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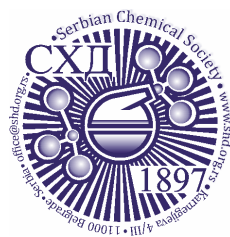
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Design of novel quinazoline–chalcone hybrids as potent epidermal growth factor receptor inhibitors

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Abstract: This study successfully designed and synthesized a novel series of quinazoline–chalcone hybrids. The key innovation lies in the molecular hybridization of the pharmacophoric quinazoline scaffold with a chalcone moiety, creating new chemical entities to exploit potential synergistic antitumor effects. A concise multi-step synthetic route was efficiently implemented. Preliminary evaluation demonstrated that a majority of these hybrids exhibited potent anti-proliferative activity against non-small cell lung cancer (NSCLC) cell lines (A549 and H1975) *in vitro*. Molecular docking studies suggested against epidermal growth factor receptor (EGFR) inhibition as a potential mechanism, with the compounds forming stable interactions with the kinase domain. Furthermore, *in silico* absorption, distribution, metabolism and excretion (ADME) and toxicity predictions by SwissADME and ProTox 3.0, respectively, indicated promising drug-like properties and safety profiles. However, the cytotoxicity was assessed only on cancer cell lines, and the selectivity against normal cells remains to be determined. Despite this limitation, the compelling initial results position these novel hybrids as promising leads for future optimization and development.

Keywords: synthesis; EGFR inhibition; molecular docking; antitumor activity; ADME prediction; structure–activity relationship.

INTRODUCTION

Targeted therapies achieve precision treatment by specifically inhibiting key signaling pathways in cancer cells.^{1–5} The 4-aminoquinazoline scaffold serves as a privileged pharmacophore that forms the structural basis of multiple clinically approved EGFR tyrosine kinase inhibitors (EGFR-TKIs),^{6–9} such as zorifertinib.¹⁰

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Its high structural versatility enables rational optimization of inhibitory activity against specific mutations. Meanwhile, natural chalcone derivatives exhibit broad-spectrum antitumor effects through their unsaturated ketone moiety,^{11–14} which modulates diverse oncogenic processes via multiple mechanisms. The present study innovatively integrates the quinazoline core with chalcone structures using flexible linkers.^{15–17} It preserves the critical hydrogen-bonding network between the quinazoline scaffold and EGFR's adenosine triphosphate (ATP)-binding pocket while leveraging chalcone's covalent binding capability to enhance target engagement.¹⁸ The systematic molecular optimization through bioisosteric replacement and pharmacophore refinement generated novel small-molecule inhibitors with improved selectivity and pharmacokinetic profiles.^{19–21}

The molecular design strategy is illustrated in Fig. 1. The third-generation EGFR inhibitor zorifertinib demonstrates a characteristic binding mode wherein the N3 nitrogen atom of the quinazoline core establishes a hydrogen-bonding interaction with the catalytic residue ASP-855 of the target protein. The molecular scaffold occupies the ATP-binding pocket delineated by ARG748, GLY857, ASP855, LYS875 and GLY874 residues, with 6- and 7-position substituents projecting into the solvent-accessible region. This binding conformation exemplifies the conserved structural motif of quinazoline-derived EGFR inhibitors. Accordingly, a rational design strategy was implemented by introducing flexible linkers containing chalcone structures at the 6-position. The unsaturated ketone moiety serves as a Michael acceptor to form selective covalent bonds with target protein residues while the aromatic system enhances binding affinity through hydrophobic inter-

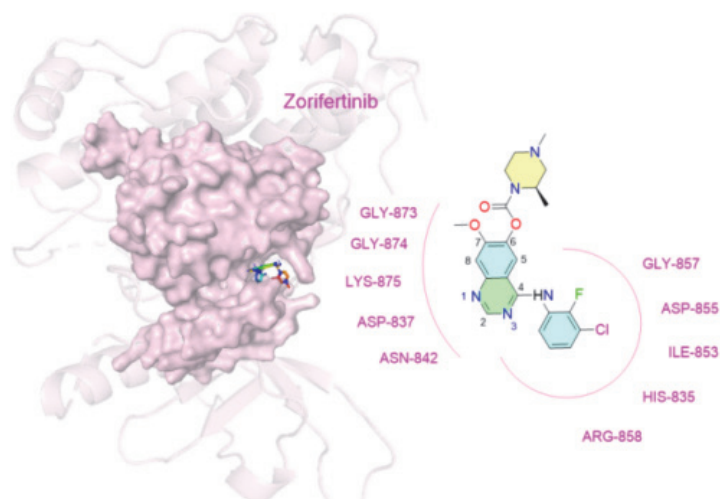


Fig. 1. Zorifertinib molecular docking interaction diagram.

actions.^{22–26} Additionally, the methoxy group at this position is retained to synergistically improve antitumor activity and mutation selectivity.²⁷ Based on the structure–activity relationship analysis, the present study adopted highly selective pharmacophores as the molecular design framework and innovatively constructed a hybrid quinazoline-chalcone molecular system. By integrating the protein-binding patterns and structure–activity relationship data of zorifertinib, this study precisely preserved the quinazoline core structure of EGFR inhibitors using the bioisosterism principle,^{28,29} while systematically optimizing the pharmacokinetic properties of candidate compounds through pharmacophore refinement and isosteric replacement strategies. Through rational design, a series of novel small-molecule EGFR inhibitors, featuring combined quinazoline and chalcone structural motifs, were successfully developed.

Based on the aforementioned research background, the present study synthesized and characterized a series of novel quinazoline–chalcone hybrids using IR, ¹H-NMR, ¹³C-NMR and mass spectrometry. Their antitumor activities were evaluated against A549 and H1975 cell lines. In addition, *in silico* ADME prediction, toxicity prediction, and molecular docking with the EGFR kinase domain (PDB ID:7OXB) were performed to assess drug-like properties and explore the binding mode of representative compound **9h**, providing mechanistic insights into its action.

EXPERIMENTAL

Chemistry

General. All reagents and solvents were commercially available and used as received unless otherwise specified. Reaction progress was monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates (Qingdao Haiyang Chemical Co., Ltd.).

Instrumentation and Characterization. Melting points were determined on an X-4 micro-melting point apparatus and are uncorrected. ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker ARX-400 spectrometer (400 MHz for ¹H-NMR, 101 MHz for ¹³C-NMR) in the indicated deuterated solvents (CDCl₃ or DMSO-*d*₆) using tetramethylsilane (TMS) as an internal standard; chemical shifts are reported in ppm and coupling constants (*J*) are given in Hz. FT-IR spectra were acquired on a Bruker Tensor II spectrometer using KBr pellets and wavenumbers are reported in cm^{–1}. Low-resolution electrospray ionization (ESI) mass spectra were recorded on a Finnigan Trace MS spectrometer. Samples were dissolved in a mixed solvent of methanol and acetonitrile and introduced *via* direct infusion in positive ion mode. All observed *m/z* values corresponded to the expected [M]⁺ or [M+H]⁺ of the target compounds.

General procedure for the synthesis of intermediates **2**

At room temperature, the mixed solution of 7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate **1** (1.20 g, 5.12 mmol), toluene (15 mL) and triethylamine (0.88 g, 8.71 mmol) were heated to 80 °C. Then, phosphorus oxychloride (1.96 g, 12.81 mmol) was added to the mixture. After completion, the reaction proceeds directly to the next step.

*General procedure for the synthesis of intermediates 3a–h*³⁰

Substituted aniline (0.48 g, 4.35 mmol) was added to intermediate **2**, and the mixture was stirred for 5 h. After completion, the solvent was concentrated under vacuum and mixed with isopropanol (15 mL) for 12 h. The product was filtered to afford intermediate **3**.

*General procedure for the synthesis of intermediates 4a–h*³⁰

Intermediate **3** (1.00 g, 3.06 mmol), methanol (15 mL) and ammonia solution (1 mL) were stirred at room temperature. After completion, the solvent was concentrated under vacuum, followed by addition of water (8 mL). It was filtered to afford intermediate **4**.

General procedure for the synthesis of intermediates 7a–c

Referred to reference,³¹ taking (2*E*)-1-(4-aminophenyl)-3-(3-methylphenyl)prop-2-en-1-one (**6a**) as an example: 4-aminoacetophenone (1.00 g, 3.70 mmol), 3-methylbenzaldehyde (0.88 g, 3.70 mmol) and ethanol (15 mL) were added sequentially; the reaction vessel was transferred to a cooling bath maintained at 5 °C. Add a 20 % aqueous sodium hydroxide (0.29 g, 7.40 mmol) solution dropwise over 0.25 h. After completion, the solvent was concentrated under vacuum to afford intermediates **7a**. The reaction proceeds directly to the next step.

*General procedure for the synthesis of intermediates 8a–c*³²

Taking *N*-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-chloroacetamide (**7a**) as an example: intermediate **7a** (1.00 g, 4.21 mmol), dichloromethane (15 mL), chloroacetyl chloride (1.43 g, 12.64 mmol) and triethylamine (0.51 g, 5.06 mmol) were stirred at 0 °C under nitrogen in a cooling bath. After completion, the mixture was warmed to 25 °C and stirred for 6 h. The solvent was concentrated under vacuum to afford intermediate **8a**.

General procedure for the synthesis of compounds 9a–k

Taking *N*-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-[[7-methoxy-4-(phenylamino)quinazolin-6-yl]oxy]acetamide (**9a**) as an example: a mixture of intermediate **4a** (0.50 g, 1.69 mmol), intermediate **8a** (0.58 g, 1.86 mmol), potassium carbonate (0.47 g, 3.39 mmol) and *N,N*-dimethylformamide (10 mL) was heated to 80 °C. After completion, water (20 mL) was added to the mixture, followed by filtration. The filter cake was collected and dried at 50 °C, then purified by column chromatography to afford the final product.

Pharmacological experiments of target compounds

Cell culture. The human NSCLC cell lines A549 and H1975 were obtained from the Shanghai Institute of Life Sciences, Chinese Academy of Sciences. Cells were cultured in RPMI 1640 medium (Invitrogen) supplemented with 10 % fetal bovine serum (FBS, Invitrogen) in a humidified incubator at 37 °C under an atmosphere of 5 % CO₂. The cells were passaged using 0.25 % trypsin (Amresco) upon reaching approximately 90 % confluence.

Cell viability assay (CCK-8). The antiproliferative activity of the synthesized compounds was assessed using the CCK-8 (Wuhan Heyan Biotechnology). Briefly, cells in the logarithmic growth phase were digested, centrifuged, and resuspended in complete medium. Cell density was adjusted to 3×10^4 cells/mL using a hemocytometer. Subsequently, 100 µL of the cell suspension was seeded into each well of a 96-well plate (NEST Biotechnology) and incubated for 24 h to allow attachment. After incubation, the medium was removed and replaced with 100 µL of fresh medium containing various concentrations of the test compounds or the positive control (zorifertinib). Cells treated with medium containing an equivalent volume of DMSO served as the negative control. The plates were then incubated for 72 h. Following the treatment period, 10 µL of CCK-8 reagent was added to each well, and the plates were incubated for an

additional 2 h. The absorbance at 450 nm was measured using a multifunctional microplate reader (Shanghai Hanfei Medical Instrument Co., Ltd.). The inhibition rate (*IR*%) was calculated using the following formula:

$$IR\% = 100 \frac{OD_{\text{sample}} - OD_{\text{negative control}}}{OD_{\text{STSP}} - OD_{\text{negative control}}} \quad (1)$$

The half-maximal inhibitory concentration (IC_{50}) values were determined from concentration–response curves using GraphPad Prism software via nonlinear regression analysis (Bliss method). All experiments were performed in triplicate wells and repeated independently at least three times.

Molecular docking protocol

Molecular docking of target derivatives with EGFR (PDB ID: 7OXB) was performed using AutoDock Vina. Small molecule ligands were prepared in ChemDraw/Chem3D and converted to PDBQT format alongside the pretreated protein. Following binding pocket configuration, 20 docking runs were conducted. Results were selected based on binding energy and conformation, with PyMOL used for interaction visualization.

The selection of the EGFR kinase domain (PDB ID: 7OXB) for molecular docking studies is based on its established relevance in elucidating the structural basis of quinazoline-based inhibitor binding. Although the anticancer activity was evaluated in whole-cell systems, docking simulations against the isolated kinase domain provide mechanistic insights into potential direct interactions with the EGFR target. The 7OXB structure represents a well-characterized model of the ATP-binding pocket and has been widely employed in structural studies of EGFR inhibitors. This approach allows for the prediction of key intermolecular interactions, such as hydrogen bonding and hydrophobic contacts, between the synthesized hybrids and critical residues (*e.g.*, ASP-855, LYS-875), thereby supporting the interpretation of the observed structure–activity relationships and guiding future design strategies.

ADME prediction introduction

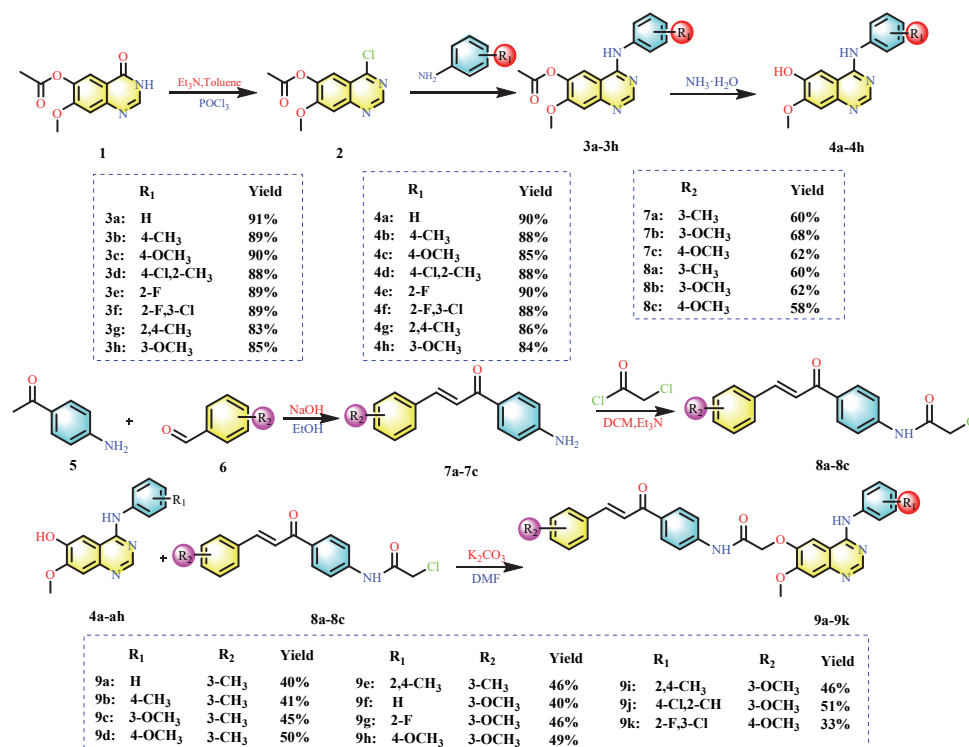
ADME prediction is vital in drug development, using computational models to evaluate a compound's absorption, distribution, metabolism and excretion. Researchers simply input the molecular structure into a prediction platform and run the analysis. The system quickly generates key parameters like partition coefficients and permeability in standardized reports, enabling efficient lead compound optimization. This computer-aided approach significantly accelerates early-stage drug screening.

Toxicity prediction introduction

Toxicity prediction is essential in drug development, using computational models to evaluate the safety profile of a compound. Researchers simply input the molecular structure into a prediction platform and run the analysis. The system quickly generates key parameters such as LD_{50} values and toxicity classes in standardized reports, enabling efficient identification of compounds with favorable safety margins. This computer-aided approach significantly reduces the risk of late-stage drug failure.

RESULTS AND DISCUSSION

Based on the synthesis methods of the references,^{31–35} we systematically optimized the synthetic route for target compounds **9a–k**, as illustrated in Scheme 1. Using 3,4-dihydro-7-methoxy-4-oxoquinazolin-6-yl acetate **1** as the starting mat-



Scheme 1. The synthesis route of target derivatives.

erial in toluene with triethylamine as the acid scavenger, we investigated the effect of reaction temperature on the chlorination with phosphorus oxychloride. As demonstrated in Table S-I of the Supplementary material to this paper, optimal yields of 85–95 % were achieved at 70 °C for 2 h, whereas higher temperatures or prolonged reaction times led to increased byproduct formation. As shown in Table S-II of the Supplementary material, intermediate **2** reacted with substituted anilines for 5 h to give intermediate **3** in high yield exceeding 90 %, with both insufficient and excessive reaction times negatively impacting the yield. Subsequent alkaline hydrolysis of **3** with aqueous ammonia yielded intermediate **4**. In the synthesis of intermediates **7a–c**, the influence of various basic conditions was systematically investigated. Using 4-aminoacetophenone and substituted benzaldehydes as starting materials, the reactions were conducted for 4 h under different basic conditions. As evidenced in Table S-III of the Supplementary material, the results demonstrated that sodium hydroxide afforded the highest product yield, while sodium carbonate showed reduced efficiency due to its weaker alkalinity and poor solubility. When triethylamine was employed as the base, the reaction yield was approximately, only 50 %. The results demonstrate that strong inorganic bases are more

effective than weaker or organic bases in promoting the condensation. For intermediates **8a–c**, optimization showed that a molar ratio of **7a–c** to chloroacetyl chloride of 1.0:2.5 (Table S-IV of the Supplementary material) and addition at 0 °C (Table S-V of the Supplementary material) afforded the best yield, avoiding incomplete conversion or bis-acylation. For the final etherification of **9a–d**, 80 °C proved optimal (Table S-VI of the Supplementary material), balancing conversion and byproduct formation. Screening of bases (Table S-VII of the Supplementary material) indicated that potassium carbonate, owing to its moderate basicity, effectively promoted alkoxide formation without triggering elimination side reactions, unlike sodium hydroxide which reduced yield through competitive elimination.

Through systematic optimization as described, we have established an efficient six-step synthetic route starting from 3,4-dihydro-7-methoxy-4-oxoquinazolin-6-yl acetate **1**, involving sequential chlorination, amination, hydrolysis, condensation, acylation and etherification reactions. Each reaction condition was thoroughly investigated and optimized, with all key steps achieving satisfactory yields to provide sufficient compound samples for subsequent structure-activity relationship studies. This synthetic route demonstrates several advantageous characteristics including readily available starting materials, mild reaction conditions, and straightforward operational procedures.

Antitumor activity

The antitumor activity of the target compounds was evaluated using the CCK-8 assay *in vitro*. Zorifertinib was employed as the positive control drug. The inhibitory effects on A549 and H1975 cell lines are summarized in Table I.

TABLE I. The inhibition rate of target compounds on tumor cells; compounds concentration: 50 μ M

Compound	R ₁	R ₂	Inhibition rate, %	
			A549	H1975
9a	H	3-CH ₃	–4.16	36.77
9b	4-CH ₃	3-CH ₃	0.12	36.17
9c	3-OCH ₃	3-CH ₃	23.80	20.06
9d	4-OCH ₃	3-CH ₃	54.27	62.22
9e	2,4-CH ₃	3-CH ₃	49.82	54.97
9f	H	3-OCH ₃	36.55	58.99
9g	2-F	3-OCH ₃	43.99	62.63
9h	4-OCH ₃	3-OCH ₃	47.80	58.17
9i	2,4-CH ₃	3-OCH ₃	14.96	35.25
9j	4-Cl,2-CH ₃	3-OCH ₃	41.63	34.45
9k	2-F,3-Cl	4-OCH ₃	47.56	61.92
Zorifertinib	–	–	62.14	49.60

The data in Table I demonstrate that the activity of target compounds is closely related to the type and position of R₁ and R₂ substituents in their structures. When R₂ was meta-methyl substituted, compounds **9d** and **9e** exhibited inhibitory rates of 49.82 and 54.27 % against A549 cells, respectively, approaching the efficacy of the positive control zorifertinib (62.14 %). Notably, these compounds demonstrated more pronounced inhibitory effects against H1975 cells, with rates reaching 54.97 and 62.22 % (compared to zorifertinib's 49.60 % in this cell line). These results indicate that meta-methyl substitution can significantly enhance the inhibitory activity of compounds against H1975 cells. This enhancement effect may originate from the steric hindrance effect of meta-methyl optimizing the binding conformation between molecules and target proteins, while its hydrophobicity strengthens interactions with active sites. Additionally, meta-substitution may reduce molecular conformational freedom, maintaining pharmacophores in a more favorable orientation, thereby improving inhibitory efficiency.

Further investigation of the meta-methoxy substituted compounds at the R₂ position revealed that **9j** (R₁: 4-chloro-2-methyl), **9g** (R₁: 2-fluoro) and **9h** (R₁: 4-methoxy) exhibited inhibition rates of 41.63, 43.99 and 47.80 % against A549 cells, respectively, all slightly lower than that of the positive control zorifertinib (62.14 %). In contrast, against H1975 cells, both **9g** (62.63 %) and **9h** (58.17 %) demonstrated significantly enhanced inhibitory activity compared to zorifertinib (49.60 %), whereas **9j** (34.45 %) showed reduced potency. These results clearly indicate that with meta-methoxy substitution, the choice of R₁ substituent significantly impacts biological activity, with the 2-fluoro-substituted compound **9g** demonstrating particularly enhanced inhibition against H1975 cells, achieving an inhibition rate of 62.63 %. The observed activity differences likely stem from the strong electronegativity of the 2-fluoro group facilitating improved hydrogen bonding interactions with the target protein, whereas the steric hindrance introduced by the 4-chloro, 2-methyl disubstitution in **9j** may impair optimal molecular binding to the target site.

Structure–activity relationship analysis demonstrated that the position of R₂ substituents critically influences biological activity. In H1975 cells, meta-substituted compounds **9e** (R₂: 3-methyl) and **9g** (R₂: 3-methoxy) demonstrated significantly superior inhibitory activities of 54.97 and 62.63 %. This marked enhancement suggests that meta-substitution facilitates stronger molecular binding to the target protein. This advantage likely arises from the optimal accommodation within the three-dimensional architecture of the target's active site, improving spatial complementarity and hydrophobic interactions to enhance binding affinity. Furthermore, the structural characteristics of R₁ substituents exert a decisive influence on the antitumor activity of these compounds. Notably, compounds **9d** (R₁: 4-methoxy) and **9e** (R₁: 2,4-dimethyl) exhibited the most prominent inhibitory activities. Specifically, **9d** demonstrated inhibition rates of 54.27 and 62.22 %

against A549 and H1975 cell lines, respectively, while **9e** showed corresponding inhibition rates of 49.82 and 54.97 %. Remarkably, compound **9g** (R₁: 2-fluoro) displayed the strongest inhibitory activity against H1975 cells with an inhibition rate of 62.63 %, although it exhibited relatively weaker activity against A549 cells (43.99 % inhibition), indicating excellent cellular selectivity. Comprehensive analysis reveals that introducing medium-sized electron-donating groups (*e.g.*, methoxy and methyl) at the R₁ position substantially enhances antitumor efficacy, with the 4-methoxy-substituted compounds **9d** and **9h** emerging as particularly promising drug candidates due to their optimal overall performance profile, rendering them promising candidates for further development.

According to the *IC*₅₀ determination results shown in Table II, these compounds exhibited superior inhibitory activity against both A549 (*IC*₅₀: 7.479 μM) and H1975 (*IC*₅₀: 6.652 μM) cell lines compared to zorifertinib (A549: 31.080 μM; H1975: 64.170 μM). Notably, compound **9e** demonstrated the lowest *IC*₅₀ values (A549: 7.479 μM; H1975: 6.652 μM), indicating the most potent inhibitory effect. Furthermore, both **9d** (A549: 8.463 μM; H1975: 7.885 μM) and **9h** (A549: 7.944 μM; H1975: 8.739 μM) displayed *IC*₅₀ values below 10 μM, further confirming their excellent antitumor potential. In conclusion, compounds **9e**, **9d** and **9h** warrant further in-depth investigation due to their remarkable inhibitory activity and structural advantages.

TABLE II. *IC*₅₀ value of preferred compounds

Compound	<i>IC</i> ₅₀ / μM	
	A549	H1975
9d	8.463	7.885
9e	7.479	6.652
9g	20.960	23.500
9h	7.944	8.739
9k	8.113	18.080
Zorifertinib	31.08	54.71

Preliminary structure–activity relationship analysis revealed several key patterns. First, the position of the R₂ substituent on the chalcone moiety had a decisive influence on activity with meta-substitution significantly outperforming para-substitution, likely due to its greater potential to form stable interactions with the target protein. Second, methoxy-substituted compounds generally exhibited stronger activity than their methyl-substituted counterparts, suggesting the importance of hydrogen bonding in target recognition. Additionally, the number of R₁ substituents on the quinazoline moiety also affected activity with mono-substituted derivatives typically outperforming di-substituted analogs, possibly due to steric hindrance effects. These findings provide important guidance for the rational design of future

antitumor drugs. In particular, the lead compound **9h** shows promising development potential and warrants further investigation into its pharmacological mechanisms and preclinical evaluation.

Molecular docking

Molecular docking of the positive control drug zorifertinib and selected target derivatives with EGFR kinase (PDB ID: 7OXB) was performed using AutoDock Vina. The binding modes between ligand molecules and receptor proteins were analyzed to further explore their interactions. The selected target derivative **9h** and the positive control drug zorifertinib were individually docked with the target protein EGFR.

The molecular docking analysis (Fig. 2, PDB ID:7OXB) reveals that compound **9h** binds to EGFR primarily through an extensive hydrogen-bonding network. The quinazoline core forms critical hydrogen bonds with residues in the catalytic pocket (GLU-1015, GLN-820), while the side-chain substituents engage additional residues (GLN-812, ASN-816, TYR-813), collectively contributing to a stable and potent inhibition.

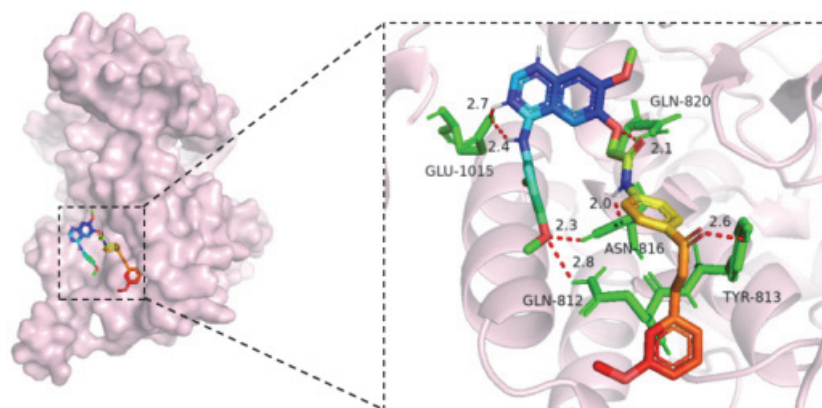


Fig. 2. Molecular docking models of compound **9h** with EGFR (PDB ID code: 7OXB).

Molecular docking of zorifertinib with EGFR (PDB ID: 7OXB, Fig. 3) reveals that its quinazoline core forms three key hydrogen bonds with the kinase domain: the 3-position nitrogen with ASP-855 (1.9 Å), the 4-position amino nitrogen with ASP-837 (2.3 Å), and the 6-position oxygen with LYS-875 (2.3 Å). These interactions, particularly the short, strong bond with ASP-855, are critical for anchoring the inhibitor tightly within the ATP-binding pocket. This binding network enhances stability and specificity, effectively competing with ATP to inhibit EGFR signaling and providing a structural basis for its potent antitumor activity.

While both compound **9h** and zorifertinib share a conserved quinazoline core that targets the ATP-binding pocket of EGFR (PDB ID:7OXB), their distinct side

chains dictate divergent binding modes and inhibitory profiles. Compound **9h**, with its flexible C-6 substituent, engages the solvent-front region (GLN-812, TYR-813), potentially conferring adaptive binding to various mutants like L858R/T790M. In contrast, zorifertinib's rigid structure deeply penetrates the back pocket, forming a strong salt bridge with ASP-855 in the DFG motif and a cation interaction with LYS-875, which may enhance its potency against wild-type EGFR. This analysis suggests that **9h**'s flexibility could be key for a broader mutant spectrum, whereas zorifertinib's pre-organization favors strong wild-type inhibition.

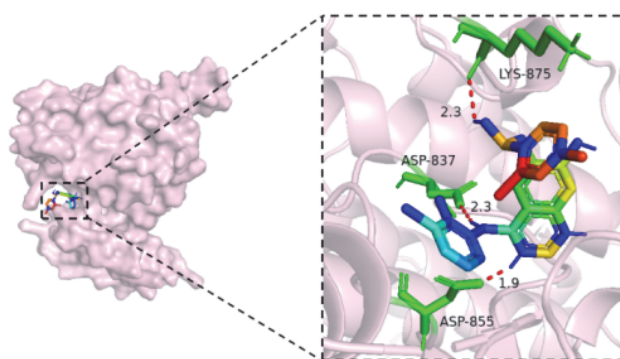


Fig. 3. Molecular docking models of zorifertinib with EGFR (PDB ID code: 7OXB).

Physicochemical properties and ADME prediction

As summarized in Table III, all synthesized compounds (**9a–k**) exhibit molecular weights exceeding 500 Da, constituting a single Lipinski violation, while

TABLE III. Physicochemical properties and ADME properties of target compounds; *RB* – rotatable bonds; *HAcc* – H-bond acceptors; *HDon* – H-bond donors; Lipinski – violation Lipinski Rule of 5; * – *MW* > 500 g/mol, Log *s* – the water solubility of the compound; GI – gastrointestinal absorption; bioavailability score: 0.55

Cmpd.	<i>MW</i> g/mol	<i>RB</i>	<i>HAcc</i> (<10)	<i>HDon</i>	<i>TPSA</i> Å (≤140)	Log <i>P_{o/w}</i>	Log <i>s</i>	GI	Lipinski
9a	544.60	11	6	2	102.44	5.52	– 7.02	Low	1*
9b	558.63	11	6	2	102.44	5.87	– 7.33	Low	1*
9c	574.63	12	7	2	111.67	5.45	– 7.11	Low	1*
9d	574.63	12	7	2	111.67	5.45	– 7.11	Low	1*
9e	572.65	11	6	2	102.44	6.21	– 7.63	Low	1*
9f	560.60	12	7	2	111.67	5.03	– 6.80	Low	1*
9g	578.59	12	8	2	111.67	5.40	– 6.96	Low	1*
9h	590.63	11	6	2	102.44	6.21	– 7.11	Low	1*
9i	588.65	12	7	2	111.67	5.73	– 7.41	Low	1*
9j	609.07	12	7	2	111.67	5.98	– 7.70	Low	1*
9k	613.03	12	8	2	111.67	5.99	– 7.56	Low	1*
Zorifertinib	459.90	6	7	1	79.82	3.65	– 5.50	High	0

other key parameters such as TPSA (102.44–111.67 Å²) and bioavailability scores (0.55) remain within favorable ranges. Despite the predicted low gastrointestinal absorption, the overall physicochemical profiles are typical of beyond-rule-of-5 kinase inhibitors, and the potent *in vitro* antiproliferative activity against NSCLC cells demonstrates that these compounds can effectively reach their intracellular targets. The consistent drug-like parameters across the series, combined with their strong biological activity, highlight the potential of the quinazoline–chalcone hybrids as promising lead compounds for further optimization and development as novel anticancer agents.

Toxicity profile of the designed compound

As shown in Table IV, all designed compounds (**9a–k**) exhibited a predicted *LD*₅₀ of 2000 mg/kg and a toxicity class of 4, whereas zorifertinib showed an *LD*₅₀ of 1150 mg/kg (class 4). The average similarity of the designed compounds ranged from 54.91 to 58.50 %, slightly higher than that of zorifertinib (50.88 %), with prediction accuracies around 67 %. These results indicate that the designed compounds possess toxicity profiles comparable to or slightly better than the reference drug.

TABLE IV. Predicted toxicity properties of target compounds

Compound	Predicted <i>LD</i> ₅₀ mg/kg	Predicted toxicity class (1 to 6)	Average similarity, %	Prediction accuracy, %
9a	2000	4	56.76	67.38
9b	2000	4	56.76	67.38
9c	2000	4	55.25	67.38
9d	2000	4	56.76	67.38
9e	2000	4	55.25	67.38
9f	2000	4	58.50	67.38
9g	2000	4	55.78	67.38
9h	2000	4	58.50	67.38
9i	2000	4	56.40	67.38
9j	2000	4	58.26	67.38
9k	2000	4	54.91	67.38
Zorifertinib	1150	4	50.88	67.38

CONCLUSIONS

Collectively, this study developed novel antitumor agents by designing and synthesizing a series of quinazoline–chalcone hybrids. Their antiproliferative activity was evaluated against A549 and H1975 cell lines, with zorifertinib as the positive control. Molecular docking revealed their stable binding to EGFR, and ADME/toxicity predictions validated their favorable drug-like and safety profiles, particularly for compound **9h**. However, the cytotoxicity was assessed only on cancer cell lines, and the selectivity against normal cells remains to be determined.

Future work will address this limitation to establish their therapeutic selectivity index.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: <https://www.shd-pub.org.rs/index.php/JSCS/article/view/13582>, or from the corresponding author on request.

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ИЗВОД

ДИЗАЈН НОВИХ ХИБРИДА ХИНАЗОЛИНА И ХАЛКОНА КАО СНАЖНИХ ИНХИБИТОРА РЕЦЕПТОРА ЕПИДЕРМАЛНОГ ФАКТОРА РАСТА

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У оквиру овог истраживања успешно је дизајнирана и синтетисана нова серија хибрида хиназолина и халкона. Најважнија иновација је молекулска хибридизација фармакофорног скелета хиназолина са халконским фрагментом, чиме су створене нове хемијске врсте за испитивање потенцијалног синергистичког антитуморног ефекта. Успешно је спроведена усмерена синтеза у више реакционих корака. Први резултати испитивања показали су да већина синтетисаних хибрида показује снажну антипролиферативну активност *in vitro* према ћелијским линијама неситноћелијског рака плућа (NSCLC) (A549 и H1975). На основу испитивања молекулским докингом предложено је да је инхибиција рецептора епидермалног фактора раста (EGFR) главни механизам деловања и да једињења остварују стабилне интеракције са киназним доменом. Осим тога, *in silico* предвиђање апсорпције, дистрибуције, метаболизма и излучивања (ADME) и предвиђања токсичности добијена на SwissADME и ProTox 3.0 платформама, редом, указују на то да једињења поседују својства слична лековима и одговарајући профил безбедности. Ипак, цитотоксичност је одређена само према ћелијским линијама рака и селективност према нетуморским, здравим, ћелијама тек треба одредити. Без обзира на ова ограничења, почетни резултати су охрабрујући и упућују на наставак оптимизације и развој ових нових хибрида једињења.

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SUPPLEMENTARY MATERIAL TO
**Design of novel quinazoline–chalcone hybrids as potent
epidermal growth factor receptor inhibitors**

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Table S-I The influence of the dropping time and temperature of POCl₃ on the yield of intermediate **2**.

No.	Temperature during POCl ₃ addition	Reaction Time (h)	Yield
1	60°C	3	71%
2	60°C	2	65%
3	60°C	1.5	60%
4	70°C	1.5	85%
5	70°C	2	95%
6	70°C	3	89%
7	80°C	2	71%
8	80°C	3	69%

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Table S-II The influence of different reaction time on the yield of intermediates **3a-3d**.

No.	Synthesized Intermediate	Reaction Time (h)	Yield
1	3a	4	68%
2		5	92%
3		6	75%
4	3b	4	63%
5		5	94%
6		6	72%
7	3c	4	68%
8		5	91%
9		6	75%
10	3d	4	65%
11		5	90%
12		6	71%

Table S-III The influence of different alkaline environment on the yield of intermediates **7a-7c**.

No.	Synthesized Intermediate	Basic Conditions	Yield
1	7a	Sodium carbonate	37%
2		Triethylamine	52%
3		Sodium hydroxide	93%
4	7b	Sodium carbonate	32%
5		Triethylamine	49%
6		Sodium hydroxide	92%
10	7c	Triethylamine	34%
11		Sodium carbonate	51%
12		Sodium hydroxide	91%

Table S-IV The influence of different molar ratio on the yield of intermediates **8a-8c**.

No.	Synthesized Intermediate	7a-7c: Chloroacetyl Chloride (molar ratio)	Yield
1	8a	1.0:2.0	41%
2		1.0:2.5	60%
3		1.0:3.0	54%
4	8b	1.0:2.0	40%
5		1.0:2.5	62%
6		1.0:3.0	52%
10	8c	1.0:2.0	35%
11		1.0:2.5	56%
12		1.0:3.0	49%

Table S-V The influence of different reaction time on the yield of intermediates **8a-8c**.

No.	Synthesized Intermediate	Addition Temperature (°C)	Yield
1	8a	10	45%
2		0	60%
3		-10	50%
4	8b	10	47%

5		0	62%
6		-10	50%
10		10	42%
11	8c	0	56%
12		-10	43%

Table S-VI The influence of different reaction temperature on the yield of target compounds **9a-9d**.

No.	Target Compound	Reaction Temperature (°C)	Yield
1		60	26%
2	9a	80	40%
3		100	27%
4		60	29%
5	9b	80	41%
6		100	29%
7		60	25%
8	9c	80	44%
9		100	27%
10		60	24%
11	9d	80	46%
12		100	25%

Table S-VII The influence of different alkaline environment on the yield of target compounds **9a-9d**.

No.	Target Compound	Basic Conditions	Yield
1		Sodium hydroxide	21%
2	9a	Potassium carbonate	40%
3		Sodium hydroxide	22%
4	9b	Potassium carbonate	41%
5		Sodium hydroxide	22%
6	9c	Potassium carbonate	44%
7		Sodium hydroxide	22%
8	9d	Potassium carbonate	46%

7-Methoxy-4-(phenylamino)quinazolin-6-yl acetate(3a).

Yield 92%, white solid, m. p. 103.4 - 105.6°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.64 (s, 1H), 8.86 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.59 (s, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 4.01 (s, 3H), 2.39 (s, 3H); IR (KBr), ν, cm⁻¹: 3256.35 (N-H), 2753.22 (CH₃), 1630.36 (C=O), 1563.35 (C=C_{Ar}), 1426.28 (C=N), 1218.82 (C-O-C).

7-Methoxy-4-[(4-methylphenyl)amino]quinazolin-6-yl acetate(3b).

Yield 94%, light-yellow solid, m. p. 112.1 - 114.5°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.62 (s, 1H), 8.87 (d, *J* = 3.8 Hz, 2H), 7.58 (d, *J* = 1.5 Hz, 2H), 7.58 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 4.00 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H); IR (KBr), ν, cm⁻¹: 3255.32 (N-H), 2753.03 (CH₃), 1642 (C=O), 1509 (C=C_{Ar}), 1397 (C-N), 1247 (C-O-C).

7-Methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-yl acetate(3c).

Yield 91%, white solid, m. p. 101.2 - 105.4°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.66 (s, 1H), 8.90 (s, 1H), 8.86 (s, 1H), 7.60 (dd, *J* = 6.6, 2.3 Hz, 3H), 7.06-7.01 (m, 2H), 3.99 (s, 3H), 3.80 (s, 3H), 2.38 (s, 3H); IR (KBr), ν, cm⁻¹: 3223.05(N-H), 2838.37(CH₃), 1670.79 (C=O), 1625.71 (C=C_{Ar}), 1465.55 (C=N), 1327.88 (C-N), 1252.17 (C-O-C).

4-[(4-Chloro-2-methylphenyl)amino]-7-methoxyquinazolin-6-yl acetate(3d).

Yield 90%, white solid, m. p. 113.3 - 115.7°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.20 (s, 1H), 8.83 (s, 1H), 8.56 (s, 1H), 7.63 (d, *J* = 6.0, 2H), 7.12-7.01 (m, 2H), 3.82 (s, 3H), 2.35 (s, 3H); IR (KBr), ν, cm⁻¹: 3266.25 (N-H), 2865.31 (CH₃), 1625.38 (C=O), 1568.51 (C=C_{Ar}), 1488.51 (C-C), 1331.57 (C-N), 1272.81 (C-O-C), 775.62 (C-Cl).

4-[(2-Fluorophenyl)amino]-7-methoxyquinazolin-6-yl acetate(3e).

Yield 89%, light-yellow solid, m. p. 109.1 - 111.3°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.31 (s, 1H), 8.90 (s, 1H), 8.74 (d, *J* = 5.2 Hz, 1H), 7.58 (s, 1H), 7.56-7.51 (m, 1H), 7.52-7.43 (m, 1H), 7.48-7.40 (m, 1H), 7.39-7.30 (m, 1H), 4.02 (s, 3H), 2.40 (s, 3H); IR (KBr), ν, cm⁻¹: 3245.21 (N-H), 2945.98 (CH₃), 1627.89 (C=O), 1532.22 (C=N), 1458.88 (C=C_{Ar}), 1371.45 (C-N), 1203.77 (C-O-C), 993.71 (C-F).

4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl acetate(3f).

Yield 89%, white solid, m. p. 112.1 - 114.9°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.71 (s, 1H), 8.85 (s, 1H), 8.58 (s, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.39 (s, 1H), 7.28-7.06 (m, 1H), 3.83 (s, 3H), 2.27 (s, 3H); IR (KBr), ν, cm⁻¹: 3261.76 (N-H), 2821.38 (CH₃), 1661.80 (C=O), 1458.28 (C=C_{Ar}), 1318.90 (C-N), 1291.04 (C-O-C), 1148.39 (C-F), 728.29 (C-Cl).

4-[(2,4-Dimethylphenyl)amino]-7-methoxyquinazolin-6-yl acetate(3g).

Yield 83%, light-yellow solid, m. p. 105.2-108.7°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.73 (s, 1H), 8.90 (s, 1H), 8.77 (s, 1H), 7.64 (s, 1H), 7.22-7.15 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 4.00 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H); IR (KBr), ν, cm⁻¹: 3015.64 (N-H), 2837.02 (CH₃), 1637.46 (C=O), 1435.26 (C=C_{Ar}), 1376.00 (C-N), 1182.06 (C-O-C).

7-Methoxy-4-[(3-methoxyphenyl)amino]quinazolin-6-yl acetate(3h).

Yield 85%, white solid, m. p. 106.1 - 109.9°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.56 (s, 1H), 8.93 (s, 1H), 8.89 (s, 1H), 7.61 (s, 1H), 7.44 - 7.32 (m, 3H), 6.94-6.87 (m, 1H), 4.01 (s, 3H), 3.79 (s, 3H), 2.39 (s, 3H); IR (KBr), ν, cm⁻¹: 3274.08 (N-H), 2927.72 (CH₃), 1639.12 (C=O), 1494.16 (C=C_{Ar}), 1267.58 (C-N), 1159.34 (C-O-C).

7-Methoxy-4-(phenylamino)quinazolin-6-ol(4a).

Yield 90%, white solid, m. p. 123.7 - 125.2°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.36 (s, 1H), 8.43(s, 1H), 7.90-7.69 (m, 3H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.20 (s, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 3.98 (s, 3H); IR (KBr), ν, cm⁻¹: 3621.25 (-OH), 3390.22 (N-H), 1605.58 (C=N), 1579.22 (C=C_{Ar}), 1243.16 (C-O-C).

7-Methoxy-4-[(4-methylphenyl)amino]quinazolin-6-ol(4b).

Yield 88%, white solid, m. p. 125.1 - 128.7°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.61 (s, 1H), 9.29 (s, 1H), 8.40 (s, 1H), 7.80 (s, 1H), 7.73 (s, 1H), 7.71 (s, 1H), 7.18 (d, *J* = 5.6 Hz, 2H), 7.15 (s, 1H), 3.97 (s, 3H), 2.30 (s, 3H); IR (KBr), ν, cm⁻¹: 3625.24 (-OH), 3304.96 (N-H), 2795.30 (CH₃), 1569.36 (C=C_{Ar}), 1531.07 (C=N), 1287.67 (C-O-C).

7-Methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-ol(4c).

Yield 85%, white solid, m. p. 121.7 - 124.2°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.29 (s, 1H), 8.36 (s, 1H), 7.80(s, 1H), 7.74-7.66 (m, 2H), 7.17 (s, 1H), 6.97-6.91 (m, 2H), 3.97 (s, 3H), 3.76 (s, 3H), 2.53-2.49 (m, 1H); IR (KBr), ν, cm⁻¹: 3625.20 (-OH), 3338.02 (N-H), 2836.80 (CH₃), 1560.35 (C=C_{Ar}), 1513.42 (C=N), 1225.60 (C-O-C).

4-[(4-Chloro-2-methylphenyl)amino]-7-methoxyquinazolin-6-ol(4d).

Yield 88%, white solid, m. p. 123.5 - 124.3°C. ¹H-NMR(400 MHz, DMSO-*d*₆) δ 9.82 (s, 1H), 8.48 (s, 1H), 8.23 (s, 1H), 7.55-7.46 (m, 2H), 7.37(s, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 3.96 (s, 3H), 2.37 (s, 3H); IR (KBr), ν, cm⁻¹: 3622.50 (-OH), 3337.01 (N-H), 2837.69 (CH₃), 1560.36 (C=C_{Ar}), 1501.42 (C=N), 1241.26 (C-O-C), 731.57 (C-Cl).

4-[(2-Fluorophenyl)amino]-7-methoxyquinazolin-6-ol(4e).

Yield 90%, white solid, m. p. 121.2 - 124.2°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.70 (s, 1H), 9.34 (s, 1H), 8.31 (s, 1H), 7.61 (d, *J* = 6.0 Hz, 2H), 7.24 (d, *J* = 9.6 Hz, 4H), 3.97 (s, 3H); IR (KBr), ν, cm⁻¹: 3634.86 (-OH), 3313.96 (N-H), 2843.21 (CH₃), 1552.69 (C=C_{Ar}), 1523.78 (C=N), 1256.97 (C-O-C), 927.20 (C-F).

4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-ol(4f).

Yield 88%, white solid, m. p. 123.2 - 125.9°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.48 (s, 1H), 8.49 (s, 1H), 8.28(s, 1H), 7.91-7.72 (m, 2H), 7.31 (s, 1H), 7.02 (s, 1H), 6.93 (s, 1H), 3.83 (s, 3H); IR (KBr), ν, cm⁻¹: 3658.18 (-OH), 3345.18 (N-H), 2859.71 (CH₃), 1568.29 (C=C_{Ar}), 1528.39 (C=N), 1279.39 (C-O-C), 929.37 (C-F), 720.18 (C-Cl).

4-[(2,4-Dimethylphenyl)amino]-7-methoxyquinazolin-6-ol(4g).

Yield 86%, white solid, m. p. 125.3 - 128.6°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.57 (s, 1H), 9.10 (s, 1H), 8.21 (s, 1H), 7.70 (s, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.10 (s, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 3.96 (s, 3H), 2.31 (s, 3H), 2.12 (s, 3H); IR (KBr), ν, cm⁻¹: 3648.79 (-OH), 3324.36 (N-H), 2814.29 (CH₃), 1569.39 (C=C_{Ar}), 1523.11 (C=N), 1249.11 (C-O-C).

7-Methoxy-4-[(3-methoxyphenyl)amino]quinazolin-6-ol(4h).

Yield 84%, white solid, m. p. 128.1 - 130.4°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.35 (s, 1H), 8.47 (s, 1H), 7.86 (s, 1H), 7.58 (t, *J* = 1.9 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.26 (t, *J* = 8.3 Hz, 1H), 7.20 (s, 1H), 6.66 (dd, *J* = 7.9, 1.9 Hz, 1H), 3.98 (s, 3H), 3.78 (s, 3H); IR (KBr), ν, cm⁻¹: 3653.90 (-OH), 3358.63 (N-H), 2819.13 (CH₃), 1602.18 (C=C_{Ar}), 1527.12 (C=N), 1273.73 (C-O-C).

N-{4-[(2E)-3-(3-Methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-chloroacetamide(8a).

Yield 60%, white solid, m. p. 126.8 - 129.1°C. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.85-7.69 (m, 3H), 7.55 (s, 1H), 7.47 (s, 2H), 7.31 (d, *J* = 7.9 Hz, 1H), 4.24 (s, 2H), 2.41 (s, 3H); IR (KBr), ν, cm⁻¹: 3335.22 (N-H), 2872.03 (CH₃), 1671.20 (C=O), 1597.10 (C=C), 1335.25 (C-N), 786.33 (C-Cl).

N-{4-[(2E)-3-(3-Methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-chloroacetamide(8b).

Yield 62%, white solid, m. p. 125.7 - 128.5°C. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 8.07 (s, 1H), 8.05 (s, 1H), 7.84-7.68 (m, 3H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.16 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 4.23 (s, 2H), 3.86 (s, 3H); IR (KBr), ν, cm⁻¹: 3354.21 (N-H), 2834.25 (CH₃), 1645.33 (C=O), 1580.72 (C=C), 1339.81 (C-N), 1259.90 (C-O-C), 779.21 (C-Cl).

N-{4-[(2*E*)-3-(4-methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-chloroacetamide(**8c**).

Yield 56%, white solid, m. p. 151.9 - 154.6°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (d, *J* = 8.6 Hz, 2H), 7.99 - 7.90 (m, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 1.0 Hz, 2H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.05-6.97 (m, 2H), 4.26 (s, 2H), 3.81 (s, 3H); IR (KBr), ν, cm⁻¹: 3333.21 (N-H), 2863.28 (CH₃), 1671.70 (C=O), 1518.66 (C=C), 1335.54 (C-N), 1264.23 (C-O-C), 777.21 (C-Cl).

N-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-[(7-methoxy-4-(phenylamino)quinazolin-6-yl]oxy}acetamide(**9a**).

Yield 40%, white solid, m. p. 121.7 - 123.9°C. ¹H NMR (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.70 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.72 (t, *J* = 9.2 Hz, 3H), 7.55 (s, 1H), 7.50 - 7.43 (m, 3H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 4.4 Hz, 3H), 4.79 (s, 2H), 4.10 (s, 3H), 2.41 (s, 3H); IR (KBr), ν, cm⁻¹: 3359.01 (N-H), 2833.91 (CH₃), 1648.58 (C=O), 1569.69 (C=C_{Ar}), 1525.58 (C=N), 1398.31 (C-N), 1205.56 (C-O-C). ¹³C NMR (101 MHz, DMSO) δ 188.03, 167.12, 157.02, 154.84, 153.78, 147.89, 147.80, 144.12, 143.26, 139.76, 138.63, 135.14, 133.25, 131.73, 130.42, 129.54, 129.25, 128.93, 128.81, 126.75, 124.00, 123.02, 122.25, 122.16, 119.42, 109.18, 108.09, 104.77, 68.89, 56.43, 56.35, 21.34. ESI-MS (m/z): calculated for C₃₃H₂₈N₄O₄: 544.61 (100%); found: 545.26 [M+H]⁺ (100%).

N-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-[(7-methoxy-4-(4-methylphenyl)amino)quinazolin-6-yl]oxy}acetamide(**9b**).

Yield 41%, light-yellow solid, m. p. 135.1 - 138.7°C. ¹H NMR (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.66 (s, 1H), 8.06 (d, *J* = 8.1 Hz, 2H), 7.82 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 6.4 Hz, 3H), 7.49 (s, 1H), 7.45 (s, 2H), 7.34 (d, *J* = 6.2 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 4.78 (s, 2H), 4.09 (s, 3H), 2.41 (s, 3H), 2.36 (s, 3H); IR (KBr), ν, cm⁻¹: 3357.00 (N-H), 2824.79 (CH₃), 1632.97 (C=O), 1568.47 (C=C_{Ar}), 1543.06 (C=N), 1398.90 (C-N), 1206.84 (C-O-C). ¹³C NMR (101 MHz, DMSO) δ 188.02, 167.12, 157.12, 154.78, 153.80, 147.76, 144.12, 143.28, 138.64, 137.09, 135.15, 133.22, 133.14, 131.75, 130.42, 129.54, 129.38, 129.28, 126.80, 123.22, 122.17, 119.39, 109.08, 108.00, 104.73, 68.83, 56.43, 21.35, 21.01. ESI-MS (m/z): calculated for C₃₄H₃₀N₄O₄: 558.64 (100%); found: 559.28 [M+H]⁺ (100%).

N-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-[(7-methoxy-4-[(3-methoxyphenyl)amino]quinazolin-6-yl]oxy}acetamide(**9c**).

Yield 45%, light-yellow solid, m. p. 118.4 - 121.7°C. ¹H NMR (400 MHz, CDCl₃) δ 8.90 (s, 1H), 8.69 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.53 (s, 1H), 7.47 - 7.39 (m, 4H), 7.32 (d, *J* = 4.6 Hz, 2H), 7.29 (s, 1H), 7.22 (s, 1H), 6.71 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.78 (s, 2H), 4.09 (s, 3H), 3.82 (d, *J* = 1.1 Hz, 3H), 2.40 (s, 3H); IR (KBr), ν, cm⁻¹: 3315.60 (N-H), 2971.93 (CH₃), 1627.83 (C=O), 1577.82 (C=C_{Ar}), 1541.91 (C=N), 1492.97 (C=C), 1390.77 (C-N), 1212.12 (C-O-C). ¹³C NMR (101 MHz, DMSO) δ 188.02, 167.11, 159.87, 156.95, 154.87, 153.71, 147.90, 147.81, 147.78, 144.12, 143.26, 140.98, 138.63, 135.14, 133.24, 131.73, 130.49, 130.42, 129.65, 129.54, 129.26, 126.77, 122.16, 119.41, 115.11, 109.23, 109.16, 108.75, 108.11, 104.80, 68.93, 56.44, 55.55, 21.34. ESI-MS (m/z): calculated for C₃₄H₃₀N₄O₅: 574.64 (100%); found: 575.26 [M+H]⁺ (100%).

N-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-[(7-methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-yl]oxy}acetamide(**9d**).

Yield 50%, light-yellow solid, m. p. 137.6 - 140.1°C. ¹H NMR (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.62 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.82 - 7.67 (m, 4H), 7.54 - 7.44 (m, 4H), 7.29 (d, *J* = 3.5 Hz, 2H), 7.23 (d, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.75 (s, 2H), 4.06 (s, 3H),

3.79 (s, 3H), 2.40 (s, 3H); IR (KBr), ν , cm^{-1} : 3356.13 (N-H), 3081.78 (CH_3), 1648.28 ($\text{C}=\text{O}$), 1568.00 ($\text{C}=\text{C}_{\text{Ar}}$), 1511.29 ($\text{C}=\text{C}$), 1471.31 ($\text{C}=\text{N}$), 1434.25 (C-C), 1338.63 (C-N), 1237.37 (C-O-C). ^{13}C NMR (101 MHz, DMSO) δ 188.02, 167.14, 157.28, 156.27, 154.67, 153.94, 147.68, 144.12, 143.28, 138.63, 135.14, 133.22, 132.48, 131.73, 130.42, 129.54, 129.26, 126.77, 125.11, 122.16, 119.39, 114.15, 108.99, 108.04, 104.70, 68.79, 56.38, 55.67, 21.34. ESI-MS (m/z): calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_5$: 574.64 (100%); found: 575.27 $[\text{M}+\text{H}]^+$ (100%).

N-{4-[(2*E*)-3-(3-methylphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({4-[(2,4-dimethylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)acetamide(**9e**).

Yield 46%, light-yellow solid, m. p. 138.7 - 141.7°C. ^1H NMR (400 MHz, CDCl_3) δ 8.92 (s, 1H), 8.59 (s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.84 - 7.73 (m, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 9.9 Hz, 1H), 7.37 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 4.8 Hz, 2H), 7.16 - 7.02 (m, 3H), 4.71 (s, 2H), 4.08 (s, 3H), 2.59 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H); IR (KBr), ν , cm^{-1} : 3362.08 (N-H), 2915.42 (CH_3), 1631.59 ($\text{C}=\text{O}$), 1569.52 ($\text{C}=\text{C}_{\text{Ar}}$), 1541.96 ($\text{C}=\text{N}$), 1400.31 (C-N), 1205.93 (C-O-C). ^{13}C NMR (101 MHz, DMSO) δ 188.00, 186.31, 167.14, 167.08, 158.31, 154.61, 154.36, 154.18, 154.09, 147.67, 147.49, 144.11, 141.99, 138.64, 138.53, 135.81, 135.55, 135.18, 135.15, 135.08, 129.21, 127.24, 126.43, 122.64, 119.33, 113.20, 112.92, 108.76, 107.93, 104.53, 68.50, 56.37, 21.36, 21.07, 18.39. ESI-MS (m/z): calculated for $\text{C}_{35}\text{H}_{32}\text{N}_4\text{O}_4$: 572.66 (100%); found: 573.25 $[\text{M}+\text{H}]^+$ (100%).

N-{4-[(2*E*)-3-(3-methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-([7-methoxy-4-(phenylamino)quinazolin-6-yl]oxy)acetamide(**9f**).

Yield 40%, white solid, m. p. 127.4 - 130.9°C. ^1H NMR (400 MHz, CDCl_3) δ 8.93 (s, 1H), 8.68 (s, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.78 (s, 1H), 7.73 (s, 2H), 7.70 (s, 2H), 7.68 (s, 1H), 7.50 (s, 1H), 7.45 (s, 2H), 7.37 (s, 2H), 7.16 (d, J = 9.4 Hz, 2H), 7.01 - 6.92 (m, 1H), 4.76 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H); IR (KBr), ν , cm^{-1} : 3357.92 (N-H), 2833.33 (CH_3), 1631.84 ($\text{C}=\text{O}$), 1570.15 ($\text{C}=\text{C}_{\text{Ar}}$), 1533.30 ($\text{C}=\text{N}$), 1397.94 (C-N), 1206.27 (C-O-C). ^{13}C NMR (101 MHz, DMSO) δ 188.05, 167.10, 160.13, 159.88, 156.98, 154.91, 153.66, 147.84, 143.99, 143.30, 140.94, 136.64, 133.18, 130.48, 130.40, 130.00, 129.67, 122.65, 122.15, 119.40, 119.28, 117.11, 115.15, 113.78, 109.22, 108.79, 104.82, 68.91, 56.46, 55.56. ESI-MS (m/z): calculated for $\text{C}_{33}\text{H}_{28}\text{N}_4\text{O}_5$: 560.61 (100%); found: 561.27 $[\text{M}+\text{H}]^+$ (100%).

N-{4-[(2*E*)-3-(3-methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({4-[(2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)acetamide(**9g**).

Yield 46%, light-yellow solid, m. p. 158.9 - 160.3°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.51 (s, 1H), 9.47 (s, 1H), 8.35 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 7.6 Hz, 2H), 7.85 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 9.7 Hz, 1H), 7.53 - 7.46 (m, 2H), 7.40 (d, J = 8.6 Hz, 1H), 7.31 (dd, J = 7.4, 4.8 Hz, 2H), 7.26 (d, J = 8.0 Hz, 3H), 7.02 (d, J = 8.1 Hz, 1H), 4.94 (s, 2H), 3.98 (s, 3H), 3.82 (s, 3H); IR (KBr), ν , cm^{-1} : 3359.45 (N-H), 1650.47 ($\text{C}=\text{O}$), 1572.11 ($\text{C}=\text{C}_{\text{Ar}}$), 1542.58 ($\text{C}=\text{N}$), 1397.92 (C-N), 1215.02 (C-O-C), 979.34 (C-F). ^{13}C NMR (101 MHz, DMSO) δ 188.06, 167.12, 160.13, 157.02, 154.85, 153.77, 147.87, 147.81, 143.99, 143.30, 139.74, 136.64, 133.18, 130.47, 130.40, 130.00, 128.94, 124.02, 123.02, 122.65, 122.14, 119.40, 117.10, 113.78, 109.16, 108.09, 104.78, 68.88, 56.44, 55.79. ESI-MS (m/z): calculated for $\text{C}_{33}\text{H}_{27}\text{FN}_4\text{O}_5$: 578.60 (100%); found: 579.23 $[\text{M}+\text{H}]^+$ (100%).

N-{4-[(2*E*)-3-(3-Methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({7-methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-yl}oxy)acetamide(**9h**).

Yield 49%, light-yellow solid, m. p. 140.3 - 143.7°C. ^1H NMR (400 MHz, CDCl_3) δ 8.94 (s, 1H), 8.62 (s, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.80 - 7.68 (m, 3H), 7.58 - 7.44 (m, 4H), 7.41 (s,

1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.23 (d, $J = 7.7$ Hz, 1H), 7.14 (s, 1H), 6.91 (d, $J = 8.6$ Hz, 2H), 4.75 (s, 2H), 4.07 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H); IR (KBr), ν , cm^{-1} : 3358.21 (N-H), 2836.70 (CH_3), 1649.02 (C=O), 1570.39 (C=C_{Ar}), 1541.06 (C=N), 1401.01 (C-N), 1234.63 (C-O-C). ^{13}C NMR (101 MHz, DMSO) δ 188.05, 167.16, 160.13, 157.27, 156.26, 154.67, 153.94, 147.68, 143.98, 143.34, 136.64, 133.16, 132.50, 130.47, 130.39, 125.10, 122.65, 122.14, 119.38, 117.09, 114.15, 113.78, 109.00, 108.05, 104.70, 68.78, 56.38, 55.78, 55.67. ESI-MS (m/z): calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_6$: 590.64 (100%); found: 591.27 $[\text{M}+\text{H}]^+$ (100%).

N-{4-[(2*E*)-3-(3-Methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({4-[(2,4-dimethylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)acetamide(**9i**).

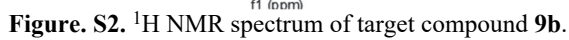
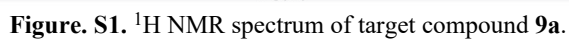
Yield 46%, light-yellow solid, m. p. 132.5 - 135.6°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.49 (s, 1H), 9.27 (s, 1H), 8.26 (s, 1H), 8.20 (d, $J = 8.5$ Hz, 2H), 7.90 (d, $J = 9.7$ Hz, 2H), 7.83 (d, $J = 8.5$ Hz, 2H), 7.49 - 7.31 (m, 3H), 7.21 (s, 1H), 7.18 - 7.06 (m, 3H), 7.02 (d, $J = 8.5$ Hz, 2H), 4.92 (s, 2H), 3.96 (d, $J = 3.9$ Hz, 3H), 3.82 (d, $J = 1.2$ Hz, 3H), 2.29 (s, 3H), 2.09 (s, 3H); IR (KBr), ν , cm^{-1} : 3319.12 (N-H), 2972.56 (CH_3), 1642.89 (C=O), 1570.77 (C=C_{Ar}), 1514.69 (C=N), 1429.55 (C-C), 1392.01 (C-N), 1276.98 (C-O-C). ^{13}C NMR (101 MHz, DMSO) δ 188.03, 167.14, 160.13, 158.32, 154.63, 154.16, 147.68, 147.42, 143.97, 143.39, 136.64, 135.82, 135.18, 135.07, 133.10, 131.46, 130.47, 130.40, 128.12, 127.24, 122.65, 122.15, 119.33, 117.10, 113.78, 108.75, 107.88, 104.55, 68.50, 56.38, 55.79, 21.07, 18.39. ESI-MS (m/z): calculated for $\text{C}_{35}\text{H}_{32}\text{N}_4\text{O}_5$: 588.66 (100%); found: 589.28 $[\text{M}+\text{H}]^+$ (100%).

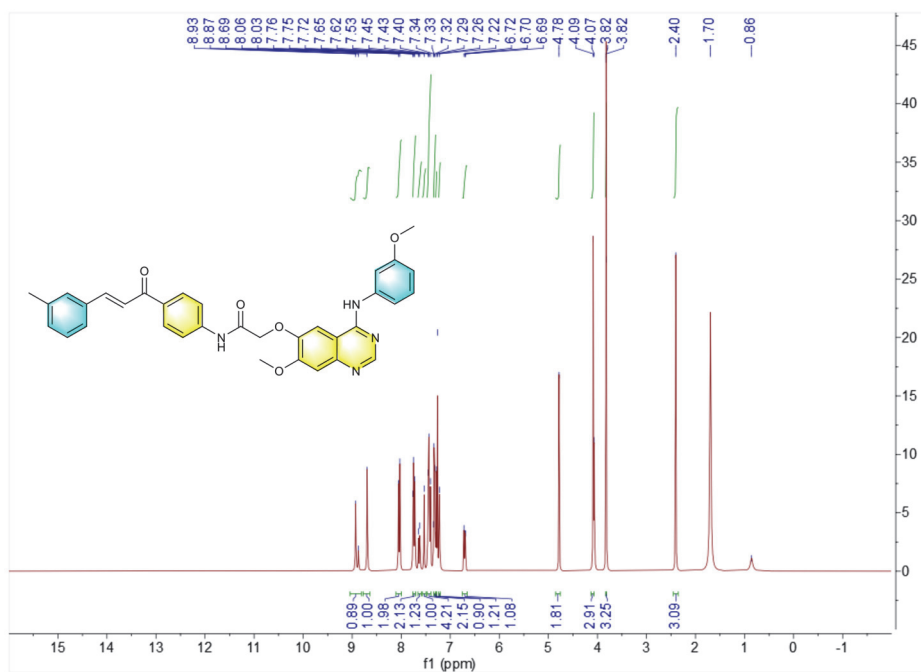
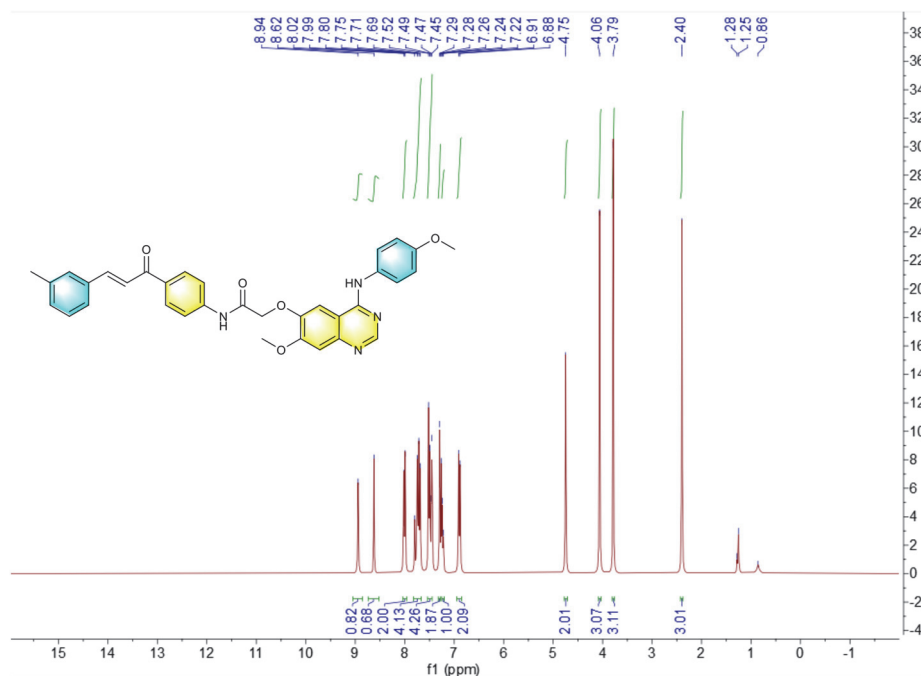
N-{4-[(2*E*)-3-(3-Methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({4-[(4-chloro-2-methylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)acetamide(**9j**).

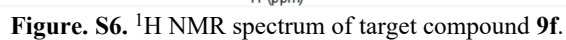
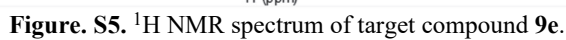
Yield 51%, light-yellow solid, m. p. 149.5 - 152.1°C. ^1H NMR (400 MHz, CDCl_3) δ 8.93 (s, 1H), 8.60 (s, 1H), 8.04 (d, $J = 8.4$ Hz, 2H), 7.85 - 7.67 (m, 3H), 7.49 - 7.43 (m, 1H), 7.33 (d, $J = 6.9$ Hz, 3H), 7.16 (s, 2H), 7.06 - 6.91 (m, 3H), 4.78 (s, 2H), 4.10 (s, 3H), 3.87 (s, 3H), 2.28 (s, 3H); IR (KBr), ν , cm^{-1} : 3365.25 (N-H), 2835.28 (CH_3), 1650.55 (C=O), 1572.46 (C=C_{Ar}), 1541.55 (C=N), 1401.62 (C-N), 1202.72 (C-O-C), 784.76 (C-Cl). ^{13}C NMR (101 MHz, DMSO) δ 188.03, 167.11, 160.13, 158.29, 154.74, 154.09, 147.77, 147.48, 143.98, 143.38, 138.32, 136.64, 134.01, 133.11, 130.47, 130.40, 130.15, 122.65, 122.15, 119.33, 117.32, 117.10, 113.78, 113.41, 113.19, 108.70, 107.92, 104.48, 68.49, 56.41, 55.79, 18.48. ESI-MS (m/z): calculated for $\text{C}_{34}\text{H}_{29}\text{ClN}_4\text{O}_5$: 609.08 (100%); found: 632.26 $[\text{M}+\text{Na}]^+$ (100%).

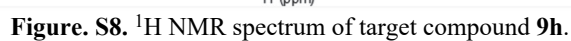
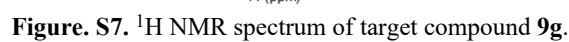
N-{4-[(2*E*)-3-(4-Methoxyphenyl)-1-oxoprop-2-en-1-yl]phenyl}-2-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)acetamide(**9k**).

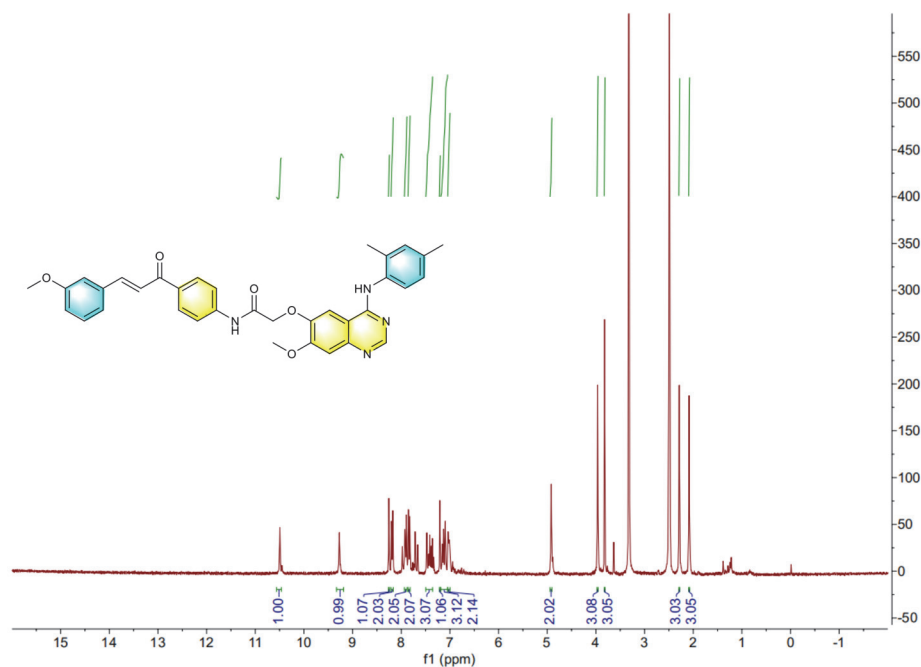
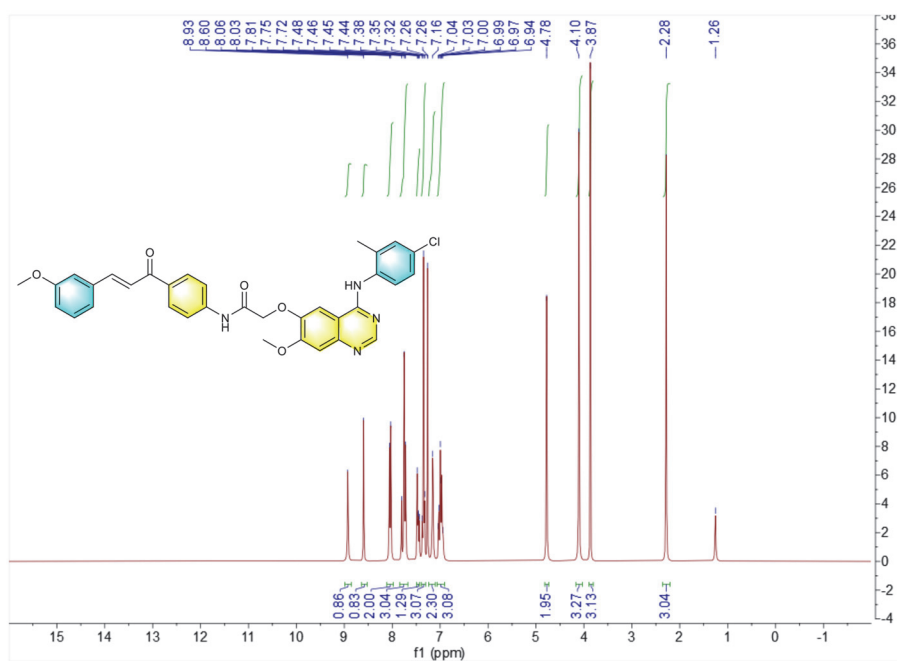
Yield 33%, white solid, m. p. 118.4 - 121.9°C. ^1H NMR (400 MHz, CDCl_3) δ 8.94 (s, 1H), 8.73 (s, 1H), 8.46 (t, $J = 8.4$ Hz, 1H), 8.07 (d, $J = 8.2$ Hz, 1H), 8.00 (d, $J = 8.6$ Hz, 1H), 7.79 - 7.70 (m, 3H), 7.61 (d, $J = 8.6$ Hz, 1H), 7.45 (s, 2H), 7.37 (s, 1H), 7.32 (d, $J = 4.1$ Hz, 1H), 7.25 - 7.09 (m, 4H), 6.95 (d, $J = 8.7$ Hz, 1H), 4.82 (d, $J = 2.8$ Hz, 3H), 4.11 (d, $J = 2.5$ Hz, 3H), 3.87 (s, 2H); IR (KBr), ν , cm^{-1} : 3352.98 (N-H), 2833.62 (CH_3), 1642.29 (C=O), 1586.70 (C=C_{Ar}), 1541.09 (C=N), 1393.64 (C-N), 1215.32 (C-O-C), 984.60 (C-F), 752.12 (C-Cl). ^{13}C NMR (101 MHz, DMSO) δ 188.05, 167.10, 160.13, 158.59, 157.83, 156.14, 154.89, 153.88, 147.94, 147.67, 143.98, 143.37, 136.64, 133.13, 130.48, 130.40, 128.96, 127.65, 126.96, 124.88, 122.65, 122.14, 119.35, 117.10, 116.54, 116.34, 113.78, 108.89, 107.87, 104.41, 68.50, 56.43, 55.79. ESI-MS (m/z): calculated for $\text{C}_{33}\text{H}_{26}\text{ClFN}_4\text{O}_5$: 613.04 (100%); found: 613.25 $[\text{M}]^+$ (100%).



**Figure. S3.** ^1H NMR spectrum of target compound **9c**.**Figure. S4.** ^1H NMR spectrum of target compound **9d**.





**Figure. S9.** ^1H NMR spectrum of target compound **9i**.**Figure. S10.** ^1H NMR spectrum of target compound **9j**.

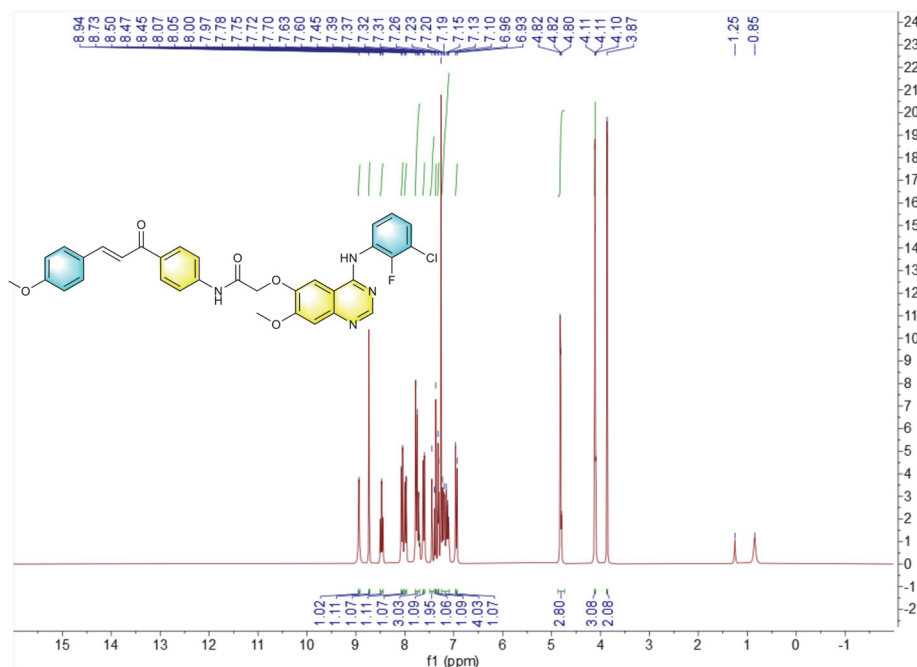


Figure. S11. ^1H NMR spectrum of target compound **9k**.

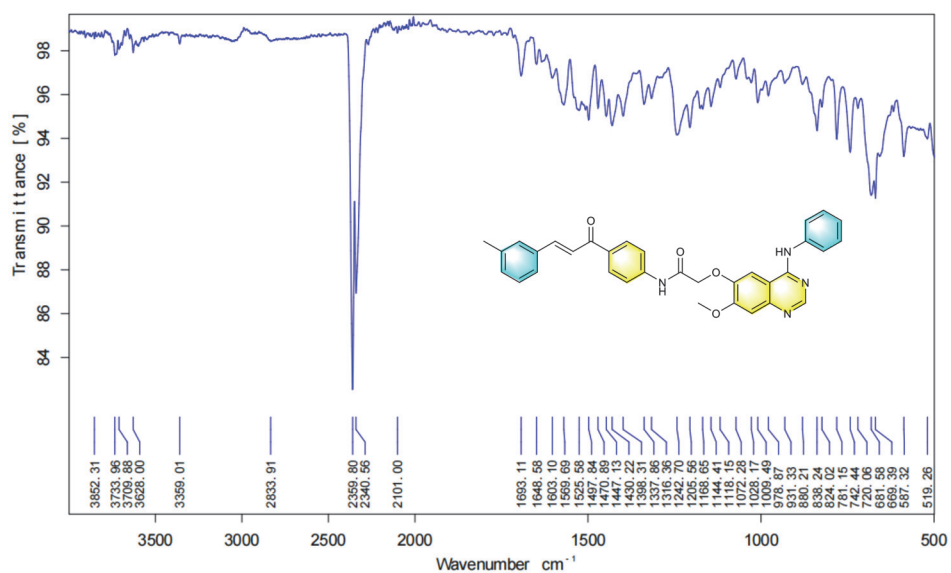


Figure. S12. IR spectrum of target compound **9a**.

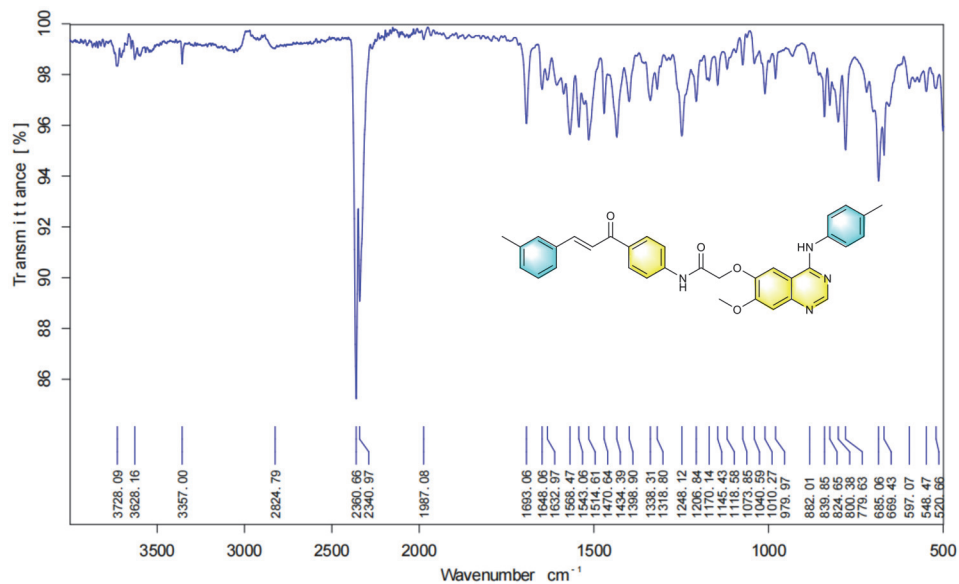


Figure. S13. IR spectrum of target compound 9b.

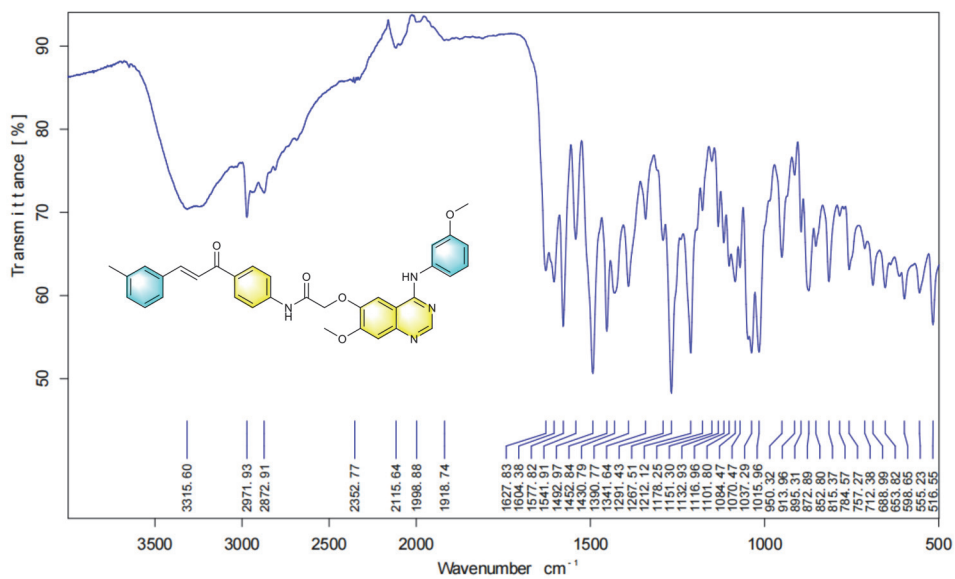


Figure. S14. IR spectrum of target compound 9c.

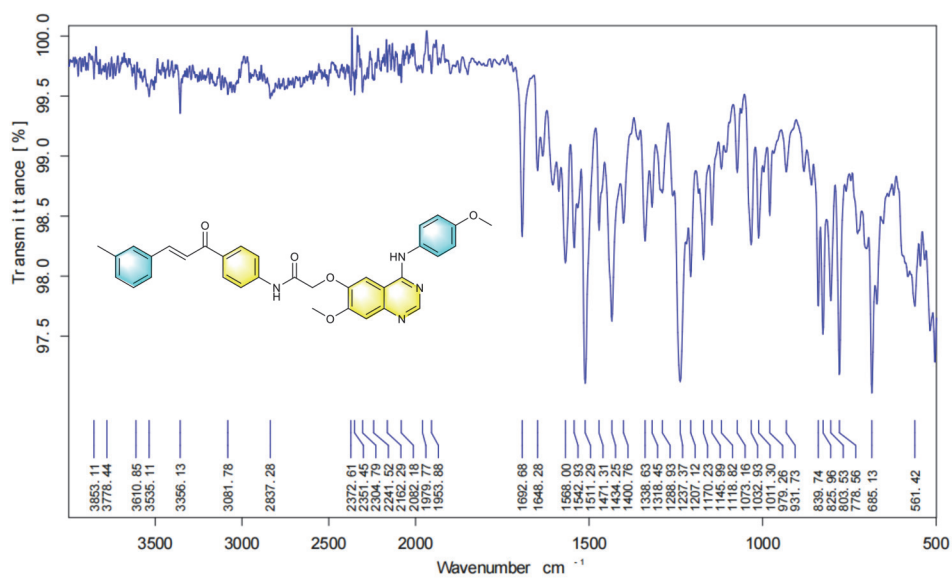


Figure. S15. IR spectrum of target compound 9d.

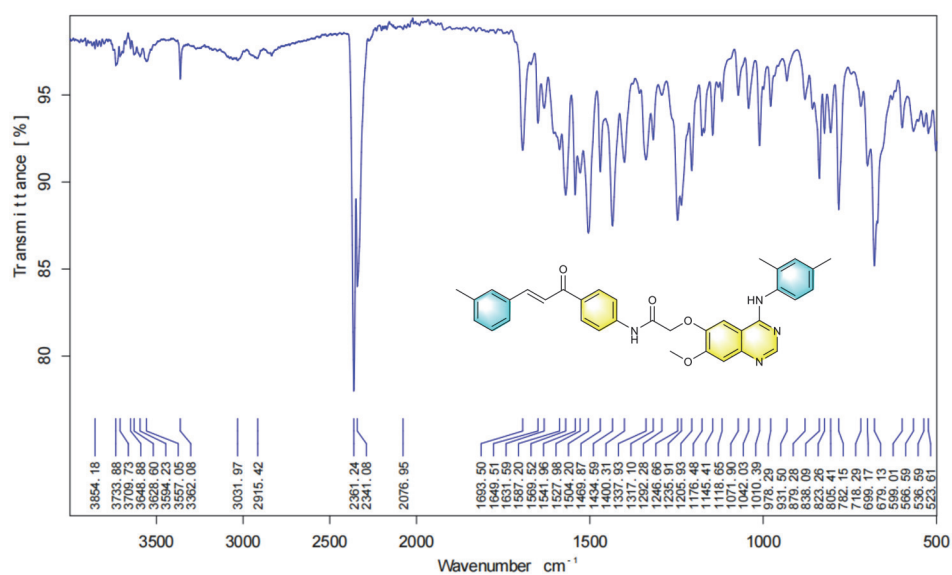
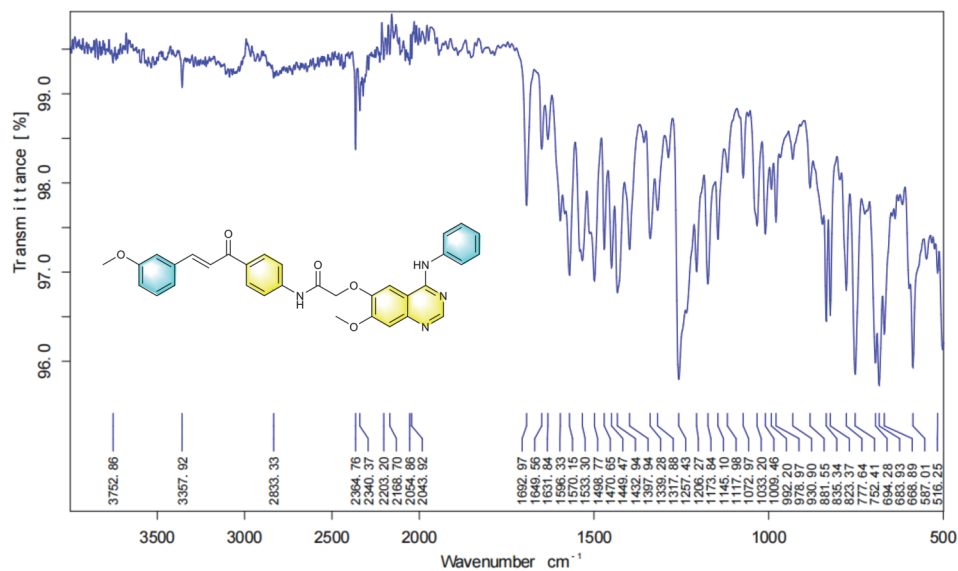
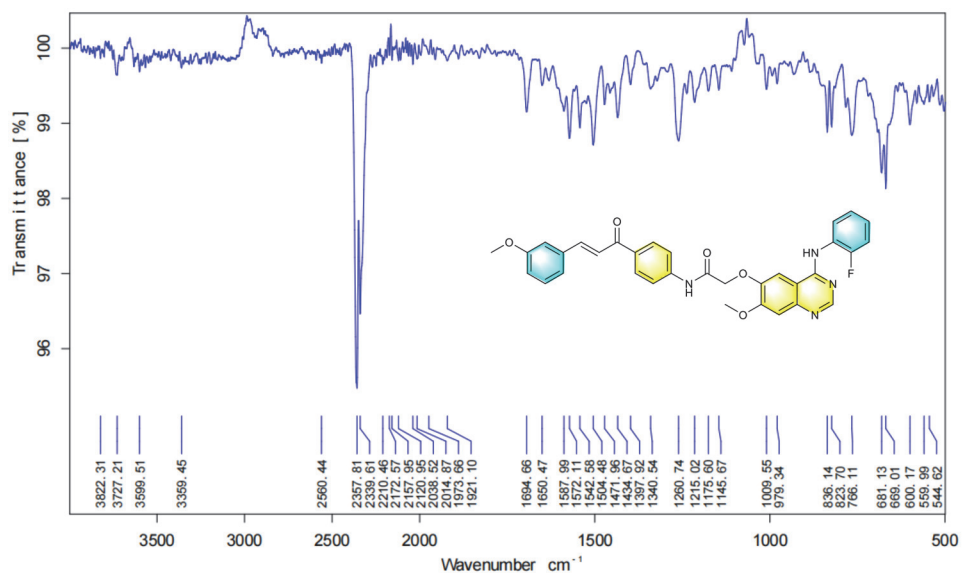


Figure. S16. IR spectrum of target compound 9e.

Figure. S17. IR spectrum of target compound **9f**.Figure. S18. IR spectrum of target compound **9g**.

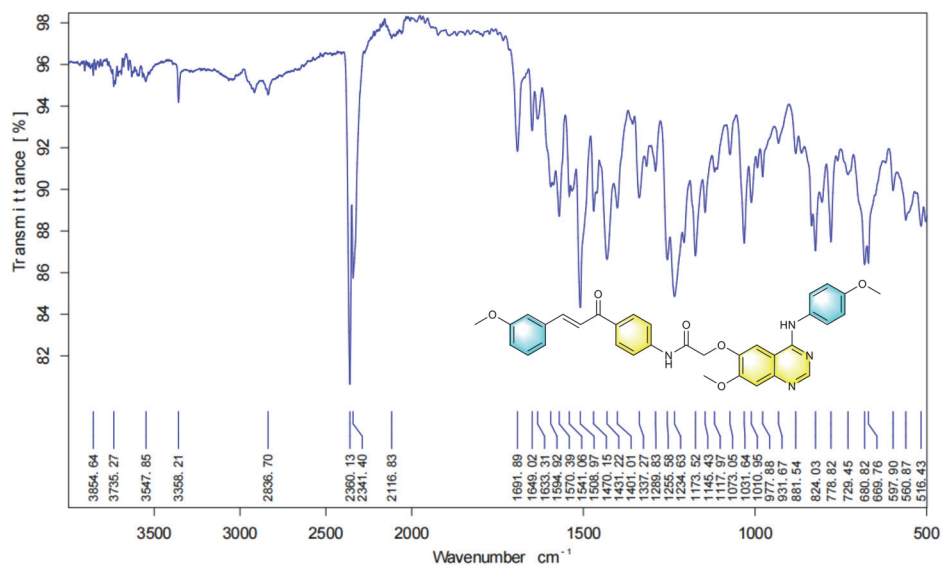


Figure. S19. IR spectrum of target compound 9h.

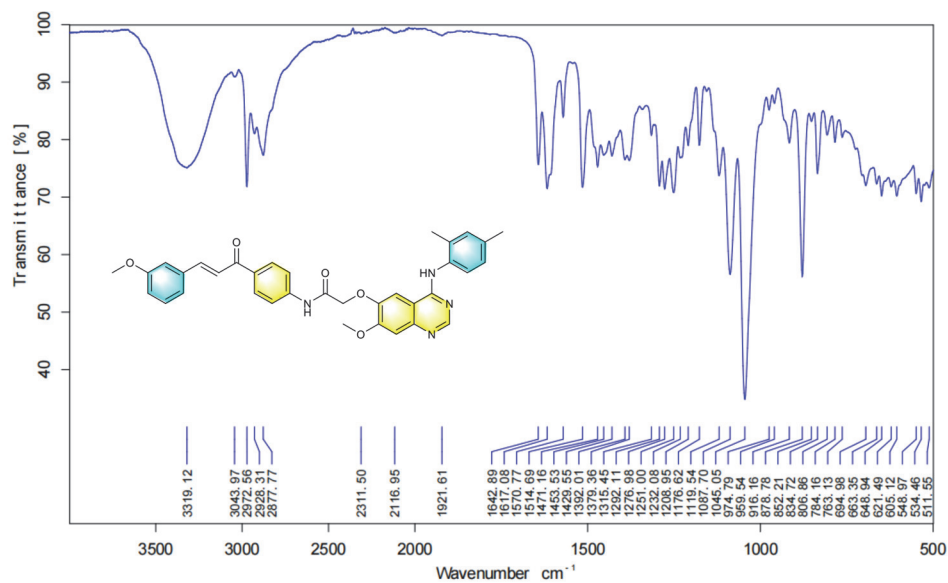


Figure. S20. IR spectrum of target compound 9i.

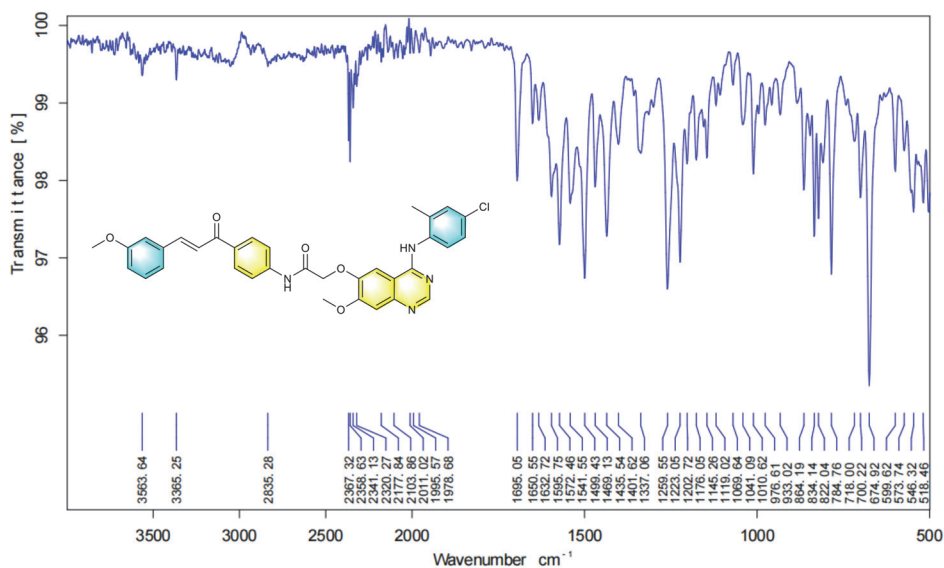


Figure. S21. IR spectrum of target compound 9j.

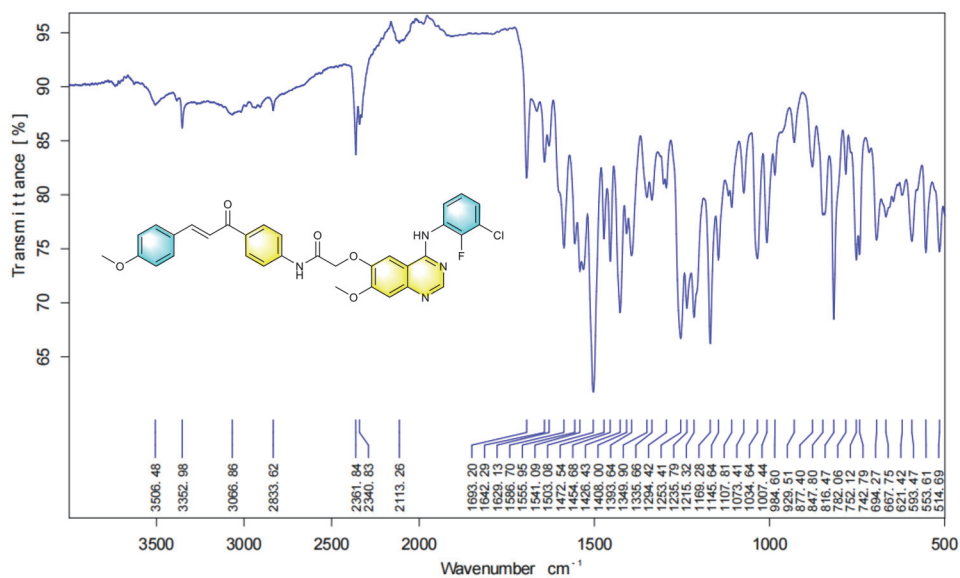


Figure. S22. IR spectrum of target compound 9k.

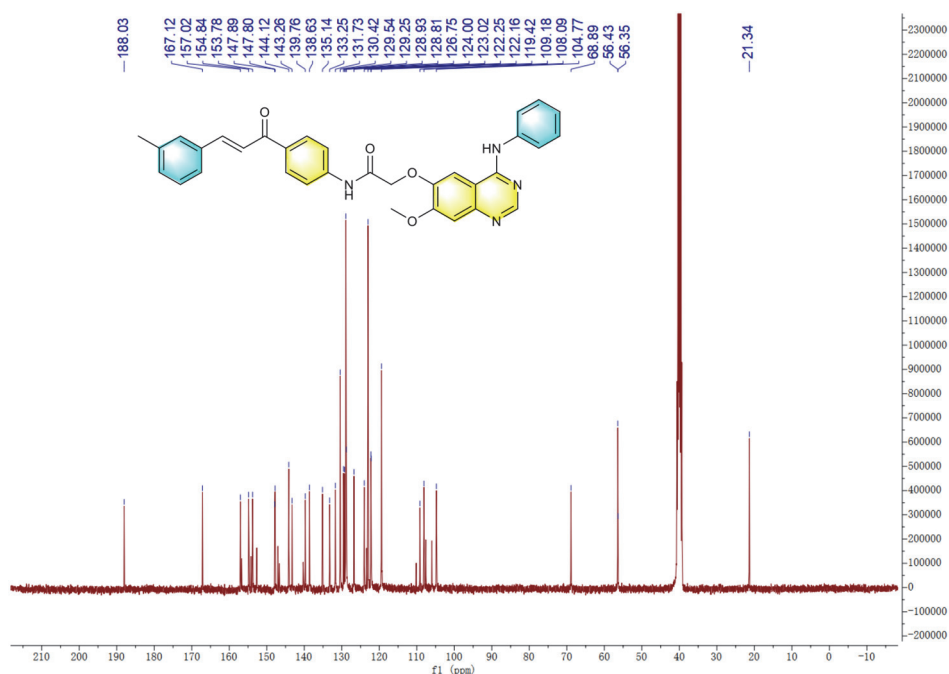


Figure. S23. ¹³C NMR spectrum of target compound 9a.

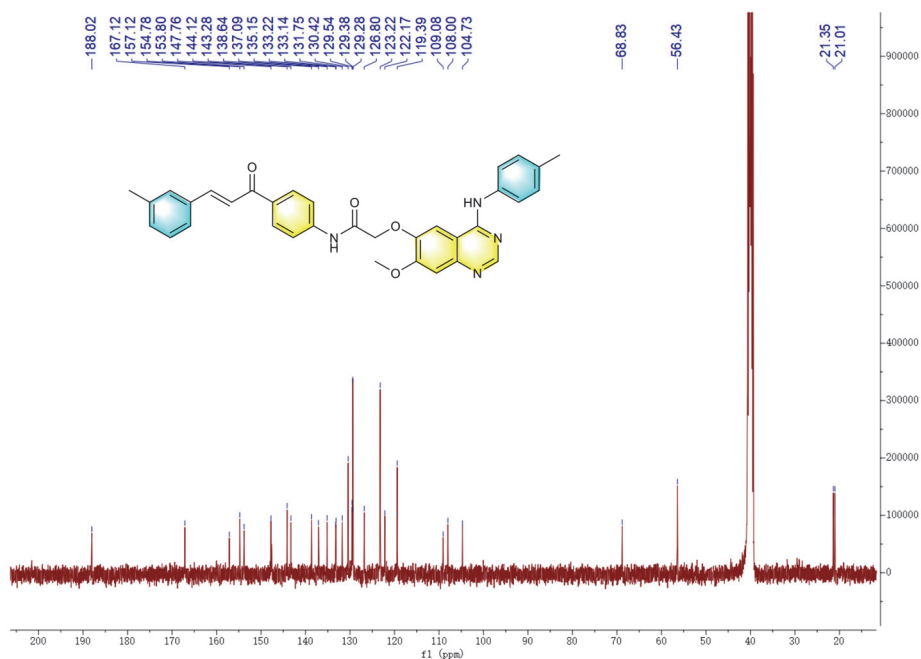


Figure. S24. ¹³C NMR spectrum of target compound 9b.

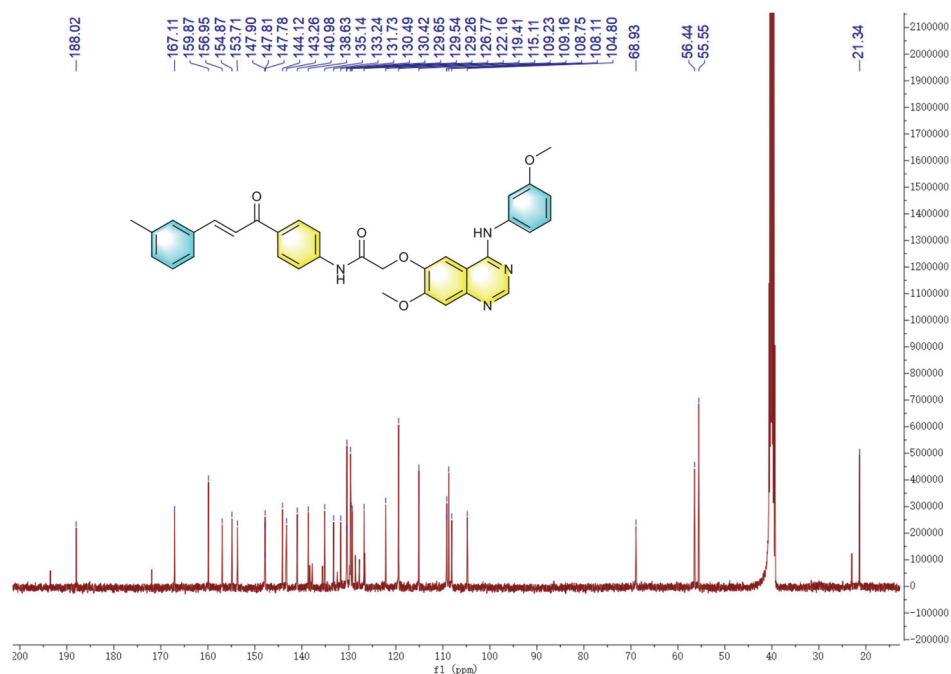


Figure. S25. ¹³C NMR spectrum of target compound 9c.

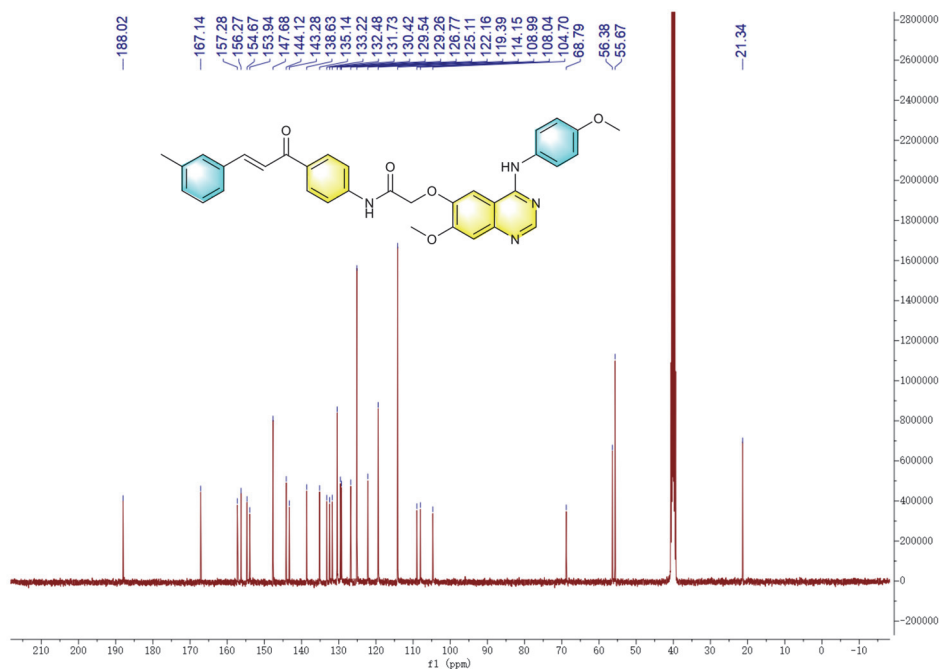
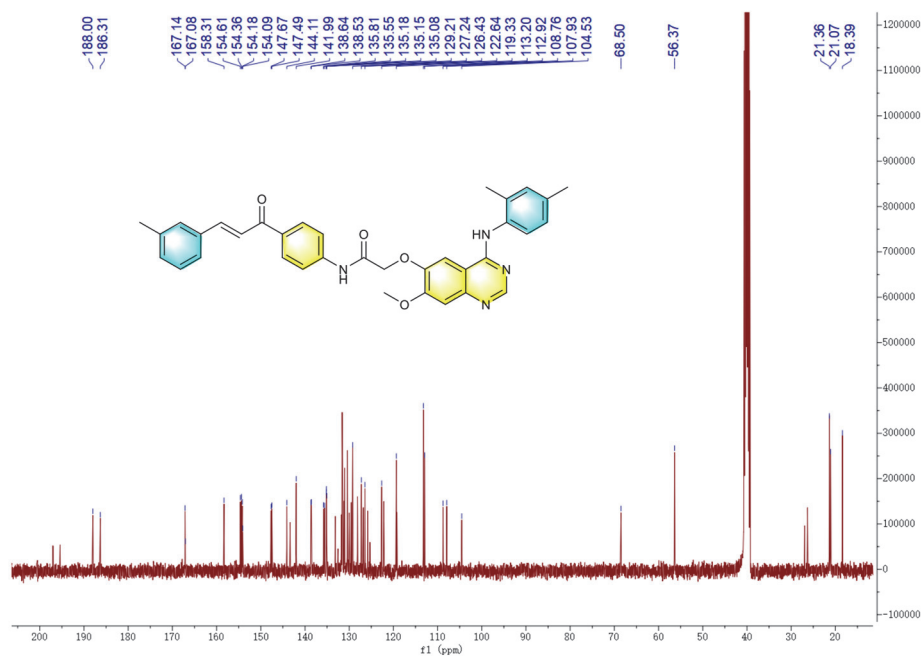
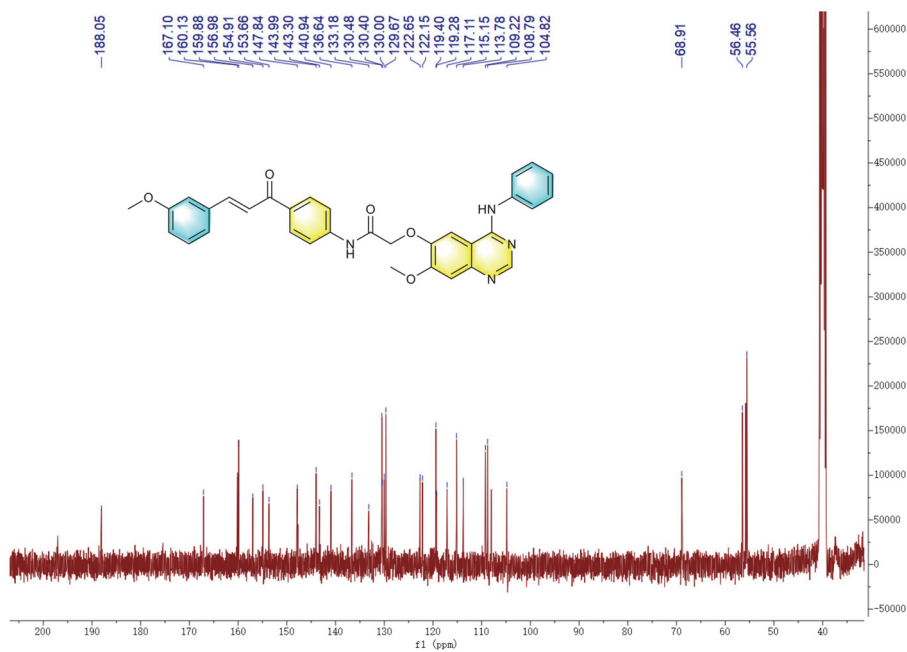


Figure. S26. ¹³C NMR spectrum of target compound 9d.

Figure. S27. ¹³C NMR spectrum of target compound 9e.Figure. S28. ¹³C NMR spectrum of target compound 9f.

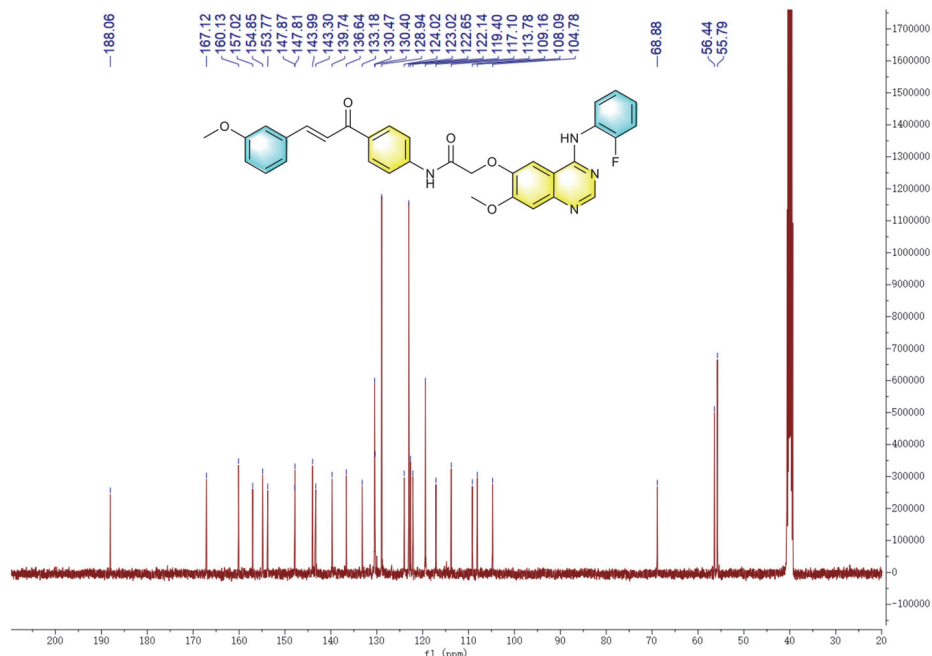


Figure. S29. ¹³C NMR spectrum of target compound 9g.

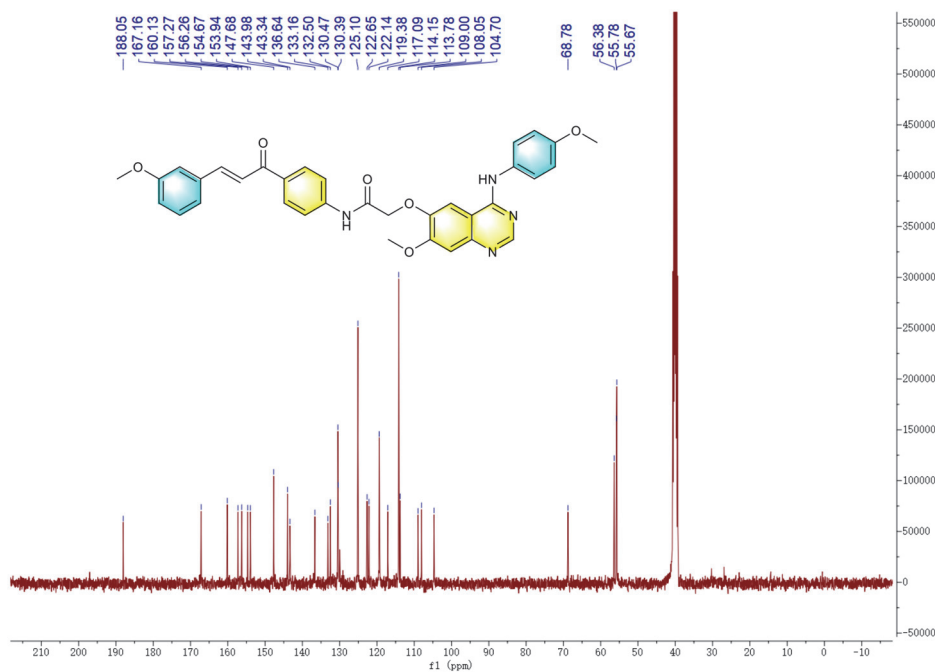
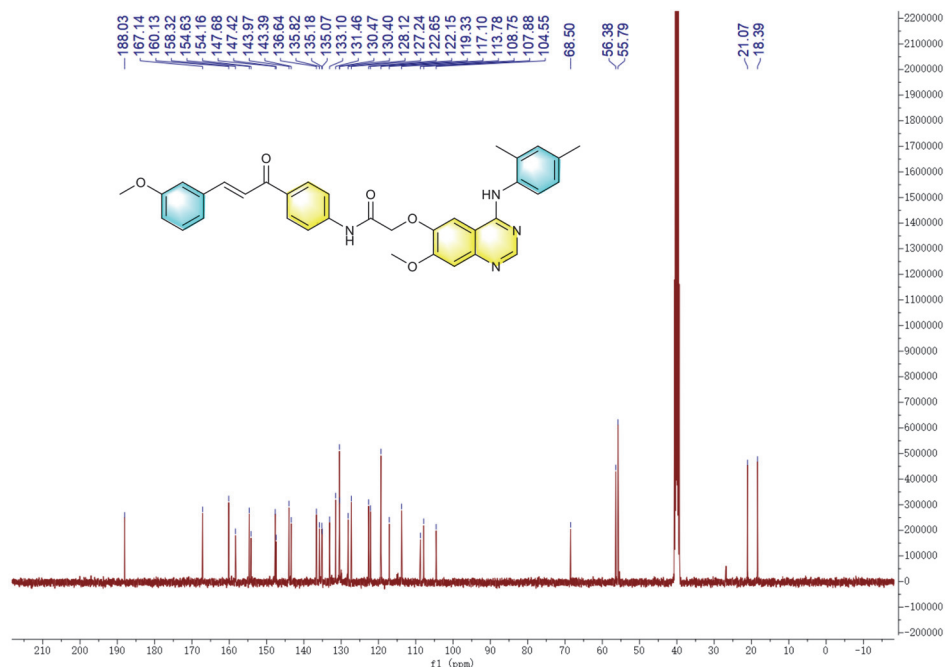
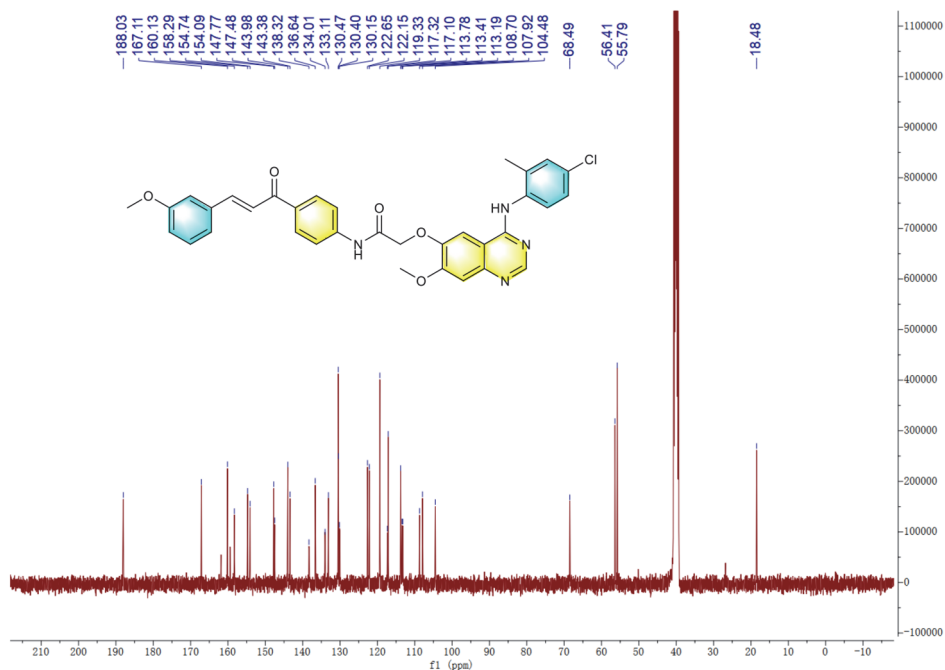


Figure. S30. ¹³C NMR spectrum of target compound 9h.

**Figure. S31.** ^{13}C NMR spectrum of target compound **9i**.**Figure. S32.** ^{13}C NMR spectrum of target compound **9j**.

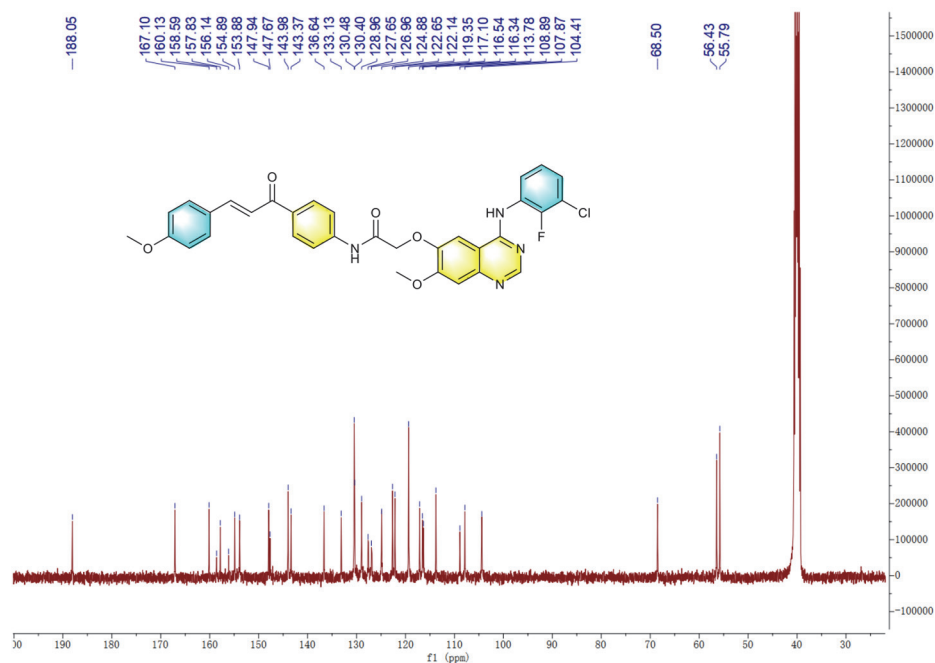
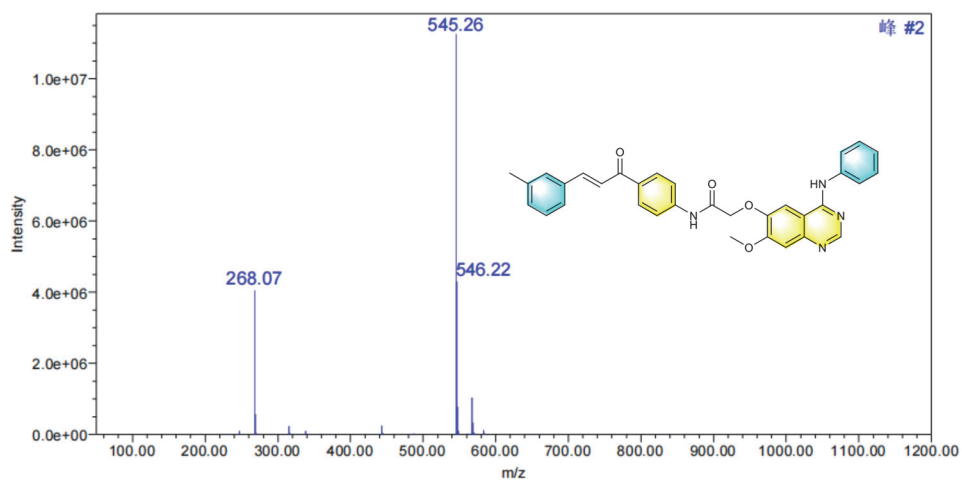
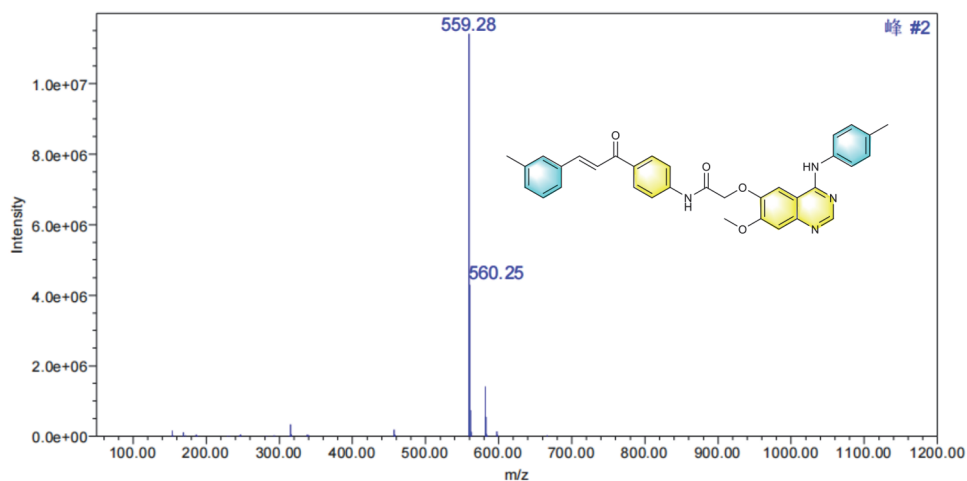
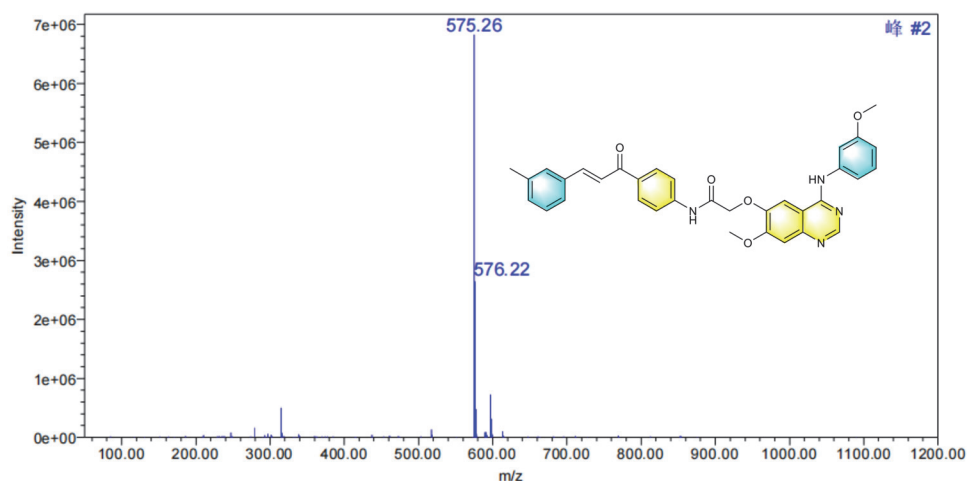
Figure. S33. ¹³C NMR spectrum of target compound 9k.

Figure. S34. MS spectrum of target compound 9a.

**Figure. S35.** MS spectrum of target compound **9b**.**Figure. S36.** MS spectrum of target compound **9c**.

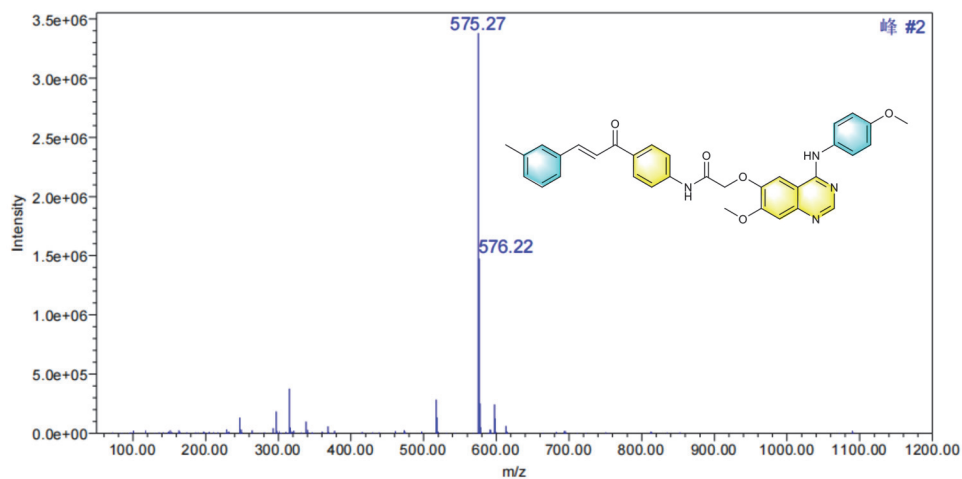


Figure. S37. MS spectrum of target compound 9d.

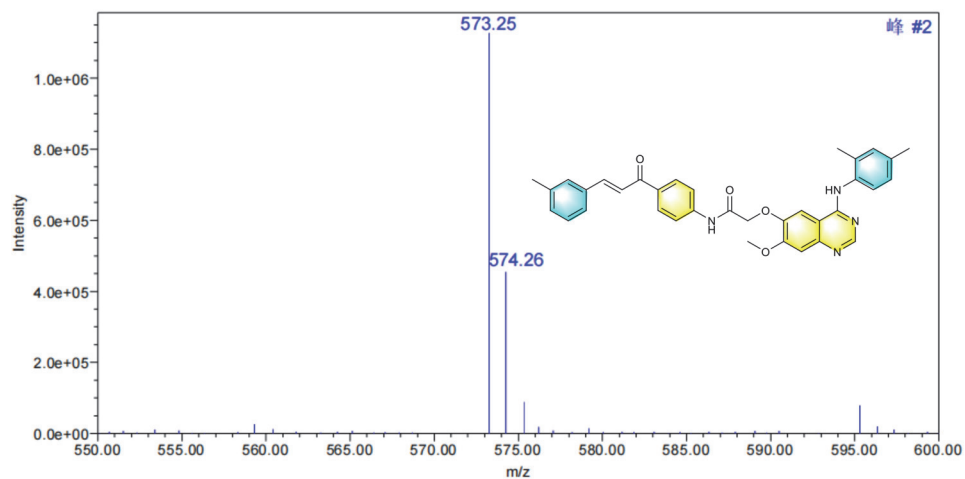
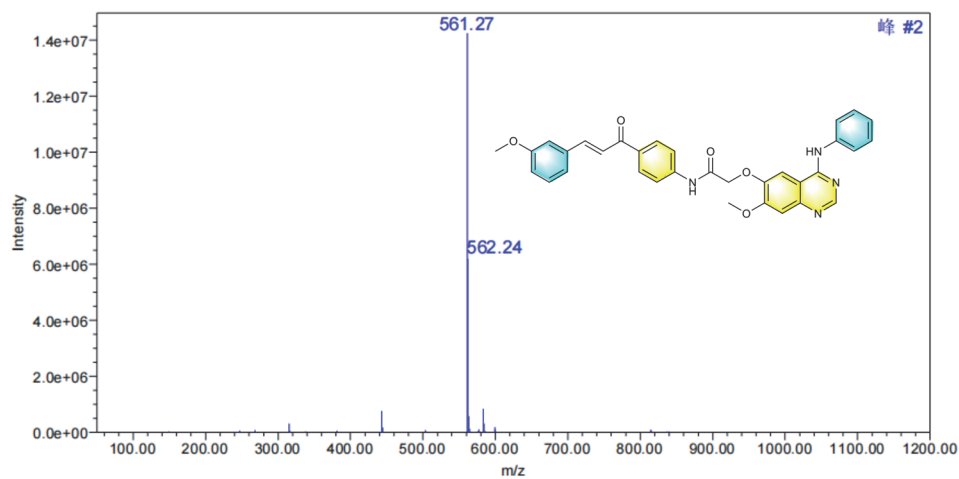
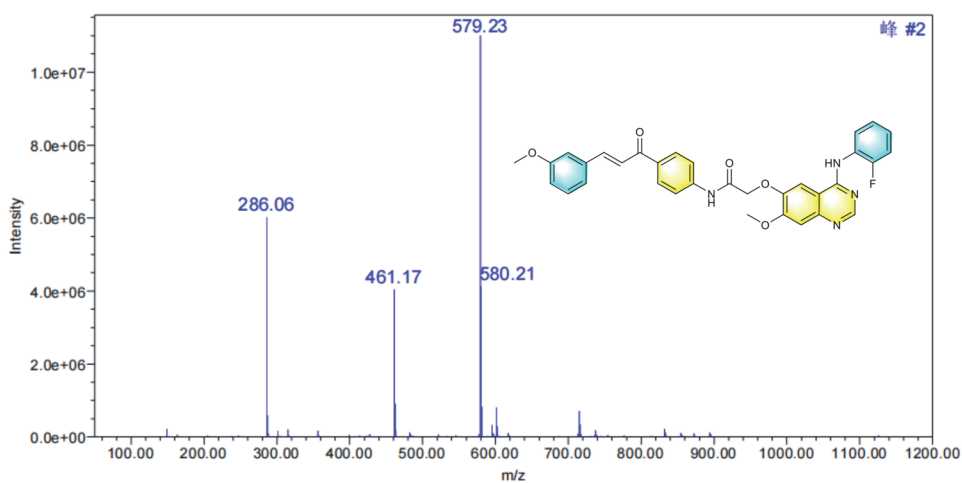


Figure. S38. MS spectrum of target compound 9e.

**Figure. S39.** MS spectrum of target compound **9f**.**Figure. S40.** MS spectrum of target compound **9g**.

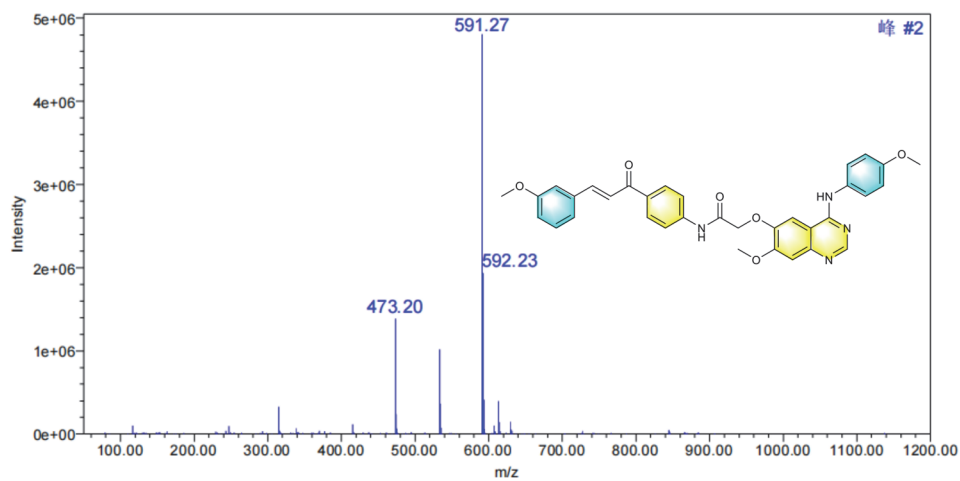


Figure. S41. MS spectrum of target compound **9h**.

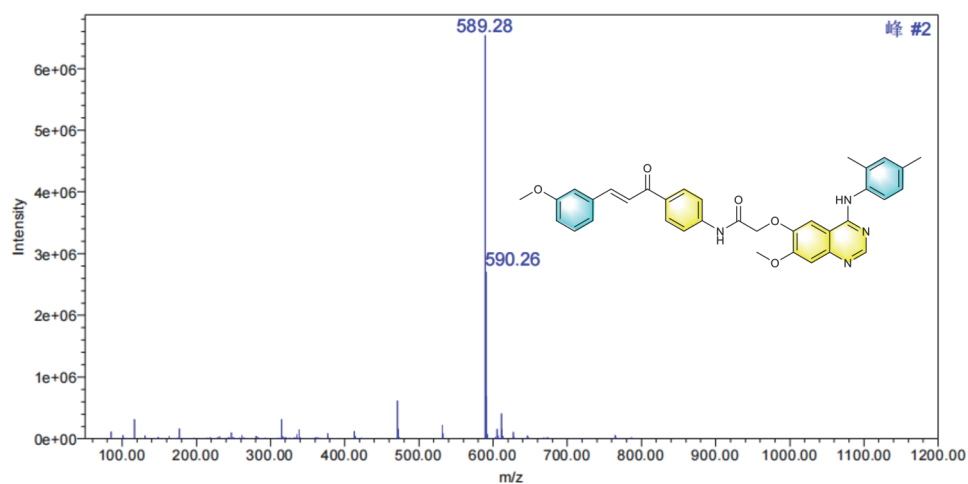


Figure. S42. MS spectrum of target compound **9i**.

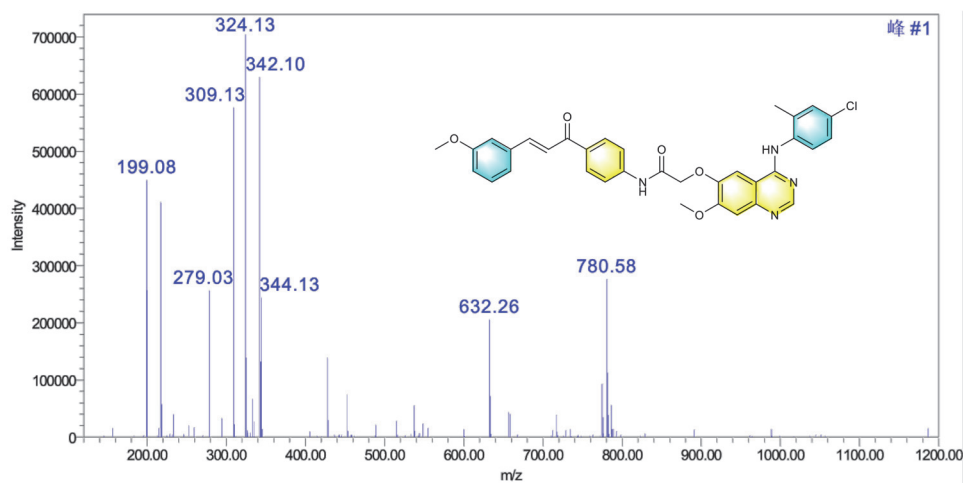


Figure. S43. MS spectrum of target compound **9j**.

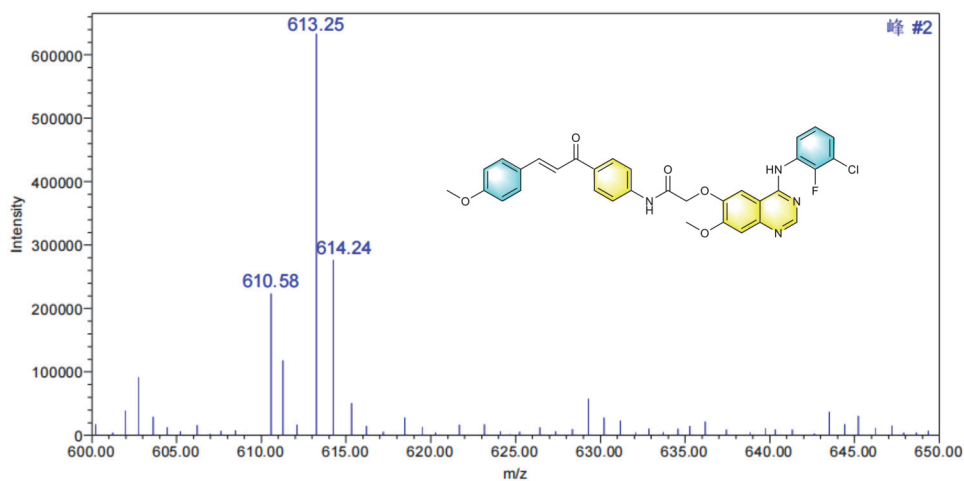


Figure. S44. MS spectrum of target compound **9k**.

Synthesis, structure and photocatalytic properties of a novel chromium compound constructed from *N*-substituted acetic acid and nitrogen-containing ligands

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Abstract: In this study, a novel Cr(III)-based coordination compound, namely [Cr(L)(phen)(COO)]₂·6H₂O (**1**), [H₂L: 3-carboxy-1-(carboxymethyl)-2-oxido-pyridinium, phen: 1,10-phenanthroline], was successfully synthesized *via* a solvothermal method. The structure of the synthesized coordination compound was confirmed by CCD single-crystal X-ray diffraction. The compound was further characterized using infrared spectroscopy, UV–Vis spectroscopy, thermogravimetric analysis and powder X-ray diffraction. The degradation of tetracycline (TC) was investigated using the coordination compound in combination with H₂O₂ under simulated ultraviolet (UV) light. Detailed catalytic reaction and kinetic studies revealed a TC degradation efficiency of 82.99 % with a rate constant of 0.0115 min^{–1}, indicating that the coordination compound exhibits promising performance in the photocatalytic degradation of antibiotics.

Keywords: coordination compound; photocatalytic degradation; tetracycline; Hirshfeld surface analyses.

INTRODUCTION

In recent years, as environmental pollution has become increasingly severe, addressing water pollution has garnered widespread attention from researchers.¹ With the design and production of pharmaceuticals, particularly antibiotics for human and animal use, the pharmaceutical sector has made groundbreaking advances. Antibiotics, in particular, constitute an important component of various medications for both humans and animals. Such developments have improved the quality of life for humans and animals; however, recent studies indicate that their

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uncontrolled discharge into terrestrial and aquatic environments has led to serious contamination of soil and water resources.² Tetracycline (TC), one of the most widely used antibiotics, poses significant risks to organisms and humans once released into water. Residual antibiotics may cause organ abnormalities or embryonic toxicity, and even at low concentrations, they can induce and disseminate antibiotic resistance genes. Due to the poor biodegradability of wastewater, conventional wastewater treatment methods are unsuitable for antibiotic removal. Therefore, identifying an effective approach for the removal of antibiotic organic pollutants is of critical importance.^{3,4} Currently, the technologies developed for antibiotic removal include adsorption, biodegradation, flocculation and photocatalysis. Guided by the principles of environmental sustainability, solar-driven photocatalytic technology is regarded as an advanced approach due to its clean, sustainable, and efficient characteristics.^{5–8} Therefore, photocatalytic degradation is widely recognized as one of the most promising methods for water remediation.⁹ Previous reports have demonstrated that semiconductors such as titanium dioxide, silver, molybdenum trioxide and iron(II,III) oxide nanoparticles have been employed as photocatalysts for pollutant degradation. However, these semiconductors suffer from low utilization efficiency of ultraviolet light and limited capacity for organic pollutant adsorption. Therefore, it is necessary to explore efficient and stable photocatalysts.^{10–13}

Coordination compounds are a class of materials capable of forming various two- and three-dimensional structures.¹⁴ Owing to their structural tunability, diverse coordination polymers can be synthesized by varying the metal centres and organic ligands, which endows them with broad application prospects in fields such as magnetism, photoluminescence, adsorption, biology and catalysis.^{15–17} Previous studies have demonstrated that introducing different organic ligands to coordinate with metal ions significantly enhances the catalytic activity of the metal centres while generating synergistic effects, thereby enabling the efficient degradation of organic pollutants.¹⁸ Coordination compounds possess wide or narrow band gaps that enable efficient absorption of UV–Vis radiation, making them effective for the photodegradation of organic molecules.¹⁹ For instance, the research group led by H. Dong developed a magnesium(II)-based coordination compound as a photocatalyst for the photocatalytic degradation of antibiotics.²⁰ In another study, A. Swargiary and colleagues reported the preparation of a copper(II)-based coordination compound as a photocatalyst for the photocatalytic degradation of organic dyes.²¹ These reports demonstrate that coordination compounds hold broad application prospects in the field of photocatalytic degradation.

In this study, a novel coordination compound, $[\text{Cr}(\text{L})(\text{phen})(\text{COO})]_2 \cdot 6\text{H}_2\text{O}$ (**1**), was synthesized using $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ as the metal source and 3-carboxy-1-(carboxymethyl)-2-oxidopyridinium (H_2L) together with 1,10-phenanthroline (phen) as mixed ligands. The structure and properties of the compound were characterized

using techniques such as X-ray single-crystal diffraction, X-ray powder diffraction and Fourier-transform infrared spectroscopy. The band gap of the compound was analyzed by UV–Vis diffuse reflectance spectroscopy (UV–Vis DRS), and its photocatalytic degradation performance was investigated.

EXPERIMENTAL

Materials and methods

All reagents were of analytical grade and purchased directly from suppliers without further purification. Analysis of the crystal structure of the compound using a Bruker-AXS Smart CCD X-ray single crystal diffractometer. Sample morphology and elemental composition were characterized using a PerkinElmer 2400 (II) analyser. The thermal stability of the compounds was evaluated with a Netzsch STA 2500 Regulus thermogravimetric analyser. Fourier-transform infrared (FT-IR) spectra were recorded on a PerkinElmer Spectrum One spectrometer. UV–Vis absorption spectra of finely ground samples were obtained using a Shimadzu UV-2550 spectrophotometer. Powder X-ray diffraction (PXRD) patterns were collected on a Rigaku Dmax 2000 diffractometer equipped with monochromatic CuK α radiation ($\lambda = 0.154$ nm). UV–Vis spectra of solution samples were measured with a TU-1901 spectrophotometer (Beijing Purkinje General Instrument Co., Ltd., China). A 12 W UV light source, assembled from commercially available UV LED strips, was used for irradiation experiments.

*Synthesis of [Cr(L)(phen)(COO)]₂·6H₂O (**1**)*

3-Carboxy-1-(carboxymethyl)-2-oxidopyridinium (H₂L)(0.05 mmol, 0.0099 g), 1,10-phenanthroline (phen) (0.1 mmol, 0.0186 g), CrCl₃·6H₂O (0.1 mmol, 0.0266 g), 1.5 mL of H₂O and 1.5 mL of DMF were added to a 10 mL glass vial. After ultrasonication for 40 min, the glass vial was placed in an oven at 88 °C for 4 days, followed by cooling to room temperature at a rate of 3 °C/h. Pink block-shaped crystals were obtained, with a yield of 50 % calculated based on the L value. Calcd. for C₄₂H₄₀Cr₂N₆O₂: C, 52.04 %; H, 2.51 %; N, 7.36 %; Found: C, 51.61 %; H, 2.47 %; N, 7.25 %.

X-ray crystallography

In this study, a single-crystal sample measuring 0.280×0.174×0.151 mm³ was mounted on a Rigaku R-Axis Rapid single-crystal X-ray diffractometer equipped with MoK α monochromated radiation ($\lambda = 0.71073$ Å). Diffraction experiments and data collection were performed at 298(2) K using the φ - ω scan method. The structural data were solved by direct methods with the SIR2014 program and refined by full-matrix least-squares on F^2 using SHELXL2018/3.^{22,23} The final structure of **1** was determined based on single-crystal data. Detailed crystallographic parameters are summarized in Table I, while selected bond lengths and bond angles are listed in Table II and hydrogen bonds in Table III.

The relevant data can be obtained free of charge from www.ccdc.cam.ac.uk or by contacting the Cambridge Crystallographic Data Centre (CCDC: 2542481), 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; email: deposit@ccdc.cam.ac.uk).

Photocatalytic measurements

To investigate the photocatalytic performance of the coordination compound **1**, a 12W UV lamp with a wavelength of 405 nm was used to simulate visible light. The **1** (20 mg) was added to 20 mL of TC solutions with concentrations of 10, 20 and 40 ppm, respectively. Additionally, 15, 20, 25 and 30 mg of the **1** were added to 20 mL of TC solution at a concentration of 20 ppm for photocatalytic degradation experiments. The mixtures were stirred in the dark for 30 min to

TABLE I. Crystallographic data and structure refinements for **1**

Parameter	Value
Chemical formula	C ₄₂ H ₄₀ Cr ₂ N ₆ O ₂₀
Formula weight	1052.80
Crystal size, mm ³	0.280×0.174×0.151
Temperature, K	290.(2) K
Radiation	0.71073
Crystal system	Orthorhombic
Space group	<i>Pbcn</i>
<i>a</i> / Å	12.980(2)
<i>b</i> / Å	24.806(5)
<i>c</i> / Å	13.641(3)
α / °	90
β / °	90
γ / °	90
<i>V</i> / Å ³	4434.8(2)
<i>Z</i>	4
ρ (calc) / g cm ⁻³	1.592
<i>F</i> (000)	2168
Absorp. coeff., mm ⁻¹	0.586
θ range, °	2.987 to 25.010
Reflns collected	42685 (<i>Rint</i> = 0.0369)
Indep. rflns	3868
Refns obs. (<i>I</i> > 2 σ (<i>I</i>))	3185
Data/restr/paras	3868/0/316
<i>GOF</i>	1.035
<i>R</i> ₁ / <i>wR</i> ₂ (<i>I</i> > 2 σ (<i>I</i>))	0.0392/0.1046
<i>R</i> ₁ / <i>wR</i> ₂ (all data)	0.0515/0.1177
Larg peak and hole, e/Å ³	0.280/−0.386

TABLE II. Selected bond distances (Å) and bond angles (°) for **1**; symmetry transformations used to generate equivalent atoms: *i*−*x*, *y*, −*z*+1/2

Bond lengths, Å			
N(1)–Cr(1)	2.062(2)	N(2)–Cr(1)	1.961(2)
O(2)–Cr(1)	1.9341(18)	O(3)–Cr(1)	1.9535(18)
O(4)–Cr(1) ^{<i>i</i>}	1.9546(19)	O(6)–Cr(1)	1.9757(19)
Bond angles, °			
O(2)–Cr(1)–O(3)	91.08(7)	O(2)–Cr(1)–O(4) ^{<i>i</i>}	87.19(8)
O(3)–Cr(1)–O(4) ^{<i>i</i>}	88.89(8)	O(2)–Cr(1)–O(6)	91.09(8)
O(3)–Cr(1)–O(6)	91.48(8)	O(4) ^{<i>i</i>} –Cr(1)–O(6)	178.25(8)
O(2)–Cr(1)–N(1)	95.05(9)	O(3)–Cr(1)–N(1)	173.78(8)
O(4) ^{<i>i</i>} –Cr(1)–N(1)	92.53(8)	O(6)–Cr(1)–N(1)	87.29(8)
O(2)–Cr(1)–N(2)	175.03(8)	O(3)–Cr(1)–N(2)	93.57(8)
O(4) ^{<i>i</i>} –Cr(1)–N(2)	94.65(8)	O(6)–Cr(1)–N(2)	87.04(8)
N(1)–Cr(1)–N(2)	80.28(9)		

TABLE III. Hydrogen bonding data for **1**; Symmetry transformations: ⁱⁱ $x-1, y, z$; ⁱⁱⁱ $x-1/2, -y+1/2, -z+1$; ^{iv} $-x, -y, -z+1$; ^v $-x+1/2, -y+1/2, z-1/2$

D–H···A	$d(\text{D–H}) / \text{\AA}$	$d(\text{H···A}) / \text{\AA}$	$d(\text{D···A}) / \text{\AA}$	$\angle \text{DHA} / ^\circ$
C(2)–H(2)···O(3W)	0.93	2.62	3.286(5)	129.1
C(7)–H(7)···O(3)	0.93	2.65	3.138(3)	113.7
C(13)–H(13)···O(3W) ⁱⁱ	0.93	2.47	3.334(4)	154.7
C(19)–H(19A)···O(1) ⁱⁱⁱ	0.97	2.60	3.206(3)	121.0
O(1W)–H(1B)···O(6) ^{iv}	0.85	2.36	2.963(4)	128.0
O(2W)–H(2A)···O(1)	0.86	1.93	2.767(3)	164.5
O(2W)–H(2B)···O(7) ^v	0.85	2.01	2.829(4)	161.7

achieve adsorption–desorption equilibrium. Subsequently, under illumination with continuous stirring (the vertical distance between the light source and the reaction vessel was 12 cm). One mL aliquots of the suspension were collected every 30 min. After centrifugation at 10,000 rpm for 1 min, the supernatant was collected, and its absorbance was measured using a UV–Vis spectrophotometer. After determining the optimal TC concentration (20 ppm) and the optimal I dosage (20 mg), three 20 mL aliquots of 20 ppm TC solution were prepared. The first aliquot was supplemented with 0.4 mL of 30 % H₂O₂ as a control, the second aliquot was supplemented with 20 mg of **1**, and the third aliquot was supplemented with both 20 mg of **1** and 0.4 mL of 30 % H₂O₂. Photocatalytic degradation experiments were then conducted on each sample.

RESULTS AND DISCUSSION

Crystal structure description of **1**

Single-crystal X-ray diffraction analysis reveals that the compound crystallizes in the orthorhombic system with the *Pbcn* space group. As illustrated in Fig. 1, the smallest asymmetric unit of **1** consists of one Cr(III) ion, one L anion, one formate ion and one 1,10-phenanthroline (phen) molecule. The Cr(III) ion adopts a distorted six-coordinate [CrN₂O₄] octahedral coordination environment. Three oxygen atoms are derived from two L ligands (O(2)–Cr(1) = 1.9341(18) Å, O(3)–Cr(1) = 1.9535(18) Å, O(4)–Cr(1) = 1.9546(19) Å), and the remaining oxygen atom originates from a formate ion resulting from the decomposition of DMF (O(6)–Cr(1) = 1.9757(19) Å). The two nitrogen atoms are provided by a bidentate chelating phen (N(1)–Cr(1) = 2.062(2) Å, N(2)–Cr(1) = 2.065(2) Å, N(1)–Cr(1)–N(2) = 80.28(9)°). Two L ligands bridge Cr(1) and symmetry-related Cr(1) cations in a tridentate (μ_2 – η^0 : η^1 : η^1 : η^0) bridging mode, forming a binuclear unit with a Cr(1)ⁱ–Cr(1)ⁱⁱ distance of 5.931 Å. As summarized in Table III, hydrogen-bonding interactions (O–H···O) lead to the formation of a two-dimensional supramolecular structure from the binuclear molecules (Figs. 2 and 3). The hydrogen-bonding parameters are as follows. O(2W)–H(2A)···O(1): O(2W)–H(2A) = 0.86 Å, H(2A)···O(1) = 1.93 Å, O(2W)···O(1) = 2.767(3) Å, O(2W)–H(2A)···O(1) = 164.5; O(2W)–H(2B)···O(7): O(2W)–H(2B) = 0.85 Å, H(2B)···O(7) = 2.01 Å, O(2W)···O(7) = 2.829(4) Å, O(2W)–H(2B)···O(7) = 161.7.

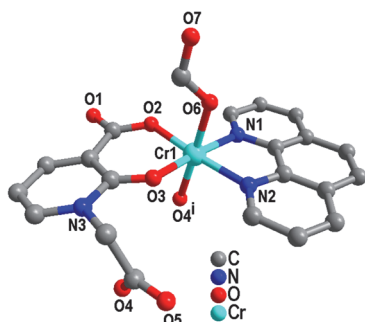


Fig. 1. Coordination environment of the **1** (symmetry code: $i-x, y, -z+1/2$).

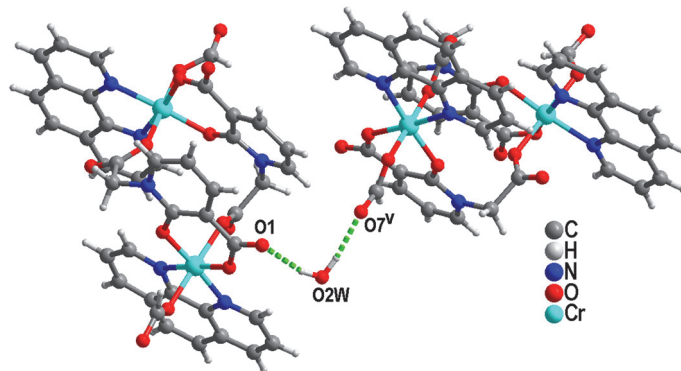


Fig. 2. Hydrogen-bonding interactions between adjacent binuclear units (symmetry code: $v-x+1/2, -y+1/2, z-1/2$).

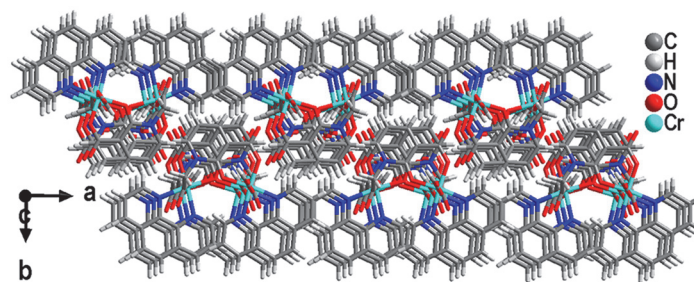


Fig. 3. Two-dimensional supramolecular structure of **1**.

The phen ligand features a planar and rigid conjugated aromatic skeleton. Distinct supramolecular π - π stacking interactions occur between phenanthroline aromatic rings of adjacent complex units, and the centroid-centroid distances of these aromatic rings are within the typical range for π - π interactions. The ordered layered π - π stacking creates continuous conjugated electron transport pathways, which drastically shorten the migration distance of photogenerated electrons and holes, efficiently restrain the rapid recombination of e^-/h^+ pairs, and boost carrier

utilization efficiency. Combined with solid-state UV–Vis spectral results, the conjugated phenanthroline skeleton together with interlayer π – π stacking synergistically widens the light absorption range of the material. Intermediate defect energy levels are introduced based on the intrinsic wide band gap, allowing the material to be excited by 405 nm near-visible light to generate active free radicals, thereby delivering satisfactory photocatalytic degradation performance against tetracycline.

Hirshfeld surface analyses

In the crystal structure, intermolecular interactions play a crucial role in maintaining structural stability. Hirshfeld surface analysis was performed to quantitatively assess these intermolecular interactions. In the dnorm map, distances greater than the sum of the van der Waals radii are represented in blue, indicating regions with negligible interactions; distances equal to the sum of the van der Waals radii of the relevant atoms are shown in white, representing relatively weak interactions; contact distances shorter than the sum of the van der Waals radii are depicted in red, corresponding to hydrogen-bonding interactions (Fig. 4). The Hirshfeld surface analysis is further complemented by two-dimensional fingerprint plots, which provide a quantitative description of the nature and types of intermolecular interactions present in the crystal. The contributions of various intermolecular interactions in **1** are as follows: H...H (36.2 %), O...H/H...O (35.8 %), C...H/H...C (20.9 %), C...O/H...O (3.4 %) and N...H/H...N (1.8 %). According to the analytical results, the H...H, O...H/H...O and C...H/H...C interactions make the largest contributions (Fig. 5).

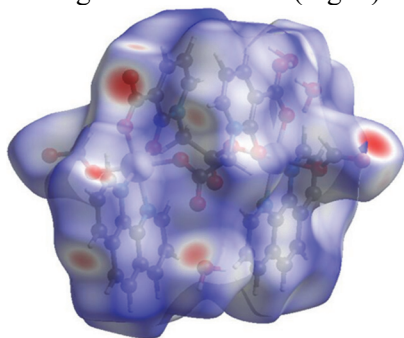
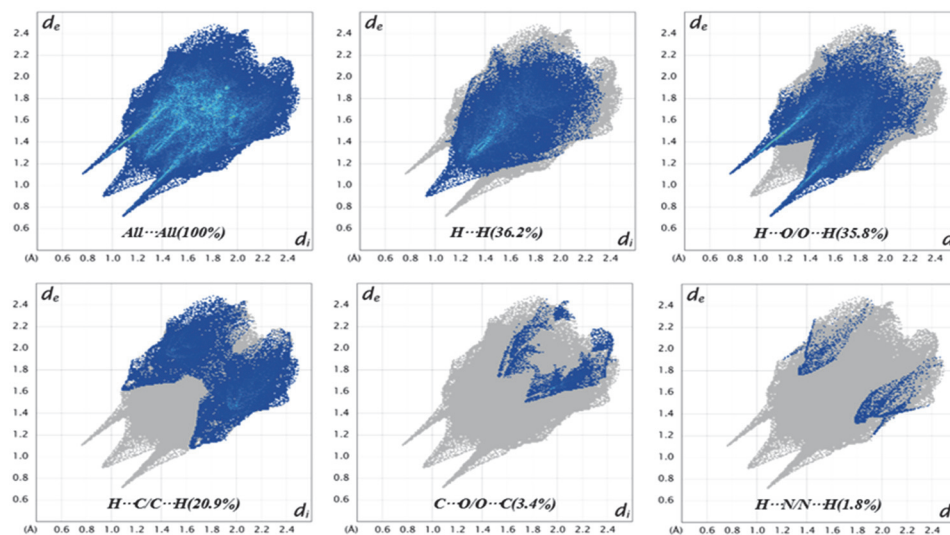
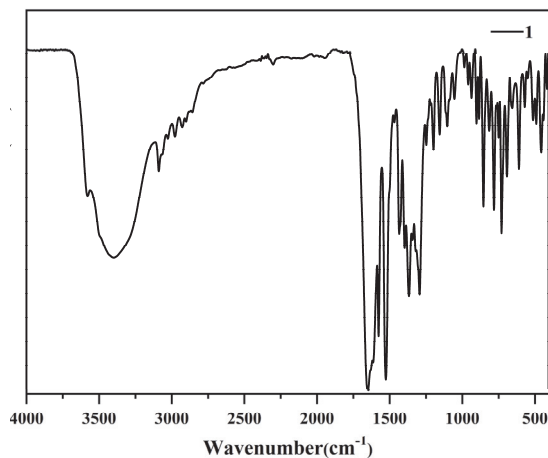


Fig. 4. Three-dimensional Hirshfeld surface of **1** mapped with dnorm.

FTIR analysis of 1

The coordination modes of the coordination compound **1** were analysed by FT-IR spectroscopy in the range of 4,000–500 cm^{-1} (Fig. 6). As shown in the spectrum, in the high-frequency region, the characteristic peak observed at 3400 cm^{-1} is attributed to the stretching vibration of water molecules within the **1**, while

Fig. 5. Two-dimensional fingerprint plot of **1**.Fig. 6. FTIR spectra of **1**.

the peak at 3083 cm^{-1} corresponds to C–H stretching vibrations.²⁴ The characteristic peak at 1650 cm^{-1} is assigned to C=O stretching vibrations. The stretching vibrations of the COO^- group appear at 1526 and 1369 cm^{-1} , which are attributed to the asymmetric stretching vibration (ν_{asym}) and symmetric stretching vibration (ν_{sym}) of the COO^- group, respectively. The difference between these two frequencies ($\Delta\nu = \nu_{\text{asym}} - \nu_{\text{sym}}$) is $< 200\text{ cm}^{-1}$, indicating that the COO^- groups of the ligand adopt a bidentate coordination mode with the metal center.²⁵ The peak at 1278 cm^{-1} is assigned to C–O stretching vibrations. Furthermore, the medium-

-intensity characteristic peaks in the low-wavenumber region at 597 and 437 cm^{-1} correspond to Cr–O and Cr–N stretching vibrations, respectively.²⁶

PXRD pattern and thermogravimetric analyzes and of 1

In this study, powder X-ray diffraction (PXRD) analysis revealed that the as-synthesized **1** exhibits characteristic diffraction peaks consistent with the simulated pattern, indicating the high phase purity of the compound (Fig. 7).

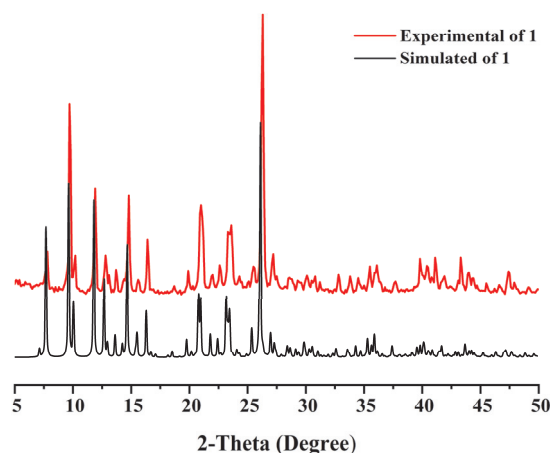
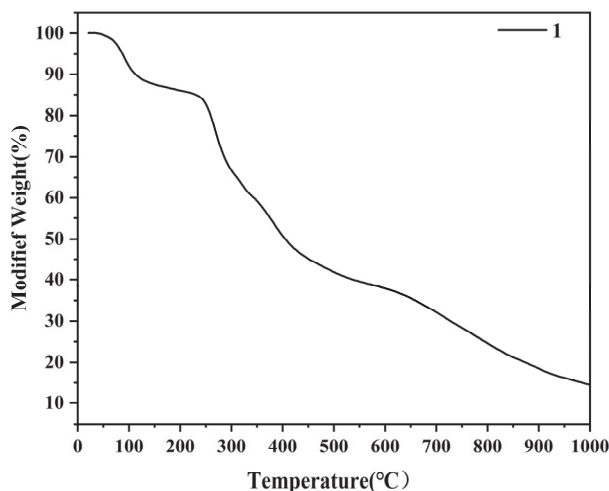


Fig. 7. PXRD patterns analysis of **1**.

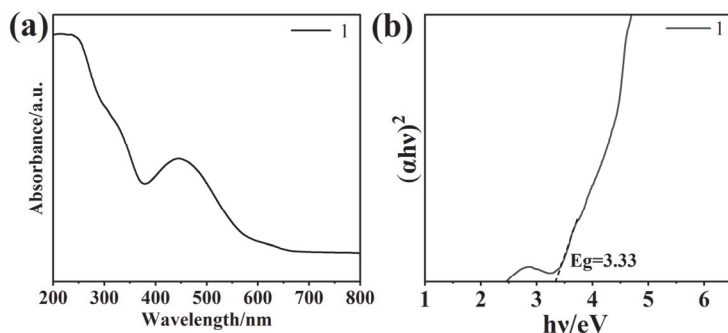
The thermal stability of compound **1** was investigated by thermogravimetric analysis (TGA) under a nitrogen atmosphere over the temperature range of 20–1000 °C (Fig. 8). The analysis results revealed an initial mass loss of 15.1 % in the range of 44–237 °C, which is attributed to the simultaneous loss of free water and most of the carboxylate ions (calculated values: free water: 10.3 %; carboxylate ions: 8.4 %). A subsequent mass loss of 70.4 % occurred between 237 and 977 °C, corresponding to the thermal decomposition of ligand L, the nitrogen-containing ligand, and the remaining carboxylate ions (calculated values: ligand L: 32.7 %; nitrogen-containing ligand: 34.2 %).²⁷ At 987 °C, the residual mass corresponds to the formation of Cr_2O_3 , with an experimental value of 14.3 % (calculated value: 14.4 %).²⁸

UV–Vis diffuse reflectance spectroscopy (UV–Vis DRS)

The solid-state UV–Vis diffuse reflectance spectrum of the **1** is shown in the Fig. 9a. The intense absorption band in the range of 200–370 nm is attributed to intra-ligand transitions, namely ligand-centred electron transfer ($\pi \rightarrow \pi^*$) and $n \rightarrow \pi^*$ transitions.²⁹ The weak absorption band in the range of 385–600 nm can be assigned to the spin-allowed d–d transitions of Cr(III) in an octahedral field.³⁰ In addition to the visible-light absorption range, the band gap energy is also one of the

Fig. 8. Thermogravimetric analysis of **1**.

key factors for evaluating the degradation efficiency of photocatalysts. To determine the optical band gap energy of the **1**, the Kubelka – Munk formula ($\alpha h\nu = A(h\nu - E_g)^n$) was used, yielding a calculated band gap value of 3.33 eV, where α , ν and E_g represent the absorption coefficient, optical frequency and band gap energy, respectively (Fig. 9b).³¹ The relatively low band gap value indicates that the compound exhibits semiconductor characteristics, and semiconductors with a narrow band gap can utilize the visible light spectrum of sunlight to initiate photocatalysis.³²

Fig. 9. UV–Vis adsorption spectrum of **1** (a) and the band gap of **1** (b).

The intrinsic main band gap of the material is 3.33 eV, and defect energy levels exist within the band gap, resulting in weak light absorption in the range of 372–405 nm. Although 405 nm light does not belong to the strong visible-light region, it falls at the junction of near-ultraviolet and visible light. Light at this wavelength can excite defect sites to generate charge carriers and further drive

catalytic reactions. The obvious degradation efficiency, observed under 405 nm irradiation, verifies that light of this wavelength can effectively activate the photocatalytic system. 3.33 eV corresponds to the band gap derived from the intrinsic transition of the crystal. Benefiting from surface defects and intermolecular charge transfer effects of the material, its light response range extends to longer wavelengths. Accordingly, near-ultraviolet light at 405 nm can still effectively excite the catalyst and drive the photocatalytic reaction.

Effects of pollutant concentration on photocatalytic degradation performance

To investigate the optimal reaction conditions for the photocatalytic degradation of TC, photocatalytic experiments were first conducted using TC solutions with concentrations of 10, 20 and 40 ppm, with a catalyst dosage of 20 mg (Fig. 10a). The results show that under the conditions of TC concentration of 20 ppm and illumination time of 150 min, the photocatalytic activity is relatively high, with a degradation efficiency of 60.71 %. However, when the TC concentration was increased to 40 ppm, the photodegradation efficiency decreased to 25.32 %, indicating a decline in photocatalytic activity (Fig. 10c). This decrease may be attributed to the coverage of the photocatalyst surface by TC, which limits its interaction with light. Furthermore, kinetic studies revealed that the kinetic rate constants (k) for initial TC concentrations of 10, 20 and 40 ppm were 0.0035, 0.0056 and 0.0020 min⁻¹, respectively (Fig. 10b). Therefore, an initial TC concentration of 20 ppm was considered optimal for degradation efficiency.

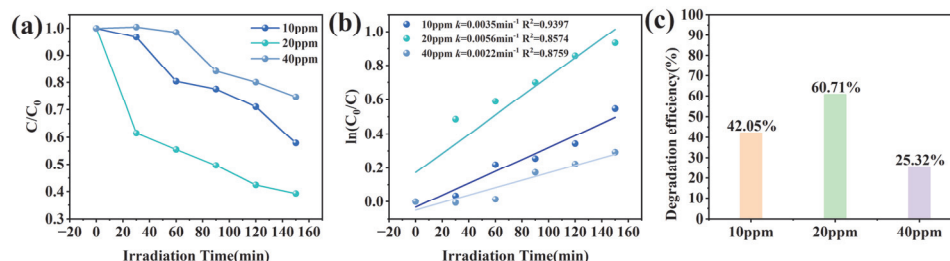


Fig. 10. Degradation curves of **1** at different TC concentrations (a); pseudo-first-order kinetics of **1** at different TC concentrations (b); degradation efficiency of **1** at different TC concentrations (c).

Effects of catalyst dosage on photocatalytic degradation performance

The catalyst dosage was optimized by varying the catalyst mass (15, 20, 25, and 30 mg), while maintaining a constant TC concentration of 20 ppm (Fig. 11a). Under the conditions of a photocatalyst amount of 15 mg and an illumination time of 150 min, the photodegradation efficiency was 33.50 %. As the catalyst amount increased from 15 to 20 mg, the catalytic performance improved, and the degrad-

ation efficiency increased to 60.71 %. This enhancement is attributed to the increase in the number of catalytically active sites with increasing catalyst dosage, which promotes the degradation of antibiotics. However, when the catalyst dosage was further increased to 25 and 30 mg, the catalytic performance declined, with degradation efficiencies of 26.59 and 22.89 %, respectively (Fig. 11c). This decrease may be ascribed to the excessive photocatalyst dosage hindering light penetration, thereby limiting the photodegradation of TC. The results indicate that the optimal photocatalytic performance is achieved at a catalyst dosage of 20 mg, with a rate constant (k) of 0.0056 min^{-1} , which conforms to a first-order kinetic model (Fig. 11b).

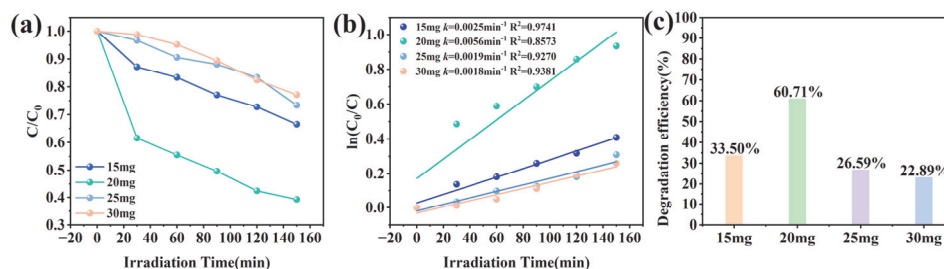


Fig. 11. Effect of different dosages of **1** on the degradation performance of TC (a); first-order kinetics at different dosages of **1** (b); degradation efficiency of TC at different dosages of **1** (c).

Effects of pH on photocatalytic degradation performance

In addition, the photocatalytic degradation performance of tetracycline (TC) varies markedly with the pH of the reaction system. The photocatalytic TC degradation activity of compound **1** was evaluated under a fixed catalyst dosage of 20 mg and an initial TC concentration of 20 ppm across different pH environments (Fig. 12a and b). The degradation efficiency reached 60.71 % under neutral aqueous conditions. In contrast, the degradation efficiencies dropped to 14.89 and 31.68 % under acidic and alkaline conditions, respectively (Fig. 12c). These results dem-

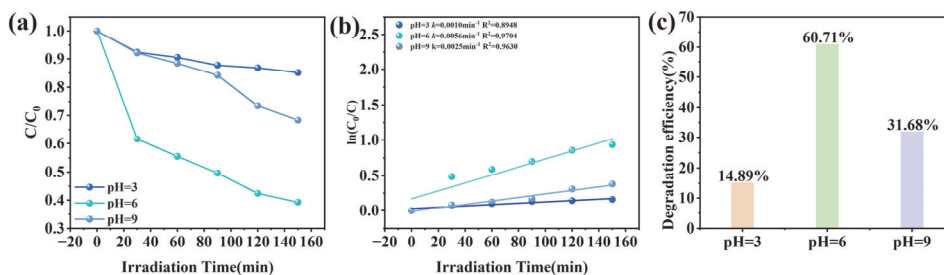


Fig. 12. Effect of pH on the degradation performance of TC by compound **1** (a); first-order degradation kinetics of TC by compound **1** at various pH values (b); TC degradation efficiency by compound **1** under different pH conditions (c).

onstrate that the catalyst exhibits optimal catalytic activity under near-neutral conditions, while its performance is substantially suppressed under strongly acidic or alkaline environments.

Effect of the combination of 1 and hydrogen peroxide on photocatalytic performance

Three comparative experiments were conducted using 20 mL of 20 ppm TC solution: *i*) degradation of TC using H_2O_2 alone, *ii*) degradation of TC using 20 mg of **1** alone and *iii*) degradation of TC using compound **1** combined with 0.4 mL of 30 % H_2O_2 (Fig. 13a). As shown in the figure, at 150 min of illumination, the H_2O_2 /TC system without the coordination polymer achieved a degradation efficiency of 44.85 %, indicating that TC undergoes gradual degradation upon exposure to H_2O_2 alone. In the **1**/TC system, the degradation efficiency was 60.71 %, while in the **1**/ H_2O_2 /TC system, the degradation efficiency reached 82.99 % (Fig. 13c). The results demonstrate that under the conditions of a photocatalyst dosage of 20 mg and a TC concentration of 20 ppm, the combination with 0.4 mL of 30 % H_2O_2 yielded the optimal degradation efficiency for TC. Furthermore, the degradation kinetics followed a first-order kinetic model with a rate constant (k) of 0.0115 min^{-1} (Fig. 13b). Furthermore, compared with the photocatalytic materials reported in previous literature, compound **1** exhibits superior degradation performance toward tetracycline (Fig. 14).^{33–36}

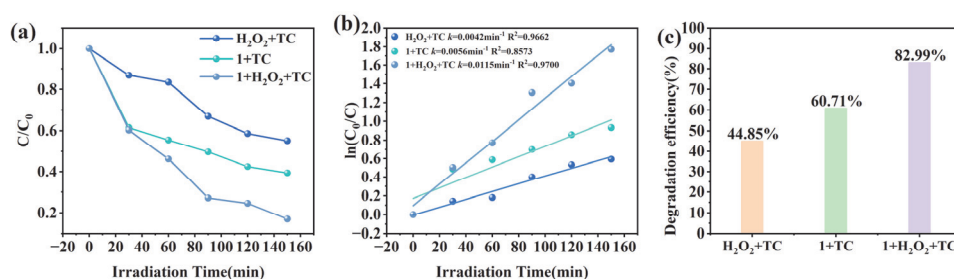


Fig. 13. Effect of different experimental group on the degradation performance of TC (a); first-order kinetics at different experimental group (b); degradation efficiency of TC a different experimental group (c).

Mechanism of photocatalytic degradation

UV–Vis diffuse reflectance spectroscopy (DRS) analysis reveals that compound **1** exhibits prominent absorption peaks in the range of approximately 200–370 nm. The high-energy photons corresponding to this short-wavelength region can accelerate the photocatalytic process and the subsequent degradation of organic pollutants. Based on these results, a series of control experiments were carried out. The addition of hydrogen peroxide as an electron acceptor markedly enhances

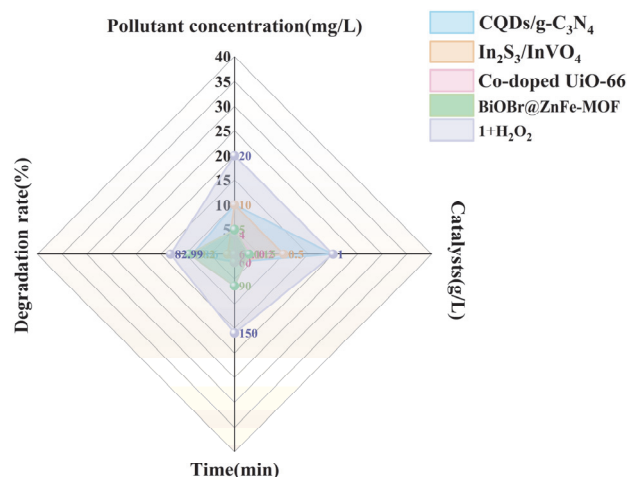
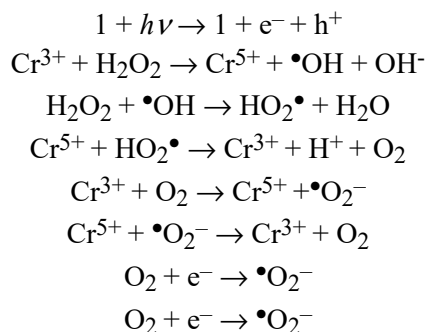


Fig. 14. Comparison of TC degradation efficiency with previously reported catalysts.

the photocatalytic activity of compound **1** toward TC degradation. The photocatalytic reaction initiates with the generation of electron-hole pairs: photogenerated holes can directly react with organic molecules or OH⁻ to produce hydroxyl radicals (•OH) for subsequent oxidation reactions. Nevertheless, the recombination of electron-hole pairs reduces the efficiency of photocatalysis. As an electron acceptor, hydrogen peroxide effectively captures photogenerated electrons and minimizes the recombination of electrons and holes.³⁷ The transfer of electrons to hydrogen peroxide facilitates the production of highly reactive •OH, thereby promoting TC degradation and boosting photocatalytic efficiency. Therefore, the introduction of an external electron acceptor is expected to suppress electron-hole recombination and improve photocatalytic performance. The superior degradation efficiency observed under UV lamp irradiation can be attributed to the strengthened capacity of hydrogen peroxide to generate •OH as well as the higher efficiency of electron excitation in the ultraviolet region.³⁸ According to previously reported literature, the plausible photocatalytic mechanism can be described by the following reaction equations:³⁹





Stability and reusability

To evaluate the stability of the photocatalyst after photocatalytic reactions, three consecutive cyclic degradation experiments of tetracycline were carried out using the same batch of photocatalyst. After each cycle, the photocatalyst was separated from the reaction mixture via centrifugation, repeatedly washed with ethanol and deionized water, and then dried in a vacuum oven at 60 °C for the subsequent cycle. The catalytic activity remained nearly unchanged after three cycles, demonstrating the recyclability of the as-prepared photocatalyst (Fig. 15a). In addition, PXRD patterns verified that the crystal structure of compound **1** barely changed before and after the photocatalytic reaction, revealing its outstanding structural stability. Therefore, the material can serve as a stable and reusable photocatalyst for the degradation of antibiotics (Fig. 15b).

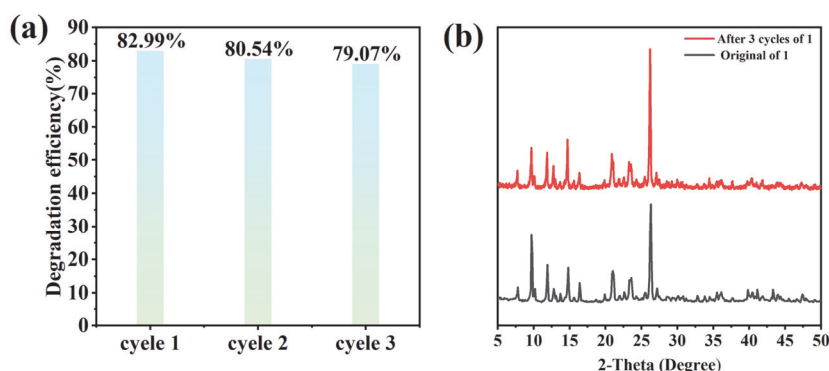


Fig. 15. Three-cycle experiment **1** for TC (a); PXRD patterns after three cycles (b).

CONCLUSION

In this study, a novel coordination compound, $[\text{Cr}(\text{L})(\text{phen})(\text{COO})]_2 \cdot 6\text{H}_2\text{O}$ (**1**), was successfully synthesized *via* a solvothermal method. Its crystal structure, optical properties and photocatalytic performance were systematically characterized. The photocatalytic degradation of tetracycline (TC) was investigated under simulated visible light irradiation. The results showed that with 20 mg dosage and 20 ppm TC concentration of **1**, the optimal degradation efficiency was achieved, reaching 60.71 % within 150 min, indicating that the **1** exhibits a certain photocatalytic degradation capability toward TC. When **1** was combined with H_2O_2 , the degradation efficiency for 20 ppm TC solution reached 82.99 % within 150 min, which conformed to a first-order kinetic model with a rate constant (k) of 0.0115 min^{-1} . This enhanced photocatalytic degradation performance demonstrates that the coordination compound holds potential application prospects in the photocatalytic degradation of antibiotics.

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ИЗВОД

СИНТЕЗА, СТРУКТУРА И ФОТОКАТАЛИТИЧКА СВОЈСТВА НОВОГ ЈЕДИЊЕЊА
ХРОМА КОЈЕ САДРЖИ *N*-СУПСТИТУИСАНУ СИРЋЕТНУ КИСЕЛИНУ И
АЗОТ-ДОНОРСКЕ ЛИГАНДЕ

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У овом раду успешно је синтетисано ново комплексно једињење хрома(III) формуле $[\text{Cr}(\text{L})(\text{phen})(\text{COO})]_2 \cdot 6\text{H}_2\text{O}$ (**1**), $[\text{H}_2\text{L} = 3\text{-карбокси-1-(карбоксиметил)-2-оксидопиридини-јум, phen} = 1,10\text{-фенантролин}]$, применом солвотермалне методе. Структура синтетисаног комплексног једињења потврђена је применом рендгенске структурне анализе. Поред тога, синтетисано једињење је окарактерисано применом инфрацрвене спектроскопије, UV–Vis спектрофотометрије, термогравиметријске анализе (TGA) и рендгенске дифракције праха. Испитивана је разградња тетрациклина (TC) применом синтетисаног комплексног једињења у комбинацији са H_2O_2 под симулираним ултраљубичастим (UV) зрачењем. Детаљно испитивање каталитичке реакције и кинетике показало је ефикасност разградње тетрациклина од 82,99 %, уз константу брзине $0,0115 \text{ min}^{-1}$, што указује на то да ово комплексно једињење показује значајан потенцијал за фотокаталитичку разградњу антибиотика.

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Voltammetric study of a detergent-stable *Actinomadura keratinilytica* lipase CPT29-cross-linked GA/BSA platinum biosensor

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Abstract: This study describes the immobilization of a native lipase (LCPT29) from *Actinomadura keratinilytica* strain CPT29 isolated from poultry compost in the northeast of Algeria in order to detect ester pollutants in an aqueous environment. For this purpose, this detergent-stable lipase was immobilized with glutaraldehyde as a cross-linker, in the presence of bovine serum albumin (BSA) onto a platinum (Pt) electrode. The prepared enzyme membrane was characterized by FT-IR spectroscopy, confirming its network formation, while its coating of the Pt-electrode was evaluated using cyclic voltammetry. The effectiveness of the cross-linked enzyme membrane-coated working electrode was evaluated electrochemically by detecting propyl 4-hydroxybenzoate (PHB) as a model analyte. Under optimal conditions and at an applied potential of –250 mV vs. Ag/AgCl, the LCPT29-based biosensor showed a linear response over the concentration range from 10^{-14} to 10^{-8} mol L⁻¹ ($r = 0.991$), with a detection limit of 10^{-14} mol L⁻¹. The biosensor exhibited high sensitivity (0.0327 mA L mol⁻¹), good stability ($RSD = 0.37\%$) and significant selectivity as well as the ability to analyse trace amounts of PHB in real water samples, demonstrating its potential for electrochemical biosensing applications.

Keywords: immobilization; enzyme membrane; biosensor; electrochemical; ester pollutant.

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INTRODUCTION

Due to their catalytic nature, which accelerates biochemical reactions in living organisms, enzymes play a crucial role in many biotechnological applications. They are essential for analytical devices used in various environmental and medical applications, including biosensors and biocatalysis.^{1,2} As recognition elements in biodetection, they provide developed biosensors with high detection capabilities, essential characteristics for analysing target compounds in complex matrices.^{3,4} Alongside these technological advances, the application of enzymes in biosensors is a current research area that is increasingly being explored.

Biosensors are devices that combine a biological recognition element, such as an enzyme, with a physicochemical transducer, thus enabling the conversion of a specific biochemical reaction into a measurable signal.⁵ Although the exploitation of commercial enzymes is widespread, their use often remains limited by their high cost, availability and sometimes their stability under specific environmental conditions.⁶ As an alternative to commercially produced enzymes, those derived from autochthonous microorganisms are cited. A wide variety of microorganisms produce enzymes, which differ in their microbial origin, chemical properties and mechanisms of action. Generally, microbial enzymes catalyze hydrolysis, oxidation or reduction reactions.⁷ Microbial lipases are the most widely used enzymes in the industrial world because they are more economical, stable and easy to culture.⁸

Lipases (EC 3.1.1.3 triacylglycerol acylhydrolase) are enzymes of the hydrolase group, mainly involved in the degradation of fats.^{9,10} They are common in nature and are made by fungi, bacteria and actinomycetes, as well as plants, animals and other microorganisms.¹¹ On an industrial scale, lipases are produced by microbes.¹² Lipase is widely employed for detecting ester-based pollutants due to its catalytic hydrolysis activity.¹³ In recent years, many enzyme electrochemical biosensors have been conceived, developed and commercialized as user-friendly and time-saving analytical methods.¹⁴ Their immobilization enhances stability, reusability, and applicability in biosensing systems.¹ Recently, numerous immobilization approaches, such as adsorption, entrapment, covalent binding and cross-linking, have been examined in the literature.¹⁵

Exploiting a detergent-stable extracellular lipase from an autochthonous strain of *Actinomyces keratinilytica* (CPT29), we developed a platinum-electrode-based enzymatic membrane. This membrane was designed to create a cost-effective, highly sensitive and selective biosensor for detecting ester-type pollutants in aquatic environments. The lipase was immobilized on a platinum electrode to form an enzymatic membrane, which was characterized by FT-IR spectroscopy and cyclic voltammetry.

EXPERIMENTAL

Chemicals and reagents

Bovine serum albumin (BSA, 99 %), aqueous solutions of glutaraldehyde (25 %), buffer solutions, glycerol (99 %) and an ester substrate were purchased from Sigma–Aldrich Chemie GmbH (Munich, Germany).

Enzyme source

In this study, the lipase¹⁶ used as a biological recognition element, was previously produced from *Actinomadura keratinilytica* strain CPT29 (GenBank accession no. KC447297) isolated from poultry compost collected from a local farm in the northeastern region of Annaba, Algeria.¹⁷

Apparatus and measurements

Electrochemical analyses were performed using a modular SP-300 potentiostat/galvanostat (Biologic Science Instruments, France), controlled by EC-Lab software (v. 11.46) for data acquisition and processing. Measurements were carried out in a three-electrode cell consisting of a platinum working electrode (0.5 cm²), a platinum wire auxiliary electrode (0.1 cm diameter), and an Ag/AgCl reference electrode. The working electrode had been previously cleaned according to a previously described procedure.¹³

Immobilization procedure

Immobilizing the enzyme on the electrode is a crucial step in biosensor development, as its efficiency depends directly on the fixation method used. Several techniques, such as adsorption, covalent bonding, or encapsulation,^{18–21} can be employed after prior activation of the surface functional groups.^{22,23}

In this study, LCPT29 was immobilized on the surface of a platinum electrode by covalent cross-linking in saturated GA vapor with BSA, in which the amino groups of proteins are expected to form a Schiff base.²⁴ During the immobilization, GA acts as a bifunctional cross-linking agent, enabling covalent bonding between the enzyme and the substrate, while BSA is often used as a stabilizing and spacing agent, promoting membrane formation on conductive surfaces. According to a previous study,²⁵ the developed biosensor was prepared by depositing a drop of lipase-based solution containing enzyme/BSA (5 %) and glycerol (10 %) in 10 mol L^{–1} PBS (90 % and pH 7.4) onto the surface of the Pt electrode. The modified working electrode was then exposed to the vapor of the saturated GA for 30 min, followed by drying at room temperature for another 30 min. Finally, it was stored at 4 °C until further use. Scanning electron microscope images (SEM, Quanta 250, FEI Company, Eindhoven, Netherlands) and FT-IR transmittance spectra (Shimadzu IRSpirit-X FTIR) were recorded to confirm the cross-linking and the membrane formation.

Enzyme activity assay

The activity of LCPT29 towards the hydrolysis of PHB was measured titrimetrically. The experiment was conducted using a method similar to that described elsewhere with slight modifications.¹³ Lipase (50 mg) was added to PHB (16.7 mol L^{–1}) in 40 mL of PBS (10 mol L^{–1}; pH 8). The mixture was stirred in a water bath at 40 °C. The kinetics of the hydrolysis reaction, were monitored using an automatic pH-stat titrator (TitroLine®7000, TitriSoft 3.0, SI Analytics GmbH, Germany). The quantity of *p*-hydroxybenzoic acid (PHBA) released was titrated by adding 0.1 mol L^{–1} of sodium hydroxide to the reaction medium. One unit (1 IU) of hydrolytic activity corresponds to 1 μmol of released acid per minute under the assay conditions used. All determinations were performed in triplicate.

RESULTS AND DISCUSSION

Characterization of GA/BSA/LCPT29

FT-IR spectroscopy analysis. Fig. 1 shows the results of the FT-IR analysis obtained after lipase immobilization. The GA spectrum shows a peak around 1680 cm^{-1} ($\text{C}=\text{O}$ stretching vibration) attributed to the carbonyl group of the aldehydic function.²⁶ In the lipase-based membrane spectrum, this peak exhibits a slight shift, suggesting the involvement of glutaraldehyde-derived aldehydes in a chemical reaction. Furthermore, the peaks recorded around 1650 and 1540 cm^{-1} can be attributed to amide I ($\text{C}=\text{O}$ stretching vibration) and amide II ($\text{C}-\text{N}$ stretching and $\text{N}-\text{H}$ bending), respectively, which are characteristic of proteins.²⁷ Although a minor contribution of residual GA in the 1650 cm^{-1} region cannot be completely excluded, this band is predominantly associated with the protein components of the membrane (BSA and immobilized enzyme). Indeed, the same band is already observed in the spectrum of pure BSA, confirming its protein origin. Furthermore, the characteristic aldehyde band of free GA around 1680 cm^{-1} is absent or strongly attenuated in the membrane spectrum, suggesting that most of the GA was consumed during the cross-linking reaction with the amino groups of BSA and the enzyme.

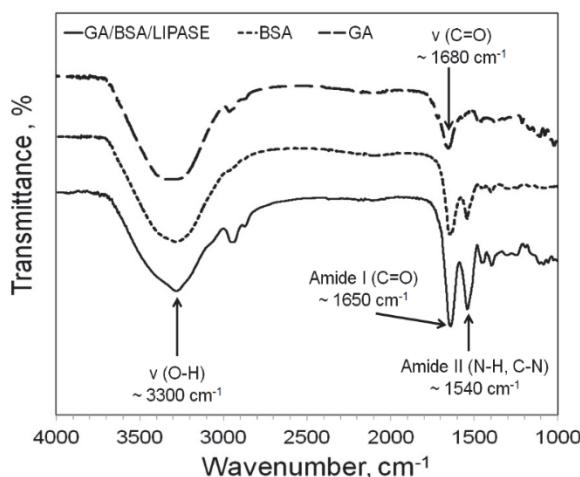


Fig. 1. FT-IR spectra of GA, BSA, and the prepared biomembrane GA/BSA/LCPT29.

The increased intensity of the amide I band in the membrane, compared with that of BSA alone, may be attributed to the combined contribution of BSA and the immobilized enzyme, as well as to structural and chemical modifications induced by GA-mediated cross-linking. These interactions likely involve Schiff base formation and/or imine bond generation between aldehyde groups of GA and amino

groups of proteins.²⁸ Since the amide I region is highly sensitive to the secondary structure of proteins, changes in its intensity and profile may reflect modifications in the local structural environment of the immobilized proteins.²⁹ The FT-IR spectrum (Fig. 1) also shows a broad absorption between 3000 and 3400 cm^{-1} , indicating O–H and N–H bonds stretching vibrations,³⁰ reflecting the presence of hydrophilic groups and bound water. These spectral characteristics together confirm the successful chemical integration of BSA and lipase within the GA-cross-linked membrane.²⁸ In this region, a weaker band is observed around 2900–3000 cm^{-1} , which may be associated with C–H bond stretching vibrations. On the other hand, the absence of a clearly resolved imine (C=N) band in the spectrum could be attributed to overlap with the intense region of amide I and the low intrinsic intensity of this feature in complex protein matrices.

Morphological analysis

In accordance with the method described above, a morphological study was performed to validate the fabrication of the enzymatic membrane on the platinum electrode using SEM analysis under an accelerating voltage of 20 kV, using CBS images at magnifications of 80 $\times$ and 600 $\times$ to compare the surface morphology before and after immersion in PHB (Fig. 2a–d). In addition, ETD images at 300 $\times$ were recorded to further examine the surface changes before and after immersion (Fig. 2a' and b').

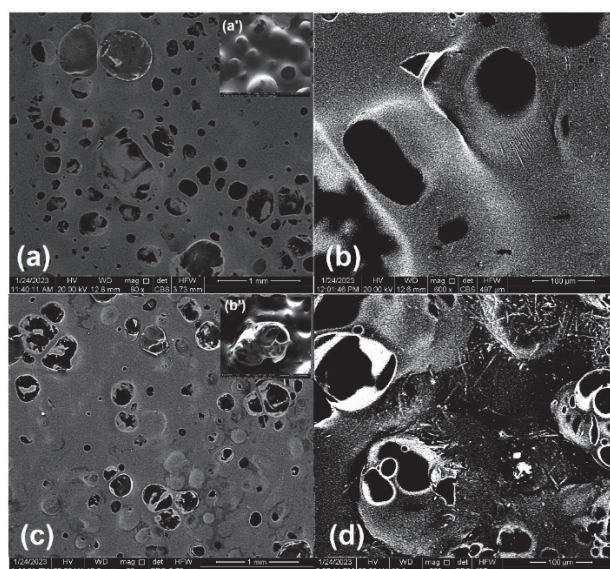


Fig. 2. SEM analysis of the platinum electrode coated with an LCPT29-based biomembrane: a and b – before; c and d – after immersion in PHB using CBS images at 80 $\times$ and 600 $\times$. Insets: ETD images at 300 $\times$ before and after immersion (a' and b', respectively).

SEM analysis (Fig. 2a and b) revealed homogeneous and stable adhesion of the biomembrane to the platinum electrode surface after deposition. The morphology of the biosensor after immersion in the target analyte was examined (Fig. 2c–d) to assess analyte diffusion to the active sites. The images show a porous structure and cavities within the BSA–GA–enzyme matrix, facilitating analyte penetration and improving access to the active sites, thus promoting mass transfer. These SEM images (Fig. 2c–d) also show brighter areas localized around the membrane pores, suggesting adsorption and/or accumulation of products resulting from the enzymatic hydrolysis of the analyte. Furthermore, ETD images (Fig. 2a' and b') confirm the surface modification before and after immersion. These observations are consistent with data from the literature¹³ and highlight the essential role of porosity in the diffusion of the analyte.

Cyclic voltammetry (CV) analysis

The SEM analysis was then validated by electrochemical characterization of the biomembrane after its deposition on the working electrode. For this purpose, CV, as a widely used technique in biosensing,^{31,32} was employed to characterize the surface of a platinum electrode³³ before and after biomembrane deposition. Measurements were performed in a 5 mmol L^{−1} [Fe(CN)₆]^{3−/4−} solution prepared in 10 mol L^{−1} PBS buffer (pH 7.4), with a scanning potential from −0.7 to 0.7 V at 25 mV s^{−1}.

The voltammograms illustrated in Fig. 3a–b show two well-defined anodic and cathodic peaks, indicating a quasi-reversible redox process. The bare electrode (Fig. 3a) exhibits the highest peak currents, indicating rapid electron transfer, while

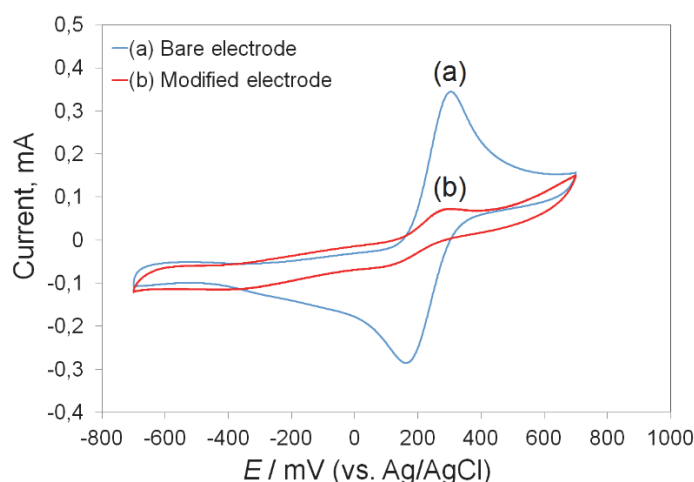


Fig. 3. Cyclic voltammograms recorded for bare and modified electrodes (a and b, respectively), using 5 mmol L^{−1} [Fe(CN)₆]^{3−/4−} in 10 mmol L^{−1} PBS buffer (pH 7.4) at a scan rate of 25 mV s^{−1}.

their decrease (Fig. 3b) after modification confirms the formation of a bioactive layer that limits access to the redox probe, without, however, completely blocking electron transfer.^{34,35}

Evaluation of enzymatic activity

In this study, enzymatic hydrolysis of PHB was performed to evaluate the hydrolytic activity of LCPT29 against this model analyte, prior to its use as a bioreceptor in the development of a novel biosensor. Initially, PHB was converted to PHBA by enzymatic hydrolysis using the titrimetric method described in the experimental section. The proposed reaction mechanism is illustrated in Fig. 4.

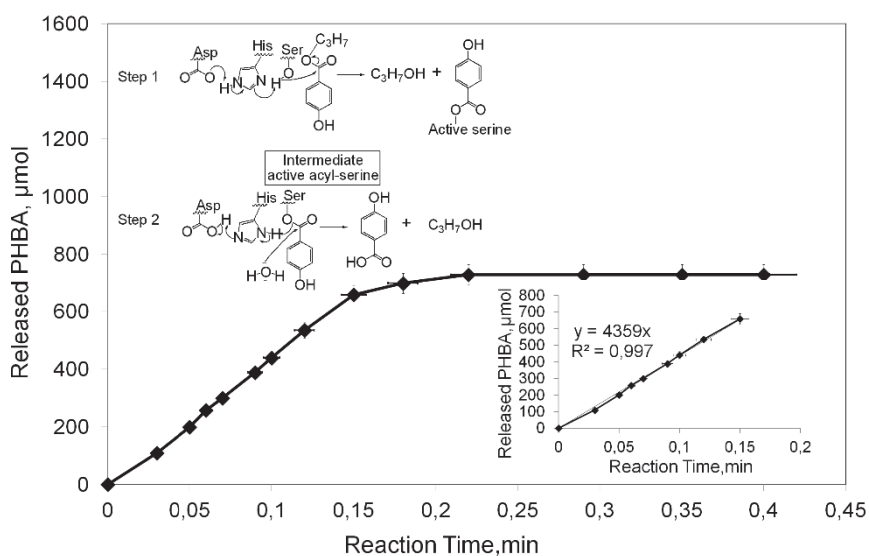


Fig. 4. Kinetic curve recorded for the hydrolysis of PHB to PHBA, catalyzed by LCPT29. The proposed mechanism for the hydrolysis of PHB and the linear portion of the curve are shown in the inset. The reactions were carried out at pH 8 and 40 °C, and their kinetics were continuously monitored using a pH meter. The error bars represent the standard deviation of three measurements.

The hydrolytic activity of the produced LCPT29 was determined from the slope of the linear portion of the kinetic curve, plotted against reaction time (inset of Fig. 4). The enzyme exhibited high activity toward the hydrolysis of PHB (4359 IU) and a higher specific activity than previously described enzymes (Table I), highlighting its potential as a novel bioreceptor in a sensitive PHB biosensor.

Optimization of biosensor response

Scan rate effect. To investigate the scan rate dependence and diffusion-controlled kinetics of the modified electrode, the $[Fe(CN)_6]^{3-/4-}$ redox couple was used as a standard quasi-reversible electrochemical probe. CV measurements of the

TABLE I. Comparison of the specific activity of LCPT29 with that of certain enzymes described in the literature, during the hydrolysis of PHB; LPP: lipase from porcine pancreas; PrbA: esterase from *Enterobacter cloacae* strain EM; rAoPrbA: *Aspergillus oryzae* esterase

Biocatalyst	Specific activity, IU mg ⁻¹ of enzyme	Reference
LCPT29	90.02±0.05	This work
LPP	53.25±0.02	10
PrbA	1.91±0.03	32
rAoPrbA	0.280±0.029	33

LCPT29-based biosensor were performed at scan rates ranging from 25 to 200 mV s⁻¹ over a potential range of -0.7 to 0.7 V vs. Ag/AgCl. All experiments were conducted in a 5 mmol L⁻¹ [Fe(CN)₆]^{3-/4-} solution prepared in 10 mmol L⁻¹ PBS buffer solution (pH 7.4), in the absence of PHB.

The modified electrode exhibited two well-defined redox peaks (Fig. 5), with peak currents increasing with the scan rate. The slight potential shift and the I_{pc}/I_{pa} ratio close to unity (1.03 at 100 mV s⁻¹, Table II) indicate quasi-reversible behavior.

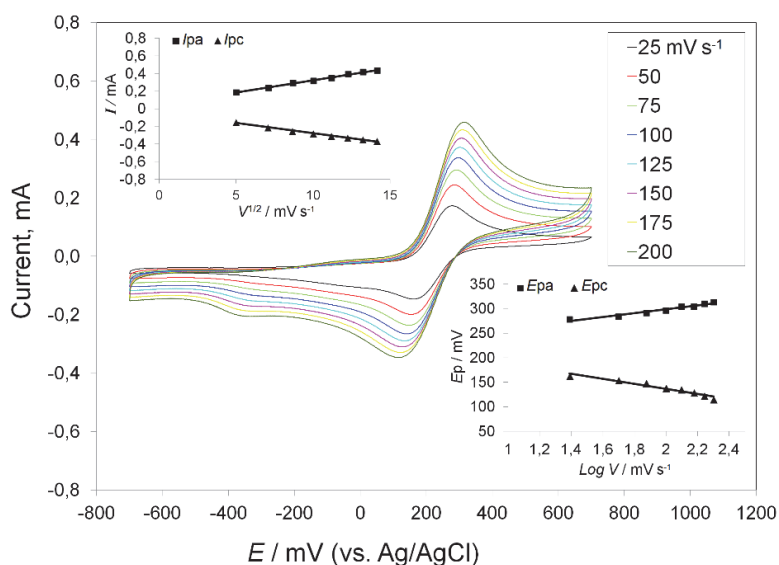


Fig. 5. Cyclic voltammograms of the modified electrode at scan rates from 25 to 200 mV s⁻¹ over -0.7 to 0.7 V vs. Ag/AgCl, using 5 mmol L⁻¹ [Fe(CN)₆]^{3-/4-} in PBS buffer (10 mmol L⁻¹, pH 7.4). Insets show plots of anodic/cathodic current vs the square root of the scan rate and anodic/cathodic potential vs the logarithm of the scan rate.

The kinetic study of the effect of the scan rate on the anodic and cathodic peak currents (I_{pa} and I_{pc}) showed a linear relationship between the peak currents and the square root of the scan rate (inset of Fig. 5):

$$I_{pa} = 0.0276v^{1/2} + 0.0468 \quad r = 0.9974 \quad (1)$$

$$I_{pc} = -0.0231v^{1/2} - 0.0458 \quad r = 0.9968 \quad (2)$$

indicating a diffusion-controlled process.³⁸ The second inset of Fig. 5 reveals a linear dependence of E_{pa} and E_{pc} on the logarithm of the scan rate, as well as an increase in ΔE_p (Table II), confirming the quasi-reversible nature of the system.¹³

TABLE II. Current and potential peaks analysis parameters recorded for the modified platinum electrode at different scan rates

Scan rate, mV s ⁻¹	I_{pa} / mA	I_{pc} / mA	$ I_{pa}/I_{pc} $	E_{pa} / mV	E_{pc} / mV	ΔE_p / mV
25	0.162	-0.133	1.22	273	159	114
50	0.269	-0.214	1.26	284	154	131
75	0.333	-0.244	1.37	286	154	131
100	0.341	-0.311	1.03	294	143	151
125	0.428	-0.296	1.44	301	136	164
150	0.455	-0.311	1.46	304	122	182
175	0.493	-0.327	1.51	313	124	188
200	0.526	-0.348	1.51	313	115	199

Concentration effect. The calibration curve developed to study the influence of analyte concentration on the response of the biosensor designed for the detection of PHB in aqueous media was established by successive additions of increasing concentrations (from 10^{-14} to 10^{-4} mol L⁻¹) to 100 mL of an electrolyte composed of 5 mol L⁻¹ of $[\text{Fe}(\text{CN})_6]^{3-/4-}$ in a 10 mol L⁻¹ PBS solution. All measurements were carried out under optimized pH and temperature conditions, within a potential window ranging from -0.7 to 0.7 V. Prior to analyte injection, the electrochemical stability and repeatability of the biosensor were evaluated by recording fourteen consecutive cyclic voltammetry cycles in the presence of the immobilized enzyme and the redox mediator $[\text{Fe}(\text{CN})_6]^{3-/4-}$. The negligible variation observed during these cycles confirmed the achievement of a stable and reproducible electrochemical response, thus ensuring reliable baseline conditions for subsequent calibration experiments. This behavior also suggests the absence of significant electrode surface passivation under the experimental conditions used.

As illustrated in Fig. 6a, the redox peak currents changed significantly with increasing PHB concentration, confirming the sensitivity of the modified electrode to PHB detection. The calibration curve (Fig. 6b) was constructed by plotting the absolute value of the cathodic peak current ($|I_{pc}|$) versus the logarithm of PHB concentration. The inset of Fig. 6b shows a strong linear relationship between the cathodic peak current and the logarithm of the PHB concentration. According to these results, this linear relationship was observed over the concentration range from 10^{-14} to 10^{-8} mol L⁻¹ (Eq. (3)). In contrast, nonlinearity between the current and the concentration was observed up to 10^{-8} mol L⁻¹, which could be due to saturation of the active sites on the surface of the biosensor.¹³

$$I_p = 0.0327 \log C + 0.4908 \quad r = 0.991 \quad (3)$$

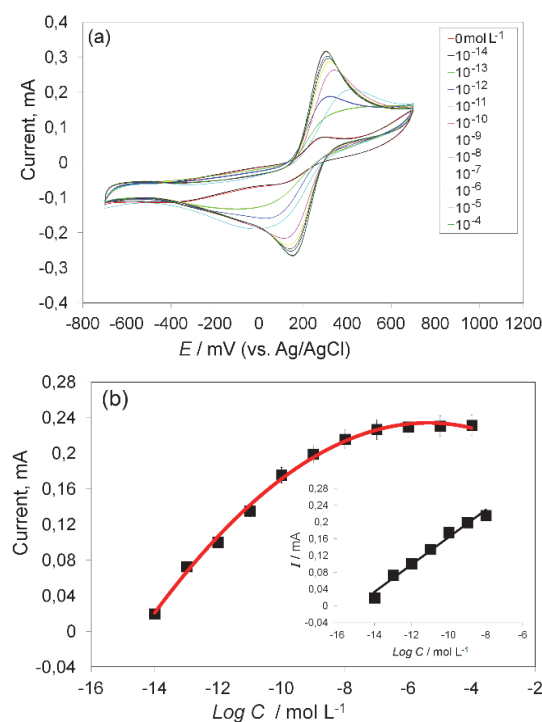


Fig. 6. Cyclic voltammograms of the LCPT29-based biosensor recorded at different PHB concentrations in PBS at optimal reaction conditions with the corresponding calibration curve of the cathodic peak current versus the logarithm of the PHB concentration (a and b, respectively). Error bars represent the standard deviation ($n = 3$).

According to this analytical curve, the LCPT29-based biosensor demonstrated significant sensitivity ($0.0327 \text{ mA L mol}^{-1}$) with a limit of detection (LOD) of $10^{-14} \text{ mol L}^{-1}$. In order to better evaluate the analytical performance of this biosensor, a comparative study was conducted with previously published studies (Table III).

TABLE III. Comparison of PHB detection characteristics with previously published studies using CV analysis

Biosensor	$LOD / \text{mol L}^{-1}$	Linear range, mol L^{-1}	Optimum pH	Reference
1	1.0×10^{-14}	10^{-14} – 10^{-8}	8.0	This work
2	3.7×10^{-15}	10^{-14} – 10^{-9}	7.4	13
3	1.1×10^{-7}	2.7×10^{-8} – 1.07×10^{-7}	6.0	39
4	8.0×10^{-8}	2.0×10^{-6} – 20.0×10^{-6}	7.0	40

Effect of pH and temperature. pH and the temperature of the reaction medium are physicochemical parameters that significantly influence enzyme activity. For example, in hydrolysis reactions, these two experimental parameters play a crucial role. pH generally affects the macromolecular stability of the enzyme protein, while temperature increases molecular collisions and improves the solubility of the substrate in the reaction medium.^{41–44} It has been shown that, in the case of enzymes such as lipases, optimizing these two parameters is essential to ensure

their stability and maximize their enzymatic activity. Bacterial lipases are generally active in media with a wide pH range, from 3 to 12, and are thermostable between 30 and 60 °C.⁴⁵ These two parameters can also affect the response of a biosensor in terms of stability, and their optimization is therefore essential.⁴⁶

For this purpose, we investigated the influence of these two physicochemical parameters on the response of the developed biosensor in order to evaluate their effect. The experiments were conducted according to the previously mentioned operating protocol, at different temperatures between 20 and 50 °C, and by testing the reaction medium at different pH values (from 4 to 10). The response obtained at pH 7.4, corresponding to the initial experimental conditions, was included in Fig. 7a as a comparative reference to evaluate the improvement achieved after pH optimization. To facilitate interpretation, the results of the CV analysis applied for this stage of the study are presented as graphs illustrating the evolution of the peak current versus pH and temperature (Fig. 7a and b, respectively).

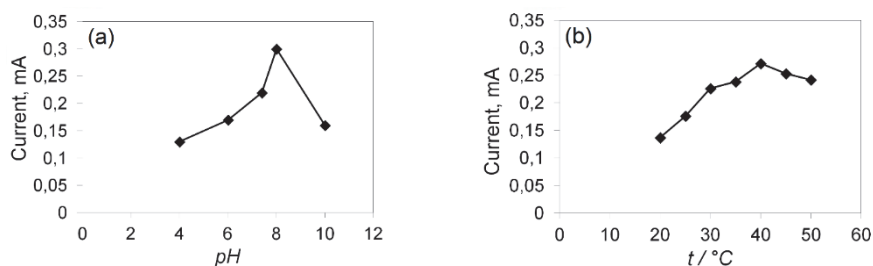


Fig. 7. Scatter plots of the current response of the biosensor as a function of pH and temperature (a and b, respectively). Experimental conditions: PBS, 10 mM; PHB, 10^{-7} M.

The results shown in Fig. 7a indicate that the peak current is highly dependent on the pH of the reaction medium. The biosensor response increases significantly between pH 4 and 8, while a marked decrease is observed at higher pH values. This reduction could be due to the accumulation of acidic products released during the reaction, which may locally lower the pH and create unfavorable conditions that reduce enzymatic activity and, consequently, the electrochemical response of the biosensor.⁴⁷

The results presented in Fig. 7b indicate that the biosensor response increases with temperature between 20 and 40 °C, reaching a maximum at 40 °C due to increased enzymatic activity and reaction kinetics. Above this temperature, a significant decrease is observed, which could be attributed to enzyme denaturation or biomembrane degradation,⁴⁸ consistent with previous studies.^{16,49}

Stability and selectivity of the biosensor

The stability of the LCPT29-based biosensor was studied by subjecting the modified working electrode to fourteen successive cycles until the response

stabilized. The results of the CV analysis were graphically represented by plotting the current (mA) *versus* cycle number (Fig. 8a) to better visualize the current response over successive cycles. Significant stability of the developed biosensor was observed, with a relative standard deviation (RSD) of 0.37 % (<5 %). The selectivity of the developed biosensor was also evaluated by comparing different potential interfering substances (α -tocopherol, glycerol, phenol, bisphenol A and cresol). α -Tocopherol and glycerol are frequently used in some industrial cosmetic formulations.^{50,51} Phenol, bisphenol A and cresol were included among the relevant environmental pollutants frequently detected in industrial effluents and wastewater.^{52,53} For consistency and reliable comparison, all interference experiments were conducted under the same experimental conditions previously optimized. The results were obtained by plotting the absolute value of the cathodic peak current versus the logarithm of PHB concentration (Fig. 8b). The significant reduction in the current signals recorded for the tested interfering substances confirms the high specificity of this biosensor for PHB.

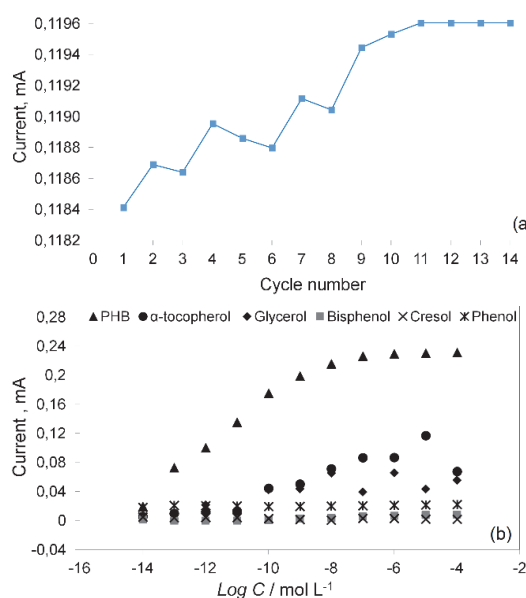


Fig. 8. Evaluation of stability and selectivity of the LCPT29-based biosensor for sensing PHB in aqueous media (a and b, respectively).

Real sample validation of PHB

In order to evaluate the LCPT29-based biosensor's performance in real matrices, recovery experiments were carried out using tap water and river water samples spiked with different known concentrations (from 10^{-8} to 10^{-11} mol L⁻¹) of the target analyte (PHB). The analyte concentrations in the real samples were determined using the calibration curve previously established with standard solutions by cyclic voltammetry (Eq. (3)), and the recovery values were calculated:⁵⁴

$$\text{Recovery} = 100 \frac{C_{\text{found}}}{C_{\text{added}}} \quad (4)$$

where C_{found} and C_{added} denote the concentrations of analyte determined in the spiked sample and the added analyte, respectively.

As shown in Table IV, recovery rates between 90 and 97 % were obtained for both matrices tested, demonstrating the good accuracy of the LCPT29-based biosensor for the analysis of real samples. These values are within the generally accepted range (70–120 %) for trace analysis in complex matrices,^{54,55} suggesting a limited matrix effect. The low *RSD* values (< 5 %) confirm the biosensor's good accuracy and repeatability. Overall, the results show that the method is reliable and suitable for analyzing the samples studied, thus confirming the applicability of the proposed biosensor to real-world sample analysis.

TABLE IV. Recovery (%) of PHB in tap and river water samples measured using the developed LCPT29-based biosensor. Blank (0 M) corresponds to unspiked samples. Results are based on three replicate measurements ($n = 3$)

Sample	$C_{\text{added}} / \text{mol L}^{-1}$	$C_{\text{found}} / \text{mol L}^{-1}$	Recovery, %	<i>RSD</i> / %
Tap water	0	—	—	—
	10^{-8}	$10^{-8.03}$	93.5	1.43
	10^{-9}	$10^{-9.02}$	94.8	1.06
	10^{-10}	$10^{-10.02}$	95.9	1.98
	10^{-11}	$10^{-11.01}$	97.3	2.52
River water	0	—	—	—
	10^{-8}	$10^{-8.04}$	90.8	1.50
	10^{-9}	$10^{-9.02}$	95.3	1.05
	10^{-10}	$10^{-10.04}$	91.4	2.10
	10^{-11}	$10^{-11.03}$	94.0	2.46

CONCLUSION

In this work, a native, detergent-stable lipase from the *Actinomadura Keratinilytica* CPT29 strain was deposited onto a platinum working electrode for the environmental detection of organic pollutants. The formation of the membrane network was confirmed by FT-IR spectroscopy and cyclic voltammetry (CV), demonstrating successful deposition on the platinum electrode. Under optimal experimental conditions, the enzyme membrane showed a markedly improved response for the detection of PHB as a model analyte, leading to a 30-fold increase in sensitivity compared to our previous study using a commercial lipase. The results obtained in this study are satisfactory, and the successful recovery of PHB from real water samples demonstrated the practical applicability of the biosensor, which has encouraged us to consider further work to more precisely evaluate its performance in different media and with different analytes, with the aim of enabling large-scale multisensory detection.

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ИЗВОД

ВОЛТАМЕТРИЈСКО ИСПИТИВАЊЕ ПЛАТИНСКОГ БИОСЕНЗОРА СА ЛИПАЗОМ CPT29 ИЗ БАКТЕРИЈЕ *Actinomadura keratinilytica* УНАКРСНО ПОВЕЗАНОМ ПОМОЋУ GA/BSA И СТАБИЛНОМ НА ДЕТЕРГЕНТЕ

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Ова студија описује имобилизацију нативне липазе (LCPT29) из која *Actinomadura keratinilytica* CPT29, изолованог из живинског компоста у североисточном Алжиру, у сврху детекције естарских загађивача у воденој средини. У ту сврху, ова липаза стабилна у детергентима имобилизована је на платинску електроду помоћу глутаралдехида као унакрсног везива, у присуству говеђег серумског албумина (БСА). Припремљена ензимска мембрана карактерисана је помоћу FT-IR спектроскопије, чиме је потврђено формирање њене мреже, као и њено наношење на платинску електроду кроз процену електрохемијских промена помоћу цикличне волтаметрије. Ефикасност радне електроде обложене унакрсно повезаном ензимском мембраном електрохемијски је процењена детекцијом пропил-4-хидроксибензоата (PHB) као модел-аналита. Под оптималним условима и при примењеном потенцијалу од -250 mV према Ag/AgCl биосензор на бази LCPT29 показао је линеаран одзив у опсегу концентрација од 10^{-14} до $10^{-8}\text{ mol L}^{-1}$ ($r = 0,991$), са границом детекције од $10^{-14}\text{ mol L}^{-1}$. Биосензор је показао високу осетљивост ($0,0327\text{ mA L mol}^{-1}$), добру стабилност ($RSD = 0,37\%$) и значајну селективност, као и могућност анализе трагова PHB у реалним узорцима воде, што доказује његов потенцијал за практичну примену.

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Advanced polypropylene random copolymer nanocomposites: Effect of natural bentonite clay and aluminum hydroxide on morphology and properties

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Abstract: This paper examines the influence of nanoparticles of the natural mineral bentonite and aluminum hydroxide in obtaining nanocomposites that are based on a compatibilized polypropylene random copolymer. A random copolymer of ethylene and propylene modified with maleic anhydride was used as a compatibilizer. The total amount of filler introduced into the polypropylene random copolymer composition was 50 wt. %. To study the synergistic effect, using a mixture of fillers, bentonite was included in the formulation at five different concentrations (5, 10, 15, 20 and 25 wt. %). The composites were obtained by mechanical mixing in the melt of a compatibilized polymer matrix. The structural, morphological, physical-mechanical, thermal properties and fire resistance of the obtained composite materials were determined. The structural and morphological properties were characterized using infrared spectroscopy (IR) and scanning electron microscopy. Based on the results of IR and scanning electron microscopy-energy dispersive X-ray spectra, the presence of elements and bonds corresponding to the composition of bentonite and aluminum hydroxide, which were used as fillers in the composition of the polypropylene random copolymer, was confirmed. Morphological study revealed minor agglomerates of bentonite nanoparticles. Thermal properties of the obtained composites were determined using thermogravimetric analysis and differential scanning calorimetry. Thermogravimetric analysis showed that the addition of bentonite increases the thermal stability of composites, as evidenced by a decrease in the rate of mass loss. Mechanical properties (tensile strength, elongation at break) decrease with increasing bentonite concentration. The synergistic effect obtained by the combined use of aluminum hydroxide and bentonite was manifested mainly in an increase in the melt flow index of the composite. The sample containing 25 wt. % natural bentonite showed the highest melt flow index values, up to 3.12 g/10 min.

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Keywords: polypropylene random copolymer; bentonite; aluminium hydroxide; physical and mechanical properties; melt flow index; surface morphological properties; thermal properties; thermomechanical properties.

INTRODUCTION

Improving the performance properties of polymer composite materials is one of the current areas in the field of materials science. When developing a recipe, it is necessary to improve the physical and mechanical properties while maintaining technological effectiveness. One of the most promising approaches to the creation of polymer composites is the use of bifunctional layered silicates as polymer fillers. The main attractive feature of bentonite clay-polymer composites is that small amounts of nanoclay can be used to enhance the functional properties of the polymer without compromising other key characteristics. Bentonite, as an inorganic mineral whose main component is montmorillonite, has advantages such as large deposits in Azerbaijan, availability and low cost. The introduction of cheap minerals into the polymer composition helps to significantly reduce the cost of the composite material. A number of studies^{1–3} have reported on the influence of bentonite on the structure and properties of various polymers. However, individual fragmentary information on the modification of the properties of polyolefins by bentonite does not allow us to systematize the research into a single, comprehensive theory. This is especially true for research in the field of developing fire-resistant materials. It is known that bentonite and montmorillonite belong to the group of clay minerals, distinguished by a unique combination of a layered structure with high flame retardancy.⁴ In the process of studying the influence of structural features of layered silicates on the combustion process of polymer composites, two mechanisms for reducing flammability were proposed.⁵ The first mechanism consisted of the formation of a carbonized layer, which affected the mass and heat transfer between the combustion zone and the polymer material. The second mechanism was based on the possible catalytic activity of aluminosilicates in the process of thermal destruction of the polymer. Also, it is necessary to take into account the fact that bentonite, at a certain content in the composition of the composite, can contribute to the improvement of their basic strength properties, in particular, tensile strength, bending strength and impact strength.^{6,7} This is due to the ability of bentonite, as a filler-reinforcer to act as a reinforcing agent, improving the overall mechanical characteristics of the composite.^{8,9}

Metal hydroxides are effective flame retardants that improve the environmental performance of fire-resistant composites. These flame retardants account for 40 % of the total polymer flame retardant materials market by weight.¹⁰ Their flame retardancy is due to strong endothermic decomposition with the release of water. Aluminum hydroxide is a flame retardant that is widely used in various types of polymers due to its ability to suppress smoke and prevent the spread of fire.¹¹

When introduced into the polymer matrix, aluminum hydroxide performs two main functions. It acts as a filler, as well as a flame retardant and smoke suppressant. For effective action, the recommended loading of aluminum hydroxide in the polymer composite is 40–65 wt. %.^{12–14} However, to achieve a satisfactory fire protection effect a large amount of aluminum hydroxide is required, which to a certain extent negatively affects the physical, mechanical and operational properties.

Yand *et al.* in their work^{15,16} showed that the addition of a mixture of aluminum hydroxide with organic montmorillonite slows down the thermal decomposition of the polymer composite and shows good thermal insulation properties while reducing heat release during combustion. Kaleg *et al.* found that the addition of aluminum hydroxide and montmorillonite did not result in significant changes in the decomposition temperature of unsaturated polyester, but tended to decrease the maximum mass loss rate.¹⁷ Based on the above ideas, we proposed a convenient strategy to replace part of the aluminum hydroxide with bentonite in a compatibilized polypropylene random copolymer.

Overall, this work allows for a simple and environmentally friendly green approach to using Azerbaijan's natural mineral resources in conjunction with flame retardants. In particular, this work examined the combined use of aluminum hydroxide with bentonite clay for use as a multifunctional flame retardant system. For this purpose, a study was conducted on the influence of different ratios of aluminum hydroxide to bentonite on the structural, morphological, physical-mechanical, thermal and fire-resistant properties of the obtained composites. The following composition was used as the base composition: polypropylene random copolymer/compatibilizer/aluminum hydroxide with a component ratio (wt. %) of 47/3/50.

EXPERIMENTAL

Materials

The properties of the polymer-based components used in the studies are presented in Table I.

TABLE I. Properties of polymer matrix and compatibilizer

Material	Name	Brand	Manufacturer	Melt flow index	Melting temp., °C
Polymer	Polypropylene random copolymer – PP-R	Topilene® R200P	Hyosung Chemical Corporation	0.2 g/10 min (230 °C, 2.16 kg)	145
Compatibiliser	Polypropylene copolymer grafted with maleic anhydride – PPC-g-MAH	DuPont™ Fusabond® P353	DuPont Company	470 g/10 min (190 °C, 2.16 kg)	135

Concentration of fillers was fixed at 50 wt. % of total amount of composite. The fillers used in studies differ in shape and size. To prepare to polymer composites aluminum hydroxide

with particle sizes $D_v(10) = 0.0197 \mu\text{m}$, $D_v(50) = 0.0559 \mu\text{m}$, $D_v(90) = 0.159 \mu\text{m}$ were used (Fig. 1).

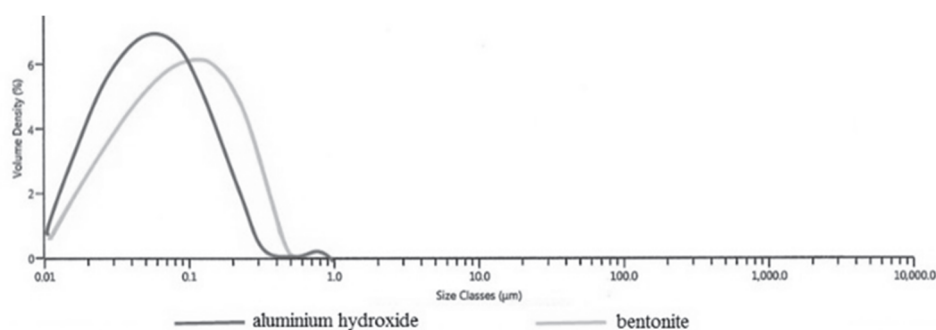


Fig. 1. Particle size of fillers.

The dosage of bentonite (origin of the Dash-Salahli deposit of the Azerbaijan Republic) varied in the range of 0–25 wt. %. The oriented particle size of the bentonite used is generally less than $0.248 \mu\text{m}$: $D_v(10) = 0.024 \mu\text{m}$, $D_v(50) = 0.0855 \mu\text{m}$, $D_v(90) = 0.248 \mu\text{m}$. The Analytical Center of the Institute of Geology and Geophysics of the Ministry of Science and Education of the Republic of Azerbaijan determined the bentonites mineralogical (XRD Miniflex 600, Rigaku, Japan) and chemical (XRF S8 Tiger, Bruker, Germany) composition (Tables II and III).

TABLE II. Chemical composition of bentonite (in %); the amount of volatile components at 950°C temperature: 0.83

Na ₂ O	MgO	Al ₂ O ₃	SiO ₂	P ₂ O ₅	SO ₃	K ₂ O	CaO
1.61	2.00	12.57	58.71	0.22	0.10	2.70	8.05
TiO ₂	MnO	Fe ₂ O ₃	BaO	SrO	V ₂ O ₅	Cl ⁻	
1.11	0.14	8.83	0.002	0.07	0.02	0.02	

TABLE III. Mineralogical composition of bentonite (in %)

SiO ₂ (α quartz)	Anorthite	Montmorillonite	Vesuvianite	Clinoptilolite
10	25	57	0	0
Lamontite	Fe ₂ O ₃ (hematite)	Fe ₃ O ₄ (magnetite)	Amorphous	Other mixtures
0	8	0	0	0

Sample preparation

The polymer composite samples based on PP-R/PPC-g-MAH/Al(OH)₃/bentonite were prepared in three stages. The first stage involved the preparation of polymer composites using a twin-roll mixer at a temperature of 170°C . The mixing time was 8–10 min and the rotor speed was 50 rpm. The mixing of components was carried out in stages. PPC-g-MAH was added to the PP-R melt, followed by fillers. At the second stage, the materials extracted from the rolls were pressed at a temperature of 190°C . The third stage involved cutting out blade samples from the pressed plates to test their strength characteristics. Table IV shows the formulations used and sample identification. The numbers in the sample designations indicate the content of

the filler used. Using the mechanical melt mixing method, composite formulations were prepared using two fillers, as shown in Table IV.

TABLE IV. Identification and formulations of all prepared samples (in wt. %)

Sample code	PP-R	PPC-g-MAH	Al(OH) ₃	Bentonite
AH ₄₅ Bt ₅	47	3	45	5
AH ₄₀ Bt ₁₀	47	3	40	10
AH ₃₅ Bt ₁₅	47	3	35	15
AH ₃₀ Bt ₂₀	47	3	30	20
AH ₂₅ Bt ₂₅	47	3	25	25

Characterization methods

Fourier transform infrared spectroscopy (FTIR). An Agilent Cary 630 FTIR device from Agilent Technologies (India) was used to record the samples infrared spectra. Every spectrum was gathered at wavenumbers between 4000 and 600 cm⁻¹.

Scanning electron microscopy (SEM) analysis. A scanning electron microscope, model JSM-6610 (JEOL, Japan), was used to investigate the surface morphology of the composites.

Particle size analysis. A Mastersizer 3000 laser analyzer from Malvern Instruments (England) used to measure the particle size of fillers (bentonite, aluminum hydroxide). The range of operation was 0.1 to 3500 μm. Measurements were made in distilled water.

Melt flow index (MFI). The CEAST MF50 branded melt flow tester (Instron company, Italy) was used to evaluate *MFI* of the filled PP-R composites in accordance with ASTM D1238. The length and diameter of the capillary were 8 and 2.095 mm, respectively. With a preheating period of 10 min and a 5 kg weight, the temperature was 190 °C. For every sample, four replicate measurements were made.

Physical and mechanical properties. Using a WPM, VEB, Thüringer industriewerk, Rauenstein R-40, TYP-2092 tensile testing machine in accordance with GOST 11262-80 (ASTM D 638), the physical and mechanical characteristics of the polymer composite materials were investigated at a speed of 50 mm/min movable grips of (four samples were tested). This study presents the average tensile strength value of the four specimens for each composite.

Thermal analysis. The thermal characteristics, decomposition process and thermal stability of the composites were ascertained using thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and differential thermogravimetric analysis (DTG). A Perkin Elmer STA 6000 simultaneous thermal analyzer was used for measurements. A nitrogen atmosphere was used to scan the sample weight of approximately 10 mg between 25.00 to 750.00 °C at a heating rate of 10.00 °C/min.

A Kanavets device was used to ascertain the samples thermomechanical characteristics. With a load of 0.5 kg/cm² and a heating rate of 50 °C/h, the deformation was recorded at sequentially varying temperatures (*T*). Tables with a flat surface that were 24 mm in diameter, 6 mm high and weighed 3.5–4 g were pressed into a special mold in order to conduct research. Thermomechanical curves $\Delta = f(T)$ showing the dependence of polymer composites were created using experimental data.

Resistance to burning. Standard Test Method for Measuring the Comparative Burning Characteristics of Solid Plastics in a Vertical Position (ASTM D3801) was used for conducting fire resistance investigations of polymer composite products.

RESULTS AND DISCUSSION

PPC-g-MAH increases the polarity of polypropylene random copolymer. The presence of a compatibilizer in the non-polar polymer matrix promotes adhesive interactions between the incompatible dispersed and dispersion phases. FTIR analysis reveals possible structural information and examines the bond interaction between all components in the composite system. Fig. 2 shows the FTIR spectra of PP-R/PPC-g-MAH/Al(OH)₃/bentonite composites.

The characteristic absorption bands observed across the FTIR spectra correspond directly to the functional groups of the polymer matrix (PP-R), the compatibilizer (PPC-g-MAH) and the inorganic fillers (Al(OH)₃ and bentonite clay). Matrix and compatibilizer bands (present in all spectra): 2950–2840 cm⁻¹ intense, sharp peaks originating from the asymmetric symmetric C – H stretching vibrations of –CH₃ and –CH₂– groups in the PP-R backbone; 1450–1460 cm⁻¹ medium peak corresponding to C–H bending deformations of –CH₃ and –CH₂– groups; 1375–1380 cm⁻¹ sharp peak assigned to the –CH₃ umbrella mode (symmetric bendix vibration of methyl side chains), a classic fingerprint for polypropylene; 1730–1750 cm⁻¹ (spectra b, c, d) a distinctive C=O carbonyl stretching vibration band introduced by the PPC-g-MAH compatibilizer (grafted maleic anhydride groups).

Aluminum hydroxide absorption bands (spectra b, c, d) are 3620–3300 cm⁻¹, a series of strong, sharp peaks (visible at approximately 3619, 3523, 3450 and 3393 cm⁻¹) representing the crystalline intermolecular and intramolecular O–H stretching vibrations of the gibbsite (Al(OH)₃) structure and 1020–960 cm⁻¹ as enhanced absorption intensity caused by the Al–OH bending/deformation modes.

As the concentration of bentonite increases from 5 (c) to 25 wt. % (d), several distinct aluminosilicate silicate bands appear and intensify. Bentonite clay absorption bands (spectra c and d) are 1030–1050 cm⁻¹, a massive, broad peak that progressively dominates the fingerprint region. It originates from the Si–O–Si in plane asymmetric stretching vibrations of the tetrahedral clay layers, 3620 cm⁻¹ overlapping with Al(OH)₃ peaks, corresponding to the structural hydroxyl stretching within the clay lattice and 520 and 460 cm⁻¹ prominent bands at lowest frequency range representing Al–O–Si stretching and Si–O–Si bending vibrations of the clay framework.

The appearances of all characteristic peaks were correlated to the distribution and dispersion of inorganic fillers in the composites. It can be confirmed from the FTIR spectroscopy that the functional groups, which were present in the individual materials had their influence in the composite formation and no new peaks were found indicating that no additional functional groups were formed. The IR spectrum of composite show characteristic band of both the PP-R and bentonite which ensures the incorporation of clay in the polymer. Referring to spectra of bentonite filled composites in comparison to the PP-R/PPC-g-MAH/50 wt. % Al(OH)₃, it was found that all spectra were very similar to each another. However, the presence

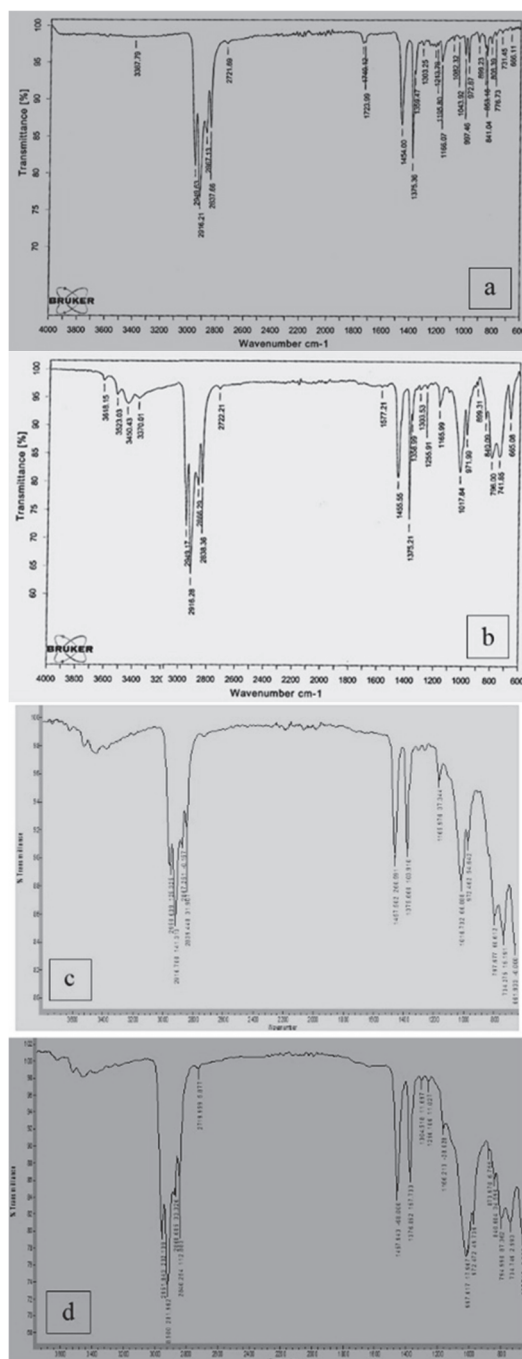


Fig. 2. IR spectra of PP-R (a), PP-R/PPC-g-MAH/50 wt. % $\text{Al}(\text{OH})_3$ (b), $\text{AH}_{45}\text{Bt}_5$ (c) and $\text{AH}_{25}\text{Bt}_{25}$ (d) polymer composites.

of bentonite caused slight changes in the position and intensity of the absorption band. Moreover, the intensities of peak related to the Si-O-Si stretching band, were more pronounced, which characterizes the presence of bentonite in the composites.

It is known that the supramolecular structure of a composite predetermines its final properties. The dispersion state of bentonite in the PP-R/PPC-g-MAH/Al(OH)₃ composition was further confirmed by SEM analysis (Fig. 3).

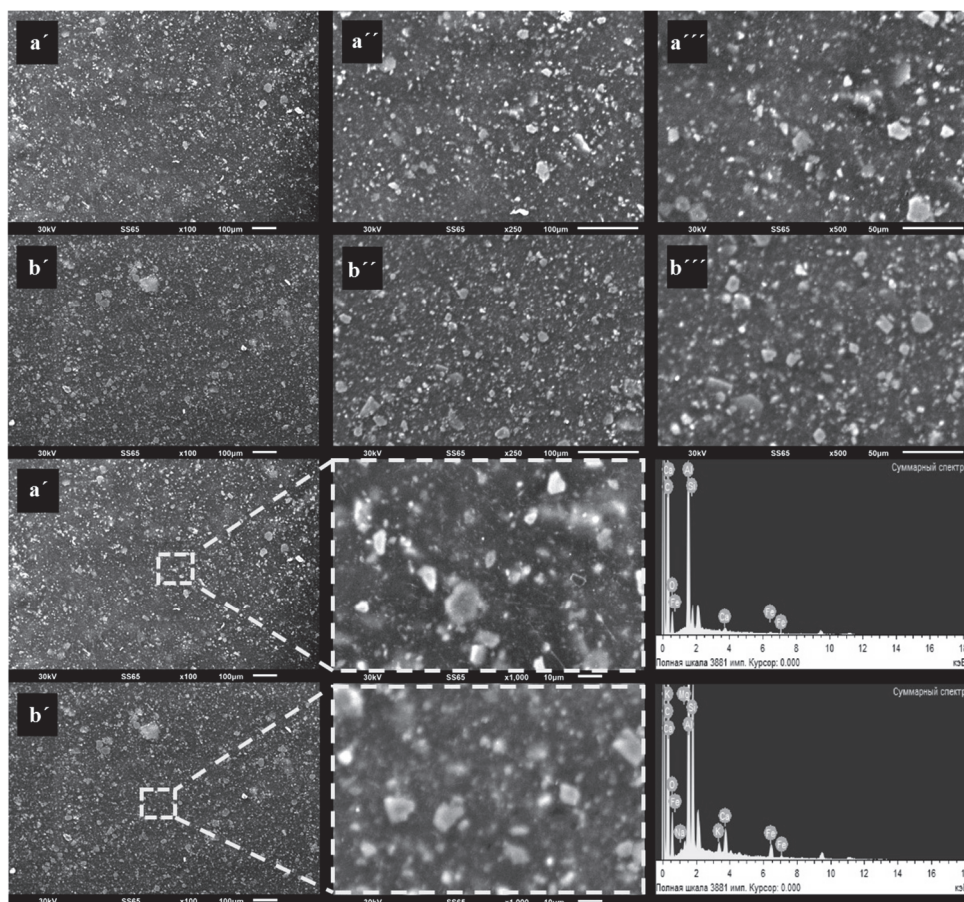


Fig. 3. SEM images and EDX spectra of AH₄₅Bt₅ (a) and AH₂₅Bt₂₅ (b) polymer composites at different magnifications.

The surface structure of AH₄₅Bt₅ and AH₂₅Bt₂₅ composites observed *via* SEM are compared in Fig. 3. Agglomeration morphology of bentonite in some areas due its poor dispersion is noticeable in SEM. The EDX analysis of composites showed the presence of K, C, Ca, O, Fe, Na, Mg, Si and Al element. The obtained results confirm the fact of obtaining a composite of the composition PP-R, PPH-g-MAH, Al(OH)₃ and bentonite.

In particular, changes in MFI can be used to judge the structural and rheological changes occurring in the polymer matrix under the influence of various factors. The study of the dependence of the MFI of PP-R/PPC-g-MAH/Al(OH)₃ on the bentonite content showed that it significantly affects the viscosity of the composite melt. As can be seen from Fig. 4, the replacing of Al(OH)₃ with bentonite leads to a fairly sharp increase in the *MFI* values of the polymer. Obviously, this behavior is associated with structural changes occurring in the polymer matrix. We do not exclude that as a result of thermomechanical action, the layered structure of bentonite decomposes with the release of surface-active substances, including glycerin, which significantly leads to an increase in the *MFI* of the composites. In general, the *MFI* values of the obtained PP-R/PPC-g-MAH/Al(OH)₃/bentonite composites are higher than those of the PP-R/PPC-g-MAH/50 wt. % Al(OH)₃, as well as the *MFI* values of industrial PP-R. This indicates that the types/nature, size, quantity and dispersion status of fillers are playing a major role in the properties of the prepared composites more than the number of the used fillers.¹⁸

Fig. 4 shows the results of studies of the physical and mechanical characteristics of polymer composite materials based on PP-R/PPC-g-MAH/Al(OH)₃/bentonite. The obtained results indicate a significant influence of bentonite concentration on physical and mechanical properties. With an increase in the concentration of bentonite, a slight decrease in the mechanical characteristics of the composite was recorded.

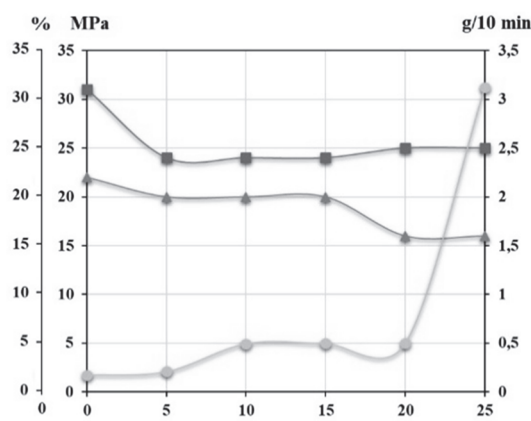


Fig. 4. Physical-mechanical properties of PP-R/PPC-g-MAH/Al(OH)₃/bentonite based polymer composites: ▲ – elongation at break, ■ – tensile strength, ● – *MFI*.

Generally, the strength properties of the composite strongly related to the interfacial interaction between the fillers and matrices. The specific surface area and particle size resulted in better dispersion of filler. The agglomeration of fillers can be a possible explanation for the reduction of tensile strength at higher filler loading. Referring to Fig. 4, it can be concluded that the tensile strength was decreased with the increase of bentonite concentration from 5 to 25 wt. %. Agglomeration of fillers may be a possible explanation for the decrease in tensile strength at

higher bentonite loading. It is believed that fillers with smaller particle sizes, such as aluminum hydroxide, provide a larger contact area with the polymer matrix due to their higher surface area compared to bentonite. The specific surface area and particle size resulted in better dispersion of the filler. This is most likely why replacing aluminum hydroxide nanoparticles with bentonite resulted in a decrease in strength.

On the other hand, Fig. 4 shows elongation at break of the studied composites. The elongation at break decreased monotonically with increasing bentonite content and decreased by approximately 27 % at a bentonite concentration of 25 wt. %. Poor interaction between $\text{Al}(\text{OH})_3$ and bentonite, and with the matrix may have contributed to lower properties in composites.

TGA has been used to evaluate the thermal stability of obtained composites. Generally, inorganic species have good thermal stability. Introduction of inorganic components into organic materials improve the thermal stability of the resulting composite. The most prominent effect of particulate fillers on the crystalline structure of semi-crystalline thermoplastics is their ability to work as a nucleation agent. Though there has been some debate over the effects of crystalline changes on macro-mechanical properties, it seems clear that by increasing crystallinity, the strength and deformability of PP-R decrease.

Thermogravimetric curves of both composites have two clearly defined stages of mass loss. The decrease in mass of both composites began above of 240 °C. The major thermal weight loss of PP-R/PPC-g-MAH/ $\text{Al}(\text{OH})_3$ / bentonite composites occurred in the range of 240–450 °C, and the mass loss was about 65–60 %. A TGA study of the obtained composites showed that their heat resistance depends on the bentonite content. The increase in heat resistance with a low bentonite content is due to intermolecular interactions and the features of the resulting phase structure. The residue obtained at the end of the TGA scan (750 °C) showed a value of approximately 34.181 % for the $\text{AH}_{45}\text{Bt}_5$ composite and 39.076 % for the $\text{AH}_{25}\text{Bt}_{25}$. The increase in solid residue is primarily driven by replacing $\text{Al}(\text{OH})_3$ with bentonite. At 750 °C, $\text{Al}(\text{OH})_3$ fully decomposes into volatile H_2O and Al_2O_3 , while bentonite is highly thermally stable, retaining a greater proportion of its mass to form a denser residual structure. Bentonite is a clay mineral composed of aluminosilicate. It is highly thermally stable and does not degrade or release volatile gases at 750 °C like the polymer or hydroxide do. Thus, an increased bentonite content leads to larger absolute mass of stable inorganic minerals in the final residue.

The thermal properties of PP-R/PPC-g-MAH/ $\text{Al}(\text{OH})_3$ /bentonite-based composites with different bentonite loading levels were also studied by DSC and the corresponding thermographs are given in Fig. 5. The melting enthalpy ΔH_m and melting temperature T_m obtained from the DSC analysis for $\text{AH}_{45}\text{Bt}_5$ and $\text{AH}_{25}\text{Bt}_{25}$ composites were summarized in Table V. The results showed that the melting temperature and melting enthalpy change of the composites increased with

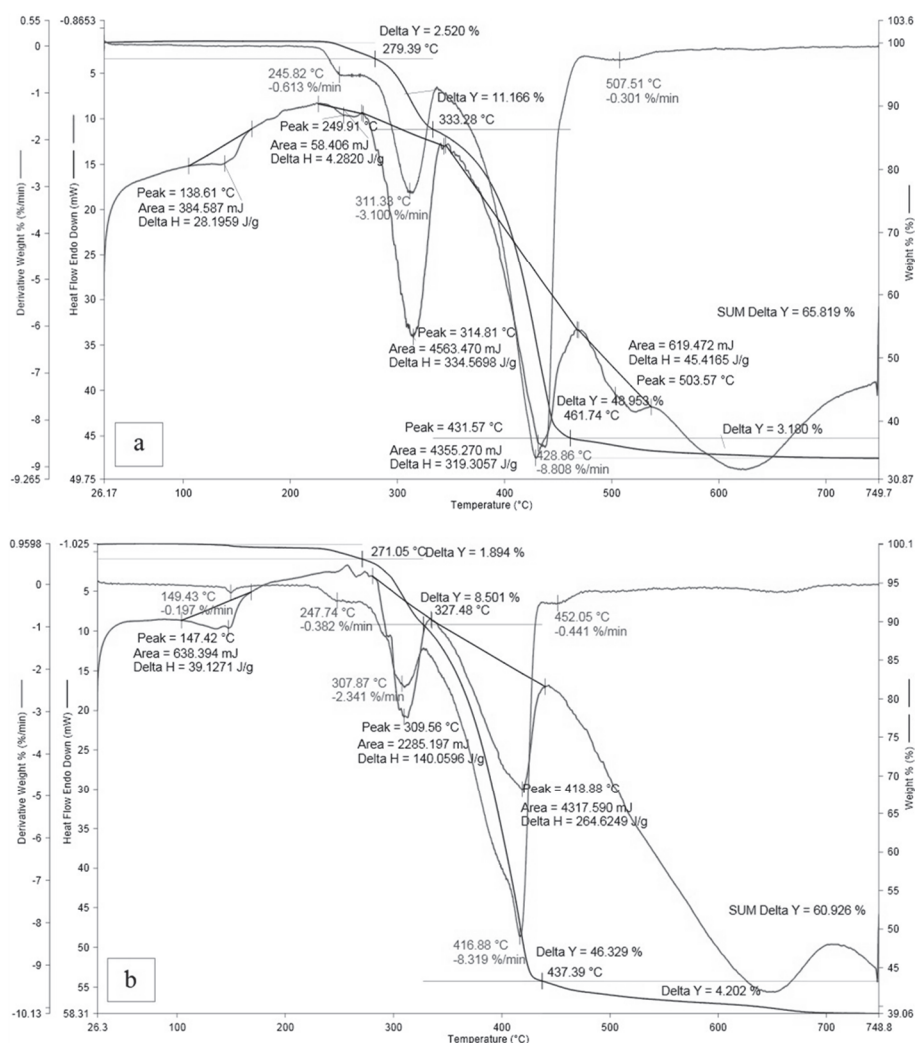


Fig. 5. Thermal analysis results for AH₄₅Bt₅ (a) and AH₂₅Bt₂₅ (b) polymer composites.

the increase of bentonite amount. A strong endothermic peak average value around 138.61 °C is visible, which is most likely associated with the melting of the crystalline domains of the AH₄₅Bt₅ composite. Double melting peaks can be associated with crystals having different morphology and, accordingly, thermal stability, crystalline perfection or crystallite sizes, polymorphism.¹⁹ The melting peak temperature T_m of PP-R/PPC-g-MAH/Al(OH)₃/bentonite composites increase with the addition of bentonite. The melting enthalpy change (ΔH_m) of PP-R/PPC-g-MAH/

/Al(OH)₃/bentonite increased with the addition of bentonite. The increase in melting enthalpy change can be explained by amount of free volume between PP-R chains capable of allowing bentonite to be intermixed.

TABLE V. Scanning calorimetry data corresponding to AH₄₅Bt₅ and AH₂₅Bt₂₅ polymer composites

Parameter	PP-R	AH ₄₅ Bt ₅	AH ₂₅ Bt ₂₅
Onset mass loss temperature, °C	345.32	279.39	271.05
Maximum weight loss rate temperature, °C	451.48	428.86	416.88
Maximum weight loss rate, %/min	-25.715	-8.808	-8.319
Solid residue under 750 °C, %	0.3 (at 700 °C)	34.181	39.076
T_m / °C	145.36	138.61	147.42
ΔH_m / Jg ⁻¹	56.6878	28.1959	39.1271

The heating thermogram of AH₂₅Bt₂₅ shows a single melting endopeak with a maximum at 147.42 °C and an enthalpy change of 39.1271 J g⁻¹. Table V shows the melting enthalpy changes of composites. The endopeak enthalpy of melting of PP-R/PPC-g-MAH/50 wt. % Al(OH)₃ was 48.2213 J g⁻¹, while that of PP-R was higher, reaching a value of 56.6878 J g⁻¹. The melting enthalpy change characterizes the energy required to break intermolecular bonds in a crystal during the transition from a solid state to a viscous flow state.²⁰ In similar PP-R, intermolecular bonds are determined by the van der Waals interaction energy. The decrease in enthalpy change for AH₂₅Bt₂₅ indicates a decrease in intermolecular interactions.

The thermogram of AH₄₅Bt₅ and AH₂₅Bt₂₅ has a regular symmetrical shape, which indicates a fairly homogeneous crystalline phase.²¹ The enthalpy change of melting of AH₂₅Bt₂₅ was greater than that of AH₄₅Bt₅. If in AH₂₅Bt₂₅ the enthalpy change of melting was only 11 J g⁻¹ higher than the enthalpy change of melting of AH₄₅Bt₅, then in PP-R the enthalpy change was 56 J g⁻¹. Obviously, this is due to a decrease in the degree of crystallinity of PP-R due to the influence of filler particles on the crystallization process.

A series of experiments with samples of different compositions showed that they all have thermograms of similar shape. The positions of the maximum melting temperature on the temperature scale are shifted relative to the melting temperature of the original PP-R. Based on the DSC data, it can be said that the introduction of 25 % bentonite into PP-R leads to an increase in the melting temperature. It has been established that the introduction of 45 % Al(OH)₃/5 % bentonite leads to a decrease in the melting temperature. When interpreting the DSC results, it can be assumed that the increase in the enthalpy change of melting of AH₂₅Bt₂₅ as a result of the introduction of 25 % of the amount of bentonite is due to the fact that bentonite promotes an increase in the number of heterogeneous nucleation centers, which contributes to an increase in the total rate of crystallization of PP-R. An increase in the rate of crystallization from two centers – homogeneous and heterogeneous

nucleation centers – leads to the simultaneous formation of many small-sized crystallites, which, as a result of steric limitations during their growth, form a crystalline phase with a minimum number of defects compared to the PP-R crystalline phase.²²

Similarly, thermomechanical analysis recorded an increase in the softening temperature and viscous flow state of the composites (Fig. 6). By analyzing the thermomechanical curves in Fig. 6, it can be established that the test samples are not subject to deformation over a wide temperature range.²³ According to this method, the melting point of the samples changed in the following sequence: AH₂₅Bt₂₅ – 149 °C, AH₃₀Bt₂₀ – 145 °C, AH₃₅Bt₁₅ – 146 °C, AH₄₀Bt₁₀ – 153 °C, AH₄₅Bt₅ – 155 °C. The difference in the values of temperature transitions obtained by the DSC method and thermomechanical analysis is interpreted by the fundamental features of the methodological approaches to assessing the value of thermo-physical indicators.

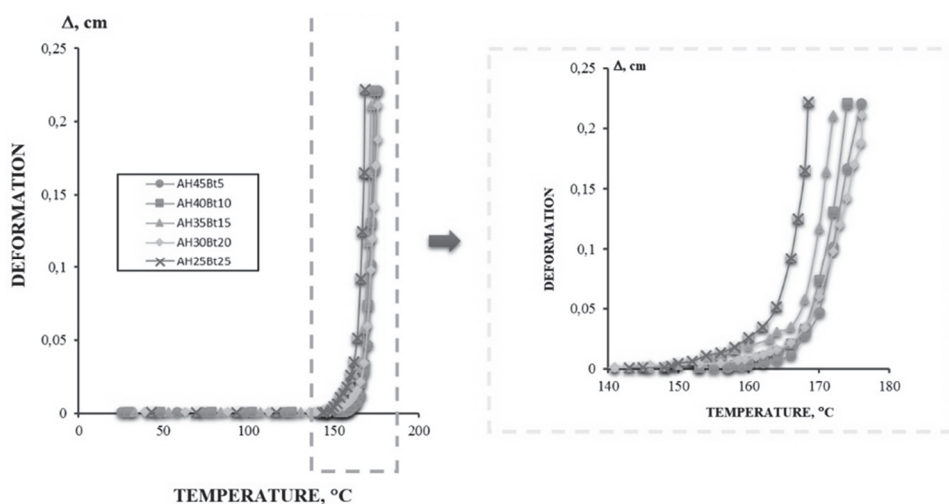


Fig. 6. Thermomechanical curves of the dependence of deformation on temperature for PP-R/PPC-g-MAH/Al(OH)₃/bentonite-based polymer composites.

Combustion tests were carried out in accordance with ASTM D3801. The Fig. 7 illustrates the results of a vertical burning flammability test performed on different polymer composite formulations over time.

As you can see from the Fig. 7, PP-R ignites quickly and burns intensely. By 30 s, a large flame is visible, and the polymer rapidly melts and drips onto the cotton. By 50 s, the sample is completely consumed, leaving the remaining time slots blank. By 80 s, the sample is entirely consumed and completely gone from the clamp, leaving nothing to record at 80 and 120 s. This indicates high flammability.

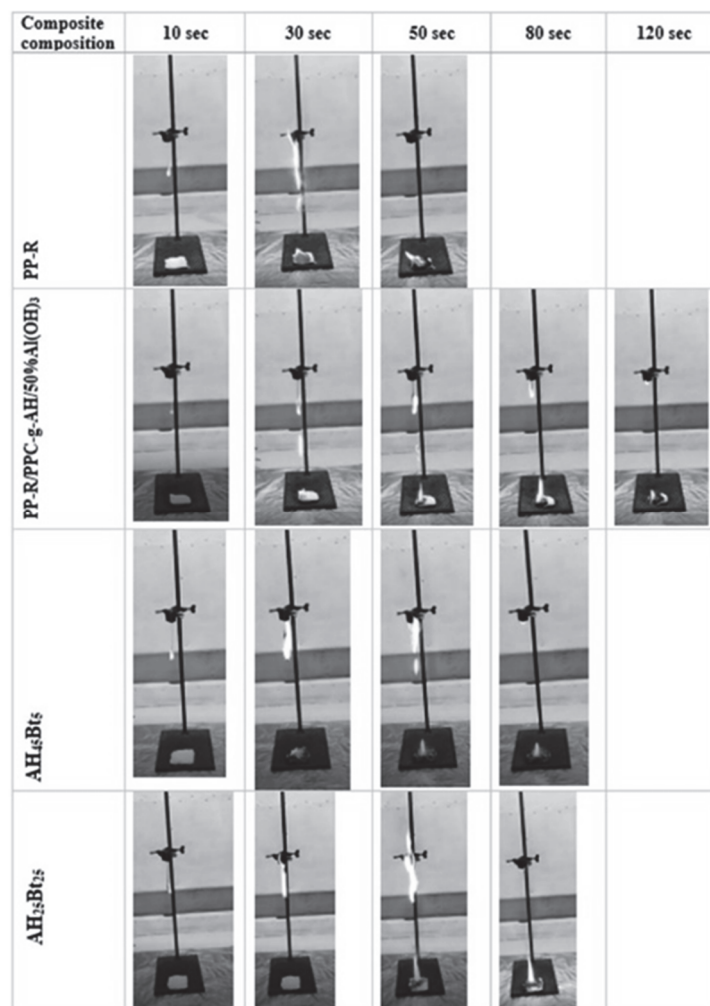


Fig. 7. Burning tests of PP-R and PP-R based composites.

For AH₄₅Bt₅, flame spread is slower compared to pure PP-R. At 30 and 50 s, a char layer begins to form, reducing the dripping behavior.^{24,25} The sample survives longer than pure PP-R, remaining clamped and burning slowly up to 80 s.

Increasing the bentonite filler to 25 wt % significantly improves performance. At 30 and 50 sec, the vertical specimen sustains much less severe structural collapse. The additive creates a thick, protective carbonaceous char layer. This layer blocks oxygen and heat transfer, delaying total degradation past 80 sec.

In samples containing bentonite, no burning droplets of the composite were released during combustion. Although the best result was obtained for the PP-R/PPC-g-AH/50 wt. %Al(OH)₃ sample, the samples filled with both fillers showed

better results than the original RPP (Fig. 7). As can be seen from the figure, while the original PP-R sample, which complies with the standard, burned for 50 s, the burning time of the samples to which both fillers were added increased to 80 s. Furthermore, unlike other samples, the sample with the addition of 25 % $\text{Al}(\text{OH})_3$ / 25 % bentonite did not burn cotton within 30 s when the alloy was dropped. The figure demonstrates that adding flame retardant and synergistic additives / clays like bentonite significantly reduces the flame spread rate and dripping of the polymer.

CONCLUSION

The obtained composites were characterized using FTIR, SEM, physical-mechanical, TGA and DSC analyses. The effectiveness of modifying the composite with bentonite was assessed by changes in the physical and mechanical properties of the composite. Physical-mechanical studies have shown that the addition of bentonite clay to PP-R/ $\text{Al}(\text{OH})_3$ composites helps maintain melt fluidity even at high contents. DSC analysis revealed changes in the melting temperature of composite samples with different bentonite concentrations. The results showed that the inclusion of bentonite clay could effectively improve the thermal stability of PP-R/PPC-g-MAH/ $\text{Al}(\text{OH})_3$ composite. Thus, taking into account the results of the assessment of the physical and mechanical properties of polymer composites, it can be stated that the optimal content of bentonite in PP-R/PPC-g-MAH/ $\text{Al}(\text{OH})_3$ /bentonite is 25 %. The results of the conducted studies provide grounds for recommending this composite as a promising material with improved operational and environmental characteristics. Enhanced fire-rated PP-R is ideal for commercial hot/cold water, heating, and sprinkler system where flame retardancy is required.

ИЗВОД

НАПРЕДНИ ПОЛИПРОПИЛЕНСКИ НАСУМИЧНИ КОПОЛИМЕРНИ НАНОКОМПОЗИТИ: УТИЦАЈ ПРИРОДНЕ БЕНТОНИТНЕ ГЛИНЕ И АЛУМИНИЈУМ-ХИДРОКСИДА НА МОРФОЛОГИЈУ И СВОЈСТВА

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У раду се испитује утицај наночестица природног минерала бентонита и алуминијум-хидроксида на добијање нанокомполита на бази компатибилизованог полипропиленског насумичног кополимера. Као компатибилизатор коришћен је насумични кополимер етилена и пропилена модификован анхидридом малеинске киселине. Укупна количина пунила у полипропиленском кополимеру била је 50 мас.%. Да би се проучио синергистички ефекат када се користи мешавина пунила, бентонит је укључен у формулацију у пет различитих концентрација (5, 10, 15, 20 и 25 мас.%). Композити су добијени механичким мешањем у растопу компатибилизоване полимерне матрице. Одређена су структурна, морфолошка, физичко-механичка, термичка својства и отпорност на

пожар добијених композитних материјала. Структурна и морфолошка својства су одређена коришћењем инфрацрвене спектроскопије (IR) и скенирајуће електронске микроскопије. На основу резултата IR спектроскопије и скенирајуће електронске микроскопије-енергетски дисперзивне рендгенске спектроскопије, потврђено је присуство елемената и веза које одговарају саставу бентонита и алуминијум-хидроксида, који су коришћени као пунила у саставу полипропиленског насумичног кополимера. Морфолошка студија открила је мање агломерате бентонитних наночестица. Термичка својства добијених композита одређена су термогравиметријском анализом и диференцијалном скенирајућом калориметријом. Термогравиметријска анализа показала је да додавање бентонита повећава термичку стабилност композита, о чему сведочи смањење брзине губитка масе. Механичка својства (затезна чврстоћа, издужење при прекиду) смањују се са повећањем концентрације бентонита. Синергистички ефекат добијен комбинованом употребом алуминијум-хидроксида и бентонита манифестовао се углавном у повећању индекса топлјења композита. Узорак који садржи 25 мас. % природног бентонита је показао највише вредности индекса топлјења до 3,12 g/10 min.

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Efficient one-pot solvothermal synthesis of lanthanum–iron oxide and its application in tenofovir adsorption

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Abstract: Novel magnetic lanthanum-iron oxide composites have been synthesized using a one-pot method. The proposed approach simplifies the synthesis process by eliminating traditional requirements such as pH adjustment and high-temperature calcination, resulting in a more streamlined procedure and the production of a magnetic material. The effects of the Fe-to-La ratio, reaction time, and reaction temperature on the properties and adsorption performance of the lanthanum–iron oxide composites were investigated. The synthesized composites were characterized by scanning electron microscopy, X-ray diffraction, vibrating sample magnetometry, Fourier-transform infrared spectroscopy, the Brunauer–Emmett–Teller method, thermogravimetric analysis and X-ray photoelectron spectroscopy, which indicated that the samples comprised of randomly oriented particles with sizes ranging from 20 to 200 nm, and possessed excellent crystallinity, magnetic responsiveness and thermal stability. Additionally, this study explored the application of lanthanum–iron oxide in tenofovir ((R)-9-(2-phosphonomethoxypropyl)adenine, PMPA) adsorption, with a maximum adsorption capacity of 34.06 mg/g under the conditions of adsorbent dosage = 0.9 g/L, pH 4, C = 50 mg/L and *t* = 25 °C. The lanthanum–iron oxide was simple to prepare and enabled rapid separation, which was beneficial for practical applications.

Keywords: one-pot synthesis; lanthanum–iron oxide; superparamagnetism; adsorption; pharmaceutical intermediates.

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INTRODUCTION

As a notable transition metal oxide, lanthanum–iron oxide predominantly comprises variations including LaFeO_3 ,¹ $\text{La}_{1-x}\text{Sr}_x\text{FeO}_{3-\delta}$ ² and $\text{Fe/La}_2\text{O}_3$,³ exhibiting diverse compositions and valencies. Its widespread research interest stems from its abundant availability, non-toxic nature and exceptional chemical stability.⁴ Lanthanum–iron oxide has been employed in various applications, such as electrodes,⁵ chemical sensors,⁶ adsorbents⁷ and catalysts.^{8,9} The performance of magnetic composites is influenced by their stoichiometric composition and microstructure, shaped during the synthesis process. Therefore, the choice of synthesis method varies depending on the intended application. Established synthesis techniques include high-energy milling,¹⁰ the citrate-gel method,¹ co-precipitation,¹¹ the hydrothermal method^{12,13} and the microwave-assisted method.¹⁴ The first three methods yield magnetic lanthanum–iron oxide compounds with particle sizes ranging from 10 to 50 nm, and require high-temperature calcination to enhance crystallinity.¹⁵ The citrate-gel and co-precipitation methods additionally necessitate pH adjustment. While microwave-assisted synthesis avoids calcination and pH adjustment,¹⁴ it produces gases during combustion, resulting in samples with weaker magnetic properties.

In a pharmaceutical context, (*R*)-9-(2-phosphonomethoxypropyl)adenine (PMPA), also known as tenofovir, is a key intermediate in immunodeficiency therapy that contains a phosphate group.¹⁶ However, the pharmaceutical wastewater generated during the production of PMPA contains about 1–2 % of the product, which is considered a harmful pharmaceutical pollutant in the environment. Therefore, it is of great importance to remove PMPA from wastewater generated during the syntheses of pharmaceutical intermediates. In recent years, there have been few reports on the removal of tenofovir, and the treatment methods for pharmaceutical wastewater can generally be divided into two categories: quantitative recovery and degradation elimination.¹⁷ Among them, quantitative recovery can alleviate the pressure on downstream wastewater treatment, which has attracted increasing attention from researchers. The commonly used methods for quantitative separation in industry include multi-effect evaporation,¹⁸ membrane separation,¹⁹ adsorption^{20,21} and recrystallization.²² Among them, adsorption has become an attractive approach owing to its economic cost, high efficiency and ease of operation.²³ Extensive investigations have revealed that metal (hydr)oxides have a strong affinity for phosphate due to the formation of inner-sphere complexes between phosphate species and the functional groups of the adsorbents.^{24,25} So far, lanthanum-based materials have received widespread attention for phosphate removal even at low concentrations due to the strong affinity of La toward phosphate and the low solubility product of LaPO_4 ($\text{p}K_{\text{sp}} = 26.15$).^{23,26} Xiong *et al.* prepared La-doped Mn–Al bimetallic oxide composites for phosphate adsorption reaching equilibrium at pH 7 after 5 h.²⁷ Qiu *et al.* fabricated a new composite

Ws-N-La by anchoring nano-La(III) (hydr)oxides within quaternary-aminated wheat straw for phosphate adsorption, the maximum adsorption capacity increased from 19.6 to 67.1 mg P/g.²⁸ However, due to the tedious separation problem caused by highly dispersed materials, magnetization has received widespread attention as an environmentally friendly approach, which can not only enhance the recovery performance of materials, but also improve their adsorption capacity.

Currently, only Ajebli *et al.*,²⁹ have conducted studies on the removal of tenofovir; they utilized activated carbon prepared through phosphoric acid thermochemical activation for PMPA adsorption. This process involved multiple steps including washing, drying, and thermal activation of corn cobs, followed by pH adjustment and drying of the resulting porous carbon. In contrast, we have developed a novel one-pot synthesis method to prepare lanthanum-iron oxide compounds, effectively avoiding the need for pH adjustment and high-temperature calcination, thus significantly streamlining the synthesis process. The resulting magnetic composite offers a rapid separation of PMPA from pharmaceutical wastewater under an external magnetic field, demonstrating a more efficient and potentially impactful approach for pharmaceutical waste management.

In summary, we have aimed to prepare lanthanum-iron oxide using a straightforward and efficient one-pot synthesis method. This novel approach not only simplifies the preparation process but also shows potential for the adsorption of PMPA from pharmaceutical wastewater. The performance of lanthanum-iron oxide was assessed using batch experiments, demonstrating its ease of preparation, rapid separation, and exceptional adsorption properties.

EXPERIMENTAL

Materials

Analytical-grade reagents were procured for the experiments. Sodium acetate trihydrate and ferric chloride hexahydrate were sourced from Shanghai McLean Biochemical Technology Co., Ltd., while lanthanum nitrate hexahydrate and ethylene glycol (EG) were purchased from Sinopharm Chemical Reagent Co., Ltd. Tenofovir (PMPA, C₉H₁₄N₅O₄P) was obtained from Jilin Sihuan Pharmaceutical Co., Ltd. The chemical structure of tenofovir is illustrated in Fig. 1.

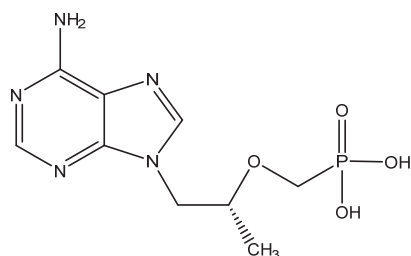


Fig. 1. Chemical structure of tenofovir.

Preparation of lanthanum–iron oxide compounds

The synthesis process involved heating 60 mL of EG to 70 °C, followed by the addition of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ in varying amounts to achieve Fe-to-La mole ratios of 0:1, 1:0, 6:1, 8:1 and 10:1. After magnetic stirring until dissolution, 7.2 g of sodium acetate trihydrate was added and stirred for 10 min. The effects of temperature and reaction time on lanthanum–iron oxide preparation were examined at 200 and 210 °C for reaction times of 6, 8, 10 and 12 h in a hydrothermal reactor. After the reaction, the product was cooled, washed and dried at 70 °C to obtain brown lanthanum–iron oxide powders. Optimal preparation conditions (such as molar ratios, temperature and time) were obtained based on the performance of lanthanum–iron oxide for PMPA removal.

Characterization of the lanthanum–iron oxide compounds

Tenofovir concentrations were determined via UV–Vis spectroscopy (UV-2550, Shimadzu, Japan). The surface morphology and crystal structure of the composites were characterized by scanning electron microscopy (SEM, Regulus-8100, Hitachi, USA) and X-ray diffraction (XRD, D8FOCUS, Bruker, Germany). The magnetic properties of the sorbents were analyzed using vibrating sample magnetometry (VSM, 7404, Lake Shore, USA). Fourier-transform infrared (FTIR) spectroscopy (Nicolet 6700, Thermo Fisher, USA), Brunauer–Emmett–Teller analysis (BET, JW-BK200B, JingWeiGaoBo, China) and X-ray photoelectron spectroscopy (XPS, AXIS, Shimadzu, Japan) were used to analyze functional groups, specific surface area, and the elemental chemical states of the samples, respectively. The thermal stability of the nanocomposites was analyzed using a blast drying oven (DHG-9070A, Yiheng Technology Co., Ltd., China) and a thermogravimetric analysis and differential scanning calorimetry (TGA–DSC) high-temperature synchronous thermal analyzer (Discovery SDT650, Swart, USA).

Adsorption experiments

Adsorption of PMPA. The adsorption properties of lanthanum–iron oxide for PMPA adsorption were extensively investigated under various conditions. The experiments assessed the impact of lanthanum–iron oxide dosage, temperature and pH on PMPA adsorption. For the dosage study, varying amounts of lanthanum–iron oxide (5 to 40 mg) were added to a three-necked flask containing 40 mL of a 50 mg/L PMPA solution at 25 °C, with stirring at 520 rpm. Upon reaching adsorption equilibrium, samples were filtered through a 0.22 μm organic membrane for UV spectrophotometric analysis of the remaining PMPA concentration. The effect of temperature on PMPA adsorption was examined by adding 35 mg of lanthanum–iron oxide to 40 mL of a 50 mg/L PMPA solution at 25, 35 and 45 °C. Additionally, the influence of pH was explored by adjusting the pH of a similar PMPA solution to values ranging from 3 to 8 using 0.1 M hydrochloric acid or sodium hydroxide, followed by the addition of 35 mg of lanthanum–iron oxide. The adsorption capacity (q_e) and removal efficiency (R in %) were calculated as:

$$q_e = \frac{V(C_0 - C_e)}{m} \quad (1)$$

$$q_e = 100 \frac{C_0 - C_e}{C_0} \quad (2)$$

where C_0 and C_e are the initial and equilibrium concentrations of PMPA (mg/L), m is the mass of the material (mg) and V is the solution volume (L).

Adsorption kinetics. A kinetic study involved dispersing 35 mg of lanthanum–iron oxide in 40 mL of a 50 mg/L PMPA solution at room temperature (RT, 20 °C). Samples were collected

at set intervals to determine the residual PMPA concentrations by UV spectrophotometric measurement.

Adsorption isotherm. Subsequently, an adsorption isotherm experiment was conducted at RT. Here, 35 mg of lanthanum-iron oxide was added to 40 mL of PMPA solution at concentrations ranging from 30 to 80 mg/L to ascertain the maximum adsorption capacity.

Adsorption thermodynamics. With all other conditions held constant, the adsorption thermodynamics of lanthanum-iron oxide were evaluated at 298, 308 and 318 K.

RESULTS AND DISCUSSION

Lanthanum-iron oxide compounds

Fig. 2a displays a histogram representing the adsorption of PMPA by samples with different Fe-to-La mole ratios. The adsorption capacities were 15.61, 31.26, 28.32, 23.98 and 9.96 mg/g for mole ratios of 0:1, 6:1, 8:1, 10:1 and 1:0, respectively. This trend indicates that the adsorption capacity decreases as the proportion of La in the sample diminishes, underscoring the crucial role of La in the adsorption process. Given its superior performance in PMPA adsorption, the sample with a 6:1 Fe-to-La mole ratio was selected for more detailed investigation in subsequent experiments. Fig. 2b shows the adsorption capacities of PMPA onto the lanthanum-iron oxide were 27.93, 28.54, 31.26 and 25.94 mg/g, at reaction times of 6, 8, 10 and 12 h, respectively. When the reaction time is less than 10 h, the adsorption capacity gradually decreases, indicating that some of the raw materials had

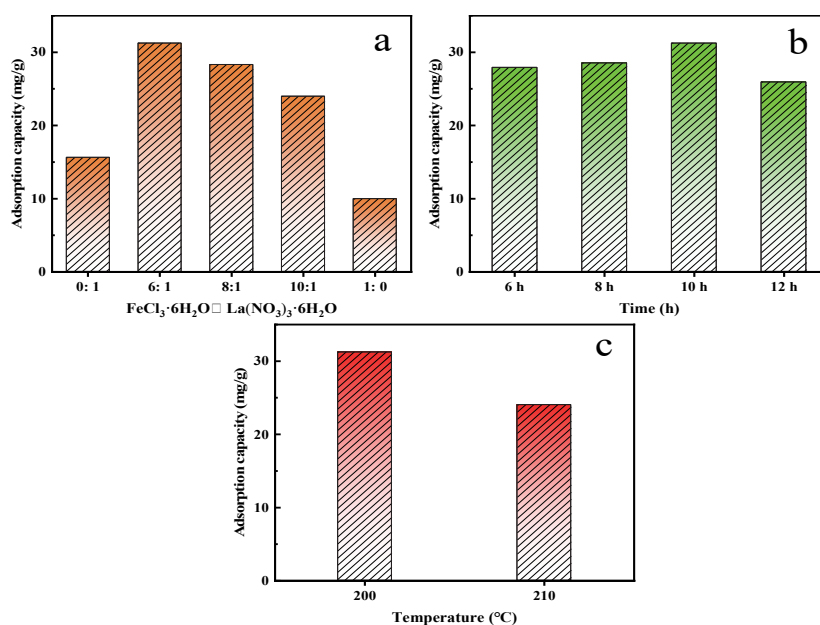


Fig. 2. The effects of Fe-to-La mole ratio (a), reaction time (b) and temperature (c) on the removal of PMPA by lanthanum-iron oxide.

not fully reacted to form lanthanum–iron oxide. The influence of temperature on the adsorption capacity of PMPA on lanthanum–iron oxide was evaluated (Fig. 2c). As can be seen, at temperatures of 200 and 210 °C, the adsorption capacities were 31.26 and 24.05 mg/g, respectively. Besides, high temperatures can cause damage to the Teflon[®]-lined stainless steel autoclave. Moreover, the choice of 200 °C was based on the objective of producing lanthanum–iron oxide with high adsorption capacity and minimum waste of energy which is very interesting from an economic point of view. Finally, it was determined that a sample with an iron–lanthanum mole ratio of 6:1, a reaction temperature of 200 °C, and a reaction time of 10 h has the highest adsorption capacity for PMPA.

Characterization of lanthanum–iron oxide

SEM characterization. The morphology of lanthanum–iron oxide samples with varying Fe-to-La mole ratios was characterized by SEM, as shown in Fig. 3. Fig. 3a shows that at a 6:1 ratio, the sample comprises densely packed, randomly oriented particles with sizes ranging from 20 to 200 nm. In contrast, at higher ratios of 8:1 (Fig. 3b) and 10:1 (Fig. 3c), the particles exhibit a spherical shape and a uniform size distribution with a diameter of approximately 170 nm. This morphological shift is attributed to the reduced mole ratio of La in the synthesis process, favoring the predominant formation of Fe₃O₄ microspheres in the product.

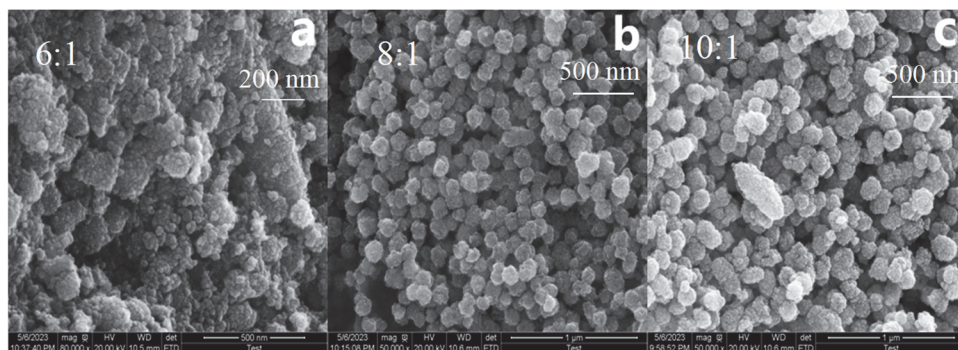


Fig. 3. SEM images of lanthanum–iron oxide compounds with different Fe-to-La mole ratios: a) 6:1, b) 8:1 and c) 10:1.

FTIR measurement. FTIR spectroscopy was utilized to analyze five lanthanum–iron oxide samples with varying Fe-to-La mole ratios, as depicted in Fig. 4a. The peaks at 1600 and 3420 cm^{−1} correspond to the stretching and bending vibrations of O–H bonds on the surface of the material.^{30,31} The peak at 1450 cm^{−1} is due to the stretching vibration of the La-bound hydroxyl groups (La–OH bonds).^{32,33} Notably, the peaks at 575 and 636 cm^{−1} are ascribed to Fe–O and La–O bonds, respectively.^{10,34} A noteworthy trend was observed: the intensity of the La–O

bond peak (636 cm^{-1}) gradually diminished with increasing Fe amount. Particularly for ratios of 8:1 and 10:1, the La–O bond peak vanished, whereas the Fe–O bond peak (575 cm^{-1}) became more prominent. At a mole ratio of 6:1, the FTIR spectrum clearly demonstrated the coexistence of both characteristic Fe–O and La–O bond peaks in the sample.

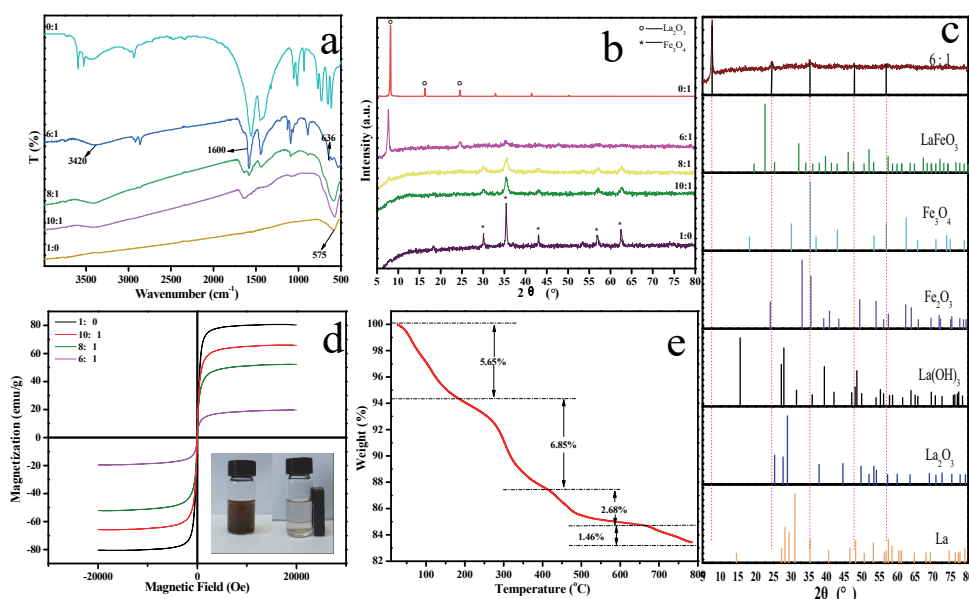


Fig. 4. a) FTIR spectra of lanthanum-iron oxides with varying Fe-to-La mole ratios: 0:1, 6:1, 10:1 and 1:0. b) XRD Patterns of lanthanum-iron oxides with Fe-to-La mole ratios of 0:1, 6:1, 10:1 and 1:0. c) Comparison of the XRD patterns of lanthanum-iron oxide with a 6:1 Fe-to-La mole ratio and reference materials. d) Vibrating sample magnetometry (VSM) analysis of lanthanum-iron oxides with Fe-to-La mole ratios of 6:1, 10:1, and 1:0. e) Thermogravimetric analysis (TGA) of lanthanum-iron oxide with a 6:1 Fe-to-La mole ratio.

XRD analysis. Fig. 4b presents the XRD patterns of lanthanum-iron oxide compounds with five different Fe-to-La mole ratios. For a mole ratio of 1:0, distinct diffraction peaks were noted at 2θ values of 30.05 , 35.43 , 43.08 , 56.96 and 62.45° , indicative of the sample's excellent crystallinity. Moreover, these peaks align precisely with the (220), (311), (400), (511) and (440) crystal planes of standard Fe_3O_4 as per JCPDS card no. 19-0629 in the XRD library.³⁵ The XRD pattern of the as-synthesized magnetic sample with a mole ratio of 6:1 did not match those of the LaFeO_3 , Fe_3O_4 , Fe_2O_3 , $\text{La}(\text{OH})_3$, La_2O_3 and La reference materials (Fig. 4c). With an increase in the $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ content and decrease in the Fe-to-La mole ratio from 10:1 to 0:1, new diffraction peaks for lanthanum oxide emerged at 7.68 , 16.39 and 24.59° , each becoming progressively more intense. The appearance of the peak at 7.68° indicates the generation of a new phase.

As the lanthanum ion content increased, the intensity of the peak at 7.68° increased, as did the crystallinity. This finding indicates that a new crystal type of lanthanum–iron oxide was obtained through the one-pot method, demonstrating the potential for adjusting the Fe-to-La mole ratio to tailor the material's structural properties.

BET measurements. The specific surface areas and pore characteristics of lanthanum–iron oxides with different mole ratios are summarized in Table I. For Fe-to-La mole ratios of 6:1, 8:1 and 10:1, large specific surface areas of 73.64, 63.02 and 79.94 m^2/g , respectively, were obtained. These observations indicate that the incorporation of Fe and La metals in the Fe-to-La 1:0 and 0:1 (hydr)oxides differs from that in the other three type. In addition, compared with Fe-to-La 1:0, the introduction of lanthanum increases the specific surface area of the lanthanum–iron oxide, which is conducive to the enrichment of target molecules.^{27,36}

TABLE I. Physical characteristics of lanthanum–iron oxides with different mole ratios

Fe:La	BET surface area	Total pore volume	Average pore diameter
	m^2/g	cm^3/g	nm
1:0	26.64	0.0136	1.92
6:1	73.64	0.0395	2.06
8:1	63.02	0.0345	2.01
10:1	79.94	0.0436	2.05
0:1	1.28	0.0009	2.6

VSM measurement. Fig. 4d illustrates the magnetic properties of the lanthanum–iron oxide compounds with varying Fe-to-La mole ratios. Notably, the saturation magnetization values for molar ratios of 1:0, 10:1, 8:1 and 6:1 were 80.5, 65.6, 51.7 and 18.8 emu/g , respectively. None samples exhibited obvious remanence or coercivity, indicating their superparamagnetic nature. The hysteresis loop diagram highlights that the saturation magnetization decreases as the amount of La increases, which is attributable to the decreasing Fe content in the compounds. Despite this, the sample with a 6:1 mole ratio maintained excellent magnetic responsiveness, as evident from the inset.

TGA analysis. The TGA of lanthanum–iron oxide have been presented in Fig. 4e. The decomposition process can be divided into three stages. The initial stage, from RT to 184°C , involves a 5.65 % weight loss due to the evaporation of surface-adsorbed water. The second stage, spanning 184 to 418°C , shows a minimal weight loss of 6.85 %, mainly due to the minimal decomposition of acetate and nitrate. The final stage, from 418 to 800°C , involves weight-loss steps: 2.68 and 1.46 %. During this stage, the oxygen-containing groups on the surface of lanthanum–iron oxides were completely eliminated, leaving 83 wt. % of lanthanum–iron ash.

XPS analysis. To further investigate the electronic valence of the elements, XPS was used to characterize the sample with a 6:1 Fe-to-La mole ratio, as shown in Fig. 5. The full spectrum (Fig. 5a) reveals characteristic peaks for La 3d, Fe 2p, O 1s and C 1s, confirming the presence of La, Fe, O and C in the synthesized material. The detection of C can be attributed to atmospheric moisture absorption, leading to minor carbonate formation. In Fig. 5b, the La 3d_{3/2} and La 3d_{5/2} peaks occur at 851.9 and 835.1 eV, respectively,²⁹ with a binding energy of 16.8 eV, indicative of La in the +3 oxidation state.³⁷ The Fe 2p spectrum in Fig. 5c exhibits Fe 2p_{1/2} and Fe 2p_{3/2} peaks at 724.4 and 710.7 eV, respectively, characteristic of both Fe²⁺ and Fe³⁺ states. The O 1s spectrum in Fig. 5d predominantly consists of lattice oxygen, along with surface-adsorbed oxygen or hydroxyl groups, corresponding to the Fe–O and La–O bonds and oxyhydroxides in the lanthanum–iron oxide compound. These findings offer a comprehensive insight into the structural and chemical properties of lanthanum-iron oxide, particularly in relation to its Fe-to-La ratio-dependent morphology and elemental composition.³⁸

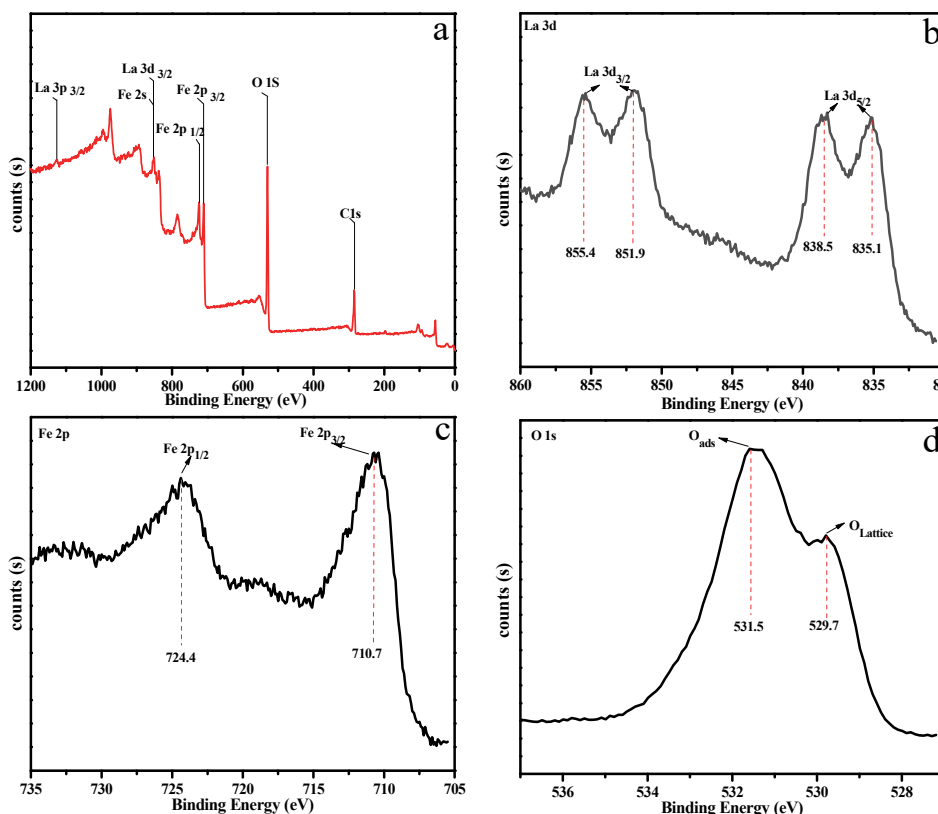


Fig. 5. XPS spectra of lanthanum–iron oxide with a 6:1 Fe-to-La mole ratio.

a) Lanthanum–iron oxide, b) La 3d, c) Fe 2p and (d) O 1s spectra.

Adsorption of PMPA

Effect of adsorbent dosage on PMPA adsorption. Fig. 6a shows the relationship between the dosage of lanthanum–iron oxide and its adsorption capacity for PMPA. With increasing dosage, there is a noticeable decrease in PMPA adsorption, while the removal rate increases significantly.^{20,39} This observation suggests an increase in the number of available adsorption sites on the lanthanum–iron oxide surface. However, the concentration of PMPA remains constant. This indicates that the adsorption process has not reached saturation. The removal rate of PMPA notably rises from 18.61 to 60.30 % as the lanthanum–iron oxide dosage increases, indicating that 35 mg is the optimal dosage.

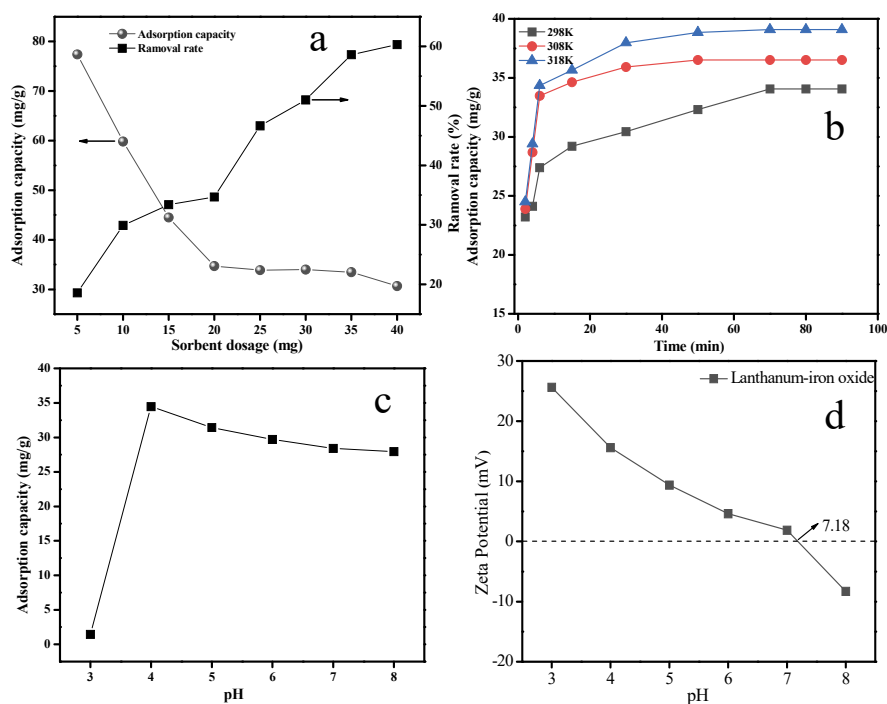


Fig. 6. Influence of adsorbent dosage (a), temperature (b) and pH (c) on PMPA adsorption and the zeta potential of lanthanum–iron oxide (d).

Effect of temperature on PMPA adsorption. Concerning the influence of temperature on adsorption, as depicted in Fig. 6b, the process appears to be endothermic. With an increase in temperature from 25 to 45 °C, the maximum adsorption capacity increases from 34.06 to 39.10 mg/g, suggesting that higher temperatures favor the adsorption process. Consequently, 25 °C was chosen as the experimental temperature based on energy-saving considerations.

Effect of pH on PMPA adsorption. Fig. 6c shows the impact of pH on PMPA adsorption by lanthanum-iron oxide. The adsorption capacity increases as the pH increases from 3 to 4, which is primarily attributed to two factors: electrostatic attraction between negatively charged PMPA and positively charged lanthanum-iron oxide (Fig. 6d). Ligand exchange occurs *via* the $-\text{OH}$ in lanthanum-iron oxide and phosphate group in tenofovir. Moreover, the protonation process that occurs under acidic conditions likely facilitates the ligand exchange process. For instance, $-\text{OH}_2^+$ (protonated state) has been reported to be more easily replaced than $-\text{OH}$ in its original state.⁴⁰ Considering these results, a possible removal mechanism was proposed, as depicted in Fig. S-1 of the Supplementary material to this paper. Therefore, these effects significantly enhance the adsorption capacity. At pH 4.0, the adsorption capacity reaches a maximum of 34.48 mg/g. Beyond pH 4.0, the removal rate gradually decreases due to competition from hydroxide ions at higher pH levels with negatively charged PMPA.^{29,41} In summary, the primary removal mechanism involves electrostatic attraction and inner-sphere complexation through ligand exchange.

Adsorption kinetics. The adsorption kinetics were analyzed using pseudo-first-order (Eq. (S-1), Supplementary material) and pseudo-second-order (Eq. (S-2), Supplementary material) kinetic models, providing a deeper understanding of the adsorption mechanisms and kinetics under different experimental conditions. Fig. S-2 of the Supplementary material presents the kinetic analysis of PMPA adsorption on lanthanum-iron oxide. The pseudo-first-order reaction model yielded a correlation coefficient (R^2) of 0.9603 (Fig. S-2a), indicating a poorer fit to the experimental data compared with the pseudo-second-order model, which displayed a higher correlation coefficient of 0.9981 (Fig. S-2b). Furthermore, Table II compares the experimentally obtained equilibrium adsorption capacity ($q_{\text{e,exp}}$) with the calculated values ($q_{\text{e,cal}}$) from the pseudo-second-order model, showing close agreement. This finding indicates that the adsorption capacity is directly related to the number of active sites on the lanthanum-iron oxide surface and suggests that chemical adsorption might be the rate-limiting step in this process.

TABLE II. Kinetic parameters for PMPA adsorption on lanthanum-iron oxide.

C_0 mg/L	$q_{\text{e,exp}}$ mg/g	Pseudo-first-order			Pseudo-second-order		
		k_1	$q_{\text{e,cal}} / \text{mg g}^{-1}$	R^2	k_2	$q_{\text{e,cal}} / \text{mg g}^{-1}$	R^2
50	33.92	2.57×10^{-2}	16.38	0.9603	8.85×10^{-3}	35.01	0.9981

Isothermal adsorption study. The study further involved fitting the adsorption data to the Langmuir (Eq. (S-3), Supplementary material) and Freundlich (Eq. (S-4), Supplementary material) isothermal adsorption models. Fig. S-3 of the Supplementary material illustrates the adsorption isotherm plots of PMPA at various initial concentrations at RT; the correlation coefficients, R_L^2 and R_F^2 , for these

models were 0.9937 and 0.5461, respectively. The higher R_L^2 value than R_F^2 suggests that the Langmuir model, which assumes monolayer adsorption, provides a better fit for the adsorption behavior of PMPA on lanthanum–iron oxide. According to Table III, the maximum adsorption capacity of lanthanum–iron oxide for PMPA, as determined by the Langmuir model, was 37.36 mg/g. This value closely aligns with the experimentally calculated maximum adsorption of 34.06 mg/g, further supporting the applicability of the Langmuir model in this context.

TABLE III. Freundlich and Langmuir isotherm parameters for the adsorption of PMPA on lanthanum–iron oxide

Temperature K	$q_{e,exp}$ mg/g	Langmuir				Freundlich	
		$q_{max} / \text{mg g}^{-1}$	$k_L / \text{L mg}^{-1}$	R^2	n	$k_F / \text{mg g}^{-1}$	R^2
298	34.06	37.36	0.49	0.9937	15.33	28.11	0.5461

Adsorption thermodynamics. The thermodynamic equations are shown in Eqs. (S5) and (S6) of the Supplementary material. As can be seen in Fig. S-4 of the Supplementary material, the ΔH and ΔS parameters for PMPA were calculated from the slope and intercept of the $\ln K_c$ vs. $1/T$ plot. The related thermodynamic values are shown in Table IV. Both ΔH and ΔS are greater than zero, indicating that the process is an entropy-increasing and heat absorption process. The preferential polar interactions, which are associated with the release of water molecules between the hydration layers of the adsorbent and adsorbate. All the values of ΔG are negative at different temperatures and the Gibbs energy change decreases with the temperature increasing, indicating that PMPA adsorption on lanthanum–iron oxide proceeds spontaneously.

TABLE IV. Thermodynamic parameters for the adsorption of PMPA on lanthanum–iron oxide.

$\Delta H / \text{kJ} \cdot \text{mol}^{-1}$	$\Delta S / \text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$	$\Delta G / \text{kJ} \cdot \text{mol}^{-1}$		
		298 K	308 K	318 K
0.0120	43.14	−12.85	−13.28	−13.78

A comparison of lanthanum–iron oxide with other adsorbents, including magnetic, non-magnetic and bimetal materials, which widely used for the treatment of pharmaceutical wastewater,^{20,29,42,43} and the relevant data are summarized in Table S-I of the Supplementary material. Clearly, it is easy for lanthanum–iron oxide to separate from the solution by an external magnetic field, which is conducive to the separation and recovery of adsorbents. In addition, lanthanum–iron oxide is easy to prepare and exhibits a high adsorption capacity.

CONCLUSION

In this study, we successfully synthesized lanthanum–iron oxide compounds using a streamlined one-pot method, employing EG as the solvent and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$

and $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ as the primary materials. This approach, in contrast to traditional methods such as high-energy milling, the citrate-gel method, and co-precipitation, eliminates the need for step-by-step sample processing. Moreover, it offers significant advantages over the microwave-assisted one-step method by obviating the need for pH adjustment, thus enhancing efficiency and energy savings. SEM analysis revealed that the lanthanum-iron oxide compound comprises densely packed particles with sizes ranging from 20 to 200 nm. FTIR analysis confirmed the existence of Fe-O (575 cm^{-1}) and La-O (636 cm^{-1}) bonds, while XRD analysis showed that a new crystal type of lanthanum-iron oxide was produced by the employed one-pot method. VSM highlighted the superparamagnetic nature of the samples, which enables rapid separation under an external magnetic field. XPS results confirmed the presence of La, Fe, O and C in the sample. The synthesized lanthanum-iron oxide was then used to study tenofovir ((*R*)-9-(2-phosphonomethoxypropyl)adenine, PMPA) adsorption. The kinetic and isothermal adsorption models suggested that the adsorption behavior was best described by the pseudo-second-order kinetic model and the Langmuir isothermal model, indicative of a monolayer chemical adsorption mechanism. Meanwhile, the spontaneous and endothermic process is indicated by adsorption thermodynamics. The mechanism of PMPA adsorption on lanthanum-iron oxide was identified as inner-sphere complexation and electrostatic attraction. This study not only presents an innovative method for synthesizing lanthanum-iron oxide materials but also demonstrates their potential as adsorbents for the treatment of actual phosphate-containing wastewater.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: <https://www.shd-pub.org.rs/index.php/JSCS/article/view/13599>, or from the corresponding author on request.

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ИЗВОД

ЕФИКАСНА СОЛВОТЕРМАЛНА СИНТЕЗА ЛАНТАН-ГВОЖЂЕ-ОКСИДА У ЈЕДНОМ КОРАКУ И ПРИМЕНА У АДОРПЦИЈИ ТЕНОФОВИРА

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Нови магнетни композити лантан-гвожђе-оксида синтетизовани су коришћењем методе у једном кораку. Предложени приступ поједностављује процес синтезе захваљујући

избегавању традиционалних захтеva као што су подешавање pH вредности и калцинација на високим температурама, што резултира ефикаснијим поступком и производњом магнетног материјала. Испитан је утицај односа Fe/La, времена реакције и температуре реакције на својства и адсорпционе перформансе композита лантан–гвожђе-оксида. Синтетизовани композити су окарактерисани методама SEM, XRD, VSM, FTIR, BET, TGA и XPS, чиме је утврђено да се узорци састоје од насумично оријентисаних честица величина од 20 до 200 nm, да поседују одличну кристалинност, магнетну осетљивост и термичку стабилност. Поред тога, у овом истраживању синтетисани лантан–гвожђе-оксиди су примењени за адсорбовање тенофовира ((R)-9-(2-фосфонометоксипропил)-аденина, РМРА), са максималним капацитетом адсорпције од 34,06 mg/g, при дози адсорбента = 0,9 g/L, pH 4, C = 50 mg/L и t = 25 °C. Ово истраживање је показало да је примењена метода једноставна за припрему лантан–гвожђе-оксида, који се лако одваја од третиране воде, што је корисно за практичну примену.

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SUPPLEMENTARY MATERIAL TO
**Efficient one-pot solvothermal synthesis of lanthanum-iron oxide
and its application in tenofovir adsorption**

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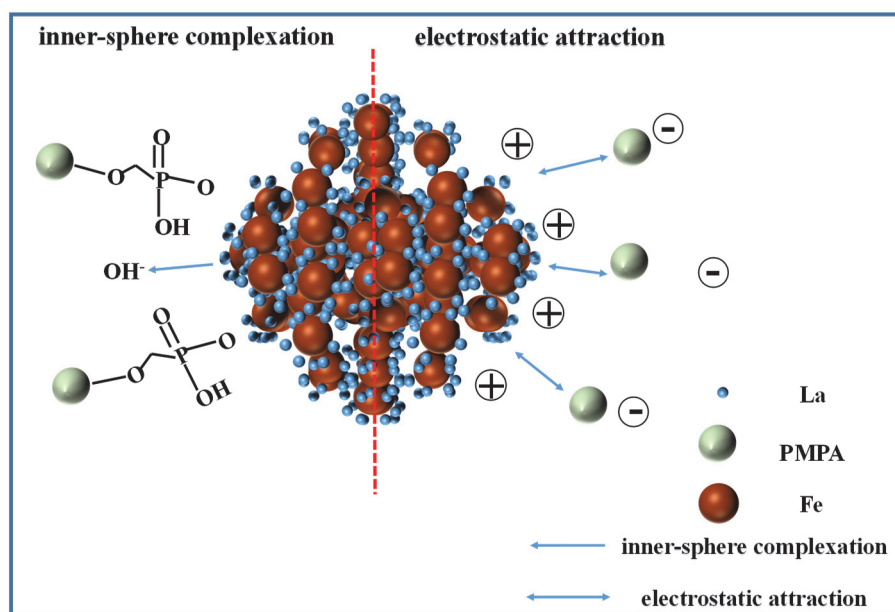


Fig. S-1. Schematic of the plausible mechanism of PMPA removal by lanthanum-iron oxide.

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Adsorption kinetics. The pseudo-first-order and pseudo-second-order kinetic models are shown below:

$$\log(q_e - q_t) = \log q_e - \frac{k_1}{2.303} t \quad (\text{S-1})$$

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{t}{q_e} \quad (\text{S-2})$$

where q_t (mg/g) represents the adsorption amount of PMPA at time t , q_e (mg/g) represents the adsorption amount at equilibrium, while K_1 (min^{-1}) and K_2 ($\text{g}/\text{mg}\cdot\text{min}$) denote the rate constants for the pseudo-first-order and pseudo-second-order reactions, respectively.

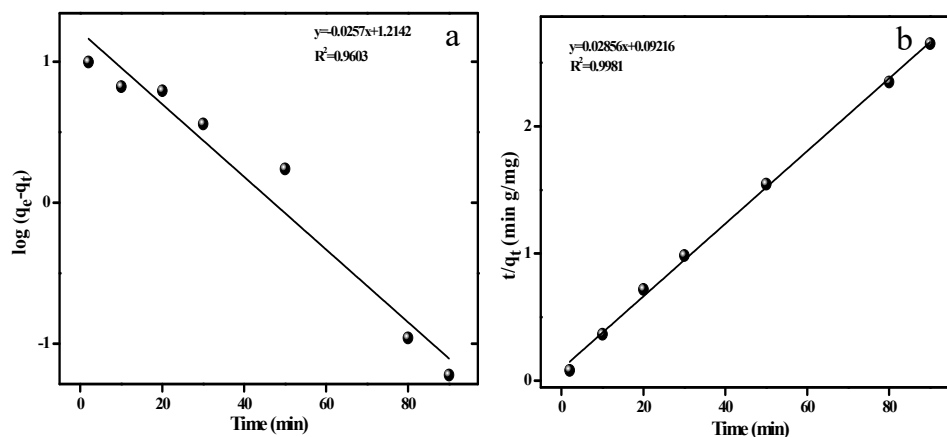


Fig. S-2. (a) Pseudo-first-order and (b) pseudo-second-order kinetic models for PMPA adsorption on lanthanum-iron oxide.

Isothermal adsorption study. Langmuir and Freundlich adsorption isotherm models can be expressed as:

$$\frac{C_e}{q_e} = \frac{1}{k_L q_{\max}} + \frac{C_e}{q_{\max}} \quad (\text{S-3})$$

$$\ln q_e = \frac{1}{n} \ln C_e - \ln k_F \quad (\text{S-4})$$

where C_e (mg/L) represents the equilibrium concentration, $q_{\max}$ (mg/g) represents the maximum adsorption capacity, and n represents the parameter characterizing medium heterogeneity and adsorption intensity. Additionally, k_L (L/mg) and k_F ($(\text{mg/g})/(\text{mg/L})^{1/n}$) denote the Langmuir and Freundlich constants, respectively.

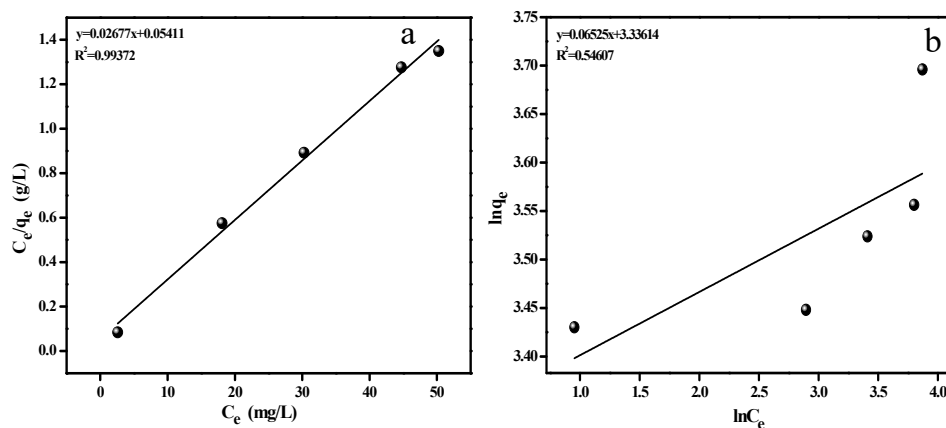


Fig. S-3. (a) Langmuir and (b) Freundlich isotherm models for the adsorption of PMPA on lanthanum-iron oxide.

Adsorption thermodynamics. The thermodynamic parametric equations are shown in Eqs. (Eq(S5), Eq(S6)):

$$\Delta G^0 = -RT \ln K_c \quad (\text{S-5})$$

$$\ln K_c = \frac{\Delta S^0}{R} - \frac{\Delta H^0}{RT} \quad (\text{S-6})$$

where ΔS^0 (J/(mol·K)), ΔH^0 (kJ/mol) and ΔG^0 (kJ/mol) are the entropy, enthalpy and Gibbs free energy changes, respectively. R (8.314 J/(mol·K)) is the ideal gas constant and K_c (L/g) is the adsorption equilibrium constant, $K_c = q_e/C_e$.

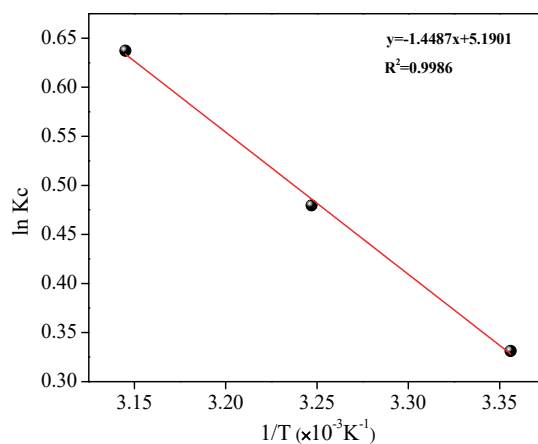


Fig. S-4. Van't Hoff's plot for PMPA uptake on lanthanum-iron oxide.

Table S-I. Comparison of lanthanum-iron oxide with other adsorbent for the treatment of pharmaceutical wastewater.

Adsorbent	Preparation method conditions	Pollutant	Adsorbent dose (g/L)	Time (min)	Adsorption capacity (mg/g)	Refs.
Lanthanum-iron oxide (magnetic)	One-pot (200 °C)	Tenofovir (50 mg/L)	0.9	50	34.06	This work
Activated carbon (non-magnetic)	Thermochemical activation with phosphoric acid (H ₃ PO ₄ , 700 °C)	Tenofovir (0.1 mM)	1.0	20	27	29
Ni@Zn-MOF (non-magnetic)	hydrothermal method	Norfloxacin (NOR) (50 mg/L)	4.0	300	11.65	20
MIL101(Fe)·Fe ₃ O ₄ (magnetic)	two-step solvothermal method	TC, DC and CFX (20 mg/L)	2.0	240	45.33, 33.20 and 31.30	42
CA-LaFeNPs	pH8.6, 200 °C combined with sol-gel	As(III)(500 mg/L)	7.0	1440	91	43

Green extraction and valorization of olive pomace using limonene: A kinetic modeling and thermodynamic approach

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Abstract: This work explores the extraction of oil from olive pomace using limonene as a green solvent, with particular emphasis on the effects of temperature on yield, kinetics and thermodynamics. Results show that oil recovery increases with time and temperature, following a two-stage mechanism: a rapid washing phase dominated by surface oil removal and a slower diffusion-controlled stage. Kinetic modeling shows that the Patricelli model best fits the process ($R^2 > 0.99$), while mass transfer coefficients confirm the predominance of washing at lower temperatures. The relatively low activation energy ($16.98 \text{ kJ}\cdot\text{mol}^{-1}$) suggests a diffusion-limited process that is thermally accessible and suitable for industrial application. Thermodynamic parameters support this interpretation, with negative Gibbs energy change confirming spontaneity, an endothermic enthalpy change ($\Delta H = 1.68 \text{ kJ}\cdot\text{mol}^{-1}$), and a positive entropy change ($\Delta S = 17.39 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$) reflecting increased molecular disorder during extraction. Overall, limonene demonstrates high efficiency and sustainability, offering a viable alternative to hexane in line with green chemistry principles.

Keywords: oil recovery; alternative solvent; azeotropic distillation; activation energy; process efficiency; spontaneous extraction.

INTRODUCTION

Olive pomace, alternatively termed olive mill cake or foot cake, is a solid byproduct resulting from oil extraction processes. This residue comprises pulp, skins, endocarp fragments, and water remaining after olive processing. Its chemical profile typically features a high moisture content (40–60 %), organic constituents including cellulose, hemicellulose, lignin and residual lipids (2–8 %), alongside various phenolic compounds, minerals, nitrogenous substances and trace fatty

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acids.^{1,2} From an environmental standpoint, olive foot cake presents distinct challenges and opportunities.³ On the negative side, its substantial organic load and phytotoxic phenolic constituents hinder biodegradation; improper management may trigger pollution, offensive odors and soil or water contamination.^{3,4} Conversely, effective valorization enables diverse sustainable applications. It can serve as combustible biomass or a substrate for biogas production *via* anaerobic digestion.¹ Following specific treatments, it can function as a soil conditioner or livestock feed, although phenolic concentrations restrict immediate utilization. Furthermore, high-value components, including polyphenols and antioxidants, are extractable for integration into cosmetic, food and pharmaceutical industries.⁵

Olive mill residue can be converted into biochar or activated carbon for environmental remediation purposes.^{6,7} This solid byproduct retains a significant amount of residual oil, typically 5 to 10 % by mass, representing a lucrative secondary source for edible and industrial applications.⁸ Valorizing olive cake *via* oil recovery facilitates waste mitigation and environmental sustainability while simultaneously bolstering the economic viability of olive oil manufacturing. Various solvent-based techniques are used for extraction, differing in efficiency and ecological footprints. Conventionally, hexane remains the predominant solvent owing to its superior lipid solubility and capacity for maximizing residual oil yields.⁸ Nonetheless, increasing apprehensions concerning its toxicity, flammability and overall environmental impact have catalyzed research into greener alternatives. Ethanol, a bio-based and less hazardous solvent, has emerged as a viable substitute, offering good extraction performance while being safer and more environmentally friendly.⁹ Additionally, limonene – a natural solvent sourced from citrus rinds – has garnered significant interest recently due to its biodegradability, minimal toxicity and exceptional solvating capacity for nonpolar substances like vegetable lipids.¹⁰ Comparative studies have shown that while hexane may achieve slightly higher yields, ethanol and limonene offer more sustainable solutions, especially when combined with process optimization strategies such as temperature control, solvent recycling, and pretreatment of the biomass.¹¹

Modeling olive pomace oil recovery using limonene as a sustainable solvent has attracted significant interest as a promising alternative to conventional hexane. Mathematical frameworks are widely used to describe extraction kinetics, providing valuable insights into mass transfer mechanisms and the influence of process variables on extraction yield, thereby facilitating process optimization.^{9,12,13} Numerous models have been proposed to explain solvent extraction from oilseeds and agro-industrial by-products, allowing the estimation of extraction rate constants, equilibrium yields, and model coefficients for process prediction and optimization.⁶ Recent studies have further highlighted the growing interest in green extraction technologies and bio-based solvents for olive pomace valorization.^{14–16} In particular, Pagliaro *et al.*¹⁷ reviewed the application of limonene as a renewable

and recyclable solvent for natural product extraction, including its successful use in microwave-assisted olive pomace oil extraction. However, despite these advances, quantitative investigations describing the extraction mechanism of olive pomace oil using limonene under conventional heating conditions remain scarce. In particular, studies combining kinetic modeling, mass-transfer analysis, activation energy determination and thermodynamic evaluation have rarely been reported. Therefore, this study employed limonene to recover residual lipids from olive pomace under conventional heating conditions and provided a comprehensive kinetic and thermodynamic assessment of the extraction process, enabling a quantitative understanding of the extraction mechanism and the feasibility of limonene as a sustainable extraction solvent.

EXPERIMENTAL

Raw materials

The olive pomace was sourced from a modern oil mill located in Tizi Ouzou (Northern Algeria). Its initial moisture content of 46.9 % was reduced to 5.4 % by oven-drying (Memmert, model 854 Schwabach) at 103 °C. The resulting olive cake was used in its raw state, without further grinding. All extraction procedures were performed using limonene with a purity of 97 %.

Oil extraction

Extractions were conducted in a double-walled glass reactor with a capacity of $5 \times 10^4 \text{ m}^3$, equipped with a mechanical stirrer to ensure homogeneity. For each experiment, $5 \times 10^{-2} \text{ kg}$ of olive pomace was mixed with $1.5 \times 10^{-4} \text{ m}^3$ of limonene, maintaining a liquid-to-solid (L/S) ratio of $3 \times 10^{-3} \text{ m}^3 \text{ kg}^{-1}$. The mixture temperature was kept constant *via* water circulation within the reactor jacket. Oil yield kinetics were investigated at four temperatures (25, 35, 45 and 65 °C) for extraction times ranging from 5 to 60 min, with a constant stirring rate of 450 rpm.

Limonene, with an average density of 0.84 kg m^{-3} at 20 °C, was used as the solvent. Each reported result represents the average of three replicates for both the kinetic and equilibrium studies. The total oil content of the samples was determined *via* exhaustive extraction for 24 h, in accordance with the NF V03-924 standard. For each procedure, a constant mass of $5 \times 10^{-2} \text{ kg}$ of olive cake was used. Following extraction, the solid and liquid phases were separated by vacuum filtration using a Busch pump (model RB 0004 B NF0), and the oil was subsequently recovered by distillation.

Following the extraction step, the separation of limonene from the extracted oil was performed *via* vacuum distillation. Due to the relatively high boiling point of limonene (175 °C at atmospheric pressure¹⁸) direct distillation requires elevated temperatures that may induce the thermal degradation of heat-sensitive components within the oil.¹⁹ To mitigate this effect and lower the distillation temperature, distilled water was added to the limonene–oil mixture to promote the formation of a heteroazeotropic system. This azeotrope exhibits a boiling point of approximately 97.4 °C,¹⁰ which is significantly lower than that of pure limonene. The formation of this azeotrope stems from the non-ideal behavior of the mixture; specifically, positive deviations from Raoult's law, resulting in a minimum-boiling point.¹⁸ Operating under reduced pressure further decreases the boiling point, facilitating efficient separation under mild thermal conditions. This strategy prevents the decomposition of heat-sensitive constituents while improving the overall energy efficiency of the process.²⁰

After azeotropic distillation, the limonene and extracted oil were recovered separately. The oil and water remaining in the distillation flask were separated by decantation, and any residual water was removed by oven-drying at 103 °C. The limonene in the distillate was similarly recovered by decantation. The oil yield was determined as:

$$\text{Oil yield (\%)} = 100 \frac{\text{Mass of oil (g)}}{\text{Mass of olive pomace sample (g)}} \quad (1)$$

Kinetic models

Various mathematical models, traditionally used to describe the falling-rate period in drying processes, were adapted to characterize the oil extraction kinetics. In this study, the Patricelli, Peleg, diffusion and logarithmic models were evaluated (Table I). For each model, R represents the yield (g oil/100 g solid), t is the contact time (min), k is a kinetic constant (min^{-1}) and a and b are model-specific constants, R_w and R_d : extraction yields associated with the washing and diffusion stages, respectively, while K_w and K_d : rate constants. The parameters k_1 and k_2 are the Peleg model constants, and k , a and b are empirical constants of the diffusion and logarithmic models.

TABLE I. Mathematical models

Name	Model	
Patricelli	$R = R_w(1 - \exp(-k_w t)) + R_d(1 - \exp(-k_d t))$	(2)
Peleg	$R = \frac{t}{k_1 + k_2 t}$	(3)
Diffusion model	$R = a \exp(-kt) + (1 - a) \exp(-kbt)$	(4)
Logarithmic model	$R = a \log t + b$	(5)

The goodness-of-fit was assessed using several statistical indicators, the coefficient of determination (R^2), the chi-square statistic (χ^2) and the mean square error (MSE). These criteria provide a quantitative basis for comparing model performance. Following established methodologies,^{13,21} the optimal model was identified by the highest R^2 and the lowest χ^2 and MSE values. The statistical parameters were calculated using the following equations:

$$\text{Residual} = \sum_{i=1}^N (R_{\text{exp},i} - R_{\text{the},i}) \quad (6)$$

$$\chi^2 = \frac{\sum_{i=1}^N (R_{\text{exp},i} - R_{\text{the},i})^2}{N - Z} \quad (7)$$

$$MSE = \left(\frac{1}{N} \sum_{i=1}^N (R_{\text{exp},i} - R_{\text{the},i})^2 \right) \quad (8)$$

R_{exp} is the experimental value, R_{the} is the calculated (predicted) value, N is the number of observations and Z is the number of constants.

RESULTS AND DISCUSSION

Oil extraction yield

Fig. 1 illustrates the evolution of oil yield as a function of time at different extraction temperatures. A detailed kinetic analysis reveals two distinct phases: a rapid initial extraction rate followed by a plateau or a significantly slower rate after approximately 30 min. Notably, at a constant extraction time of 15 min, the oil yield rose from 12 to 37 % when the temperature was increased from 25 to 65 °C. In comparison, at a constant temperature of 25 °C, extending the extraction time from 5 to 60 min resulted in a more substantial yield increase – approximately 87 %. This behavior suggests that the extraction process is initially driven by the solubilization of surface oil, followed by a diffusion-controlled mechanism that prevails as the easily accessible oil is depleted. These findings indicate that extraction time exerts a more pronounced influence on oil yield than temperature, particularly during the early stages. This trend aligns with the observations of Meziane *et al.*,⁹ regarding hexane extraction from olive pomace, where a rapid initial phase was followed by a slower, diffusion-limited stage.

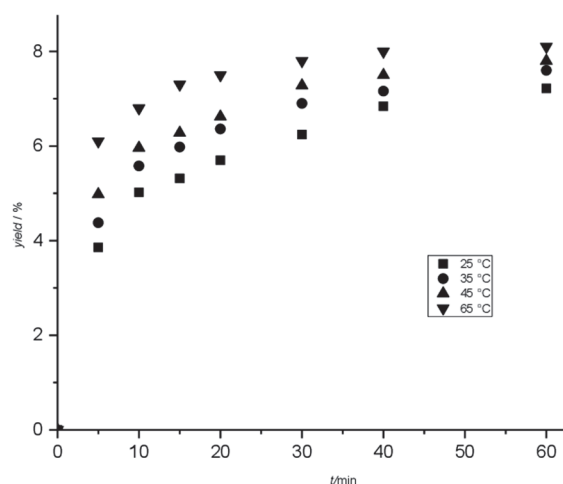


Fig. 1. Evolution of extraction efficiency with time ($L/S=3$, $V=450$ rpm) at temperatures of 25, 35, 45 and 65 °C.

Similar results were reported by Chemat *et al.*²² regarding the microwave-assisted extraction of essential oils, where the bulk of the oil was recovered within the first few minutes, with longer extraction times yielding only marginal improvements. In the context of supercritical CO₂ extraction of rapeseed oil, it was also noted²³ that extraction time exerted a more pronounced effect on recovery than moderate variations in pressure or temperature, particularly during the initial phase

dominated by external mass transfer. Likewise, Soxhlet extraction studies of peanut and sesame oil by Luque-Garcia *et al.*²⁴ demonstrated that yield increases significantly with time up to a threshold, beyond which a plateau is reached regardless of further temperature increases. Collectively, these findings underscore the dominant role of extraction time in oil recovery kinetics, especially in solid–liquid systems where rapid initial solubilization is followed by slow diffusion from internal cellular structures.

Modeling results

The experimental data shown in Fig. 1 were fitted to the mathematical models listed in Table I, with the resulting model constants for each temperature summarized in Table II. Nonlinear regression analysis was performed using Statistica 7 software to estimate the parameters, providing a quantitative description of the extraction kinetics across the investigated temperatures.

TABLE II. Model constants at 25, 35, 45 and 65 °C and comparison criteria χ^2 , CME and R^2 for the different models

Model	Constant	Temperature, °C			
		25	35	45	65
Patricelli	R_w	4.063	4.724	4.695	5.367
	R_d	3.943	3.274	3.348	2.752
	k_w	0.356	0.341	0.501	0.731
	k_d	0.028	0.035	0.045	0.076
	R^2	0.999	1	0.999	1
	χ^2	0.01050	0.00200	0.00625	0.00175
	CME	0.07246	0.03162	0.05590	0.02958
Peleg	k_1	0.720	0.549	0.430	0.234
	k_2	0.132	0.126	0.124	0.120
	R^2	0.991	0.997	0.995	0.999
	χ^2	0.01946	0.05383	0.03750	0.00917
	CME	0.12081	0.20094	0.16771	0.08292
Diffusion	k	0.196	0.205	0.256	0.324
	a	−4.259	0.205	−5.192	−6.118
	b	−0.028	−0.020	−0.016	−0.008
	R^2	0.969	0.974	0.973	0.997
	X^2	0.22696	0.21297	0.23858	0.22824
	CME	0.37663	0.36483	0.38615	0.37769
Logarithmic	a	3.053	2.866	3.756	1.953
	b	1.780	2.577	1.647	4.857
	R^2	0.991	0.989	0.799	0.966
	X^2	0.01237	0.01272	0.19607	0.01719
	CME	0.09632	0.09767	0.38347	0.11354

Fig. 2a–d compares the experimental extraction yields and the values predicted by the different kinetic models at each temperature. All models demonstrated strong agreement with the experimental data, as evidenced by the close overlap between the predicted and experimental curves. This strong agreement, further supported by Fig. 3a–d, indicates that each model accurately captures the extraction kinetics across the entire temperature range studied.

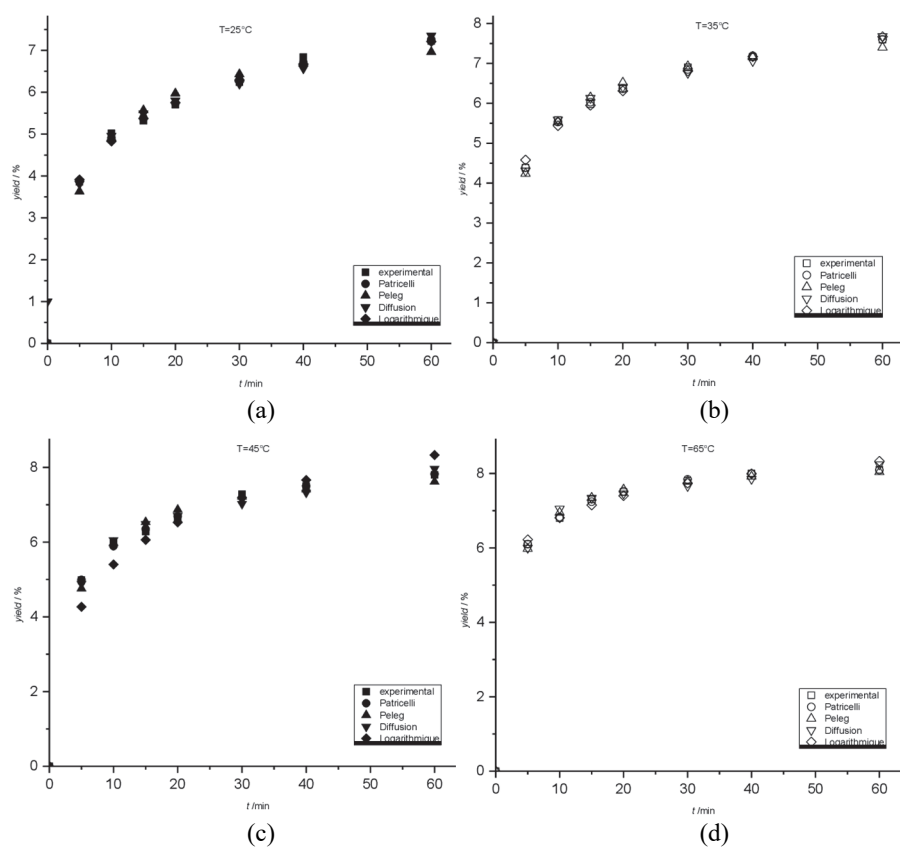


Fig. 2. Time courses of the experimental and calculated yield values at different temperatures. a) 25; b) 35; c) 45; d) 65 °C.

The coefficients of determination (R^2), chi-square (χ^2) values and mean square errors (MSE) calculated for each model at the different extraction temperatures are summarized in Table II.^{25,26} Among the tested models, the diffusion model showed the weakest agreement with the experimental data, with R^2 values ranging from 0.969 to 0.997. In contrast, the Patricelli and Peleg models demonstrated superior fits, with R^2 values between 0.991 and 1, indicating a much closer correspondence with the observed data.

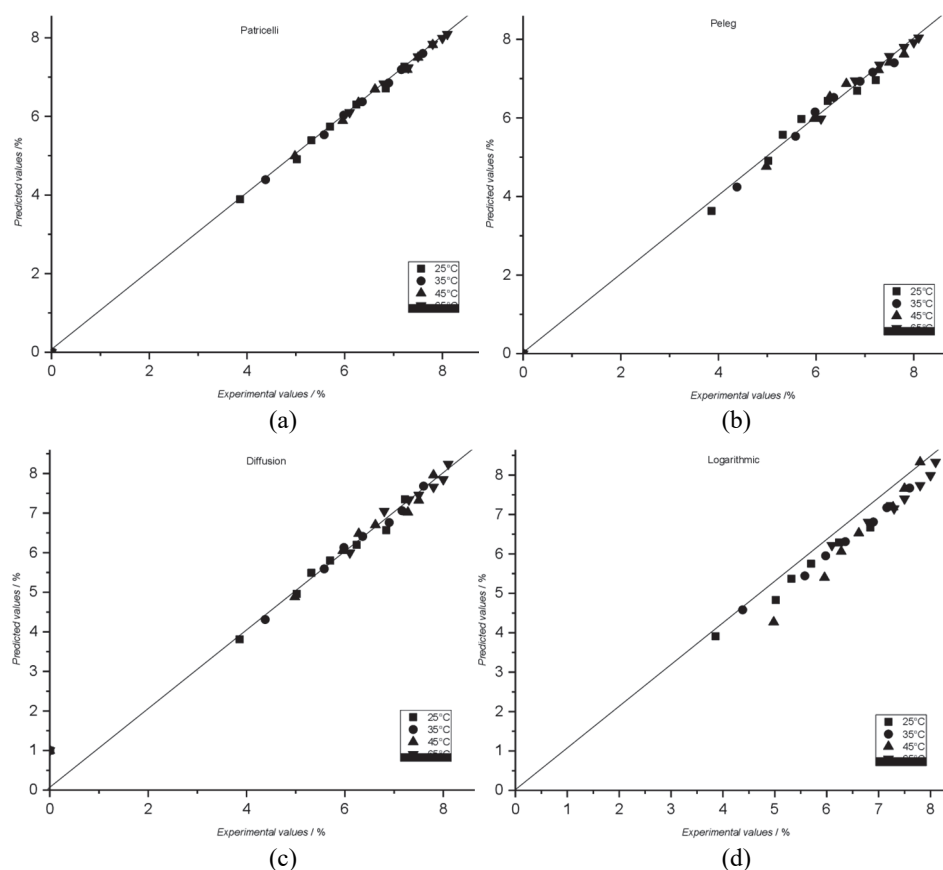


Fig. 3. Comparison between experimental and calculated values for the various models considered: a) Patricelli; b) Peleg; c) diffusion model; d) logarithmic model.

The use of multiple statistical indicators strengthens the evaluation of model performance. While R^2 provides a general measure of fit quality, the χ^2 and MSE values are more sensitive to discrepancies between observed and predicted values. The fact that the Patricelli model performs best across all three indicators reinforces its validity and suitability for representing the extraction process. This makes it a reliable tool for further kinetic modeling and potential scale-up of the extraction process.

Evaluation of the Patricelli model

Oil extraction from oleaginous seeds, fundamentally based on lipid solubilization in a solvent, is primarily governed by diffusive mechanisms. The proposed mathematical model characterizes the extraction as a two-stage process:

i) Surface wash: the initial rapid removal of accessible surface oil *via* immediate solvent contact.

ii) Internal diffusion: the subsequent recovery of intracellular lipids through a biphasic diffusion process. This internal phase comprises a relatively slow, unhindered diffusion from ruptured cells (Step 1), followed by a significantly more constrained diffusion from intact cellular structures (Step 2).

The extraction of oil from olive cake is fundamentally governed by the solvent's capacity to solubilize lipophilic compounds sequestered within the solid matrix. Various kinetic models have been developed to characterize this phenomenon; among them, the Patricelli model has proven particularly robust, especially in applications involving olive oil recovery.⁹

In the current study, the application of the Patricelli model demonstrated close agreement with the experimental results, validating its predictive accuracy under the investigated parameters. These findings are in strong agreement with the work of Meziane *et al.*,⁹ who similarly observed a high degree of correlation between empirical data and model simulations during hexane-based extraction.

Consequently, the present results not only substantiate the validity of the Patricelli model for olive cake extraction but also underscore its robustness and versatility across diverse solvents and operational parameters. The extraction yield is thus defined by Eq. (2).

The mass transfer coefficients k_w and k_d and equilibrium oil yields R_w and R_d were numerically determined using a nonlinear least-squares fitting method using Statistica software. Table II summarizes these kinetic parameters across the investigated temperature range. At all temperatures, the yield attributed to the washing stage consistently exceeded that of the diffusion phase. Notably, at 65 °C, the washing yield was approximately double that of the diffusion yield, underlining the predominance of surface oil removal during the initial extraction phase.

The calculated mass transfer coefficients further corroborate this trend. At 25 °C, the washing coefficient (k_w) was approximately 12-fold higher than the diffusion coefficient (k_d), reflecting the rapid desorption of accessible surface oil. Both coefficients exhibited a linear temperature dependence, indicating that thermal energy enhances both surface washing and internal diffusion mechanisms. However, while k_w roughly doubled between 25 and 65 °C, the diffusion coefficient increased by a factor of three. This disparity suggests that temperature exerts a more pronounced influence on internal mass transfer resistance than on surface washing kinetics.

Extraction rate

The kinetic behavior is further elucidated by the extraction profiles. As illustrated in Fig. 1, the oil yield exhibits a sharp initial increase followed by an asymptotic plateau, signifying the transition from the rapid washing phase to the rate-limiting diffusion-controlled phase. This kinetic pattern is corroborated by the extraction rate calculations derived from Eq. (4). The data in Table III indicate that

the initial extraction rate (V_0) is highest at the onset of the process but undergoes a rapid exponential decay over time. Furthermore, the natural logarithm of the initial rate ($\ln V_0$) displays a linear correlation with temperature. This relationship confirms that mass transfer processes are thermally activated, following a temperature-dependent acceleration consistent with Arrhenius-type behavior.

TABLE III. Variation in the extraction rate with time

Time, min	Rate of extraction, % min ⁻¹			
	25 °C	35 °C	45 °C	65 °C
0	1.55761	1.72547	2.50257	4.13347
5	0.33927	0.38901	0.31343	0.24443
10	0.12414	0.13398	0.11225	0.10043
15	0.07921	0.07746	0.07820	0.06696
20	0.06407	0.05866	0.06140	0.04575
30	0.04765	0.04016	0.03893	0.02139
40	0.03605	0.02826	0.02473	0.01001
60	0.02066	0.01403	0.00998	0.00219

The extraction rate is determined by the first derivative of the Patricelli equation with respect to time:

$$V = \frac{dR}{dt} = k_w R_w \exp(-k_w t) + k_d R_d \exp(-k_d t) \quad (9)$$

The initial extraction rate is defined at $t = 0$ and can be expressed as follows:

$$V_0 = \left(\frac{dR}{dt} \right)_{t=0} = k_w R_w + k_d R_d \quad (10)$$

Parameters of the Arrhenius equation

The activation energy for the extraction process was calculated using rate constants derived from mass transfer coefficients *via* the Patricelli model (Eq. (11)). These constants were used to determine the Arrhenius equation parameters:²⁷

$$k = A \exp\left(\frac{-E_a}{RT}\right) \quad (11)$$

where k is the rate constant (min⁻¹), E_a is the activation energy (J mol⁻¹), A is the frequency factor (min⁻¹), R is the universal gas constant (J mol⁻¹ K⁻¹), T is the absolute temperature (K).

The linear Arrhenius equation facilitates the determination of activation energy from the slope ($-E_a/R$) of the $\ln k$ versus ($1/T$) (Fig. 4), while the intercept yields $\ln A$. The analysis yielded an activation energy of 16.98 kJ·mol⁻¹. This relatively low value has significant implications for process design and industrial scalability. Primarily, it suggests that the rate-limiting step is governed by physical

phenomena – such as solvent penetration, lipid solubilization and matrix diffusion – rather than chemical transformations. From a process engineering perspective, this is advantageous, as physical mechanisms are generally more predictable and easier to optimize than chemically controlled reactions. Furthermore, this low energy barrier indicates reduced sensitivity to temperature fluctuations, potentially enhancing operational stability and minimizing energy consumption in large-scale applications. Consequently, moderate temperatures can be effectively used to achieve high extraction efficiencies, supporting the economic and technical feasibility of using limonene as a sustainable alternative.

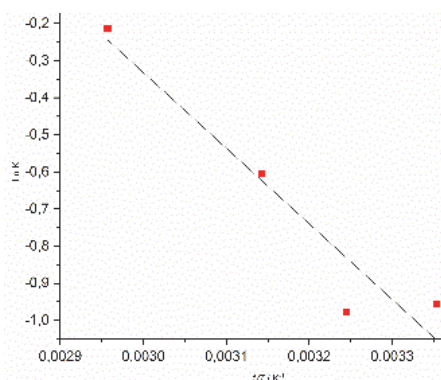


Fig. 4. Arrhenius plot of the extraction rate constant as a function of reciprocal temperature.

In this study, the activation energy was determined to be 16.98 kJ mol⁻¹, indicating a diffusion-controlled mechanism. This result aligns closely with literature values for solvent-based lipid recovery from oleaginous matrices. For instance, Meziane *et al.* reported an E_a of approximately 17.4 kJ mol⁻¹ for olive pomace extraction using hexane, which is highly comparable to the current findings.⁹ Conversely, Usenu *et al.* identified E_a values of 6 508 kJ mol⁻¹ for palm kernel oil,²⁸ while Perez *et al.* documented values ranging from 11 to 33 kJ mol⁻¹ for soybean oil, depending on specific conditions.²⁹ Furthermore, Baidoo *et al.*, observed activation energies near 60 kJ mol⁻¹ during oil extraction from cashew kernels, confirming that such processes are predominantly governed by internal mass transfer (diffusion).³⁰ The strong correlation between our data and established values further supports the experimental methodology and supports the applicability of the kinetic framework employed in this research.

Thermodynamic study

The Gibbs energy change (ΔG) associated with the oil extraction process was calculated using the following thermodynamic relation:

$$\Delta G = -RT \ln K_e \quad (12)$$

where R is the universal gas constant ($\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$), T is the absolute temperature (K) and K_e is the equilibrium constant, which quantifies the distribution of oil between the solvent (miscella) and the solid phase at equilibrium. The equilibrium constant K_e is defined as:

$$K_e = \frac{R_{\text{miscella}}}{R_{\text{solid}}} \quad (13)$$

Here, R_{miscella} represents the equilibrium yield of oil extracted at a given temperature, while R_{solid} is the residual oil content remaining in the solid matrix at equilibrium at the same temperature. The residual oil content was calculated based on the initial oil content of the sample, determined to be 9.94 %, through exhaustive extraction using 97 % limonene.

The ΔG values presented in Table IV provide critical insights into the spontaneity of the extraction process. Negative ΔG values indicate that oil recovery occurs spontaneously under the investigated conditions. Elevated temperatures generally yield more negative ΔG values, reflecting improved solubilization and accelerated mass transfer. Similar trends were documented by Meziane *et al.*, for olive cake extraction with hexane, where ΔG decreased from -4.52 to -6.80 kJ mol^{-1} between 30 and 60 °C.⁹ Dagostin *et al.*³⁰ reported ΔG values ranging from -0.41 to -15.86 kJ mol^{-1} for soybean oil extraction using ethanol between 25 and 55 °C. Similarly, Sunday *et al.* observed negative ΔG values (-1.37 to -3.61 kJ mol^{-1}) for neem oil recovery between 50 and 74 °C. Collectively, these findings confirm that lipid extraction is thermodynamically spontaneous and enhanced at elevated temperatures due to improved diffusivity and solute–solvent interactions. To further elucidate the thermodynamic behavior of the system, ΔH and ΔS were determined utilizing the van't Hoff equation, expressed as follows:

$$\ln K_e = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} \quad (14)$$

The linear relationship observed in the $\ln K_e$ versus $1/T$ plot (Fig. 5) aligns with the van't Hoff equation, where the slope represents $(-\Delta H/R)$ and the intercept denotes $\Delta S/R$. Linear regression analysis yielded ΔH of 1.68 $\text{kJ}\cdot\text{mol}^{-1}$ and ΔS of 17.39 $\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$.

TABLE IV. Thermodynamic parameters and equilibrium constants for olive pomace oil extraction using limonene.

$t / ^\circ\text{C}$	K_e	$\Delta G / \text{kJ mol}^{-1}$
25	4.14	-3.53
35	3.10	-3.62
45	4.24	-3.83
65	4.46	-4.21

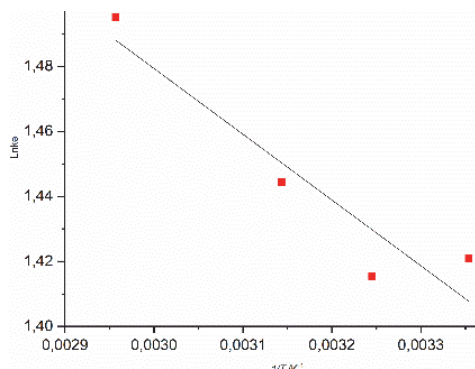


Fig. 5. Van't Hoff plot used to determine the enthalpy (ΔH) and entropy (ΔS) changes of the extraction process.

The positive ΔH value indicates that olive pomace oil extraction is an endothermic process requiring thermal input. The positive ΔS reflects increased molecular disorder resulting from matrix disruption and oil diffusion into the liquid phase. Thermodynamic parameters (ΔH , ΔS) thus provide insight into the extraction mechanism. Comparable behavior was reported by Liauw *et al.*³¹ for neem oil extraction using hexane ($\Delta H = 25.33 \text{ kJ mol}^{-1}$; $\Delta S = 0.09 \text{ kJ K}^{-1} \cdot \text{mol}^{-1}$), confirming an endothermic and irreversible process. Dagostin *et al.* similarly observed elevated ΔH (95 kJ mol^{-1}) and ΔS ($320 \text{ kJ K}^{-1} \cdot \text{mol}^{-1}$) values during soybean oil recovery.³⁰ Furthermore, Meziane and Kadi reported a ΔH of $12.91 \text{ kJ mol}^{-1}$ for olive pomace oil extraction with hexane, indicating substantial energy requirements. Collectively, these investigations indicate that lipid extraction is generally endothermic and thermodynamically favored at higher temperatures due to accelerated diffusion and enhanced solute–solvent interactions.

CONCLUSION

This investigation evaluated olive pomace oil recovery using limonene, specifically examining temperature's influence on yield, kinetics, and thermodynamic properties. The findings indicated that oil yields correlate positively with both extraction time and temperature. The process follows a biphasic progression: an initial rapid “washing” stage characterized by surface oil removal, followed by a slower diffusion-limited phase. Statistical evaluation of various kinetic models revealed that the Patricelli model provided the most accurate representation of experimental observations. This was rigorously validated by high correlation coefficients ($R^2 > 0.99$) and low error values (χ^2 and MSE), confirming its suitability for predicting extraction behavior.

Calculated mass transfer coefficients confirmed that the washing mechanism dominates the early extraction stages, especially at lower temperatures, whereas both washing and diffusion rates enhance near-linearly with thermal increase. The determined activation energy ($16.98 \text{ kJ mol}^{-1}$) is relatively low, indicating a physical extraction process that is diffusion-limited and thermally accessible – essential

characteristics for industrial scalability. Thermodynamic evaluation yielded negative Gibbs energy changes (ΔG), confirming process spontaneity which intensifies at higher temperatures. The extraction was identified as endothermic ($\Delta H = 1.68 \text{ kJ}\cdot\text{mol}^{-1}$) and characterized by a positive entropy change ($\Delta S = 17.39 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$), suggesting increased molecular disorder as lipids transition from the solid matrix into the solvent phase. These parameters collectively validate limonene as an efficient, thermodynamically favorable green alternative for the sustainable recovery of residual olive oil. In summary, limonene demonstrates efficacy as an environmentally benign solvent for olive pomace oil recovery, achieving performance comparable to hexane while adhering to green chemistry principles. The process is thermodynamically favorable and kinetically predictable, exhibiting significant potential for sustainable industrial integration as a viable alternative to conventional, petroleum-based extraction methods.

ИЗВОД

ЗЕЛЕНА ЕКСТРАКЦИЈА И ВАЛОРИЗАЦИЈА КОМИНЕ МАСЛИНЕ ПРИМЕНОМ
ЛИМОНЕНА: ПРИСТУП ЗАСНОВАН НА КИНЕТИЧКОМ МОДЕЛОВАЊУ И
ТЕРМОДИНАМИЧКОЈ АНАЛИЗИ

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У овом раду извршено је експериментано испитивање екстракције уља из комине маслине применом лимонена као зеленог растварача, са посебним нагласком на утицај температуре на принос, кинетику и термодинамику процеса. Резултати показују да се искоришћење уља повећава са временом и температуром, пратећи двостепени механизам: брзу фазу испирања, којом доминира уклањање површинског уља, и спорију фазу контролисану дифузијом. Кинетичко моделовање је показало да Патричелијев модел најбоље описује процес ($R^2 > 0,99$), док коефицијенти преноса масе потврђују доминацију механизма испирања на нижим температурама. Релативно ниска енергија активације ($16,98 \text{ kJ}\cdot\text{mol}^{-1}$) указује на то да је процес ограничен дифузијом, који је термички приступачан и погодан за индустријску примену. Термодинамички параметри потврђују овакво тумачење: негативне вредности промене Гибсове енергије потврђују спонтаност процеса, док ендотермна промена енталпије ($\Delta H = 1,68 \text{ kJ}\cdot\text{mol}^{-1}$) и позитивна промена ентропије ($\Delta S = 17,39 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$) указују на повећање молекулског не reda током екстракције. У целини посматрано, лимонен показује високу ефикасност и одрживост, представљајући одрживу алтернативу хексану у складу са принципима зелене хемије.

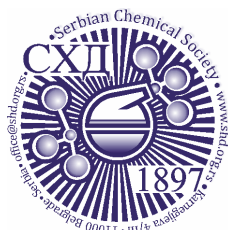
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Phenolic compounds adsorption from olive oil industry effluent using experimental design methodology: Screening and central composite design optimization

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Abstract: The experimental design methodology was investigated to model and optimize the adsorption process for removing phenolic compounds (PC) from olive mill wastewater (OMW) using magnesium–aluminum layered double hydroxide (LDH). The LDH powders were synthesized by the co-precipitation method. The structural, textural and morphological characterizations were performed. To evaluate quickly and effectively the effects of five parameters (initial PC content, contact time, solid/liquid ratio, initial pH and temperature) on the adsorption efficiency, a Hadamard matrix was employed for screening. Subsequently, a central composite design was utilized to optimize the adsorption process based on four key parameters. The correlation coefficient for the polynomial model was found to be 94 %. Predicted values generated from the response function matched the experimental data closely, indicating a good agreement. Under the selected optimal conditions, a maximum PC removal efficiency of 80.85 % was achieved. The reusability of the regenerated LDH by calcination at 500 °C in the adsorption process was assessed over four consecutive runs under the selected optimal conditions. The removal percentages of PC and chemical oxygen demand indicated that calcined LDH could be a viable alternative for treating OMW.

Keywords: olive mill wastewater; magnesium-aluminum layered double hydroxide; chemical oxygen demand; Hadamard matrix; regeneration.

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INTRODUCTION

The olive oil industry is constantly innovating to improve the oil production process in Mediterranean countries. Paradoxically, this industry generates by-products with a high environmental impact, in particular olive mill wastewater (OMW).¹ OMW constitutes the residual liquid effluent from the two- or three-phase extraction process, which is characterized by a high pollution load due to its high content of biodegradable organic matter, toxic phenolic compounds, suspended solids and fatty compounds.² Every year, olive-growing countries produce large quantities of this effluent. In Algeria, the production of 30,000 tons of olive oil generates 105,000 tons of OMW.³

The polluting activity of OMW is linked with its high organic load represented especially by an important phenol compound content, a very high chemical oxygen demand (*COD*), an equally high biological oxygen demand *BOD*₅ and an acid pH.⁴

As a source of harmful pollution to the environment, OMW must be treated to remove the phenolic content fraction before being discharged in receiving water bodies or soils. Among the various studied approaches proposed for treating this effluent, chemical processes offer effective solutions for reducing its toxicity. Techniques such as advanced oxidation (Fenton, electro-oxidation, ozonation, *etc.*),^{5,6} coagulation–flocculation,⁷ adsorption on activated materials⁸ and co-precipitation⁹ were used to degrade or extract the PC responsible of OMW's pollutant load.

The adsorption technique is a promising technology widely used for treating various types and removing pollution from the environment. Its advantages include simplicity, short treatment, ease of operation and handling, high efficiency and the ability to regenerate adsorbents.^{10,11}

Activated carbon was considered as a primary adsorbent for removing organic and inorganic pollutants from wastewater due to its high specific surface area. However, the high costs of manufacturing and regenerating after saturation limit its widespread use. To find alternatives, several studies have explored inorganic adsorbents that are more accessible and cost-effective, offering increased regenerability and recyclability, which is crucial for sustainable large-scale applications for treating wastewater, including OMW. In this sense, Yahiaoui *et al.*⁹ studied the co-precipitation of PC and organic matter from OMW using synthetic hydroxyapatite as adsorbent, achieving reduction rates of 87.30 % for PC and 76.30 % for *COD*. Additionally, Beccari *et al.*¹² demonstrated that bentonites can reduce the *COD* of OMW by approximately 61.6 % at a pH of 6.5. Other researchers applied this adsorption process to Fes clays and, after optimizing the treatment system, achieved a *COD* reduction rate of nearly 86 %.¹³

Lamellar double hydroxides, whether in their original form or after thermal decomposition, represent a unique family of clay materials characterized by distinct chemical and physicochemical properties, such as varied composition, easy

synthesis, low cost, low toxicity and high specific surface area. The general formula of the LDH materials is $[M_{1-x}M'_x(OH)_2]^{x+}(X)_{x/m} \cdot nH_2O$, where M and M' are bivalent and trivalent cations, respectively, with similar radii, and X is the interlayer anion. The cations in the layer can be changed using a wide range of main group cations (Mg and Al) or transition metal cations (V, Zn, Cr, Mn, Fe, Co, Ni,...). All these materials, having various compositions, share typical common characteristics: layered structure and the formation of mixed-metal oxides after thermal treatment.¹⁴ Moreover, the "memory effect" is a very interesting property of this kind of compound that is based on the ability of the oxides derived from the calcination of LDH in reconstructing, the layer structure when rehydrated in the presence of anions.¹⁵ Consequently, the literature has documented numerous studies related to their applications in industrial, medical, and environmental fields.^{16,17}

Due to their high specific surface area and the flexibility of their inter-filament space, LDHs can effectively trap negatively charged species through surface adsorption and anion exchange, such as nitrate, phosphate, and chromate anions,¹⁸ as well as toxic molecules like agricultural pesticides¹⁹ from wastewater. Several researchers have utilized these compounds as adsorbents for PC in OMW.^{20,21} The obtained results showed that the adsorption capacity is significantly influenced by the nature and structure of the LDHs used. A study conducted by Zhang *et al.*²² demonstrated that aluminum- and magnesium-based LDHs (Mg–Al LDHs) have a strong affinity for anionic compounds due to their exceptional stability and high positive charge density. Their structure is similar to that of the natural LDH known as brucite, making them environmentally friendly, non-toxic and cost-effective.²³ Calcining these LDHs at temperatures between 400 and 600 °C produces mixed oxides with high porosity and specific surface area. Additionally, the memory effect resulting from hydration enhances their adsorption capacity for both organic and inorganic compounds.¹⁵

These interesting results led us to investigate and optimize the adsorption efficiency of Mg–Al LDH, and its calcined product at 500 °C (LDH-500), in reducing the load of PC from OMW using experimental design methodology.

The experimental design approach is a powerful tool for understanding and optimizing experimental parameters by combining multiple variables in a single study; rather than conducting separate studies for each one, the number of required trials is significantly decreased. This approach allows for the extraction of more information with less experimentation, ultimately leading to reduced costs.²⁴

The centred composite design (CCD) is one of the methods used in response surface methodology (RSM) that allows for the study of a phenomenon across a broad experimental range. This is achieved by including axial points, which enhances the reliability and accuracy of the modeling, especially when interaction and quadratic effects are present, all while minimizing the number of required experiments.²⁴

This study aims to optimize the adsorption process for the removal of PC from OMW by using experimental design. Consequently, an empirical relationship (a second-degree polynomial) was established using CCD to calculate the optimal rate of PC removal accurately. The reusability of the LDH was also investigated.

EXPERIMENTAL

Fresh OMW used in this study was obtained by crushing Chemlal olives harvested during the 2024/2025 olive growing season. This vegetation water was extracted using a continuous system at a modern oil mill located in Tizi-Ouzou, northern Algeria.

To remove solids and fats, the raw OMW was first filtered and then centrifuged at 5000 rpm for 20 min, to eliminate suspended matter. The mixture was further decanted using a separating funnel to remove any remaining fat. The pretreated and homogenized OMW was stored in plastic bottles in a freezer at $-5\text{ }^{\circ}\text{C}$ until needed. Table I presents the main characteristics of the effluent.

TABLE I. Physicochemical characteristics of OMW

Parameter	Unit	Value
pH	–	4.96
Conductivity	$\text{mS}\cdot\text{cm}^{-1}$ at $25\text{ }^{\circ}\text{C}$	16.42
Turbidity	NTU	109
Dry matter content	$\text{g}\cdot\text{L}^{-1}$	49.25
Water content	%	95.02
Ashes	$\text{g}\cdot\text{L}^{-1}$	5.75
Volatile matter content	$\text{g}\cdot\text{L}^{-1}$	43.50
Chemical oxygen demand (COD)	$\text{gO}_2\cdot\text{L}^{-1}$	167
PC content	$\text{g}\cdot\text{L}^{-1}$	4.21

The measured chemical oxygen demand (COD) of the crude OMW was $167\text{ gO}_2\cdot\text{L}^{-1}$, indicating a high concentration of organic matter, particularly PC ($4.21\text{ g}\cdot\text{L}^{-1}$). This value is significantly higher than those reported in the literature by Yahiaoui *et al.*⁹ and Lateb *et al.*⁷, which recorded COD values of 86 and $131\text{ gO}_2\cdot\text{L}^{-1}$, respectively. The discrepancy can be attributed to differences in the nature and/or method of olive crushing used during oil extraction.

LDH with chloride in the interlayer particles was prepared by a direct co-precipitation process at room temperature following the procedure described previously by Ulibarri *et al.*²⁵ Briefly, A solution containing MgCl_2 ($0.25\text{ mol}\cdot\text{L}^{-1}$) and AlCl_3 ($0.125\text{ mol}\cdot\text{L}^{-1}$) was added dropwise under vigorous stirring at room temperature to NaOH solution at pH 10. The suspension was kept at this pH by adding $2\text{ mol}\cdot\text{L}^{-1}$ Na_2CO_3 solution. After complete addition, the resulting mixture was aged for 24 h under thermal treatment at $80\text{ }^{\circ}\text{C}$. The obtained precipitate was washed several times with distilled water, then recovered by vacuum filtration through a porcelain funnel containing a filter cloth. The obtained compound was dried in an oven at $70\text{ }^{\circ}\text{C}$ for 24 h. The prepared LDH was crushed, and sieved to have a uniform particle size and calcined at $500\text{ }^{\circ}\text{C}$ in an oven for 4 h, to improve the structural properties and those of porous exchange. The final compound is denoted LDH-500.

Characterization

The surface morphology of the synthesized LDH and LDH-500 was performed using a scanning electron microscope (SEM) (Philips ESEM XL30 with tungsten filament). The

elemental composition of the powder's surface was analyzed by energy dispersive spectroscopy (EDS). The specific surface area, volume, and mean pore diameter of the powder particles were measured through a nitrogen physisorption at -196°C using a Quantachrome Nova 2000e apparatus. The specific surface area was determined using the Brunauer–Emmet–Teller (BET) method; while the average pore volume was calculated using the Barrett–Joyner–Halenda (BJH) method.

The crystalline structure was analyzed *via* X-ray diffraction (Panalytical Empyrean X-ray diffractometer with $\text{CuK}\alpha$ (1.5406 Å) radiation at 45 kV) over a 2θ range from 0 to 80° . The synthesized particles were also characterized by Raman spectroscopy (spectrometer from Renishaw) using a visible laser with a wavelength of 632.8 nm.

The infrared spectroscopic analysis was conducted using a Shimadzu brand FTIR8400 Fourier transform spectrophotometer in the wavenumber range of $400\text{--}4000\text{ cm}^{-1}$ to identify the functional groups present in the products.

Sorption experiments

Preliminary tests were performed to identify the most effective adsorbent. Specifically, we investigated the batch adsorption of PC from OMW using LDH and LDH-500 over different time intervals. A mass of 0.5 g of each adsorbent was added to 25 mL of OMW, and the mixture was continuously stirred at 300 rpm for contact times ranging from 5 to 120 min.

Sorption experiments for PC were conducted in 200 mL glass beakers using two doses (1 g and 10 g) of LDH-500 mixed with 100 mL of OMW at varying concentrations of PC (1.40 and $2.80\text{ g}\cdot\text{L}^{-1}$). The pH of the solutions was adjusted to 7 and 12 by adding a 2 M NaOH solution. The mixture was continuously stirred at 300 rpm for 5 and 90 min at temperatures of 25 and 45°C . Once the designated contact time was reached, the suspension was centrifuged at 5000 rpm for 10 min. The recovered supernatant was analyzed for PC content, $\text{g}\cdot\text{L}^{-1}$ by the Folin–Ciocalteu colorimetric method using gallic acid for calibration, as described by Macheix *et al.*²⁶ The analysis were expressed as gallic acid equivalents, with $R^2 = 0.996$.

The percentage removal R , %, of PC was calculated using the following equation:

$$R = 100 \frac{C_0 - C_f}{C_0} \quad (1)$$

C_0 and C_f , $\text{g}\cdot\text{L}^{-1}$, represent the initial and final concentrations of the PC, respectively.

A study was conducted using experimental design methodology (EDM) to quickly and accurately identify the factors that significantly affect the PC removal rate. The process began with screening the factors, followed by optimization. This step aims to identify the factors that significantly influence the removal rate of PC from OMW. To estimate the weight of each factor, a Hadamard matrix was implemented.²⁷ Table II presents the factors considered and their corresponding experimental domains.

TABLE II. Factors and their levels in experimental design

Factor	Unit	Symbol	Code	Level (–)	Level (+)
Contact time	min	τ	X_1	5	90
Solid/liquid ratio (S/L ratio)	$\text{g}\cdot\text{L}^{-1}$	S/L	X_2	1	10
pH	–	pH	X_3	7	12
Temperature	$^{\circ}\text{C}$	t	X_4	25	45
Initial PC content	$\text{g}\cdot\text{L}^{-1}$	C	X_5	1.40	2.80

In screening factors with a Hadamard matrix, the number of experiments, N , must be a multiple of 4 and should satisfy the condition $N \geq k + 1$. In our study, with $k = 5$, the minimum number of experiments required was $N = 8$. However, this experimental design didn't provide enough degrees of freedom to accurately calculate the experimental variance and assess with precision the significance of the factors' effects. To resolve this issue, we doubled the design to $N = 16$ experiments.^{24,28} Table III presents the experimental matrix using both coded and real variables. The response being investigated is the PC removal percentage, denoted as R .

TABLE III. Design matrix of screening and results obtained for the studied response (R)

Run	Code variables					Real variables					$R / \%$
	X_1	X_2	X_3	X_4	X_5	τ / min	S/L	pH	$t / ^\circ\text{C}$	$C / \text{g}\cdot\text{L}^{-1}$	
1	1	1	1	-1	1	90	10	12	25	2.80	83.45
2	1	1	1	-1	1	90	10	12	25	2.80	79.14
3	-1	1	1	1	-1	5	10	12	45	1.40	33.81
4	-1	1	1	1	-1	5	10	12	45	1.40	25.18
5	-1	-1	1	1	1	5	1	12	45	2.80	76.26
6	-1	-1	1	1	1	5	1	12	45	2.80	74.10
7	1	-1	-1	1	1	90	1	7	45	2.80	56.47
8	1	-1	-1	1	1	90	1	7	45	2.80	54.68
9	-1	1	-1	-1	1	5	10	7	25	2.80	67.27
10	-1	1	-1	-1	1	5	10	7	25	2.80	73.02
11	1	-1	1	-1	-1	90	1	12	25	1.40	49.64
12	1	-1	1	-1	-1	90	1	12	25	1.40	43.17
13	1	1	-1	1	-1	90	10	7	45	1.40	10.43
14	1	1	-1	1	-1	90	10	7	45	1.40	15.11
15	-1	-1	-1	-1	-1	5	1	7	25	1.40	33.09
16	-1	-1	-1	-1	-1	5	1	7	25	1.40	39.92

The four parameters used for this modeling were selected based on the results of the screening experiments for the central composite design: S/L , pH, temperature and initial PC content, referred to coded variables X_2 , X_3 , X_4 and X_5 , respectively. A centered composite matrix with four factors was employed to develop the mathematical model, enabling the calculation of response values throughout the experimental domain.²⁴ The experimental range of factors was consistent with that established in the screening stage (Table II). This matrix comprises $N = 34$ experiments, which are divided into:

$N_f = 2^4 = 16$ factorial points;

$N_a = 2 \times 4 = 8$ axial points;

$N_0 = 5$ central points (to determine the experimental variance);

$N_t = 5$ test points (to check the validity of the postulated model);

The postulated mathematical model, which is a polynomial of the second degree, is given by the following equation:

$$R = a_0 + a_2X_2 + a_3X_3 + a_4X_4 + a_5X_5 + a_{22}X_2^2 + a_{33}X_3^2 + a_{44}X_4^2 + a_{55}X_5^2 + a_{23}X_2X_3 + a_{42}X_2X_4 + a_{25}X_2X_5 + a_{34}X_3X_4 + a_{35}X_3X_5 + a_{45}X_4X_5 \quad (2)$$

where X_2 , X_3 , X_4 and X_5 represent the coded variables of the system; a_0 , a_i ($i = 2,3,4,5$), a_{ii} ($i = 2,3,4,5$) and a_{ij} ($i = 2,3,4; j = 3,4,5$) are the regression coefficients for intercept, linear,

quadratic and interaction terms, respectively. Table IV displays the experimental matrix, including both coded and real values as well as the response values for all experiments. The experimental data were used to estimate the model coefficients *via* the least squares method with Nemrodw software (version 2007.3).²⁹

TABLE IV. Central composite design and the resulting experimental results obtained for the response (*R*)

Run	Coded variables				Real variables				<i>R</i> / %
	X_2	X_3	X_4	X_5	<i>S/L</i>	pH	<i>t</i> / °C	<i>C</i> / g·L ⁻¹	
1	-1	-1	-1	-1	1.00	7.00	25.00	1.40	77.70
2	+1	-1	-1	-1	10.00	7.00	25.00	1.40	78.42
3	-1	+1	-1	-1	1.00	12.00	25.00	1.40	79.86
4	+1	+1	-1	-1	10.00	12.00	25.00	1.40	79.14
5	-1	-1	+1	-1	1.00	7.00	45.00	1.40	78.10
6	+1	-1	+1	-1	10.00	7.00	45.00	1.40	76.26
7	-1	+1	+1	-1	1.00	12.00	45.00	1.40	78.42
8	+1	+1	+1	-1	10.00	12.00	45.00	1.40	79.86
9	-1	-1	-1	+1	1.00	7.00	25.00	2.80	44.60
10	+1	-1	-1	+1	10.00	7.00	25.00	2.80	43.88
11	-1	+1	-1	+1	1.00	12.00	25.00	2.80	42.25
12	+1	+1	-1	+1	10.00	12.00	25.00	2.80	49.76
13	-1	-1	+1	+1	1.00	7.00	45.00	2.80	37.41
14	+1	-1	+1	+1	10.00	7.00	45.00	2.80	41.01
15	-1	+1	+1	+1	1.00	12.00	45.00	2.80	41.01
16	+1	+1	+1	+1	10.00	12.00	45.00	2.80	42.45
17	-1	0	0	0	1.00	9.50	35.00	2.10	59.71
18	+1	0	0	0	10.00	9.50	35.00	2.10	56.83
19	0	-1	0	0	5.50	7.00	35.00	2.10	70.75
20	0	+1	0	0	5.50	12.00	35.00	2.10	64.62
21	0	0	-1	0	5.50	9.50	25.00	2.10	64.62
22	0	0	+1	0	5.50	9.50	45.00	2.10	57.11
23	0	0	0	-1	5.50	9.50	35.00	1.40	66.46
24	0	0	0	+1	5.50	9.50	35.00	2.80	47.77
25	0	0	0	0	5.50	9.50	35.00	2.10	59.00
26	0	0	0	0	5.50	9.50	35.00	2.10	59.00
27	0	0	0	0	5.50	9.50	35.00	2.10	59.71
28	0	0	0	0	5.50	9.50	35.00	2.10	52.52
29	0	0	0	0	5.50	9.50	35.00	2.10	57.57
30	-0.40	-0.23	-0.16	-0.13	3.72	8.93	33.39	2.01	58.64
31	+0.40	-0.23	-0.16	-0.13	7.28	8.93	33.39	2.01	59.26
32	0	+0.46	-0.16	-0.13	5.50	10.64	33.39	2.01	61.15
33	0	0	+0.48	-0.13	5.50	9.50	39.84	2.01	51.14
34	0	0	0	0.50	5.50	9.50	35.00	2.45	49.61

RESULTS AND DISCUSSION

Fig. 1 displays SEM micrographs and EDS spectra of LDH powders synthesized before (Fig. 1a–c) and after (Fig. 1d–f) calcinations at 500 °C. The samples exhibit irregular morphology, with grains stacked in layers, indicating the formation of a lamellar structure. As shown in Fig. 1d, the flat stacked structure was maintained after the calcination process. However, a reduction in particle size was observed and the resulting particles formed agglomerates. The EDS spectra reveal the presence of O, Al, Mg, Cl and C. Compared to LDH, the LDH-500 sample shows a slight decrease in Cl, Na and C content probably due to the rinsing process for Cl and Na and desorption of carbon dioxide from the surface of the formed oxides for C content. The results of the elemental composition of the powder surface analysis were summarized in Table V.

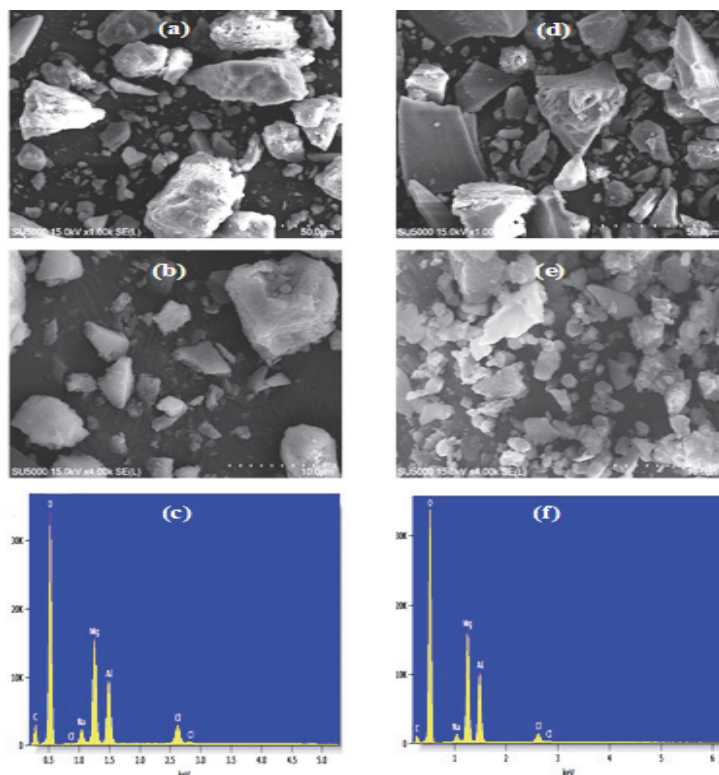


Fig. 1. SEM images and EDS spectra of: a–c) LDH and d–f) LDH-500 samples.

Nitrogen adsorption/desorption analysis was conducted on LDH and LDH-500 powders. The specific surface area was determined using the BET method, while pore size and volume were obtained through the BJH method. The results, including specific surface area, pore volume and mean pore diameter, are presented

in Table VI. The results indicate that the synthesized LDH is mesoporous, featuring a medium specific surface area and small pore diameters. For LDH-500, a slight increase in the average pore volume and an enlargement of the average pore diameter were observed, without affecting the specific surface area. These changes can be attributed to the development of more porous structures due to the formation of thermally stable oxide phases such as spinel, MgO and AlO, as well as likely the formation of grain boundaries within the agglomerates.

TABLE V. Quantitative results of LDH and LDH-500 powders (wt. %)

Element	Powder	
	LDH	LDH-500
O	63.34	63.29
Na	3.55	2.02
Mg	17.95	19.34
Al	11.67	13.70
Cl	3.49	1.66

TABLE VI. Textural properties of the LDHs

Powder	Specific area, $\text{m}^2 \cdot \text{g}^{-1}$	Average porous volume, $\text{cm}^3 \cdot \text{g}^{-1}$	Average pore diameter, nm
LDH	45.67	0.085	3.73
LDH-500	46.38	0.107	4.65

X-ray diffraction (XRD) analysis was performed on both the layered double hydroxide (LDH) and the LDH-500. Fig. 2 displays the corresponding diffraction patterns. Phase identification and diffraction peak indexing, conducted using HighScore-Plus software, reveal a predominant phase corresponding to dialuminum tetramagnesium dodecahydroxide trihydrate, with the chemical formula $\text{Mg}_4\text{Al}_2(\text{OH})_{12}\text{CO}_3 \cdot 3\text{H}_2\text{O}$, as referenced in the JCPDF database (98-017-2994). This phase crystallizes in a hexagonal lattice ($R3m$ symmetry), characteristic of double-layer hydroxides.

The characteristic peaks of LDHs are observed at low angles of 2θ of 11.81° and 23.53° , corresponding to the (003) and (006) planes, respectively. These peaks indicate the interlayer spacing of the material and illustrate the lamellar structure of LDHs. A high value of $d_{003} = 7.587 \text{ \AA}$, typical for hydrated carbonate LDH, confirms the presence of water molecules and carbonate anions (CO_3^{2-}) in the interlayer space of the structure.³⁰

Additionally, indexing reveals peaks corresponding to aluminum(II) oxide with a cubic structure (JCPDF 01-075-0278), where the main peak (200) is observed at 2θ of 31.86° , corresponding to an interlayer spacing of approximately $2.83 \text{ \AA}$. This phase may result from partial decomposition or impurities in the LDH material during synthesis.

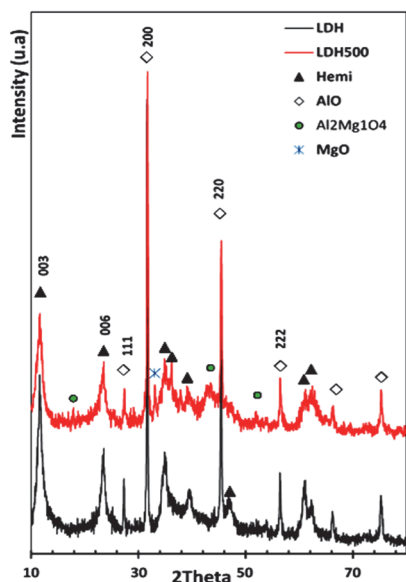


Fig. 2. X-Ray diffraction patterns of LDH and LDH-500 samples.

The presence of the hydrated LDH phase in both samples enhances the adsorption of PC, as the layered structure and hydroxylated surface provide numerous sites for ion exchange and hydrogen bonding interactions.³¹

The XRD pattern of LDH-500 shows additional peaks attributed to the formation of a spinel phase Al_2MgO_4 (JCPDF 98-009-6839) and magnesium oxide (JCPDF 98-016-2607). These phases appear after calcination at 500 °C, which induces the decomposition of the hydrated LDH phase and the recombination of the oxides.

It is important to note that the intensity of the characteristic peaks of the hydrated phases (LDH and AlO) decreases, indicating a partial loss of crystallinity and the thermochemical transformation of the material during heat treatment.

The Raman spectra obtained for the samples are illustrated in Fig. 3. They reveal several characteristic bands corresponding to the phase identified by XRD as $\text{Mg}_4\text{Al}_2(\text{OH})_{12}\text{CO}_3 \cdot 3\text{H}_2\text{O}$. The intense band observed around 1060 cm^{-1} for LDH and the band at approximately 1057 cm^{-1} for LDH-500 correspond to the symmetric ν_1 stretching mode of the carbonate group intercalated between the layers. This is in good agreement with the values reported for similar carbonate hydrotalcites. Frost *et al.*³² report peaks between 1055 and 1086 cm^{-1} for carbonated LDHs, while Frederick *et al.*³³ identify two distinct bands at 1046 and 1062 cm^{-1} for natural quintinite. A clear band at 560 cm^{-1} can be attributed to M–O or M–OH vibrations in the octahedral layers, involving Mg–O and Al–O bonds.^{34,35} These studies systematically associate this spectral range ($540\text{--}560\text{ cm}^{-1}$) with the

vibrational modes of the hydroxyl network. Finally, the presence of a low-frequency mode at $150\text{--}155\text{ cm}^{-1}$, which is rarely discussed in the literature, can be interpreted as an M–O–M deformation vibration^{34–36} or as OH vibrations.³²

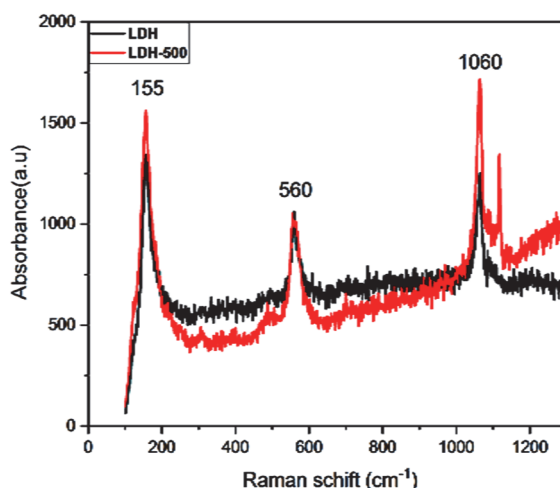


Fig. 3. Raman spectra of LDH and LDH-500 samples.

As shown in Fig. 4, the infrared spectra of the hydrotalcite samples exhibit characteristic bands of the double-lamellar hydroxide phase. In the uncalcined sample, the intense band at 3375 cm^{-1} , is attributed to O–H stretching vibrations of hydroxyl groups, water molecules within the lamellar structure, and physically adsorbed water.³⁷ The significant band around 1348 cm^{-1} is associated with the presence of carbonates in the interlayer galleries.³⁸ The bands observed around 947 , 783 and 551 cm^{-1} correspond to metal–oxygen stretching modes.²¹ Additionally, Luiz. *et al.*³⁹ attributed the band near 653 cm^{-1} to Mg–O or Al–O bonds. After calcination, a decrease in the intensity of most previously mentioned bands was observed. The reduction in intensity in the spectral region, corresponding to hydroxyl groups indicates dihydroxylation and the conversion of metal hydroxides to metal oxides.²¹ Additionally, the decrease in intensity of the band at 1348 cm^{-1} , associated with interlayer carbonates, can be attributed to the desorption of carbon dioxide from the surface of the formed oxides.⁴⁰ This result is consistent with that of EDS, XRD and Raman results.

The kinetic adsorption results shown in Fig. 5 reveal that calcined LDH-500 achieved the highest elimination rate of 70.40 % for PC within just 5 min. In contrast, LDH reached equilibrium after 60 min, with an elimination rate of 63.50 %. The higher adsorption capacity of LDH-500 can be attributed to its larger

porous surface area developed during thermal treatment, which promoted the formation of metal oxides.⁴¹ Additionally, the memory effect, which upon rehydration gave a native LDH with increased adsorption capacity.⁴²

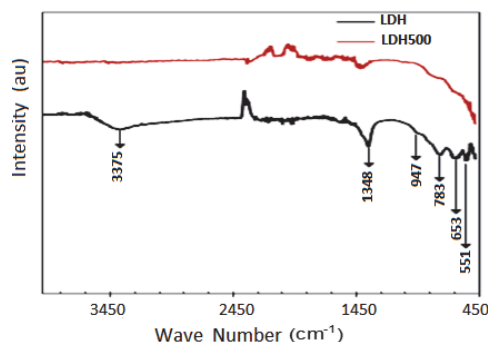


Fig. 4. FTIR spectra of LDH and LDH-500 samples.

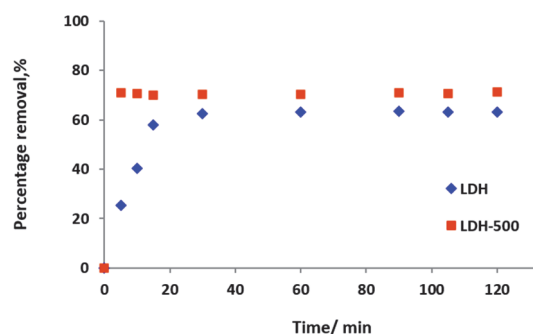


Fig. 5. Removal percentage of PC over time.

Referring to the literature data, particularly the research on LDHs, the rapid adsorption followed by a plateau observed in the case of LDH-500 indicates a two-step mechanism. This mechanism involves initial surface adsorption followed by a second step controlled by diffusion, which typically aligns with second-order or interparticle diffusion kinetic models.^{21,43,44}

Based on these findings, calcined LDH-500 was chosen for the subsequent phase focused on optimizing the adsorption process for PC using experimental designs.

The experimental values of the response R (Table III) were used in screening to determine the coefficients b_1 , b_2 , b_3 , b_4 and b_5 , which represent the weights associated to the variables τ , S/L , pH, t and C , respectively; b_0 is the intercept.

Using the Student's t experimental (t_{exp}) and the degrees of freedom (ddl), the significance level (%) was determined according to Student's t -distribution. The coefficients and other statistical parameters were calculated with Nemrodw software.²⁷ The results are presented in Table VII.

TABLE VII. Estimates and statistics of coefficients (screening); ^a – significant at the level of 95 %; ^b – significant at the level of 99.9 %; Standard deviation: 0.891

Name	Coefficient	Inflation factor	t_{exp}	Significance, %
b_0	50.921	–	57.13	< 0.01 ^b
b_1	–1.910	1.00	–2.14	5.8
b_2	–2.495	1.00	–2.80	1.88 ^a
b_3	7.173	1.00	8.05	< 0.01 ^b
b_4	–7.666	1.00	–8.60	< 0.01 ^b
b_5	19.627	1.00	22.02	< 0.01 ^b

It is established that an effect is considered significant if the significance level is below 5 %. The results presented in Table VII indicate that initial PC content, pH, *S/L* and temperature were the main factors influencing the response. However, the contact time had no significant effect ($p = 5.8$ %) on the PC removal. Fig. 6. presents the Pareto chart established to support these statistical results and showed the standardized effects in decreasing order as follows: initial PC content (76.24) > temperature (11.63) > pH (10.18) > *S/L* (1.23) > contact time (0.72), clearly indicating that contact time didn't influence the retention of PC by this material. Therefore, the contact time for the remainder of the study was fixed at its minimum level of 5 min.

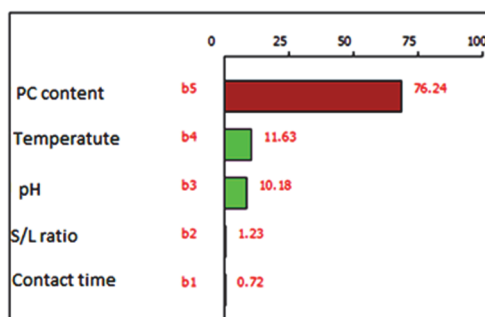


Fig. 6. Pareto chart displaying the standardized effects of factors (screening).

Before carrying out experiments, it is necessary to verify the quality of prediction given by the variance function and isovariance by rotation.

A variance function (d) is considered to provide an acceptable prediction if its maximum value, d_{max} , is less than or equal to unity $d_{\text{max}} \leq 1$, in the studied matrix, $d_{\text{max}} = 0.79$. Since this value is less than unity, any response predicted by the model within the experimental domain will have an accuracy that is at least equal to that obtained from actual experiments. Additionally, the isovariance by rotation was verified, indicating that the responses calculated by the postulated model had the same prediction error for all the points located at the same distance from the center of the studied domain (Fig. 7).

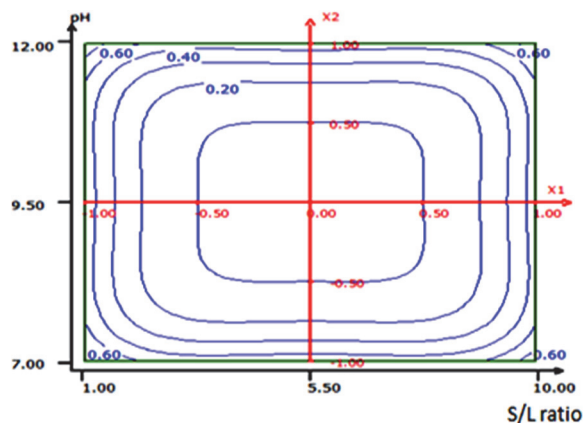


Fig. 7. Isovariance by rotation in the S/L – pH plane with: temperature = 35°C and $C = 2.10 \text{ g}\cdot\text{L}^{-1}$.

To establish the mathematical model that describes the relationship between the factors, a central composite design was applied in the experimental domain outlined in Table II. The experimental results for the response R , as shown in Table IV, were used to determine the 15 coefficients of the second-degree polynomial model, without the inclusion of checkpoints.

The coefficient of determination of 0.95 and the adjusted determination coefficient of 0.91 indicate that the model fits well. The postulated model, expressed in coded variables, is represented by the following equation:

$$R = 59.21 + 0.51X_3 - 16.89X_5 + 7.10X_3^2 \quad (3)$$

To validate the model's accuracy, we carried out experiments on test points located as far as possible from the experimental points. The results of statistical tests performed at these points indicated clearly that the differences between the experimental and predicted responses $R_{\text{exp}} - R_{\text{the}}$ for each test point fell within the range of experimental error, meaning that they were not statistically significant according to the t -test. Additionally, the coefficient of determination value of 0.94 and the adjusted coefficient of determination value of 0.90 indicated that the model is significant.

To enhance the previous model, the response values obtained from checkpoints were included in the coefficient calculation. The refined model was expressed as follows:

$$R = 58.07 + 0.52X_3 - 16.79X_5 + 7.57X_3^2 \quad (4)$$

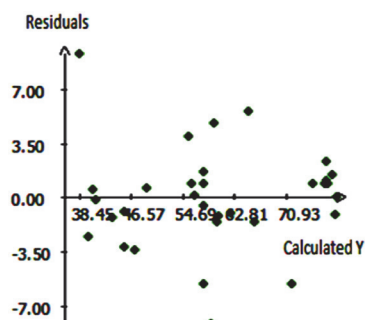
Table VIII compares the coefficients of the two models. Most effects remain unchanged after including the test points; however, slight differences have been observed for the intercept effect a_0 and the quadratic effects a_{22} , a_{33} and a_{55} . A

change in sign has been noted for the a_{44} effect; this discrepancy is likely due which does not significantly impact predictions or optimization. All these non-significant variations justified the better refining of the model using test points.

TABLE VIII. Model coefficients with and without test points

Coefficient	Without test points	Whit test points
a_0	59.21	58.07
a_2	0.48	0.48
a_3	0.51	0.52
a_4	-1.59	-1.77
a_5	-16.89	-16.79
a_{22}	-2.32	-1.88
a_{33}	7.10	7.57
a_{44}	0.28	-0.07
a_{55}	-3.47	-2.83
a_{23}	0.49	0.49
a_{24}	-0.13	-0.14
a_{25}	0.16	0.16
a_{34}	0.76	0.76
a_{35}	0.11	0.11
a_{45}	-1.01	-0.98

Fig. 8 illustrates that the residuals are randomly distributed around zero, showing no discernible pattern. This confirms the validity of the model and indicates a strong agreement between the predicted and the experimental response values.

Fig. 8. Residuals distribution according to the calculated response R .

Furthermore, the variance analysis results applied to the refined model (Table IX) indicated that the probability significance of the risk was greater than 5 %. However, the main effect of the regression was significant p -value < 0.05 ; therefore, we concluded that the proposed empirical model was suitable for predicting the removal of PC from OMW.

Response surface methodology (RSM) and the desirability function were combined to identify the optimal values of the process variables for maximum PC removal, based on the model generated from the experimental data. The optimal conditions and maximum response zone was pinpointed using RSM, while the desirability function provided precise values for these parameters²⁴.

TABLE IX. Variance analysis results; ^b – significant at the level of 99.9 %

Source of variation	Sum of squares	Degrees of freedom	Mean square	<i>F</i> ratio	Significance, %
Regression	5468.30	14	390.59	21.617	< 0.01 ^b
Residuals	343.30	19	18.07		
Lack-of-fit	309.13	15	20.61	2.412	20.4
Pure error	34.17	4	8.54		
Total	5811.60	33			

Fig. 9a–f show the 2D contour plots and the three-dimensional (3D) response surfaces plots which play a crucial role in demonstrating the relationship between independent variables and their corresponding responses while maintaining a variable at the zero-level. Fig. 9 a and b illustrates a significant interaction between pH and initial PC concentration. The percentage reduction increases with pH, indicating a positive quadratic effect on the response, while it decreases significantly with initial concentration. The optimal region was found at high pH and low *C* values, peaking at around pH 12 and *C* of 1.4 g·L⁻¹. The other response surfaces in 9 c and d and 9e and f illustrate the effects of temperature and *S/L*, which result in only slight variations in response within the studied range. Consequently, these parameters were maintained at their central levels: temperature at 35 °C and *S/L* at 5.5 g·L⁻¹. The percentage removal achieved was 82.40 %.

Desirability function is a widely used method. The values of this function (*d_i*) range from 0 to 1. A desirability of 0, referred to as “elementary desirability”, indicates an unacceptable solution for the selected objective, while a desirability of 1 signifies maximum performance, meaning no further improvement is possible.⁴⁵ In our study, the aim was to maximize the removal percentage of PC to achieve a target desirability of 100 %.

The desirability function applied to the refined model indicated that the maximum theoretical value of PC removal was 80.85 % reached at pH 12, *C* 1.4 g·L⁻¹, *S/L* 5.58 g·L⁻¹ and temperature 35.58 °C; these results align with those obtained using the RMS. To validate the model, a test was carried out by setting the operating parameters at their optimal values; the laboratory findings yielded 80.60 ± ±0.44 %, which was quite close to the predicted optimal value. The difference between the experimental and the predicted PC removal was in the range of 5 %, confirming the validity of the model.

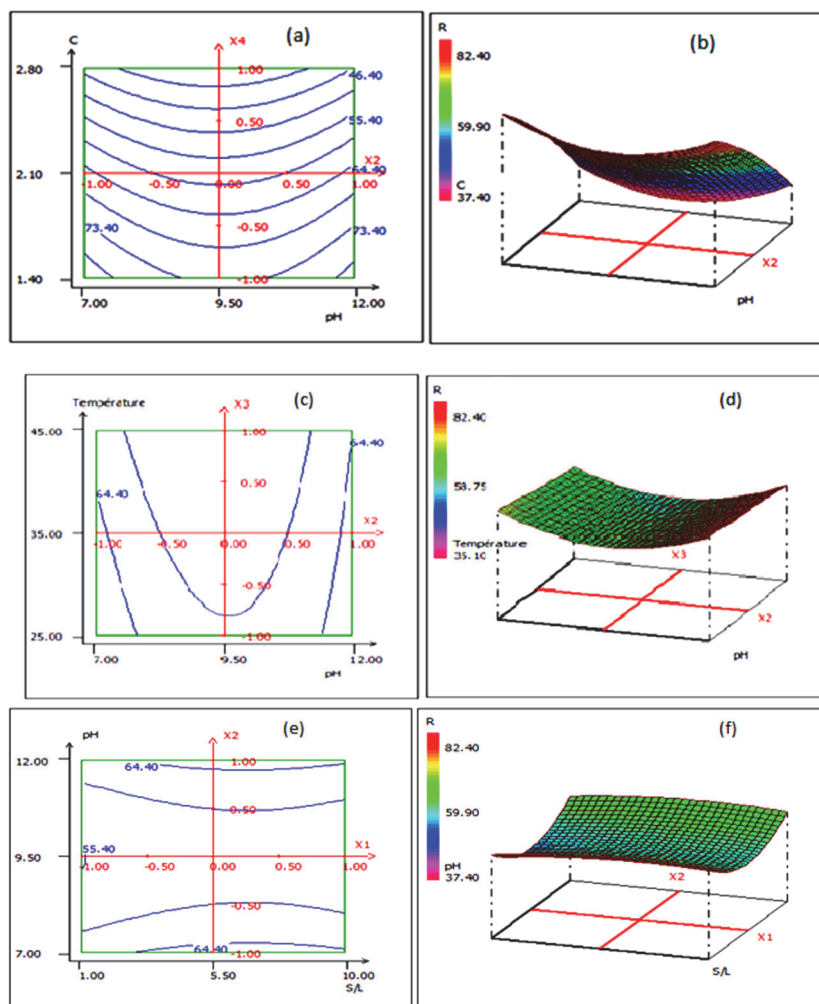


Fig. 9. The 2D contour plot (a,c,e) and the 3D surface plot (b,d,f); a,b) interaction effect of pH and C on PC removal, $t = 35\text{ }^{\circ}\text{C}$ and $S/L = 5.5\text{ g}\cdot\text{L}^{-1}$; c,d) interaction effect of pH and temperature on PC removal, $C = 2.5\text{ g}\cdot\text{L}^{-1}$ and $S/L = 5.5\text{ g}\cdot\text{L}^{-1}$; interaction effect of pH and S/L ratio on PC removal, $t = 35\text{ }^{\circ}\text{C}$ and $C = 2.1\text{ g}\cdot\text{L}^{-1}$.

Table X summarizes the adsorption efficiency of various adsorbents for the removal of CP from OMW in recent years. The results indicate that the adsorption capacity of Mg–Al LDH (500 $^{\circ}\text{C}$) powder, studied in this work, is relatively high compared to other adsorbents reported in the literature, such as Zn–Al LDH (500 $^{\circ}\text{C}$), polymeric resins, zeolite, clay soil and bentonite. This suggests that Mg–Al LDH is a favorable material for CP removal from aqueous solutions. Additionally,

its adsorption capacity is comparable to that of other adsorbents like hydroxyapatite, silicas and activated carbons, highlighting its potential as an effective alternative for treating liquid effluents.

Table X. Capacities of different adsorbents used for PC removal from OMW

Adsorbent	Conditions	Efficiency, %	Reference
Zn-Al LDH (450 °C)	Batch experiment, shaking, 25 °C, S/L 1.25 mass ratio, 24 h, natural pH sorbent/sorbate	73	De Martino <i>et al.</i> ²⁰
Activated carbon	Batch experiment, shaking, 25–27 °C, adsorbent dosage 0.45 g·L ⁻¹	87	Baransi <i>et al.</i> ⁴⁶
Activated carbon	Batch experiment, 100–450 rpm, 10–50 °C, pH 1.0–10.0, 0–30 min, adsorbent dosage 5–50 g·L ⁻¹	98	Bouharat <i>et al.</i> ⁴⁷
clay soil, bentonite and zeolite	Continuous experiment, adsorbent dosage 67 g·L ⁻¹	67 for clay soil, 29 for bentonite and 37 for zeolite	Santi <i>et al.</i> ⁴⁸
Hydroxyapatite	Batch experiments, 200 rpm, 25 °C, 30 min, pH 12, adsorbent dosage 10 g·L ⁻¹	87	Yahiaoui <i>et al.</i> ⁹
Polymeric resins	Batch experiment, 200–1000 rpm, 25 °C, 1 h, adsorbent dosage 10–200 g·L ⁻¹	75	Vavouraki <i>et al.</i> ⁴⁹
Silicas and activated carbon	Batch experiment, 150 rpm, 22 °C, 24 h, adsorbent dosage 60 g·L ⁻¹	87 for activated carbon, 67–75 for silicas	Yangui <i>et al.</i> ⁵⁰
Volcanic tuff, natural clay, activated charcoal and combinations	Batch experiment, shaking, 30 °C, 18–24 h, adsorbent dosage 40 g·L ⁻¹	21–80	Azzam ⁵¹
Mg–Al LDH (500 °C)	Batch experiments, 300 rpm, 5 min, pH 12, C 1.4 g·L ⁻¹ , S/L 5.58 g·L ⁻¹ , 35.58 °C	80.60±0.44	This work

The LDH recovered from treating OMW under the selected optimal conditions was first dried in an oven at 100 °C for 24 h. It was then calcined in a muffle furnace at 500 °C for 1 h. Following calcination, the treated LDH was reused for OMW treatment using the adsorption method under optimal conditions.

The reusability of LDH in the adsorption process was evaluated over four consecutive runs and the removal percentages of PC and COD were recorded. As shown in Fig. 10, the percentage of PC removal decreased slightly from 80.60 to 79.4 % at the third cycle, remaining stable during the fourth cycle. However, a gradual decline in COD was observed, decreasing from 76 % in the first cycle to 67 % in the second cycle, and further to 60 and 59 % in the third and fourth cycles, respectively. Furthermore, the error bars displayed on the graph indicate that the

experimental results are highly reproducible, demonstrating the stability of LDH during its repeated use for PC removal, in contrast of COD which shows significant error variability.

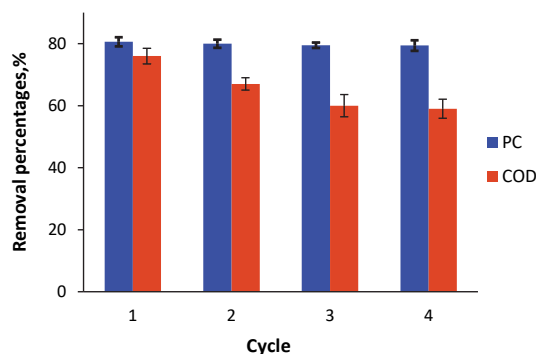


Fig. 10. Reusability of the LDH in the adsorption process.

The observed COD removal percentages after each decontamination cycle can be explained by the sorption of phenols and other polar compounds, such as sugars, organic acids and polyalcohols present in OMW.²⁰ Additionally, the decline in these reduction rates is likely attributable to the decrease in the LDH pore surface area after each calcination, which is in accordance with reported result.⁹

CONCLUSION

The optimization strategy by CCD of phenolic compounds removal for OMW treatment with the adsorption process was conducted successfully. The experimental conditions were optimized by considering the effects of some factors, namely *S/L*, pH, temperature and initial PC content on PC removal using a CCD. The results demonstrated that the predicted values were close to the experimental ones and the high R^2 value confirmed that the accuracy of the proposed polynomial model was acceptable. The regenerability and reusability of the LDH was confirmed in four successive adsorption batches without producing any new pollution. Therefore, this eco-friendly process is suitable and presents a promising technology for eliminating the organic pollution from wastewaters.

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ИЗВОД

АДСОРПЦИЈА ФЕНОЛНИХ ЈЕДИЊЕЊА ИЗ ОТПАДНИХ ВОДА НАСТАЛИХ У
ПРОИЗВОДЊИ МАСЛИНОВОГ УЉА ПРИМЕНОМ МЕТОДОЛОГИЈЕ
ЕКСПЕРИМЕНТАЛНОГ ДИЗАЈНА: СКРИНИНГ И ОПТИМИЗАЦИЈА ЦЕНТРАЛНИМ
КОМПОЗИТНИМ ДИЗАЈНОМ

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Методологија експерименталног дизајна примењена је за моделовање и оптимизацију процеса адсорпције у циљу уклањања фенолних једињења из отпадних вода насталих у производњи маслиновог уља, коришћењем двослојних магнезијум–алуминијум–хидроксида (LDH). Прашкasti LDH синтетисан је методом копреципитације. Извршена је његова структурна и морфолошка карактеризација. У циљу брзе и ефикасне процене утицаја пет процесних параметара (почетна концентрација фенолних једињења, време контакта, однос чврсте и течне фазе, почетна рН вредност и температура) на ефикасност адсорпције, примењена је Адамарова матрица. Након тога, за оптимизацију процеса адсорпције примењен је централни композитни дизајн, заснован на четири кључна процесна параметра. Коефицијент корелације полиномног модела износио је 94 %. Вредности предвиђене функцијом одзива биле су у доброј сагласности са експериментално добијеним резултатима, што потврђује адекватност развијеног модела. Под оптимално дефинисаним експерименталним условима постигнута је максимална ефикасност уклањања фенолних једињења од 80,85 %. Могућност поновне употребе регенерисаног LDH, добијеног калцинацијом на 500 °C, испитана је током четири узастопна циклуса адсорпције при утврђеним оптималним условима. Резултати који се односе на уклањања фенолних једињења као и на хемијску потрошњу кисеоника, показали су да калцинисани LDH представља перспективну алтернативу за пречишћавање отпадних вода из процеса производње маслиновог уља.

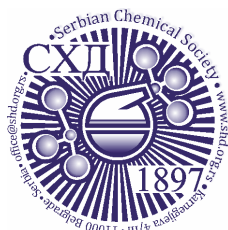
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The significance of chemistry curriculum for educational profiles in secondary medical vocational education

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Abstract: Investment in fundamental chemical research represents a key factor in the advancement of healthcare, which is increasingly facing the challenges of modern society. Nevertheless, the importance of chemistry in medical education is often insufficiently recognized, resulting in a weak connection between theoretical and practical aspects of instruction. Numerous studies highlight the need for a deeper integration of chemical content into vocational medical subjects. This paper analyses the attitudes of vocational subject teachers in secondary medical schools regarding the impact of chemistry curriculum reform on the quality and effectiveness of vocational instruction. The research was conducted using a descriptive method and an anonymous questionnaire on a sample of 73 teachers from medical schools across the Republic of Serbia. The findings indicate the importance of chemistry education for vocational medical training and suggest the need for improved curricular integration in secondary medical schools. These findings may serve as guidelines for the development of educational policies in the field of vocational education.

Keywords: chemical education; curriculum reform; teaching syllabus; medical profession; interdisciplinarity.

INTRODUCTION

In order for healthcare systems to adequately respond to the growing health-related challenges of modern society, continuous investment in fundamental chemical research is essential, as it represents a critical foundation for the future development of medicine.¹ Many aspects of medical practice rely on a basic conceptual understanding of chemistry, and scholars emphasize that the significance of chemical concepts in the healthcare profession is of vital importance for the advancement of society as a whole.² In secondary vocational schools with a healthcare focus, chemistry is often insufficiently integrated with vocational subjects,

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which limits students' ability to connect theoretical knowledge with professional practice. Curricula commonly treat chemistry as an isolated theoretical subject, lacking a functional connection with professional disciplines.

Students often struggle to recognize the relevance and applicability of chemical knowledge within the context of their future professional roles. The lack of interdisciplinary integration and practical application contributes to the perception of chemistry as an abstract and disconnected body of knowledge.³ As Hofstein and Mamlok-Naaman emphasize, "the effectiveness of science education is determined not only by the content delivered, but also by the extent to which students are able to connect that content with real-life and professional experiences."⁴ Contemporary didactic approaches, such as problem-based learning, contextualized instruction and laboratory work, demonstrate significant potential for increasing student motivation and fostering deeper understanding of scientific concepts.⁵ Practical applications of chemistry in healthcare contexts, including diagnostic procedures and sterilization processes, may contribute to more positive student attitudes and deeper cognitive engagement.⁶ Such teaching requires active collaboration between chemistry teachers and vocational subject teachers, clearly defined priorities and the use of methods that promote functional and interdisciplinary knowledge.⁷ As Fraser notes, teacher enthusiasm, instructional flexibility, and a supportive classroom atmosphere significantly influence students' perception of science, fostering curiosity, critical thinking and long-term motivation for learning chemistry.⁸

Curriculum reforms represent an important contextual factor influencing science teaching in vocational education. In the Republic of Serbia, the reform of secondary vocational education, introduced in 2014 through official national curriculum regulations⁹ was part of a broader educational modernization process aimed at aligning vocational education with labor market demands, improving the efficiency of schooling and optimizing the structure of subject curricula in accordance with European educational standards. The reform was implemented within the framework of national educational policy initiatives focused on increasing the relevance of vocational programs and improving student employability through curriculum rationalization. In this context, changes included a reduction in the number of chemistry teaching hours in secondary medical schools, as well as the revision and partial removal of certain chemistry contents specific to medical educational profiles. These modifications were intended to increase curricular efficiency but also raised concerns regarding the adequacy of students' chemical preparation for vocational subjects and professional practice.⁹

Although the study is grounded in the 2014 curriculum reform, available secondary sources indicate that chemistry education in secondary vocational schools in Serbia, including medical vocational programs, has not remained static in the period 2014–2025. A continuous reduction in the number of chemistry teaching

hours in secondary schools, particularly within vocational education, together with a decline in chemistry-related content and instructional emphasis, has been reported, leading to calls for increased support and greater consideration of teachers' views in the implementation of educational reforms.¹⁰ These changes are considered to have implications for students' foundational chemical knowledge and their preparedness for vocational and further academic studies.

In addition, the Institute for the Improvement of Education has published multiple amendments and updates to curricula for secondary vocational education in recent years, including programs in the field of chemistry, non-metals and graphic technologies.^{11,12} These updates indicate that curriculum development has been a continuous process rather than a single reform event.

Furthermore, this suggests that the prior chemical knowledge of students entering secondary medical schools may not be fully homogeneous across cohorts. Consequently, differences in curriculum content and teaching hours over time represent an important contextual factor that may influence teachers' perceptions of students' prior knowledge and its relevance for vocational subjects.

In secondary vocational education, chemistry represents an important foundation for understanding vocational subjects and clinical practice. However, a decline in student interest in chemistry, particularly in higher grades, has been widely observed and is often associated with insufficient connections between curriculum content and professional practice.^{4,13} Strengthening the relationship between chemistry and vocational subjects may therefore contribute to greater student motivation and improved applicability of acquired knowledge.

EXPERIMENTAL

This study investigates teachers' perceptions of chemistry education in secondary medical and social care schools, with emphasis on the integration of chemical content within vocational subjects and curriculum reform effects.

Research objectives

The research objectives include:

1. Determining the significance of students' prior chemical knowledge for vocational subject teachers in the process of vocational education.
2. Investigating the impact of reduced chemistry teaching hours on the implementation of instructional units in vocational subjects.
3. Conducting a quantitative analysis of teachers' attitudes toward the quality of vocational subject learning before and after the chemistry curriculum reform.

Research hypotheses

The following hypotheses were formulated:

1. Prior knowledge of chemistry represents an essential foundation for the successful mastery of most vocational subjects in medical schools.
2. Vocational subject teachers frequently need to explain chemical concepts, particularly within interdisciplinary teaching areas.

3. Vocational subject teachers perceive that the reduction in chemistry teaching hours negatively affects the quality of learning and understanding vocational content.

Research instrument

The study uses an anonymous electronic questionnaire applied in a cross-sectional design. The questionnaire consisted of twelve questions and was administered online using the Google Forms platform. The internal consistency (reliability) of the questionnaire was not formally tested (*e.g.*, Cronbach's alpha was not calculated), which is acknowledged as a methodological limitation due to the exploratory nature of the study and the use of a non-standardized instrument adapted for this specific research context. The data were statistically processed, and the results presented in textual, tabular, and graphical formats.

Research sample

The study was conducted on a sample of 73 vocational subject teachers from secondary medical schools in the Republic of Serbia. The research was carried out anonymously, and the questionnaire did not include any questions that would allow identification of participants (such as name, surname, or email address), while participation was voluntary. The surveyed teachers are directly involved in the vocational education process and are relevant for assessing the effects of the chemistry curriculum reform.

RESULTS AND DISCUSSION

Research results are presented using tables and a chart. The questions were grouped into three sections: Demographic Characteristics, Work Experience, and Teachers' Attitudes toward the Reform of Chemistry Education.

Demographic characteristics

The sample included 73 vocational subject teachers employed in secondary medical schools across the Republic of Serbia. Respondents provided basic demographic information (gender, age, and years of experience), which served as the basis for further analysis. A total of 81 % of respondents were female, while 19 % were male. Similar trends are reported in Horvat *et al.* (2023), where near 88 % of the 497 surveyed chemistry teachers were women, demonstrating a consistent pattern in both general and vocational science education.¹⁴ Regarding age distribution, the largest proportion of respondents belongs to the 35–45 age group (38 %), followed by 46–54 (34 %), Chart 1. This indicates that mid-career teachers represent the largest group in the sample. Comparable findings were reported previously.¹⁴

Work experience of respondents

Most respondents (39.7 %) have more than 20 years of teaching experience, while 31.5 % have between 11 and 20 years of service. Teachers with fewer than 5 years of experience constitute 15.1 %, and the smallest category includes teachers with less than one year of experience (1.4 %), Table I.

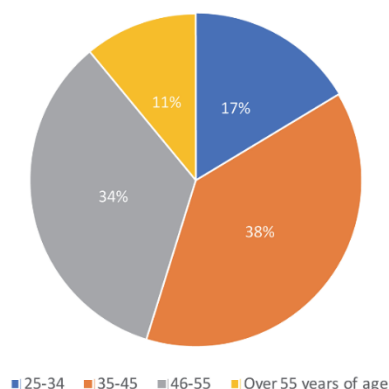


Chart 1. Age of respondents.

TABLE I. Work experience of respondents

Experience	Frequency	Percentage, %
1–5 years	11	15.1
11–20 years	23	31.5
6–10 years	9	12.3
Less than 1 year	1	1.4
More than 20 years	29	39.7
Total	73	100.0

This distribution shows a strong presence of highly experienced teachers, while younger teachers are less represented in the sample. Similar results appear in previous research.¹⁴

The fourth survey question examined the educational profiles in which teachers are engaged (Chart 2). Most participants teach in the medical nurse–technician program, which is included among the educational profiles affected by the chemistry curriculum reform.

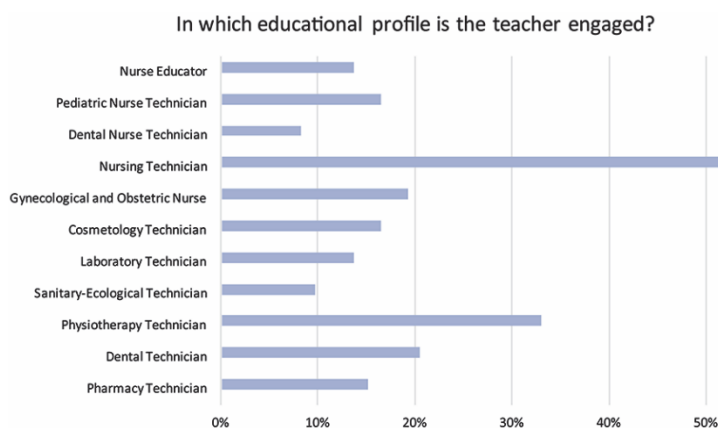


Chart 2. Educational profiles in which teachers are engaged.

Teachers' attitudes towards the reform of chemistry education

Within the framework of statistical data analysis, particular emphasis was placed on examining teachers' attitudes regarding the impact of the reform on the functional acquisition of content in vocational subjects within the fields of health and social care. The fifth question examined how frequently chemistry content is integrated into vocational subject. Respondents were offered the following options to choose from: very often, often, occasionally, rarely, never.

The results obtained from this question are presented in Table II.

TABLE II. Teachers' attitudes towards the importance of chemistry in vocational subjects

To what extent is chemistry content integrated into the vocational subjects in which the teacher is engaged?		
Extent	Percentage, %	Frequency
Very often	22	30.1
Often	30	41.1
Occasionally	19	26.1
Rarely	2	2.7
Never	0	0
Total	73	100.0

According to the results presented in Table II, the majority of teachers (41.1 %) report that chemical content is often integrated within the framework of professional subjects. An additional 30.1 % of teachers consider this integration to be very frequent. Thus, more than 71 % of teachers acknowledge frequent interdisciplinary integration. Comparable results are found at the University of San Francisco, where chemistry was identified as a foundational discipline for understanding core health science competencies.¹⁵

Teachers were also asked to evaluate the role of chemical literacy in vocational subjects (Table III).

TABLE III. Teachers' attitudes regarding the importance of chemical literacy for studying professional subjects

To what extent do you consider chemical literacy important for the effective study of professional subjects in the fields of healthcare and social care?		
Importance	Percentage, %	Frequency
Very important	36	49.3
Important	29	39.7
Moderately important	8	11.0
Slightly important	0	0
Not important	0	0
Total	73	100.0

The results indicate a high level of agreement among teachers regarding the functional role of chemistry in vocational learning. This finding is consistent with contemporary literature on critical chemical literacy, which views chemistry as a multidimensional tool for professional and societal engagement.¹⁶ In addition, the findings parallel the perspective that socio-scientific issues help students integrate conceptual knowledge with real-world contexts, thereby strengthening motivation and applicability.¹⁷

In the subsequent phase of the study, participants were presented with statements related to the reform of chemistry education, aimed at examining their attitudes toward its impact. Teachers expressed their level of agreement using a Likert scale from 1 to 5, where 5 indicated “strongly agree” and 1 “strongly disagree.” For analytical purposes, the values were interpreted within three categories: negative attitude (1–2), neutral attitude (3) and positive attitude (4–5), in accordance with the validation conducted by Xu and Lewis.¹⁸ The results are presented in Table IV.

TABLE IV. Assessment of teachers' attitudes as descriptive statistics; $N = 73$

Question	Minimum	Maximum	Mean value	Standard deviation
Has the reduction in the number of chemistry lessons affected the quality of learning in professional subjects?	2	5	4.36	0.788
Do students experience difficulties in studying instructional units that involve integrated chemical content?	2	5	4.18	0.839
Does the reduction in the number of chemistry lessons necessitate additional instructional time in professional subjects that require a solid foundation in chemistry?	1	5	4.05	1.039

Teachers strongly agree that reducing chemistry teaching hours negatively affects the quality of learning in vocational subjects. They also report that students struggle with content requiring chemical understanding. Opinions on whether additional chemistry lessons should be introduced within vocational subjects are somewhat more varied ($M = 4.05$), indicating differences in the perceived feasibility of such measures.

The following question addressed the importance of prior knowledge in chemistry for teaching vocational instructional units, offering a binary choice of answers (“yes” or “no”). The results indicate a high level of agreement among teachers regarding the importance of prior knowledge in chemistry for the successful mas-

tery of vocational instructional units, with 91.8 % of respondents stating that chemical literacy is essential for this process. Only 8.2 % of teachers expressed an opposing view. These findings are consistent with existing literature emphasizing the role of chemistry in healthcare education.¹⁹

In the next question, the study examined teachers' perceptions regarding the impact of the reduced number of chemistry lessons in upper secondary grades on the need for additional explanations during vocational instruction. The question posed was: "Do you believe that the absence of chemistry as a subject in the upper grades requires vocational subject teachers to explain related chemical concepts?" A large majority (89 %) believe that eliminating chemistry from upper secondary grades requires vocational teachers to explain chemical concepts themselves. These findings correspond with Pienta's perspective on the importance of chemistry in professional formation.²

The next question focused on assessing the teachers' self-evaluation of their competence in explaining chemical concepts. It was phrased as follows: „Do you consider yourself, as a vocational subject teacher, sufficiently competent to explain to students the chemical concepts included in the teaching units? Only 37 % of vocational subject teachers consider themselves sufficiently competent to explain chemical concepts, whereas 63 % do not. In the following question, teachers were presented with various options as potential solutions to this issue. The research results indicate that a significant proportion of the surveyed teachers (78.1 %) support increasing chemistry hours and initiating a new curriculum reform. Furthermore, 15 % of teachers emphasize aligning chemistry and vocational curricula. On the other hand, a relatively small percentage of teachers (5.5 %) support the need for additional professional development in chemistry. The remaining 1.4 % of respondents selected other responses not specified within the predefined categories.

Regarding the impact of the reform on the quality of students' knowledge, three options were examined: positive impact, negative impact, and inability to assess, with the aim of obtaining a comprehensive picture of teachers' perceptions concerning the effects of the reform. The results indicate that 46.6 % of teachers believe that the reduction in the number of chemistry classes has negatively affected the quality of learning in vocational subjects, while 30.1 % did not recognize a significant impact. The remaining 23.3 % of respondents were either uncertain or lacked sufficient data to form a clear opinion. In the subsequent analysis, a possible correlation was examined between the teaching experience of respondents and their views on the impact of the chemistry curriculum reform. The aim was to determine whether teachers with more extensive professional experience exhibit a more critical stance toward the reform changes, or whether the opinions are evenly distributed regardless of years of service. The results presented in Table V.

Although negative perceptions of the reform were predominant at the overall sample level, the distribution of responses within individual experience groups

revealed a more differentiated pattern of attitudes. Positive assessments were more frequent in several categories of teaching experience, whereas more critical views were observed among some groups of more experienced teachers. However, statistical analysis showed no significant relationship between years of teaching experience and perceptions of the reform's impact ($r = 0.153$, $p = 0.197$). These findings suggest that teachers' attitudes toward the reform cannot be explained by differences in professional experience alone.

TABLE V. Correlation between teachers' years of service and their attitudes (in %) toward the impact of the curriculum reform

Attitude	Years of service				
	<1	1–5	6–10	11–20	20+
Positive	100	54.55	66.67	30.43	51.72
Unable to assess	0	18.18	22.22	30.43	20.69
Negative	0	27.27	11.11	39.13	27.59

CONCLUSION

The results of this study indicate that the majority of vocational subjects' teachers recognize the importance of prior chemistry knowledge for the successful mastery of those subjects. In the context of the reduced presence of chemistry in the curriculum, vocational subject teachers increasingly assume the role of explaining fundamental chemical concepts, thereby revealing perceived challenges associated with the educational reform.

A considerable proportion of teachers reported that the reduction in the number of chemistry hours has negatively affected the quality of vocational education. Although some respondents consider themselves capable of compensating for these deficiencies, the findings point to the need for improved curricular coherence and stronger integration between chemistry and vocational subjects in secondary medical education. However, the findings also suggest that teachers' perceptions are not entirely uniform and should not be interpreted as strictly predominantly negative. Instead, the results indicate a more nuanced and differentiated pattern of responses across the sample.

The results of this study largely support the proposed research hypotheses. The first hypothesis was confirmed, indicating that prior chemistry knowledge represents an important foundation for the successful learning of vocational subjects in medical secondary schools. The second hypothesis was also confirmed, as vocational subject teachers reported a frequent need to explain chemical concepts, particularly within interdisciplinary teaching contexts. The third hypothesis was only partially supported, suggesting that although many teachers perceive reduced chemistry teaching hours as having a negative impact on learning vocational content, this perception was not equally strong across all respondents. Overall, the

findings emphasize the close relationship between chemistry and vocational subjects in medical education. They further highlight the importance of maintaining adequate chemistry instruction and strengthening the integration of chemical concepts within vocational curricula. Such efforts may contribute to improving students' understanding of professional content and the development of relevant competencies.

The findings provide partial support for the initial research assumptions regarding the importance of chemistry knowledge and the perceived impact of curriculum reform on vocational education. Although differences were observed among teachers with varying levels of professional experience, the correlation between years of service and attitudes toward the importance of prior chemistry knowledge was not statistically significant ($r = 0.153$, $p = 0.197$).

Overall, the findings highlight the importance of aligning curriculum reforms with the educational and professional needs of vocational education, particularly through stronger interdisciplinary integration and the functional application of chemistry knowledge in professional practice. Rather than indicating a uniform negative evaluation of the reform, the results point to a complex set of perceptions that reflect both perceived challenges and adaptive responses among teachers.

The findings of this study should be interpreted in light of several limitations. First, the research was conducted on a small sample of vocational subject teachers, which may limit the generalizability of the results. Second, the study was based only on teachers' perceptions, students' opinion was not included. Finally, the questionnaire was developed specifically for this study and did not undergo formal psychometric validation, which should be taken into consideration when interpreting the findings. Future research will include larger samples, validated instruments and student opinions in order to provide a more comprehensive evaluation of the impact of chemistry curriculum reforms.

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ИЗВОД

ЗНАЧАЈ НАСТАВНОГ ПЛАНА И ПРОГРАМА ХЕМИЈЕ ЗА ОБРАЗОВНЕ ПРОФИЛЕ У СРЕДЊЕМ МЕДИЦИНСКОМ СТРУЧНОМ ОБРАЗОВАЊУ

ДАНИЦА РАШИЋ, САША А. ХОРВАТ, ДУШИЦА Д. РОДИЋ И ТАМАРА Н. РОНЧЕВИЋ

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Улагање у фундаментална хемијска истраживања представља кључни фактор у напретку здравствене заштите, која се све више суочава са изазовима савременог друштва. Ипак, значај хемије у медицинском образовању често није довољно препознат, што доводи до слабе повезаности теоријских и практичних аспеката наставе. Бројне

студије указују на потребу за дубљом интеграцијом хемијских садржаја у медицинске стручне предмете. Овај рад анализира ставове наставника стручних предмета у средњим медицинским школама о утицају реформе наставног плана и програма хемије на квалитет и ефикасност стручне наставе. Истраживање је спроведено дескриптивном методом и анонимним упитником, на узорку од 73 наставника из медицинских школа широм Републике Србије. Резултати делимично потврђују полазне хипотезе и указују на потребу за систематским унапређивањем наставе хемије у медицинским школама. Ови налази могу послужити као смернице за развој образовних политика у области стручног образовања.

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ERRATUM

Correction of author's name in the article: Bimetallic polyaniline/silver–palladium nanocomposite for rapid and sustainable degradation of eosin yellow dye from wastewater

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This corrects the article “Bimetallic polyaniline/silver–palladium nanocomposite for rapid and sustainable degradation of eosin yellow dye from wastewater” published in volume 91, number 1, page 55 (<https://doi.org/10.2298/JSC2507020-73Z>).

CONTENT OF THE CORRECTION

For author **Aamna Balouch**, the name was incorrectly written in the list of authors.

Previous list of authors was:

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