**Table 1. Structure of the prepared chalcones.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Compound name** | **R1** | **R2** | **R3** | **R4** | **R5** |
| LSD - 1 | - | - | -NO2 | - | - |
| LSD - 2 | - | - | - | - | - |
| LSD - 3 | -Cl | - | - | - | - |
| LSD - 4 | - | - | -OCH3 | - | - |
| LSD - 5 | - | - | -N(CH3)2 | - | - |
| LSD - 6 | -OH | -C6H5 | - | - | - |
| LSD - 7 | - | -OH | - | - | - |
| LSD - 8 | - | -NO2 | - | - | - |
| LSD - 9 | -OCH3 | - | -OCH3 | -OCH3 | - |
| LSD - 10 | - | - | -(CH3)2 | - | - |
| LSD - 11 | - | - | -CH3 | - | - |
| LSD - 12 | -OH | - | - | -Cl | - |
| LSD - 13 | - | -OC6H5 | - | - | - |
| LSD - 14 | - | -CH3 | -OC7H8 | -CH3 | - |
| LSD - 15 | -NO2 | - | - | - | - |

**Table 2. Synthesis of Chalcone Derivatives**

|  |  |  |  |
| --- | --- | --- | --- |
| **CODE** | **STRUCTURE** | **IUPAC NAME**  | **YIELD (%)** |
| LSD 2 | Picture1 | **(2*E*)-1-(4-bromophenyl) -3-phenylprop-2-en-1-one** | 62 |
| LSD 4 | Picture2 | **(2*E*)-1-(4-bromophenyl)-3-(4- methylphenyl)prop-2-en-1-one**  | 72 |
| LSD 7 | Picture3 | **(2*E*)-1-(4-bromophenyl)-3-(3- hydroxyphenyl)prop-2-en-1-one** | 70 |
| LSD 8 | Picture4 | **(2*E*)-1-(4-bromophenyl)-3-(3-nitrophenyl)prop-2-en-1-one**  | 70 |
| LSD 9 |  | **(2*E*)-1-(4-bromophenyl)-3-(2,4,5- trimethoxyphenyl)prop-2-en-1-one** | 74 |
| LSD 10 | Picture6 |  **(2*E*)-1-(4-bromophenyl)-3-[4-(propan-2- yl)phenyl]prop-2-en-1-one** | 76 |
| LSD 11 | Picture12 crcted | **(2*E*)-1-(4-bromophenyl)-3-(4-methylphenyl)prop-2-en-1-one** | 70 |
| LSD 12 | Picture7 | **(2*E*)-1-(4-bromophenyl)-3-(5-chloro-2-hydroxyphenyl)prop-2-en-1-one** | 76 |
| LSD 13 | Picture9 | **(2*E*)-1-(4-bromophenyl)-3- (3-phenoxyphenyl) prop-2-en-1-one** | 72 |
| LSD 14 | Picture10 |  **(2*E*)-3-[4-(benzyloxy)-3,5-dimethylphenyl]- 1-(4-bromophenyl)prop-2-en-1-one** | 70 |
| LSD 15 | Picture11 | **(2*E*)-1-(4-bromophenyl)-3-(2-nitrophenyl)prop-2-en-1-one** | 72 |

**Table 3. Docking Score and Interactions of Designed Chalcone Derivatives**

|  |  |  |  |
| --- | --- | --- | --- |
| S.NO. | COMPOUNDS | Binding Energy (Kcal/mol)PDB ID: 2H9I | Binding Interaction(Kcal/mol) PDB ID: 2H9I |
| 01. | LSD - 2 | -8.23 | ILE 194 |
| 02. | LSD - 4 | -8.6 | ILE 194 |
| 03. | LSD - 7 | -8.44 | ILE 194, ASP 150 |
| 04. | LSD - 8 | -9.74 | THR 39, GLY 96, PHE 41 |
| 05. | LSD - 9 | -8.11 | TYR 158 |
| 06. | LSD - 10 | -8.31 | ---- |
| 07. | LSD - 11 | -8.7 | ILE 194 |
| 08. | LSD - 12 | -7.96 | ASP 150 |
| 09. | LSD - 13 | -10.4 | 1LE 194 |
| 10. | LSD - 14 | -9.29 | LYS 185 |
| 11. | LSD - 15 | -8.31 | GLY 96 |
|  | Isoniazid | -4.6 | GLY 96,ILE 194 |
|  | Pyrazinamide | -5.72 | ILE 194, TYR 158 |

**Table 4. Physicochemical Properties of the designed Inhibitors**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **S.No.** | **COMPOUNDS** | **TPSA** | **Log P** | **nON** | **nOHNH** | **nviolations** | **nrotb** | **BBB Prediction** |
| 01. | LSD - 1 | 62.90 | 4.58 | 4 | 0 | 0 | 4 | 0.9732 |
| 02. | LSD - 2 | 17.07 | 4.62 | 1 | 0 | 0 | 3 | 0.9952 |
| 03. | LSD - 3 | 17.07 | 5.07 | 1 | 0 | 1 | 3 | 0.9873 |
| 04. | LSD - 4 | 17.07 | 5.07 | 1 | 0 | 1 | 3 | 0.9959 |
| 05. | LSD - 5 | 20.31 | 4.72 | 2 | 0 | 0 | 4 | 0.9927 |
| 06. | LSD - 6 | 37.30 | 5.33 | 2 | 1 | 1 | 3 | 0.8061 |
| 07. | LSD - 7 | 37.30 | 4.12 | 2 | 1 | 0 | 3 | 0.8936 |
| 08. | LSD - 8 | 62.90 | 4.55 | 4 | 0 | 0 | 4 | 0.9732 |
| 09. | LSD - 9 | 44.77 | 4.07 | 4 | 0 | 0 | 6 | 0.9618 |
| 10. | LSD - 10 | 17.07 | 6.13 | 1 | 0 | 1 | 4 | 0.9959 |
| 11. | LSD - 11 | 17.07 | 5.07 | 1 | 0 | 1 | 3 | 0.9959 |
| 12. | LSD - 12 | 37.30 | 5.04 | 2 | 1 | 1 | 3 | 0.8858 |
| 13. | LSD - 13 | 26.30 | 6.35 | 2 | 0 | 1 | 5 | 0.9548 |
| 14. | LSD - 14 | 26.30 | 7.03 | 2 | 0 | 1 | 6 | 0.9685 |
| 15. | LSD - 15 | 62.90 | 4.35 | 4 | 0 | 0 | 4 | 0.9702 |

**Table 5. Toxicity Profile of the designed Chalcone Derivatives**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| S.NO. | ChemicalConstituents | Mutagenicity | Tumorigenic | Irritant | ReproductiveEffect | Drug likeness | Drug Score |
| **01.** | LSD1 | Green | Green | Green | Green | -12.43 | 0.44 |
| **02.** | LSD2 | Green | Green | Green | Green | -5.20 | 0.42 |
| **03.** | LSD3 | Green | Red | Green | Green | -1.23 | 0.28 |
| **04.** | LSD4 | Green | Green | Green | Green | -3.58 | 0.41 |
| **05.** | LSD5 | Red | Red | Green | Green | -6.02 | 0.15 |
| **06.** | LSD6 | Orange | Orange | Green | Green | -3.70 | 0.23 |
| **07.** | LSD7 | Green | Green | Green | Green | -1.78 | 0.49 |
| **08.** | LSD8 | Green | Green | Green | Green | -7.21 | 0.44 |
| **09.** | LSD9 | Green | Green | Green | Green | -0.60 | 0.54 |
| **10.** | LSD10 | Green | Green | Green | Green | -4.54 | 0.34 |
| **11.** | LSD11 | Green | Green | Green | Green | -3.58 | 0.41 |
| **12.** | LSD12 | Green | Green | Green | Green | -1.10 | 0.49 |
| **13.** | LSD13 | Green | Green | Green | Green | -1.83 | 0.36 |
| **14.** | LSD14 | Green | Green | Green | Green | -8.32 | 0.27 |
| **15.** | LSD15 | Green | Green | Green | Green | -8.95 | 0.44 |

**\*Green - Non Toxic ; Red – Highly Toxic**

**Table 6. In-silico Pharmacokinetic Profile of the designed Chalcone Derivatives**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| S.No. | Compounds | **GIA****(**% Absorbed) | **P-gp S** | **CaCo2**(log Papp in 10-6 cm/s) | **CYP 3A4** | **CYP 2D6** | **Log Kp**(-cm/s) | **BA** | **Hepatotoxicity** |
| 01. | LSD - 1 | 93.54 | No | 1.39 | No | No | -5.31 | 0.55 | No |
| 02. | LSD - 2 | 94.528 | No | 1.671 | No | No | -5.37 | 0.55 | No |
| 03. | LSD - 3 | 93.958 | No | 1.523 | No | No | -4.57 | 0.55 | Yes |
| 04. | LSD - 4 | 94.681 | No | 1.111 | No | Yes | -5.20 | 0.55 | No |
| 05. | LSD - 5 | 95.571 | No | 1.064 | No | Yes | -4.76 | 0.55 | Yes |
| 06. | LSD - 6 | 93.336 | No | 1.513 | No | No | -4.71 | 0.55 | No |
| 07. | LSD - 7 | 92.431 | No | 1.417 | No | No | -5.08 | 0.55 | No |
| 08. | LSD - 8 | 93.467 | No | 1.384 | No | No | -5.32 | 0.55 | No |
| 09. | LSD - 9 | 96.504 | No | 1.418 | Yes | Yes | -5.55 | 0.55 | No |
| 10. | LSD - 10 | 94.291 | No | 1.07 | Yes | Yes | -4.83 | 0.55 | Yes |
| 11. | LSD - 11 | 94.681 | No | 1.111 | No | Yes | -5.20 | 0.55 | Yes |
| 12. | LSD - 12 | 91.645 | No | 1.383 | Yes | No | -5.06 | 0.55 | No |
| 13. | LSD - 13 | 94.276 | Yes | 1.084 | No | No | -4.42 | 0.55 | No |
| 14. | LSD - 14 | 95.918 | Yes | 1.091 | Yes | No | -4.20 | 0.55 | No |
| 15. | LSD - 15 | 93.811 | No | 1.381 | No | No | -5.49 | 0.55 | No |
|  | Isoniazid | 92.601 | No | 0.52 | No | No | -7.63 | 0.55 | No |
|  | Pyrazinamide | 92.813 | No | 0.634 | No | No | -7.48 | 0.55 | No |

**\*GIA - Gastrointestinal Absorption ; P - gp S - P glycoprotein Substrate ; Log Kp - Skin Permeability; BA – Bioavailability**

**Table 7. Bioactivity Score and Medicinal Chemistry of the designed Chalcone Derivatives**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| S.No. | Compounds | **GPCR** | **1CM** | **KI** | **NRL** | **PI** | **EI** | **Pain****Alerts** | **Synthetic** **Accessibility** |
| 01. | LSD - 1 | -0.47 | -0.29 | -0.57 | -0.47 | -0.61 | -0.25 | 0 | 2.49 |
| 02. | LSD - 2 | -0.49 | -0.26 | -0.62 | -0.58 | -0.68 | -0.19 | 0 | 2.45 |
| 03. | LSD - 3 | -0.44 | -0.28 | -0.70 | -0.49 | -0.67 | -0.26 | 0 | 2.63 |
| 04. | LSD - 4 | -0.47 | -0.34 | -0.59 | -0.53 | -0.67 | -0.23 | 0 | 2.57 |
| 05. | LSD - 5 | -0.28 | -0.25 | -0.34 | -0.33 | -0.47 | -0.13 | 1 | 2.55 |
| 06. | LSD - 6 | -0.15 | -0.13 | -0.23 | -0.10 | -0.26 | 0.03 | 0 | 2.75 |
| 07. | LSD - 7 | -0.35 | -0.20 | -0.49 | -0.29 | -0.58 | -0.08 | 0 | 2.42 |
| 08. | LSD - 8 | -0.49 | -0.30 | -0.56 | -0.48 | -0.62 | -0.27 | 0 | 2.54 |
| 09. | LSD - 9 | -0.25 | -0.33 | -0.32 | -0.25 | -0.41 | -0.17 | 0 | 3.00 |
| 10. | LSD - 10 | -0.28 | -0.22 | -0.44 | -0.26 | -0.44 | -0.10 | 0 | 2.76 |
| 11. | LSD - 11 | -0.47 | -0.34 | -0.59 | -0.53 | -0.67 | -0.23 | 0 | 2.57 |
| 12. | LSD - 12 | -0.33 | -0.24 | -0.48 | -0.33 | -0.56 | -0.14 | 0 | 2.59 |
| 13. | LSD - 13 | -0.14 | -0.19 | -0.18 | -0.07 | -0.19 | -0.05 | 0 | 2.87 |
| 14. | LSD - 14 | -0.16 | -0.22 | -0.24 | -0.06 | -0.20 | -0.09 | 0 | 3.11 |
| 15. | LSD - 15 | -0.48 | -0.30 | -0.64 | -0.50 | -0.73 | -0.32 | 0 | 2.75 |
|  | Isoniazid | -1.39 | -1.45 | -1.05 | -2.33 | -1.23 | -0.66 | 0 | 1.24 |
|  | Pyrazinamide | -1.97 | -1.45 | -1.71 | -2.87 | -1.84 | -1.43 | 0 | 1.47 |

**\*GPCR - G Protein coupled receptor; ICM -Ion channel modulator ; KI -Kinase inhibitor ; NRL- Nuclear receptor ligand ; PI - Protease inhibitor ; EI -Enzyme inhibitor**

**Table 8. Antimycobacterial activity of Chalcone Derivatives**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| COMPOUNDS | 100 µg/ml | 50 µg/ml | 25 µg/ml | 12.5µg/ml | 6.25µg/ml | 3.125µg/ml | 1.6µg/ml | 0.8µg/ml |
| LSD - 2 | **S** | **S** | **S** | **S** | **S** | **R** | **R** | **R** |
| LSD - 4 | **S** | **S** | **S** | **S** | **R** | **R** | **R** | **R** |
| LSD - 7 | **S** | **S** | **S** | **S** | **R** | **R** | **R** | **R** |
| LSD - 8 | **S** | **S** | **S** | **S** | **R** | **R** | **R** | **R** |
| LSD - 9 | **S** | **S** | **S** | **R** | **R** | **R** | **R** | **R** |
| LSD - 10 | **S** | **S** | **S** | **R** | **R** | **R** | **R** | **R** |
| LSD - 11 | **S** | **S** | **S** | **R** | **R** | **R** | **R** | **R** |
| LSD - 12 | **S** | **S** | **S** | **S** | **S** | **R** | **R** | **R** |
| LSD - 13 | **S** | **S** | **S** | **S** | **S** | **R** | **R** | **R** |
| LSD - 14 | **S** | **S** | **S** | **S** | **R** | **R** | **R** | **R** |
| LSD - 15 | **S** | **S** | **S** | **S** | **S** | **R** | **R** | **R** |

**\*S - Sensitive ; R - Resistant**