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Synthesis, molecular docking, and biological activities of new cyanopyridine derivatives containing phenylurea

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Abstract

A new class of cyanopyridine derivatives (**10a–e** and **11a–e**) containing the phenylurea unit was synthesized and tested against some metabolic enzymes including acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and α-glycosidase (α-Gly). The new cyanopyridine derivatives showed K_i values in the range of 40.73 ± 6.54 to 87.05 ± 16.98 μM against AChE, 29.17 ± 4.88 to 124.03 ± 22.43 μM against BChE, and 3.66 ± 0.93 to 26.33 ± 5.05 μM against α-Gly. These inhibition effects were compared with standard enzyme inhibitors like tacrine (for AChE and BChE) and acarbose (for α-Gly). Also, these cyanopyridine derivatives with the best inhibition score were docked into the active site of the indicated metabolic enzymes. Finally, molecular docking calculations were made to compare the biological activities of the compounds against AChE (−8.81 kcal/mol for molecule **11d**), BChE (−3.52 kcal/mol for molecule **11d**), and α-Gly (−2.98 kcal/mol for molecule **11a**). After molecular docking calculations, the ADME/T analysis was performed to examine the future drug use properties of the new cyanopyridine derivatives containing phenylurea.

KEYWORDS
acetylcholinesterase, carbonic anhydrase, chalcone, cyanopyridine, molecular docking

1 | INTRODUCTION

Synthesis of heterocyclic compounds is of importance in organic and medicinal chemistry.[1] Pyridines and their analogs are a very important class of heterocyclic compounds.[2] They are known to exhibit various biological activities such as antimicrobial,[3,4] antiparkinsonian,[5] anti-inflammatory,[6] antihypertensive,[7] antiviral,[8] and anticancer activities.[9] In addition, some substituted pyridine derivatives are used as organic light-emitting devices,[10] metal ion sensors,[11] liquid crystalline polymers,[12] nonlinear optical materials,[13] and chelating agents.[14] Therefore, the synthesis of pyridines and their analogs has attracted much attention in organic chemistry.

In addition, diaryl urea derivatives are increasingly used in medicinal chemistry and drug design. The diaryl urea derivatives

have diversified biological activities including antimicrobial,[15] anticonvulsant,[16] antibacterial,[17] antimalarial,[18] antiproliferative,[19] and anticancer[20] activities.

Alzheimer's disease (AD), the most common cause of dementia, is characterized by presynaptic cholinergic deficiencies and also decreased levels and function of acetylcholine (ACh) in the body.[21,22] AD patients have elevated rates of fracture associated with vitamin D shortage, elevated falls, and lower average compression of the bone. Acetylcholinesterase (AChE), expressed in brain tissues and acting in a controlled manner to characterize ACh functioning in the central neural system, is a very powerful enzyme for hydrolyzing ACh.[23] α-Glycosidase (α-Gly) as a type of glycoside hydrolase hydrolyzing the α-glycosidic bonds in carbohydrate molecules[24] breaks the α-1,4-linked sugar molecular terminals. It also causes carbohydrate molecules' breakdown. The α-Gly inhibition helps to release the monosaccharide molecules into the bloodstream after a meal. Diabetes mellitus (DM) condition occurs after the meal due to the action of insulin resistance. Indeed, to regulate the hyperglycemic situation after the meal, α-Gly inhibitor compounds are utilized as therapeutic factors.[23]

Recent studies have shown that there exist theoretical studies besides many experimental studies. The resulting theoretical data have enabled more effective and more active molecules to be synthesized.[25,26] At present, there are many methods and programs to compare the biological activities of molecules, whether theoretical or experimental.[27,28] The most widely used among these is molecular docking. This method gives important information about the biological activities of the molecules before the experimental processes. For molecular docking calculations, numerical values of biological activities against many enzymes were calculated.

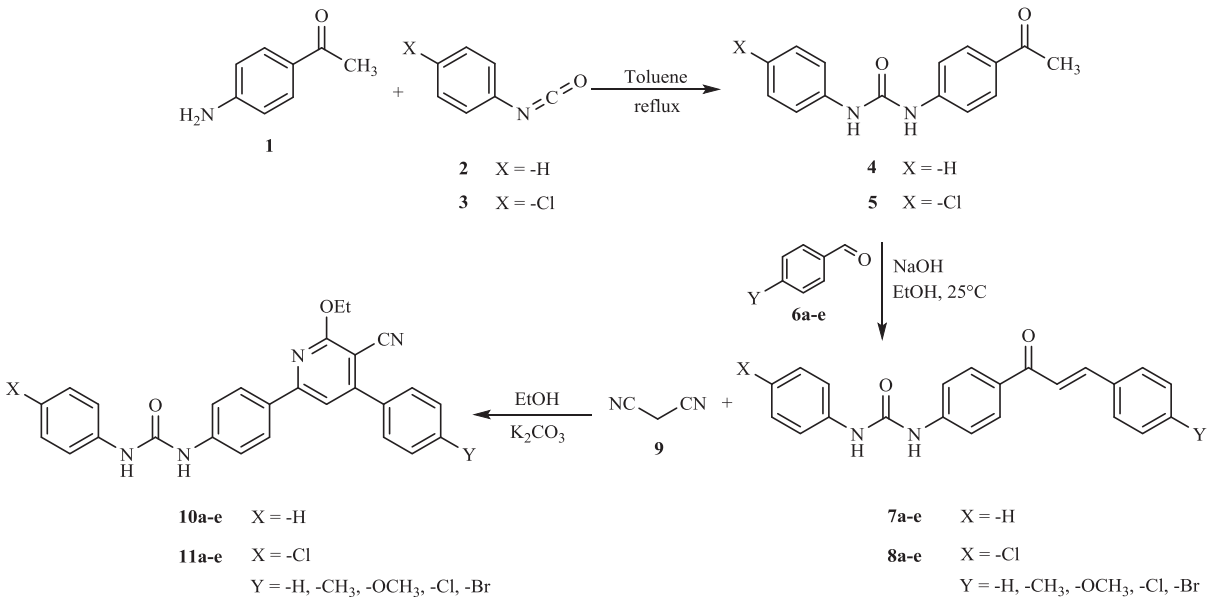
In light of this information, in this study, we aimed to synthesize new compounds containing diaryl urea and cyanopyridine units, whose pharmacophore properties have been reported in the literature, and to examine their inhibition activities against some metabolic enzymes. Thus, the synthesis of cyanopyridine derivatives containing phenylurea (**10a–e** and **11a–e**) was carried out from the reaction of phenylurea-substituted chalcone derivatives (**7a–e** and **8a–e**) with malononitrile (**9**). The structures of all synthesized compounds were elucidated by spectroscopic methods (nuclear magnetic resonance [NMR], infrared [IR], and elemental analysis).

Then, six of the synthesized compounds (**10a**, **10c**, and **11a–d**) were tested to determine their inhibition properties against some metabolic enzymes including AChE, butyrylcholinesterase (BChE), and α-Gly. In the last stage, for comparison of the obtained activity results, molecular docking calculations of the new compounds were performed against the proteins of enzymes, which are AChE (PDB ID: 4M0E),[29] BChE (PDB ID: 5NN0),[30] and α-Gly (PDB ID: 1R47).[31] After these calculations, the ADME/T (absorption, distribution, metabolism, excretion, and toxicity) analysis was performed for these compounds. With this analysis, the potential of these molecules to be used as a drug was investigated.[32]

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

Synthetic routes for the cyanopyridine derivatives (**10a–e** and **11a–e**) are outlined in Scheme 1. First, the starting compounds phenylurea-substituted acetophenone derivatives **4** and **5** were synthesized by refluxing 4-aminoacetophenone (**1**) with isocyanate (**2**) and 1-chloro-4-isocyanatobenzene (**3**) according to the published



SCHEME 1 Synthetic routes for the cyanopyridine derivatives (**10a–e** and **11a–e**)

procedure.[33] Compounds **4** and **5** were then reacted with benzaldehyde derivatives (**6a–e**) in a basic medium to synthesize phenylurea-substituted chalcones derivatives (**7a–e** and **8a–e**).[33–36] At the last stage of the study, the synthesis of cyanopyridine derivatives (**10a–e** and **11a–e**) containing the phenylurea unit, which are the resultant target compounds, by the reaction of the phenylurea-substituted chalcone derivatives (**7a–e** and **8a–e**) with malononitrile was carried out (Scheme 1 and Table 1).

The ^{1}H NMR spectra of the new cyanopyridine derivatives (**10a–e** and **11a–e**) were acquired in dimethyl sulfoxide (DMSO)-d_6 solution. The amide H-atoms of the urea unit, $-NH_a$ and $-NH_b$, gave a singlet at δ 8.62–9.05 and 8.57–8.93 ppm, respectively,[37] whereas the H–C2 proton on the cyanopyridine ring gave a singlet in the range of δ 7.47–7.78 ppm (Figure 1). The characteristic doublet of doublets of the H–C7 protons and the triplet of the H–C8 protons in the ethyl group were observed. The H–C7 protons resonated in the range of δ 4.47–4.65 ppm with the coupling constant J = 14.0, 6.8–7.2 Hz, whereas the H–C8 protons were manifested in the range of δ 1.40–1.46 ppm with the coupling constant J = 6.8–7.6 Hz. In the ^{13}C NMR spectra of **10a–e** and **11a–e**, C5 of the carbon atoms on the pyridine ring resonated in the range of δ 164.1–164.6 ppm, whereas C2 resonated between 118.4 and 110.6 ppm and C4 between 91.2 and 106.0 ppm. In addition, nitrile carbon C6 and amide carbonyl carbon C9 in the structure resonated between δ 106.1 and 114.6 ppm and 151.8 and 152.9 ppm, respectively. Other signals were in harmony with the structure.

2.2 | Enzyme inhibition results

The inhibition of metabolic enzymes was investigated, and their results are reported as follows:

i. The cholinesterase inhibition effects of novel cyanopyridine derivatives **10b**, **10c**, and **11a–d** were evaluated according to the spectrophotometric Ellman's method using tacrine (TAC) as a reference compound,[38] as described previously.[39,40] AChE was obtained from the electric eel (E.C. 3.1.1.7) and BChE from equine serum (E.C. 3.1.1.8). Both cholinergic enzymes' inhibition results are reported in Table 2. Novel cyanopyridine derivatives **10b**, **10c**, and **11a–d** had K_i values ranging from 40.73 ± 6.54 to 87.05 ± 16.98 μM for AChE (Table 2). Also, novel cyanopyridine derivatives **10b**, **10c**, and **11a–d** had K_i values ranging from 29.17 ± 4.88 to 124.03 ± 22.43 μM for BChE. However, TAC had K_i values of 116.33 ± 17.45 and 157.13 ± 23.55 μM against indicated AChE and BChE, respectively. It could be seen from the table that all novel targets, **10b**, **10c**, and **11a–d**, demonstrated marked inhibitory effects against both cholinesterase with K_i values in the nanomolar range; however, compound **11d** showed a perfect inhibition effect against AChE and BChE (K_i: 40.73 ± 6.54 μM; $K_{i\,TAC}/K_{i\,\mathbf{11d}}$: 2.86; K_i: 29.17 ± 4.88 μM; $K_{i\,TAC}/K_{i\,\mathbf{11d}}$: 5.38, respectively). Our results have shown potent results, as represented in the present study.

ii. Finally, for the α-Gly inhibition, novel cyanopyridine derivatives **10b**, **10c**, and **11a–d** showed K_i values between 3.66 ± 0.93 and 26.33 ± 5.05 μM (Table 2). The results demonstrated that all novel cyanopyridine derivatives, **10b**, **10c**, and **11a–d**, exhibited effective α-Gly inhibition effects as compared with acarbose (K_i: 20.33 ± 4.31 μM) as a standard α-Gly inhibitor. Also, highly effective K_i values were calculated for compound **11a** (K_i: 3.66 ± 0.93 μM).

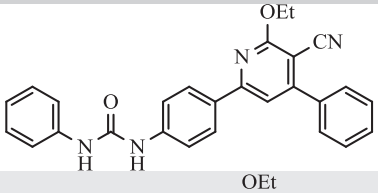
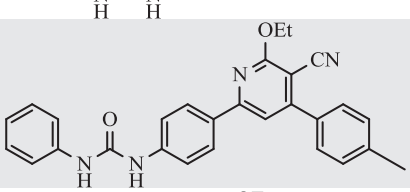
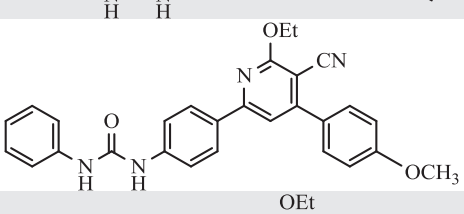
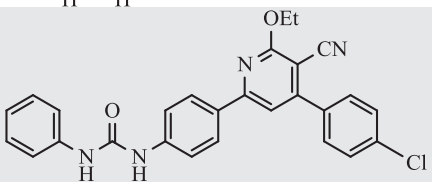
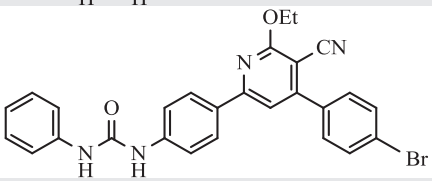
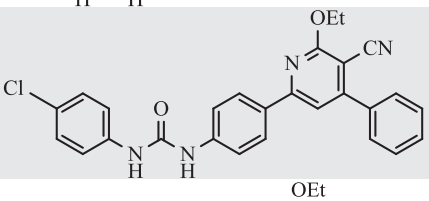
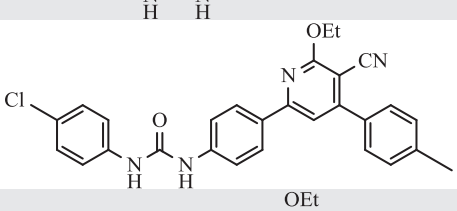
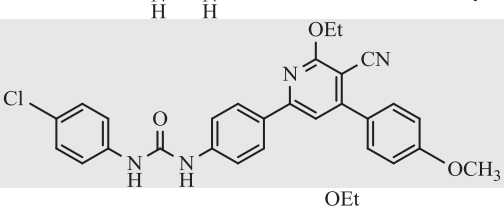
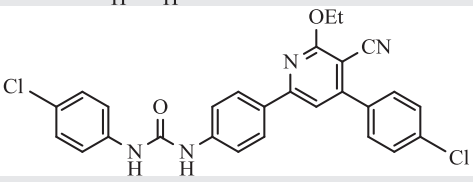
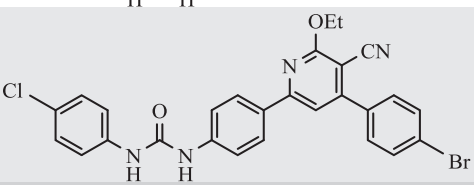
2.3 | Molecular docking results

In molecular docking calculations, calculations were performed using the Maestro Molecular modeling platform (version 12.2) by Schrödinger program to examine the interactions of ligands and proteins. For these calculations, proteins were prepared with the protein preparation module and the molecules were prepared with the LigPrep module. Finally, with the docking module, molecules and enzymes were made to interact with each other. Many parameters were calculated from this interaction. These parameters given in Table 3 are obtained from molecular docking calculations. It should be noted that the most important factor affecting the biological activities of molecules is the interactions between molecules and proteins in enzymes.[41,42] As these interactions increase, the biological activity of the molecule increases. These interactions include hydrogen bonds, polar and hydrophobic interactions, π–π interactions, and halogen interactions,[43–49] and they are presented in Figures 2–4.

The two most important parameters obtained from the molecular docking calculations of the new cyanopyridine derivatives containing phenylurea are docking score and Glide Emodel parameters. The numerical values of these parameters provide important information about the biological activities of the molecules. The molecule with a small numerical value of docking score and Glide Emodel parameters has the highest biological activity against that enzyme. The high biological activity of molecules against enzymes shows that the interaction between the molecule and the proteins in enzymes is very high. It should be noted that as the interactions between molecules and proteins in enzymes increase, the molecule attaches more to the enzyme, which increases the biological activity of the molecule.[32,41,42,50] Another parameter obtained from molecular docking calculations is Glide ligand efficiency, which is the numerical value of the effectiveness of new cyanopyridine derivatives containing phenylurea against enzymes. Another parameter is Glide H-bond, which is the numerical value of the number of hydrogen bonds that occur in interactions between molecules and proteins in enzymes. Another parameter is Glide Evdw, which is the numerical value of van der Waals interactions between molecules and proteins in enzymes. Another parameter is Glide Ecoul, which is the numerical value of Coulomb interactions between molecules and proteins in enzymes. The last one of the parameters obtained as a result of these calculations is Glide Einternal, which is the numerical value of the combination of many parameters obtained.[32,51,52]

The docking results show that the docking score parameter of the molecules and the experimental results are in great agreement,

TABLE 1 The synthesized compounds **10a–e** and **11a–d**

Entry	Synthesized compounds		M. p. (°C)	Yield (%)
1		**10a**	225–228	86
2		**10b**	245–248	93
3		**10c**	194–197	91
4		**10d**	215–218	89
5		**10e**	217–220	93
6		**11a**	268–271	89
7		**11b**	244–247	94
8		**11c**	265–268	90
9		**11d**	263–266	86
10		**11e**	272–274	81

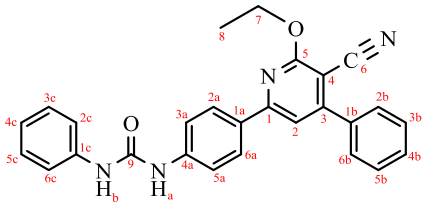


FIGURE 1 The carbon atom numbering of **10a**

such that the molecule with the most negative docking score parameter against the AChE enzyme is molecule **11d** with −8.81 kcal/mol. Also, the molecule with the most negative docking score parameter against the BChE enzyme is molecule **11d** with −3.52 kcal/mol. Finally, the molecule with the most negative docking score parameter against the α-Gly enzyme is molecule **11a** with −2.98 kcal/mol. These results are consistent with experimental results.

Comparing these results with control compounds, it is observed that although TAC molecule has a numerical value of −7.53 kcal/mol of docking score parameter against AChE enzyme, the numerical value of the docking score parameter of molecule **11d** is better than all of them. However, although the docking score parameter of TAC molecule versus the BChE enzyme has a numerical value of −3.95 kcal/mol, the numerical value of the docking score parameter of molecule **11d** is not better than TAC. Finally, although the docking score parameter of acarbose molecule versus α-Gly enzyme is −7.07 kcal/mol, the numerical value of the docking score parameter of molecule **11a** is not better than the acarbose molecule.

If the interactions of molecules with enzymes are examined in detail, it is observed that there are many interactions between molecules and enzymes. First, the molecule with the highest biological activity value against AChE enzyme is **11d**. The oxygen atom bound to the carbonyl carbon in molecule **11d** forms a hydrogen bond with the amino acid TYR337. In addition, there appears to be a π–π stacking interaction between the *N*-(4-chlorophenyl) group in molecule **11d** and TYR337. In addition, there appears to be a π–π stacking interaction between the benzene ring at the center of molecule **11d** and the amino acid TYR124. The 4-chlorophenyl end of molecule **11d** forms polar interactions with TYR119, GLY120, and GLY121 (Figure 2). Besides, the molecule with the highest biological activity value against the BChE enzyme is **11d**. The polar interaction with THR300, ASP301, and MET302 occurs with the ethoxy chain in molecule **11d** (Figure 3). Finally, the molecule with the highest biological activity against the α-Gly enzyme is **11a**. There appears to be a π–π stacking interaction between the 4-methylphenyl ring in molecule **11a** and the amino acid TRP19 (Figure 4).

After comparing the biological activity of new cyanopyridine derivatives containing phenylurea against enzymes, the ADME/T analysis was conducted to theoretically predict the effects and responses of new cyanopyridine derivatives containing phenylurea in human metabolism. As a result of this theoretical analysis, many parameters were obtained, which are presented in Table 4. The first parameter is the solute molecular weight, which requires the molecule to have a certain molecular weight. Another parameter is PISA, which is also called solute total solvent-accessible surface area (SASA). This parameter is the carbon (carbon and attached hydrogen) component of the SASA. Another parameter is QP polarizability, which is the predicted polarizability in cubic angstroms. Another important parameter is QPlog HERG, which is the numerical value of the estimated IC_{50} value when the HERG K channels are blocked. The next parameter is QPPCaco, which is Caco-2 cell permeability in the gut–blood barrier for inactive transport. Another parameter is QPlog BB, which is the coefficient of the brain–blood barrier of an orally taken drug. The next parameter is human oral absorption, which is the predicted qualitative human oral absorption: 1, 2, or 3 for low, medium, or high, respectively.[32,51,52]

The two most important parameters among all ADME/T parameters are the rule of five and the rule of three. The rule of five[53,54] and rule of three[55] parameters are more important than any other parameter, and the numerical value of these two parameters is expected to be zero. The rule of five parameter is also the Lipinski's fifth

TABLE 2 Enzyme inhibition results of the novel compounds against butyrylcholinesterase (BChE), acetylcholinesterase (AChE), and α-glycosidase (α-Gly) enzymes

	IC_{50} (μM)						K_i (μM)		
Compounds	AChE	r^2	BChE	r^2	α-Gly	r^2	AChE	BChE	α-Gly
10b	83.03	.9830	88.35	.9432	9.03	.9821	68.04 ± 14.30	74.87 ± 17.23	13.25 ± 3.51
10c	102.36	.9924	154.30	.9035	14.88	.9903	83.28 ± 10.44	124.03 ± 22.43	19.05 ± 3.88
11a	88.20	.9411	111.84	.9880	2.01	.9942	59.03 ± 11.55	97.23 ± 19.02	3.66 ± 0.93
11b	100.01	.9889	89.08	.9118	5.83	.9424	87.05 ± 16.98	80.32 ± 13.05	7.91 ± 1.05
11c	74.31	.9547	90.43	.9553	11.21	.9919	66.41 ± 18.32	68.45 ± 9.13	15.47 ± 3.40
11d	48.04	.9483	32.05	.9523	21.24	.9430	40.73 ± 6.54	29.17 ± 4.88	26.33 ± 5.05
Tacrine[a]	141.34	.9736	178.03	.9894	–	–	116.33 ± 17.45	157.13 ± 23.55	–
Acarbose[b]	–	–	–	–	15.32	.9243	–	–	20.33 ± 4.31

[a]Used as a control for AChE and BChE enzymes.

[b]Used as a control for α-glycosidase enzyme.

TABLE 3 Numerical values of the parameters obtained from the interactions of the studied molecules with some metabolic enzymes

	Molecule	Docking score	Glide ligand efficiency	Glide H-bond	Glide Evdw	Glide Ecoul	Glide Emodel	Glide energy	Glide Einternal	Glide posenum
AChE	**10a**	−7.64	−0.23	−0.05	−35.71	−6.67	−56.80	−42.38	9.25	365
	10b	−8.18	−0.24	−0.45	−49.63	−3.10	−71.59	−52.73	10.17	238
	10c	−8.18	−0.23	−0.45	−51.13	−2.49	−70.78	−53.62	14.08	234
	10d	−7.99	−0.24	−0.44	−49.52	−2.35	−69.97	−51.88	9.76	2
	10e	−7.72	−0.23	−0.25	−50.28	−2.45	−68.79	−52.72	13.23	2
	11a	−6.91	−0.20	−0.27	−48.48	−1.51	−62.07	−49.99	14.09	379
	11b	−8.19	−0.23	−0.40	−54.90	−1.51	−76.43	−56.40	8.74	211
	11c	−6.81	−0.19	−0.45	−47.35	−1.58	−61.29	−48.94	13.60	328
	11d	−8.81	−0.25	−0.45	−47.35	−1.58	−73.29	−58.94	13.60	328
	11e	−7.03	−0.20	−0.28	−48.07	−0.88	−60.99	−48.96	14.92	363
	Tacrine	−7.53	−0.50	−0.16	−22.45	−10.78	−53.38	−33.23	0.00	358
BChE	**10a**	−2.62	−0.08	0.00	−25.75	−2.47	−31.19	−28.22	3.06	138
	10b	−2.74	−0.08	−0.22	−25.77	−1.61	−30.86	−27.38	2.06	63
	10c	−3.11	−0.09	−0.32	−27.45	−3.79	−35.92	−31.23	2.31	28
	10d	−2.73	−0.08	−0.53	−25.66	−3.23	−32.46	−28.90	2.75	345
	10e	−2.20	−0.06	−0.03	−27.69	−0.26	−30.65	−27.96	2.20	155
	11a	−2.60	−0.07	−0.16	−27.92	−1.80	−29.07	−29.71	9.11	56
	11b	−2.52	−0.07	−0.14	−28.14	−1.74	−28.59	−29.88	8.67	149
	11c	−2.52	−0.07	0.00	−30.36	−0.94	−34.24	−31.30	3.29	281
	11d	−3.52	−0.07	0.00	−25.36	−0.94	−36.24	−32.30	2.29	281
	11e	−2.36	−0.07	−0.06	−27.94	−0.48	−31.60	−28.42	2.12	262
	Tacrine	−3.95	−0.26	0.00	−13.58	−4.67	−23.94	−18.25	0.00	47
α-Gly	**10a**	−2.51	−0.08	0.00	−29.87	−1.69	−34.99	3.11	−34.77	86
	10b	−2.51	−0.07	0.00	−30.49	−1.69	−35.43	3.17	−29.60	242
	10c	−2.73	−0.08	0.00	−31.28	−3.48	−39.66	2.25	−35.47	29
	10d	−2.13	−0.06	0.00	−27.67	−2.96	−33.78	2.35	−32.18	183
	10e	−2.72	−0.08	0.00	−26.47	−3.13	−30.75	8.59	−31.56	205
	11a	−2.98	−0.06	0.00	−31.78	−0.01	−41.90	9.16	−36.00	355
	11b	−2.63	−0.07	0.00	−31.87	−3.60	−35.31	12.27	−32.49	52
	11c	−2.18	−0.06	0.00	−29.51	−2.98	−32.01	9.82	−32.49	352
	11d	−2.18	−0.06	0.00	−29.51	−2.98	−32.01	9.82	−30.62	352
	11e	−2.38	−0.07	−0.03	−29.23	−2.77	−35.21	3.75	−29.78	252
	Acarbose	−7.07	−0.16	−0.47	−26.85	−25.83	−85.08	−52.68	22.11	118

Abbreviations: AChE, acetylcholinesterase; BChE, butyrylcholinesterase; α-Gly, α-glycosidase.

rule of Pfizer. The rules are as follows: mol MW < 500, QPlog *P* o/w < 5, donorHB ≤ 5, accptHB ≤ 10 (the "five" refers to the limits, which are multiples of 5). However, the rule of three parameter is known as the three rules of Jorgensen. The three rules are as follows: QPlog *S* > −5.7, QPPCaco > 22 nm/s, and #Primary Metabolites < 7. If the numerical value of the rule of three parameter is zero, this molecule can be used orally as a medicine. These two parameters are among the parameters that must be examined for the molecules to be theoretical drugs.

Experimentally and theoretically, the two molecules with the highest biological activity are **11a** and **11d**. When the ADME/T results of these two molecules were examined in detail, the molecular masses of the molecules were calculated as 483 and 503, respectively. However, the numerical value of the total SASA parameter is 837 and 823. One of the most important parameters in ADME/T calculations is the QPPCaco parameter, the numerical value of this parameter is 223 for both. There are many other parameters. The numerical values of these calculated parameters are within the normal range.

3 | CONCLUSIONS

In conclusion, a series of novel cyanopyridine derivatives (**10a**–**e** and **11a**–**e**) containing the phenylurea unit was synthesized in high yields (81%–94%) and investigated for their inhibition properties against AChE, BChE, and α-Gly. Among the compounds whose inhibitory activity was examined, compound **11d** showed the best activity against AChE and BChE enzymes, whereas compound **11a** showed the best

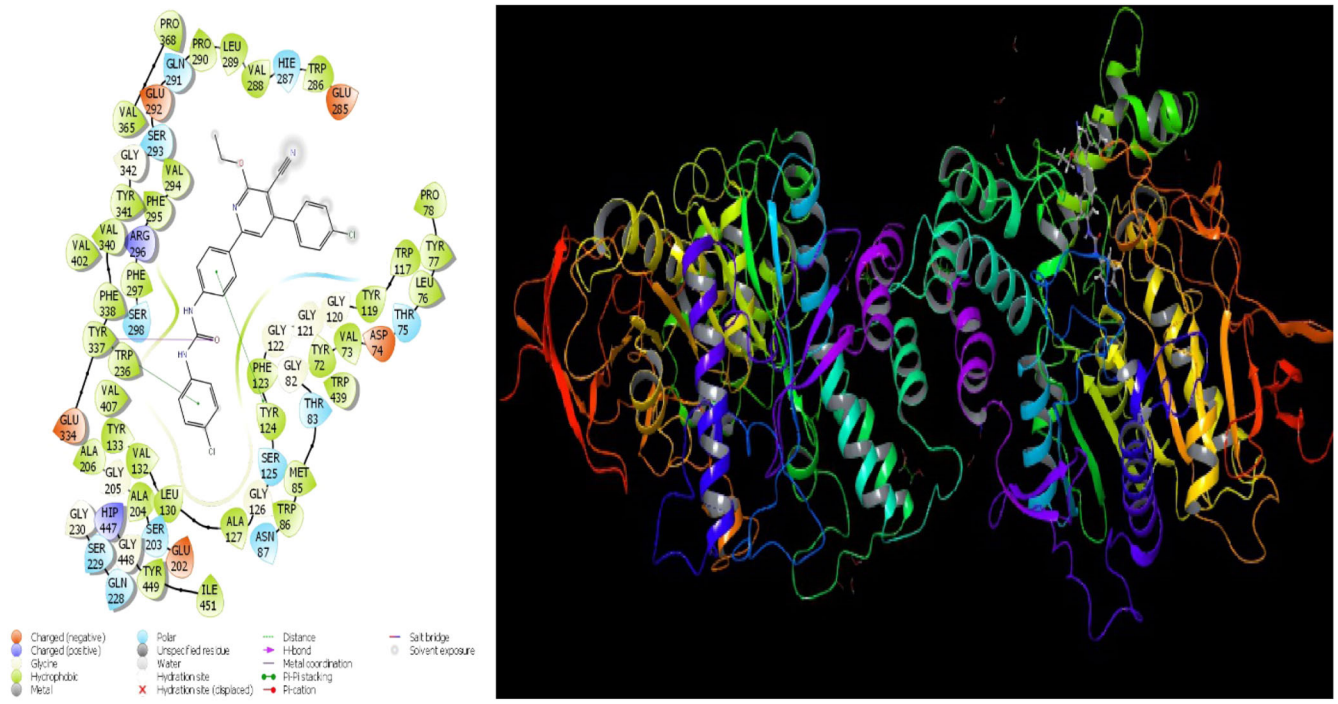


FIGURE 2 Interaction of molecule **11d** with the acetylcholinesterase enzyme

activity against the α-Gly enzyme. It was observed that the data obtained from molecular docking calculations were in harmony with the experimental study. The biological activities of molecules against enzymes were determined by molecular docking calculations. A comparison is made with the numerical values obtained as a result of these calculations. With the data obtained as a result of these calculations, it is possible to synthesize more effective and more active molecules. Afterward, the ADME/T analysis of these molecules was performed theoretically. As a result of this analysis, these molecules were examined with many parameters. The analysis of the numerical values of the parameters obtained may lead to the discovery of new drug candidates using in vivo and in vitro studies in future.

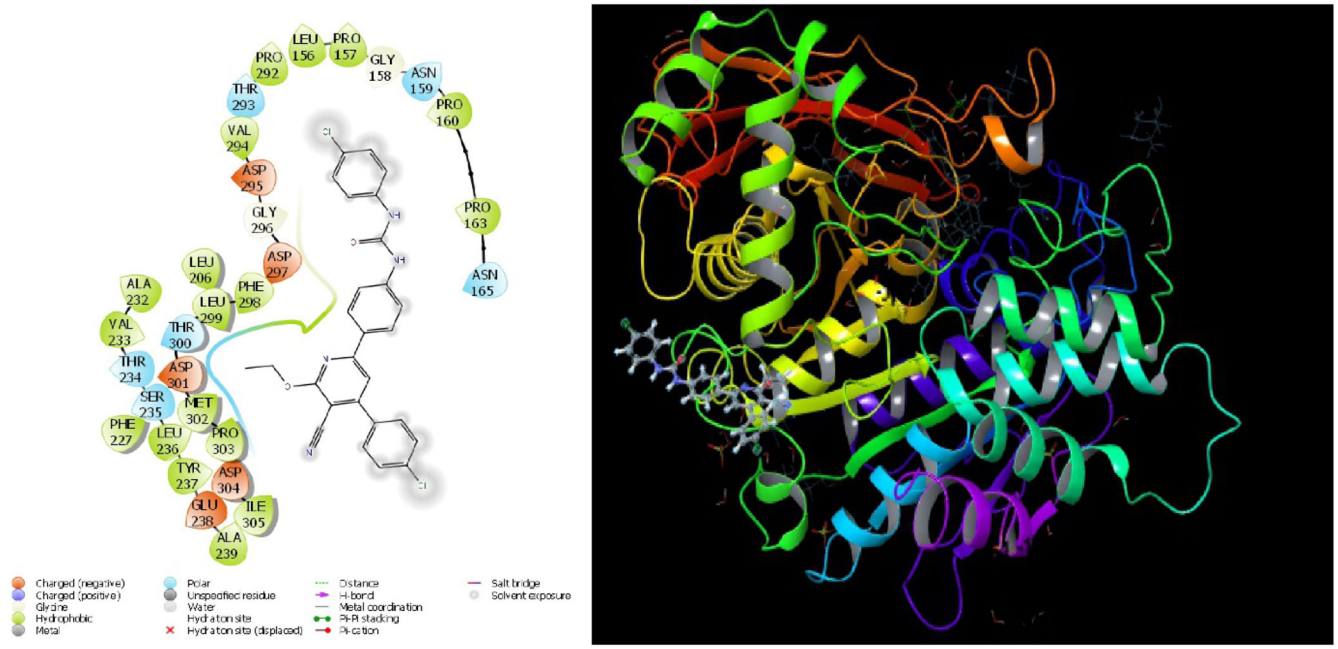


FIGURE 3 Interaction of molecule **11d** with the butyrylcholinesterase enzyme

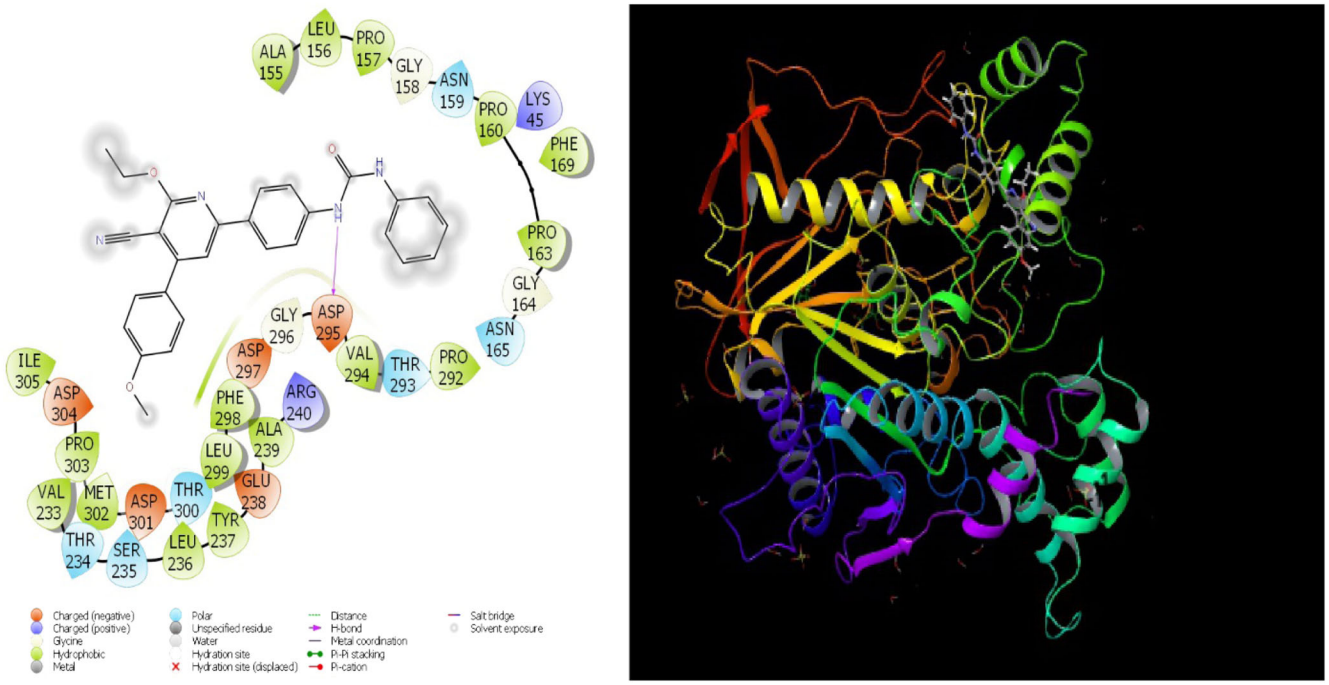


FIGURE 4 Interaction of molecule **11a** with the α-glycosidase enzyme

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All chemicals and solvents were obtained from Merck (Germany) and Fluka (Germany). Melting points were measured using an Electrothermal 9100 apparatus. The ^{1}H and ^{13}C NMR spectra (see Supporting Information) were recorded with a Bruker Avance DPX-400 instrument. Elemental analyses were obtained from a LECO CHNS 932 Elemental Analyzer.

The InChI codes of the investigated compounds, together with some biological activity data, are provided as Supporting Information.

4.1.2 | Synthesis of the phenylurea-substitued acetophenone derivatives 4 and 5

The phenylurea-substituted acetophenone derivatives **4** and **5** were synthesized in accordance with the published procedures.[33]

4.1.3 | General method for the synthesis of phenylurea-substituted chalcone derivatives 7a–e and 8a–e

The phenylurea-substituted chalcone derivatives (**7a–e** and **8a–e**) were synthesized in accordance with the published procedures.[33,36]

4.1.4 | General method for the synthesis of cyanopyridine derivatives containing the phenylurea unit (10a–e and 11a–d)

To a solution of chalcones (**7a–e** or **8a–e**; 1 mmol) in 20 ml of ethanol, malononitrile (**9**; 4 mmol) and K_2CO_3 (8 mmol) were added and refluxed for 4 h. The mixture was neutralized by adding HCl. Then, it was diluted with $CHCl_3$ (50 ml) and dried over Na_2SO_4. The solvent was evaporated, and the crude product was crystallized in $CHCl_3$/ethanol (3:7) mixture. Their structures were confirmed using IR, ^{1}H NMR, and ^{13}C NMR.

*1-[4-(5-Cyano-6-ethoxy-4-phenylpyridin-2-yl)phenyl]-3-phenylurea (**10a**)*

Yield: 86%, Mp: 225–228°C. IR (KBr, cm^{-1}): 3385, 2966, 2221, 1708, 1634, 1589, 1539, 1493, 1450, 1424, 1377, 1332, 1319, 1233, 1172, 1148, 1035, 827, 752, 698, 642, 511. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.02 (s, 1H), 8.78 (s, 1H), 8.21 (d, J = 8.8 Hz, 2H), 7.73 (s, 1H), 7.64–7.58 (m, 6H), 7.50–7.47 (m, 2H), 7.33–7.29 (m, 3H), 7,02–6.98 (m, 1H), 4.62 (dd, J = 14.0, 7.2 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.43, 157.58, 156.62, 152.77, 142.79, 139.90, 136.57, 132.34, 129.50 (2C), 129.29 (2C), 129.05 (2C), 128.84 (2C), 127.51, 122.58, 118.85 (2C), 118.77 (2C), 116.07, 113.07, 91.64, 63.45, 14.87. Anal. calc. for $C_{27}H_{22}N_4O_2$: C, 74.64; H, 5.10; N, 12.89. Found: C, 74.56; H, 5.07; N, 12.80.

*1-{4-[5-Cyano-6-ethoxy-4-(p-tolyl)pyridin-2-yl]phenyl}-3-phenylurea (**10b**)*

Yield: 93%, Mp: 245–248°C. IR (KBr, cm^{-1}): 3380, 2976, 2220, 1703, 1631, 1582, 1539, 1499, 1444, 1419, 1371, 1339, 1315, 1237, 1176,

TABLE 4 ADME properties of the molecules

	10a	10b	10c	10d	10e	11a	11b	11c	11d	11e	Reference range
Solute molecular weight	434	449	465	469	513	483	499	503	503	548	130 to 725
Solute dipole moment (*D*)	5.9	5.8	5.3	6.1	6.9	6.2	4.8	6.2	6.2	6.6	1.0 to 12.5
SASA	781	812	809	799	810	837	833	823	823	834	300 to 1000
FOSA	107	194	195	107	107	194	195	107	107	107	0 to 750
FISA	140	140	139	140	140	140	139	140	140	140	7 to 330
PISA	534	478	475	486	485	430	427	438	438	437	0 to 450
WPSA	0	0	0	66	77	72	72	138	138	149	0 to 175
Solute molecular volume ($Å^3$)	1391	1450	1461	1425	1444	1494	1506	1469	1469	1488	500 to 2000
Solute as hydrogen bond donor	2	2	2	2	2	2	2	2	2	2	0 to 6
Solute as hydrogen bond acceptor	4.5	4.5	5.25	4.5	4.5	4.5	5.25	4.5	4.5	4.5	2.0 to 20.0
Solute globularity (sphere = 1)	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.75 to 0.95
QP polarizability ($Å^3$)	50.1	51.9	51.7	51.0	51.8	53.3	53.0	52.3	52.3	53.1	13.0 to 70.0
QPlog *p* for hexadecane/gas	16.5	16.7	16.8	17.0	17.3	17.4	17.4	17.6	17.6	17.9	4.0 to 18.0
QPlog *p* for octanol/gas	22.7	23.2	23.4	23.2	23.6	23.9	24.1	23.9	23.9	24.3	8.0 to 35.0
QPlog *p* for water/gas	14.9	14.6	15.1	14.7	14.7	14.4	14.9	14.4	14.4	14.5	4.0 to 45.0
QPlog *p* for octanol/water	5.0	5.3	5.0	5.4	5.5	5.8	5.5	5.9	5.9	6.0	−2.0 to 6.5
QPlog *S* aqueous solubility	−7.2	−7.8	−7.3	−7.8	−8.1	−8.5	−8.0	−8.6	−8.6	−8.8	−6.5 to 0.5
QPlog *S* conformation-independent	−8.0	−8.2	−8.3	−8.7	−9.6	−9.0	−9.0	−9.4	−9.4	−10.3	−6.5 to 0.5
QPlog HERG	−6.4	−6.3	−6.1	−6.3	−6.3	−6.2	−6.0	−6.1	−6.1	−6.2	[a]
QPPCaco (nm/s)	223	223	229	223	223	223	229	223	223	223	[b]
QPlog BB	−1.4	−1.5	−1.5	−1.3	−1.3	−1.3	−1.3	−1.1	−1.1	−1.1	−3.0 to 1.2
QPPMDCK (nm/s)	214	214	220	492	568	532	546	1221	1221	1411	[b]
QPlog Kp	−1.6	−1.8	−1.6	−1.7	−1.7	−1.9	−1.8	−1.9	−1.9	−1.9	Kp in cm/h
IP (eV)	9.3	9.3	9.3	9.0	9.3	9.3	9.3	9.0	9.0	9.4	7.9 to 10.5
EA (eV)	0.8	0.8	0.9	0.8	0.9	0.8	0.9	0.8	0.8	0.9	−0.9 to 1.7
#metab	2	3	3	2	2	2	2	1	1	1	1 to 8
QPlog Khsa	0.8	1.0	0.8	0.9	1.0	1.1	0.9	1.0	1.0	1.1	−1.5 to 1.5
Human oral absorption	1	1	1	1	1	1	1	1	1	1	–
Percent human oral absorption	100	87	86	87	75	90	89	77	77	78	[c]
PSA	93	93	102	93	93	93	102	93	93	93	7 to 200
Rule of five	0	1	1	1	2	1	1	2	2	2	Maximum is 4
Rule of three	1	1	1	1	1	1	1	1	1	1	Maximum is 3
Jm	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	–

[a]Corcern below −5.

[b]<25 is poor and >500 is great.

[c]>80% is high.

1142, 1032, 821, 748, 691, 640, 509. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.99 (s, 1H), 8.75 (s, 1H), 8.20 (d, *J* = 8.8 Hz, 2H), 7.69 (s, 1H), 7.63 (t, *J* = 8.0 Hz, 4H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 8.0 Hz, 2H), 6.99 (t, *J* = 7.6 Hz, 1H), 4.64 (dd, *J* = 14.0, 7.2 Hz, 2H), 2.42 (s, 3H), 1.45 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.48, 157.43, 156.30, 152.67, 142.30, 139.92, 139.48, 133.67, 129.56, 128.86 (2C), 128.36 (2C), 128.18 (3C), 122.34 (2C), 118.66 (2C), 118.16 (2C), 115.87, 112.33, 91.61, 63.08, 21.36, 14.63. Anal. calc. for $C_{28}H_{24}N_4O_2$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.86; H, 5.21; N, 12.37.

*1-{4-[5-Cyano-6-ethoxy-4-(4-methoxyphenyl)pyridin-2-yl]phenyl}-3-phenylurea (**10c**)*

Yield: 91%, Mp: 194–197°C. IR (KBr, cm^{-1}): 3400, 2218, 1725, 1584, 1538, 1442, 1375, 1339, 1314, 1233, 1174, 1024, 823, 748, 682, 634, 574. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.98 (s, 1H), 8.74 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.68 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 8.0 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (t, J = 7.2 Hz, 1H), 4.63 (dd, J = 14.0, 7.2 Hz, 2H), 3.86 (s, 3H), 1.45 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.56, 161.21, 157.38, 156.19, 152.77, 142.69, 139.90, 130.60 (2C), 130.46, 129.26 (2C), 128.74 (2C), 128.66, 122.56, 118.87 (2C), 118.38 (2C), 116.30, 114.74 (2C), 112.79, 91.26, 63.33, 55.89, 14.87. Anal. calc. for $C_{28}H_{24}N_4O_3$: C, 72.40; H, 5.21; N, 12.06. Found: C, 72.37; H, 5.18; N, 12.01.

*1-{4-[4-(4-Chlorophenyl)-5-cyano-6-ethoxypyridin-2-yl]phenyl}-3-phenylurea (**10d**)*

Yield: 89%, Mp: 215–218°C. IR (KBr, cm^{-1}): 3316, 2979, 2357, 2222, 1649, 1597, 1544, 1495, 1443, 1424, 1379, 1342, 1314, 1234, 1206, 1093, 1035, 1013, 821, 745, 693, 647, 509, 484. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.89 (s, 1H), 8.73 (s, 1H), 8.14 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.78 (s, 1H), 7.60–7.57 (m, 4H), 7.47 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 8.4 Hz, 2H), 6.99 (t, J = 7.6 Hz, 1H), 4.49 (dd, J = 14.0, 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.20, 154.89, 152.88, 150.39, 141.28, 140.04, 136.89, 134.51, 132.08, 130.98, 129.45 (2C), 129.37 (2C), 129.27 (2C), 127.79 (2C), 122.44, 118.78 (2C), 118.40 (2C), 110.52, 106.03, 61.69, 15.07. Anal. calc. for $C_{27}H_{21}ClN_4O_2$: C, 69.15; H, 4.51; N, 11.95. Found: C, 69.10; H, 4.48; N, 11.86.

*1-{4-[4-(4-Bromophenyl)-5-cyano-6-ethoxypyridin-2-yl]phenyl}-3-phenylurea (**10e**)*

Yield: 93%, Mp: 217–220°C. IR (KBr, cm^{-1}): 3416, 2923, 1645, 1597, 1542, 1496, 1444, 1377, 1341, 1314, 1236, 1209, 820, 745, 693. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.90 (s, 1H), 8.74 (s, 1H), 8.14 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.77 (s, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 8.0 Hz, 2H), 6.97 (t, J = 6.8 Hz, 1H), 4.47 (dd, J = 14.0, 6.8 Hz, 2H), 1.40 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.22, 154.93, 152.89, 150.46, 141.35, 140.10, 136.99, 132.37 (2C), 132.24, 131.18, 129.64 (2C), 129.26 (2C), 127.78 (2C), 123.19, 122.43, 118.79 (2C), 118.42 (2C), 110.46, 105.98, 61.69, 15.07. Anal. calc. for $C_{27}H_{21}BrN_4O_2$: C, 63.17; H, 4.12; N, 10.91. Found: C, 63.08; H, 4.09; N, 10.81.

*1-(4-Chlorophenyl)-3-[4-(5-cyano-6-ethoxy-4-phenylpyridin-2-yl)phenyl]urea (**11a**)*

Yield: 89%, Mp: 268–271°C. IR (KBr, cm^{-1}): 3410, 2222, 1585, 1540, 1491, 1445, 1399, 1373, 1339, 1309, 1234, 1175, 828, 762, 698, 607, 505. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.05 (s, 1H), 8.92 (s, 1H), 8.22 (d, J = 8.8 Hz, 2H), 7.75–7.73 (m, 3H), 7.62 (d, J = 8.8 Hz, 2H), 7.60–7.58 (m, 3H), 7.51 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 4.65 (dd, J = 14.0, 6.8 Hz, 2H), 1.46 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.44, 157.57, 156.66, 152.69, 142.60, 138.93, 136.56, 130.51, 130.42, 129.29 (2C), 129.12 (2C), 129.03 (2C), 128.82 (2C), 126.38, 121.47 (2C), 118.52 (2C), 116.34, 114.65, 91.90, 67.04, 14.86. Anal. calc. for $C_{27}H_{21}ClN_4O_2$: C, 69.15; H, 4.51; N, 11.95. Found: C, 69.03; H, 4.38; N, 11.82.

*1-(4-Chlorophenyl)-3-{4-[5-cyano-6-ethoxy-4-(p-tolyl)pyridin-2-yl]phenyl}urea (**11b**)*

Yield: 94%, Mp: 244–247°C. IR (KBr, cm^{-1}): 3338, 2227, 1694, 1694, 1581, 1535, 1492, 1444, 1397, 1377, 1338, 1310, 1237, 1214, 1177, 1145, 1089, 1034, 1011, 819, 616, 508. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.03 (s, 1H), 8.90 (s, 1H), 8.20 (d, J = 8.0 Hz, 2H), 7.70 (s, 1H), 7.65–7.61 (m, 4H), 7.51 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 4.63 (dd, J = 14.0, 7.2 Hz, 2H), 2.48 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.50, 157.48, 156.62, 152.69, 142.55, 140.31, 138.93, 133.68, 130.58, 129.85 (2C), 129.13 (2C), 128.95 (2C), 128.79, 127.32, 126.12, 120.41 (2C), 118.53 (2C), 116.11, 112.97, 91.58, 63.40, 21.36, 14.86. Anal. calc. for $C_{28}H_{23}ClN_4O_2$: C, 69.63; H, 4.80; N, 11.60. Found: C, 69.59; H, 4.78; N, 11.53.

*1-(4-Chlorophenyl)-3-{4-[5-cyano-6-ethoxy-4-(4-methoxyphenyl)-pyridin-2-yl]phenyl}urea (**11c**)*

Yield: 90%, Mp: 265–268°C. IR (KBr, cm^{-1}): 3381, 1722, 1607, 1578, 1535, 1494, 1445, 1315, 1295, 1259, 1236, 1174, 1024, 870, 827, 637, 517, 501. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.77 (s, 1H), 8.64 (s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 4.57 (dd, J = 14.0, 7.2 Hz, 2H), 3.81 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.51, 161.00, 157.26, 155.93, 152.52, 142.22, 138.59, 130.62, 130.14 (2C), 128.75 (2C), 128.65 (2C), 128.31, 126.35, 120.02 (2C), 118.28 (2C), 116.01, 114.42 (2C), 112.39, 91.36, 63.06, 55.55, 14.72. Anal. calc. for $C_{28}H_{23}ClN_4O_3$: C, 67.40; H, 4.65; N, 11.23. Found: C, 67.34; H, 4.59; N, 11.18.

*1-(4-Chlorophenyl)-3-{4-[4-(4-chlorophenyl)-5-cyano-6-ethoxypyridin-2-yl]phenyl}urea (**11d**)*

Yield: 86%, Mp: 266–263°C. IR (KBr, cm^{-1}): 3304, 2975, 1644, 1595, 1546, 1491, 1427, 1398, 1379, 1344, 1303, 1236, 1207, 1090, 1012, 821, 654, 515, 482. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.62 (s, 1H), 8.57 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.50 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.41 (m, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 4.57 (dd, J = 14.0, 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.08, 154.77, 152.65, 150.35, 140.77, 138.66, 137.07, 134.60, 132.44, 129.17 (2C), 128.71 (2C), 128.68 (2C), 127.42 (2C), 126.28, 119.92 (2C), 118.31 (2C), 110.25, 106.07, 92.44, 61.50, 14.89. Anal. calc. for $C_{27}H_{20}Cl_2N_4O_2$: C, 64.42; H, 4.00; N, 11.13. Found: C, 64.38; H, 3.89; N, 11.10.

*1-(4-Chlorophenyl)-3-{4-[4-(4-bromophenyl)-5-cyano-6-ethoxypyridin-2-yl]phenyl}urea (**11e**)*

Yield: 81%, Mp: 272–274°C. IR (KBr, cm^{-1}): 3300, 2968, 1621, 1585, 1541, 1487, 1426, 1389, 1374, 1338, 1300, 1236, 1201, 1089, 1009,

820, 659, 505, 474. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.98 (s, 1H), 8.93 (s, 1H), 8.14 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.78 (s, 1H), 7.60–7.57 (m, 4H), 7.51 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 4.51 (dd, J = 14.0, 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.6, 155.7, 154.5, 151.8, 140.6, 138.66, 137.07, 134.60, 132.44, 129.17 (2C), 128.71 (2C), 128.68 (2C), 127.42 (2C), 126.28, 119.92 (2C), 118.31 (2C), 110.25, 106.07, 92.44, 61.50, 14.89. Anal. calc. for $C_{27}H_{20}ClBrN_4O_2$: C, 59.20; H, 3.68; N, 10.23. Found: C, 59.18; H, 3.61; N, 10.20.

4.2 | Enzymes studies

The inhibitory effect of novel cyanopyridine derivatives on AChE and BChE activities was examined according to the spectrophotometric method of Ellman,[38] as described previously.[39] The α-Gly inhibition effect of the novel cyanopyridine derivatives was evaluated according to the method of Tao et al.[40] The absorbance of samples was recorded at 405 nm.[32]

4.3 | Molecular docking method

Theoretical calculations provide good assistance to experimental studies. By theoretical calculations, biological activities of molecules against enzymes are compared. There are many programs and methods in theoretical calculations. The most commonly used among these is molecular docking. The numerical values of many parameters obtained from molecular docking calculations provide important information about the biological activities of molecules. These numerical values can be used for the discovery of new drugs.

In this study, molecular docking calculations were performed to compare the biological activities of molecules using Maestro Molecular modeling platform (version 12.2) by Schrödinger. Proteins and molecules must be prepared for calculations. In the calculations, a different process was performed for the molecules at each stage. First, the Gaussian software program[56] was used to obtain optimized structures of molecules, which created files with the extension *.sdf using these structures. Using these files, all calculations were performed with Maestro Molecular modeling platform (version 12.2) by Schrödinger, LLC.[57] The Maestro Molecular modeling platform (version 12.2) by Schrödinger consists of many modules. First, the protein preparation module[58,59] was used to prepare the proteins for calculations. The studied enzymes consisted of a combination of many small proteins. The crystal structures of these enzymes have been downloaded from the Protein Data Bank site. These enzymes were initially minimized and water molecules in crystal structures were removed. In the next step, the active regions of the enzymes were determined for calculations, in which all the proteins in this active region were given freedom of movement. Therefore, these proteins were enabled to interact with molecules more easily. In the next step, the LigPrep module[60,61] was used to prepare the working molecules for calculations.

Calculations were performed to find high-energy isomers with physiological pH values of new cyanopyridine derivatives containing phenylurea 3D structures and the correct protonation conditions. In the next step, the prepared protein and molecules were docked with each other. The Glide ligand docking module[62] was used for this step. In this module, the OPLS3e method was used in all calculations for docking calculations of molecule and proteins. The numerical value of many parameters obtained as a result of molecular docking calculations using this module is used. After the docking calculations, the ADME/T analysis was performed to examine the molecule's ability to be used as a drug in the future. The Qik-prop module[63] of the Schrödinger software was used for the ADME/T analysis.

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CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interests.

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