in the presence of synthesized compounds
V0 = enzyme activity in the absence of synthesized compounds

3. RESULTS AND DISCUSSION

Chemistry

2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfono hydrazide I was reacted with some aromatic aldehydes under refluxing condition in glacial acetic acid to afford the hydrazones 1 – 6 as shown in Scheme 1. Furthermore, N-(E)- (2-oxoindole-3-ylideneamino)-6- (quinoxaline-2,3-(1H,4H)-dione) sulfonamide 7 was prepared by
the reacting I with indoline-2,3-dione as shown in Scheme 1. The reaction of I with acetophenone under refluxing condition in glacial acetic acid afforded the hydrazone 8. Generally, studying the infrared spectra of the compounds the absorption bands due to the stretching vibrations of N-H and OH was observed between 3135 and 3390 cm\(^{-1}\), the C=O vibrations was observed between 1676 and 1692 cm\(^{-1}\), C=C and C=N between 1607 and 1580 cm\(^{-1}\), SO2 at 1310 - 1391 cm\(^{-1}\) and 1140 - 1167 cm\(^{-1}\) for asymmetric and symmetric vibrations. The \(^1\)H-NMR spectral data of compounds 1-8 in DMSO-d6 showed signal for NH between 8.37 ppm and 12.51 ppm, the signals for CH=N between 7.68-ppm and 9.59 ppm, the signals for aromatic protons were observed between 6.40 ppm and 9.50 ppm, the signals for methyl protons (CH\(_3\)) were seen at 2.50 ppm and the signals for methoxy protons (OCH\(_3\)) were observed between 3.75 ppm and 3.78 ppm.

**SCHEME 1: Synthetic procedure for compounds 1-8**

**Biology**

Alzheimer disease (AD) is one of the most ordinary neurodegenerative diseases resulting in progressive dysfunction in the brain which has become a major health problem among the aged all over the world. Alzheimer disease brains show extensive cell loss, particularly of cholinergic neurons [21], and reduction of the neurotransmitter acetylcholine, producing the cholinergic dysfunction characteristic of AD [21]. It is also established that AChE levels decrease in AD, while BuChE activity does not [22]. BuChE co-regulates acetylcholine metabolism as demonstrated by the fact that AChE-knockout mice are viable [23-24]. The accumulation of BuChE in AD pathology is especially notable in cortical grey matter, an area that normally has very little BuChE activity [25-28]. Therefore, inhibition of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), the enzymes responsible for hydrolysis of ACh at the cholinergic synapse and grey matter respectively, is currently the most established approach for treating Alzheimer disease [29-30]. The present study established that the synthetic compounds show a dual inhibition of both AChE and BuChE, with more preference to BuChE. All the tested compounds exhibit a very strong inhibition towards BuChE more than AChE as observed from their IC\(_{50}\). This might be as a result of larger size of the compounds which makes them fit properly into the active site of BuChE more than AChE, thereby resulting into higher inhibition.

**Fig. 1. Inhibition (%) of AChE by Compounds 1-8**
Fig. 2. Inhibition (%) of BChE by Compounds 1-8

Fig. 3. $IC_{50}$ of AChE by Compounds 1-8

Fig. 4. $IC_{50}$ of BChE by Compounds 1-8
The results also established that compounds 1, 2, 5, 6, 7 and 8 have a higher inhibitory activity towards BChE when compared to the reference compound i.e. eserine, which shows that they can serve as a potent and lead compounds which can be optimized for treatment of Alzheimer disease. A study also demonstrated that selective BuChE inhibitors reduced amyloid precursor protein processing and Aβ level in vivo and in vitro [31]. These results suggest that the effects may arise from the interaction of these compounds with amyloid cascade, influencing the expression and metabolic processing of APP and thereby slowing down the major pathological consequences of aggregation [32-33]. Therefore, cholinesterase inhibitors not only increase the level of ACh but also prevent the formation of β-amyloid plaques thereby protecting the neurons from neurodegeneration.

4. CONCLUSION

The results obtained from this study clearly indicate that the synthesized compounds have a potent cholinesterase inhibitory activity under in vitro study. The most probable reason for their potential cholinesterase inhibitory activity might be related to their large size and chemical structure. This can be further characterized, and they can be evaluated for their bioavailability and potential toxicity in vivo.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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