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Synthesis: Small library of hybrid scaffolds of benzothiazole having hydrazone and evaluation of their β-glucuronidase activity

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ABSTRACT

Due to the great biological importance of β-glucuronidase inhibitors, here in this study, we have synthesized a library of novel benzothiazole derivatives (**1**–**30**), characterized by different spectroscopic methods and evaluated for β-glucuronidase inhibitory potential. Among the series sixteen compounds *i.e.* **1**–**6**, **8**, **9**, **11**, **14**, **15**, **20**–**23** and **26** showed outstanding inhibitory potential with IC_{50} value ranging in between 16.50 ± 0.26 and 59.45 ± 1.12 when compared with standard D-Saccharic acid 1,4-lactone (48.4 ± 1.25 μM). Except compound **8** and **23** all active analogs showed better potential than the standard. Structure activity relationship has been established.

1. Introduction

The chemistry of fused ring heterocycles is recognized to be a key field of investigation in medicinal chemistry, subsequently, they have been establishing to show enhanced biological activity. Heterocyclic compounds display important role in medicinal chemistry and their structures in natural products. One of them is benzothiazole scaffold which have gain considerable attention in synthetic organic chemistry with valuable applications in the pharmaceutical industry. From the literature survey, benzothiazole analog have shown numerous biological activities [1–3] used in material science and in other wide range industrial applications [4,5]. Furthermore, these benzothiazole compounds have also shown enzymes inhibition, like protoporphyrinogen oxidase, which give free radicals that result in simultaneous toxicological effects on plants and animals [6,7]. The benzothiazole is an exceptional scaffold for further molecular study to synthesize innovative compounds. Benzothiazole analogs have been reported as antimicrobial agents [8,9], if having pyrazole or isatin moiety then exhibit significant antimicrobial potential [10–13].

β-Glucuronidase is an exoglycosidase enzyme catalyzes the cleavage of glucuronosyl-O-bonds [14]. This enzyme is broadly distributed in anaerobic bacteroides, also occur in human blood cells, gastric juice, body fluids, spleen, serum, urine and organs like liver, lung, bile kidney and muscle [15,16]. The deficit of β-glucuronidase in human body leads to Sly syndrome which is linked with the increase of glycosaminoglycans in cells [17,18]. Certain hepatic diseases and AIDS are reported due to the overreaction of the enzyme. Though, it over expressed in some pathological conditions like cancer, inflammation, epilepsy, in hepatic as well as renal diseases, in joints, bladder, and neoplasm of breast, testes, and larynx [19–21]. Literature survey revealed that the bacterial β-glucuronidase inhibitor lead to a reduction in carcinogen prompted colonic tumors [22]. Consequently, inhibitors of this enzyme are immediate need of the day to cure numerous pathological conditions.

Recently our group has reported various classes of heterocyclic compounds as a potent inhibitor of β-glucuronidase [23]. In this connection here we are reporting the synthesis of new benzothiazole analogs and its β-glucuronidase inhibitory potential.

2. Experimental

All nuclear magnetic resonance experiments had been carried out using an AvanceBruker 600 MHz. Elemental analysis was performed on Carlo Erba Strumentazion-Mod-1106, Italy. Electron impact mass spectra (EI-MS) were recorded on a Finnigan MAT-311A, Germany. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany).

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2.1. Synthetic procedure of methyl 4-(5-chlorobenzo[d]thiazol-2-yl) benzoate (I)

The methyl 4-(5-chlorobenzo[*d*]thiazol-2-yl) benzoate (I) was prepared by the treatment of aldehyde (1 mmol) and 4-chloro-2-aminothiophenol (1 mmol) in the presence of DMF for 5 h. After completion of reaction as determined by TLC analysis, the contents were cooled and dried. The impurities were removed washing with ethyl acetate and hexane.

2.2. Synthetic procedure of 4-(5-chlorobenzo[d]thiazol-2-yl)benzohydrazide (II)

In second step, 4-(5-chlorobenzo[*d*]thiazol-2-yl) benzohydrazide (II) was synthesized by treating of the equimolar amount of methyl 4-(5-chlorobenzo[*d*]thiazol-2-yl) benzoate (I) (1 mmol) and hydrazine hydrate (1 mmol) in the presence of methanol for 6 h. The reaction completion was monitored by TLC.

2.3. Synthetic procedure of (E)-4-(5-chlorobenzo[d]thiazol-2-yl)-N′-(3-hydroxybenzylidene) benzohydrazide (**1**–**30**)

In third step, 4-(5-chlorobenzo[*d*]thiazol-2-yl)benzohydrazide (II) (1 mmol) was further treated with different benzaldehydes (1 mmol) in the presence of acetic acid for 3 h. The reaction completion was monitored by TLC. Different spectroscopic techniques such as ESI-MS, ^{1}H NMR and ^{13}C NMR were used to determine the structure of all analogs.

2.3.1. (E)-4-(5-chlorobenzo[d]thiazol-2-yl)-N′-(3-hydroxybenzylidene)benzohydrazide (**1**)

White solid, Yield: 81%. ^{1}H NMR (500 MHz, DMSO d_6):δ 8.32 (s, 1H, —CH), 8.21 (s, 1H, Ar), 8.10 (d, J = 8.8 Hz, 2H, Ar), 7.94 (d, J = 8.6 Hz, 2H, Ar), 7.88 (d, J = 8.01 Hz, 1H, Ar), 7.54 (d, J = 7.8 Hz, 1H, Ar), 7.43 (s, 1H, Ar), 7.37 (d, J = 6.8 Hz, 1H, Ar), 7.23 (t, 1H, Ar), 7.01 (d, J = 6.6 Hz, 1H, Ar), 5.34 (s, 1H, —OH); ^{13}C NMR (126 MHz, DMSO d_6): δ 170.2, 164.3, 159.4, 156.7, 147.3, 146.6, 139.3, 133.4, 132.5, 131.6, 131.4, 130.5, 130.3, 128.3, 128.1, 125.2, 123.5, 122.4, 121.6, 115.5, 118.4; HR-ESI-MS: m/z calcd for $C_{21}H_{14}ClN_3O_2S$, $[M]^+$ 407.0752; Found 407.0751.

2.3.2. (E)-4-(5-chlorobenzo[d]thiazol-2-yl)-N′-(2,3-dihydroxybenzylidene)benzohydrazide (**2**)

White solid, Yield: 81%. ^{1}H NMR (500 MHz, DMSO d_6):δ H 8.75 (s, 1H, —CH), 8.21 (s, 1H, Ar), 8.10 (d, J = 8.8 Hz, 2H, Ar), 7.95 (d, J = 8.6 Hz, 2H, Ar), 7.91 (d, J = 8.01 Hz, 1H, Ar), 7.53 (d, J = 7.8 Hz, 1H, Ar), 7.20 (s, 1H, Ar), 6.83 (d, J = 7.2 Hz, 1H, Ar), 6.80 (t, J = 7.2 Hz, 1H, Ar), 5.33 (s, 2H, —OH); ^{13}C NMR (126 MHz, DMSO d_6): δC 170.2, 164.3, 157.7, 146.6, 156.2, 152.4, 147.4, 147.1, 146.2, 134.1, 133.2, 131.4, 130.6, 130.4, 128.2, 128.1, 125.5, 125.1, 124.2, 123.4, 122.1, 120.5, 120.2; HR-ESI-MS: m/z calcd for $C_{21}H_{14}ClN_3O_3S$, $[M]^+$ 423.0503; Found 423.0501.

2.3.3. (E)-4-(5-chlorobenzo[d]thiazole-2-yl)-N′-(4-hydroxybenzylidene)benzohydrazide (**3**)

Yellow solid, Yield: 86%. ^{1}H NMR (500 MHz, DMSO d_6): δH 8.34 (s, 1H, —CH), 8.22 (s, 1H, Ar), 8.11 (d, J = 8.8 Hz, 2H, Ar), 7.96 (d, J = 8.6 Hz, 2H, Ar), 7.92 (d, J = 8.01 Hz, 1H, Ar), 7.75 (d, J = 8.1 Hz, 2H, Ar), 7.54 (d, J = 7.8 Hz, 1H, Ar), 6.83 (d, J = 7.3 Hz, 2H, Ar), 5.34 (s, 1H, —OH); ^{13}C NMR (126 MHz, DMSO d_6): δC 170.2, 164.3, 161.4, 156.2, 147.3, 147.2, 133.4, 132.0, 131.3, 131.3, 130.8, 130.6, 130.6, 128.4, 128.4, 127.2, 125.2, 124.2, 122.1, 117.1, 117.1; HR-ESI-MS: m/z calcd for $C_{21}H_{14}ClN_3O_2S$, $[M]^+$ 407.0315; Found 408.0312.

2.3.4. (E)-4-(5-chlorobenzo[d]thiazol-2-yl)-N′-(2,5-dihydroxybenzylidene)benzohydrazide (**4**)

Yellowish solid, Yield: 83%. ^{1}H NMR (500 MHz, DMSO d_6):δH 8.73 (s, 1H, —CH), 8.21 (s, 1H, Ar), 8.08 (d, J = 8.8 Hz, 2H, Ar), 7.95 (d, J = 8.5 Hz, 2HAr), 7.93 (d, J = 8.01 Hz, 1H, Ar), 7.55 (d, J = 7.8 H z, 1H, Ar), 7.27 (s, 1H, Ar), 6.83(d, J = 6.9 Hz, 2H, Ar), 5.33 (s, 2H, —OH); ^{13}C NMR (126 MHz, DMSO d_6): δC 170.2, 164.3, 156.2, 154.4, 152.3, 147.2, 146.4, 133.4, 132.2, 131.4, 130.6, 130.6, 128.4, 128.4, 125.2, 124.2, 122.1, 121.4, 120.2, 119.8, 117.3; HR-ESI-MS: m/z calcd for $C_{21}H_{14}ClN_3O_3S$, $[M]^+$ 423.0404; Found 423.0401.

2.3.5. (E)-4-(5-chlorobenzo[d]thiazol-2-yl)-N′-(3,4,dihydroxybenzylidene)benzohydrazide (**5**)

White solid, Yield: 84%. ^{1}H NMR (500 MHz, DMSO d_6):δH 8.34 (s, 1H, —CH), 8.21 (s, 1H, Ar), 8.07 (d, J = 8.8 Hz, 2H, Ar), 7.95 (d, J = 8.6 Hz, 2H, Ar), 7.92 (d, J = 8.01 Hz, 1H, Ar), 7.53 (d, J = 7.8 Hz, 1H, Ar), 7.32 (d, J = 8.1 Hz, 1H, Ar), 7.26 (s, 1H, Ar), 6.82 (d, J = 7.0 1 Hz, 1H, Ar), 5.32 (s, 2H, —OH); ^{13}C NMR (126 MHz, DMSO d_6): δC 170.2, 164.3, 156.2, 150.5, 147.4, 147.1, 146.2, 133.4, 133.2, 132.0, 131.6, 130.8, 130.6, 130.6, 128.4, 128.4, 125.2, 124.2, 123.6, 118.4, 117.3; HR-ESI-MS: m/z calcd for $C_{21}H_{14}ClN_3O_3S$, $[M]^+$ 423.0314; Found 424.0311.

2.3.6. (E)-4-(5-chlorobenzo[d]thiazol-2-yl)-N′-(2,4-dihydroxybenzylidene)benzohydrazide (**6**)

Yellowish solid, Yield: 82%. ^{1}H NMR (500 MHz, DMSO d_6):δH 8.73 (s, 1H, —CH), 8.22 (s, 1H, Ar), 8.06 (d, J = 8.8 Hz, 2H, Ar), 7.94 (d, J = 8.5 Hz, 2H, Ar), 7.91 (d, J = 8.01 Hz, 1H, Ar), 7.62 (d, J = 7.02 Hz, 1H, Ar), 7.52 (d, J = 7.8 Hz, 1H, Ar), 7.50 (s, 1H, Ar), 6.38 (d, J = 6.2 Hz, 1H, Ar), 5.34 (s, 2H, —OH); ^{13}C NMR (126 MHz, DMSO d_6): δC170.2, 164.3, 162.8, 162.7, 156.2, 147.1, 146.4, 134.1, 133.4, 132.0, 130.8, 130.6, 130.6, 128.4, 128.4, 125.2, 124.2, 121.4, 111.6, 109.3, 104.1; HR-ESI-MS: m/z calcd for $C_{21}H_{14}ClN_3O_3S$, $[M]^+$ 423.0412; Found 424.0414.

2.3.7. (E)-4-(5-chlorobenzo[d]thiazol-2-yl)-N′-(4-methylbenzylidene) benzohydrazide (**7**)

Yellowish solid, Yield: 76%. ^{1}H NMR (500 MHz, DMSO d_6):δH 8.34 (s, 1H, —CH), 8.23 (s, 1H, Ar), 8.06 (d, J = 8.8 Hz, 2H, Ar), 7.95 (d, J = 8.6 Hz, 2H, Ar), 7.91 (d, J = 8.01 Hz, 1H, Ar) 7.53 (d, J = 7.8 H z, 1H, Ar), 7.67 (d, J = 8.1 Hz, 2H, Ar), 7.23 (d, J = 7.9 Hz, 2H, Ar), 2.31 (s, 3H, —CH_3); ^{13}C NMR (126 MHz, DMSO d_6): δC 170.2, 164.3, 156.2, 147.4, 147.1, 141.1, 133.4, 132.0, 131.2, 130.8, 130.6, 130.6, 129.6, 129.6, 128.4, 128.4, 126.7, 126.7, 125.2, 124.2, 121.4, 21.7; HR-ESI-MS: m/z calcd for $C_{22}H_{16}ClN_3OS$, $[M]^+$ 405.0518; Found 406.0515.

2.3.8. (E)-4-(5-chlorobenzo[d]thiazol-2-yl)-N′-(4-nitrobenzylidene) benzohydrazide (**8**)

Yellow solid, Yield: 82%. ^{1}H NMR (500 MHz, DMSO d_6):δH 8.32 (s, 1H, —CH), 8.29 (d, J = 8.3 Hz, 2H, Ar), 8.21 (s, 1H, Ar), 8.05 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.8 Hz, 2H, Ar), 7.94 (d, J = 8.6 Hz, 2H, Ar), 7.92 (d, J = 8.02 Hz, 1H, Ar), 7.54 (d, J = 7.8 Hz, 1H, Ar); ^{13}C NMR (126 MHz, DMSO d_6): δC 170.2, 164.3, 156.2, 150.7, 147.4, 147.1, 140.2, 133.4, 132.0, 130.8, 130.6, 130.6, 128.4, 128.4, 125.2, 124.6, 124.6, 124.5, 124.3, 124.2, 124.2; HR-ESI-MS: m/z calcd for $C_{21}H_{13}ClN_4O_3S$, $[M]^+$ 436.0321; Found 437.0318.

2.3.9. (E)-4-(5-chlorobenzo[d]thiazol-2-yl)-N′-(2-hydroxybenzylidene) benzohydrazide (**9**)

Brown solid, Yield: 72%. ^{1}H NMR (500 MHz, DMSO d_6):δH 8.73 (s, 1H, —CH), 8.20 (s, 1H, Ar), 8.06 (d, J = 8.8 Hz, 2H, Ar), 7.93 (d, J = 8.6 Hz, 2H, Ar), 7.91 (d, J = 8.01 Hz, 1H, Ar), 7.64 (d, J = 7.8 Hz, 1H, Ar), 7.59 (d, J = 8.4 Hz, 1H, Ar), 7.04 (m, 1H, Ar), 7.48 (m, 1H), 7.01 (d, J = 7.2 Hz, 1H, Ar), 5.34 (s, 1H, —OH); ^{13}C NMR (150 MHz,