RESEARCH PAPER

Synthesis, Characterization and Molecular Docking of γ-lactone with Human Serum Albumin (HSA)

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Abstract: C-H bond activation using Palladium (Pd) as a catalyst is a powerful tool in synthetic organic chemistry. The carboxylate moiety has been recognized as a promising model substrate for the regioselective transformations, since its functionalization is challenging. It is also gaining attention for its varied applications. For generating Pd-catalyzed C-H functionalized products, allyl alcohols have been in use. This paper involves the synthesis of γ-lactone from the reaction of pivalic acid and allyl alcohol, taking the help of a Pd-catalyst and N-, O-, and N-, S-containing ligands, followed by the study of the interactions and binding of γ-lactone with the Human Serum Albumin (HSA) through Molecular Docking studies. The prepared γ-lactone binds the HSA active site *via* hydrophobic interactions.

Keywords: Molecular Docking, HSA, Pd-catalyzed reactions, allyl alcohols, aliphatic carboxylic acids, C-H activation

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1. Introduction

Transition-metal-catalyzed synthetic transformations offer broad strategies for the discovery and development of novel and useful molecules with diverse applications. Palladium (Pd)-catalyzed coupling reaction between aliphatic carboxylic acids and allyl alcohols offers a sophisticated route toward the synthesis of γ-lactone, which is a quintessential scaffold for natural products and pharmaceuticals. Pd serves as an exceptional catalyst in this context (***Docherty et al., 2023***) due to its high regioselectivity and its unique ability to shuttle between Pd(0) and Pd(II) oxidation states (***Curto et al., 2015***), facilitating complex C-H activation and oxidative cyclization without requiring harsh reaction conditions

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(***Hong et al., 2019***). Utilizing aliphatic carboxylic acids as coupling partners is highly beneficial as they are stable, abundant (***Ghosh et al., 2020***), and provide a versatile saturated framework (***Uttry et al., 2020***). The majority of C-(sp3)-H functionalization of carboxylic acids is reported using Pd catalysts, which speaks volumes about its potential to slice C-(sp^3)-H bonds. The robust nature of Pd is owed to its electrophilicity and facile electro-palladation of C-H bonds. The carboxylates are weakly coordinated, and hence, ligands come into play, controlling the reactivity and selectivity of their reactions (***Das et al., 2022***). The use of solvents such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) plays a major role. HFIP acts as a secondary ligand, interacting with the acidic directing group *via* hydrogen bonding and stabilizing the catalytically active Pd-catalyst. N-acetyl containing bidentate ligands have a crucial role carboxylates directed C-(sp^3)-H functionalization (***Das et al., 2021***). Carboxylate groups are abundant in pharmaceuticals and agrochemicals. Therefore, Pd-catalyzed functionalization involving carboxylic acids has drawn attention in recent years (***Dutta et al., 2022***). Meanwhile, allyl alcohols act as powerful, atom-economical building blocks (***Butt et al., 2015***) that allows for the direct construction of the lactone ring. This catalytic approach circumvents the need for pre-functionalized starting materials, making the process more sustainable and streamlined (***Sundararaju et al., 2012***). In 2012, δ-bromo-γ,δ-unsaturated carbonyls were synthesized *via* a Pd-catalyzed, selective tandem reaction between alkynes, $CuBr_2$, and allylic alcohol (***Wen et al., 2012***). In 2017, a group of scientists led by Zhu reported the first example of a general, Pd-catalyzed, selective arylation of β-C(sp^3)–H bonds of aliphatic acids (***Zhu et al., 2017***). Later, in 2018, Gooßen et al. used allyl alcohols for *ortho* allylation of aromatic acids using Ru-catalyst (***Gooßen et al., 2018***). Once the γ-lactone is synthesized, molecular docking serves as a vital computational tool to evaluate its biological "fit" within a protein's binding pocket (***Singh and Singh, 2012***). γ-lactones are common motifs in pheromones and antifungal agents, docking studies help visualize the non-covalent interactions (***Theetharappan et al., 2017***) between the lactone carbonyl and active-site residues (***Salama et al., 2017***) that determine their potency (***Neelakantan et.al., 2018***).

In this paper, we aim to study the interactions and binding of γ-lactone with the Human Serum Albumin (HSA) protein using Schrödinger software to assess their potency against the target protein. γ-lactones were synthesised by reaction between pivalic acid and pent-1-en-3-ol (allyl alcohol) using a Pd-catalyst and N, O and N, S-containing ligands. To compare and, in the hope of improved lactone yield, different ligands have been prepared and tested.

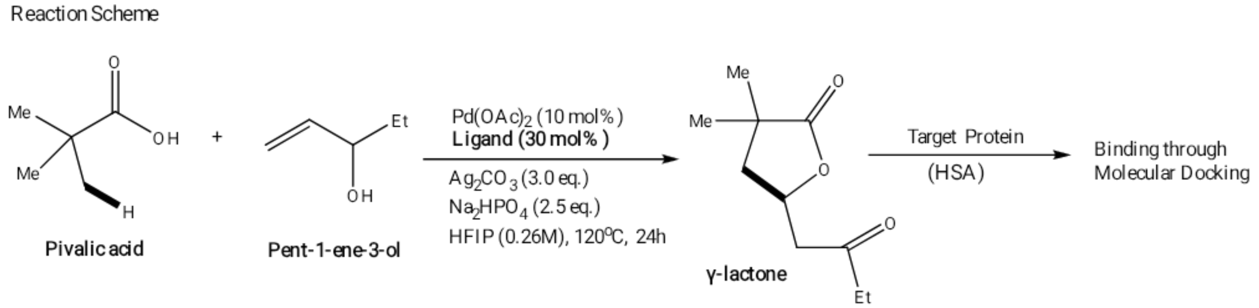
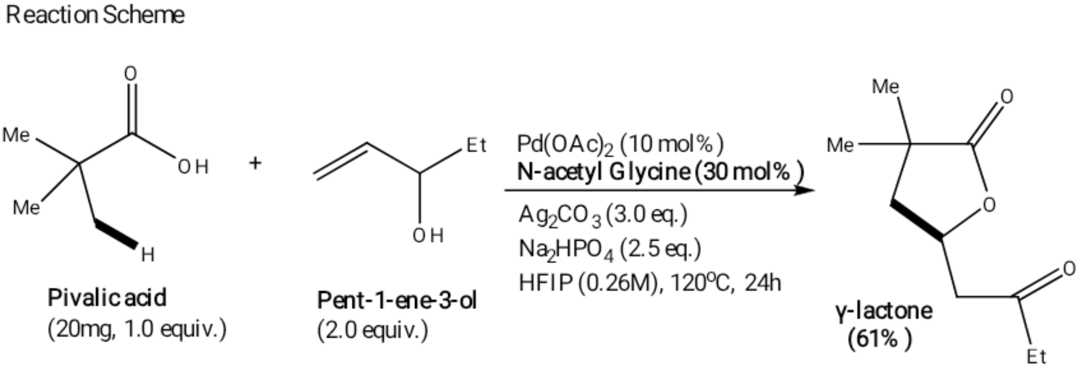


Fig 1: General scheme depicting work strategy

2. Experimental Details

1.0 equiv (20 mg) of pivalic acid substrate and 2.0 equiv of pent-1-en-3-ol coupling partner, 10 mol% $Pd(OAc)_2$ catalyst, 30 mol% N-acetyl glycine ligand, 3.0 equiv of silver carbonate (Ag_2CO_3) oxidant, 2.5 equiv of sodium biphosphate (Na_2HPO_4) base, were treated at 120 ºC in 0.26 molar hexafluoro-isopropanol (HFIP) for 24 hours. The desired γ-lactone was obtained in 61% yield (Figure 2).

Fig 2: Reaction Scheme for the synthesis of γ-lactone



2.1 Screening of Ligands

We started with N-acetyl glycine as the ligand. To improve product yield, we performed the reaction with two additional ligands.

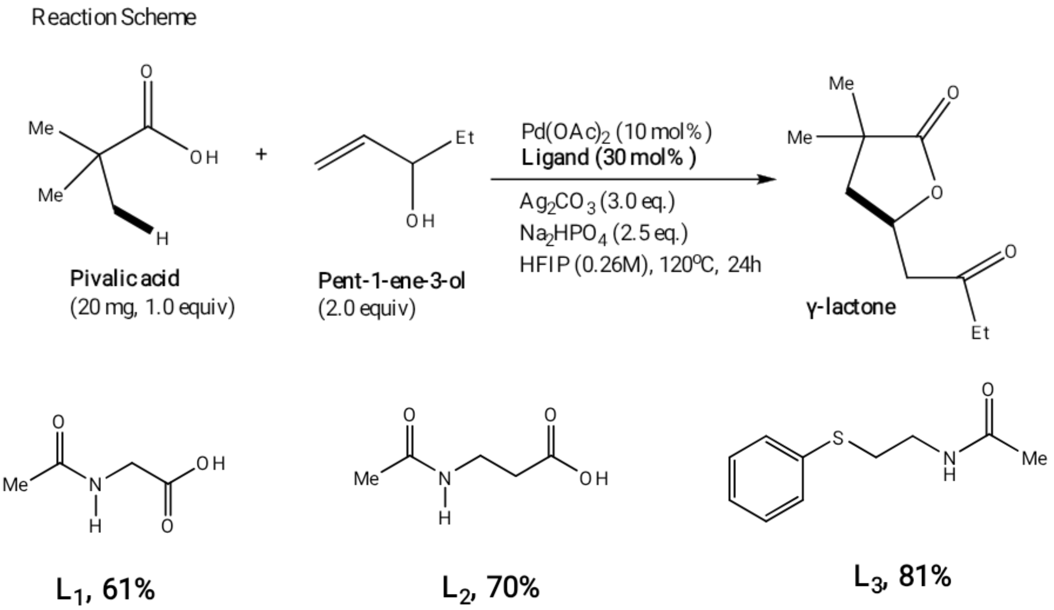


Fig 3: Reaction Scheme for the synthesis of γ-lactones prepared using three different ligands

Initially, the reaction was carried out with ligand L_1 (N-acetyl glycine). The observed yield was 61% (Figure 3). Upon changing the ligand to L_2 (N-acetyl β-alanine), the yield increased to 70% (Figure 3). Further, with the ligand L_3 (N-acetyl ethyl phenyl thioether), the observed yield was 81% (Figure 3). Hence, the best yield obtained was 81% with ligand L_3 (N-acetyl ethyl phenyl thioether).

2.2 Synthesis of Ligands

Ligand L_1: N-acetyl Glycine

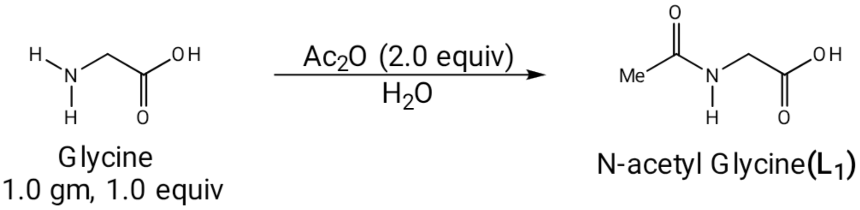


Fig 4: Preparation of N-acetyl glycine

In a clean round-bottom flask, 1.0 g of glycine and 4.0 mL of water were taken. It was mounted on a magnetic stirrer, and the mixture was stirred till glycine dissolved. Then 2.7 mL (2.0 equiv) of acetic anhydride was added. The mixture was further stirred for fifteen to twenty minutes, leading to crystallization of N-acetyl glycine (L1) (Figure 4). The solution was kept in the freezer overnight for effective crystallization. The final precipitate was collected, rinsed with water, and dried at 100–110 °C.

Ligand L_2: N-acetyl β-alanine

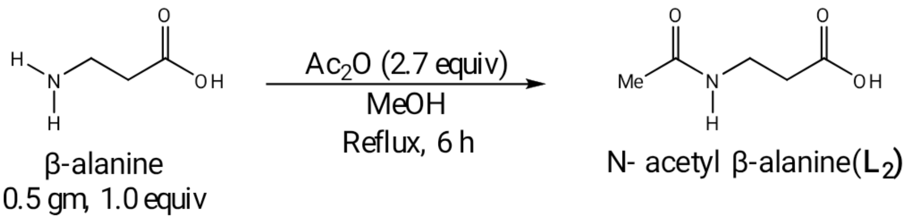
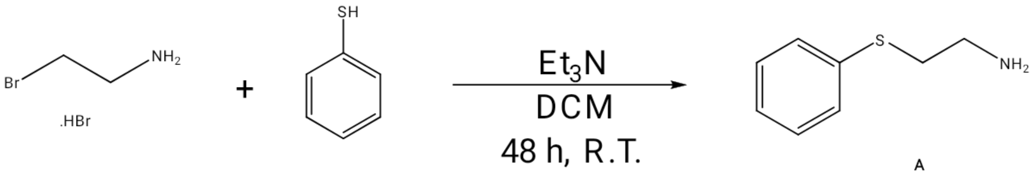


Fig 5: Preparation of N-acetyl β-alanine

To a solution of the amino acid (0.5 g, 1.0 equiv) in MeOH (20 mL), acetic anhydride (2.7 equiv) was added. The mixture was refluxed for 6 hours, then cooled to room temperature. All the volatiles were then removed. The colorless oil obtained was kept in the open air overnight for crystallization. It was dried over a hot-water bath at 100 °C. The *N*-acetyl β-alanine (**L_2**) was observed as a colorless oil (Figure 5).

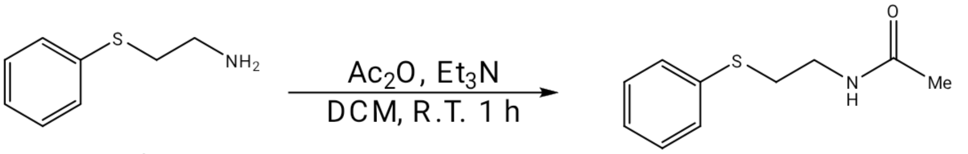
Ligand L_3: N-acetyl ethyl phenyl thioether



A

Fig 6: Preparation of Compound A

Thiophenol (2.12 g, 1.0 equiv) and 2-bromoethylamine hydrobromide (2.0 g, 1.0 equiv) were dissolved in 50 mL DCM. Afterwards, a solution of triethylamine (5.6 mL, 2.1 equiv) in 20 mL DCM was added. The mixture was stirred for 48 hours at room temperature. It was then washed with water, resulting in the separation of the organic phase. It was dried with Na_2SO_4. The solvent was evaporated, and the raw product was cleaned by column chromatography (DCM/MeOH 97:3 V/V). The compound **A** (1.5 gm, 51%) was received as a yellow oil (Figure 6).



A

N-acetyl ethyl phenyl thio ether(**L_3**)

Fig 7: Preparation of N-acetyl ethyl phenyl thioether

Triethyl amine (1.1 mL, 1.2 equiv) and Ac_2O (1.64 mL, 1.2 equiv) were added to the solution of compound **A** (1.5 g) in DCM (25 mL). It was stirred for 1 hour, concentrated in vacuo, and purified by column chromatography, yielding the thioether ligand **L_3** (Figure 7).

2.3 Computational Details

The structure of camptothecin bound to HSA (PDB ID: 4L9K) (Wang et al., 2013) was imported from the open-access Protein Data Bank (www.rcsb.org), maintained by the Research Collaboratory for Structural Bioinformatics (RCSB). The protein was imported and prepared using the Protein Preparation wizard of Schrödinger software (*Schrödinger, Inc.*). For molecular docking, a receptor grid was generated within the prepared protein. For the validation of the docking methodology, bound-camptothecin was used, followed by energy minimization using the Macromodel module (*Mohamadi et al., 1990*) with OPLS-2005 force field (*Jorgensen et al., 1996*) and re-docked. The LigPrep module of Schrödinger was used to prepare ligands, and for docking, the Glide module (*Friesner et al., 2004*) was used.

3. Result and Discussion

For the reaction, pivalic acid and pent-1-en-3-ol were purchased from BLD Pharm. For the synthesis of different ligands, β-alanine, thiophenol, 2-bromoethylamine hydrobromide, and triethylamine were purchased from CDH company. Glycine, acetic anhydride, dichloromethane and sodium sulphate were present in the laboratory.

3.1 Reaction Procedure to Synthesize γ -lactone

To a pressure tube with a magnetic stir bar, $Pd(OAc)_2$ (10 mol%), *N*-acetyl ethyl phenyl thioether (30 mol%), Ag_2CO_3 (3.0 equiv), Na_2HPO_4 (2.5 equiv), pivalic acid, (40 mg) and pent-1-en-3-ol, (2.0 equiv) were added, followed by the addition of HFIP (0.26 M). The pressure tube was tightly sealed with a screw cap and stirred for 5 minutes. Then the sealed tube was placed in an oil bath at 120 °C and stirred for 24 hours, cooled to room temperature and diluted using ethyl acetate. Filtration was performed using a celite/silica plug, and the concentrate was concentrated *in vacuo*. The residual reaction mixture was purified using column chromatography to obtain the pure γ -lactone products. The yield of yellow oil (γ-lactone) was 96%.

3.2 Characterisation of Product (γ-lactone)

3.2.1 Elemental Analysis

Element	No. of Atoms	Atomic Wt.	Mass Contribution	Theoretical %
Carbon(C)	10	12.011	120.11	65.19%
Hydrogen(H)	16	1.008	16.13	8.75%
Oxygen(O)	3	15.999	47.99	26.06%

Total			184.23	100.00%

3.2.2 FT-IR Analysis

Major peaks originating in the graph include carbonyl peak of γ-lactone ring and ketonic group, sp^3 C-H bond stretching and bending peaks and C-O stretching bands. Multiple medium peaks corresponding to sp^3 C-H stretching from the methyl and methylene groups appear at 2850–2980 cm^{-1}. A very strong and sharp peak for the lactone C=O stretch is reflected around 1780 cm^{-1}, and for the ketone C=O stretch, around 1718 cm^{-1}. Bending vibrations for the methyl groups are observed at 1370–1385 cm^{-1} (you may see a "split" here due to the gem-dimethyl group on the ring). Strong C-O stretching bands typical of esters and lactones appear at 1150–1250 cm^{-1} (Fig. 8).

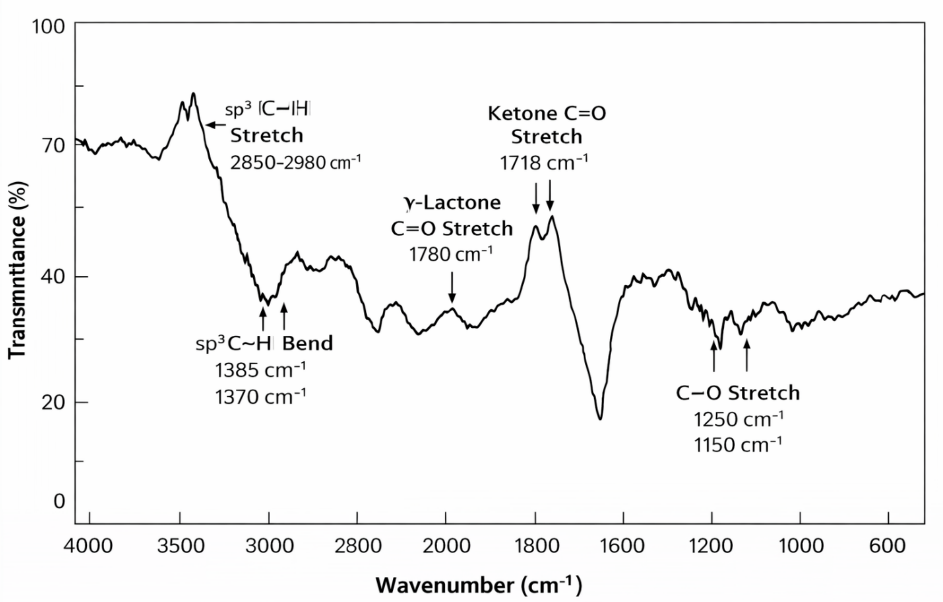


Fig 8: FT-IR of γ-lactones

3.2.3 NMR Analysis

^{1}H NMR (400 MHz, Chloroform-*d*): δ 4.84 (dq, *J* = 12.1, 6.2 Hz, 1H), 2.96 (dd, *J* = 16.9, 6.7 Hz, 1H), 2.62 (dd, *J* = 16.9, 6.0 Hz, 1H), 2.54 – 2.42 (m, 2H), 2.30 (dd, *J* = 12.8, 5.9 Hz, 1H), 1.72 (t, *J* = 11.4 Hz, 1H), 1.25 (s, 6H), 1.05 (t, *J* = 7.3 Hz, 3H) (Fig. 9)

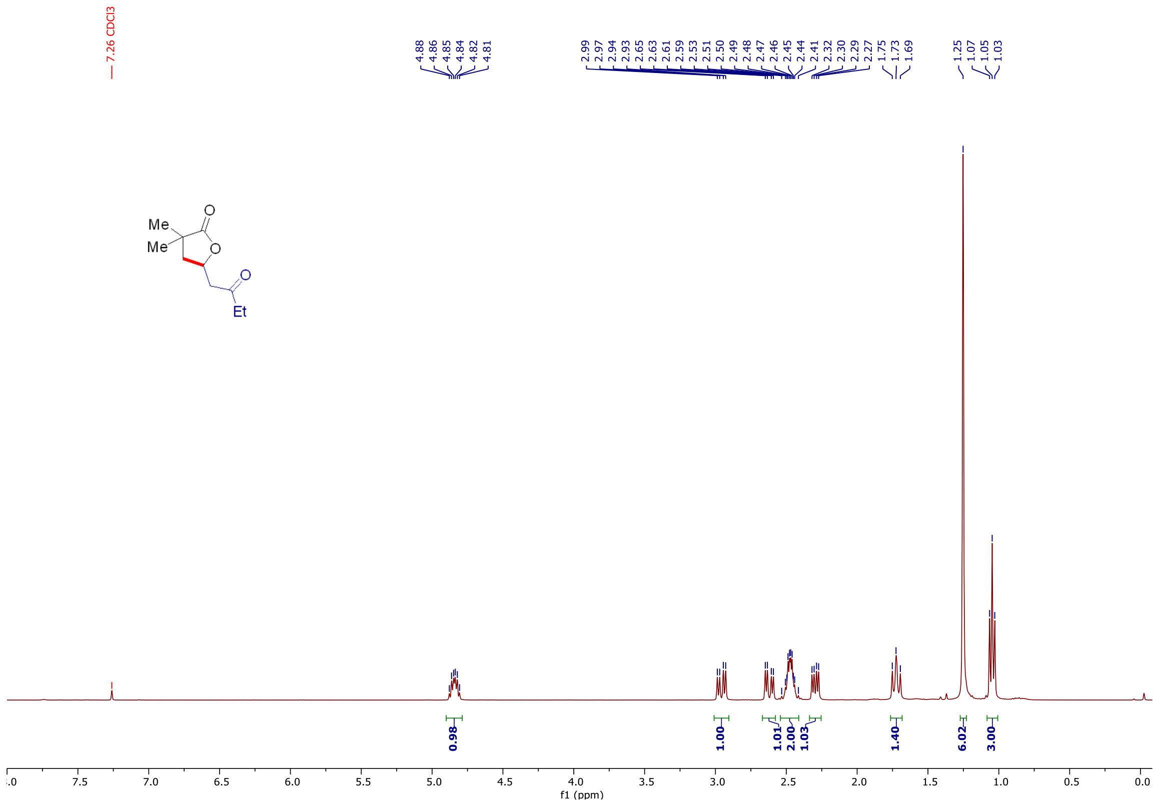


Fig 9: NMR of γ-lactones

3.3 Molecular Docking Studies of the synthesized Ligands

Docking begins with validating the methodology used. For this, the bound inhibitor was re-docked into the prepared protein, and root mean square deviation (RMSD) with respect to the original structure was computed (Fig. 10). The RMSD value has to be less than 2 Å (*Gohlke et al., 2000*), and in our case, it was 0.44 Å, validating the methodology.

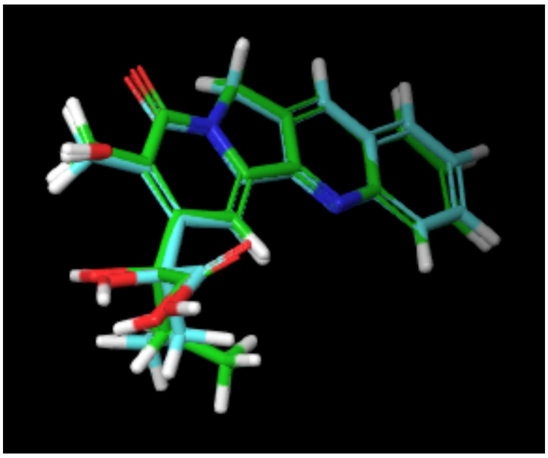


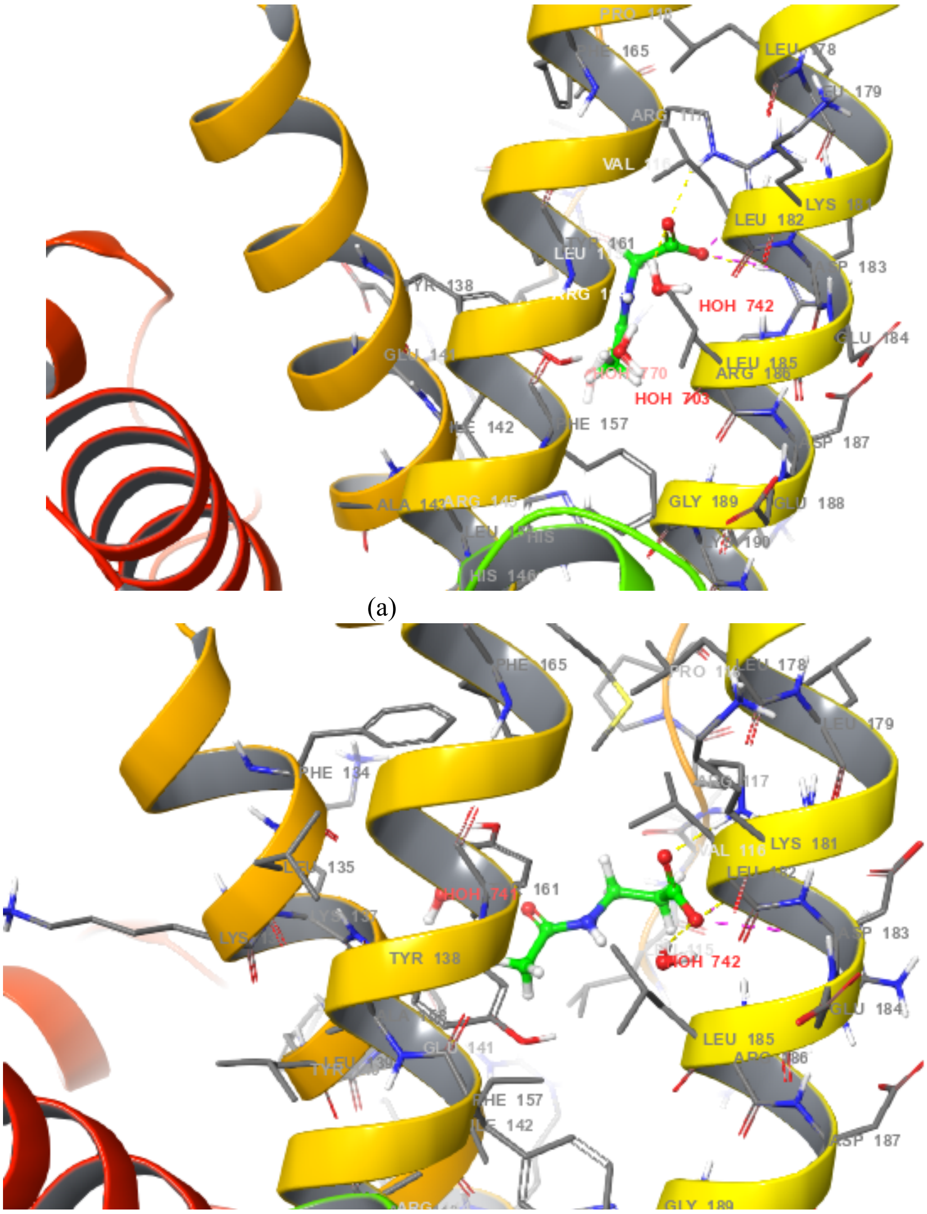
Fig 10: Superimposed structures of bound ligand (cyan) and re-docked ligand (green).

After validating the methodology used, the ligands (L1-L3) were docked into the active site of human serum albumin. Table 1 shows the molecular docking results for the ligands and the bound inhibitor.

Table 1 Docking results of the ligands

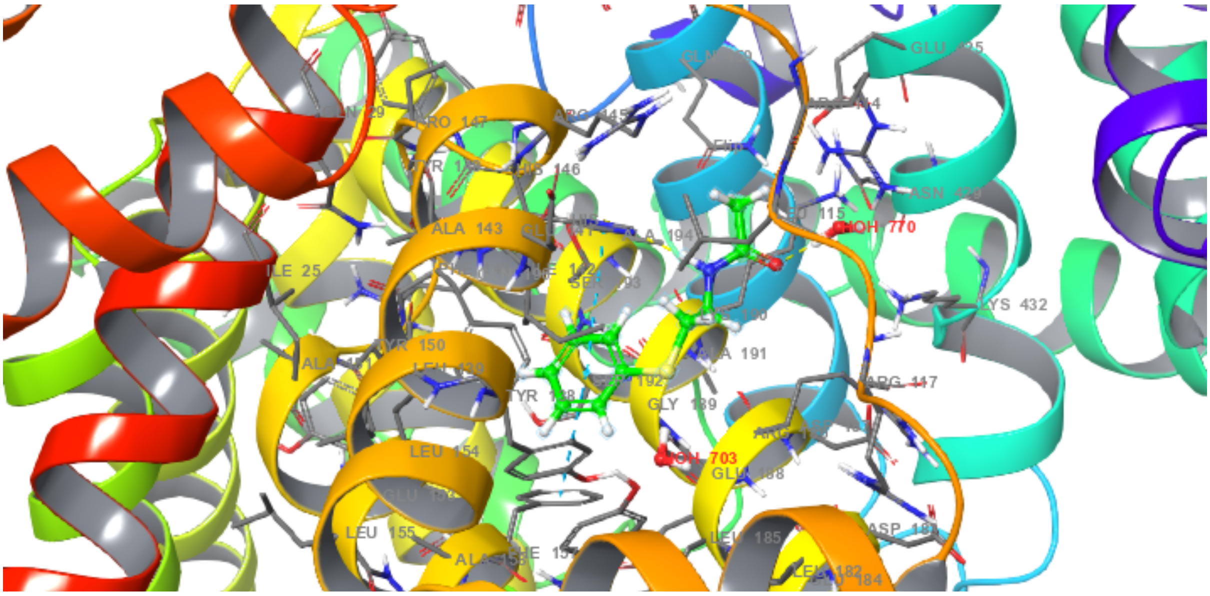
Ligands	Docking Score	Glide E_{vdW}	Glide E_{coul}	Glide Energy
L1	-4.30	-8.35	-10.31	-18.66
L2	-4.47	-10.25	-10.84	-21.09
L3	-5.17	-19.04	-4.30	-23.34
Camptothecin	-9.42	-40.69	-13.99	-54.68

A quick comparison of the docking scores showed that all three synthesized ligands are comparatively less effective in binding to human serum albumin, as compared to camptothecin. However, if a comparison is made among the synthesized ligands, the L3 performs well in comparison to L2 and L1, as reflected by a more negative docking score and glide energy values (Table 1). Figure 11 shows the docked pose of the ligands into the receptor active site. The ligand binding here is governed by the hydrophobic interactions, as reflected by the negative value of van der Waals energy (Glide E_{vdW}) (Table 1). Owing to its larger hydrophobic area, the ligand L3 shows stronger hydrophobic interactions and thus displays better binding efficiency than L1 and L2.



(a)

(b)



(c)

Fig 11: Docking pose of (a) L1, (b) L2 and (c) L3 into the active site of human serum albumin (PDB Id: 4L9K).

3.4 Molecular Docking of γ-lactone

Armed with this knowledge, we proceeded to perform the docking calculations for γ-lactone. The γ-lactone binds to the HSA with a docking score of -5.64. The observed docking score is comparable with respect to L3 (-5.17) but greater than those observed for L1 (-4.30) and L2 (-4.47). Figure 12 shows the binding pose of γ-lactone inside the HSA active site. The γ-lactone primarily interacts with the residue Arg117 through hydrogen bonds with an XP Hbond value of -1.53, a measure of hydrogen bond interaction energy. The carbonyl oxygen of the side chain is involved in making two hydrogen bonds with -HN of Arg117, with CO-----HN bond distances of 2.10 Å and 2.36 Å. The XP Hbond values for L1-L3 were very low, ranging from -0.44 to -0.55. Thus, we can say that the γ-lactone shows better hydrogen bond interactions than the three ligands. The hydrophobic interactions observed in the case of L3 are also present for γ-lactone, with a Glide E_{vdW} value of -18.89.

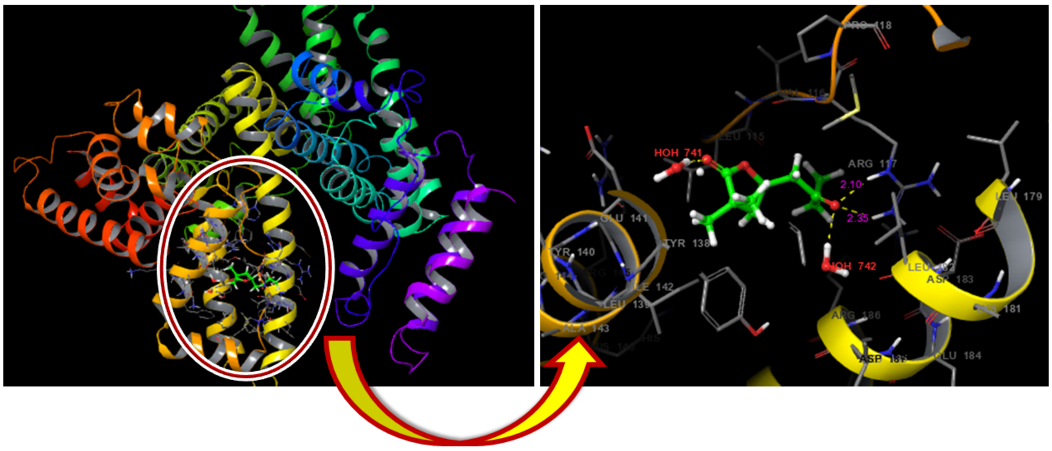


Fig 12: Docking pose of γ-lactone.

3.5 ADMET of the synthesized ligands and γ-lactone

The drug-likeness of the ligands was assessed by performing ADMET studies. Table 2 shows the results of ADMET calculations.

Table 2 ADMET results of the ligands

L	#Star	QPCaco	QPlogBB	QPPMDCK	QPlogKp	QPlogKhsa	Human Oral Absorption	% Human Oral Absorption	Rule of Five	Rule of Three
L1	5	28.432	-0.955	27.874	-4.538	-1.286	2	48.508	0	0
L2	3	34.689	-0.996	31.928	-4.336	-1.187	2	53.345	0	0

L3	1	1429.084	-0.151	2125.293	-1.556	-0.456	3	94.068	0	0
γ-lactone	1	1119.659	-0.445	602.285	-3.013	-0.357	3	87.08	0	0

All three synthesized ligands and γ-lactone show zero violation of the rule of five of Lipinski (Table 2). A compound with zero or fewer violations is more drug-like. Further, the ligands, as well as the γ-lactone, do not violate Jorgensen's rule of three (Table 2). Ligands that do not violate these rules or violate fewer times imply their oral availability. Furthermore, the #star value falls within the recommended range (0-5). It is a measure of the number of properties that fall outside the 95% range of similar values for known drugs. A molecule with a few stars suggests it is more drug-like. The Caco-2 cell (QPPCaco) and MDCK cell permeability (QPPMDCK) are in the acceptable range for all three ligands (> 25 nm/s). L3 and γ-lactone show greater cell permeability than L1 and L2, as reflected by much higher QPPCaco and QPPMDCK values (Table 2). The predicted values for QPlogKhsa, a measure of binding efficiency to human serum albumin, are also in the acceptable range (-1.5-1.5), and L3 and γ-lactone show higher binding efficiency than L1 and L2, as seen from a less negative QPlogKhsa value, which is in accord with docking studies (Table 2). The predicted brain/blood partition coefficient (QPlogBB) and predicted skin permeability are also in the recommended range for all the studied molecules (Table 2). Further, the human oral absorption value is moderate (2) for L1 and L2, but is high (3) for L3 and γ-lactone (Table 2). The percentage human absorption is also high (94.068%) for L3 and γ-lactone (87.080%), but moderate for L1 (48.508%) and L2 (53.345%).

4. Conclusion

γ -lactone is prepared from the reaction of pivalic acid and pent-1-en-3-ol using $Pd(OAc)_2$ as a catalyst, *N*-acetyl ethyl phenyl thioether as a ligand, Ag_2CO_3 as an oxidant, Na_2HPO_4 as a base and HFIP as a solvent. The optimized reaction produced the desired lactone as yellow oil in 96% yield. Various characterization techniques were used to elucidate the structure and formation of γ -lactone. Molecular docking studies of the prepared ligands and γ -lactone was performed against Human Serum Albumin (HSA). The prepared γ-lactone displayed effective binding to HSA, as evidenced by a high docking score and favourable ADMET properties.

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