RESEARCH PAPER

Synthesis, Spectral Characterization and Biological Evaluation of Adamentanecarboxamides Copmounds

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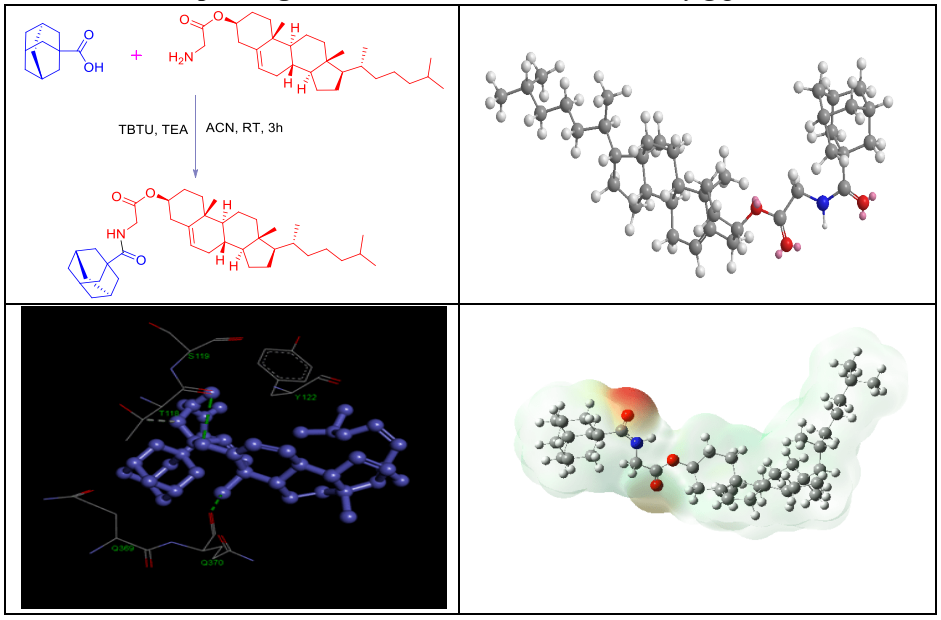

ABSTRACT:

The synthesis of adamentanecarboxamides compounds. The diclofenac sodium was used to reference drug to compare the inhibition of synthesized compounds. **9a** showed highest activity and **7a** good activity than standard at lower concentrations like 10 and 50 µg/ml respectively. But the **3a** and **5a** were showed lower activity. The anti-inflammatory activities of **3a, 5a, 7a** and **9a** are similar to standard diclofenac sodium. Antidiabetic activity was observed for N-((3S,5S)-adamantan-1-yl)benzamide **(3a)** is highest inhibitory activity against the α-amylase enzyme. The N-((3S,5S)-adamantan-1-yl)quinoline-2-carboxamide **(5a)** good inhibition activity. The **(7a)** and **(9a)** exhibited relatively moderate activitys. All the compounds characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR, Mass spectral and CHN analysis.

KEYWORDS: Adamentane carboxamides, Anti-inflammatory activity, Antidiabetic activity and Molecular docking study.

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1. INTRODUCTION:

The incorporation of adamantane fragments in pharmaceuticals has an effect of improving the lipophilicity and stability of drugs. The examples of nitrogen-containing pharmaceuticals derived from adamantane are numerous and usually exhibit antiviral, anti-Parkinsonian or anti-Alzheimer properties[1,2]. The growing interest in materials chemistry in the use of diamondoids for diamond formation, which is an area of research that we are focused on. It has been shown that diamondoids such as adamantine[3–7], (poly) haloadamantanes[8–10], azaadamantanes[11], pentamantane[12] can be used as precursors or seeds of nanodiamonds under high-pressure high-temperature conditions

(HPHT synthesis) and for chemical vapor deposition methods (CVD synthesis).

The drug resistance has been recognized as a major health concern. A leading strategy to fight against resistant pathogens is the development of new effective antimicrobials. Adamantane analogues known for their manifold pharmacological activities. Since the discovery of 1-aminoadamantane (amantadine) and its methyl analogue (rimantadine) as effective M2 inhibitors against influenza virus type A[13], more attention has been paid to the adamantane scaffold. Despite the rapidly acquired resistance to M2-blockers and later to the second approved class of drugs (neuraminidase inhibitors-oseltamivir, zanamivir), the combination therapy of both class of inhibitors represents a good option for the control of resistant influenza viral infections[14]. In addition to the antiviral activity, several newly adamantyl analogues have been found to possess bactericidal or fungicidal activities[15-20]. The adamantine was celebrated (2023) 90 years of adamantane chemistry, since the first isolation of the molecule from Hodonín crude oil and its structural elucidation at the university of chemistry and technology in prague[21]. Since then, this tricyclic molecule has appeared as a building block in organic synthesis alongside other common aliphatic compounds[22]. Many reviews have already summarized original works describing its first preparation[23], industrial synthesis[24], properties[25], reactivity and functionalization[26], and applications of its derivatives in medicine[27–31], catalysis[32], material science[33–36], and other fields. Compounds with a repeating adamantane unit are sometimes called diamondoids (after the diamond crystal lattice)[37,38] and are also extracted from crude oil[39]. Diamantane can be effectively synthesized[40], while higher diamondoids such as triamantane, tetramantane, etc., are typically separated from petroleum by column chromatography[41]. For any other alkane, the first functionalization of adamantane or its congeners is based on the oxidation of the C–H bond to a selected functional group[42]. More recently we have reported the synthesis, spectral characterization, molecular docking, DFT studies and biological evaluation of N-(2-oxo-2-(phenylamino)ethyl)picolinamide derivatives as anti-inflammatory and antidiabetic activity[43]. We report the synthesis, spectral characterization and biological evaluation of adamentanecarboxamides compounds.

2. MATERIALS AND METHODS:

2.1. Experimental:

All chemicals, solvents and reagents were purchased from spectrochem, TCI chemicals, Sigma-Aldrich (AR grade). Reaction progress was monitored by thin-layer chromatography on 0.2 mm precoated aluminum sheet silica gel merck 60 (F254). Melting points of the synthesized compounds were determined by open glass capillary tubes and are uncorrected. FT-IR spectrum of all the products was recorded on PerkinElmer FT-IR-4400 using KBr pellet technique. Proton ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance spectrometer 400 MHz and 100 MHz respectively, DMSO-d_6 or $CDCl_3$ solvents using tetra methylsilane (TMS) as the internal standard. Chemical shift values are given in δ (ppm) scale and the signals are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet), whereas coupling constants (*J*) are expressed in Hz. Mass spectra (ESI-MS) were recorded on SHIMADZU mass spectrometer.

2.1. Typical experimental general procedure for the synthesis of adamentanecarboxamides compounds:

The carboxylic acid was dissolved in acetonitrile, TBTU and triethyl amine was added. The reaction mixture was stirred for 30min and corresponding amine was added. The reaction mixture was stirred for 3h and the completion of the reaction was monitored by thin layer chromatography. The reaction mixture was diluted with ethyl acetate, washed with water and brine solution. The organic layer was separated and dried anhydrous sodium sulfate. The ethyl acetate layer was separated and concentrated under vacuum and the concentrated product was purified by column chromatography on silica gel (Merck, 200-400 mesh, ethyl acetate/petroleum ether, 1:4) to give the products adamentanecarboxamides **(3a)** in 75.0 % yield.

N-((3S,5S)-adamantan-1-yl)benzamide (3a):

FT- IR (KBr) V_{max} cm^{-1}: 3000, 1705, 1632, 1345, 706; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 7.73-7.69 (d, 2H), 7.46-7.40 (d, 3H), 5.81 (s, NH, 1H), 1.79 (s, 6H), 2.13(s, 9H); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 166.6, 136.0, 130.9, 128.4, 126.7, 52.2, 41.6, 36.4, 29.5; **MS**: m/z: 255 (M^+); **Anal. Calcd. for** $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49; **Found**: C, 78.57; H, 8.20; N, 5.34.

N-((3S,5S)-adamantan-1-yl)quinoline-2-carboxamide (5a):

FT- IR (KBr) V_{max} cm^{-1}: 2960, 1612, 1401, 1344, 717; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 8.50 (d, 1H), 8.35 (d, 3H), 7.91 (d, 1H), 7.67 (d, 1H), 7.64 (1H, NH), 2.16 (d, 9H), 1.70 (t, 6H); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 161.8,

150.3, 144.6, 139.3, 131.1, 129.3, 128.4, 128.3, 127.8, 119.4, 52.5, 41.5, 36.5, 29.6; **MS**: m/z: 306 (M^+); **Anal. Calcd. for** $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14; **Found**: C, 78.35; H, 7.19; N, 9.08.

(3R,5R)-N-((3S,5S)-adamantan-1-yl)adamantane-1-carboxamide (7a):

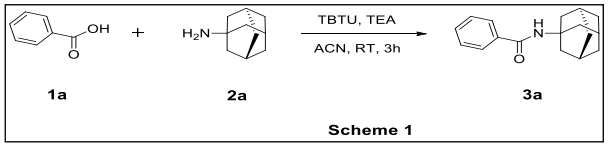
FT- IR (KBr) V_{max} cm^{-1}: 2985, 1619, 1408, 1351, 711; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 5.23 (1H, NH), 2.06-1.92 (m, 15H), 1.80-1.67 (m, 15H); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 177.3, 51.2 41.6 40.9, 39.4, 38.7, 36.6, 36.4, 29.5, 28.2, 27.9; **MS**: m/z: 313 (M^+); **Anal. Calcd. for** $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47; **Found**: C, 80.37; H, 9.79; N, 4.33.

(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11, 12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl-2-((3S,5S)-adamantane-1-carboxamido) acetate (9a):

FT- IR (KBr) V_{max} cm^{-1}: 3400, 2910, 1704, 1633, 1505, 1422, 1324, 1216; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 7.27 (s, 1H, NH), 5.37 (d, 1H), 4.63 (t, 1H), 4.10 (d, 1H), 3.98 (t, 2H), 2.35 (s, 2H), 2.04-1.25 (m, 43H), 1.10 (d, 3H), 0.90 (s, 3H), 0.85 (d, 3H), 0.67 (s, 3H); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 178.1, 169.8, 139.4, 123.0, 75.5, 56.8, 56.2, 50.1, 42.4, 41.6, 40.7, 39.6, 39.2, 37.0, 36.6, 31.9, 28.3, 28.2, 23.9, 22.9, 22.6, 21.1, 19.4, 18.8, 11.9; **MS**: m/z: 605 (M^+); **Anal. Calcd. for** $C_{40}H_{63}NO_3$: C, 79.29; H, 10.48; N, 2.31; **Found**: C, 79.13; H, 10.29; N, 2.22.

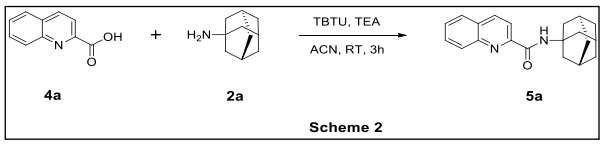
3. RESULTS AND DISCUSSION:

The benzoic acid **(1a)** was dissolved in acetonitrile, TBTU and triethyl amine was added. The reaction mixture was stirred for 30min and adamantan-1-amine **(2a)** was added. The reaction mixture was stirred at RT for 3h. The reaction mixture was monitored by TLC. The synthesis of N-((3S,5S)-adamantan-1-yl) benzamide **(3a)** in good yields **(Scheme 1)**.



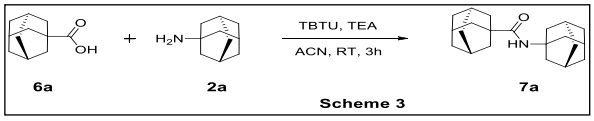
Scheme 1: Synthesis of N-((3S,5S)-adamantan-1-yl)benzamide

The reaction of quinoline-2-carboxylic acid **(4a)** was dissolved in acetonitrile, TBTU and triethylamine was added. The reaction mixture was stirred for 30min and corresponding adamantan-1-amine **(2a)** was added. The reaction mixture was stirred at RT for 3h. The reaction was monitored by TLC. The effective synthesis of N-((3S,5S)-adamantan-1-yl)quinoline-2-carboxamide **(5a)** in good yields **(Scheme 2)**.



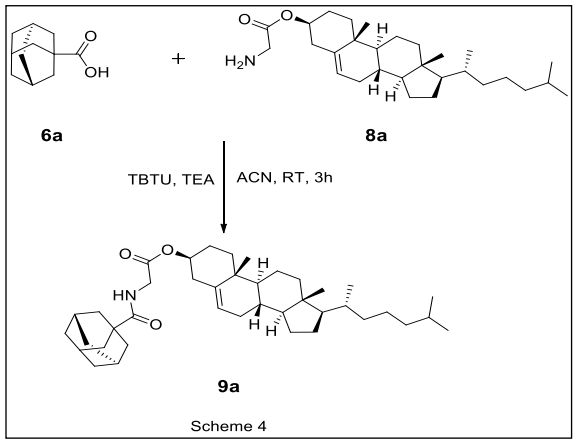
Scheme 2: Synthesis of N-((3S,5S)-adamantan-1-yl)quinoline-2-carboxamide

The synthesis of (3R,5R)-N-((3S,5S)-adamantan-1-yl)adamantane-1-carboxamide **(7a)** in good yields by reacting (3R,5R)-adamantane-1-carboxylic acid **(6a)** was dissolved in acetonitrile, TBTU and triethylamine was added. The reaction mixture was stirred for 30min and corresponding adamantan-1-amine **(2a)** was added. The reaction mixture was stirred at room temperature for 3h. The reaction mixture was monitored by TLC. The synthesis of (3R,5R)-N-((3S,5S)-adamantan-1-yl)adamantane-1-carboxamide **(7a)** in good yields **(Scheme 3)**.



Scheme 3: Synthesis of (3R,5R)-N-((3S,5S)-adamantan-1-yl)adamantane-1-carboxamide

The (3R,5R)-adamantane-1-carboxylic acid **(6a)** was dissolved in acetonitrile, TBTU and triethylamine was added. The reaction mixture was stirred for 30min and corresponding (3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11, 12,13,14,15,16,17-tetrade cahydro-1H-cyclopenta[a]phenanthren-3-yl-2-aminoacetate **(8a)** was added. The reaction mixture was stirred at RT for 3h. The reaction mixture was monitored by TLC. The synthesis of (3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl-2-((3S,5S)-adamantane-1-carboxamido) acetate **(9a)** in good yields **(Scheme 4).**



Scheme 4: Synthesis of (3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11, 12,13,14,15,16,17-tetradecahydro-1H-cyclopenta [a]phenanthren-3-yl-2-((3S,5S)-adamantane-1-carboxamido) acetate

3.1. Ultraviolet Visible Spectral Analysis:

The UV - Visible spectrum was calculated by the time-dependent (TD)-DFT method for the optimized structure using B3LYP/6-311þþG (d, p) basis set associated with the polarizable continuum model (PCM). The observed electronic absorption is 200nm. The calculated electronic absorption is identified as 190nm. This absorption has appeared due to the p- p* transition. The experimental and theoretical absorption spectrums are represented in **Fig. 1**.

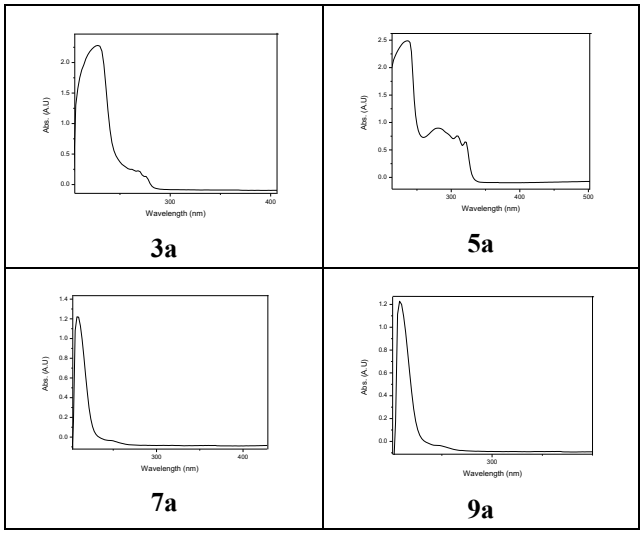


Fig 1 UV spectrum of synthesized (3a, 5a, 7a & 9a) compounds

3.2. FT-IR Spectrum:

The FT-IR spectroscopy studies were effectively; identify the functional groups present in the synthesized adamentanecarboxamides compounds. The range of 400-4000cm^{-1}, the various bands obtained in FT-IR spectrum by using KBr pellet technique are shown in figure 2. The absorption band at 3400cm^{-1} indicates the presence of carboxamide NH. The stretching vibrations are observed at 2910cm^{-1} indicates the presence of aromatic CH group. The sharp absorption band at 11705cm^{-1} indicates the presence of a carbonyl group. The C-N stretching vibrations are observed at 1216cm^{-1}. The C-H bending vibrations are observed at 717cm^{-1}.

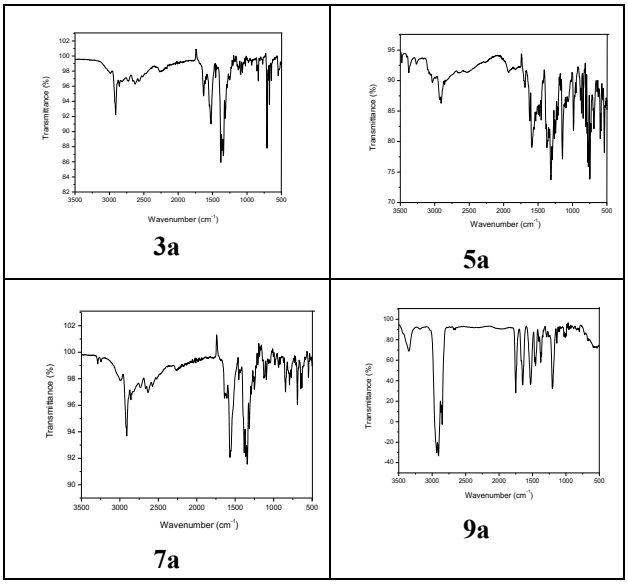


Fig 2 FT-IR spectrum of synthesized (3a, 5a, 7a & 9a) compounds

4. BIOLOGICAL STUDIES:

4.1. Anti-inflammatory Activity:

The standard diclofenac sodium was screened for anti-inflammatory activity by using the inhibition of albumin denaturation technique with minor modification. The compound were dissolved in minimum quantity of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, PH 7.4). The final concentration of DMF in all solution was less than 2.5%. Test solution (2.5ml) containing different concentrations of the drug was mixed with 1ml of 1mm bovine serum albumin solution in phosphate buffer and incubated at 37^{0}C in an incubator for 10min. Denaturation was induced by keeping the reaction mixture at 70^{0}C in a water bath for 10min. After cooling, the turbidity was measured at 660nm. The percentage inhibition of denaturation was calculated by using the formula.

The mechanism of the anti-inflammation activity of adamentane carboxamides to inhibit protein

denaturation was studied using the BSA denaturation technique. The diclofenac sodium used to reference drug. The **9a** is highest activity and **7a** good activity. The lower concentrations like 10 and 50µg/ml respectively. But the **3a** and **5a** were showed lower activity than standard. The anti-inflammatory activities of **3a, 5a, 7a** and **9a** are similar to standard drug. **Fig. 3.**

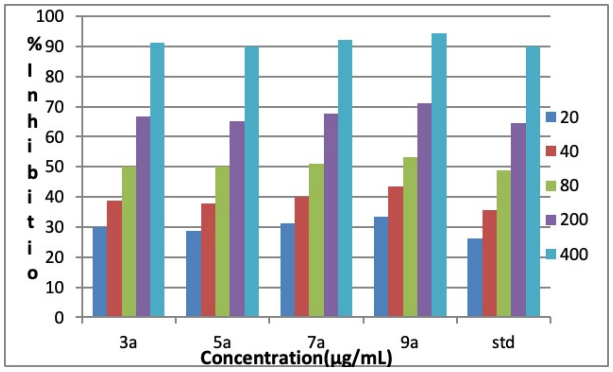


Fig 3 Anti-inflammatory activity of synthesized compounds

4.2. Antidiabetic Activity:

The antidiabetic activity of the samples by using α-amylase inhibition method. Amylase (0.2%) was incubated with and without samples (1.5ml) and standard for 10min at 25^0C. This experiment was performed in 0.2M phosphate buffer (pH 6.9). After pre incubation, the 1% starch solution (0.5ml) was added and the reaction mixture was incubated for 30 min at 25^0C. In order to stop the enzymatic reaction, DNSA reagent (0.5ml) was added as the color reagent and then incubated in a boiling water bath for 90min. After cooling down to the room temperature, 0.5 ml of samples was diluted to 2.5ml of distilled water and the absorbance measured at 540nm using a UV-Visible spectrophotometer.

The α-amylase is a reduction of postprandial hyperglycemia in diabetic conditions. The percentage inhibitions are different concentrations 20, 50, 100, 250 and 400µg/ml respectively **(Fig. 4).** The N-((3S,5S)-adamantan-1-yl)benzamide **(3a)** showed highest inhibitory activity against the α-amylase enzyme. The N-((3S,5S)-adamantan-1-yl)quinoline-2-carboxamide **(5a)** showed the good inhibition activity. The **(7a)** and **(9a)** exhibited relatively moderate activity to standard acarbose.

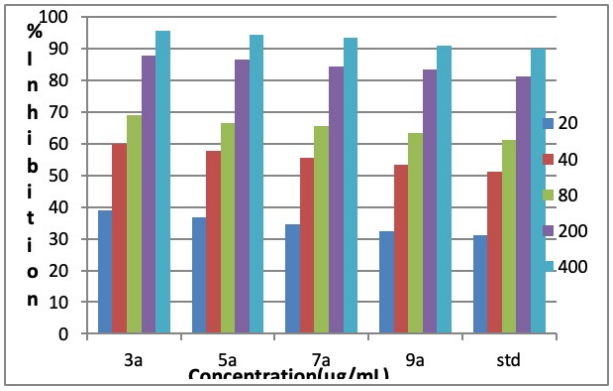


Fig 4 Anti-diabetic activity of synthesized compounds

4.3. Molecular Docking Study:

Molecular docking of synthesized compounds into the α-amylase, **3a, 5a, 7a** and **9a** was carried out by using the Auto-Dock Vina software. Accelrys discovery studio client 4.1 visualizer was used for the visualizing protein-ligand complex. Three dimensional structures of synthesized compounds were constructed using ChemBio 3D ultra 13.0 software and then they were energetically minimized by using MMFF94 with 5000 iterations and minimum RMS gradient of 0.10. The crystal structure of α-amylase (1HNY, 1PGG, 4COX and 3V03) were taken from protein data bank. The ligand were eliminated from the protein and polar hydrogen was added. All the docking a grid box size of 60x60x60 points in X, Y and Z direction. A grid spacing of 0.375Å and ten runs were generated by using lamarckian genetic algorithm searches.

The α-amylase (1HNY) was selected as enzyme [44] and the discovery studio was used for visualizing the enzyme-ligand complexes. The preparation of the target for docking, polar hydrogen was added with Kollman charges. The target file was saved as pdb format and the grid box was generated. The preparation of ligand, adamentanecarboxamides were drawn by ChemDraw software and optimized using Gaussian 09W software. The prepared ligands were saved in pdb format.

3a formed three hydrogen bonds, two conventional hydrogen bonds with amino acid residue (HIS299, ASP300) with corresponding bond distances of 2.72Å and 2.91Å, one pi-donor hydrogen bond with amino acid residue (TYR62) with corresponding bond distances of 3.56Å with better binding energy -6.46. **5a** formed three hydrogen bonds, two conventional hydrogen bonds with amino acid residue (ASP300, HIS299) with corresponding bond distances of 2.94Å

and 2.79Å, one pi-donor hydrogen bond with amino acid residue (TYR62) with corresponding bond distances of 3.37Å with better binding energy -7.53. **7a** formed two conventional hydrogen bonds with amino acid residue (GLN63, ASP300) with corresponding bond distances of 3.24Å and 3.18Å with better binding energy -7.73. **9a** formed one pi-donor hydrogen bond interaction with amino acid residue (TYR62) with corresponding bond distances of 3.95Å with better binding energy -9.16. The corresponding interaction of designed compounds against α-amylase enzyme (1HNY) as given below **fig: 5**. The **3a, 5a, 7a and 9a** no hydrogen bonds formed. The corresponding interaction of designed compounds against α-amylase enzyme (1HNY) as given below **fig: 6.**

3a formed five hydrogen bonds, one conventional hydrogen bonds interaction with amino acid residue (ALA527) with corresponding bond distances of 3.12Å, two carbon hydrogen interaction with amino acid residue (GLY524 & SER530) with corresponding bond distances of 3.12Å & 2.94Å, two pi-donor hydrogen bond interaction (TYR385 & PHE518) with corresponding bond distances of 3.68Å & 4.17Å with better binding energy -8.29. **5a** no hydrogen bonds formed. **7a** formed seven hydrogen bonds, four conventional hydrogen bonds interaction with amino acid residue (THR212, PHE210, PHE210 & GLN289) with corresponding bond distances of 3.27Å, 2.68Å, 2.72Å and 2.92Å, two carbon hydrogen interaction with amino acid residue (LSY211 & HIS201) with corresponding bond distances of 3.57Å and 3.52Å, one pi-donor hydrogen bond interaction (HIS201) with corresponding bond distances of 4.09Å, with better binding energy -7.29, **9a** formed three hydrogen bonds, two conventional hydrogen bonds interaction with amino acid residue (GLN370 & THR118) with corresponding bond distances of 2.76Å & 3.27Å, carbon hydrogen bond interaction (THR118) with corresponding bond distances of 3.11Å with better binding energy -3.43. The corresponding interaction of designed compounds against α-amylase enzyme (4COX) as given below **fig: 7.**

The enzyme 4COX, **7a** is good docking results and inhibition constant, **3a** & **9a** better docking results. The enzyme 1HNY, **3a, 5a, 7a & 9a** moderate docking results. The similar results were obtained in the experimental α-amylase inhibitory assay. The docked complexes were represented in **Fig. 5, Fig. 6 and Fig. 7** Molecular docking of protein-ligand were represented in **Table 1.**

Sample Code	Enzyme Code	Binding Energy (Kcal/mol)	Inhibition Constant	No of Hydrogen bonding	Hydrogen bonding amino acid Residue
3a	1HNY	-6.46	18.55μM	3	HIS299(2.72Å) conventional hydrogen bond interaction, ASP300(2.91Å) conventional hydrogen bond interaction and TYR62(3.56Å) pi-donor hydrogen bond interaction
5a	1HNY	-7.53	3.03μM	3	ASP300(2.94Å) conventional hydrogen bond interaction, HIS299(2.79Å) conventional hydrogen bond interaction and TYR62(3.37Å) pi-donor hydrogen bond interaction
7a	1HNY	-7.73	2.16μM	2	GLN63(3.24Å) conventional hydrogen bond interaction and ASP300(3.18Å) conventional hydrogen bond interaction
9a	1HNY	-9.16	194.67nM	1	TYR62(3.95Å) pi-donor hydrogen bond interaction
3a	1PGG	-5.81	54.74μM	0	-
5a	1PGG	-7.18	5.5μM	0	-
7a	1PGG	-7.01	7.33μM	0	-
9a	1PGG	-7.14	5.84μM	0	-
3a	4COX	-8.29	835.91nM	5	ALA527(3.12Å) conventional hydrogen bond interaction, GLY524(3.12Å) carbon hydrogen bond interaction, SER530(2.94Å) carbon hydrogen bond interaction, TYR385(3.68Å) pi-donor hydrogen bond interaction and PHE518(4.17Å) pi-donor hydrogen bond interaction
5a	4COX	-7.34	4.17μM	0	-
7a	4COX	-7.29	4.56μM	7	THR212(3.27Å) conventional hydrogen bond interaction, PHE210(2.68Å) conventional hydrogen bond interaction, PHE210(2.72Å) conventional hydrogen bond interaction, GLN289(2.92Å) conventional hydrogen bond interaction, LSY211(3.57Å) carbon hydrogen bond interaction, HIS201(3.52Å) carbon hydrogen bond interaction and HIS207(4.09Å) pi-donor hydrogen bond interaction
9a	4COX	-3.43	3.04mM	3	GLN370(2.76Å) conventional hydrogen bond interaction, THR118(3.27Å) conventional hydrogen bond interaction and THR118(3.11Å) carbon hydrogen bond interaction

Table: 1 Parameter calculated from molecular docking experiments

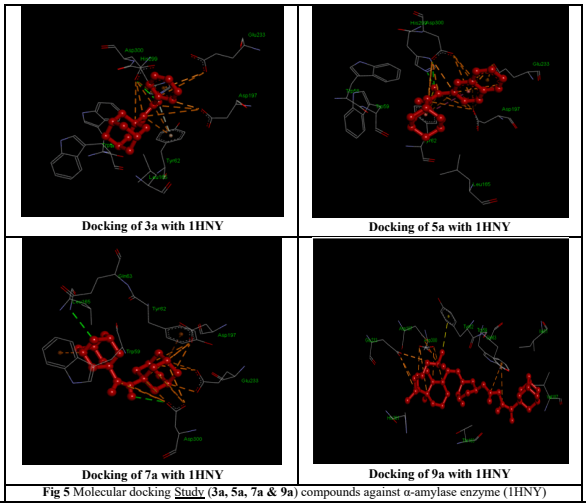


Fig 5 Molecular docking Study (**3a, 5a, 7a & 9a**) compounds against α-amylase enzyme (1HNY)

4.4. Computational Calculations:

The computational calculations including representation of HOMO, LUMO, molecular electrostatic potential (MEP) and mulliken population

analysis (MPA). The checkpoint file was developed the gaussian 09W program using DFT methods. The chemical structure of the QCKs was optimized with B3LYP/6-31G basis set. The gauss view used to visualize the computed structures including frontier molecular orbitals, MEP representation.

4.5. Frontier Molecular Orbital's:

HOMO is an electron donor, the highest energy orbital. LUMO is an electron acceptor, the lowest energy orbital. HOMO, LUMO is orbital energy are important role of electrical properties, biological activities and chemical properties of the compounds [45-47]. The HOMO and LUMO energy gap predict the stability and chemical reactivity of the compounds.

The negative value of HOMO and LUMO indicated that the adamentanecarboxamides are stable molecules. The energy gap of **3a** in the range of -6.2974 to -0.1561 eV. The band gap is role in chemical reactivity and stability. The lower band gap value is more chemical reactivity. Soft molecules more reactive than hard molecules because easily electrons acceptor.

The **3a**, band gap of **7a** is lower than **5a** and **9a**, the **7a** is the more reactive. The other parameters like chemical potential, hardness, softness and electrophilicity the**7a** is more reactive compounds. The binding energy of **7a** is better than others (**Table 2)**. The frontier molecular orbitals are represented in **Fig. 8** and **9.**

Table 2 DFT calculations

S. No	Compound Name	HOMO eV	LUMO eV	Band gap(ΔE)	Electro negativity	Chemical potential	Global hardness
1	**3a**	-6.2974	-0.1561	6.1412	3.2267	-3.2267	3.0706
2	**5a**	-6.3463	-1.8849	4.4614	4.1156	-4.1156	2.2307
3	**7a**	-6.1463	0.7366	6.8830	2.7048	-2.7048	3.4415
4	**9a**	-6.2443	-0.5562	5.6881	3.4002	-3.4002	2.8440

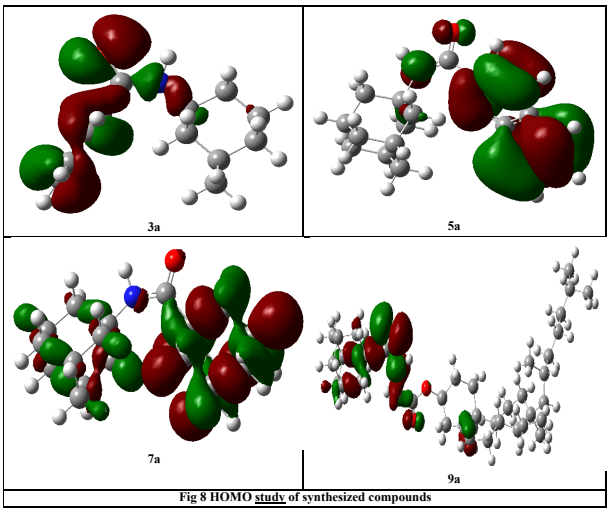


Fig 8 HOMO study of synthesized compounds

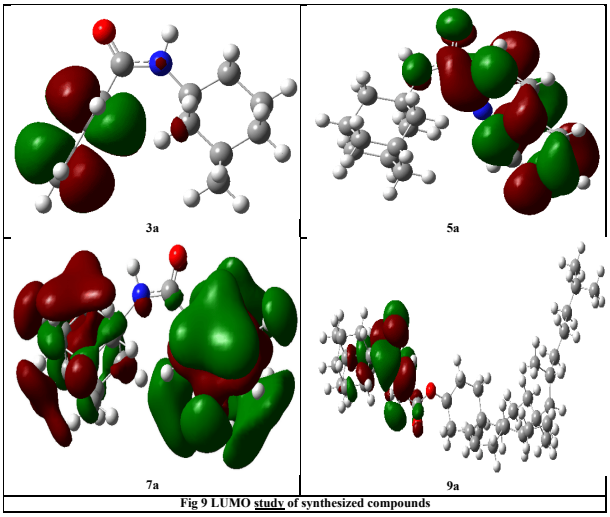


Fig 9 LUMO study of synthesized compounds

4.6. Molecular Electrostatic Potential (MEP):

MEP is used to electrophilic and nucleophilic sites of the molecules. The different colors and values in MEP are indicated the electrostatic potential. Red, blue and green colour indicates the electrophilic, nucleophilic reactivity and zero electrostatic potential respectively. The blue colour indicates the strongest attraction and red colour indicates the strongest repulsion [25]. The negative potential has been used to identify the binding region of the ligand for the interaction of biomolecule. The **3a** most negative potential at the carbonyl of carboxamide. The **5a** negative potential at pyridine ring and carbonyl of carboxamide. The **7a** and **9a** negative potential is carbonyl of carboxamide. The representation of MEP was given in **Fig. 10.**

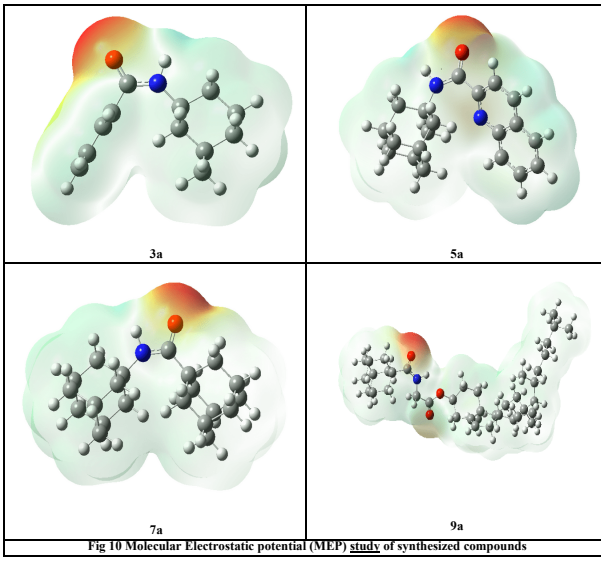


Fig 10 Molecular Electrostatic potential (MEP) study of synthesized compounds

5. CONCLUSION:

The synthesis of adamentanecarboxamides compounds. The anti-inflammatory activity of synthesized compounds. The diclofenac sodium was used as a reference drug to compare the inhibition of synthesized compounds. **9a** showed highest activity and **7a** good activity than standard at lower concentrations like 10 and 50µg/ml respectively. The anti-inflammatory activities of **3a, 5a, 7a** and **9a** are similar to standard diclofenac sodium. Antidiabetic activity was observed for N-((3S,5S)-adamantan-1-yl)benzamide **(3a)** showed highest inhibitory activity against the α-amylase enzyme. The N-((3S,5S)-adamantan-1-yl)quinoline-2-carboxamide **(5a)** showed the good inhibition activity. The **(7a)** and **(9a)** exhibited relatively moderate activity. The molecular docking studies clearly showed that the enzyme 4COX, **7a** is good docking results and inhibition constant, **3a** & **9a** better docking results. The enzyme 1HNY, **3a, 5a, 7a & 9a** moderate docking results.

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