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Research article

Synthesis, α-glucosidase inhibition, α-amylase inhibition, and molecular docking studies of 3,3-di(indolyl)indolin-2-ones

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ABSTRACT

The synthesized 3,3-di(indolyl)indolin-2-ones **1a-p** showed desired higher α-glucosidase inhibitory activities and lower α-amylase inhibitory activities than standard drug acarbose. Particularly, compound **1i** showed favorable higher α-glucosidase % inhibition of 67 ± 13 and lower α-amylase % inhibition of 51 ± 4 in comparison to acarbose with % inhibition activities of 19 ± 5 and 90 ± 2, respectively. Docking studies of selected 3,3-di(indolyl)indolin-2-ones revealed key interactions with the active sites of both α-glucosidase and α-amylase, further supporting the observed % inhibitory activities. Furthermore, the binding energies are consistent with the % inhibition values. The results suggest that 3,3-di(indolyl)indolin-2-ones may be developed as suitable Alpha Glucosidase Inhibitors (AGIs) and the lower α-amylase activities should be advantageous to reduce the side effects exhibited by commercial AGIs.

1. Introduction

Diabetes mellitus is a metabolic disease associated with high levels of sugars in the blood (hyperglycemia) [1]. Diabetes Type 1 accounts for ~10% and occurs in patients whose pancreas is not able to produce enough insulin. Type 2 diabetes accounts for ~90% and occurs when the body cannot use the secreted insulin effectively [2, 3]. Diabetes causes severe problems including cardiovascular diseases, nephropathy, neuropathy, retinopathy, etc [2, 3].

There are several approaches to control hyperglycemia in the blood each with its advantages and disadvantages. Such approaches mainly enhance insulin availability or remove sugar more effectively [1, 2]. An effective approach to limit the amount of sugar entering the bloodstream is to uses α-glucosidase inhibitors (AGIs) [4] which inhibit the α-glucosidase enzyme. Unfortunately, commercial AGIs cause undesired strong inhibition of α-amylase enzymes and are associated with severe side effects. α-Amylase enzymes in the saliva and pancreatic juices hydrolyze α-1,4-glycosidic bonds of starch to simpler dextrins, disaccharides, and oligosaccharides [5, 6]. As the food travels to the small intestine, the brush border cells of the epithelium secrets α-glucosidase enzymes which hydrolyze disaccharides and oligosaccharides giving α-D-glucose that pass to the bloodstream [7]. Consequently, inhibition of α-glucosidase limits the amount of α-D-glucose that passes to the bloodstream [8]. Current commercial AGI drugs represented by Acarbose, Miglitol, and Voglibose are effective inhibitors of α-glucosidase. However, they cause flatulence, diarrhea, bloating, abdominal pain, and discomfort [4]. It is thought that the side-effects result from fermentation of undigested carbohydrates due to strong inhibition of α-amylase [9]. Therefore, it is desirable to design new selective AGIs having strong inhibition of α-glucosidase and low inhibition of α-amylase.

Indole-based compounds are abundant in the plant kingdom and show many bioactivities including antimalarial [10], antifungal [11], anticancer [12], antibacterial [12], anti-diabetic [13], antihelmintic [14] activities. Several indole-based drugs such as Sunitinib, indolidan, delaverdine, indomethacin, indoxole, and vinblastine are marketed for the treatment of various diseases while others are at various stages of clinical trials [15, 16, 17].

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Oxindoles also exhibit many activities including antiviral, antimicrobial, antifungal, anticancer, anti-inflammatory, antihypertensive, serotonergic, analgesic and sleep-inducing activities [17]. Oxindoles of the 3,3-di(indolyl)indolin-2-ones type (Scheme 1) show antidiabetic [18], antimicrobial [19], anticancer [20], and spermicidal [21] activities. Recently, Wang and co-workers [18] reported promising α-glucosidase inhibition activities of several 3,3-di(indolyl)indolin-2-ones. However, the authors did not examine the α-amylase inhibition activities which are important for developing next-generation AGIs having minimal gastrointestinal side-effects. They also did not elucidate the structure-activity relationship of 3,3-di(indolyl)indolin-2-ones with aromatic substituents as well as strongly donating and withdrawing moieties on inhibition of α-glucosidase. Therefore, at this stage, the overall inhibitory activity profile of 3,3-di(indolyl)indolin-2-ones remains unclear.

Herein, we report the synthesis of diverse 3,3-di(indolyl)indolin-2-ones and examine their α-glucosidase and α-amylase activities to provide a clear understanding of their overall inhibition effectiveness. To complement our study, we also report molecular docking studies to elucidate the mechanism of action of these compounds.

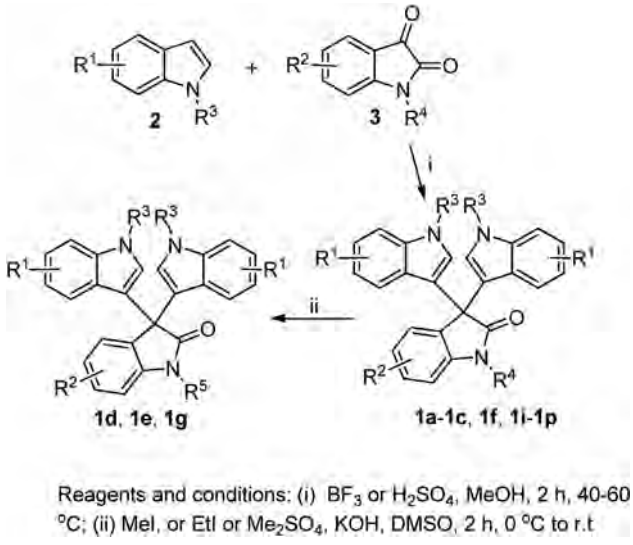
2. Materials and methods

The starting materials, solvents, and reagents were purchased from Sigma-Aldrich, Merck, and Fluka, and were used without further purification unless stated. Thin-layer chromatography was performed on Merck 0.20 mm precoated silica gel aluminum plates (Kieselgel 60, F254) and visualized using a UV lamp operating at 245 nm. Melting points were measured using the Fischer-John apparatus and are uncorrected. Infrared spectra were recorded using KBr disc on FTIR Shimadzu 8400S. ^{1}H NMR spectra were recorded using Jeol JNM-ECA300 (300 MHz), Jeol JNM-ECS400 (400 MHz), Bruker Avance DPX 300 (300 MHz), or Hitachi R-1900 FT NMR (90 MHz). ^{13}C NMR spectra were recorded at 75 MHz on Jeol JNM-ECA300 (300 MHz), 100 MHz on Jeol JNM-ECS400 (400 MHz), and 75.47 MHz on a Bruker Avance DPX 300. Mass spectra were obtained using a Xevo G2-XS QTof, Hitachi QP-5000, or Waters LCT Premier XE instrument.

2.1. Chemistry

2.1.1. General procedure for the synthesis of 3,3-di(indolyl)indolin-2-one

A solution of the isatin or its alkyl derivative and indole or its alkyl derivative in methanol (~100 ml per 1g of isatin) was treated with a catalytic amount of BF_3 or H_2SO_4 (2–3 drops per 1 g of isatin) and stirred at 40–60 °C for 1–2 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with ice-cold water (50 mL per 1g of isatin). The resulting precipitates were filtered under vacuum, washed with an excess of ice-cold water (3 x 50 mL), and then were dried under vacuum to give the pure product. This general procedure was used to prepare 3,3-di(indolyl)indolin-2-one derivatives **(1a-1c, 1f, 1i-1p)**.



Scheme 1. Synthesis of 3,3-di(indolyl)indolin-2-ones **1a-p**.

3,3-Di(1*H*-indole-3-yl)indolin-2-one **(1a)**: Isatin (0.30 g, 2.04 mmol) and indole (0.47 g, 4.00 mmol) reacted to give **1a** as white powder, 0.71 g, 97% yield), m.p. 320–321 °C (lit [22]. 317–319 °C). ^{1}H NMR (90 MHz, DMSO-d_6): δ 6.70–7.40 (m, 14H), 10.54 (s, 2H), 10.91 (s, 1H). Mass spectrum (EI): *m/z* 363 (M, 80%), 334 (100), 247 (10), 219 (50).

3,3-Di(1-methyl-1*H*-indole-3-yl)indolin-2-one **(1b)**: Isatin (0.25 g, 1.70 mmol) and 1-methylindole (0.44 g, 3.35 mmol) reacted to give **1b** as white powder (0.58 g, 88% yield), m.p. 329–330 °C (lit [23]. 330–332 °C). ^{1}H NMR (90 MHz, $(CD_3)_2CO$): δ 3.76 (s, 6H), 6.74–7.45 (m, 14H), 9.45 (bs, 1H). Mass spectrum (EI): *m/z* 392 (M+1, 10%), 391 (M, 60), 376 (5), 362 (100), 233 (20).

3,3-Di(1-ethyl-1*H*-indole-3-yl)indolin-2-one **(1c)**: Isatin (0.052 g, 0.35 mmol) and 1-ethylindole (0.10 g, 0.69 mmol) reacted to give **1c** as white powder (0.13 g, 93% yield), m.p. 340–341 °C (lit [24]. mp 273–275 °C). ^{1}H NMR (90 MHz, $(CD_3)_2CO$): δ 1.28 (t, J = 7.2 Hz, 6H), 4.14 (q, J = 7.2 Hz, 4H), 6.73–7.47 (m, 14H), 10.56 (s, 1H). Mass spectrum (EI): *m/z* 420 (M+1, 10%), 419 (M, 65), 390 (100), 275 (15), 247 (10).

3,3-Di(1*H*-indole-3-yl)-5-bromoindolin-2-one **(1f)**: 5-Bromoisatin (0.050 g, 0.22 mmol) and indole (0.050 g, 0.45 mmol) reacted to give **1f** as brown solid (0.090 g, 92% yield), m.p. 282–283 °C (lit [19]. 299–301 °C). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 6.80 (t, J = 7.3 Hz, 2H), 6.87 (s, 2H), 6,95 (d, J = 8.2 Hz, 1H), 7.01 (t, J = 7.2 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.28 (s, 1H), 7.35 (d, J = 8,0 Hz, 2H), 7.39 (d, J = 8.3 Hz, 1H), 10.74 (s, 1H), 10.99 (s, 2H). Mass spectrum (EI): *m/z* 443 (M, ^{81}Br, 10%), 441 (M, ^{79}Br, 10), 327 (5), 325 (5), 299 (5), 297 (5), 44 (100).

3,3-Di(5-hydroxy-1*H*-indole-3-yl)-5-nitroindolin-2-one **(1i)**: 5-Nitroisatin (0.096 g, 0.50 mmol) and 5-hydroxyindole (0.13 g, 1.00 mmol) reacted, and after column chromatography (ethyl acetate:*n*-hexane, 2:1), gave **1i** as brown solid (0.15 g, 68 % yield), m.p. 302–303 °C. IR (KBr disk): 3524, 3349, 3117, 1697, 1626, 1605, 1582, 1528, 1468, 1338, 1202, 1062 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.53 (dd, J = 8.4, J = 2.4 Hz, 4H), 6.57 (d, J = 2.4 Hz, 2H), 6.78 (d, J = 2.4 Hz, 2H), 7.12–7.16 (m, 3H), 7.90 (d, J = 2.0 Hz, 1H), 8.20 (dd, J = 8.4, J = 2.4 Hz, 1H), 8.52 (s, 2H), 10.72 (s, 2H), 11.20 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.1, 105.1, 110.3, 112.2, 112.6, 120.5, 125.6, 125.7, 125.9, 126.7, 132.1, 136.0, 142.7, 148.4, 150.5, 179.5.

3,3-Di(1*H*-indole-3-yl)-5-nitroindolin-2-one **(1j)**: 5-Nitroisatin (0.072 g, 0.38 mmol) and indole (0.088 g, 0.75 mmol) reacted to give the **1j** as yellow solid (0.13 g, 87% yield), m.p. 272–273 °C (lit [22]. 281–282 °C). IR (KBr disc): 3385, 3123, 3059, 1709, 1620, 1528, 1481, 1456, 1420, 1340, 1246, 1215, 1175, 1129, 1086, 1013, 941 cm^{-1}. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 6.87 (t, J = 4.6 Hz, 2H), 7.05–7.09 (m, 4H), 7.07 (s, 1H), 7.32 (d, J = 9.1 Hz, 1H), 7.42 (d, J = 5.1 Hz, 4H), 7.44 (d, J = 4.8 Hz, 2H), 8,15 (d, J = 1.5 Hz, 1H), 8.27 (dd, J = 4.0, 1.5 Hz, 1H), 10.20 (bs, 1H), 10.29 (s, 2H). ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 53.9, 110.6, 112.6, 114.7, 119.8, 121.6, 121.9, 122.5, 125.6, 126.1, 126.9, 136.6, 138.5, 143.9, 148.6, 179.5. MS (ES): *m*/z calcd for $C_{24}H_{15}N_4O_3$, $[M-H]^-$ 407.1144; Found 407.1124.

3,3-Di(1-methyl-1*H*-indole-3-yl)-5-nitroindolin-2-one **(1k)**: 5-Nitroisatin (0.29 g, 1.51 mmol) and 1-methylindole (0.39 g, 2.97 mmol) reacted to give **1k** as yellow solid (0.61 g, 94% yield), m.p. 291–292 °C (lit [25]. >300 °C). ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 3.78 (s, 6H), 6.88 (t, J = 4.1 Hz, 2H), 7.00 (s, 2H), 7.12 (t, J = 4.6 Hz, 2H), 7.31 (d, J = 5.2 Hz, 1H), 7.37 (d, J = 4.8 Hz, 2H), 7.41 (d, J = 4.8 Hz, 2H), 8.12 (d, J = 1.5 Hz,1H), 8.26 (dd, J = 4.5, 1.4Hz, 1H), 10.29 (bs, 2H). ^{13}C NMR (125 MHz, $(CD_3)_2CO$): δ 32.9, 53.7, 110.6, 110.6, 113.6, 119.7, 121.6, 122.1, 122.5, 126.1, 127.3, 129.8, 136.6, 138.9, 143.9, 148.6, 179.4. MS (ES): *m*/z calcd for $C_{26}H_{19}N_4O_3$, $[M-H]^-$ 435.1457; Found 435.1436.

3,3-Di(1*H*-indole-3-yl)-1-benzyl-5-nitroindolin-2-one **(1l)**: 1-Benzyl-5-nitroisatin (0.070 g, 0.25 mmol) and indole (0.060 g, 0.51 mmol) reacted to give **1l** as a yellow solid (0.10 g, 83% yield), m.p. 237–238 °C. IR (KBr disc): 3458, 3352, 3125, 3061, 1711, 1603, 1518, 1487, 1454, 1335, 1211, 1173, 1105, 1080, 748 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 5.09 (s, 2H), 6.74 (t, $J = 7.6$ Hz, 2H), 6.95 (d, $J = 2.4$ Hz, 2H), 7.01 (d, $J = 7.6$ Hz, 2H), 7.07 (d, $J = 8.6$ Hz, 2H), 7.28–7.37 (m, 8H), 8.00 (d, $J = 2.4$ Hz, 1H), 8.24 (dd, $J = 8.6$, 2.4 Hz, 1H), 11.09 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 43.9, 52.7, 110.2, 112.4, 113.0, 119.1, 120.4, 120.9, 121.8, 125.2, 125.8, 125.9, 128.2, 128.3, 129.3, 135.0, 136.3, 137.6, 143.4, 148.2, 177.9. HRMS (ES): *m/z* calcd for $C_{31}H_{21}N_4O_3$, $[M\text{-}H]^-$ 497.1614; Found 497.1636.

3,3-Di(1*H*-indole-3-yl)-1-benzyl-5-bromoindolin-2-one **(1m)**: 1-Benzyl-5-bromoisatin (0.030 g, 0.10 mmol) and indole (0.020 g, 0.20 mmol) reacted to give **1m** as yellow solid (0.043 g, 81% yield), m.p. 188–189 °C (lit [19]. 268–270 °C). IR (KBr disc): 3428, 3356, 3131, 3063, 1699, 1603, 1546, 1479, 1454, 1422, 1341, 1242, 1213, 1173, 1101, 1065, 1013, 749 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 5.00 (s, 2H), 6.74 (t, $J = 8.0$ Hz, 2H), 6.89 (d, $J = 2.8$ Hz, 2H), 7.01 (t, $J = 7.6$ Hz, 2H), 7.08 (t, $J = 7.0$ Hz, 3H), 7.26–7.45 (m, 10H), 11.03 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 43.6, 53.0, 112.0, 112.3, 113.7, 114.7, 119.0, 121.0, 121.7, 125.0, 125.9, 127.8, 128.1, 129.2, 131.3, 136.7, 136.7, 137.5, 141.6, 177.1. MS (ES): *m/z* calcd for $C_{31}H_{31}N_3OBr$, $[M\text{-}H]^-$ 530.0868; Found 530.0910.

3,3-Di(1*H*-indole-3-yl)-1-(4-bromobenzyl)-5-bromoindolin-2-one **(1n)**: 1-(4-Bromobenzyl)-5-bromoisatin (0.19 g, 0.48 mmol) and indole (0.12 g, 1.02 mmol) reacted to give **1n** as ivory coloured solid (0.28 g, 97% yield), m.p. 248–249 °C. IR (KBr disc): 3416, 3287, 3056, 1715, 1601, 1537, 1422, 1333, 1244, 1206, 1167, 1101, 1071, 1013, 741 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 4.97 (s, 2H), 6.73 (t, $J = 7.4$ Hz, 2H), 6.87 (s, 2H), 7.00 (dd, $J = 12.8$, 8.0 Hz, 4H), 7.13 (d, $J = 8.0$ Hz, 1H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 7.4$ Hz, 3H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.49 (d, $J = 8.0$ Hz, 2H), 11.02 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 42.5, 52.4, 111.5, 111.9, 113.1, 114.3, 118.5, 120.5, 120.8, 121.2, 124.6, 125.4, 127.3, 130.0, 130.8, 131.6, 135.7, 136.1, 137.0, 140.9, 176.6. MS (ES): *m/z* calcd for $C_{31}H_{21}N_3OBr_2$, $[M + Na]^+$ 633.9929; Found 633.9542.

3,3-Di(1*H*-indole-3-yl)-5-chloroindolin-2-one **(1o)**: 5-Chloroisatin (0.051 g, 0.28 mmol) and indole (0.065 g, 0.56 mmol) reacted to give **1o** as brown solid (0.10 g, 98% yield), m.p. 275–276 °C (lit [22]. 290–291 °C). ^1H NMR (90 MHz, $CDCl_3$): δ 6.81–7.42 (m, 13H), 10.70 (s, 1H), 10.98 (s, 2H). Mass spectrum (EI): *m/z* 399 (M, ^{37}Cl, 10%), 397 (M, ^{35}Cl, 30), 368 (15), 246 (50), 117 (35), 44 (100).

3,3′-Di(1-methyl-1*H*-indole-3-yl)-5-chloroindolin-2-one **(1p)**: 5-Chloroisatin (0.083 g, 0.46 mmol) and 1-methylindole (0.12 g, 0.92 mmol) reacted to give **1p** as pink solid (0.17 g, 89% yield), m.p. 278–279 °C (lit [26]. >300 °C). IR (KBr disc): 3223, 2932, 1717, 1616, 1541, 1476, 1429, 1371, 1333, 1290, 1248, 1200, 739 cm^{-1}. ^1H NMR (90 MHz, DMSO-d_6): δ 3.72 (s, 6H), 6.77–7.44 (m, 3H), 10.74 (s, 1H). Mass spectrum (EI): *m/z* 427 (M, ^{37}Cl, 5), 425 (M, ^{35}Cl, 15), 399 (30), 397 (10), 269 (9), 267 (3), 44 (100).

2.1.2. General procedures for the synthesis of substituted 3,3-di(indolyl) indolin-2-one through N-alkylation

A mixture of the 3,3-di(indolyl)indolin-2-one and freshly crushed KOH in anhydrous DMSO was stirred at room temperature for 1 h. After cooling to ice-bath temperature, the alkylating agent was added and the mixture was stirred further at room temperature for 1 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with ice-cold water (~50 mL per 0.5 mmol of starting indolin-2-one). The resulting precipitate was filtered under vacuum, washed with an excess of ice-cold water (3 x 50 mL), and dried to give the pure product. This general procedure was used to make compounds **1d**, **1e**, and **1g**.

3,3-Di(1-methyl-1*H*-indole-3-yl)-1-methylindolin-2-one **(1d)**: A mixture of **1b** (0.20 g, 0.51 mmol) and KOH (0.11 g, 1.96 mmol) in anhydrous DMSO (15 mL) reacted with methyl iodide (0.06 mL, 0.96 mmol) to give **1d** as white solid (0.19 g, 90% yield), m.p. 218–219 °C (lit [23]. 232–234 °C). ^1H NMR ($CDCl_3$): δ 3.32 (s, 3H), 3.66 (s, 6H); 6.82–7.48 (m, 14H). Mass spectrum (EI): *m/z* 406 (M+1, 30%), 405 (M, 100), 390 (10), 376 (90), 275 (40), 247 (70), 233 (20).

3,3-Di(1-ethyl-1*H*-indole-3-yl)-1-ethylindolin-2-one **(1e)**: A mixture of **1c** (0.10 g, 0.24 mmol) and KOH (0.066 g, 1.18 mmol) in anhydrous DMSO (10 mL) reacted with ethyl iodide (0.04 mL, 0.48 mmol) to give **1e** as white solid (0.10 g, 91% yield), m.p. 169–170 °C (lit [27]. 272–274 °C). ^1H NMR ($CDCl_3$): δ 1.23–1.29 (m, 9H), 3.83 (q, $J = 6.0$ Hz, 2H), 4.13 (q, $J = 6.0$ Hz, 4H), 6.83 (t, $J = 9,0$ Hz, 2H), 6.92 (s, 2H), 6.98–7.10 (m, 3H), 7.17–7.27 (m, 3H), 7.32 (d, $J = 6.0$ Hz, 2Hz), 7.43 (d, $J = 9.0$ Hz, 2H). Mass spectrum (EI): *m/z* 448 (M+1, 30%), 447 (M, 100), 418 (75), 404 (30), 390 (20), 303 (40), 275 (40), 247 (70), 233 (20).

3,3-Di(5-bromo-1-methyl-1*H*-indole-3-yl)-5-bromo-1-methylindolin-2-one **(1g)**: A mixture of 3,3-di(5-bromo-1-methyl-*1H*-indole-3-yl)-5-bromoindolin-2-one (0.030 g, 0.048 mmol) and KOH (0.036 g, 0.64 mmol) in anhydrous DMSO (15 mL) reacted with dimethyl sulfate (0.06 mL, 0.63 mmol) to give **1g** as light orange solid (0.029 g, 94% yield), m.p. 287–288 °C. IR (KBr disc): 2918, 1713, 1607, 1537, 1474, 1422, 1368, 1337, 1273, 1219, 1144, 1094, 1049, 789 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.25 (s, 3H), 3.73 (s, 6H), 7.02 (s, 2H), 7.21 (d, $J = 8.4$ Hz, 1H), 7.23 (d, $J = 2.0$ Hz, 1H), 7.25 (d, $J = 2.0$ Hz, 1H), 7.27 (d, $J = 2.0$ Hz, 1H), 7.31 (d, $J = 2.0$ Hz, 1H), 7.43 (d, $J = 9.1$ Hz, 2H), 7.59 (dd, $J = 8.4$, 2.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.5, 32.7, 51.7, 111.2, 111.6, 111.7, 112.4, 114.4, 122.5, 123.9, 127.2, 130.2, 131.2, 134.8, 136.2, 141.8, 175.9. Mass spectrum (ES): *m/z* calcd for $C_{27}H_{21}Br_3N_3O$, $[M + H]^+$ 639.9235; Found 639.9280.

2.1.3. Reduction of *1j* to *1h*

3,3′-Di(1*H*-indole-3-yl)-5-5-aminoindolin-2-one **(1h)**: A mixture of **1j** (0.10 g, 0.25 mmol) and Pd/C (0.01 g) in ethanol (10 mL) was brought to reflux. To this mixture, a solution of hydrazine hydrate (0.49 mL, 0.01 mmol) in ethanol (10 mL) was added dropwise. The resulting mixture was heated to reflux for 90 min, allowed to cool and then diluted with THF (5 mL). The cooled mixture was filtered and the mother liquor was diluted with water (50 mL). The resulting precipitates were filtered under vacuum, washed with excess of ice-cold water (3 x 50 mL), dried over $MgSO_4$, purified by column chromatography (chloroform:ethyl acetate, 1:2) to give **1h** as brown-yellow solid (0.068 g, 72% yield), m.p. 258–259 °C. IR (KBr disc): 3626, 3364, 3315, 3121, 3057, 1666, 1614, 1491, 1456, 1421, 1335, 1244, 1207, 1103, 1014 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 5.11 (bs 2H), 6.44 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.52 (s, 1H), 6.66 (d, $J = 8.8$ Hz, 1H), 6.75 (t, $J = 7.6$ Hz, 2H), 6.79 (d, $J = 2.4$ Hz, 2H), 6.97 (t, $J = 7.2$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 7.6$ Hz, 2H), 10.15 (s, 1H), 10.88 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.4, 110.3, 112.0, 113.1, 114.0, 115.3, 118.6, 121.4, 121.5, 124.8, 126.3, 132.3, 136.0, 137.4, 142.8, 179.0. Mass spectrum (ES): *m/z* calcd for $C_{24}H_{19}N_4O$, $[M + H]^+$ 379.1559; Found 379.3989.

2.2. α-Glucosidase inhibition assay

In principle, Kang and co-workers method was used to examine the α-glucosidase inhibitory activity of the synthesized compounds [28]. In this method, a solution of 50 μg/mL final concentration was prepared for each compound in DMSO. 8 μL of this solution was added to 115 μL of 0.1 M sodium phosphate buffer pH 7.0 in a 96 well microtiter plate. To this mixture, 50 μL of α-glucosidase enzyme solution (0.5 U/mL of yeast α-glucosidase in buffer solution) was introduced. The 'Blank', was prepared similarly but 50 μL of buffer was added instead of the enzyme, and 8 μL of DMSO was added instead of the inhibitor. Positive control was also prepared in a similar fashion where no inhibitor is replaced by 8 μL of DMSO. Acarbose was used as the standard drug in this procedure. The microtiter plate was shaken for 15 min at 37 °C then 25 μL of 2.5 mM of 4-nitrophenyl β-D-glucopyranoside (PNPG) was introduced to each well. The plate was shaken for another 15 min at the same temperature and the

absorbance was measured at 405 nm. The percentage of inhibition was calculated as Eq. (1):

$$\left(\frac{(Abs_{positive\ control} - Abs_{compound})}{Abs_{positive\ control}}\right) \times 100\% \quad (1)$$

All measurements are performed in triplicates and the values are represented as mean ± standard deviation.

2.3. α-Amylase inhibition assay

Phan and co-workers method was used for testing α-amylase inhibitory activity [29]. Solution corresponding to 50 μg/mL in DMSO was prepared. To each test tube, 50 μL of these test solutions, 100 μL of α-amylase (5U/mL of porcine pancreatic α-amylase in 0.05 sodium phosphate buffer pH 6.8) and 460 μL of 0.05 M sodium phosphate buffer pH 6.8 were added. 'Blank' and 'Positive Control' were prepared similarly but 50 μL of DMSO was added instead of the inhibitor. In the case of 'Blank', the enzyme solution was replaced by 100 μL of the buffer. Results were compared to Acarbose as the standard drug. The test tubes were shaken for 10 min at 37 °C whereupon 450 μL of 0.5% starch solution was added to each tube and the shaking continued for another 20 min. At this point, 500 μL of dinitro salicylic acid (DNSA) reagent was added to each tube. The tubes were introduced in a boiling water bath for 15 min and the absorbance was then measured at 540 nm. The 0.5% starch solution was prepared by dissolving 0.5 g of starch in 99.5 mL of buffer. The starch solution was heated in a boiling water bath for 5 min to ensure starch dissolved completely. The percentage inhibition was calculated using Eq. (1). All measurements were performed in triplicates and the values are represented as mean ± standard deviation. Note that the DNSA solution is prepared by dissolving 1 g of DNSA in 50.0 mL of ultrapure water followed by slow addition of 30.0 g of sodium tartrate and 20.0 mL of 2N NaOH solution. Finally, the volume was topped up to 100 mL with ultrapure water.

2.4. Molecular docking

Docking simulations were performed to reveal the binding modes of 3,3-di(indolyl)indolin-2-ones **1a**, **1i**, and **1n** with α-glucosidase and α-amylase enzymes. The structure of the human lysosomal α-glucosidase [30] and human pancreatic α-amylase [31] was directly downloaded from the protein data bank (PDBID: 5NN5 and 6OCN, respectively) and was optimized after removing the co-factors, water molecules, and heteroatoms. The structures of the ligands were directly drawn using MarvinSketch program [32]. The docking simulation was conducted using Autodock 4.2.6 software [33]. The docking center was set to be the center of protein and the docking pocket size was set to be large enough to cover the whole protein molecule. The docking results were visualized using Discovery studio (Dassault Systèmes, San Diego) [34].

3. Results and discussions

3.1. Synthesis of 3,3-di(indolyl)indolin-2-ones *1a-p*

The route to synthesize 3,3-di(indolyl)indolin-2-ones **1a-p** is shown in Scheme 1. The reaction between indoles **2** and isatins **3** in the presence of a catalytic amount of BF_3 or H_2SO_4 at 40–60 °C afforded the desired products **1a-1c**, **1f,** and **1i-1p** in high 68–97% yields within 2 h. Compounds **1d, 1e,** and **1g** were obtained conveniently in high 90–94% yields by alkylating their corresponding counterparts. The 3,3-di(indolyl) indolin-2-ones **1a-p** were characterized using MS, IR, ^{1}H NMR and ^{13}C NMR and the spectral data were consistent with the structures and are typical for oxindole systems.[18] For an illustrative example, the ^{1}H NMR spectrum of **1n** recorded in DMSO-*d*6 showed 21 protons. Singlet signals at δ_H 4.97 and 11.02 ppm were assigned to methylene group protons and –NH protons respectively. The ^{13}C NMR spectrum showed signals at δ_C 42.5 and 52.4 ppm correspond to a methylene carbon and a spiro carbon respectively, and a signal at δ_C 176.6 ppm indicates the presence of carbonyl carbon. The IR spectrum of compound **1n** showed peak at 1715 revealing the presence of lactam amide (–NH–CO-). MS data was acquired in the positive ionization mode, exhibited peak at $m/z = 633.9542$ $[M + Na]^+$.

3.2. α-Glucosidase and α-amylase inhibition studies

The α-glucosidase and α-amylase % inhibition activities of the synthesized 3,3-di(indolyl)indolin-2-ones **1a-p** along with that of acarbose as the positive standard drug are summarized in Table 1. In general, while the compounds showed high to excellent inhibition activities for both enzymes, they showed stronger α-glucosidase inhibitory activity and desired lower α-amylase inhibitory activity in comparison to standard AGI drug acarbose.

Table 1. Percentage inhibition of α-glucosidase and α-amylase by 3,3-di(indolyl)indolin-2-ones **1a-p** with acarbose as the reference standard.

No	Indolin-2-one	R^1	R^2	R^3	R^4/R^5	% α-glucosidase inhibition[a]	% α-amylase inhibition[a]
1	**1a**	H	H	H	H	16 ± 6	92 ± 4
2	**1b**	H	H	CH_3	H	37 ± 11	81 ± 6
3	**1c**	H	H	CH_3CH_2	H	73 ± 6	72 ± 5
4	**1d**	H	H	CH_3	CH_3	86 ± 7	77 ± 8
5	**1e**	H	H	CH_3CH_2	CH_3CH_2	50 ± 11	74 ± 9
6	**1f**	H	Br	H	H	76 ± 8	86 ± 10
7	**1g**	Br	Br	CH_3	CH_3	61 ± 1	79 ± 4
8	**1h**	H	NH_2	H	H	17 ± 3	79 ± 9
9	**1i**	OH	NO_2	H	H	67 ± 13	51 ± 4
10	**1j**	H	NO_2	H	H	79 ± 5	93 ± 6
11	**1k**	H	NO_2	CH_3	H	86 ± 6	91 ± 5
12	**1l**	H	NO_2	H	Benzyl	76 ± 8	86 ± 0
13	**1m**	H	Br	H	Benzyl	92 ± 3	80 ± 3
14	**1n**	H	Br	H	4-Br-benzyl	94 ± 3	73 ± 5
15	**1o**	H	Cl	H	H	83 ± 2	87 ± 6
16	**1p**	H	Cl	CH_3	H	84 ± 2	81 ± 7
17	Acarbose[a]					19 ± 5	90 ± 2

[a] Inhibition was measured at a concentration of 50 μg/ml. Inhibition values are expressed as means ± SD; n = 3.

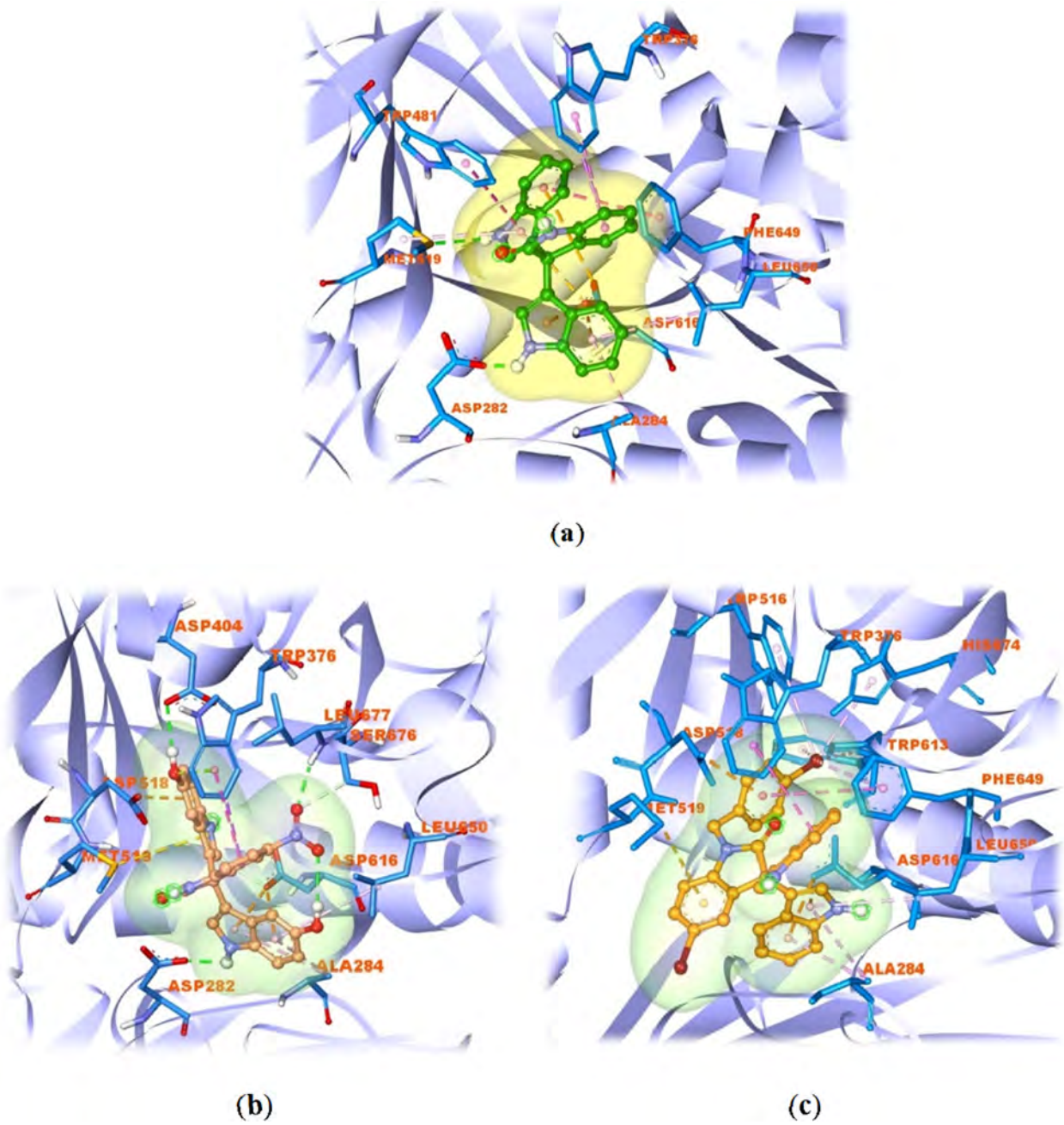


Figure 1. Binding interaction of (**a**) indolin-2-one **1a**; (**b**) indolin-2-one **1i**; and (**c**) indolin-2-one **1n** in with α-glucosidase (PDB ID: 5NN5).

3.2.1. α-Glucosidase inhibition activities

All the compounds showed higher % α-glucosidase inhibition activities ranging from 37 ± 11 to 94 ± 3 in comparison to acarbose with % inhibition activity of 19 ± 5, all measured at a concentration of 50 μg/ml. Exceptions are compounds **1a** and **1h** which showed % inhibition activities of 16 ± 6 and 17 ± 3, respectively (Table 1, entries 1 and 8). Considering the compounds in Table 1, the type of substituent and their position played a role in the inhibition activities to different extents. Compound **1a** with no substituents showed the lowest % inhibition activity of 16 ± 6. In the study conducted by Wang *et.al.* [18], the same compound **1a** showed the lowest IC_{50} value of 145.95 ± 0.46 μM. Introduction of a methyl moiety at the indole rings as in **1b** lead to doubling of the % inhibition activity to 37 ± 11 while the introduction of an ethyl moiety as in **1c** increases the activity to more than four folds to 73 ± 6. Interestingly, while the introduction of methyl moiety to the oxindole ring increased the inhibition activity of **1d** to 86 ± 7, the introduction of a corresponding ethyl moiety as in **1e** reduced the activity to 50 ± 11. This unpredicted result underscores the effect of small structural changes on inhibitory activity. Compound **1f** with bromine moiety enhanced the % inhibition activity of its parent **1a** by five-folds from 16 ± 6 to 76 ± 8. However, compound **1g** with the bromine at the same position but with another at the indole rings gave lower inhibition activity of 61 ± 1 in comparison to its parent **1d** with inhibition activity of 86 ± 7. The introduction of strong electron-donating NH_2 group on the oxindole ring of **1a** to give **1h** did not significantly affect the % inhibition activity (17 ± 3 *vs* 16 ± 6, entry 8 *vs* entry 1, Table 1). However, the introduction of additional OH groups on the indole rings of **1h** and replacing its NH_2 group with NO_2 group to give **1i**, significantly increased the % inhibition activity from 17 ± 3 to 67 ± 13 (Table 1, entry 8 *vs* entry 9). Additionally, stronger electron-withdrawing NO_2 groups of

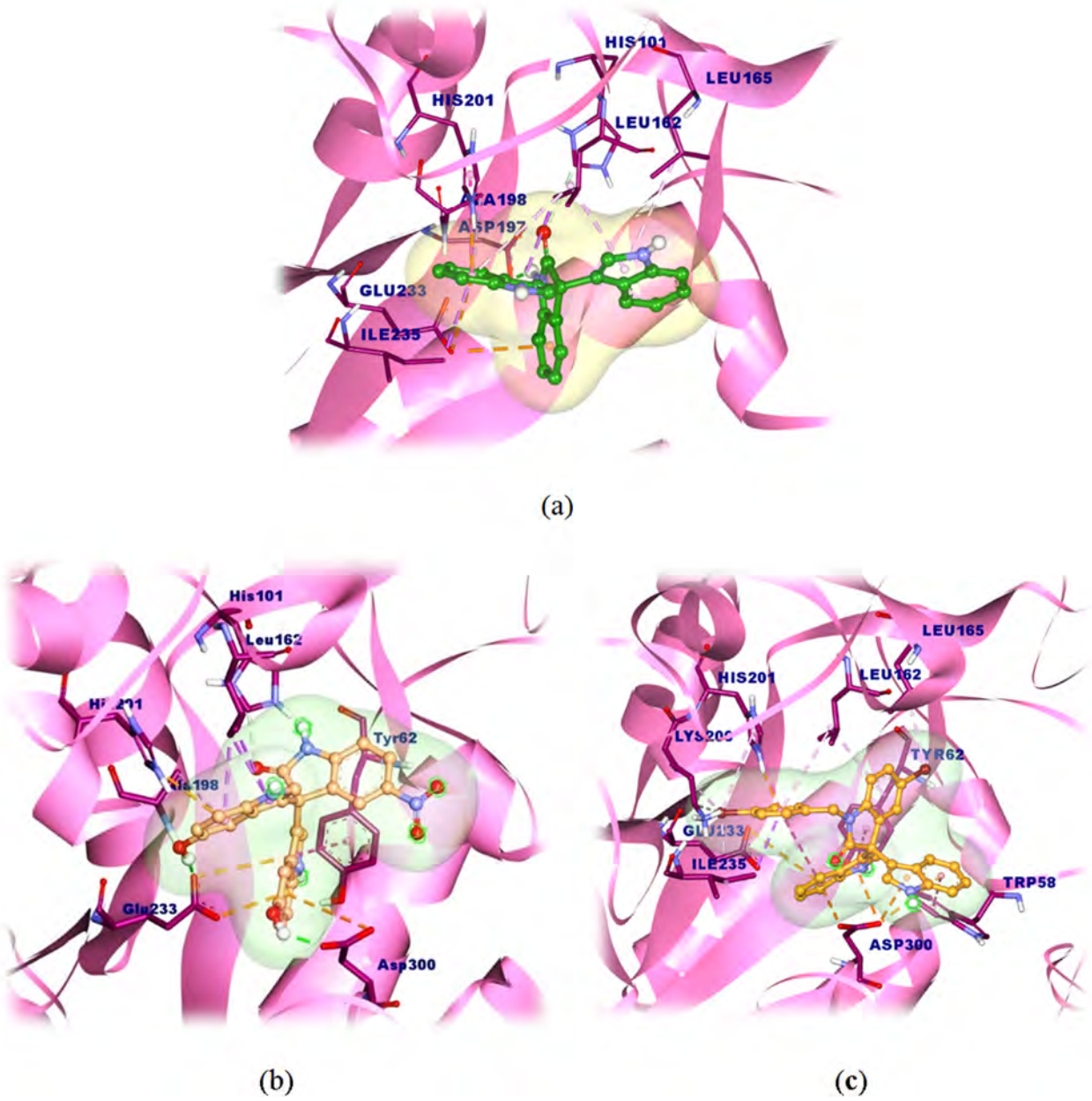


Figure 2. Binding interaction of (a) indolin-2-one **1a**, (b) indolin-2-one **1i**, and (c) indolin-2-one **1n** with α-amylase (PDB ID: 6OCN).

1j increased its activity to almost five-fold (79 ± 5 *vs* 16 ± 6, Table 1, entry 10 *vs* entry 1). At this stage, we predicted that the introduction of *N*-alkyl substituents to **1j** will increase its inhibition activities. However, while compound **1k** with methyl substituents showed a moderate increase in the % inhibition activity to 86 ± 6, compound **1l** with benzyl substituent decreased the % inhibition activity to 76 ± 8 perhaps due to stearic effects which prevented better fitting with the enzyme active sites. A significant increase in the activity occurred by changing the strong electron-withdrawing NO_2 group of **1l** to bromine as in **1m** which showed % inhibition of 92 ± 3, or related **1n** which showed % inhibition of 94 ± 3. Replacement of bromine of **1f** with chlorine to get **1o** resulted in a small increase in the % inhibition activity (Table 1, entry 6 *vs* entry 15). Methylation of **1o** with to obtain **1p** did not increase the % inhibition activity.

3.2.2. α-Amylase inhibition activities

The tested compounds in Table 1 showed high to very high α-amylase % inhibition activities ranging from 72 ± 5 to 92 ± 4, except **1i** which showed a % inhibition value of 51 ± 4, all measured at a concentration of 50 μg/ml. Overall, the differences in activities between structurally related compounds are not as pronounced as in the α-glucosidase case. Interestingly, compound **1a** which showed the lowest α-glucosidase inhibitory activity exhibited one of the highest α-amylase % inhibition activity of 92 ± 4. The inhibition activity varied with the size/number of the substituents. For example, as the size/number of the substituents increases in compounds **1a-e**, the corresponding inhibition values decrease (Table 1, entries 1–5). The same is also observed for compounds **1f** and **1g**. The situation becomes ambiguous when we consider the effects of electron-withdrawing and donating substituents which gave no obvious trend. For example, the parent compound **1a** showed very high % inhibition activity similar to compounds **1j** with 93 ± 6 and **1k** with 91 ± 5 having strong electron-withdrawing group NO_2 and donating methyl moieties. The inhibition values in Table 1 suggest that compounds **1a-h** and **1j-p** have a similar mode of interactions with α-amylase enzymes and that mode is different in the case of **1i**. As mentioned in the introduction section, lower α-amylase inhibition is desired to overcome the

gastrointestinal side-effects. Therefore, compound **1i** serves this purpose considering that it has the lowest α-amylase activity and high α-glucosidase activity.

3.3. Molecular docking studies

Docking simulations were performed on 3,3-di(indolyl)indolin-2-ones **1a**, **1i,** and **1n** to predict the binding interaction of these compounds in the active site of both enzymes. These compounds were selected because they showed the highest contrasting α-glucosidase and α-amylase inhibition values (Table 1, entries 1, 9, and 14). In the docking simulation, all the 3,3-di(indolyl)indolin-2-ones **1a**, **1i,** and **1n** recognized the binding pocket of both enzymes correctly. These indolin-2-ones formed stable key interactions with the active sites of both enzymes.

In the case of α-glucosidase, the binding affinities of the three indolin-2-ones is in the order **1a** (−7.45 kcal/mol) > **1i** (−7.84 kcal/mol) > **1n** (−8.26 kcal/mol) which is consistent with the experimental % inhibition trend values $16 \pm 6 < 67 \pm 13 < 94 \pm 3$, respectively. The theoretical binding modes of compounds **1a**, **1i,** and **1n** with α-glucosidase are shown in Figure 1. Indolin-2-one **1a** formed hydrophobic π-σ interaction with the Trp376. One of the indole rings formed π-π T-shaped interaction with Phe649 and Trp481 while the other indole rings formed π-alkyl with Leu650 and Ala284. Both of the indole rings also formed π-anion interaction with Asp616. From the docking analysis, hydrogen bonds were observed between NH of each indole rings with Met519 (bond length: 2.93 Å) and Asp282 (bond length: 1.88 Å). Indolin-2-one **1i** which has an NO_2 and OH groups formed new hydrogen bonds with Leu677 (bond length: 2.34 Å) and Asp404 (bond length: 2.76 Å), respectively, while maintaining the hydrogen bond between the NH of the other indole rings and Asp282 (bond length: 2.06 Å). Additionally, the NO_2 group not only formed a conventional hydrogen bond, but also a non-classical or carbon-hydrogen bond with the Ser676. The OH group formed π-lone pair interaction with Trp376. However, it was different from indolin-2-one **1n** which did not show the presence of any hydrogen bonds. The *p*-bromobenzyl group on the indolin-2-one ring in indolin-2-one **1n** formed hydrophobic π-π stacking and π-alkyl interactions with Phe649, His674, Trp613, and Trp516 residues. In addition, the benzene ring of the *p*-bromobenzyl group formed a π-anion interaction with Asp518. Besides, both indolin-2-ones **1i** and **1n** maintained the hydrophobic interaction with Trp376, Leu650, and Ala284 residues.

In the case of docking with α-amylase, the binding affinities of indolin-2-ones were in the order **1i** (−8.42 kcal/mol) > **1a** (−8.47 kcal/mol) > **1n** (−8.75 kcal/mol) which is different from the trend with α-glucosidase. The binding modes of indolin-2-ones **1a**, **1i,** and **1n** with α-amylase are shown in Figure 2. The protein-ligand complex analysis of compound **1a** showed there were two kinds of hydrogen bonds observed on the indolin-2-one ring which were conventional and non-classical hydrogen bonds. The NH of the indolin-2-one ring formed the conventional hydrogen bond with Asp197 (bond length: 1.74 Å) while the carbonyl group of the indolin-2-one ring formed the non-classical hydrogen bond with His101 (bond length: 3.52 Å). The indole rings of compound **1a** formed several hydrophobic interactions which were π-σ interaction with Ile235 and Leu162, π-alkyl interaction with Ala198, Leu165, and Leu162. Moreover, there were electrostatic interactions via a π-cation interaction between the indolin-2-one ring and Glu233 then a π-anion interaction between one of the indole rings and His201. From the docking analysis, the carbonyl group of the indolin-2-one ring in compound **1i** formed a non-classical hydrogen bond with His101 (bond length: 3.02 Å). One of the indole rings of compound **1i** formed π-alkyl, π-σ, and π-anion interactions with Ala198, Leu162, and His 201, respectively. The other indole rings formed π-π T-shaped and π-anion interactions with Tyr62 and GLu233, respectively. Meanwhile, the substitution of the OH group in the indole rings formed hydrogen bonds with Glu233 (bond length: 1.72 Å) and Asp300 (bond length: 1.83 Å). In this receptor, again, compound **1n** showed no hydrogen bond but had five types of hydrophobic interaction in its protein-ligand complex. The bromo group of the indolin-2-one ring formed an alkyl hydrophobic interaction with Leu165, while bromo group of the *p*-bromobenzyl of the indolin-2-one ring formed alkyl and π-alkyl interaction with Ile235 and His201, respectively. The *p*-bromobenzyl group also formed π-σ and π-cation interaction with Ile235 and His201, respectively. The indole rings of compound **1n** formed π-π stacking and π-π T-shaped interactions with Trp58 and Tyr62, respectively. Also, the indole rings formed π-anion interaction with Asp300 and Glu233.

4. Conclusions

We have synthesized a series of 3,3-di(indolyl)indolin-2-ones **1a-p** and examined their α-glucosidase and α-amylase inhibitory activities. Overall, the compounds showed desired higher α-glucosidase activities and desired lower α-amylase activities than standard drug AGI acarbose. The inhibitory activity against α-glucosidase varied greatly in comparison to α-amylase concerning the substituents on the core structure. Molecular docking studies showed that the tested compounds interacted with the active sites of both α-glucosidase and α-amylase and the trend in the binding energy values parallel with the % inhibition values. The results suggest that 3,3-di(indolyl)indolin-2-ones, especially indolin-2-one **1i**, are promising AGIs.

Declarations

Author contribution statement

Mardi Santoso, Azminah Azminah, Zaher M. A. Judeh: Conceived and design the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Li Lin Ong, Nur Pasca Aijijiyah, First Ambar Wati, Rose Malina Annuur, Arif Fadlan: Performed the experiments; Analyzed and interpreted the data.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] A. Mitra, D. Dewanjee, B. Dey, Mechanistic studies of lifestyle interventions in type 2 diabetes, World J. Diabetes 3 (2012) 201–207.
[2] M. Blair, Diabetes mellitus review, Urol. Nurs. 36 (2016) 27–36 [PMID: 27093761].
[3] R.A. DeFronzo, E. Ferrannini, L. Groop, R.R. Henry, W.H. Herman, J.J. Holst, F.B. Hu, C.R. Kahn, I. Raz, G.I. Shulman, D.C. Simonson, M.A. Testa, R. Weiss, Type 2 diabetes mellitus, Nat Rev Dis Primers 1 (2015) 15019.
[4] G. Derosa, P. Maffioli, Management of diabetic patients with hypoglycemic agents α-Glucosidase inhibitors and their use in clinical practice, Arch. Med. Sci. 8 (2012) 899–906.
[5] A.F. Afifi, E.M. Kamel, A.A. Khalil, M.F.E. Fawzi, M.M. Houseny, Purification and characterization of oc-amylase from *Penicillium olsonii* under the effect of some antioxidant vitamins, Glob. J. Biotechnol. Biochem. 3 (2008) 14–21.
[6] Y.-I. Kwon, E. Apostolidis, K. Shetty, Evaluation of Pepper (Capsicum Annuum) for Management of diabetes and Hypertension, J. Food Biochem. 31 (2007) 370–385.

[7] Y.-M. Kim, Y.-K. Jeong, M.-H. Wang, W.-Y. Lee, H.-I. Rhee, Inhibitory effect of pine extract on α-glucosidase activity and postprandial hyperglycemia, Nutrition 21 (2005) 756–761.

[8] M. Yoshikawa, T. Murakami, K. Yashiro, H. Matsuda, Kotalanol, a potent α-glucosidase inhibitor with Thiosugar Sulfonium sulfate structure, from antidiabetic Ayurvedic Medicine Salacia reticulata, Chem. Pharm. Bull. 46 (1998) 1339–1340.

[9] D.E. Kelley, P. Bidot, Z. Freedman, B. Haag, D. Podlecki, M. Rendell, D. Schimel, S. Weiss, T. Taylor, A. Krol, J. Magner, Efficacy and Safety of acarbose in insulin-treated patients with type 2 diabetes, Diabetes Care 21 (1998) 2056–2061.

[10] S.A. Santos, A.K. Lukens, L. Coelho, F. Nogueira, D.F. Wirth, R. Mazitschek, R. Moreira, A. Paulo, Exploring the 3-piperidin-4-yl-1H-indole scaffold as a novel antimalarial chemotype, Eur. J. Med. Chem. 102 (2015) 320–333.

[11] Y. Song, F. Wu, C. Zhang, G. Liang, G. Zhou, J. Yu, Ionic liquid catalyzed synthesis of 2-(indole-3-yl)-thiochroman-4-ones and their novel antifungal activities, Bioorg. Med. Chem. Lett. 25 (2015) 259–261.

[12] R. Gali, J. Banothu, R. Gondru, R. Bavantula, Y. Velivela, P.A. Crooks, One-pot multicomponent synthesis of indole incorporated thiazolylcoumarins and their antibacterial, anticancer and DNA cleavage studies, Bioorg. Med. Chem. Lett 25 (2015) 106–112.

[13] M. Nazir, M.A. Abbasi, Aziz-ur-Rehman, S.Z. Siddiqui, K.M. Khan, Kanwal, U. Salar, M. Shahid, M. Ashraf, M.A. Lodhi, F. Ali Khan, New indole based Hybrid Oxadiazole Scaffolds with N-substituted Acetamides: as potent anti-diabetic agents, Bioorg. Chem. 81 (2018) 253–263.

[14] S.K. Srivastava, A. Agarwal, P.M. Chauhan, S.K. Agarwal, A.P. Bhaduri, S.N. Singh, N. Fatima, R.K. Chatterjee, Potent 1, 3-disubstituted-9H-pyrido [3, 4-b] indoles as new lead compounds in antifilarial chemotherapy, Bioorg. Med. Chem. 7 (1999) 1223–1236.

[15] N. Chadha, O. Silakari, Indoles as therapeutics of interest in medicinal chemistry: Bird's eye view, Eur. J. Med. Chem. 134 (2017) 159–184.

[16] M.Z. Zhang, Q. Chen, G.F. Yang, A review on recent developments of indole-containing antiviral agents, Eur. J. Med. Chem. 89 (2015) 421–441.

[17] M. Khan, M. Yousaf, A. Wadood, M. Junaid, M. Ashraf, U. Alam, M. Ali, M. Arshad, Z. Hussain, K.M. Khan, Discovery of novel oxindole derivatives as potent α-glucosidase inhibitors, Bioorg. Med. Chem. 22 (2014) 3441–3448.

[18] G. Wang, J. Wang, Z. Xie, M. Chen, L. Li, Y. Peng, S. Chen, W. Li, B. Deng, Discovery of 3, 3-di (indolyl) indolin-2-one as a novel scaffold for α-glucosidase inhibitors: in silico studies and SAR predictions, Bioorg. Chem. 72 (2017) 228–233.

[19] A.R. Karimi, Z. Dalirnasab, G.H. Yousefi, A.R. Akbarizadeh, Synthesis of mono and bis-[3, 3-di (indolyl) indolin-2-ones] and evaluation of their antimicrobial activity, Res. Chem. Intermed. 41 (2015) 10007–10016.

[20] B.V.S. Reddy, N. Rajeswari, M. Sarangapani, Y. Prashanthi, R.J. Ganji, A. Addlagatta, Iodine-catalyzed condensation of isatin with indoles: a facile synthesis of di (indolyl) indolin-2-ones and evaluation of their cytotoxicity, Bioorg. Med. Chem. Lett. 22 (2012) 2460–2463.

[21] P. Paira, A. Hazra, S. Kumar, R. Paira, K.B. Sahu, S. Naskar, P. Saha, S. Mondal, A. Maity, S. Banerjee, N.B. Mondal, Efficient synthesis of 3, 3-diheteroaromatic oxindole analogues and their in vitro evaluation for spermicidal potential, Bioorg. Med. Chem. Lett. 19 (2009) 4786–4789.

[22] B. Suresh, G. Brahmeshwary, T. Swamy, I. Gopi, V. Ravinder, Efficient synthesis of bis-indolyloxindoles from (phenylimino) indolin-2-ones and 1 H-indole catalyzed by p-toluenesulfonic acid, Russ. J. Gen. Chem. 86 (2016) 1144–1150.

[23] J. Bergman, N. Eklund, Synthesis and studies of tris-indolobenzenes and related compounds, Tetrahedron 36 (1980) 1445–1450.

[24] S. Mathavan, K. Kannan, R. Yamajala, Thiamine hydrochloride as a recyclable organocatalyst for the synthesis of bis(indolyl)methanes, tris(indolyl)methanes, 3,3-di(indol-3-yl)indolin-2-ones and biscoumarins, Org. Biomol. Chem. 17 (2019) 9620–9626.

[25] K. Rad-Moghadam, M. Sharifi-Kiasaraie, H. Taheri-Amlashi, Synthesis of symmetrical and unsymmetrical 3, 3-di (indolyl) indolin-2-ones under controlled catalysis of ionic liquids, Tetrahedron 66 (2010) 2316–2321.

[26] G. Brahmachari, B. Banerjee, Facile and one-pot access of 3, 3-bis (indol-3-yl) indolin-2-ones and 2, 2-bis (indol-3-yl) acenaphthylen-1 (2 H)-one derivatives via an eco-friendly pseudo-multicomponent reaction at room temperature using sulfamic acid as an organo-catalyst, ACS Sustain. Chem. Eng. 2 (2014) 2802–2812.

[27] J. Kothandapani, S.M.K. Reddy, S. Thamotharan, S.M. Kumar, K. Byrappa, S.S. Ganesan, TBHP Mediated Substrate controlled Oxidative dearomatization of indoles to C2/C3-quaternary indolinones, Eur. J. Org Chem. 2018 (2018) 2762–2767.

[28] W.Y. Kang, Y.L. Song, L. Zhang, α-Glucosidase inhibitory and antioxidant properties and antidiabetic activity of Hypericum ascyron L, Med. Chem. Res. 20 (2011) 809–816.

[29] M.A.T. Phan, J. Wang, J. Tang, Y.Z. Lee, K. Ng, Evaluation of α-glucosidase inhibition potential of some flavonoids from Epimedium brevicornum, LWT - Food Sci. Technol. (Lebensmittel-Wissenschaft -Technol.) 53 (2013) 492–498.

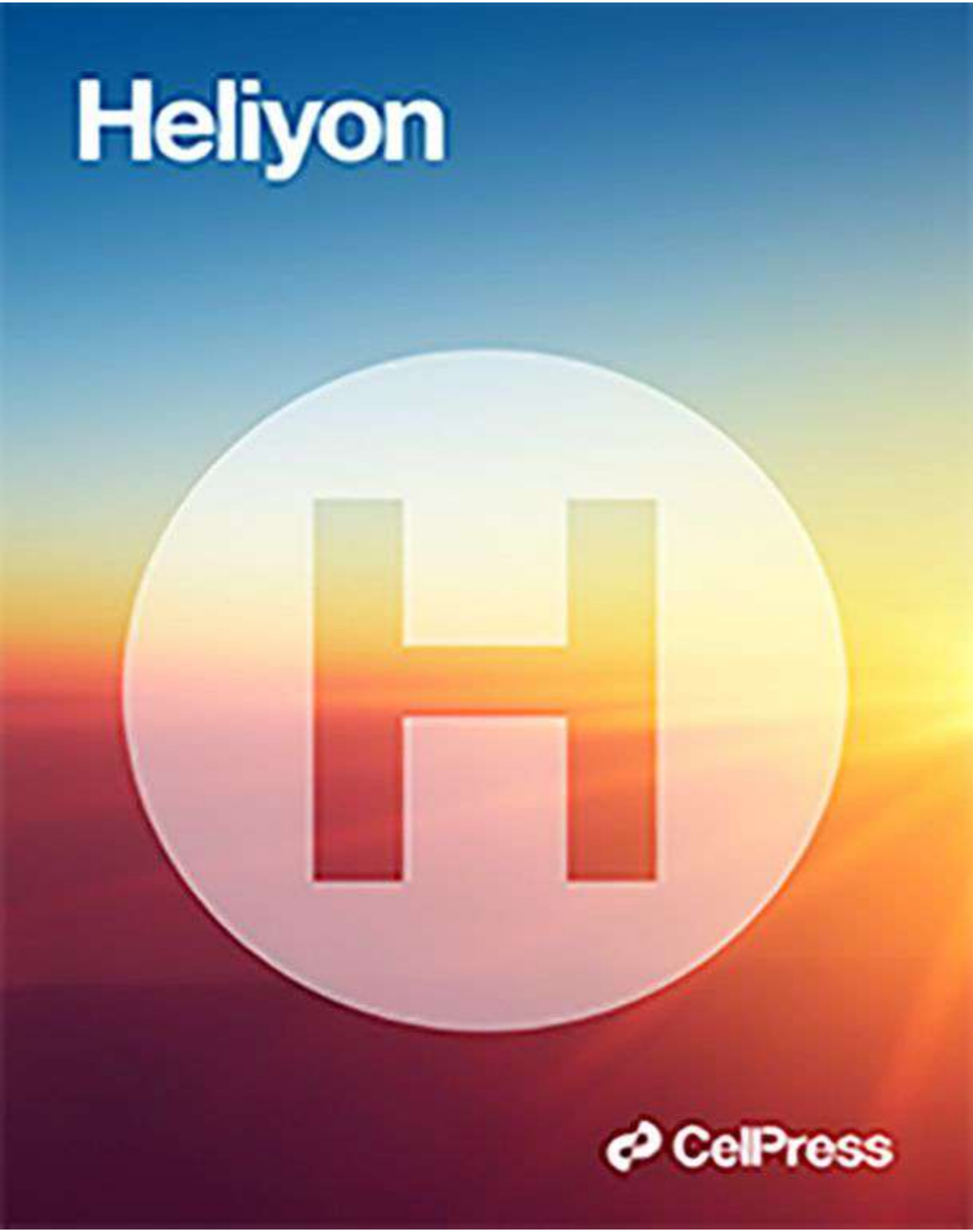
[30] S. Mor, S. Sindhu, Synthesis, Type II diabetes inhibitory activity, antimicrobial evaluation and docking studies of indeno [1, 2-c] pyrazol-4 (1 H)-ones, Med. Chem. Res. 2020 (29) (2020) 46–62.

[31] C.R. Tysoe, S. Caner, M.B. Calvert, A. Win-Mason, G.D. Brayer, S.G. Withers, Synthesis of montbretin A analogues yields potent competitive inhibitors of human pancreatic α-amylase, Chem. Sci. 10 (2019) 11073–11077.

[32] I. Miladiyah, J. Jumina, S.M. Haryana, M. Mustofa, Biological activity, quantitative structure–activity relationship analysis, and molecular docking of xanthone derivatives as anticancer drugs, Drug Des. Develop. Ther. 12 (2018) 149–158.

[33] M.S. Hussain, F. Azam, H.A. Eldarrat, I. Alkskas, J.A. Mayoof, J.M. Dammona, H. Ismail, M. Ali, M. Arif, A. Haque, Anti-inflammatory, analgesic and molecular docking studies of Lanostanoic acid 3-O-α-D-glycopyranoside isolated from *Helichrysum stoechas*, Arab. J. Chem. 13 (2020) 9196–9206.

[34] R.K. Mohapatra, L. Perekhoda, M. Azam, M. Suleiman, A.K. Sarangi, A. Semenets, L. Pintilie, S.I. Al-Resayes, Computational investigations of three main drugs and their comparison with synthesized compounds as potent inhibitors of SARS-CoV-2 main protease (Mpro): DFT, QSAR, molecular docking, and in silico toxicity analysis, J. King Saud Univ. Sci. 33 (2021) 101315.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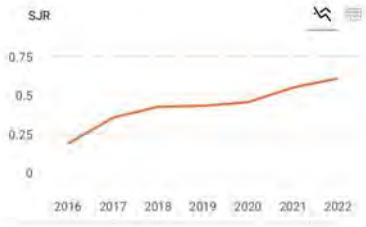

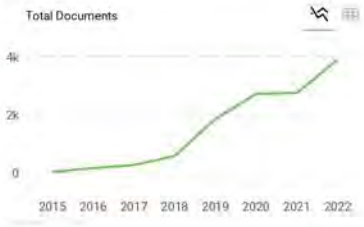

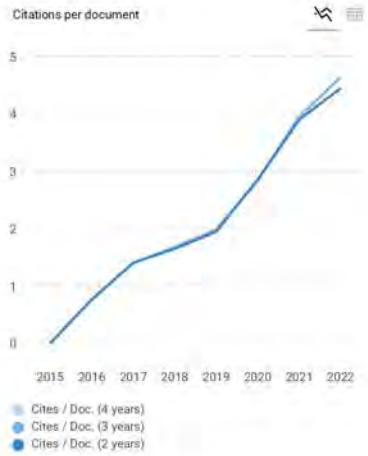

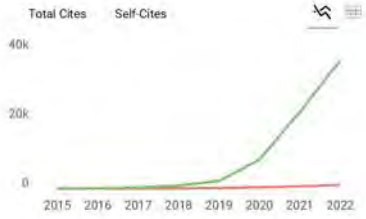

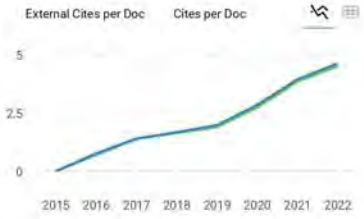

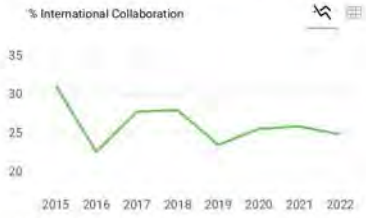

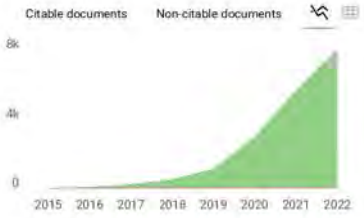

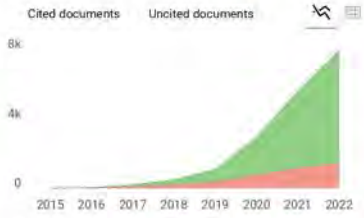

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Mubbasher munir 6 months ago

Hi

What is the status of journal in 2022?

Is it recognized yet?

reply

SCImago Team

Melanie Ortiz 6 months ago

Dear Mubbasher,
Thank you very much for your comment.
All the metadata have been provided by Scopus /Elsevier in their last update sent to SCImago, including the Coverage's period data. The SJR for 2021 was released on 11 May 2022. We suggest you consult the Scopus database directly to see the current index status as SJR is a static image of Scopus, which is changing every day.
The Scopus' update list can also be consulted here:
https://www.elsevier.com/solutions/scopus/how-scopus-works/content
Best Regards, SCImago Team

S **Safa** 1 year ago

Dear Sir,

Could you provide me if this journal is included in the Scopus and Clarivate lists?

Regards
Safa

Source details

Heliyon

Open Access

Scopus coverage years: from 2015 to Present

Publisher: Elsevier

E-ISSN: 2405-8440

Subject area: Multidisciplinary

Source type: Journal

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4.0

SJR 2021
0.550

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1.270

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CiteScore | CiteScore rank & trend | Scopus content coverage

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CiteScoreTracker 2022

$$5.5 = \frac{61{,}884 \text{ Citations to date}}{11{,}184 \text{ Documents to date}}$$

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