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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, α-amylase inhibition and molecular docking study of bisindolylmethane sulfonamide derivatives

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Abstract

We have synthesized nineteen (**1**–**19**) bisindolylmethane sulfonamide analogs, characterized by different spectroscopic techniques such as ^{1}HNMR and EI-MS and tested for α-amylase inhibitory potential. All compounds showed excellent to moderate degree of α-amylase inhibitory potential with IC_{50} values ranging between 1.192 ± 0.51 to 3.057 ± 0.18 µM as equated with standard acarbose (IC_{50} values 0.83 ± 0.36 µM). Among the series, six analogs such as **1**, **4**, **5**, **6**, **10**, and **14** showed potent α-amylase inhibition with IC_{50} values 1.747 ± 0.2, 1.208 ± 0.15, 1.192 ± 0.51, 1.858 ± 0.08, 1.358 ± 0.27 and 1.527 ± 0.17 µM, respectively, as equated with standard acarbose. The structure-activity relationship based upon different substituents on phenyl part. Molecular docking studies performed to recognize the binding interaction of the most active compounds.

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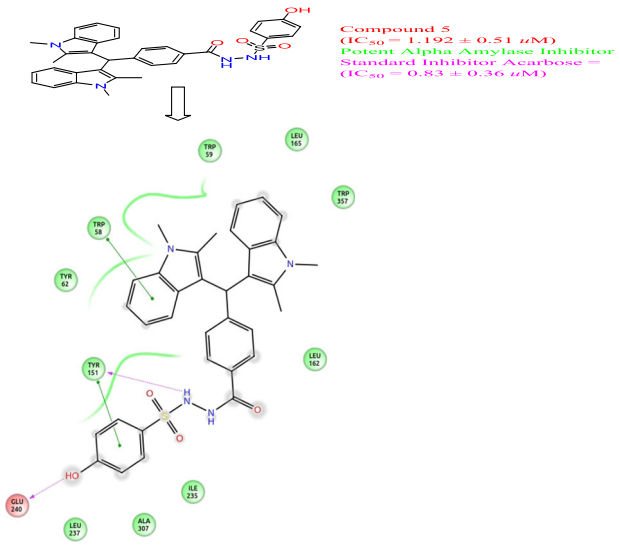
Graphical Abstract



Keywords Synthesis · Bisindolylmethane sulfonamide · α-Amylase Inhibitory Potential · Molecular docking · SAR

Introduction

The most of energy in the body is achieved by intake of starch. The most useful enzymes which break down starch to use are alpha-amylases in salivary, pancreatic as well as alpha-glucosidases presents in small intestinal (Liu et al. 2011).

α-Amylase catalyze the breaking down of starch to shorter useful sugar by cleavage of internal α-D-(1-4) glycosidic bonds that yielded α-anomeric products. The main products of α-amylase action are the dextrins as well as oligosaccharides (Sales et al. 2012; Sivaramakrishnan et al. 2006).

The excessive intake of starchy food is main culprit for developing diabetic II (Kwon et al. 2006; Tadera et al. 2006). In diabetic II the sugar level in the blood arises uncontrollably which causes hyperglycemic situations in body. The main treatment for hyperglycemia to induce insulin production from the β-cells of pancreatic islets. Other way stops the generation of sugar degradation by two main enzymes α-amylase and α-glucosidase (Jarald et al. 2008). So, α-amylase inhibitors are considered as most important tool to control the diabetic II (Adisakwattana et al. 2011).

The indole compounds considered as most important class for medicinal and bioorganic chemistry research (Sundberg 1996; Pelletier 1999). Indole two cyclic frameworks allows to have rigid skeleton which is useful for the interactions with enzymes or receptors (Shaheen et al. 1999). The indole compounds are reported in natural products as well as biologically (Ali et al. 2013; Nencki 1874; Asghari et al. 2014; Stöckly 1881). Additionally, indole is reported as antioxidant and showed very interesting results various types of cancer (Nematollahi and Hedayatfar 2011).

Indole derivatives showed very interesting results α-amylase inhibitory as well as alpha-glucosidases in recent past (Taha et al. 2019; Gollapalli et al. 2018; Javid et al. 2018)

Our group is uninterruptedly working on synthesis of biological compounds (Aziz et al. 2014; Musharraf et al. 2012; Anouar et al. 2013; Khan et al. 2011; Khan et al. 2010; Khan et al. 2009; Khan et al. 2008) and hydrazones (Khan et al. 2014; Taha et al. 2013; Taha et al. 2014). Due to wide range application of indole, here in this study we are going to report α-amylase inhibitory potential and molecular docking analysis of bisindolylmethane sulfonamide derivatives.

Experimental

General method

Avance Bruker 600 MHz was used for NMR experiments. Elemental analysis results got by Carlo Erba Strumentazion-Mod-1106, Italy. Finnigan MAT-311A (Germany) recorded EI-MS.

Synthetic Procedure for the synthesis of bisindolylmethane ester (I)

1,2-dimethyl indole 20 mmol was refluxed with 10 mmol of methyl 4-formylbenzoate in the presence of acetic acid as solvent for 6 h. The reaction checked by TLC and the reaction mixture was poured in cold water, the ppt formed was filtered and washed with cold water.

Synthetic procedure for the synthesis of 4-(bis(1,2-dimethyl-1H-indol-3-yl) methyl) benzohydrazide (II)

Bisindolylmethane ester refluxed with mixture of hydrazine-hydrate/methanol for 4 h. The reaction completion confirmed by TLC and after completion of reaction the reaction mixture was dried by rotary evaporator, the ppt formed was filtered and washed with cold water.

Yield: 88%. M.p.194 °C; Brown crystal; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.33 (s, 1H, HN), 7.94–7.84 (m, 2H), 7.76 (dd, $J = 7.5$, 1.4 Hz, 2H), 7.49 (d, $J = 7.5$ Hz, 2H), 7.42 (s, 2H), 7.34 (td, J = 7.4, 1.5 Hz, 2H), 7.26 (td, $J = 7.4$, 1.5 Hz, 2H), 5.73 (s, 1H), 4.08 (s, 2H, NH_2), 3.76 (s, 6H 2xCH_3), 2.36 (s, 6H 2xCH_3); δ ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.5, 137.3, 137.3, 132.6, 132.6, 131.2, 113.1, 129.2, 129.2, 127.7, 127.7, 127.4, 127.4, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2: HR-ESI-MS: m/z calcd for $C_{28}H_{28}N_4O$, $[M]^+$ 436.2263 found: 436.2067; Anal. Calcd for,$C_{28}H_{28}N_4O$,C, 77.04; H, 6.46; N, 12.83; Found: C, 77.06; H, 6.47; N, 12.85.

General Procedure for the synthesis of bisindolylmethane sulfonamide derivatives (1–19)

Equimolar amount of 4-(bis(1,2-dimethyl-1H-indol-3-yl) methyl) benzohydrazide reacted with different aryl sulfonyl chloride in the presence of pyridine to give us bisindolylmethane sulfonamide derivatives. After reaction completion, the reaction mixture was poured in cold water and filtered, washed and dried.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-4-chlorobenzenesul-fonohydrazide (1)

Yield: 80%. M.p.195 °C; Light purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 12.4.2 (s, 1H, NH), 11.62 (s, 1H, NH), 7.80 (d, $J = 8.1$ Hz, 2H), 7.72 (d, $J = 7.0$ Hz, 2H), 7.51 (t, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.31 (d, $J = 7.9$ Hz, 2H), 7.13 (t, $J = 7.0$ Hz, 2H), 6.93 (t, $J = 7.0$ Hz, 2H), 6.84 (s, 2H), 5.98 (s, 1H), 3.74 (s, 6H); 3.29 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.5, 137.8, 137.5, 137.3, 137.3, 132.6, 132.6, 131.2, 129.2, 129.2, 129.2, 129.2, 128.7, 128.7, 127.7, 127.7, 127.4, 127.4, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2 HR-ESI-MS: m/z calcd for $C_{34}H_{31}ClN_4O_3S$, $[M]^+$ 610.1805; Found 610.1828; $[M+2]^+$ 612. 1760: Anal. Calcd for $C_{34}H_{31}ClN_4O_3S$,C, 66.82; H, 5.11; N, 9.17; Found C, 66.81; H, 5.09; N, 9.18.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-4-nitrobenzenesulfonohydrazide (2)

Yield: 83%. M.p.195 °C; Brown powder; ^{1}H NMR (600 MHz, DMSO-d_6):δ 12.56 (s, 1H, NH), 12.15 (s, 1H, NH), 7.96 (d, $J = 7.0$ Hz, 2H), 7.80 (d, $J = 7.5$ Hz, 2H), 7.50 (d, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.31 (d, $J = 7.5$ Hz, 2H), 7.10 (t, $J = 7.0$ Hz, 2H), 6.90 (t, $J = 7.5$ Hz, 2H), 6.89 (s, 2H), 5.96 (s, 1H), 3.73 (s, 6H), 2.65 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 151.6, 145.8, 141.5, 137.3, 137.3, 132.6, 132.6, 131.2, 129.2, 129.2, 128.2, 128.2, 127.7, 127.7, 127.4, 127.4, 122.2, 122.2, 121.4, 121.4, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2HR-ESI-MS: m/z calcd for $C_{34}H_{31}N_5O_5S$, $[M]^+$ 621.2046; Found 621.2061; Anal. Calcd for,$C_{34}H_{31}N_5O_5S$,C, 65.68; H, 5.03; N, 11.26; Found C, 65.67; H, 5.02; N, 11.28.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-2-nitrobenzenesulfonohydrazide (3)

Yield: 83%. M.p.138 °C; Light purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 12.30 (s, 1H, NH), 11.73 (s, 1H, NH), 7.79–7.67 (m, 5H), 7.31 (dd, $J = 7.5$, 1.6 Hz, 2H), 7.28–7.17 (m, 4H), 7.08 (dd, $J = 7.5$, 1.5 Hz, 2H), 6.98 (td, $J = 7.4$, 1.6 Hz, 2H), 5.38 (d, $J = 1.2$ Hz, 1H), 3.62 (s, 6H), 2.32 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 145.4, 141.5, 137.3, 137.3, 135.2, 134.4, 132.9, 132.6, 132.6, 131.2, 129.2, 129.2, 128.2, 127.7, 127.7, 127.4, 127.4, 122.2, 122.2, 121.4, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{31}ClN_4O_3S$, $[M]^+$ 621.2046; Found 621.2038; Anal. Calcd for $C_{34}H_{31}N_5O_5S$,C, 65.68; H, 5.03; N, 11.26; Found C, 65.66; H, 5.02; N, 11.25.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-4-fluorobenzenesulfonohydrazide (4)

Yield: 83%. M.p.166 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 12.30 (s, 1H, NH), 11.82 (s, 1H, NH), 7.83–7.76 (m, 4H), 7.52 (d, $J = 7.0$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.31 (d, $J = 7.5$ Hz, 2H), 7.30–7.24 (m, 2H), 7.11 (t, $J = 7.0$ Hz, 2H), 6.92 (t, $J = 7.0$ Hz, 2H), 5.92 (s, 1H), 3.75 (s, 6H), 2.91 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 166.1 (d, $J_{(C\text{-}F)} = 160$ Hz), 164.9, 141.5, 137.3, 137.3, 135.3, 132.6, 132.6, 131.2, 129.2, 128.9, 128.9, 128.9, 127.7, 127.7, 127.4, 127.4, 122.2, 122.2,

120.1, 120.1, 119.0, 119.0, 115.8, 115.8, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{31}FN_4O_3S$, $[M]^+$ 594.2101; Found 594.2117; Anal. Calcd for$C_{34}H_{31}FN_4O_3S$,C, 68.67; H, 5.25; N, 9.42; Found C, 68.69; H, 5.26; N, 9.41.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-4-hydroxybenzenesulfonohydrazide (5)

Yield: 83%. M.p.151 °C; Light purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.58 (s, 2H, 2xNH), 9.92 (s, 1H, OH), 7.78 (d, $J = 8.0$ Hz, 2H), 7.52 (d, $J = 8.0$ Hz, 2H), 7.45 (d, $J =$ 7.5 Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 7.5$ Hz, 2H), 7.10 (t, $J = 7.0$ Hz, 2H), 6.90 (t, $J = 7.0$ Hz, 2H), 6.80 (d, $J = 80$ Hz, 2H), 5.92 (s, 1H), 3.72 (s, 6H) 2.60 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 163.9, 141.5, 137.3, 137.3, 132.6, 132.6, 132.0, 131.2, 129.2, 129.2, 128.3, 128.3, 127.7, 127.7, 127.4, 127.4, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 114.6, 114.6, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{32}N_4O_4S$, $[M]^+$ 592.2144; Found 592.2247; Anal. Calcd for$C_{34}H_{32}N_4O_4S$,C, 68.90; H, 5.44; N, 9.45; Found C, 68.92; H, 5.47; N, 9.46.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-4-bromobenzenesulfonohydrazide (6)

Yield: 83%. M.p.131 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.82 (s, 1H, NH), 9.71(s, 1H, NH), 7.72 (t, $J = 7.0$ Hz, 2H), 7.56 (d, $J = 7.0$ Hz, 2H), 7.41 (d, $J =$ 8.0 Hz, 2H), 7.30 (d, $J = 7.0$ Hz, 2H), 7.30–7.21 (m, 4H), 7.10 (t, $J = 7.0$ Hz, 2H), 6.96 (t, J = 7.5 Hz, 2H), 5.95 (s, 1H), 3.74 (s, 6H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.5, 138.7, 137.3, 137.3, 132.6, 132.6, 132.0, 132.0, 131.2, 129.5, 129.5, 129.2, 129.2, 127.7, 127.7, 127.4, 127.4, 126.3, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{31}BrN_4O_3S$, $[M]^+$ 654.1300; Found 654.1314; $[M + 2]^+$ 656.1288; Anal. Calcd for,$C_{34}H_{31}BrN_4O_3S$,C, 62.29; H, 4.77; N, 8.55; Found C, 62.30; H, 4.75; N, 8.54.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-2-methylbenzenesulfonohydrazide (7)

Yield: 86%. M.p.141 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 12.23 (s, 1H, NH), 11.63 (s, 1H, NH), 7.86 (s, 1H), 7.72–7.66 (m, 2H), 7.62–7.58 (m, 2H), 7.47–7.30 (m, 4H), 7.21 (dd, $J = 7.4$, 1.6 Hz, 3H), 7.04–6.95 (m, 4H), 5.94 (s, 1H) 3.75 (s, 6H), 2.45 (s, 6H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.5, 139.0, 137.3, 137.3, 136.6, 132.6, 132.6, 131.9, 131.2, 129.4, 129.2, 129.2, 127.7, 127.7, 127.4, 127.4, 127.2, 126.1, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 16.4, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{35}H_{34}N_4O_3S$, $[M]^+$ 590.2352; Found 590.2350; Anal. Calcd for$C_{35}H_{34}N_4O_3S$,C, 71.16; H, 5.80; N, 9.48; Found C, 71.14; H, 5.81; N, 9.49.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-3-nitrobenzenesulfonohydrazide (8)

Yield: 90%. M.p.178 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 12.77 (s, 1H), 12.07 (s, 1H), 8.21 (d, $J =$ 7.5 Hz, 1H), 7.86–7.80 (m, 2H), 7.62 (t, $J = 7.0$ Hz, 1H), 7.52 (dd, $J = 7.5$ Hz, 2H), 7.43–7.36 (m, 4H), 7.22 (dd, $J =$ 7.5 Hz, 2H), 7.13–705 (m, 4H), 5.95 (s, 1H), 3.79 (s, 6H), 2.78 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 148.7, 141.5, 140.6, 137.3, 137.3, 133.4, 132.6, 132.6, 131.2, 130.0, 129.2, 129.2, 127.7, 127.7, 127.4, 127.4, 124.3, 122.2, 122.2, 120.6, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{31}N_5O_5S$, $[M]^+$ 621.2046; Found 621.2037; Anal. Calcd for,$C_{34}H_{31}N_5O_5S$,C, 65.68; H, 5.03; N, 11.26; Found C, 65.69; H, 5.04; N, 11.27.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-4-methylbenzenesulfonohydrazide (9)

Yield: 94%. M.p. 150 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.70 (s, 1H), 11.06 (s, 1H), 7.85–7.79 (m, 2H), 7.67–7.61 (m, 2H), 7.40–7.23 (m, 8H), 7.14 (dd, $J =$ 7.4, 1.6 Hz, 2H), 7.04 (td, $J = 7.4$, 1.5 Hz, 2H), 5.93 (s, 1H), 3.68 (s, 6H), 2.68 (s, 6H), 2.17 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.6, 141.5, 137.3, 137.3, 136.7, 132.6, 132.6, 131.2, 129.4, 129.4, 129.2, 129.2, 127.7, 127.7, 127.4, 127.4, 127.2, 127.2, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 24.3, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{31}ClN_4O_3S$, $[M]^+$ 590.2352; Found 590.2349; Anal. Calcd for,$C_{35}H_{34}N_4O_3S$,C, 71.16; H, 5.80; N, 9.48; Found C, 71.15; H, 5.81; N, 9.47.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-3,4-dichlorobenzenesulfonohydrazide (10)

Yield: 93%. M.p.150 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.50 (s, 1H, NH), 9.55 (s, 1H, NH), 7.62 (d, $J = 7.0$ Hz, 2H), 7.40 (dd, $J = 7.5$ Hz, 2H), 7.38–7.27 (m, 4H), 7.18 (dd, $J = 7.5$, 1.5 Hz, 2H), 6.98–6.89 (m, 4H), 6.78 (d, $J = 7.5$ Hz, 1H), 5.918 (s, 1H), 3.72 (s, 6H), 2.21 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.5, 139.2, 137.3, 137.3, 136.6, 133.7, 132.6, 132.6, 131.2, 130.6, 129.2, 129.2, 128.0, 127.7, 127.7, 127.4, 127.4, 126.8, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS:

m/z calcd for $C_{34}H_{31}ClN_4O_3S$, $[M]^+$ 644.1416; Found 644.1421; $[M+1]^+$ 645.1452; $[M+2]^+$ 646.1382; Anal. Calcd for $C_{34}H_{30}Cl_2N_4O_3S$, C, 63.25; H, 4.68; N, 8.68; Found C, 63.23; H, 4.67; N, 8.65.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-2,4-dichlorobenzenesulfonohydrazide (11)

Yield: 83%. M.p.124 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.75 (s, 1H, NH), 11.50 (s, 1H, NH), 7.46 (dd, $J = 7.0$, 2.0 Hz, 1H), 7.41 (dd, $J = 7.0$, 2.0 Hz, 2H), 7.32 (d, $J = 7.0$ Hz, 1H), 6.95–6.84 (m, 4H), + 6.38 (dd, $J = 7.5$, 1.5 Hz, 1H), 6.28 (td, $J = 7.4$, 1.5 Hz, 2H), 5.98 (s, 1H), 3.82 (s, 6H), 2.51 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.5, 138.9, 137.8, 137.3, 137.3, 132.9, 132.6, 132.6, 131.2, 130.7, 130.1, 129.2, 129.2, 127.7, 127.7, 127.4, 127.4, 127.3, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{30}Cl_2N_4O_3S$, $[M]^+$ 644.1416; Found 644.1411; $[M+1]^+$ 645.1445; $[M+2]^+$ 646.1378; Anal. Calcd for$C_{34}H_{30}Cl_2N_4O_3S$, C, 63.25; H, 4.68; N, 8.68; Found C, 63.25; H, 4.68; N, 8.67.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-2,5-dichlorobenzenesulfonohydrazide (12)

Yield: 93%. M.p.136 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 12.04 (s, 1H, NH), 10.70 (s, 1H, NH), 7.60 (d, $J = 7.0$ Hz, 2H), 7.40 (dd, $J = 7.5$, 2.0 Hz, 2H), 7.38 (d, $J = 7.5$ Hz, 2H), 7.17–7.06 (m, 3H), 6.90–6.78 (m, 6H), 5.97 (s, 1H), 3.81 (s, 6H), 2.70 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.5, 141.1, 137.3, 137.3, 133.5, 132.7, 133.5, 132.7, 132.6, 132.6, 131.2, 130.6, 129.6, 129.2, 129.2, 128.0, 127.7, 127.7, 127.4, 127.4, 122.2, 122.2, 120.1, 120.1, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{30}Cl_2N_4O_3S$, $[M]^+$ 644.1416; Found 644.1403; $[M+1]^+$ 645.1455; $[M+2]^+$ 646.1374; Anal. Calcd for-$C_{34}H_{30}Cl_2N_4O_3S$, C, 63.25; H, 4.68; N, 8.68; Found C, 63.24; H, 4.69; N, 8.66.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-2,3-dichlorobenzenesulfonohydrazide (13)

Yield: 99%. M.p.133 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 12.10 (s, 1H, NH), 11.20 (s, 1H, NH), 7.95 (dd, $J = 7.5$, 2.0 Hz, 2H), 7.50 (dd, $J = 7.0$, 2.0 Hz, 2H), 7.36–7.29 (m, 4H), 7.20 (dd, $J = 7.5$, 1.5 Hz, 2H), 6.93–6.84 (m, 4H), 6.80 (dd, $J = 7.0$, 1.5 Hz, 2H), 5.95 (s, 1H), 3.84 (s, 6H), 2.73 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.5, 141.1, 137.3, 137.3, 133.7, 133.5, 132.6, 132.6, 131.2, 131.2, 129.2, 129.2, 128.6, 127.7, 127.7, 127.4, 127.4, 126.8, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{30}Cl_2N_4O_3S$, $[M]^+$ 644.1416; Found 644.1407; $[M+1]^+$ 645.1447; $[M+2]^+$ 646.1380; Anal. Calcd for$C_{34}H_{30}Cl_2N_4O_3S$, C, 63.25; H, 4.68; N, 8.68; Found C, 63.24; H, 4.66; N, 8.67.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-3,5-dichlorobenzenesulfonohydrazide (14)

Yield: 91%. M.p. 122 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.62 (s, 1H, NH), 9.42 (s, 1H, NH), 7.62 (dd, $J = 7.5$, 2.0 Hz, 2H), 7.55 (dd, $J = 7.0$, 2.0 Hz, 2H), 7.49 (d, $J = 7.0$ Hz, 2H), 7.20 (dd, $J = 7.5$, 1.5 Hz, 2H), 6.92–6.84 (m, 4H), 6.62 (d, $J = 7.5$ Hz, 2H), 6.31 (s, 1H), 5.92 (s, 1H), 3.84 (s, 6H), 2.73 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 142.5, 141.5, 137.3, 137.3, 136.0, 136.0, 133.6, 132.6, 132.6, 131.2, 129.2, 129.2, 127.7, 127.7, 127.7, 127.7, 127.4, 127.4, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{30}Cl_2N_4O_3S$, $[M]^+$ 644.1416; Found 644.1419; $[M+1]^+$ 645.1458; $[M+2]^+$ 646.1386; Anal. Calcd for-$C_{34}H_{30}Cl_2N_4O_3S$, C, 63.25; H, 4.68; N, 8.68; Found C, 63.23; H, 4.66; N, 8.67.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-2,4,5-trichlorobenzenesulfonohydrazide (15)

Yield: 91%. M.p.122 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.73 (s, 1H, NH), 10.65 (s, 1H), 7.54 (dd, $J = 7.5$, 2.0 Hz, 2H), 7.31–7.20 (m, 4H), 7.19 (dd, $J = 7.5$, 2.0 Hz, 2H), 6.91 (d, $J = 7.0$ Hz, 2H), 6.84 (t, $J = 7.0$ Hz, 2H), 6.81(s, 1H), 6.32 (s, 1H), 5.92 (s, 1H), 3.75 (s, 6H), 2.74 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.5, 139.2, 138.0, 137.3, 137.3, 132.6, 132.6, 132.1, 131.8, 131.0, 131.2, 129.4, 129.2, 129.2, 127.7, 127.7, 127.4, 127.4, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{29}C_{l3}N_4O_3S$, $[M]^+$ 678.1026; Found 678.1031; $[M+1]^+$ 679.1054; $[M+2]^+$ 680.0990; $[M+3]^+$ 681.1026; $[M+4]^+$ 682.0962; Anal. Calcd for-$C_{34}H_{29}C_{l3}N_4O_3S$, C, 60.05; H, 4.30; N, 8.24; Found C, 60.03; H, 4.32; N, 8.25.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-2-fluorobenzenesulfonohydrazide (16)

Yield: 84%. M.p.129 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.94 (s,1H, NH), 11.25 (s, 1H, NH), 7.91 (dd, $J = 7.4$, 2.0 Hz, 2H), 7.52–7.46 (m, 2H), 7.41–7.31 (m, 4H), 7.31–7.20 (m, 4H), 7.16 (dd, $J = 7.0$, 2.0 Hz, 2H), 6.91 (td, $J = 7.0$, 2.0 Hz, 2H), 5.91 (s, 1H), 3.80 (s, 6H), 2.74 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9 (d, $J_{(C\text{-}F)} =$

190 Hz), 158.3, 141.5, 137.3, 137.3, 133.6, 132.6, 132.6, 131.2, 129.2, 129.2, 128.9, 127.7, 127.7, 127.4, 127.4, 126.3, 124.7, 122.2, 122.2, 120.1, 120.1 119.0, 119.0, 115.8, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{31}FN_4O_3S$, $[M]^+$ 594.2101; Found 594.2117; Anal. Calcd for $C_{34}H_{31}FN_4O_3S$,C, 68.67; H, 5.25; N, 9.42; Found C, 68.68; H, 5.26; N, 9.41.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-2-chlorobenzenesulfonohydrazide (17)

Yield: 84%. M.p.113 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.73 (s, 1H, NH), 11.20 (s, 1H, NH), 7.92–7.86 (m, 3H), 7.52 (dd, $J = 7.5$, 2.0 Hz, 2H), 7.41 (d, $J = 7.5$ Hz, 2H), 7.22–7.16 (m, 3H), 7.18 (dd, $J = 7.5$, 2.0 Hz, 2H), 6.91 (dd, $J = 7.5$, 2.0 Hz, 2H), 6.85 (d, $J = 7.5$, Hz, 2H), 5.91 (s, 1H), 3.75 (s, 6H), 2.34 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6):δ 164.9, 141.5, 139.7, 137.3, 137.3, 133.4, 132.6, 132.6, 131.5, 131.2, 129.2, 129.2, 129.2, 128.7, 127.7, 127.7, 127.4, 127.4, 127.2, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{31}ClN_4O_3S$, $[M]^+$ 610.1805; Found 610.1826; $[M+2]^+$ 612. 1764: Anal. Calcd for$C_{34}H_{31}ClN_4O_3S$,C, 66.82; H, 5.11; N, 9.17; Found C, 66.81; H, 5.10; N, 9.16.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-2,4-dinitrobenzenesulfonohydrazide (18)

Yield: 87%. m.p. 164 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.93 (s, 1H, NH), 11.65 (s, 1H, NH), 7.52 (dd, $J = 7.5$, 2.0 Hz, 2H), 7.43–7.38 (m, 3H), 7.35 (d, $J = 7.5$ Hz, 2H), 7.12 (d, $J = 7.0$ Hz, 2H), 6.93 (dd, $J = 7.5$, 2.0 Hz, 2H), 6.88 (d, $J = 7.5$, Hz, 2H), 6.48–6.40 (m, 2H), 5.92 (s, 1H), 3.75 (s, 6H), 2.34 (s, 6H); ^{13}C NMR (150 MHz, DMSO -d_6):δ 164.9, 152.5, 146.3, 141.5, 140.5, 137.3, 137.3, 132.6, 132.6, 131.2, 129.2, 129.2, 129.1, 127.7, 127.7, 127.5, 127.4, 127.4, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{30}N_6O_7S$, $[M]^+$ 666.1897; Found 666.1913; Anal. Calcd for,$C_{34}H_{30}N_6O_7S$,C, 61.25; H, 4.54; N, 12.61; Found C, 61.26; H, 4.55; N, 12.62.

N′-(4-(bis(1,2-dimethyl-1H-indol-3-yl)methyl)benzoyl)-3-bromobenzenesulfonohydrazide (19)

Yield: 89%. m.p.125 °C; purple; ^{1}H NMR (600 MHz, DMSO-d_6):δ 11.69 (s, 1H, NH), 9.49 (s, 1H, NH), 7.77 (dd, $J = 7.5$, 2.0 Hz, 2H), 7.65 (d, $J = 7.5$ Hz, 2H), 7.32–7.07 (m, 8H), 6.87 (td, $J = 7.4$, 2.0 Hz, 2H), 6.77 (dd, $J = 7.0$ Hz, 2H), 5.92 (s, 1H), 3.76 (s, 6H), 2.70 (s, 6H); ^{13}C NMR (150 MHz, DMSO -d_6):δ 164.9, 141.9, 141.5, 137.3, 137.3, 134.9, 132.6, 132.6, 131.3, 131.2, 129.2, 129.2, 129, 127.7, 127.7, 127.4, 127.4, 126.3, 123.4, 122.2, 122.2, 120.1, 120.1, 119.0, 119.0, 113.1, 113.1, 111.1, 111.1, 42.7, 35.9, 35.9, 6.2, 6.2; HR-ESI-MS: m/z calcd for $C_{34}H_{31}BrN_4O_3S$, $[M]^+$ 654.1300; Found 654.1313; $[M+2]^+$ 656.1280; Anal. Calcd for$C_{34}H_{31}BrN_4O_3S$,C, 62.29; H, 4.77; N, 8.55; Found C, 62.30; H, 4.78; N, 8.53.

α-Amylase inhibitory assay

Zhang and coworkers method (Zhang et al. 2011) was used with small modification for α-Amylase inhibitory activity. We used sample protocol as we used in our previous publications (Adegboye et al. 2018; Bale et al. 2018; Salar et al. 2017).

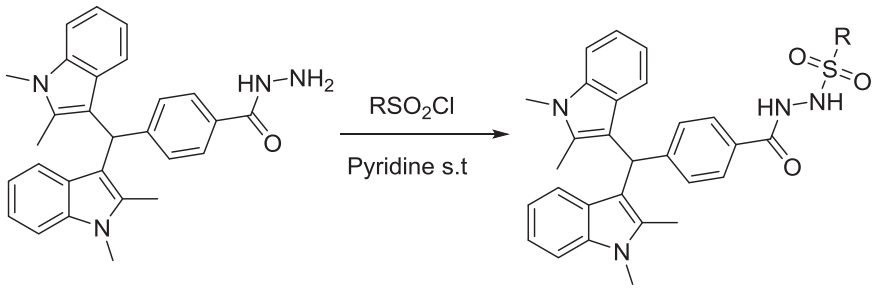
Molecular docking studies with amylase

We used sample protocol as we used in our previous publications (Noreen et al. 2017; Imran et al. 2017; Taha et al. 2017).

Results and discussion

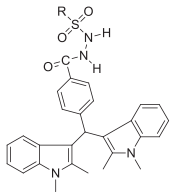
Chemistry

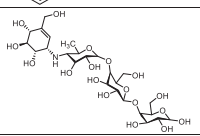
Synthesis of N'-(4-(bis(1,2-dimethyl-1H-indol-3-yl) methyl) benzoyl) arylsulfonohydrazide is carried out by the reaction of equimolar 4-(bis(1,2-dimethyl-1H-indol-3-yl) methyl) benzohydrazide and aryl sulfonyl chloride with pyridine. The reaction mixture was dried and washed with cold water. The crude product recrystallized and categorized by different spectroscopy methods (Scheme 1 and Table 1).



Scheme 1 Synthesis of bisindolylmethane sulfonamide derivatives **1–19**

Table 1 Bis-indolylmethane sulfonamide analogs (**1–19**) synthesis and α-amylase inhibitory potential



S. No	R	IC_{50} ±SEM[a]
1		1.747±0.2
2		3.057±0.18
3		2.101±0.05
4		1.208±0.15
5		1.192±0.51
6		1.858±0.08
7		2.485±0.11
8		3.008±0.02
9		2.174±0.05
10		1.358±0.27
11		2.108±0.08
12		2.037±0.06
13		2.206±0.14
14		1.527±0.17
15		2.161±0.07
16		2.517±0.06
17		2.169±0.04
18		2.372±0.04
19		2.392±0.02
Acarbose (standard drug)		0.83±0.36

In vitro α-amylase inhibitory potential

We have synthesized nineteen (**1**–**19**) bisindolylmethane sulfonamide analogs. They were evaluated for α-amylase inhibitory potential. They showed α-amylase inhibition with IC_{50} values ranging between 1.192 ± 0.51 to 3.057 ± 0.18 μM as compared with standard acarbose IC_{50} values 0.83 ± 0.36 μM. Among the series, six compounds such as **1**, **4**, **5**, **6**, **10**, and **14** showed potent α-amylase inhibition with IC_{50} values 1.747 ± 0.2, 1.208 ± 0.15, 1.192 ± 0.51, 1.858 ± 0.08, 1.358 ± 0.27 and 1.527 ± 0.17 μM, respectively, when compared with the standard acarbose. All other compounds such as **2**, **3**, **7**, **8**, **9**, **11**, **12**, **13**, **15**, **16**, **17**, **18**, and **19** having IC_{50} values 3.057 ± 0.18, 2.101 ± 0.05, 2.485 ± 0.11, 3.008 ± 0.02, 2.174 ± 0.05, 2.108 ± 0.08, 2.037 ± 0.06, 2.206 ± 0.14, 2.161 ± 0.07, 2.517 ± 0.06, 2.169 ± 0.04, 2.372 ± 0.04 and 2.392 ± 0.02 μM, respectively, showed good to moderate α-amylase inhibition.

The most potent compound is compound **5** with IC_{50} value 1.192 ± 0.51 μM having *para*-hydroxy substituent at the phenyl part. The great potential of this compound is seems to be due to the hydroxy group which is electron-donating. The second most active analog among the series is compound **4** with IC_{50} value 1.208 ± 0.15 μM having *para*-fluoro at the phenyl part while the third most active analog among the series is compound **10** with IC_{50} value 1.358 ± 0.27 μM having *meta*, *para*-chloro at the phenyl part. Both of the substituents are electron-withdrawing groups which might play some role in these inhibitions (Fig. 1).

If we compare analog **10** having IC_{50} value 1.358 ± 0.27 μM with analog **11** having IC_{50} value 2.108 ± 0.08 μM, analog **12** having IC_{50} value 2.037 ± 0.06 μM, analog **13** having IC_{50} value 2.206 ± 0.14 μM and analog **14** with IC_{50} value 1.527 ± 0.17 μM, all five analogs have chloro groups, with different pattern of substitution in them which authorized that the difference in position of substituents momentously affect the inhibitory potentials of the compounds (Fig. 2).

Similarly compound **2**, a 4-nitro analog (IC_{50} = 3.057 ± 0.18 μM) if compared with other nitro compounds like **3**, a 2-nitro analog (IC_{50} = 2.101 ± 0.05 μM) and **8**, a 3-nitro analog (IC_{50} = 3.008 ± 0.02 μM). The little bit difference in potential of these analogs showed that position of substituent also play role in this inhibition (Fig. 3).

If we compare compound **7**, a 2-methyl analog having IC_{50} value 2.485 ± 0.11 μM with compound **9**, a 4-methyl analog having IC_{50} value 2.174 ± 0.05 μM. The compound **9** was found to be superior (Fig. 4).

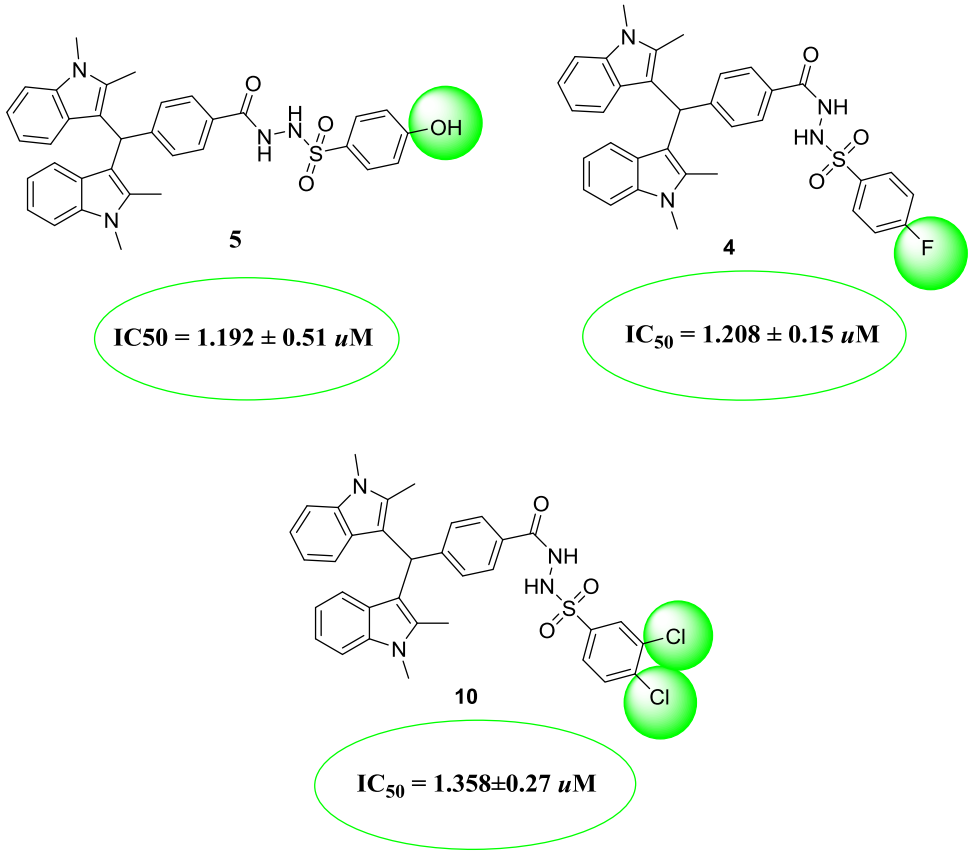


Fig. 1 Comparison between compounds **4**, **5**, and **10**

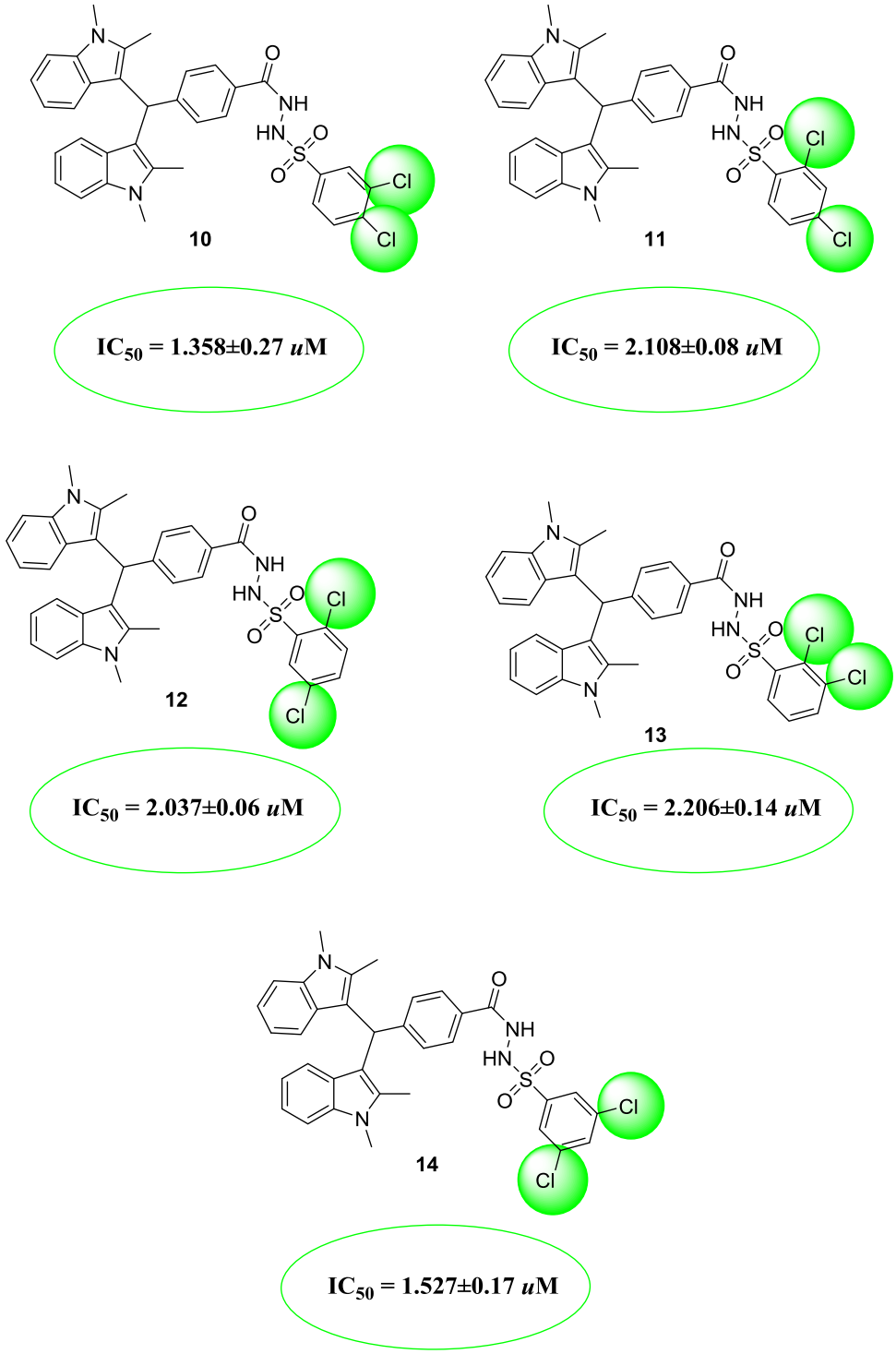


Fig. 2 Comparison of structure-activity relationship between compounds **10**, **11**, **12, 13**, and **14**

Docking study

The docking studies show the binding mode of the bis-indolylmethane sulfonamide derivatives bound to the active site of the amylase enzyme. Here in this paper, we only show the top most four compounds binding mode.

Figure 5a shows the binding mode of the compound **5** is the most active among the bisindolylmethane sulfonamide derivatives. The phenon oxygen and the hydrazide NH forms hydrogen bond with Glu240 and Tyr151, respectively. Further, the phenol ring and one of the bisindole ring forms π–π stacking with Trp151 and Trp58, respectively. In

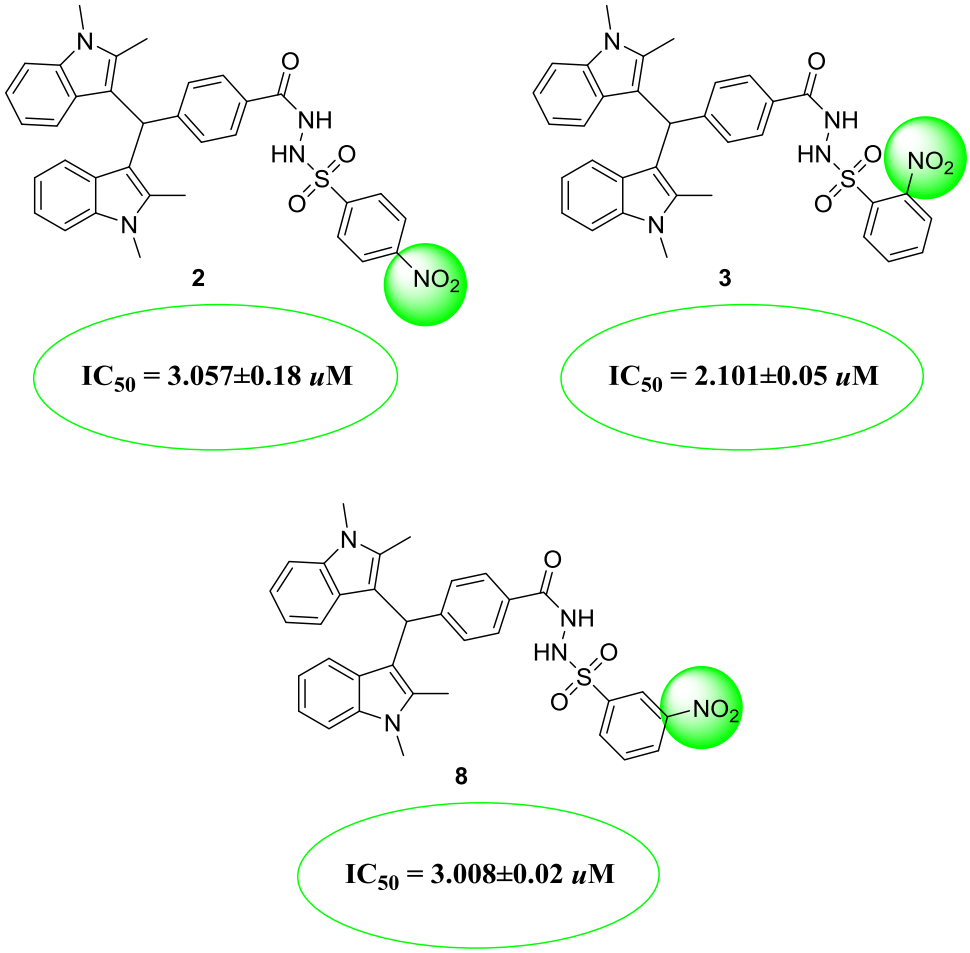


Fig. 3 Comparison of structure-activity relationship between compounds **2**, **3**, and **8**

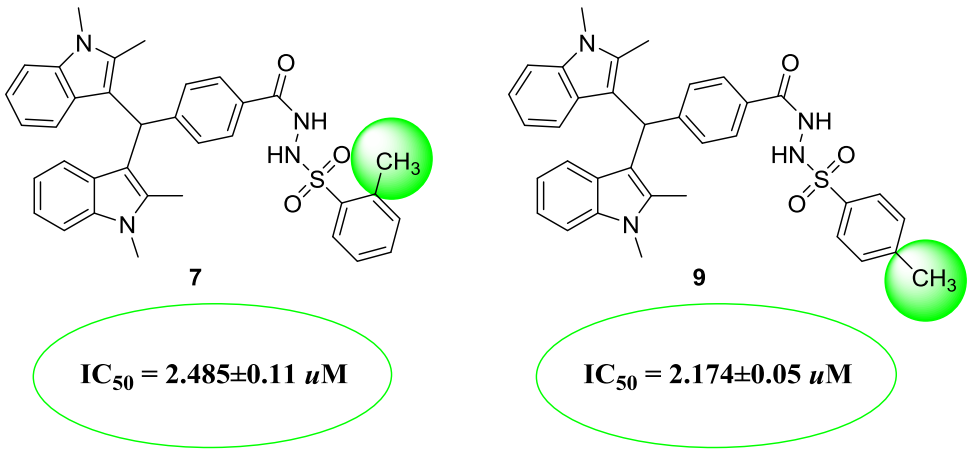


Fig. 4 Comparison of structure-activity relationship between compounds **7** and **9**

addition interactions the bisindole ring forms hydrophobic interaction with Trp59, Tyr62, Leu162, Leu165, Trp357 and the phenol ring forms similar interactions with Ile235, Leu237, and Ala307.

In the case of the compound **4**, the complex was stabilized by theπ- π stacking of the the florophenyl ring with His201, the bisindole rings with Trp58, Tyr62 and with Trp59, respectively. Next the presence of the π-cationic interaction of the His299 with one of the bisindole ring and addtional hydrophobic interaction with Leu165 and Trp357. Moreover, the presence of hydrophobic contacts of the florophenyl ring with residues such as Tyr151, Leu162, Ala198, Val 234 and Ile235, stablilizes the complex furthermore (Fig. 5b).

The compound **10** shows that the hydrazide NH forms hydrogen bond with Try151. While there is stable π- π

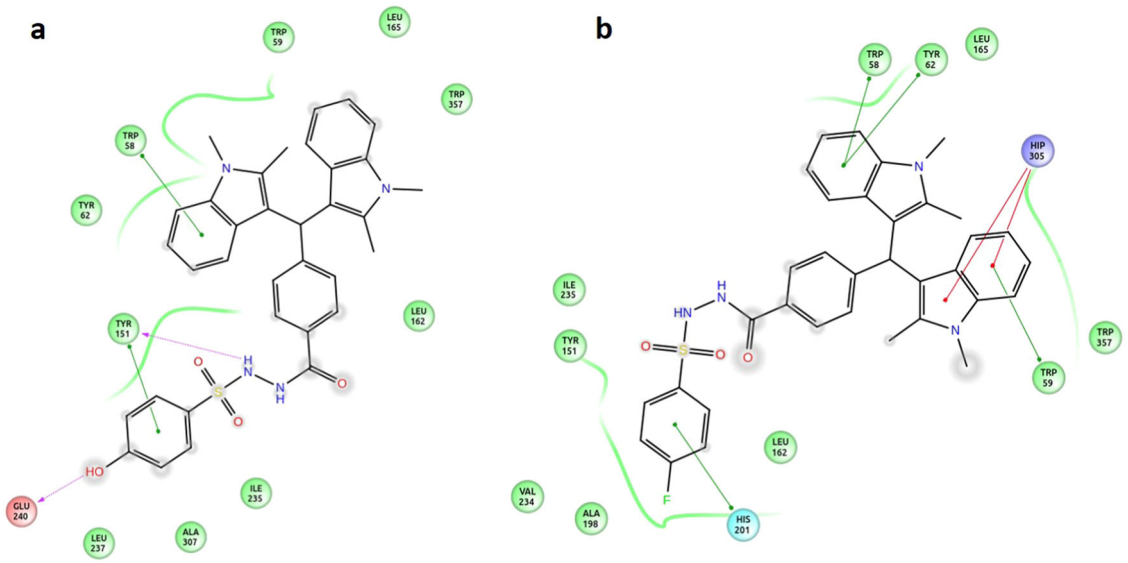


Fig. 5 Illustrates the predicted binding modes of active sulfonyl derivatives. Binding modes of **a** compound **5**, **b** compound **4**. Key residues are represented in spear and labeled. The potential of H-bond interaction are represented by magenta color arrow, π–π interactions are shown in green color lines and cationep interactions are shown in red color lines. Compounds are shown in line form

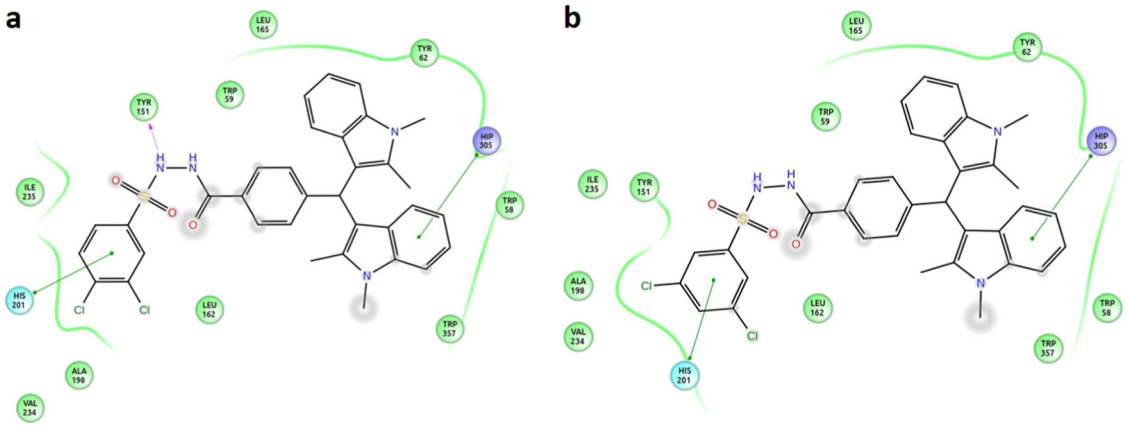


Fig. 6 Illustrates the predicted binding modes of active sulfonyl derivatives. Binding modes of **a** compound **10**, **b** compound **14**. Key residues are represented in spear and labeled. The potential of H-bond interaction are represented by magenta color arrow, π–π interactions are shown in green color lines. Compounds are shown in line form

stacking between diclorophenyl ring with His201 and similar π- π interaction is is also observed between one of the bisindole ring with the His305. Moreover the complex was also found to have hydrophobic contacts of the diclorophenyl ring with Leu162, Ala198, Val234, and Ile235. Similarly, the bisindole ring forms non polar contacts with Trp58, Trp59, Tyr62, Leu165, and Trp357 (Fig. 6a).

The Fig. 6b shows the binding mode of the compound **14**, where the dicholo ring forms π–π stacking with His201 and one of the bisindole ring forms similar interaction with His305. In addition the dicholorpheny ring also forms nonpolar interaction with Tyr151, Leu162, Ala198, and Val234. Finally, the bisindole ring forms hydrophobic contacts with Trp58, Trp59, Tyr62, Leu165, and Trp357, respectively.

Conclusion

In this study, we have synthesized nineteen bisindolylmethane sulfonamide analogs and screened for α-amylase inhibitory activity. All analogs showed a variable degree of α-amylase inhibition with IC_{50} values ranging between 1.192 ± 0.51 to 3.057 ± 0.18 µM when compared with standard acarbose having IC_{50} values 0.83 ± 0.36 µM. Among the series, six compounds such as **1, 4, 5, 6, 10** and **14** showed potent α-amylase inhibition while all other remaining compounds showed good to moderate α-amylase inhibition. The structure-activity relationship has reveals that difference of substituents nature and position on phenyl part of compounds effect their potential greatly.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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