

# Synthesis, Spectral Characterization, *in Vitro* and *in Silico* Studies of Benzodioxin Pyrazoline derivatives

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**Abstract:** The present study deals with the *in silico* and *in vitro* studies of DBDP derivatives, which is formed from the Michal-addition reaction of DihydroBenzo[b]Dioxin Chalcone Derivatives(DBDD) with hydrazine hydrate and carboxyethane. The DBDD were synthesized via Claisen condensation between substituted aldehyde and 1,4-(benzodioxan-6-yl)-methyl ketone. The newly arrived compounds were characterized by IR and NMR spectra. The structurally confirmed synthesized compounds were screened against 1UAG microbial protein, 1OQA cancer protein using auto dock software, and ADME properties also found by using (*in silico*) Swissadme and Molinspiration online tools. All the newly arrived DBDP compounds have passed the acceptable values of ADME (drug-likeness), medicinal property, and lead likeness in ADME prediction. Compound DBDP-9 scored better values in drug-likeness. It obeys the five basic rules (Lipinski, Ghose, Verber, Egan, and Muegge) of medicinal chemistry property, passed the PAINS, Brenk filters with 0 violation, and also have better lead likeness value. All the other compounds in this series also passed the above-mentioned properties with 1 or 2 violations only present in PAINS and Brenk filter. This theoretical results incitement to performed docking and *in vitro* studies of the DBDP derivatives. Docking studies results that the good I.S averse to 1 UAG bacterial protein than standard drugs and also give impact values in the docking against 1OQA breast cancer protein. Overall observation from the above studies, DBDP-9 has a maximum oral absorption value 91.36% with 0 violation alert in drug-likeness, medicinal property, and pharmacokinetics filter. DBDP-4 has a good I.S (-8.8), DBDP-2 has 4 numbers of HBI as standard, and all the DBDP 1-9 compounds have higher I.S than the standard and also have impact I.S against 1OQA breast cancer protein.

**Keywords:** Multicomponent; Dihydro Dibenzo-dioxan; ADME; *In vitro*; *In silico*.

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## 1. Introduction

In the 21<sup>st</sup> century, the world handshake with electronic gadgets and enters in the digitalized pathway. The computers lead in all the aspects, and it is also done tremendous help in the research area of science and the medicinal field. Computational methods are one of the most essential ones to predict the pharmacokinetics and biological properties of the designed organic compounds [1]. The information's about the drug-likeness property, binding affinity towards protein, toxicity, and absorption, distribution, metabolism, excretion (ADME) of the organic molecules are carried by using online protocols.

Low availability and scarcity of natural compounds [2] limited their chemotherapeutic importance. Due to this, the synthesis process of the hetero compound has more important. One of the most interesting and important five-membered heterocyclic systems is pyrazole, which

has two “N” atom in its adjacent position [3,4], and it has played the most important role in pharmacology. It has special attention in the field of medicinal and agro-chemistry and the pyrazole moiety present at the marketed drugs which are used as an anti-inflammatory (*Celebrex*), insecticide (Fipronil<sup>®</sup>), neuroprotective agent (Endaravone), COX-2 inhibitor (Celecoxib) [5,6], antipyrine (prostaglandin G/H synthase 2 inhibitors), anticoagulant (resaxaban<sup>®</sup>) [7], and it also possessed anti-cancer activity, anti-viral agent [8, 9], antimicrobial [10,11], analgesic [12,13], antidepressant [14], antitumor [15,16], anti-hyperglycemic [17]. Pyrazole moiety has N-N linkage, which helps to its pharmacological property [18], and this N-N linkage present in natural compounds is less in amounts. The creation of the N-N bond is very difficult for living micro-organisms, so this pyrazole moiety less abundant in natural compounds [19]. The most important and common method for synthesis of pyrazoline derivatives is the addition reaction of hydrazine hydrate with  $\alpha,\beta$ -unsaturated compound [20]. The antimicrobial activity of 1,4-benzodioxane moiety was first proven by Mallesha *et al.* in the year 2011[21] as well in the year 2014, Sang *et al.* proved that the benzodioxane moiety could target FabH and play an important role against bacteria [22,23]. Dioxino substituted coumarin derivatives have antihepatotoxic activity [24], methylamine substituted dioxino derivative function as antipsychotic agent [25] and propionic acid substituted benzodioxane moiety has anti-inflammation property [26, 27].

Among this investigation, at present, we designed, synthesized benzodioxin substituted dihydro pyrazole derivatives (DBDP), and its electronic structure was confirmed with the help spectral data's taken from Bruker NMR and Shimadzu IR instruments. Then the targets are screened *in silico* and *in vitro* studies by using suitable online software and methods.

## 2. Materials and Methods

### 2.1. Spectral devices.

The melting point of the compounds was measured with the help of the MELT-TEMP apparatus. The IR values were recorded in the SHIMADZU FT-IR spectrometer using KBr as a reference. The <sup>1</sup>H and <sup>13</sup>C spectral values for BDP were noted from the BRUKER instrument at 400 Hz and 100 Hz with the help of TMS ILR (Internal Reference) and CDCl<sub>3</sub> as a solvent. The preparation of DBDD compounds is followed by our previous work [28].

### 2.2. Synthesis of DBDP.

0.025 mol chalcone derivatives dissolved in the 40 ml of carboxyethane present at the 250 ml RB flask, and then nearly 1 ml of hydrazine hydrate was added, shaken well, and it refluxed for 12-16 hours in the HM (Heating Mantle). The reaction was monitored by TLC; when completion occurs, the mixture poured into crushed ice to get a solid. The product finally it was filtered, dried, and its purity was checked by using TLC. The synthesis procedure of the DBDP compounds is followed by our previous work[29].

#### **1-(4,5-dihydro-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-(4-chlorophenylpyrazol-1-yl)propan-1-one (DBDP-1):**

Yield 89; Pale yellow; molecular formula C<sub>20</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>3</sub>; IR (KBr, cm<sup>-1</sup>): 1650.77 (C=N), 1694.16 (C=O), 1591.95 (C=C), 1134.09 (C-N), 2982.37 (Aromatic CH), 2884.02 (Aliphatic CH), 688.46,717.39,779.10,830.20; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz): 1.150-1.192 (3H,t), 2.75-2.809 (2H,d), 3.03 ppm (dd, J<sub>4a,4e</sub>= 4Hz & J<sub>4a,5a</sub> = 17.6Hz); 3.66 ppm (dd, J<sub>4e,4a</sub> = 12 Hz & J<sub>4e,5a</sub>= 17.4 Hz); 5.50 ppm (dd, J<sub>5a,4a</sub>= 4.2 Hz & J<sub>5a,4e</sub> = 11.4 Hz), 4.29-4.33 (dddd, J= 3.6 Hz);

6.881-7.756 (m, Ar-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm): 172.16 (C=O); 27.54 (C-2'); 9.20 (C-3'); 153.20 (C-3); 42.04 (C-4); 59.46 (C-5); 64.57,64.27 (C<sub>a</sub>,C<sub>b</sub> of dioxin); 133.24 (C-Cl); 115.59-145.69 (Ar-C).

**1-(4,5-dihydro-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-(4-nitrophenylpyrazol-1-yl)propan-1-one (DBDP-2):**

Yield 80; dark yellow; molecular formula C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>; IR (KBr, cm<sup>-1</sup>): 1652.17 (C=N), 1693.16 (C=O), 1592.31 (C=C), 1142.12 (C-N), 2982.31 (Aromatic CH), 2886.12 (Aliphatic CH), 689.26,765.43,825.34; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz): 1.149-1.183 (3H,t), 2.742-2.799 (2H,d), 3.04 ppm (dd, J<sub>4a,4e</sub>= 3.4Hz & J<sub>4a,5a</sub> = 18Hz); 3.62 ppm (dd, J<sub>4e,4a</sub> = 11.6 Hz & J<sub>4e,5a</sub> = 17.4 Hz); 5.47 ppm (dd, J<sub>5a,4a</sub>= 3.6 Hz & J<sub>5a,4e</sub> = 11.6 Hz), 4.31-4.33 (dddd, J= 3.6 Hz); 6.811-7.866 (m, Ar-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm): 172.10 (C=O); 27.58 (C-2'); 9.02 (C-3'); 153.24 (C-3); 42.19 (C-4); 59.54 (C-5); 64.24,64.53 (C<sub>a</sub>,C<sub>b</sub>); 114.23-148.16 (Ar-C).

**1-(4,5-dihydro-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-(4-methoxyphenylpyrazol-1-yl)propan-1-one (DBDP-3):**

Yield 85; yellowish white; molecular formula C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>; IR (KBr, cm<sup>-1</sup>): 1654.21 (C=N), 1692.93 (C=O), 1590.42 (C=C), 1139.42 (C-N), 2985.10 (Aromatic CH), 2887.32 (Aliphatic CH), 692.63,728.21,785.63,825.34; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz): 1.150-1.187 (3H,t), 2.74-2.79 (2H,d), 3.07 ppm (dd, J<sub>4a,4e</sub>= 3.8Hz & J<sub>4a,5a</sub> = 17.4Hz); 3.64 ppm (dd, J<sub>4e,4a</sub> = 11.8 Hz & J<sub>4e,5a</sub> = 17.4 Hz); 5.49 ppm (dd, J<sub>5a,4a</sub>= 3.6 Hz & J<sub>5a,4e</sub> = 11.6 Hz), 4.29-4.31 (dddd, J= 3.4 Hz); 6.819-7.599 (m, Ar-H); 3.76 (OCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm): 172.40 (C=O); 27.51 (C-2'); 8.92 (C-3'); 153.05 (C-3); 41.88 (C-4); 59.53 (C-5); 64.29,64.59 (C<sub>a</sub>,C<sub>b</sub>); 161.56 (C-OCH<sub>3</sub>); 115.64-149.16 (Ar-C).

**1-(4,5-dihydro-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-(2,3-dichlorophenylpyrazol-1-yl)propan-1-one (DBDP-4):**

Yield 76; white; molecular formula C<sub>20</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>; IR (KBr, cm<sup>-1</sup>): 1656.18 (C=N), 1690.32 (C=O), 1593.54 (C=C), 1139.12 (C-N), 2981.92 (Aromatic CH), 2888.63 (Aliphatic CH), 689.72,715.33,784.54,832.34; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz): 1.148-1.188 (3H,t), 2.746-2.781 (2H,d), 3.09 ppm (dd, J<sub>4a,4e</sub>= 3.8Hz & J<sub>4a,5a</sub> = 17.6Hz); 3.68 ppm (dd, J<sub>4e,4a</sub> = 11.6 Hz & J<sub>4e,5a</sub> = 17.6 Hz); 5.45 ppm (dd, J<sub>5a,4a</sub>= 3.4 Hz & J<sub>5a,4e</sub> = 11.4 Hz), 4.31-4.33 (dddd, J= 3.2 Hz); 6.799-7.432 (m, Ar-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm): 172.18 (C=O); 27.60 (C-2'); 9.05 (C-3'); 153.22 (C-3); 42.10 (C-4); 59.52 (C-5); 64.22,64.58 (C<sub>a</sub>,C<sub>b</sub>); 130,132.22 (C-Cl); 114.20-127.78 (Ar-C); 143.43-147.79 (Ipsso Carbon).

**1-(4,5-dihydro-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-(2-chlorophenylpyrazol-1-yl)propan-1-one (DBDP-5):**

Yield 80; Pale yellow; molecular formula C<sub>20</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>3</sub>; IR (KBr, cm<sup>-1</sup>): 1651.18 (C=N), 1693.53 (C=O), 1592.18 (C=C), 1135.21 (C-N), 2980.92 (Aromatic CH), 2887.92 (Aliphatic CH), 679.42,724.52,791.45,836.24; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz): 1.152-1.175 (3H,t), 2.738-2.789 (2H,d), 3.02 ppm (dd, J<sub>4a,4e</sub>= 3.6Hz & J<sub>4a,5a</sub> = 17.8Hz); 3.60 ppm (dd, J<sub>4e,4a</sub> = 11.4 Hz & J<sub>4e,5a</sub> = 17.4 Hz); 5.39 ppm (dd, J<sub>5a,4a</sub>= 3.8 Hz & J<sub>5a,4e</sub> = 11.8 Hz), 4.31-4.32 (dddd, J= 3.6 Hz); 6.810-7.652 (m, Ar-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm): 172.21 (C=O); 27.53 (C-2'); 9.07 (C-3'); 153.29 (C-3); 42.15 (C-4); 59.55 (C-5); 64.26,64.56 (C<sub>a</sub>,C<sub>b</sub>); 134.43 (C-Cl); 115.21-127.60 (Ar-C); 143.20-147.62 (Ipsso Carbon).

**1-(4,5-dihydro-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-(4-bromophenylpyrazol-1-yl)propan-1-one (DBDP-6):**

Yield 76; brownish yellow; molecular formula C<sub>20</sub>H<sub>19</sub>BrN<sub>2</sub>O<sub>3</sub>; IR (KBr, cm<sup>-1</sup>): 1654.32 (C=N), 1694.25 (C=O), 1594.63 (C=C), 1141.52 (C-N), 2986.45 (Aromatic CH), 2893.56 (Aliphatic

CH), 668.85,731.47,786.56,815.87; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz): 1.151-1.177 (3H,t), 2.740-2.785 (2H,d), 3.11 ppm (dd, J<sub>4a,4e</sub>= 3.6Hz & J<sub>4a,5a</sub> = 17.6Hz); 3.69 ppm (dd, J<sub>4e,4a</sub> = 11.6 Hz & J<sub>4e,5a</sub> = 17.8 Hz); 5.49 ppm (dd, J<sub>5a,4a</sub>= 3.4 Hz & J<sub>5a,4e</sub> = 11.4 Hz), 4.32-4.35 (dddd, J= 3.4 Hz); 6.795-7.821 (m, Ar-H): <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm): 172.30 (C=O); 27.55 (C-2'); 9.04 (C-3'); 153.42 (C-3); 42.08 (C-4); 59.52 (C-5); 64.25,64.55 (C<sub>a</sub>,C<sub>b</sub>); 115.30-149.62 (Ar-C).

**1-(4,5-dihydro-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-(4-methylphenylpyrazol-1-yl)propan-1-one (DBDP-7):**

Yield 85; light yellow; molecular formula C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>; IR (KBr, cm<sup>-1</sup>): 1656.84 (C=N), 1695.78 (C=O), 1593.18 (C=C), 1145.48 (C-N), 2984.67 (Aromatic CH), 2886.34 (Aliphatic CH), 672.45,724.78,768.87,826.54; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz): 1.154-1.178 (3H,t), 2.739-2.786 (2H,d), 3.06 ppm (dd, J<sub>4a,4e</sub>= 3.4Hz & J<sub>4a,5a</sub> = 17.6Hz); 3.59 ppm (dd, J<sub>4e,4a</sub> = 11.8 Hz & J<sub>4e,5a</sub> = 17.2 Hz); 5.49 ppm (dd, J<sub>5a,4a</sub>= 3.4 Hz & J<sub>5a,4e</sub> = 11.6 Hz), 4.34-4.36 (dddd, J= 3.6 Hz); 3.74,3.89 (3H of CH<sub>3</sub>); 6.802-7.874 (m, Ar-H): <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm): 172.34 (C=O); 27.49 (C-2'); 9.06 (C-3'); 153.10 (C-3); 41.98 (C-4); 59.56 (C-5); 64.23,64.45 (C<sub>a</sub>,C<sub>b</sub>); 114.59-148.25 (Ar-C).

**1-(4,5-dihydro-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-(4-fluorophenylpyrazol-1-yl)propan-1-one (DBDP-8):**

Yield 76; yellow; molecular formula C<sub>20</sub>H<sub>19</sub>FN<sub>2</sub>O<sub>3</sub>; IR (KBr, cm<sup>-1</sup>): 1655.45 (C=N), 1693.28 (C=O), 1591.36 (C=C), 1144.25 (C-N), 2985.34 (Aromatic CH), 2884.75 (Aliphatic CH), 667.54,732.42,756.51,815.24; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz): 1.151-1.181 (3H,t), 2.731-2.779 (2H,d), 3.04 ppm (dd, J<sub>4a,4e</sub>= 3.6Hz & J<sub>4a,5a</sub> = 17.8Hz); 3.64 ppm (dd, J<sub>4e,4a</sub> = 11.6 Hz & J<sub>4e,5a</sub> = 17.2 Hz); 5.49 ppm (dd, J<sub>5a,4a</sub>= 3.4 Hz & J<sub>5a,4e</sub> = 11.8 Hz), 4.30-4.32 (dddd, J= 3.8 Hz); 6.791-8.114 (m, Ar-H): <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm): 172.22 (C=O); 27.49 (C-2'); 8.94 (C-3'); 153.35 (C-3); 42.21 (C-4); 59.59 (C-5); 64.23,64.51 (C<sub>a</sub>,C<sub>b</sub>); 114.46-148.56 (Ar-C).

**1-(4,5-dihydro-3-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-phenylpyrazol-1-yl)propan-1-one (DBDP-9):**

Yield 72; pale yellow; molecular formula C<sub>20</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>; IR (KBr, cm<sup>-1</sup>): 1650.63 (C=N), 1690.96 (C=O), 1589.42 (C=C), 1141.87 (C-N), 2981.57 (Aromatic CH), 2880.42 (Aliphatic CH), 675.12,754.86,808.75; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz): 1.151-1.181 (3H,t), 2.731-2.779 (2H,d), 3.02 ppm (dd, J<sub>4a,4e</sub>= 3.2Hz & J<sub>4a,5a</sub> = 17.6Hz); 3.64 ppm (dd, J<sub>4e,4a</sub> = 11.4 Hz & J<sub>4e,5a</sub> = 17.8 Hz); 5.45 ppm (dd, J<sub>5a,4a</sub>= 3.2 Hz & J<sub>5a,4e</sub> = 11.4 Hz), 4.35-4.38 (dddd, J= 3.8 Hz); 6.665-7.899 (m, Ar-H): <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, ppm): 172.38 (C=O); 27.39 (C-2'); 8.98 (C-3'); 153.18 (C-3); 42.11 (C-4); 59.51 (C-5); 64.21,64.51 (C<sub>a</sub>,C<sub>b</sub>); 114.12-147.88 (Ar-C).

*2.3. Antimicrobial screening test.*

The disk diffusion method is used to screen the antimicrobial studies of synthesized compounds DBDP, and MIC values are calculated by the microdilution method. The inoculums and sterile swabs are constructed and sterilized. Ciprofloxacin is used as a standard drug. The gram-positive *S. aureus*, *St. pyogenes*, and the gram-negative *E. coli*, *P. aeruginosa* bacterial strains and *C.albicans* fungal strain agar nutrient medium were prepared for the test. The reference procedures were adapted to do antimicrobial work[30].

#### 2.4. Computational method.

##### 2.4.1. Molecular docking.

The Auto dock 4.2.5.1 version program was used for molecular docking studies of synthesized DBDP derivatives. The given literary method followed to find the docking scores [31].

##### 2.4.2. ADME.

Absorption, distribution, metabolism, and excretion (ADME) properties of all newly arrived DBDP were predicted using Swissadme online tool. That tool gave information about molecular weight (MW),  $\log P_{o/w}^c$  (octanol-water partition co-efficient, Log s(Solubility),  $\log k_p$  (skin permeation), hydrogen bond acceptor (HyA), number of hydrogen bond donor(HyD), polar surface area(TSPA), molar refractivity (M.Ref), bioavailability score. The given parameters help to understand the ADME property of any drugs or organic molecules. The molecule or the compounds which satisfy the Lipinski rule of five and some other below mentioned criteria are known as active drug molecule. The criteria for effective drug molecules are Molecular weight  $\leq 500$ , Hydrogen bond acceptor  $\leq 10$ , hydrogen bond donor  $\leq 5$ ,  $\log p \leq 5$ , molar refractivity  $\leq 140$  satisfy the rule of five and then  $\log P_{o/w}$  range between -2 to 6.5, polar surface area range between 7 to 200,  $\log S$  range lie above -4 and the drug score value above 0.5 is accepted one for synthesized compounds. The pharmacokinetics, medicinal chemistry, and drug-likeness are also predicted from this tool.

The % Abs are calculated using the known formula [32, 33],

$$\% \text{Abs} = 109 - 0.345 * \text{TPSA}$$

The molinspiration tool kit is used to predict the Bioactivity score of the synthesized compounds. Likewise GPCR ligand, Ion channel modulator, Kinase inhibitor, nuclear receptor ligand, Protease inhibitor, and Enzyme inhibitor values of DBDP compounds [32]. All DBDP compounds have a good drug-like score of 0.55.

### 3. Results and Discussion

#### 3.1. Chemistry.

The synthesis of DBDP molecules was achieved by adopting the Michal addition reaction of DBDD derivatives with hydrazine hydrate in the presence of sodium ethanoate as a multicomponent reaction (MCR). MCR reaction is the one of time-saving method which reduces the work time and solvent usage in the synthesis lab. It is also economical, product efficient. The starting DBDD (1-9) synthesized by Claisen-Schmidt condensation between various substituted benzaldehyde and 1,4-benzodioxan-6-yl-methyl ketone in the presence of a base medium. The pathway of the target is given in figure1.

#### 3.2. Computational analysis.

##### 3.2.1. ADME prediction.

A good drug is a compound in which one has an effective metabolism, absorbed at the required time, and well in distribution. The ADME study exhibits drug-likeness, medicinal property, pharmacokinetics property, and lead likeness of the compounds. The target molecules

DBDP (1-9) ADME property predicted with the help of Swiss-ADME online software. This *in silico* method, plays a major role in helping to optimize the pharmacokinetic property of new molecules and increase the success rate. The target compounds DBDP (1-9) derivatives all obey the Lipinski's rule of five and also exhibit good solubility and absorption values. The ADME prediction values are given in table 1.

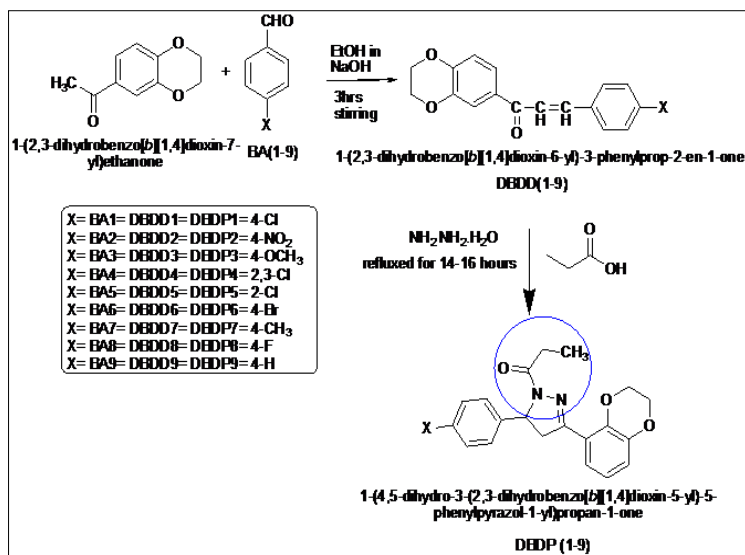


Figure 1. Representation of the schematic pathway of DBDP compounds.

### 3.2.2. Oral absorption.

DBDP compounds showed the best oral absorption values 91.63 ( $\geq 80\%$ ), except DBDP-2 compound, which has a moderate absorption value of 74.22 (30 to  $\leq 80\%$ ). The halogenated substituted and electron-donating group substituted compounds DBDP-1,4,5,6,7,8 also have the best oral absorption value 91.63%, and DBDP-3 has 88.17% oral absorption values.

### 3.2.3. Drug-likeness.

The compound DBDP-1, 5, 6, 8 are halogen-substituted ones. In that compounds DBDP-1 and DBDP-5 are chlorine substituted in the position 2 and 4, they two are having same ABME prediction values. While comparing the compounds DBDP-1,6,8, notable changes have occurred there. The Fluoro substituted DBDP-8 compound shows low solubility value, Log P-value, and M.Rty. values than the other two. Let us find the other two compounds DBDP-1,6 the DBDP-1 have less MW, low solubility, Log P, and M.Rty. values than DBDP-6. This shows that the molecular weight of the compounds heavily influencing the ADME values.

Compounds DBDP-2, 3 & 7 are the compounds having electron-withdrawing and electron-donating substituents. All have acceptable values in drug-likeness prediction. While DBDP-3 & 7 have lower values in MW, solubility, Log P, n-HyA, n-HyD, and M.Rty than DBDP-2 compound. This ADME study results stimulated our research work towards docking and *in vitro* studies of the DBDP compounds.

The compounds DBDP (1-9) showed the 0 violations for Lipinski rule of five, solubility value in the range -3.62 to -4.92, polar surface area 51.13 except DBDP-2 and 3 and permeability range is -5.83 to -7.04. All these values are satisfied, good, and all targets are has a moderate drug score value is 0.55.

### 3.3. Drug likeness and medicinal chemistry.

The medicinal chemistry of the targeted compounds DBDP (1-9) is done by using the same Swissadme software. The Medicinal chemistry contains 5 basic rules, which are Lipinski, Ghose, Veber, Egan, and Muegge. These are the basic rules for finding the medicinal chemistry of the compounds which are synthesized one. The target compounds DBDP- 1to 9 are having 0 violations in all the rules. The PAINS and Brenk are the physicochemical filters to predict the compounds which are responsible for poor pharmacokinetics property. The PAINS is a filter that helps to identify the molecule, whether it is a response or not against the biological assays, and Brenk is a filter to identify compounds that have the accepted toxic level, chemical reactivity, and metabolically unstable. Lead-likeness is one of the parameters similar to drug-likeness. There is 0 violation in the PAINS filter of all the DBDP compounds, and it exhibits a potent response of DBDP compounds against biological assays. Except for DBDP-2, all the compounds have 0 violations in Brenk filter exhibits that all the compounds are good pharmacokinetics property with including acceptable toxic level, chemically inactive, and proper metabolic stability. The Drug-likeness, lead likeness, pharmacokinetic property (PAINS, Brenk), and synthetic accessibility of the compounds are shown in table 2.

Particularly, the compound DBDP-9 attains 0 violations in lead likeness property. The compounds which are substituted by CH<sub>3</sub>, OCH<sub>3</sub>, F, NO<sub>2</sub> have only one violation in MW > 350, but it obeys all five basic rules and their molecular weight < 500. The other four compounds that are 4-Cl, 2-Cl, 2,3-Cl, and 4-Br substitutions have two violations MW> 350, XLOGP3> 3.5 in the lead likeness parameter.

The identified values showed that all the DBDP compounds moderately active towards G-protein coupled receptor ligand. The entire compound also showed that moderately active towards Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor, and Enzyme inhibitor. The values are represented in Table-3.

### 3.4. Docking studies.

The target molecule DBDP (1-9) subjected molecular docking studies against bacterial protein 1UAG and cancer cell line protein 1OQA. The docking resulted are given in Table-4 and Table-5, respectively. The cell wall mechanism involved in the *in silico* screening studies. The compound DBDP-4 has a high I.S. (Interaction Score) compared to other DBDP derivatives as well as standard drug ciprofloxacin. DBDP-4 scored -8.8 for I.S. and good H-bond interaction; it has two HBI (Hydrogen Bond Interaction) ARG A: 37 at C=O group of propionyl group attached in the 1<sup>st</sup> position of pyrazole ring, THR A: 36 obtained in the oxygen of dioxane moiety and three HPI (Hydrophobic Interaction) of ILE A: 74, PRO A: 72 & LEU A: 15 present at the phenyl rings of the target compound. This compound has mark able binding score compared with standard and other compounds in the series.

DBDP-2 compound has the best I.S -7.2 with one HBI and one HPI. HBI formed GLN A: 104 substituted carbonyl group in the pyrazoline moiety and HPI PRO A: 59 formed at phenyl ring.

All the compounds in the series have a high I.S. score compare with standard drugs. In that, DBDP-3-9 compounds I.S. higher than -8.0 with one HBI at HIS A: 267 with bond length 2.06 and two HPI at LEU A: 263, ARG A: 302 with bond length 5.09, 5.12, the compound DBDP-5 has two H-bond interaction at ILE A:139, LEU A:141 and bond length is 2.82, 2.78 as like as the compound DBDP-4 but DBDP-5 have two hydrophobic interaction with VAL

A:135, PRO A:300 amino acids at bond length 4.32,4.17. The DBDP-6,9 compounds have good I.S. -8.3,-8.4, but did not have any HBI and HPI.

The DBDP (1-9) compounds binding with the 1OQA protein, which belongs to the breast cancer cell line. The 9 target compounds have a good I.S. averse to 1OQA cell line with a notable number of HBI, and the maximum numbers of DBDP compounds form a HBI with GLN A: 104 at the C=O of propionyl group, which is attached in the 1<sup>st</sup> position of pyrazoline ring.

The electron-withdrawing substitution compound DBDP-1 and electron-donating substitution compound DBDP-3 are considerable I.S. with the maximum number of HBI at GLN A:104, GLY A: 72, GLN A: 73 and PHE A:68. This phenomenon shows that the substitution, even electron-donating or an electron-withdrawing enhances the binding affinity of the compounds averse to 1OQA protein. This interaction study also shows that all the 9 compounds may have a better ability to act as an anti-cancer drug. Docking studies established the mechanism for the interaction of protein and ligand binding. The docking results of some of the compounds showed in figure 2, figure3, figure 4, and figure 5.

### 3.5. Antimicrobial study.

The ADME and Molinspiration (*in silico*) study values incitement to carry out the *in vitro* studies of the compounds are treated antagonistically to gram-positive *S. aureus*, *St. pyogenes* gram-negative *E. coli*, *P. aeruginosa*, and fungal strain *C. albicans*. The study was done by 1 mg/mL concentration, and their results are exhibited in Fig 4. Ciprofloxacin used as a standard drug for bacterial strains *S. aureus*, *E. coli*, *St. pyogenes*, and *P. aeruginosa*, and Clotrimazole consider as a standard for fungal strain *C. albicans*.

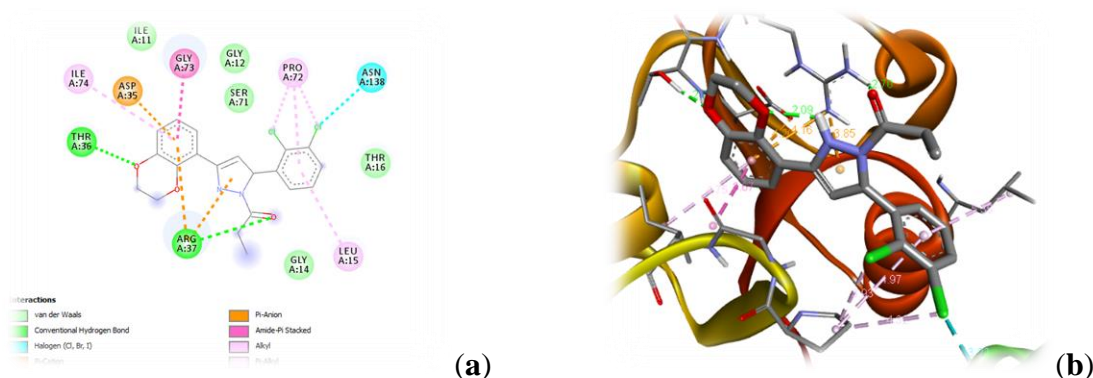


**Figure 2.** This is the figure belongs to the DBDP-2 compounds docking study averse to 1UAG protein: (a) 2-D image of DBDP-2 against 1UAG ; (b) 3-D image of DBDP-2 against 1UAG.

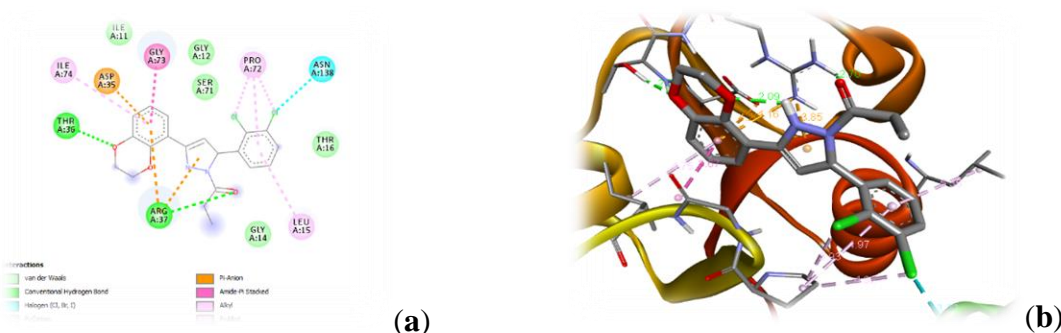
Compounds DBDP-4, 5 showed better results while compared with standard, and they have a good zone of inhibition averse to bacterial strains. Especially, DBDP compounds show the best zone of inhibition against *E. coli* reveals the compound follow the cell wall synthesis mechanism. The compounds DBDP-1, 6, and 9 have good activity against *S. pyogenes* such as a standard. Compound DBDP-9 had a good inhibition against *E. coli* compared with standard and DBDP-6, 9 also had 90% activity against *P. aeruginosa* compared with ciprofloxacin. DBDP-2,3 and 7 are substituted by electron-withdrawing, and electron-donating groups show a better activity against all the bacterial strains.

The results in figure 6 showed that the maximum DBDP compounds have a maximum inhibition activity averse to taken bacterial strains, and they had better activity against fungal strain.

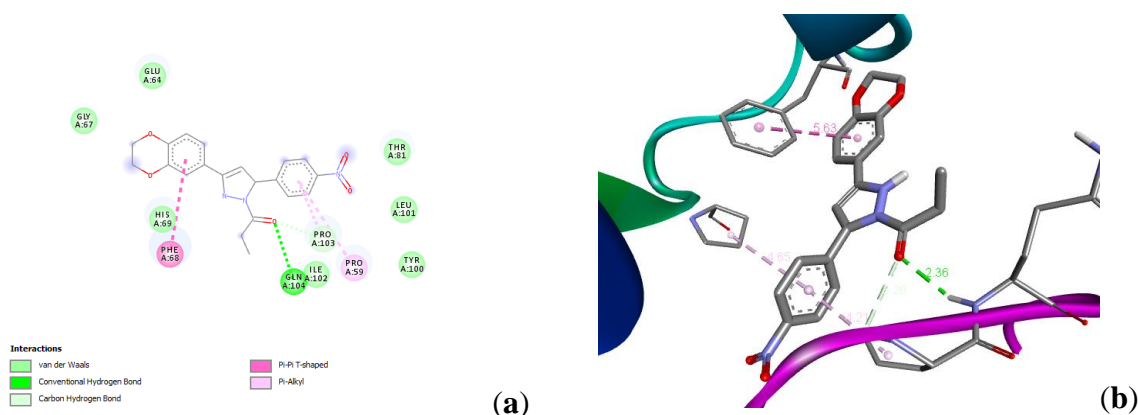




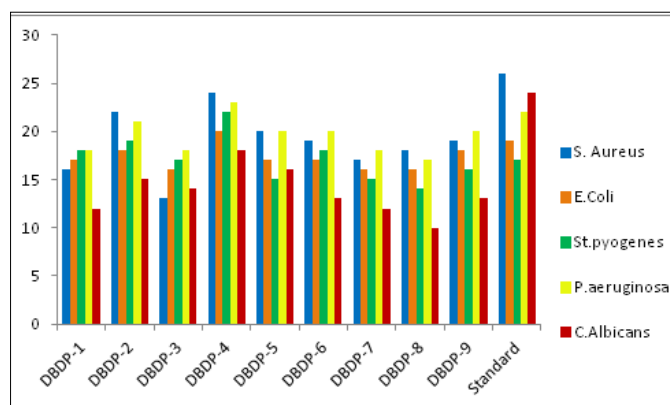
**Figure 3.** This is the figure belongs to the DBDP-5 compounds docking study averse to 1UAG protein: (a) 2-D image of DBDP-5 against 1UAG ; (b) 3-D image of DBDP-5 against 1UAG.



**Figure 4.** This is the figure belongs to the DBDP-4 compounds docking study averse to 1UAG protein: (a) 2-D image of DBDP-4 against 1UAG ; (b) 3-D image of DBDP-4 against 1UAG.



**Figure 5.** This is the figure belongs to the DBDP-2 compounds docking study averse to 1OQA protein: (a) 2-D image of DBDP-2 against 1OQA ; (b) 3-D image of DBDP-2 against 1OQA.



**Figure 6.** *In vitro* studies, results of compound DBDP (1-9) compounds at 1.0 mg/mL with a standard.

**Table 1.** ADME prediction values of DBDP (1-9) compounds.

| Compound | n-Heavy atoms | MW     | Log P | n-HyA | n-HyD | M.Rty. | n-violation of rule of five | Log S | TSPA in Å | Drug Score | %Abs  |
|----------|---------------|--------|-------|-------|-------|--------|-----------------------------|-------|-----------|------------|-------|
| DBDP-1   | 26            | 370.83 | 3.59  | 4     | 0     | 107.71 | 0                           | -4.28 | 51.13     | 0.55       | 91.36 |
| DBDP-2   | 27            | 382.39 | 1.00  | 6     | 1     | 109.95 | 0                           | -4.00 | 100.79    | 0.55       | 74.23 |
| DBDP-3   | 26            | 366.41 | 3.06  | 5     | 0     | 109.20 | 0                           | -3.79 | 60.36     | 0.55       | 88.18 |
| DBDP-4   | 26            | 405.27 | 4.12  | 4     | 0     | 107.72 | 0                           | -4.92 | 51.13     | 0.55       | 91.36 |
| DBDP-5   | 27            | 370.83 | 3.59  | 4     | 0     | 107.71 | 0                           | -4.28 | 51.13     | 0.55       | 91.36 |
| DBDP-6   | 26            | 415.28 | 4.21  | 4     | 0     | 110.41 | 0                           | -4.34 | 51.13     | 0.55       | 91.36 |
| DBDP-7   | 28            | 350.41 | 3.39  | 4     | 0     | 107.67 | 0                           | -4.00 | 51.13     | 0.55       | 91.36 |
| DBDP-8   | 25            | 354.37 | 3.38  | 5     | 0     | 102.67 | 0                           | -3.73 | 51.13     | 0.55       | 91.36 |
| DBDP-9   | 26            | 336.38 | 3.07  | 4     | 0     | 102.71 | 0                           | -3.62 | 51.13     | 0.55       | 91.36 |

Acceptable values: n-Heavy atoms, MW<500, Log P < 5, n-HyA ≤ 10, n-HyD ≤ 5, M.Rty < 120, Log S ≤ -5, TPSA (30 ≤ to ≥ 140), Drug Score ≥ 0.5, %Abs (≤ 80% (best), 30-80 (moderate), ≥ 30% (poor)).

**Table 2.** Drug likeness and medicinal chemistry.

| Compound | Lipinski           | Ghose | Veber | Egan | Muegge | PAINS   | Brenk                     | Lead likeness            | Synthetic accessibility |
|----------|--------------------|-------|-------|------|--------|---------|---------------------------|--------------------------|-------------------------|
| DBDP-1   | Y with 0 violation | Y     | Y     | Y    | Y      | 0       | 0                         | N (2 MW>350, XLOGP3>3.5) | 3.60                    |
| DBDP-2   | Y with 0 violation | Y     | Y     | Y    | Y      | 0       | 1 (NO <sub>2</sub> group) | N (1 violation, MW> 350) | 3.75                    |
| DBDP-3   | Y with 0 violation | Y     | Y     | Y    | Y      | 0       | 0                         | N (1 violation, MW> 350) | 3.85                    |
| DBDP-4   | Y with 0 violation | Y     | Y     | Y    | Y      | 0       | 0                         | N (2 MW>350, XLOGP3>3.5) | 3.78                    |
| DBDP-5   | Y with 0 violation | Y     | Y     | Y    | Y      | 0       | 0                         | N (2 MW>350, XLOGP3>3.5) | 3.76                    |
| DBDP-6   | Y with 0 violation | Y     | Y     | Y    | Y      | 0       | 0                         | N (2 MW>350, XLOGP3>3.5) | 3.73                    |
| DBDP-7   | Y with 0 violation | Y     | Y     | Y    | Y      | 0       | 0                         | N (1 violation, MW> 350) | 3.80                    |
| DBDP-8   | Y with 0 violation | Y     | Y     | Y    | Y      | 0       | 0                         | N (1 violation, MW> 350) | 3.71                    |
| DBDP-9   | Y with 0 violation | Y     | Y     | Y    | Y      | 0 alert | 0 alert                   | Y                        | 3.70                    |

**Table 3.** Bioactivity of DBDP compounds by Molinspiration online tool.

| Compound      | GPCR ligand | Ion channel modulator | Kinase inhibitor | Nuclear receptor ligand | Protease inhibitor | Enzyme inhibitor |
|---------------|-------------|-----------------------|------------------|-------------------------|--------------------|------------------|
| DBDP-1        | -0.36       | -0.92                 | -0.59            | -0.54                   | -0.49              | -0.46            |
| DBDP-2        | -0.48       | -0.90                 | -0.66            | -0.58                   | -0.56              | -0.50            |
| DBDP-3        | -0.38       | -0.93                 | -0.57            | -0.53                   | -0.47              | -0.44            |
| DBDP-4        | -0.35       | -0.91                 | -0.65            | -0.60                   | -0.49              | -0.52            |
| DBDP-5        | -0.38       | -0.97                 | -0.64            | -0.62                   | -0.52              | -0.54            |
| DBDP-6        | -0.46       | -0.99                 | -0.62            | -0.63                   | -0.56              | -0.50            |
| DBDP-7        | -0.35       | -0.93                 | -0.54            | -0.50                   | -0.48              | -0.44            |
| DBDP-8        | -0.40       | -0.98                 | -0.61            | -0.55                   | -0.51              | -0.48            |
| DBDP-9        | -0.37       | -0.95                 | -0.59            | -0.55                   | -0.47              | -0.44            |
| Ciprofloxacin | 0.12        | -0.04                 | -0.07            | -0.19                   | -2.0               | -0.28            |

**Table 4.** I.S., HBI and HPI of compounds DBDP (1-9) averse to 1UAG protein.

| Compound      | I.S  | HBI-bond length        | HBI  | HPI- bond length | HPI                             |
|---------------|------|------------------------|--|------------------|---------------------------------|
| DBDP-1        | -7.9 | 2.07                   | HIS A: 267                                     | 5.12, 6.08       | LEU A: 263, ARG A: 302          |
| DBDP-2        | -7.9 | 2.01, 2.16, 2.40, 2.63 | LYS A: 319, SER A: 116, LYS A: 115, GLY A: 114 | 5.40             | ALA A: 414                      |
| DBDP-3        | -8.3 | 2.06                   | HIS A: 267                                     | 5.09, 5.12       | LEU A: 263, ARG A: 302          |
| DBDP-4        | -8.8 | 2.09, 2.70             | THR A: 36, ARG A: 37                           | 4.97, 4.75, 5.35 | ILE A: 74, PRO A: 72, LEU A: 15 |
| DBDP-5        | -8.0 | 2.82, 2.78             | ILE A: 139, LEU A: 141                         | 4.32, 4.17       | VAL A: 135, PRO A: 300          |
| DBDP-6        | -8.3 | -                      | -  | -                | -                               |
| DBDP-7        | -8.6 | 2.27                   | ASN A: 268                                     | -                | -                               |
| DBDP-8        | -8.6 | 2.31                   | ASN A: 268                                     | -                | -                               |
| DBDP-9        | -8.4 | -                      | -  | -                | -                               |
| Ciprofloxacin | -7.7 | 2.05, 2.65, 2.47       | ASN A: 178, ASN A: 271, GLU A: 327             | 4.12             | ALA A: 328                      |

**Table 5.** I.S., HBI and HPI of compounds DBDP (1-9) averse to 1OQA protein.

| Compound | I.S  | HBI- bond length    | HBI  | HPI- bond length    | HPI  |
|----------|------|---------------------|--|---------------------|--|
| DBDP- 1  | -7.0 | 2.69,2.59,2.65,2.27 | GLN A: 104, GLY A: 72,<br>GLN A: 73, PHE A: 68 | 5.40                | ILE A: 105   |
| DBDP- 2  | -7.2 | 2.36                | GLN A: 104                                     | 4.65                | PRO A: 59  |
| DBDP- 3  | -6.6 | 2.34,2.52,2.64,2.68 | GLN A: 104, GLN A: 73,<br>GLY A: 72, PHE A: 68 | -                   | -  |
| DBDP- 4  | -6.9 | 2.52,2.32           | PHE A: 68,<br>HIS A: 69                        | 4.69,4.20,4.90      | PRO A: 59, PRO A: 103,<br>ILE A: 102               |
| DBDP- 5  | -7.0 | 2.65,2.83           | GLN A: 73,<br>GLN A: 104                       | 5.35                | PRO A: 59  |
| DBDP- 6  | -7.0 | 2.37                | GLN A: 104                                     | 4.65                | PRO A: 59  |
| DBDP- 7  | -6.8 | 2.41,2.59           | HIS A: 69,<br>PHE A: 68                        | 5.16,4.94,4.82,4.74 | PRO A: 59, PRO A:<br>103, ILE A: 102, VAL<br>A: 57 |
| DBDP- 8  | -6.6 | 2.31,2.55           | HIS A: 69,<br>PHE A: 68                        | 4.71,4.62,5.23      | PRO A: 59, PRO A: 103,<br>ILE A: 102               |
| DBDP- 9  | -6.8 | 2.63,2.89           | GLN A: 73,<br>GLN A: 104                       | 5.29,5.40           | PRO A: 59,<br>ILE A: 102                           |

#### 4. Conclusions

The newly designed DBDP derivatives were successfully synthesized, and their skeleton sketch was confirmed by using spectral data values. The derivatives subjected to *in silico* study known as docking and ADME prediction. The compound DBDP-4 has better active against bacterial strain also had high I.S., HBI, HPI values in the *in silico* study averse to 1 UAG with acceptable ADME prediction values, and it has a moderate bioactive score. DBDP-2 has better I.S. with a high number of HBI, which leads to better binding between the protein and the ligand with a moderate ADME score. DBDP-9 has a good oral absorption value with 0 violations of all the ADME study. It moderates averse to 1UAG bacterial protein but better I.S. averse to 1OQA breast cancer protein with notable HBI and HPI interactions.

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#### Conflicts of Interest

The authors declare no conflict of interest.

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