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β-amino carbonyl derivatives: Synthesis, Molecular Docking, ADMET, Molecular Dynamic and Herbicidal studies.

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In the current report, 3D structures of the enzyme **Lathyrus aphaca Ribulose bisphosphate carboxylase (LArbcL)** was modeled using homology modeling. The structures of the synthesized β-amino carbonyl derivatives were made by means of "Chem Draw ultra-12.0", ADMET prediction were conducted to compute physicochemical properties. Pharmacokinetics studies and the molecular docking study of the synthesized compounds were performed against Lathyrus aphaca **Ribulose bisphosphate carboxylase**. Docking experiments verified a significant Docking Score values between 6.2 to 7.3 kcal mol^{-1}. The highest-ranking complexes obtained from docking results were subjected to 100 ns Molecular Dynamics simulations using Gromacs program to investigate the constancy of the docked "protein–ligand complexes" as well as the oscillation and conformational variations that occur during protein–ligand interaction. The synthesized derivatives were screened for pre-emergence and post-emergence herbicidal activity adjacent to weed species named Lathyrus aphaca with concentrations of "0.005 M, 0.01 M and 0.02 M", and the activity was compared with Butachlor and penoxulum which are standard herbicide. Every single synthesized compounds show good to moderate activity.

Introduction

"β-aminocarbonyl compounds" are vital construction block designed for the production of physiologically and medicinally significant substances. They serve as significant intermediates in the production of compounds such as "β-amino alcohols, β-amino acids, and lactams", which are used in a variety of "pharmaceutical and natural product syntheses".[1–5] Antimicrobial, anti-inflammatory, anticonvulsant, anticancer, and other medicinal medicines have been developed from derivatives of β-aminocarbonyl molecules.[6–8]

Rubisco [ribulose-1,5-bisphosphate (RuBP) carboxylase] is the most abundant protein in plants,[9] and it is an enzyme that catalyses the CO_2 fixation reaction in photosynthesis, forming phosphoglycerate (PGA), as well as photorespiration, forming phosphorglycolate and PGA with the reaction to O_2.[10] Because it accounts for about 30% of total protein in *"Lathyrus aphaca"* leaves, it is of great interest in terms of plant nitrogen nutrition. The catalytic mechanisms, lack of specificity, control, and turnover features have all piqued biochemists' curiosity. Physiologists have been concerned about the effects of Rubisco's features on the gas exchange characteristics of photosynthetic tissues, as well as the amount of nitrogen bound up in the enzyme and it's recycling during leaf senescence.

"Lathyrus aphaca" is a medium-height rambling or scrambling annual broad-leafed weed. It is a member of the Fabaceae family that attacks wheat crops in both rain-fed and irrigated environments. In the rice-wheat cropping system, it is a problematic weed. It germinates from October to November and matures in early April, just ahead of the wheat crops. It scatters its seeds in the field beforehand wheat harvest, expanding the soil weed seed bank and causing problems in the winter crop.[11,12]

Herbicide is a chemical which is used to destroy or slow down the expansion of undesired plants such as weeds and insidious genus in housing and agricultural area. Weeds compete for sunlight, water, and nutrients with other plant kinds. "Weeds" are also able to control plant spreading out, causing a reduction in crop assembly and dominance.[13–15] Chemical herbicides supply numeral reward over mechanical weed management, which include effortlessness of application, which can save money and labor. Although most herbicides are generally safe to animals and people, they can kill non target plants and the insects that rely on them, especially when used aerially. The defense of crops has repeatedly expressed a desire for the discovery of new innovative herbicides. Herbicides, on the other hand, can be used to achieve automatic and extensive cropping. Herbicide can be classified on the basis of mode of action as selective and nonselective which may further be classified into contact, systemic and residual and on the basis of

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time of action they may classified as pre-planting, pre-emergence and post-emergence herbicides. Farmers' weed-killing herbicides also assist to amplify food production and the financial system also represents a concealed threat to people, animals, and the environment. Herbicides supply to effluence and ailments range from skin annoyance to tumor. Novel herbicides with a known or maybe new mode of action and no hazardous or harmful effects on humans, animals, or the environment are being required.[16] Chemical compounds' physicochemical properties are frequently used to guide the design and selection of chemical libraries.[17] These characteristics properties are mostly related to chemical compounds' "absorption, distribution, metabolism, and excretion (ADME)" characteristics, which have a significant impact on their pharmacokinetic profiles. For many pesticides, including diverse subsets of herbicides, the distributions of physicochemical character and straightforward structural features have been investigated. For many pesticides, including diverse subsets of herbicides, the distributions of physicochemical qualities and simple structural features have been investigated. Herbicide-likeness rules (analogy to drug-likeness rules) have been discovered as a result of these investigations, making it easier to design and create new herbicide compounds.[18,19] Many software and online tools such as OSIRIS Property Explorer,[20] Swiss ADME,[21] "ALOGPS 2.1 (http://www.vcclab.org/lab/alogps/) and CERTARA (https://www.certara.com/software/)" are used for ADME prediction.

Medicine finding is extensive procedures that take about 10–12 years and can be highly expensive when it comes to bringing a medicine to sell. It is a multistep procedure that begins by way of the recognition of a feasible drug object, follow through drug target justification, strike to escort finding, lead molecule optimization, and preclinical and experimental research. "Computer-aided drug design" is a novel computer tool designed for identifying and developing a promising lead in the drug discovery process.[22] "Computer-aided drug design" has a long history of success and continues to play an important role in medication development. These are mathematical tools for manipulating and quantifying the attributes of possible drug candidates. A variety of publicly and commercially available software applications are among them.[23] CADD can be performed through many approaches as "structure based drug design, molecular docking, Virtual screening, Inverse docking, Ligand based drug design and molecular dynamics simulation".[24] "Molecular docking" is a computer technique that generates a obligatory representation by predicting the interaction of two molecules.[25] For molecular docking, there are numerous servers, suites, and tools available such as AUTODOCK Vina,[26,27] GOLD,[28] Moldock,[29] AUTODOCK,[30] Chimera.[31] Chemdraw[32] is used to draw the ligands and the receptor molecules are downloaded from Protein data bank.[33] MD simulations anticipate how each atom in a protein or other molecular system will move over time based on a common understanding of the physics underlying inter-atomic interactions. They might unveil the positions of every atom at little second chronological accuracy and allow them to imprison a broad choice of serious bio molecular processes such as "conformational change", "ligand binding, and protein folding". Importantly, these simulations preserve to anticipate the response to bio molecules through perturbations like "mutation, phosphorylation, protonation", or the accumulation or elimination of a ligand at the atomic stage. Numerous forces field are usually used in "molecular dynamics simulations" are "AMBER,[34] CHARMM,[35] and GROMOS".[36,37] These vary mainly in the mode of parameterized but usually provide comparable outcome. In this report we have worked on the preparation of novel, green and nontoxic herbicide.

Result and Discussion

Homology modeling of Lathyrus aphaca Ribulose bisphosphate carboxylase (LArbcL) and the target template sequence alignment

SWISS-MODEL was used to create a 3D structure of LArbcL, which had a GMQE of 0.97 and a QMEAN of 0.88, and was found to be the contiguous template to LArbcL with a correspondence identity of 94.23 percent and a sequence resemblance of 0.61. The QMEAN score of 0.88 and the GMQE value of 0.97 designate that the modeled arrangement is dependable and of high-quality. The reference protein and its alignment with modeled protein are shown in Figure 1. Evaluating superposition across all 433 fully populated columns in the final alignment: RMSD of align.pdb, chain A with modeled protein.pdb, chain A : 0.263

Overall RMSD: 0.263; Sequence lengths: 465 433; SDM (cutoff 5.0): 5.257; Q-score: 0.924

Structure validation of modeled protein

The projected local resemblance to target was shown against the predicted 3D arrangement of the modeled protein's residue number in a graphic (Figure 2a). The majority of the residues had values close up to 1, signifying that the anticipated model's restricted quality assessment of the residues is good. Low-quality residues were defined as those with values less than 0.6. The modeled protein arrangement is also inside the range of other protein structures in the Protein Data Bank, indicating that it is reliable (Figure 2b)

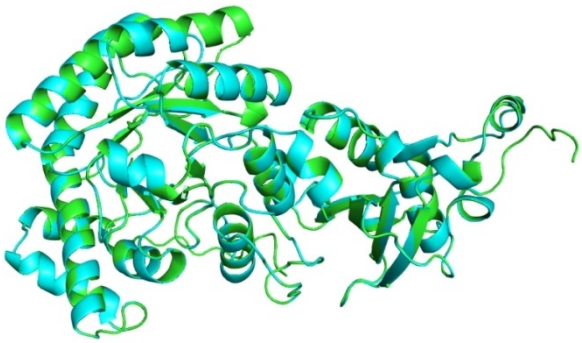


Figure 1. Structure of reference protein (green color) is aligned to the modeled protein (cyan color)

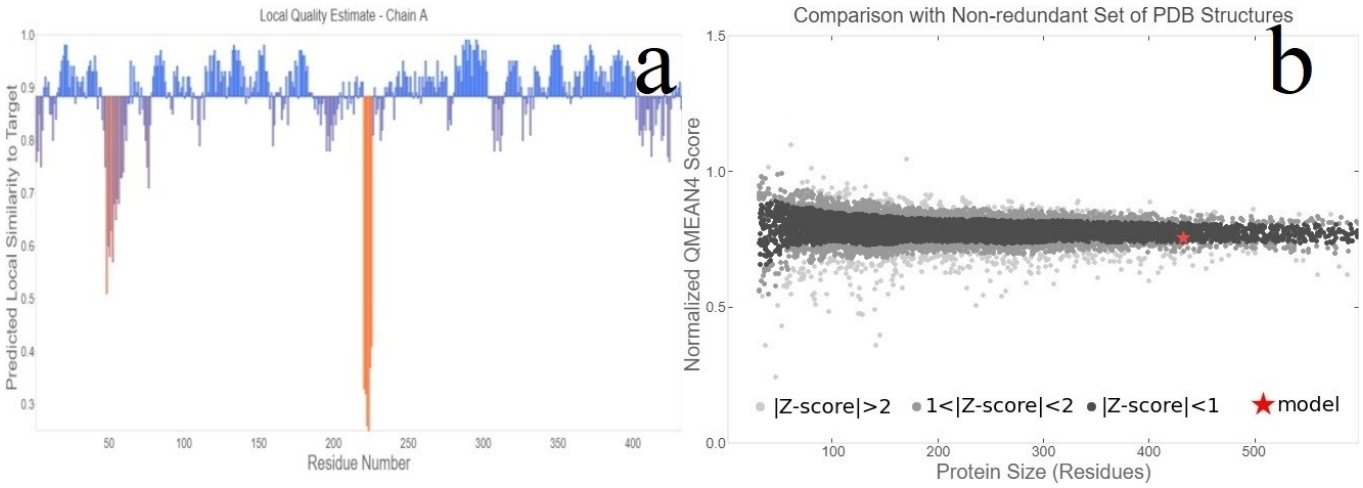


Figure 2. Structure validation of modeled LArbcL: (a) Local quality estimate of the residues of the predicted LArbcL model (b) comparison of the predicted LArbcL structure with nonredundant set of PDB structures.

The PDB sum web service provided both the "Ramachandran plot (Figure 3A) and the Ramachandran plot statistics" (Figure 3B). 92.9 percent of the residues in the modeled 3D structure of LArbcL are in the most favored regions of the Ramachandran plot, 6.8% are in additional allowed regions, 0.0 percent are in generously allowed regions, and 0.3 percent are in disallowed regions, according to the Ramachandran plot statistics. This also verifies the great quality of the modeled 3D structure. Also acquired for the structural validation server[38] was the Verify Errat plot of the modeled protein (Figure 4), which demonstrated PASS. The overall quality factor in the 3D environment profile is 83.493 percent, indicating that the model is legitimate.

In silico results of risks and Herbicide-likeness of ligands

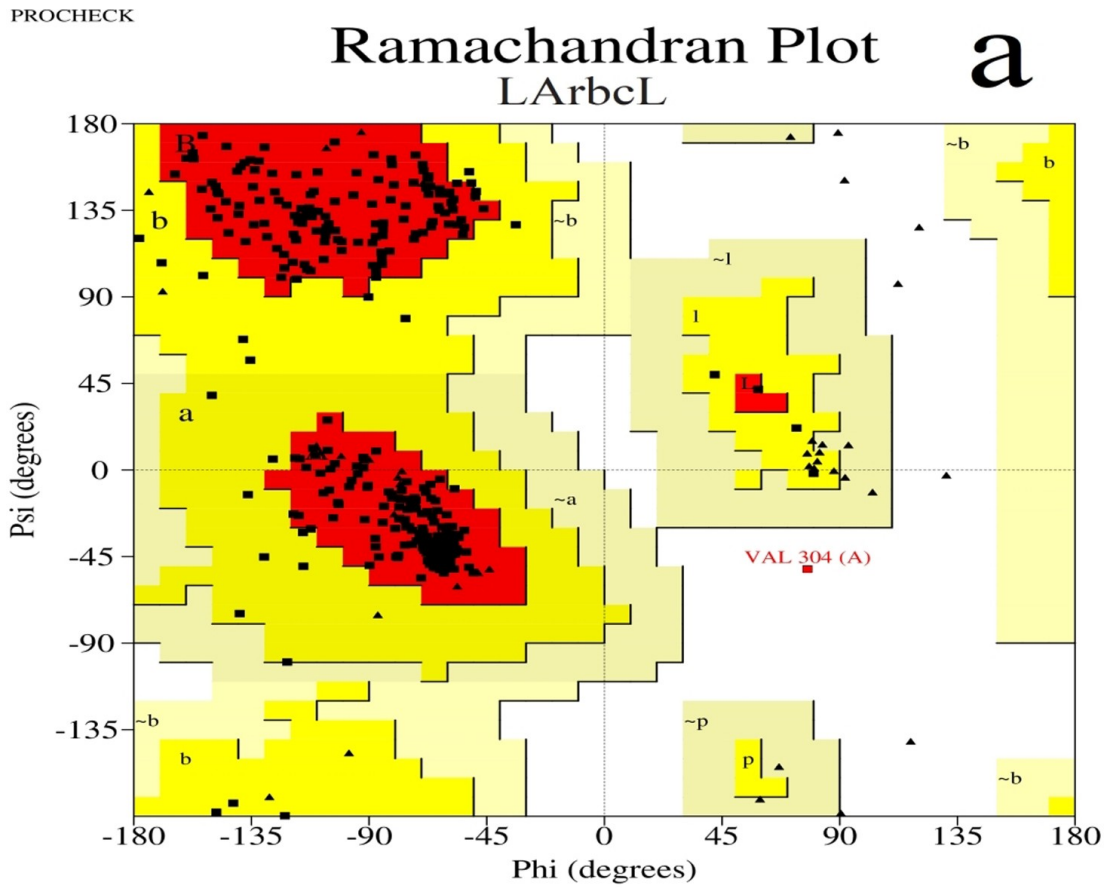
The radar diagram analysis for the BAC_1–BAC_{11} and Butachlor is depicted in Figure 5. The radar map displays key characteristics of BAC_1–BAC_{11} and Butachlor that are similar to those of herbicides, such as lipophilicity, molecular weight, polarity, insolubility, instauration, and rotatable bond flexibility. The lead compounds' bioavailability radars were acceptable and within range. Compounds BAC_1–BAC_{11} barely deviated from the radar's necessary instauration zone. To investigate their herbicidal capabilities, the chemicals BAC_1–BAC_{11} and Butachlor were represented by a boiled egg diagram. All of the substances produced positive outcomes (Figure 6).

All of the "compounds had molecular weights less than 500," indicating that they are expected to be captivated and arrive at the site of act, LogP values of less than 5 were found in all substances, including the standard (Butachlor), indicating good absorption and penetration across cell membranes, according to data warrior results.[39]

Except for the standard Butachlor, which was expected to have a high mutagenic toxicity risk, all of the developed compounds were predicted to have no "mutagenic, tumorigenic, irritating, and reproductive effective toxicity risks" (Table 1)), It is proved that in this report we have worked on the preparation of novel, green and nontoxic herbicide. 95% of herbicides have clogP values ranging from 0.5 to 5 according to Tice 2002.[19] The cLogP values are ranging from 3.097–4.625 for compounds BAC_1–BAC_{11} which is 4.603 for Butachlor.

Table 1. Physicochemical properties and toxicity risks of compounds BAC_1- BAC_{11} in comparison with Butachlor as predicted using DATA Warrior.

Comp.	Formula	MW	cLogP	Mutagenic	Tumorigenic	Reproductive effective	Irritant
BAC_1	$C_{21}H_{19}NO$	301.38	4.0194	None	None	None	None
BAC_2	$C_{21}H_{18}ClNO$	335.83	4.6254	None	None	None	None
BAC_3	$C_{21}H_{18}ClNO$	335.83	4.6254	None	None	None	None
BAC_4	$C_{22}H_{21}NO_2$	331.41	3.9494	None	None	None	None
BAC_5	$C_{21}H_{18}FNO$	319.37	4.1202	None	None	None	None
BAC_6	$C_{22}H_{20}FNO_2$	349.4	4.0502	None	None	None	None
BAC_7	$C_{21}H_{17}ClN_2O_3$	380.82	3.7038	None	None	None	None
BAC_8	$C_{21}H_{18}ClNO$	335.83	4.6254	None	None	None	None
BAC_9	$C_{21}H_{18}N_2O_3$	346.38	3.0978	None	None	None	None
BAC_{10}	$C_{21}H_{18}ClNO$	335.83	4.6254	None	None	None	None
BAC_{11}	$C_{21}H_{18}N_2O_3$	346.38	3.0978	None	None	None	None
Butachlor	$C_{17}H_{26}ClNO_2$	311.85	4.603	High	High	High	High



Plot statistics

b

Residues in most favoured regions [A,B,L]	341	92.9%
Residues in additional allowed regions [a,b,l,p]	25	6.8%
Residues in generously allowed regions [~a,~b,~l,~p]	0	0.0%
Residues in disallowed regions	1	0.3%
Number of non-glycine and non-proline residues	367	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	43	
Number of proline residues	21	
Total number of residues	433	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Figure 3. Structure validation using (a) Ramachandran plot; (b) Ramachandran plot statistics of the homology modeled LArbcL

"The numbers of hydrogen bond acceptors (NHA) and hydrogen bond donors (NHD) in " BAC_1–BAC_{11} (Table 2) follow Lipinski et al's rule of five[18]. All of the compounds were moderately soluble in general, according to the LogS prediction of −5.86 to −4.16, and their synthetic accessibility (2.32–2.90) was contained by the range of easy synthetic accessibility. It's also worth noting that none of the compounds broke the Lipinski rule of five, indicating that all of the ligands might be used as lead compounds in therapeutic development. According to Tice 2002,[19] herbicides must have *TPSA* values within the

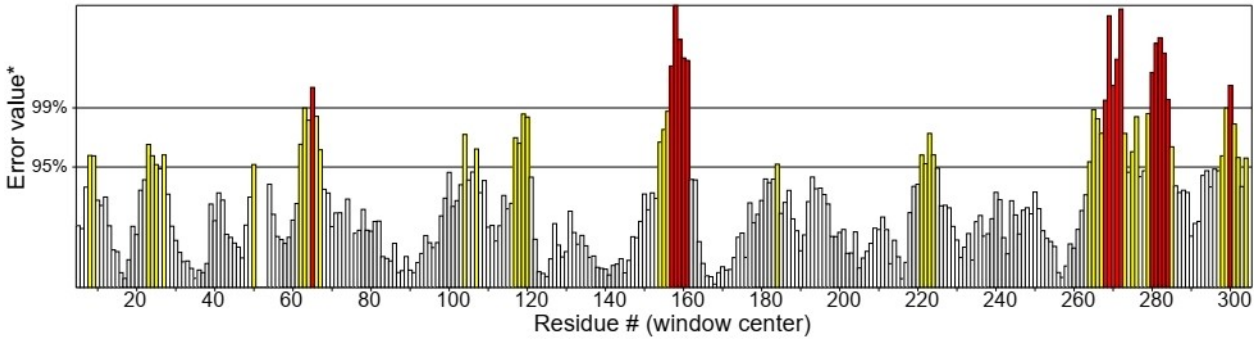


Figure 4. Structure validation using Errate

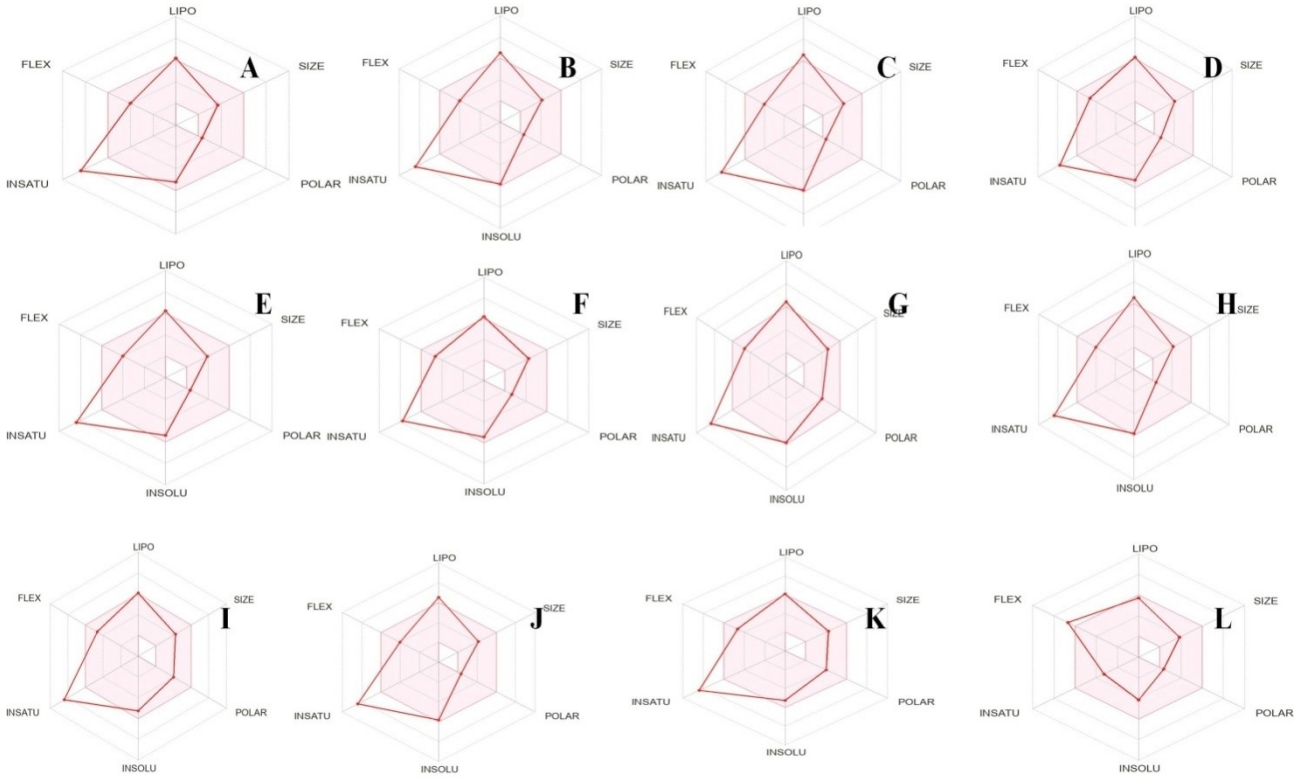


Figure 5. Radar Map of (A) BAC_1 (B) BAC_2 (C) BAC_3 (D) BAC_4 (E) BAC_5 (F) BAC_6 (G) BAC_7 (H) BAC_8 (I) BAC_9 (J) BAC_{10} (K) BAC_{11} (L) Butachlor

Table 2. ADME prediction of compounds BAC_1–BAC_{11} in comparison with Butachlor, predicted by Swiss ADME.

Comp.	Formula	MW	NHD	NHA	NRB	TPSA(A^0)	Log P (iLogP)	Log S(E SOL)	Synthetic Accessibility
BAC_1	$C_{21}H_{19}NO$	301.38	1	1	6	29.1	2.73	−5.23	2.32
BAC_2	$C_{21}H_{18}ClNO$	335.83	1	1	6	29.1	3	−5.82	2.55
BAC_3	$C_{21}H_{18}ClNO$	335.83	1	1	6	29.1	3	−5.82	2.47
BAC_4	$C_{22}H_{21}NO_2$	331.41	1	2	7	38.33	3.37	−5.29	2.63
BAC_5	$C_{21}H_{18}FNO$	319.37	1	2	6	29.1	2.87	−5.38	2.48
BAC_6	$C_{22}H_{20}FNO_2$	349.4	1	3	7	38.33	3.46	−5.44	2.7
BAC_7	$C_{21}H_{17}ClN_2O_3$	380.82	1	3	7	74.92	2.81	−5.86	2.8
BAC_8	$C_{21}H_{18}ClNO$	335.83	1	1	6	29.1	3.19	−5.82	2.43
BAC_9	$C_{21}H_{18}N_2O_3$	346.38	1	3	7	74.92	2.62	−5.27	2.9
BAC_{10}	$C_{21}H_{18}ClNO$	335.83	1	1	6	29.1	3.09	−5.82	2.43
BAC_{11}	$C_{21}H_{18}N_2O_3$	346.38	1	3	7	74.92	2.5	−5.27	2.74
Butachlor	$C_{17}H_{26}ClNO_2$	311.85	0	2	10	29.54	3.62	−4.16	3.07

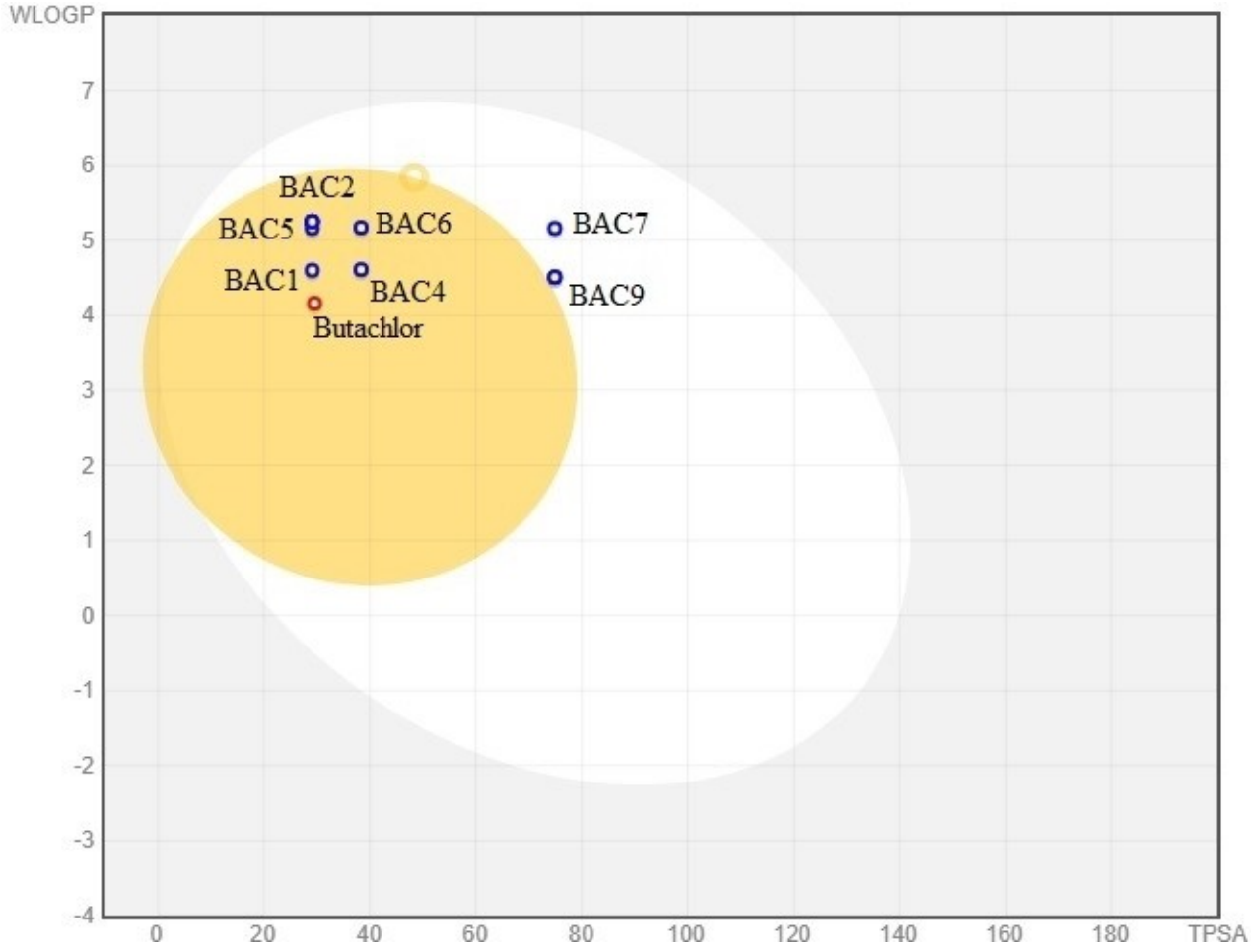


Figure 6. Boiled Egg diagram of BCA_1–BCA_{11} and Butachlor

relatively narrow ranges 20 $A^0 < TPSA < 100\ A^0$, the TPSA values are 29.1–74.92 for compounds BAC_1–BAC_{11} which is 29.54 for Butachlor.

Active site identification

Amino acid residues were predicted to be the active sites (Figure 7) for the modeled protein. conversely these were selected as the favorable site for the "docking analyses" due to the similarity observed from the arrangement of the modeled arrangement to the template arrangement: Arg 23, Arg 116, Glu118, Tyr242, Arg 268, His 271, Val 273, Ile 274, Asp 275, Arg 276, Gln 277, Lys 278, His 283, Phe 284, Arg 285, Leu 287, Lys 307, Leu 308, Glu309, Glu 311, Ile 316, Thr 315, Leu 316, Phe 318, Arg 331, Arg 333, Tyr 336.

Molecular docking results

Table 3 provides information on the "binding energies and hydrogen bonds" of BAC_1–BAC_{11}. While Figures 8 shows the docked conformation of BAC_{11} and Butachlor in the active regions of LArbcL. Furthermore, the dock score values for each of the created compounds ranged from −6.2 to −7.3 kcal/mol, indicating that they had lower binding energies than the butachlor, which had a "binding energy" of −5.2 kcal/mol. Using the lowest auto dock score and the most beneficial interactions, the compound with the best conformation was found.[40]

Among the synthesized β-amino carbonyl derivatives, molecule BAC_{11} had the best dock score of −7.3 kcal/mol. The practical and structural firmness of the "ligand-protein complex" is further validated by the six hydrogen bonds generated among compound BAC_{11} and the amino acid residues of LArbcL's active site. As a result of the obligatory model revealed in this study, these substituted β-amino carbonyl derivatives behave as herbicides and exhibit several critical structural features to consider for in vitro activities of compounds with Lathyrus aphaca.

Molecular dynamic simulation studies

To assess the variation of compounds for a 100 ns trajectory period, the Root Mean Square Deviation (RMSD) of compound BAC_1, BAC_7, BAC_{11} with protein was determined and compared with Butachlor-protein complex (Figure 9). The RMSD plot of all

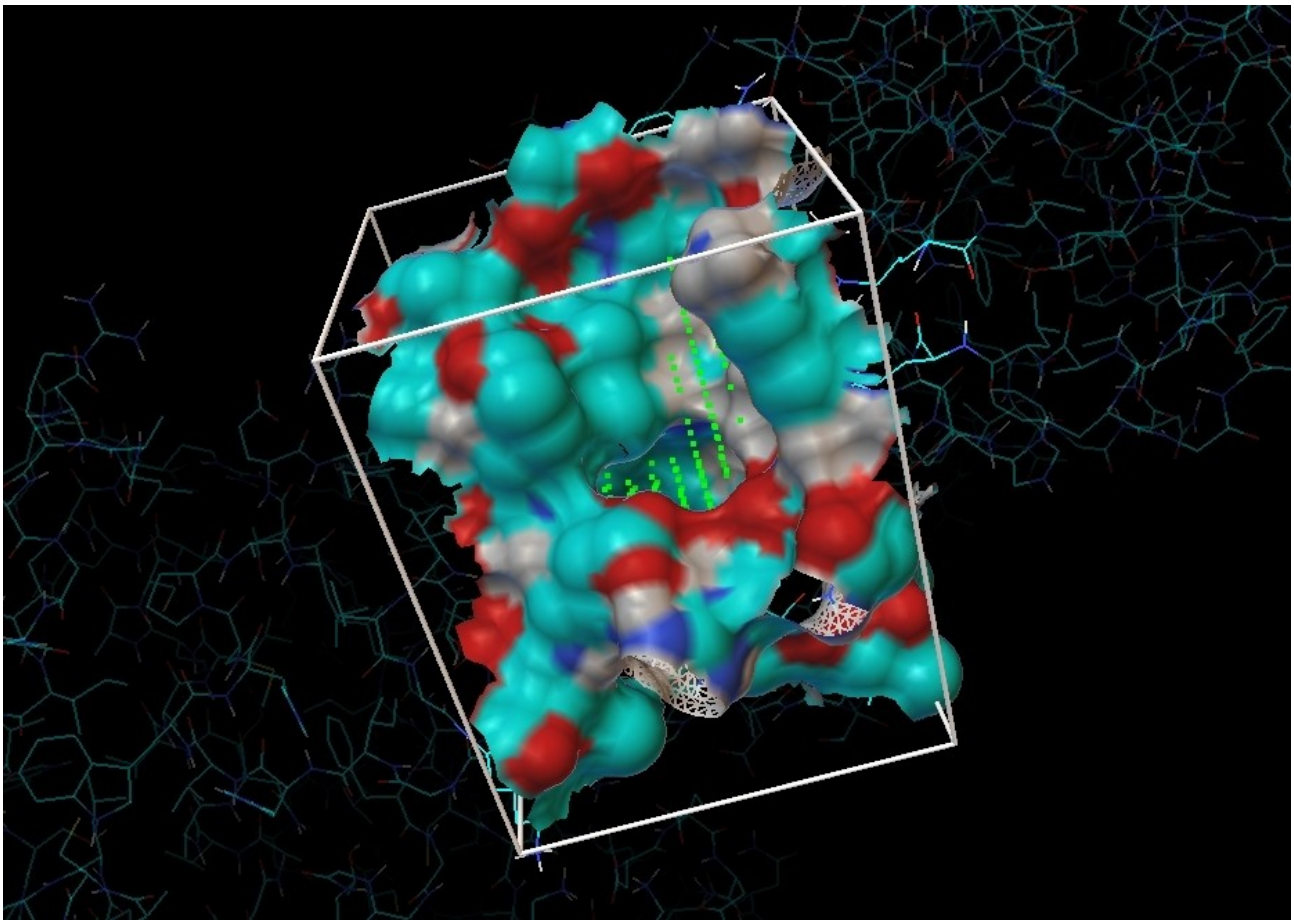


Figure 7. The surface of the binding pocket of the modeled protein as computed using AGFR 1.0

protein–ligand complexes revealed their protein stability. The average RMSD values in this investigation are 0.456 nm for BAC_1-protein complex and 0.4725 nm for ligand, 0.396 nm for BAC_7-protein complex and 0.832 nm for ligand, 0.351 nm for BAC_{11}-protein complex and 0.308 nm for ligand compared to the reference value of butachlor protein complex 0.388 nm and for ligand 0.674 nm. In general, RMSD allows us to measure a molecule's divergence from a reference structure to get a good idea of the simulation protocol's stability and validity. According to[41] Instability and large conformational changes are implied by high RMSD values for the target. As a result of the RMSD plot analysis of all the three complexes with reference to Butachlor, it was discovered that BCA_{11}-protein complex attained good stability in 100 ns, resulting in a stable trajectory for further exploration.

The Root Mean Square Fluctuation (RMSF) measurement was used to examine the local changes in chemicals as well as the protein chain residues at a specific temperature and pressure (Figure 10). There were very few alterations in the constituent residues of the protein–ligand complexes during the 100 ns trajectory period, which were plotted to compare the flexibility of each residue in the protein and the complex. Finally, it was discovered that the fluctuation in complex residues is significantly similar to the reference, resulting in minimal fluctuation and improved stability.

By estimating the structural compactness along the MD trajectories, the Radius of gyration (Rg) study was used to determine the stability of protein-ligand complexes (Figure 11). The Rg computation was also influenced by the protein and complexes system's ability to stay folded or unfolded. The Radius of gyration analysis was performed using 100 ns trajectories in this investigation. When compared to the reference 2.29 nm, the average Rg value of complexes BAC_{11} is 2.29 nm, BAC_7 2.32 nm and for BCA_1 2.40 nm which are significant. When compared to the native and reference Butachlor, the result demonstrates that all complexes have Rg values that are reasonably similar and constant, indicating that they are perfectly overlaid and have good stability.

To calculate the proportion of the protein surface that was accessed by aqueous solvent during MDS, the "solvent accessible surface area (SASA)" parameter was used. During interaction energy simulation, SASA can anticipate the magnitude of conformational changes. The plot of SASA value vs. time for all "protein-ligand complexes" is shown in Figure 12. Through a molecular dynamics simulation of 100 ns trajectory period, the average SASA of BCA_1-protein complex is 188.69 nm^2, BCA_7-protein complex is 185.86 nm^2, and BCA_{11}-protein complex is

Table 3. Molecular Docking activity of β-amino carbonyl derivatives *Lathyrus aphaca* (jangli matar).

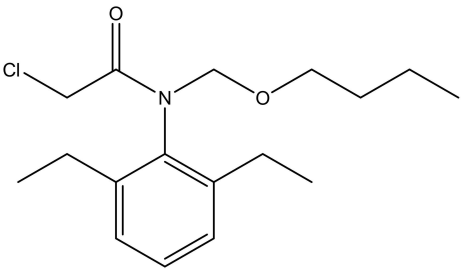
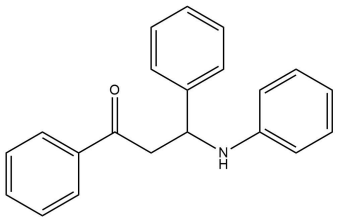
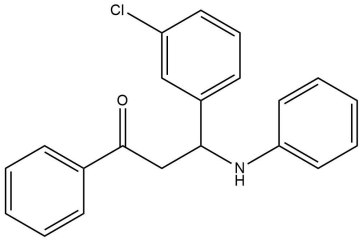
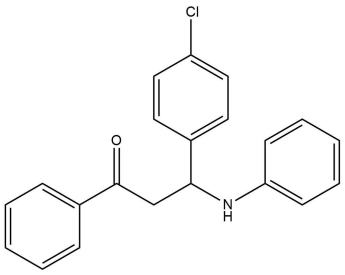
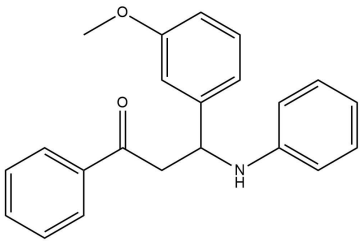
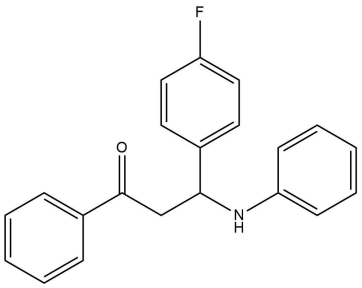
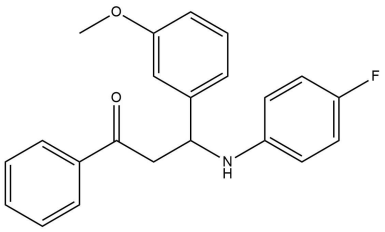
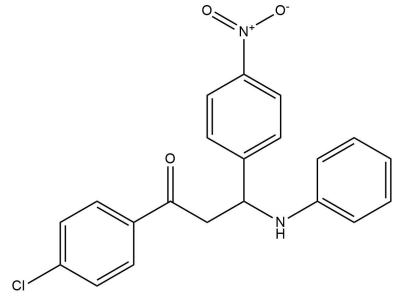
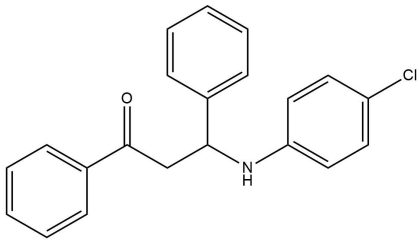
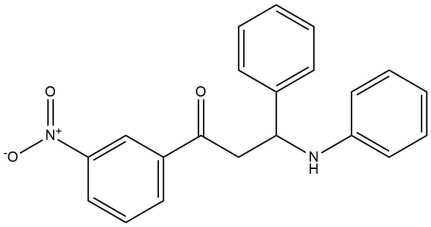
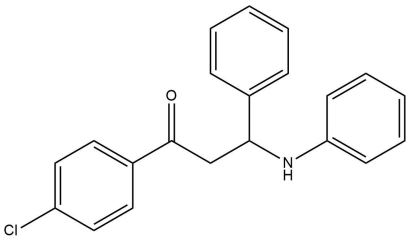
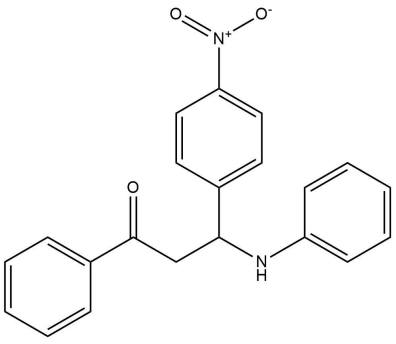
Compound	Nomenclature	Chemical Structure	Docking Score (kcal mol^{-})
Butachlor	*N*-(butoxymethyl)-2-chloro-*N*-(2,6-diethylphenyl)acetamide		−5.2
BAC_1	1,3-diphenyl-3-(phenylamino)propan-1-one		−6.4
BAC_2	3-(3-chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one		−6.6
BAC_3	3-(4-chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one		−6.2
BAC_4	3-(3-methoxyphenyl)-1-phenyl-3-(phenylamino)propan-1-one		−6.5
BAC_5	3-(4-fluorophenyl)-1-phenyl-3-(phenylamino)propan-1-one		−6.5

Table 3. continued

Compound	Nomenclature	Chemical Structure	Docking Score (kcal mol^{-})
BAC_6	3-((4-fluorophenyl)amino)-3-(3-methoxyphenyl)-1-phenylpropan-1-one		−6.8
BAC_7	1-(4-chlorophenyl)-3-(4-nitrophenyl)-3-(phenylamino)propan-1-one		−7.2
BAC_8	3-((4-chlorophenyl)amino)-1,3-diphenylpropan-1-one		−6.6
BAC_9	1-(3-nitrophenyl)-3-phenyl-3-(phenylamino)propan-1-one		−6.6
BAC_{10}	1-(4-chlorophenyl)-3-phenyl-3-(phenylamino)propan-1-one		−6.7
BAC_{11}	3-(4-nitrophenyl)-1-phenyl-3-(phenylamino)propan-1-one		−7.3

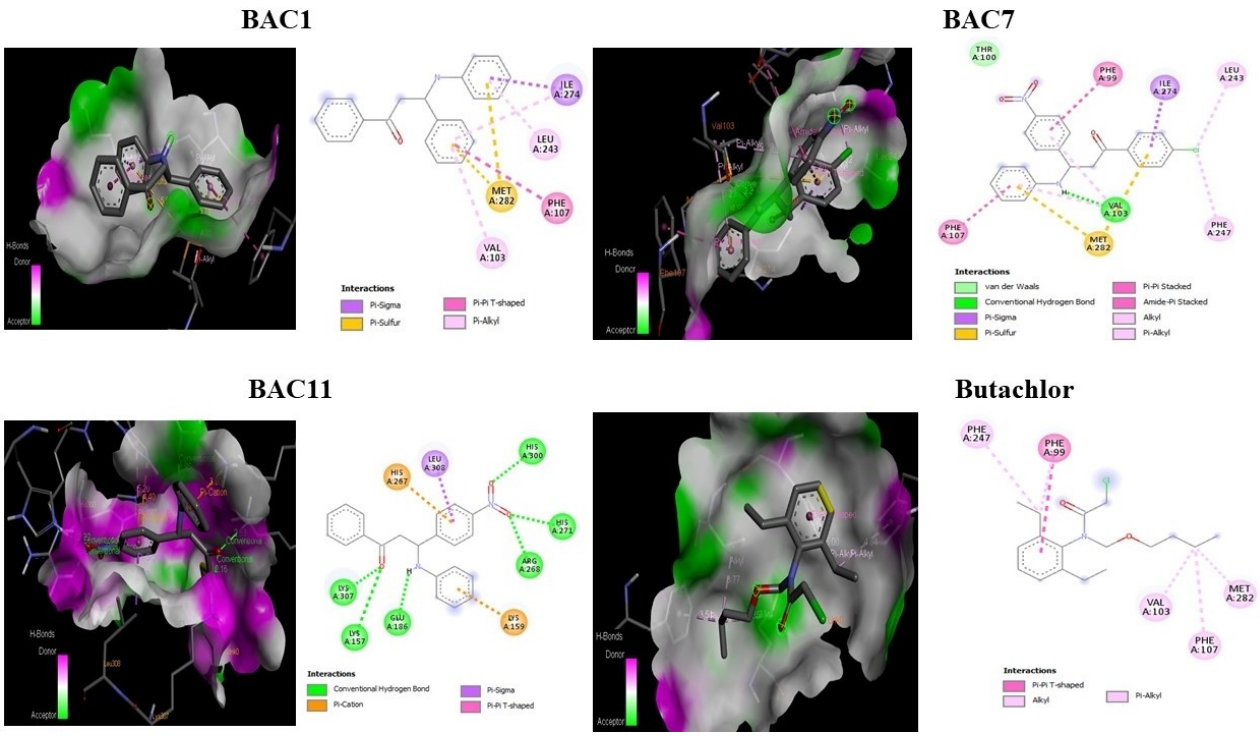


Figure 8. Molecular docking interactions between BAC and the binding sites of LArbcL: 3D and 2D model of the interactions between $BAC_{1,}$ $BAC_{7,}$ BAC_{11} and Butachlor and LArbcL.

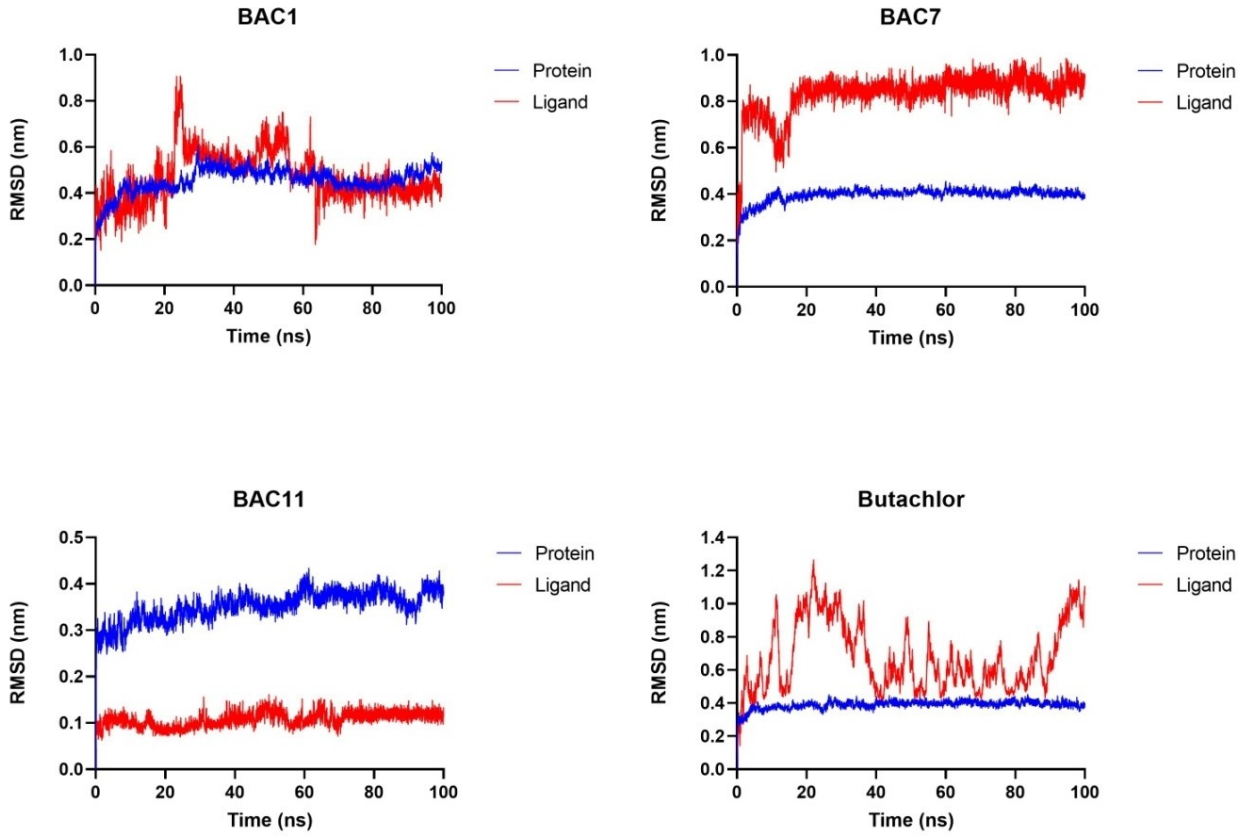


Figure 9. RMSD graph of BAC_1 complex, BAC_7 complex, BAC_{11} complex, RMSD Butachlor complex

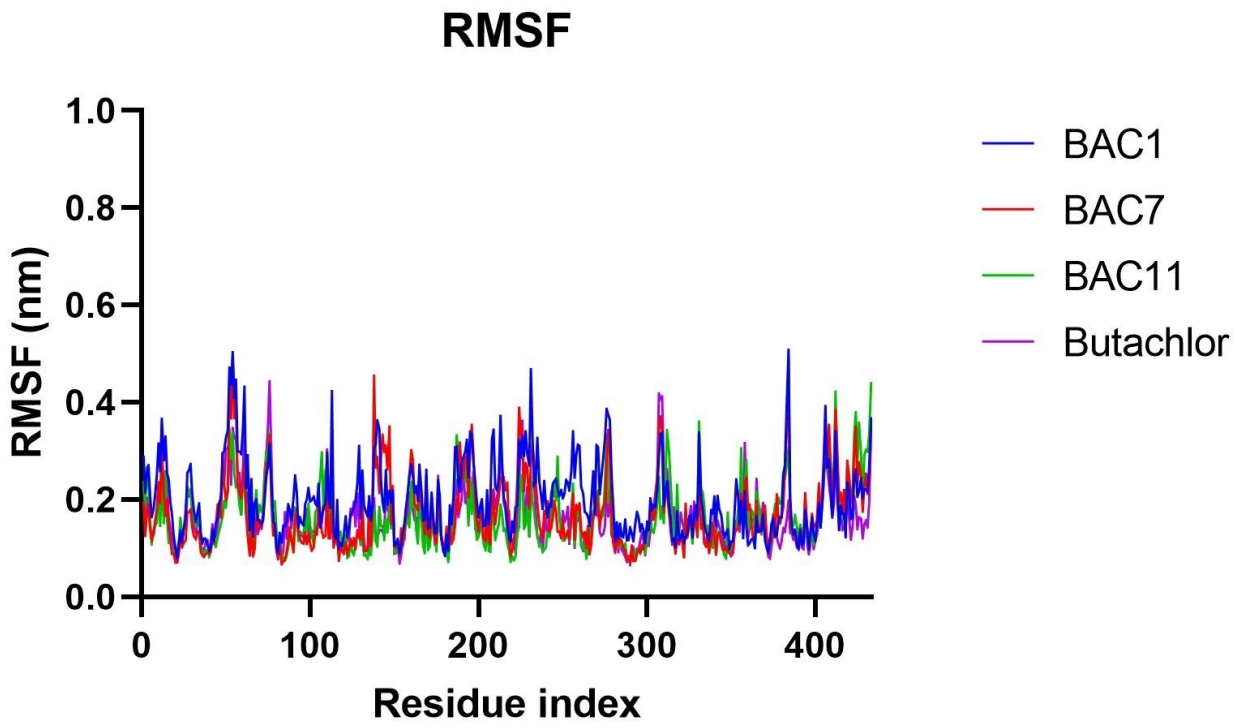


Figure 10. RMSF graph of BAC_1 complex, BAC_7 complex, BAC_{11} complex and Butachlor complex

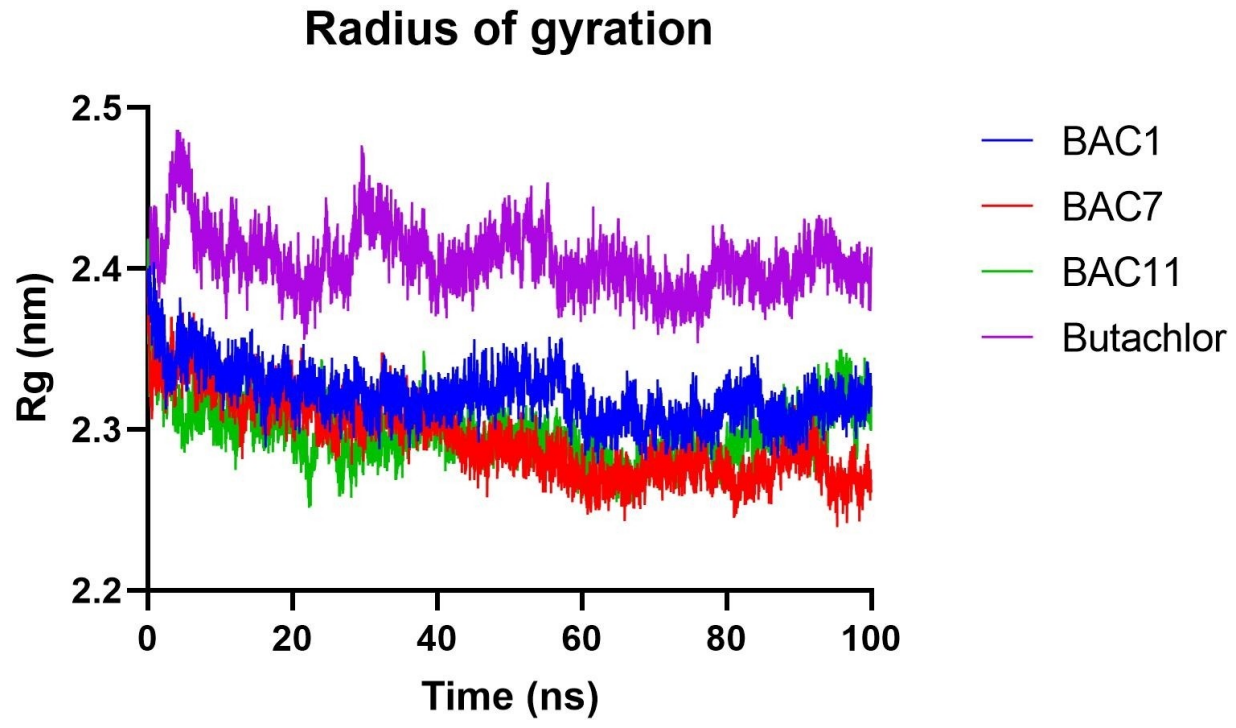


Figure 11. Radius of gyration of BAC_1 complex, BAC_7 complex, BAC_{11} complex and Butachlor complex

176.93 nm^2, as opposed to the reference 182.34 nm^2. All of the complexes had an SASA value of 182.34 nm^2, which was remarkably similar to the reference Butachlor-protein complex. We found from the SASA study that the BCA_{11}-protein complex is relatively most stable.

Because it impacts drug selectivity, metabolization, and adsorption, the hydrogen bond is critical in ligand binding to

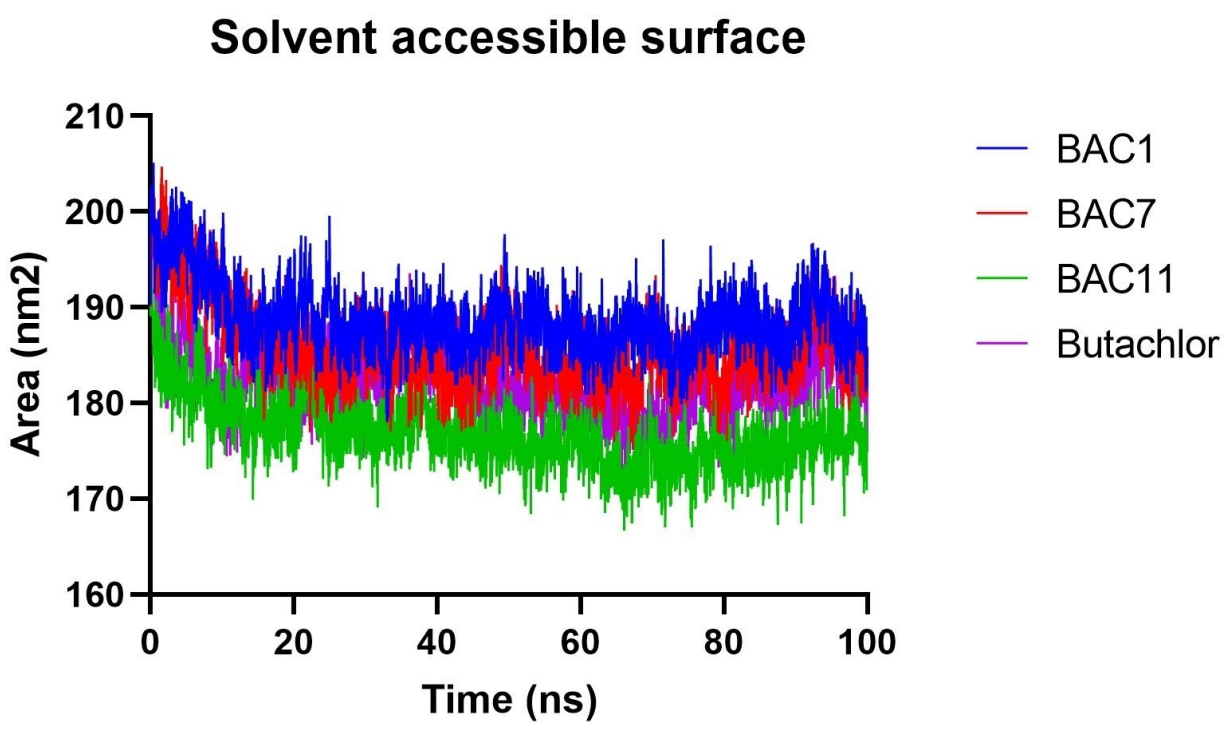


Figure 12. Solvent accessible surface area (SASA) of BAC_1 complex, BAC_7 complex, BAC_{11} complex and Butachlor complex

receptors. As a result, the total number of hydrogen bonds that may be present in the complexes was approximated during the 100 ns simulation phase. In the reference Butachlor-protein complex, no hydrogen bonds were found (Figure 13). The observed bonding properties of all the ligand-protein complexes revealed that the BAC11-protein complex has the maximum 4 hydrogen bond, which is the greatest of all, implying that it is more stable than Butachlor-protein complex.

The binding free energy calculations of BAC_1, BAC_7, BAC_{11} and Butachlor complexes yielded values ranging between −23.291 and 58.251 KJ/mol. The calculated MM-GBSA binding energies were further decomposed into separate components to recognize the vigour in the binding of protein with ligands (Table 4), Van der Waals binding energy was found to be a considerable contributor to in complex BCA_1 with average binding free energy values of 58.251 +/−109.622. Among the calculated parameters the △Gbind for all the complexes were in the same vicinity, which was consistent with the previous molecular docking results. Results also showed that polar solvation energy (ΔG Bind Lipo) and Van der Waals interactions (ΔG Bind vdW) were vital contributors to the ligand binding.

Pre- emergence herbicidal activity of β-amino carbonyl derivatives (BAC_1–BAC_{11})

The synthesized derivatives of β-amino carbonyl (BAC_1–BAC_{11}) were screened for their pre-emergence herbicidal activity against seeds of rabi crop weed "*Lathyrus aphaca*". The "seed germination inhibition activity" of synthesized compounds and standard (butachlor) was studied at three "concentrations (0.005 M, 0.01 M and 0.02 M)". The mean percent germination inhibition values of synthesized compounds and standard with their CD values are presented in Table 5. Perusal of Table 5 clearly indicates that with increase in concentration from 0.005 M to 0.01 M for the compounds BAC_4, BAC_7 and BAC_9 including standard there is significant increase in activity while with amplify in concentration from 0.01 M to 0.02 M there is noteworthy raise in activity intended for the compounds BAC_1, BAC_7 and BAC_{11}. Evaluating the activity of compounds at 0.005 M

Table 4. ΔGbind for the complexes along with ΔG Bind Lipo and ΔG Bind vdW were determined via MM/PBSA method. The standard deviation was reported as an error (±) associated with free energy differences.

Entry	vander Waal energy (kJ/mol)	Electrostatic energy (kJ/mol)	Polar Solvation energy (kJ/mol)	SASA energy (kJ/mol)	Binding energy (kJ/mol)
BCA_1	−193.345 +/−16.557	−303.039 +/−91.453	578.738 +/−190.293	−24.103 +/−1.558	58.251 +/−109.622
BCA_7	0.000 +/−0.000	1.583 +/−0.261	−4.214 +/−55.561	−0.084 +/−1.276	−2.715 +/−55.432
BCA_{11}	−3.469 +/−3.143	−3.822 +/−6.586	−15.008 +/−62.737	−0.992 +/−2.017	−23.291 +/−62.483
Butachlor	−64.243 +/−11.848	−16.338 +/−22.720	52.106 +/−25.814	−8.717 +/−1.168	−37.193 +/−11.341

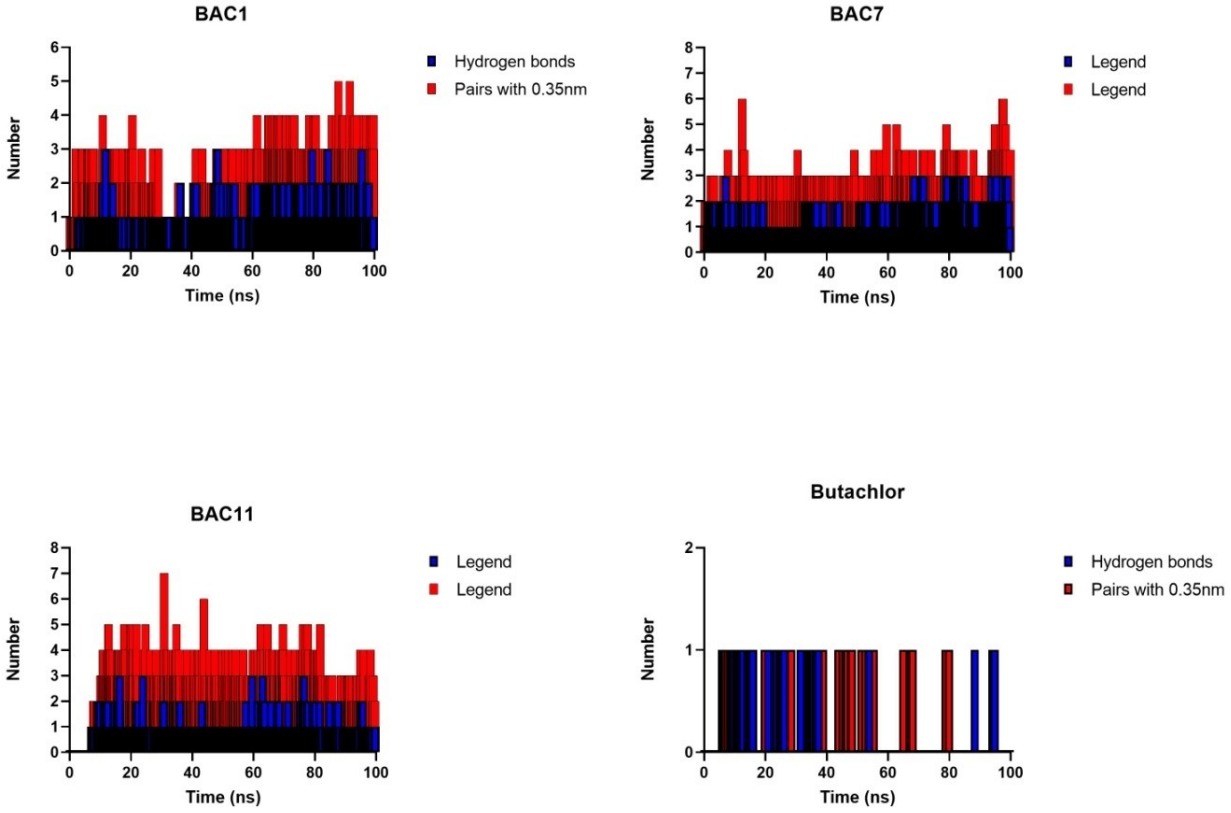


Figure 13. Ligand Hydrogen Bonds of BAC_1 complex, BAC_7 complex, BAC_{11} complex and Butachlor complex

Table 5. Mean percent germination inhibition values of synthesized β-amino carbonyl derivatives (BAC_1–BAC_{11}) against rabi crop weed *Lathyrus aphaca* (jangli matar).

Compound Code	Mean percent germination inhibition			
	0.005 M	0.01 M	0.02 M	CD at 5%
BAC_1	56.7	76.7	96.7	41.3
BAC_3	26.7	70.0	70.0	17.9
BAC_4	63.3	86.7	93.3	11.8
BAC_5	30.0	53.3	80.0	6.8
BAC_6	46.7	66.7	86.7	16.6
BAC_7	63.3	86.7	96.7	11.8
BAC_8	36.7	53.3	83.3	11.7
BAC_9	43.3	56.7	80.0	15.2
BAC_{10}	53.3	86.7	93.3	11.7
BAC_{11}	63.3	76.7	96.7	11.7
Stand. (Butachlor)	53.3	73.3	83.3	11.7
CD at 5%	9.4	11.9	11.1	

concentration among standard reveals that only the compounds BAC_4 (63.3%), BAC_7 (63.3%) and BAC_{11} (63.3%) exhibit activity at par with standard (53.3%). At concentration 0.01 M the compounds BAC_4 (86.7%), BAC_7 (86.7%) and BAC_9 (86.7%) exhibit activity at par with standard (73.3%). At concentration 0.02 M also, the compounds BAC_1 (96.7%), BAC_7 (96.7%) and BAC_{11} (96.7%) exhibit activity at par with standard (83.3%) (Figure 14 a-d).

Post- emergence herbicidal activity of β-amino carbonyl derivatives (BAC_1–BAC_{11})

The herbicidal activity of β-amino carbonyl derivatives (BAC_1–BAC_{11}) against the weed variety Lathyrus aphaca cultivated in a greenhouse was tested (Figure 15 a–b). Table 6 shows the results of herbicidal activities 15 days after treatment on a visual ranking scale ranging from 0 for no result to 5 for total control. Compounds BAC_1, BAC_7, and BAC_{11} had the maximum activity against Lathyrus aphaca, according to the results. The results of both pre-emergence and post-emergence herbicide bioassays indicate that compounds BAC_1, BAC_7, and BAC_{11} have a substantial inhibitory effect on weed species, and that these three compounds are the most phytotoxic of all the compounds.

Although all of the compounds had excellent activity, three of them – BAC_1, BAC_7, and BAC_{11} – were shown to be the most active. The inhibition of compound BAC_7 and BAC_{11} against the weed species substantially increased with the addition of a nitro group to the benzene ring. These results suggest that electronic effects of substituent are also crucial for compound herbicidal actions.

Proposed mode of Action

The results of pre-emergence herbicidal bioassay, post emergence herbicidal bioassay, molecular docking and molecular dynamic studies clearly indicate that β-amino carbonyl deriva-

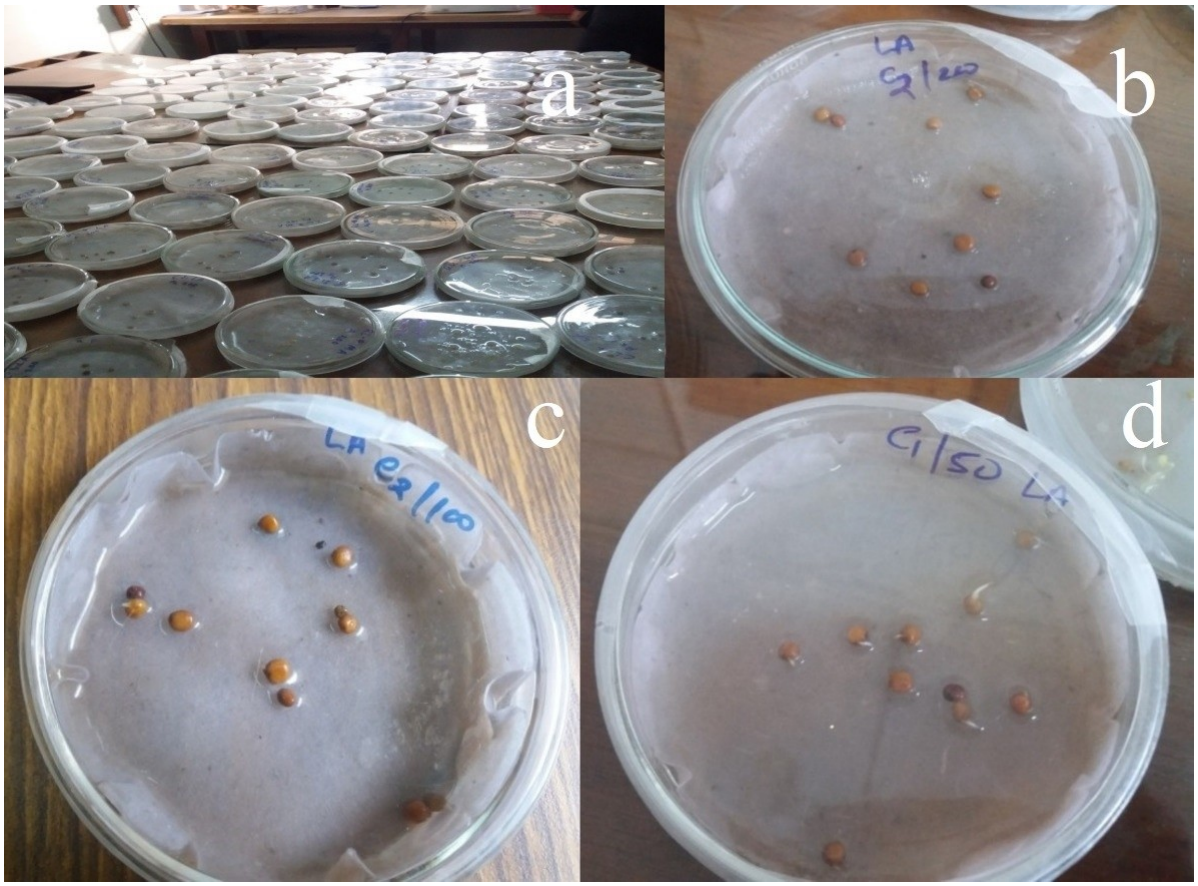


Figure 14. (a) *Lathyrus aphaca* (jangli matar) weed seeds in petri dishes (b) Use of BAC_1 on *Lathyrus aphaca* (jangli matar) weed seeds (c) Use of BAC_7 on *Lathyrus aphaca* (jangli matar) weed seeds (d) Use of BAC_7 on *Lathyrus aphaca* (jangli matar) weed seeds

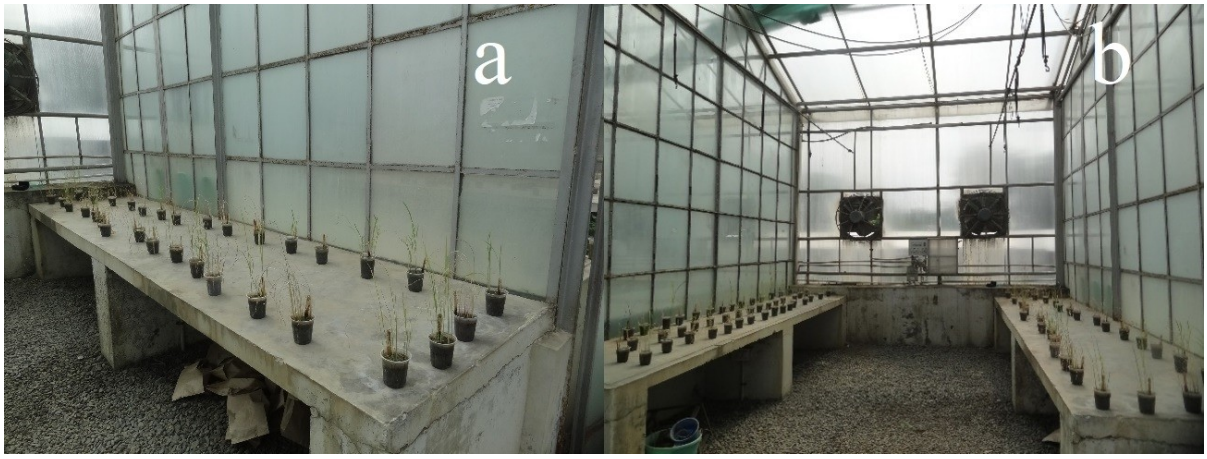


Figure 15. Effect of β-amino carbonyl derivatives (BAC_1–BAC_{11}) on *Lathyrus aphaca* plant grown up in soil.

tives family belongs to photosynthesis inhibitors. These herbicides work by inhibiting the photosynthetic pathway, specifically the Photosystem II enzyme (PSII).[42] It inhibit Rubisco which is an enzyme that catalyses the CO_2 fixation reaction in photosynthesis, forming phosphoglycerate (PGA), as well as photorespiration, forming phosphor-glycolate and PGA with the reaction to O_2.

Table 6. Effect of β-amino carbonyl derivatives (BAC_1–BAC_{11}) on Lathyrus aphaca.

Code	Herbicidial Activity against *Lathyrus aphaca*
BAC1	5
BAC3	3.5
BAC4	3
BAC5	1.5
BAC6	2
BAC7	5
BAC8	0.5
BAC9	0.2
BAC10	1
BAC11	4.5
Control	0
Penoxulam	5

Conclusion

The study reveals to develop and foresee likely binding affinities and interaction patterns of "β-amino carbonyl derivatives" (BAC_1–BAC_{11}) molecules using homology modelled LArbcL. Among the synthesized ligands, BAC_{11} "(3-(4 nitrophenyl)-1-phenyl-3-(phenylamino)propan-1-one)" exhibit the maximum dock score value and hydrogen bonds. The in silico ADMET properties of each of the synthesized compounds show that they are all suitable for further manufacture and development into herbicides with broad commercial application. The activity of the synthesized compounds was compared to that of the standard herbicide, in pre-emergence herbicidal and post-emergence herbicidal bioassay against "Lathyrus aphaca" seeds at 0.005 M, 0.01 M, and 0.02 M concentrations. All of the compounds had great activity but out of eleven compounds the three BAC_1, BAC_7, and BAC_{11} were found to be most active. The main benefits of the entire procedure are the ability to design unique, green, and nontoxic herbicides.

Experimental

Material and Methods

Synthesis of β-amino carbonyl derivatives (BAC_1–BAC_{11})

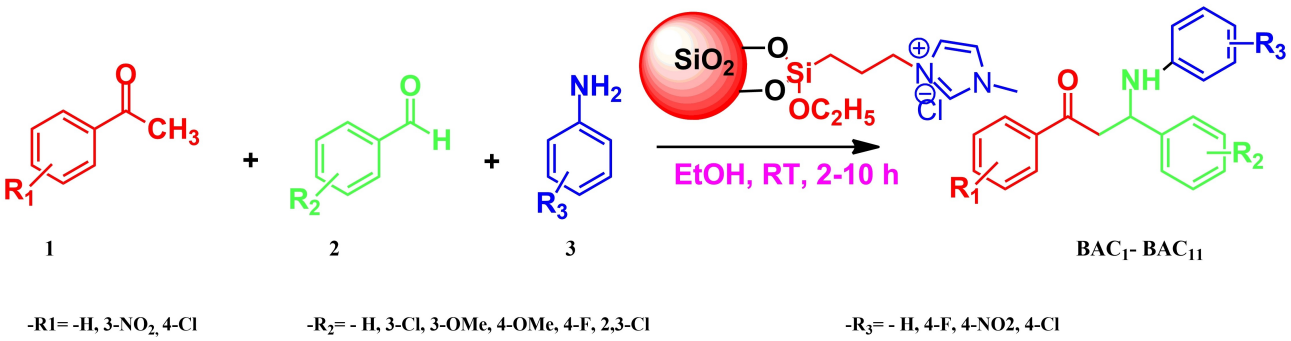
β-amino carbonyl derivatives were synthesized using a method in our previous report[43] "[SNsipmim]Cl as a proficient, Green and Recyclable Heterogeneous Catalyst through Mannich Type Reaction" In the whole procedure, Benzaldehyde (10 mmol), acetophenone (12 mmol), and aniline (10 mmol) were added to a round bottom flask containing 15 ml ethanol and 5 mol percent ([SNsipmim]Cl) catalyst, which was stirred for 2 hours at room temperature and the reaction development was checked using TLC with Ethyl acetate (4): hexane(1) solvent (Scheme 1). The residue washed via water and ethanol after extracting the desired product before being recrystallized with ethanol to obtain a pure product. The separated solid catalyst was washed in ethanol, dried, and reused in the subsequent cycle.

Ligand modeling

The "2-dimensional (2D) structures" of the substituted β-amino carbonyl derivatives (BAC_1- BAC_{11}) were built using Chem Draw Ultra Professional 12.0 b, also transformed to the equivalent "3D structures" by means of Chem Draw Ultra 3D conformation generator and saved in .pdb format. In addition, Auto-Dock software[31] was used to convert the .pdb files to the (pdbqt) format, which was additional used for the "docking studies".

Homology modeling of Lathyrus aphaca Ribulose bisphosphate carboxylase (LArbcL) and the target pattern series arrangement

Because LArbcL experimental's crystal composition is not in the "Protein Data Bank (PDB)",[44] its 3D arrangement was modeled. The "protein ID" of the object Lathyrus aphaca Ribulose bisphosphate carboxylase (LArbcL) was retrieved with the accession number A0 A0 A7NX29 from UniProt Knowledgebase (UniProtKB).[45] "The protein ID" was then sent to the "SWISS-MODEL"[46] online server, which created a representation with adequate query progression treatment and progression uniqueness. Based on the "Global Model Quality Estimation (GMQE)"[47] and "Qualitative Model Energy Analysis (QMEAN)"[48] values the most dependable 3D structure was chosen. The "GMQE" values are typically between 0–1, with the superior the number, the more reliable the predicted arrangement, whereas a assessment under 4.0 indicates consistency for QMEAN.[49]



Scheme 1. Synthesise of β-amino ketones during the Mannich process(Taken from[43]).

Structure validation of modeled protein

Based on the geometry, relations, and solvent prospective of the "protein model", the "SWISS-MODEL" online server calculates the "QMEAN" score role for assessment of the narrow and comprehensive model excellence. It also provides us a "z-score" between 0 and 1, which you may compare to the predicted value for any structure. The quality of the modeled 3D structure of LArbcL obtained by "SWISS-MODEL" was checked by means of "PROCHECK"[50]. The modeled LArbcL's.pdb file format was uploaded to the European Bioinformatics Institute's PDB sum web server[51] for structural validation. The modeled LArbcL's.pdb file format was submitted to the server to acquire the Rama-Chandran plot as well as the Rama-Chandran "plot statistics". The Rama-chandran "plot statistics" provide data regarding the entire quantity of amino acid residues discovered within the favorable, acceptable, and prohibited region, whereas the "Ramachandran plot" is used to examine the excellence of a modeling protein.

In silico Herbicide-likeness predictions

Herbicide-likeness is a criterion for determining whether a pharmacological drug possesses qualities that would make it an orally active herbicide. This prediction is based on the "Lipinski rule of five", which was developed by Lipinski et al.[52] The "in silico" herbicide-likeness and toxicity prediction of the considered ligands were conceded through DATA Warrior and "Swiss ADME"[21] predictor. The DATA Warrior program calculates mutagenic, tumorigenic, irritating, and reproductive risks, as well as total polar surface area (TPSA), cLogP, "hydrophilicity (LogP), solubility (LogS), molecular weight" for each molecule. Meanwhile, the Swiss ADME predictor gives data on the quantity of "hydrogen donors, acceptors, and rotatable bonds", as well as the compounds' synthetic accessibility. Radar and boiled eggs analysis have been done to assess the bioavailability and absorption of compound BCA_1–BCA_{11} and Butachlor.

Protein preparation

SWISS-MODEL provided the homology modeled 3D structure of the target protein, LArbcL, in.pdb format. Furthermore, using AutoDock-Tools 1.5.7, the protein was produced by calculating "Gasteiger charges, adding polar hydrogens, and merging nonpolar hydrogens".

Prediction of active sites in the modeled protein

The active sites contained in the modeled protein structure were predicted using Autogrid FR (AGFR 1.0).

Molecular docking analysis

Docking studies were performed using "Autodock- Vina of The Scrips Research Institute". "Microsoft Windows 10 professional Version, operating System on Intel (R) i5 (TM), CPU @ 3.30 GHz and 8.0 GB of RAM of Intex Machine" were used. At the following coordinates: centre x = 16.151, centre y = 19.928, centre z = −10.673, and size 40, 40, and 40 in X, Y, and Z axes, the grid box was set to encompass the greatest portion of proteins and ligand. The docked structure's interactions and binding energy, as well as the lowest energy states of proteins and ligand complexes, were examined using Pymol, Discovery studio, Molegro Molecular Viewer, and Ligplot+.

Molecular dynamic simulation study

"GROMACS version 2020.4" with the "GROMOS96 43 a1 force field" was used to run molecular dynamics simulations of the most powerful complexes BAC1, BAC7, BAC11 and the standard Butachlor produced through molecular docking. However, because the force field employed for biomolecular modelling lacks a parameter for small molecules, ligand parameterization is required. "Prodrug server" "(http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg)" was used for this, which uses a pre-defined mathematical methodology to generate ligand parameters suitable with the force field. To achieve this, the system was initially reduced for a maximum of 5000 steps, after which it was exposed to NVT and NPT equilibrium for 5000 steps each at 300 K. Finally, the complex was examined using "RMSD (Root Mean Square Deviation), RMSF (Root Mean Square Fluctuation), Rg (Radius of Gyration), SASA (Solvent-Accessible Surface Area), and Hbonds for 100 ns with 5000 steps (average number of H-bonds)." Mmpbsa (Molecular Mechanic/ Poisson-Boltzmann Surface Area)[53,54] were also studied for the Binding free Energy calculation using the following equation:

$$\Delta GBinding = Gcomplex - (Gprotein + Gligand)$$

In this equation, $G_{complex}$ is the energy of the compound and protein complex, and $G_{protein}$ and G_{ligand} are the protein and ligand energy in water bounded surroundings.

Pre- emergence herbicidal activity of β-amino carbonyl derivatives (BAC_1–BAC_{11})

The synthesized derivatives of β-amino carbonyl (BAC_1–BAC_{11}) were screened for their pre-emergence herbicidal activity against seeds of rabi crop weed *Lathyrus aphaca.* at three concentrations (0.005 M, 0.01 M and 0.02 M). The herbicide butachlor was used as a reference point. The CD values of synthesized derivatives of β-amino carbonyl (BAC_1–BAC_{11}) and standard (butachlor) were derived using the mean percent germination inhibition values.

Post- emergence herbicidal activity of β-amino carbonyl derivatives (BAC_1–BAC_{11})

Post emergence herbicidal bioassay of β-amino carbonyl (BAC_1–BAC_{11}) were analyzed next to weed variety *Lathyrus aphaca*, grown-up in greenhouse at three concentrations (0.005 M, 0.01 M and 0.02 M). Flora grew in a 10×10 cm planter filled with filthy soil. Each species received ten pots. Every day, all of the pots were watered and stored in the greenhouse. Every variety was divided into two categories. The primary group was given a hydroethanolic dispersion that contained Tween 20 (0.5%) and ethanol at the preferred concentration for up to 15 days (10 percent by volume). As a positive control, penoxulam (21.7%) was used. A flat fan nozzle was used to apply the herbicide over the top. Tween 20 (0.5%) and ethanol are present in the second group (control) treated with hydroethanolic solution (10 vol percent). At the time of treatment, the plants had grown to a height of 10–12 cm. Herbicidal activity was assessed 15 days after treatment using a visual rating scale ranging from 0 to 5, with 0 representing no result and 5 representing entire control. The percentage of injured leaves observed on treated plants compared to controls is referred to as visual ranking.[55]

Supporting Information Summary

All the 3D docked images and the link of simulation video are given in supporting information.

Acknowledgment

We are grateful to Govind Ballabh Pant University of Agriculture and Technology, Pantnagar (Uttarakhand), India, for providing the essential research facilities, as well as the KIET Group of Institutions for their unwavering support and assistance throughout the research process.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: β-amino carbonyl · Herbicide · Lathyrus aphaca · AFMET · Molecular Docking Molecular dynamics simulations

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