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 11 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 undesirable 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 secretes α-glucosidases 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], anti helminthic [14] activities. Several indole-based drugs such as Sunitinib, indolidan, dela verdine, 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(indoly)indolin-2-ones type (Scheme 1) show antidiabetic [18], antimicrobial [19], anticancer [20], and spemidial [21] activities. Recently, Wang and co-workers [18] reported promising \( \alpha \)-glucosidase inhibition activities of several 3,3-di(indoly)indolin-2-ones. However, the authors did not examine the \( \alpha \)-amylase inhibition activities pro of several 3,3-di(indoly)indolin-2-ones. Therefore, at this stage, the overall inhibitory activity profile of 3,3-di(indoly)indolin-2-ones remains unclear.

Herein, we report the synthesis of diverse 3,3-di(indoly)indolin-2-ones and examine their \( \alpha \)-glucosidase and \( \alpha \)-amylase inhibition 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 examined under UV light. 1H and 13C 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). 1H NMR spectra were recorded at 270 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(indoly)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\(_2\)SO\(_4\) (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 1 g 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(indoly)indolin-2-one derivatives (1a-1c, 1f, 1-1p).

3,3-Di(1H-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). \( \alpha \) NMR (90 MHz, DMSO-d\(_6\)): \( \delta \) 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(1H-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). \( \alpha \) NMR (90 MHz, CD\(_3\)SO\(_2\)CO): \( \delta \) 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).

Reagents and conditions: (i) BF\(_3\) or H\(_2\)SO\(_4\), MeOH, 2 h, 40–60 °C; (ii) Mel, or EtI or Me\(_2\)SO\(_4\), KOH, DMSO, 2 h, 0 °C to r.t.

Scheme 1. Synthesis of 3,3-di(indoly)indolin-2-ones 1a-1p.
3,3-Di(1H-indole-3-yl)-1-benzyl-5-nitroindolin-2-one (1l): 1-Benzyl-5-nitroisatin (0.070 g, 0.25 mmol) and 1-methylindole (0.060 g, 0.51 mmol) reacted to give 1l as a yellow solid (0.10 g, 9% yield), m.p. 219–219°C (lit [23]. 232–234°C).1H NMR (CDCl3): 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-1H-indole-3-yl)-1-ethylindolin-2-one (1e): A mixture of 1e (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 (CDCl3): 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, 2H), 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(1-methyl-1H-indole-3-yl)-5-bromo-1-methylindolin-2-one (1q): A mixture of 3,3-di(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 1q as light orange solid (0.029 g, 94% yield), m.p. 287–288°C.1H NMR (KBr disc): 2918, 1713, 1507, 1474, 1422, 1326, 1337, 1273, 1219, 1144, 1049, 1049, 789 cm–1.1H NMR (500 MHz, CDCl3): δ 3.25 (s, 3H), 3.73 (s, 6H), 7.02 (s, 2H), 7.21 (d, J = 8.8 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).13C NMR (125 MHz, CDCl3): δ 26.5, 32.7, 51.7, 111.2, 111.6, 111.7, 114.2, 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 C29H21BrN2O3, [M + H]+ 639.9235; Found 639.9280.

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 crude 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 resulting mixture was diluted with ice-cold water (~50 mL per 0.5 mL of stirring 3-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(1H-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 (CDCl3): 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).
absorbance was measured at 405 nm. The percentage of inhibition was calculated as Eq. (1):

\[
\left( \frac{Abs_{\text{positive control}} - Abs_{\text{compound}}}{Abs_{\text{positive control}}} \right) \times 100\% 
\]  

(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 a 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 incubated in a boiling water bath for 15 min and the absorbance was then measured at 405 nm. The percentage of 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 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 BF3 or H2SO4 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, 1H NMR and 13C NMR and the spectral data were consistent with the structures and are typical for oxindole systems.18 For an illustrative example, the 1H NMR spectrum of 1n recorded in DMSO-d6 showed 21 protons. Singlet signals at δ4.97 and 11.02 ppm were assigned to methylene group protons and –NH protons respectively. The 13C NMR spectrum showed signals at δc 42.5 and 52.4 ppm correspond to a methylene carbon and a spiro carbon respectively, and a signal at δc 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 | R1 | R2 | R3 | R4 | % α-glucosidase inhibition | % α-amylase inhibition |
|----|---------------|----|----|----|----|---------------------------|------------------------|
| 1  | 1a            | H  | H  | H  | H  | 16 ± 6                    | 92 ± 4                 |
| 2  | 1b            | H  | H  | CH3| H  | 37 ± 11                   | 81 ± 6                 |
| 3  | 1c            | H  | H  | CH3|CH2| 73 ± 6                    | 72 ± 5                 |
| 4  | 1d            | H  | H  | CH3| CH2| 86 ± 7                    | 77 ± 8                 |
| 5  | 1e            | H  | H  | CH3|CH2| 50 ± 11                   | 74 ± 9                 |
| 6  | 1f            | H  | Br | H  | H  | 76 ± 8                    | 86 ± 10                |
| 7  | 1g            | Br | Br | CH3|CH2| 61 ± 1                    | 79 ± 4                 |
| 8  | 1h            | H  | NH2| H  | H  | 17 ± 3                    | 79 ± 9                 |
| 9  | 1i            | OH | NO2| H  | H  | 67 ± 13                   | 51 ± 4                 |
| 10 | 1j            | H  | NO2| H  | H  | 79 ± 5                    | 93 ± 6                 |
| 11 | 1k            | H  | NO2| CH3| H  | 86 ± 6                    | 91 ± 5                 |
| 12 | 1l            | H  | NO2| H  | Benzy| 76 ± 8                   | 86 ± 0                 |
| 13 | 1m            | H  | Br | H  | Benzy| 92 ± 3                   | 80 ± 3                 |
| 14 | 1n            | H  | Br | H  | 4-Br-benzy| 94 ± 3                   | 73 ± 5                 |
| 15 | 1o            | H  | Cl | H  | H  | 83 ± 2                    | 87 ± 6                 |
| 16 | 1p            | H  | Cl | CH3| 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.
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 IC50 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 NH2 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 NH2 group with NO2 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 NO2 groups of

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).
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 NO2 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, 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 NO2 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 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 NO2 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 ± 6 < 67 ± 13 < 94 ± 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-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 NO₂ 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 NO₂ 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-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-T-shaped and π-anion interactions with Tyr62 and GluA233, 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-σ 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 Ajiyija, 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**

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