

Computational Modelling of Drug-Likeness, Absorption, Distribution, Metabolism and Putative Biological Targets of Ethyl Esters 4-Chlorethoxy(Aryl Phosphoryl)Acetic Acids

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ABSTRACT

This study presents an *in silico* evaluation of four synthesized organophosphate derivatives as potential drug candidates. Physicochemical properties, pharmacokinetic parameters, drug-likeness criteria, and predicted biological targets were assessed using SwissADME and SwissTargetPrediction platforms. All compounds demonstrated molecular weights below 500 g/mol, optimal topological polar surface area (62–66 Å²), moderate lipophilicity (Consensus LogP 2.28–2.83), and acceptable aqueous solubility. The BOILED-Egg model predicted high gastrointestinal absorption for all derivatives and potential blood–brain barrier permeability, with no indication of P-glycoprotein-mediated efflux. The compounds complied with Lipinski, Ghose, Veber, Egan, and Muegge rules and showed moderate synthetic accessibility. Target prediction suggested possible interactions with oxidoreductases, serine hydrolases, and central nervous system-related enzymes and receptors. The balanced polarity–lipophilicity profile, combined with favorable ADME characteristics, indicates promising oral bioavailability and potential CNS exposure. These findings support further molecular modeling, biochemical validation, and experimental pharmacokinetic studies to confirm therapeutic potential and safety profiles of the investigated organophosphate derivatives.

Keywords: organophosphate derivatives; SwissADME; ADME; drug-likeness; blood-brain barrier; *in silico* analysis; Target Prediction

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I. INTRODUCTION(10 Bold)

Organophosphate compounds are a broad class of substances with significant pharmaceutical potential. The presence of phosphorus-containing functional groups, such as phosphonate and phosphoryl fragments, contributes to the formation of stable donor-acceptor and electrostatic interactions with biological macromolecules [1].

In recent years, there has been an increase in interest in low-molecular-weight organophosphorus structures as promising pharmacophores. Their chemical flexibility and ability to vary lipophilicity and spatial configuration make it possible to optimize pharmacokinetic parameters and selectivity of action [1].

At the same time, the organophosphate chemical class is highly heterogeneous and cannot be considered synonymous with therapeutic safety. Some organophosphorus compounds are potent pesticides, while others, including nerve agents such as sarin, soman, VX and Novichok-type agents, are associated with severe or lethal toxicity, primarily through inhibition of acetylcholinesterase (AChE) and disruption of cholinergic neurotransmission [2–5]. Accordingly, favorable drug-likeness or ADME predictions alone should not be interpreted as evidence of therapeutic safety. For the compounds studied here, the absence or presence of predicted interactions with AChE, butyrylcholinesterase (BChE), relevant receptors, ion channels, metabolic enzymes and other critical

proteins must be explicitly considered before any pharmacological development is proposed. The present study therefore treats beneficial pharmacokinetic features and potential toxicological liabilities as complementary aspects of early-stage compound prioritization.

One of the key tasks in modern medicinal chemistry is the early assessment of the drug-like properties of compounds. The use of *in silico* methods can significantly reduce the time and financial costs of preclinical development.

The SwissADME [7] and SwissTargetPrediction [6,8] platforms are widely used to assess the absorption, distribution, metabolism, excretion, and potential biological targets of small-molecule compounds.

This study aimed to comprehensively characterize four novel organophosphate derivatives *in silico* by assessing their physicochemical and pharmacokinetic profiles, compliance with established drug-likeness criteria, and putative biological targets, while also considering potential safety-related liabilities and off-target interactions [9]. The four compounds were selected because they constitute a structurally related series of newly synthesized 4-chloroethoxy(aryl phosphoryl)acetic acid ethyl esters that differ systematically in the aromatic substituent (unsubstituted phenyl, methylphenyl, chlorophenyl, and dimethylaminophenyl groups). This design provides a useful structure–property comparison and enables assessment of how electronic and lipophilic substituent effects influence ADME characteristics and predicted biological interactions. The selection was therefore based on the availability of a coherent synthesized series rather than on any assumption that all organophosphate compounds are intrinsically safe or therapeutically active.

Extended literature review 2020–2025 with reference to the results of the study.

A review of the literature has shown that organophosphate structures (including phosphonates/phosphonate esters and related motifs) remain of high interest in medicinal chemistry because of their variable electronic properties, ability to fine-tune lipophilicity, and participation in specific interactions with active enzyme sites [10]. Reviews [10–12] note that phosphorus-containing fragments are often considered as "functional enhancers" of binding (including through donor-acceptor and electrostatic contributions) and can support the formation of a favorable ADME profile with a limited molecular weight.

In recent years, it has been emphasized that phosphates/phosphonates often face the "polarity-membrane $\leftrightarrow$ permeability" trade-off, so pro-dosage form approaches are actively used to balance solubility and absorption. The "remdesivir paradigm" and a broader class of phosphate/phosphonate pro-drugs as a means of increasing systemic exposure and delivery to tissues are discussed separately [12].

SwissADME remains one of the most widely used tools for the primary assessment of ADME and medicinal chemistry friendliness. A 2022 review [9] highlighted the prevalence of SwissADME for calculating LogP/TPSA/solubility and applying Lipinski-Veber-Egan-Muegge filters when ranking candidates.

Simultaneously, applied research in 2024 demonstrates a typical scheme: the calculation of physicochemical parameters + the use of drug-likeness rule sets (Lipinski, Ghose, Veber, Egan, Muegge) as a preliminary stage before docking/biological tests [13].

In recent years, there has been an accumulation of a large body of work showing that BBB permeability is determined not only by passive diffusion, but also by the flux/efflux balance involving transporters. A large article in the *Journal of Medicinal Chemistry* (2023) demonstrated that the explanation of BBB permeability requires the integration of transport mechanisms and physicochemical traits [13–20].

Reviews and studies [18] summarizing experimental and computational approaches for assessing BBB permeability emphasize the central role of optimizing physical and chemical parameters (including TPSA, H-bond capacity, and lipophilicity) at the design cycle stage.

Some papers [19–20] on AI/ML models of BBB permeability confirm the trend towards ensemble and interpretable models, where TPSA/LogP-like descriptors remain key features along with H-bonding parameters and molecule size.

The literature [20] emphasizes that even with the "right" TPSA/LogP molecules, molecules can show weak brain exposure if they are substrates of P-gp on BBB.

At the same time, in silico models for predicting P-gp substrates are being developed (including for estimating the probability of sufficient brain exposure), which supports the idea of combining "property-based" and "transporter-aware" filters [21].

The 2025 reviews further highlighted the effect of P-gp on the distribution of CNS drugs and response variability and discussed methods for identifying P-gp substrates [22-24].

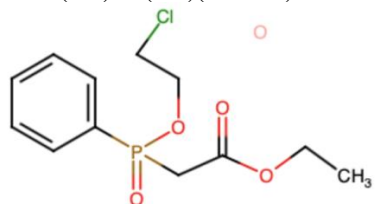
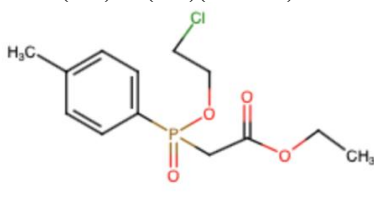
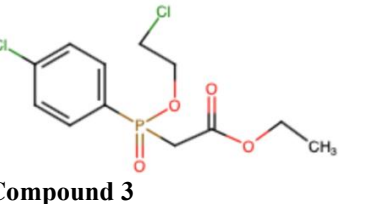
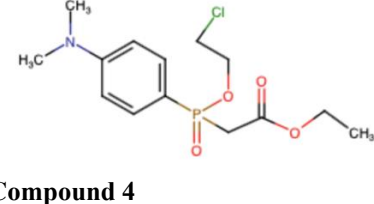
Modern research on target prediction resources emphasizes that "reverse screening" web servers remain a practical tool for generating hypotheses on targets in the absence of experimental data. However, limitations include the probability of false-positive signals, dependence on ligand base coverage, and the need for subsequent validation (docking/biochemical tests) [25].

Research in the field of computational toxicology emphasizes that the combination of ADME predictions and toxicological models is becoming the standard for lead prioritization (including the integration of tools such as SwissADME as a source of basic descriptors/rules) [25-27].

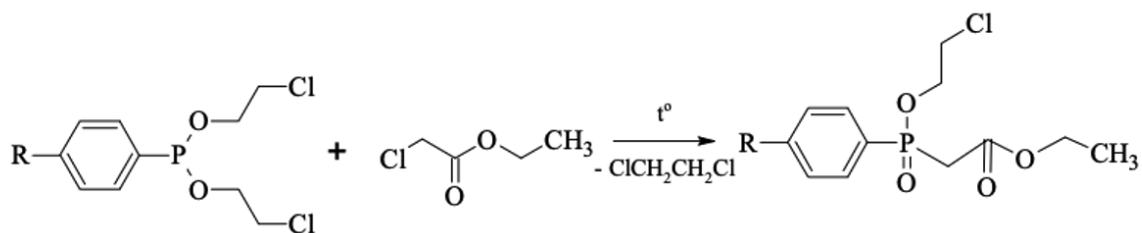
II. MATERIAL AND METHODS

In this study, four organophosphorus derivatives with different substituents in the aromatic moiety and alkyl chains were analyzed. The structures of the studied compounds and their SMILES notations are presented in Table 1.

Table 1. SMILES and structures of investigated compounds

<chem>CCOC(=O)CP(=O)(OCCCl)C1=CC=CC=C1</chem>  Compound 1 ethyl 2-[2-chloroethoxy(phenyl)phosphoryl]acetate	<chem>CCOC(=O)CP(=O)(OCCCl)C1=CC=C(C)C=C1</chem>  Compound 2 ethyl 2-[2-chloroethoxy-(4-methylphenyl)phosphoryl]acetate
<chem>CCOC(=O)CP(=O)(OCCCl)C1=CC=C(Cl)C=C1</chem>  Compound 3 ethyl 2-[2-chloroethoxy-(4-chlorophenyl)phosphoryl]acetate	<chem>CCOC(=O)CP(=O)(OCCCl)C1=CC=C(C(=C1)N(C)C)</chem>  Compound 4 ethyl 2-[2-chloroethoxy-(4-dimethylaminophenyl)phosphoryl]acetate

These compounds were synthesized by the reaction of di-β,β-chloroethyl esters of arylphosphonic acids with ethyl chloroacetate, which resulted in the formation of ethyl esters of 4-chloroethoxy(aryl phosphoryl)acetic acids [27].



R=H (I); CH₃ (II); Cl (III); Me

The assessment was conducted using the following web-based platforms:

SwissADME [7] – for analysis of physicochemical parameters and ADME profile;
SwissTargetPrediction [6,8] – for predicting possible biotargets.

The following indicators were calculated.

- Molecular Weight
- TPSA
- Number of hydrogen bond donors and acceptors
- Lipophilicity (LogP)
- Solubility (LogS)
- Gastrointestinal absorption
- penetration through the BBB
- Belonging to P-gp substrates compliance with the Lipinski rules and other drug-likeness criteria
- Synthetic Availability

In addition, the revised assessment framework included a safety-oriented screening strategy. Potential biological activities and safety-related effects were evaluated using PASS Online, while predicted interactions with critical proteins and receptors were considered for further target-specific investigation. Particular attention was directed toward AChE and BChE, CNS receptors, ion channels, and other off-targets identified through reverse screening. This combined workflow was selected to avoid interpreting favorable ADME properties in isolation from potential toxicity.

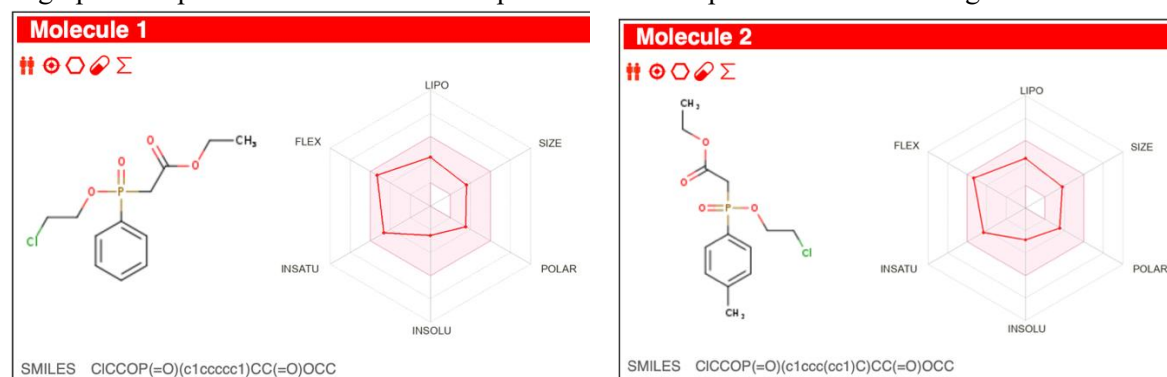
The BOILED-Egg model, implemented in the SwissADME platform, was used to visually assess the potential gastrointestinal absorption and passive blood–brain barrier (BBB) permeation of the investigated compounds [27].

III. RESULTS

Analysis of physical and chemical parameters

The in silico analysis of the four studied organophosphorus derivatives made it possible to establish their compliance with the main criteria for drug-like compounds.

A graphical representation of the ADME profile of the compounds is shown in Fig. 1



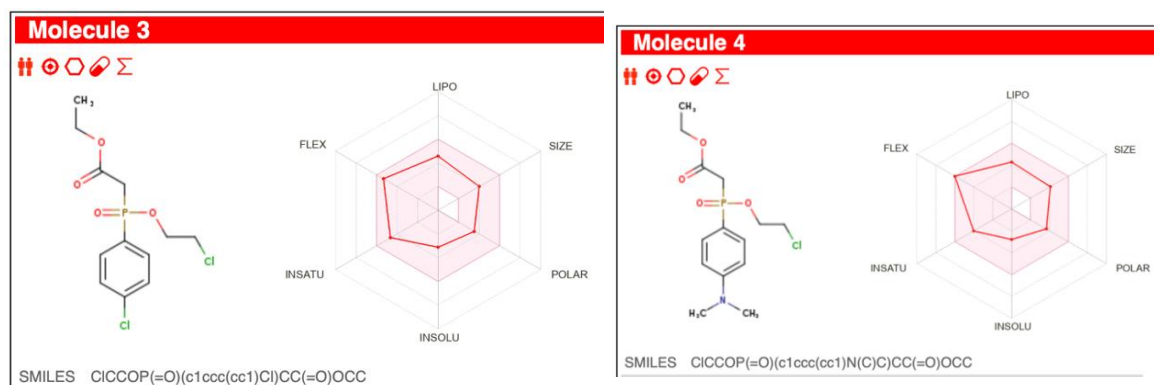


Figure 1. ADME profile of compounds 1-4 (Molecules 1-4).

The molecular weights of the compounds varied in the range of 290.68–333.75 g/mol, which is well below the limit value of 500 g/mol according to the Lipinski rule. This indicator suggests favorable prerequisites for membrane permeability and oral bioavailability.

The topological polar surface area (TPSA) was 62.41–65.65 Å². TPSA values of less than 90 Å² are generally correlated with high intestinal absorption, and values below 70 Å² are often associated with the potential for penetration of the blood-brain barrier (BBB). Thus, the compounds under study demonstrated an optimal balance between polarity and lipophilicity.

The number of hydrogen bond donors was 0, and the number of acceptors was 4. The absence of hydrogen bond donors may contribute to better lipophilicity and penetration through biological membranes but may somewhat limit water solubility.

The fraction of sp³-hybridized carbon atoms (0.42–0.50) indicates the presence of a moderately three-dimensional structure. Current research shows that an increase in the Csp³ fraction is associated with an increase in binding selectivity and a decrease in nonspecific toxicity.

Lipophilicity and aqueous solubility

The Consensus LogP varied from 2.28 to 2.83, which corresponds to moderate lipophilicity. Values in the range of 1-3 are considered optimal for oral drug candidates because they allow for efficient diffusion across membranes while maintaining solubility.

The calculated solubility values (LogS = –2.53 – –3.13) indicate that the compounds are moderately soluble. This level of solubility is acceptable for early development, although further optimization may require structural modifications to increase water solubility.

Pharmacokinetic profile (ADME)

High GI absorption was predicted for all compounds. This is consistent with the moderate LogP values and low TPSA. Thus, these molecules show promise for oral administration.

The predicted ability to penetrate the blood-brain barrier indicates potential activity against central nervous system targets. This is particularly important when considering compounds as possible inhibitors of neuroenzymes or central nervous system (CNS) receptor proteins.

The absence of P-glycoprotein substrates is a positive factor, as it reduces the likelihood of active elimination of the drug from the cells and the development of multidrug resistance.

Drug-likeness and synthetic accessibility

All connections demonstrate the following:

0 violations of the Lipinski rule

No violations of the Ghose, Veber, Egan and Muegge criteria

Bioavailability Score = 0,55

The Synthetic Accessibility score (4.39–4.48) indicates moderate synthesis complexity, making these structures realistic candidates for further chemical modification (Table 1).

Table 2. Comparison of Physicochemical and ADME Parameters

Parameter	Compound 1	Compound 2	Compound 3	Compound 4
Molar weight (g/mol)	290,68	305,71	320,73	333,75
TPSA ($\text{\AA}^2$)	62,41	63,02	64,88	65,65
HBA	4	4	4	4
HBD	0	0	0	0
Consensus LogP	2,28	2,46	2,71	2,83
LogS (ESOL)	-2,53	-2,76	-2,94	-3,13
GI absorption	High	High	High	High
BBB permeant	Yes	No	No	No
P-gp substrate	No	No	No	No
Bioavailability score	0,55	0,55	0,55	0,55
Synthetic accessibility	4,39	4,42	4,45	4,48

Relationship of the ADME profile to the intended biotargets

Based on the previously conducted analysis of the prediction of biological targets (Swiss Target Prediction), it is possible to assume a possible interaction of the studied compounds with the following:

- enzymes of the oxidoreductase class,
- serine hydrolases,
- carbonyl-containing active sites of enzymes,
- receptors in the central nervous system.

Moderate lipophilicity and the presence of hydrogen bond acceptor sites are prerequisites for interaction with catalytic amino acid residues (Ser, His, Asp/Glu). Phosphorus-containing fragments can participate in coordination interactions or the formation of donor-acceptor complexes.

The predicted ability of these compounds to penetrate the blood–brain barrier suggests their potential suitability as modulators of central nervous system targets, including acetylcholinesterase, monoamine oxidase, and GABAergic or glutamatergic receptor systems.

Such a profile may be relevant for the development of compounds with neuroprotective or neuromodulatory activities.

Moderate lipophilicity and good cell permeability can promote intracellular accumulation, which is important for the inhibitors of enzymes involved in cell proliferation.

Reverse pharmacophore screening using the SwissTargetPrediction platform demonstrated a wide range of putative molecular targets for the organophosphate derivatives under study. According to the data obtained, the probable biotargets mainly belong to the classes of enzymes (lyases, oxidoreductases, hydrolases, proteases), as well as to kinases, nuclear receptors and receptors coupled to the G protein or ion channels. For a number of compounds, the highest probability of interaction was predicted for carbonic anhydrase isoforms (CA I, CA II, CA IX, CA XII), acetylcholinesterase, as well as for monoamine oxidases A and B, indicating the potential for influencing enzyme systems involved in the regulation of acid-base balance, neurotransmitter metabolism and cell proliferation processes. In addition, serine proteases (e.g., leukocyte elastase), cyclooxygenase-2, as well as metabotropic glutamate receptors are present in the list of suspected targets, which expands the potential pharmacological profile of the compounds. The identified spectrum of targets indicates a predominant targeting of compounds on enzyme systems and neurotransmitter receptors, which is consistent with the calculated ADME profile and the predicted ability to penetrate the blood-brain barrier (Fig.2).

The four compounds investigated in the present study constitute a structurally related series of ethyl 2-[2-chloroethoxy(aryl)phosphoryl]acetates. They share the same phosphonate-containing molecular framework but differ in the substituent attached to the aromatic ring: Compound 1 contains

an unsubstituted phenyl group, Compound 2 a methyl-substituted phenyl group, Compound 3 a chlorine-substituted phenyl group, and Compound 4 a dimethylamino-substituted phenyl group. This systematic structural variation provides an appropriate basis for evaluating the relationship between aromatic substitution and physicochemical, pharmacokinetic, and predicted biological properties.

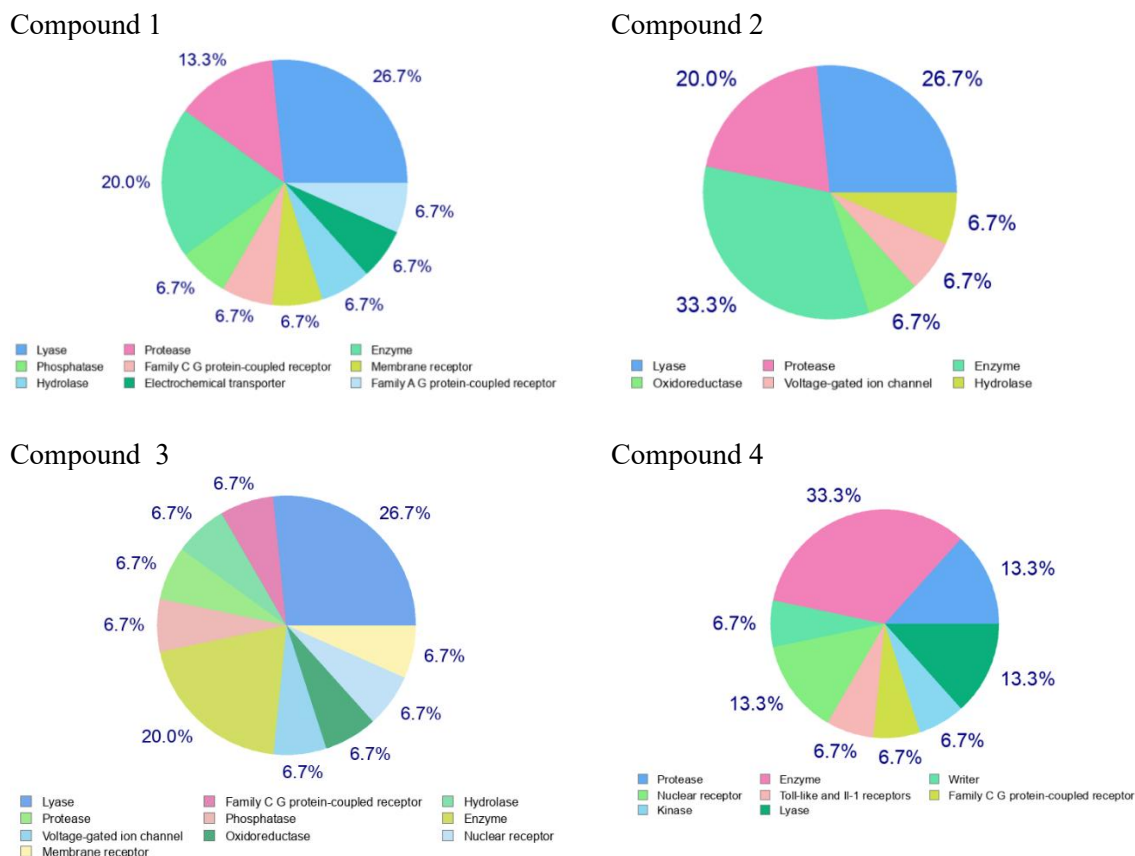


Figure 2. Pharmacophore screening of compounds 1-4 by SwissTarget Prediction

Comparative Assessment of the Biological and Toxicological Relevance of the Studied Organophosphorus Compounds

The biological and toxicological relevance of the four compounds can also be considered in comparison with other major groups of organophosphorus substances. Organophosphorus pesticides, including compounds such as chlorpyrifos, diazinon, malathion, and parathion, have historically been developed primarily for agricultural applications. Many of these compounds exert their insecticidal effects through inhibition of acetylcholinesterase (AChE), although their toxicity profiles and mechanisms of metabolic activation differ considerably. In humans and other mammals, exposure to sufficiently high concentrations may lead to cholinergic toxicity. The investigated Compounds 1–4 should not, however, be classified as agricultural pesticides solely on the basis of their organophosphorus functionality. Their molecular structures differ substantially from those of many classical organophosphorus pesticides, and their biological effects require independent experimental or computational assessment.

An even more distinct subgroup comprises organophosphorus nerve agents used as chemical warfare agents, including sarin, soman, VX, and Novichok-type agents. These compounds are among the most toxic organophosphorus substances known and exert their characteristic toxicity primarily through inhibition of acetylcholinesterase, resulting in excessive accumulation of acetylcholine and severe disruption of cholinergic neurotransmission. The comparison with nerve agents is relevant not because Compounds 1–4 are structurally or functionally equivalent to such agents, but because it

demonstrates the importance of evaluating acetylcholinesterase and related biological targets when investigating novel organophosphorus molecules. The presence of an organophosphorus group should therefore be regarded as a structural feature requiring comprehensive biological and toxicological characterization rather than as an indicator of either safety or toxicity by itself.

The four investigated compounds can consequently be positioned within a broader spectrum of organophosphorus chemistry. Compound 1, which showed the lowest molecular weight and lipophilicity and was the only derivative predicted to penetrate the BBB, may require particular attention in subsequent studies of potential CNS activity and toxicity. Compound 2, containing a methyl substituent, demonstrated a moderate increase in lipophilicity and molecular weight while maintaining high predicted gastrointestinal absorption. Compound 3, containing a chlorine substituent, exhibited a further increase in lipophilicity and a reduction in predicted aqueous solubility, which may influence membrane interactions and tissue distribution. Compound 4, bearing a dimethylamino group, had the highest molecular weight, LogP, and TPSA values and the lowest predicted aqueous solubility among the four derivatives. However, its higher lipophilicity should not automatically be interpreted as evidence of increased biological activity or toxicity.

The comparison of the predicted biological targets further indicates that the investigated compounds may interact with a broad range of protein classes, including enzymes, receptors, ion channels, and other molecular targets. Of particular relevance is the predicted association with acetylcholinesterase and other enzymes involved in neurotransmitter metabolism. Such predictions require careful interpretation because reverse pharmacophore screening does not establish actual inhibition or activation. Nevertheless, they provide a rational basis for prioritizing acetylcholinesterase and butyrylcholinesterase for further molecular docking and experimental validation.

The comparative analysis therefore suggests that the four compounds represent a chemically coherent series with gradually changing physicochemical properties rather than a group of compounds with identical biological behavior. The differences in aromatic substitution appear to influence lipophilicity, solubility, and predicted distribution, while the common phosphonate-containing scaffold may contribute to similarities in the predicted target spectrum. Nevertheless, the present *in silico* findings do not provide sufficient evidence to classify any of the compounds as therapeutic agents, pesticides, or toxic organophosphorus agents. Instead, they identify structural and pharmacokinetic features that should guide further biological investigation.

In particular, the next stage of the study should include a systematic assessment of the potential interaction of Compounds 1–4 with acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and other relevant enzymes and receptors. PASS-based prediction of pharmacological and toxicological activity spectra, combined with molecular docking against prioritized targets, could provide additional information for distinguishing potentially beneficial biological activities from undesirable toxicological effects. Such an integrated approach would allow the four compounds to be evaluated not only in terms of drug-likeness and ADME properties but also in terms of their potential biological risks, thereby providing a more balanced assessment of their prospects for further pharmacological development.

Graphical analysis of absorption and distribution (BOILED-Egg model)

The BOILED-Egg model is an *in silico* graphical model used to predict two important pharmacokinetic properties of small molecules: passive gastrointestinal absorption (HIA) and passive blood–brain barrier (BBB) permeation.

It was developed by Daina and Zoete (2016) [27] and subsequently incorporated into the SwissADME platform. The model is based on two physicochemical descriptors:

WLOGP — a measure of molecular lipophilicity;

TPSA (topological polar surface area) — a descriptor of molecular polarity.

The model represents compounds on a two-dimensional WLOGP–TPSA plot that resembles a fried egg:

White region (the "white") — compounds located in this region are predicted to have a high probability of passive gastrointestinal absorption.

Yellow region (the "yolk") — compounds located in this region are predicted to have a high probability of passive penetration across the BBB and therefore potential access to the central nervous system.

Overlap between the white and yolk is possible, meaning that a compound can be predicted to have both high gastrointestinal absorption and high BBB permeability.

Outside the egg — compounds located outside the relevant regions are predicted to have lower passive gastrointestinal absorption and/or limited passive BBB penetration.

From a mathematical perspective, the model is a classification plane partition (WLOGP, TPSA), in which the probability of penetration through biological barriers is approximated by empirically derived boundaries obtained from training samples of known drugs.

The probability of intestinal absorption (P_{HIA}) and BBB penetration (P_{BBB}) are considered to be functions of two independent variables:

An increase in WLOGP increases membrane permeability due to increased lipophilic interaction with the phospholipid bilayer, and an increase in TPSA reduces the likelihood of passive diffusion due to increased hydration of the molecule. Based on the analysis of large datasets, the following areas were empirically identified:

"Protein" (HIA-region) is a zone with a high probability of gastrointestinal absorption.

The "yolk" (BBB region) is a subset of the HIA region that corresponds to a high probability of penetration through the BBB.

The boundaries of these regions are not hard thresholds but reflect the maximization of the a posteriori probability for the corresponding pharmacokinetic properties.

In the resulting diagram (Fig. 3), all the studied organophosphorus derivatives were localized.

- inside the white area, corresponding to a high probability of gastrointestinal absorption.
- inside the yellow area, indicating the ability to penetrate the blood-brain barrier.

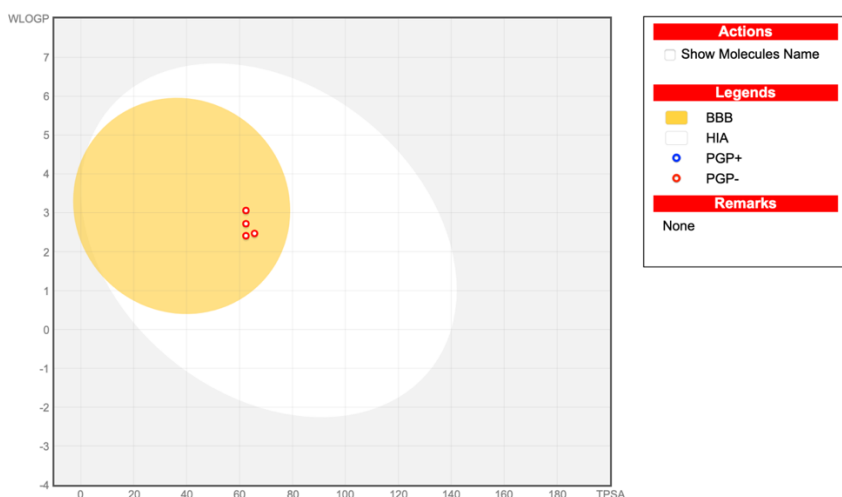


Figure 3. BOILED-EGG of compounds 1-4.

TPSA values in the range of $\sim 62\text{--}66 \text{ \AA}^2$ and WLOGP around 2.4–3.1 form an optimal compromise between polarity and lipophilicity. From a mathematical perspective, such values lie in a region where the derivative of the WLOGP permeability function remains positive, and the negative influence of TPSA has not yet become a dominant factor.

In addition, the model considers the classification of compounds based on their belonging to P-glycoprotein substrates. In the diagram, the compounds under study are marked with red markers corresponding to the PGP– category, indicating the absence of predicted active efflux.

From a pharmacokinetic perspective, this implies that the total flux of a substance through the membrane (J_{total}) is primarily determined by passive diffusion:

In contrast to PGP+ compounds, active reverse transport (J_{efflux}) plays an essential role.

The compact arrangement of dots in the diagram indicates the structural homogeneity of the studied series and the similarity of the pharmacokinetic profile. Small offsets along the WLOGP axis reflect a moderate increase in lipophilicity while maintaining the TPSA within the optimal range.

Compounds 2 and 3 were located closer to the center of the yellow region, indicating the most balanced combination of factors determining absorption and distribution, allowing them to be considered priority candidates for further research.

Thus, the BOILED-Egg model demonstrated that the studied organophosphate derivatives have a high probability of oral absorption, can potentially penetrate the blood-brain barrier, are not subject to active efflux from P-glycoprotein, and are characterized by an optimal ratio of lipophilicity and polarity.

The results of graphical analysis complement the numerical parameters of ADME and confirm the prospects for further experimental studies of these compounds, including molecular modeling and in vitro and in vivo pharmacokinetic studies.

Prospects for further pharmacological and safety evaluation

Although the presented results are based on in silico evaluation (SwissADME/Swiss Target Prediction) and require experimental validation, the combination of parameters (moderate lipophilicity, TPSA $\sim 62\text{--}66 \text{ \AA}^2$, high predicted GI absorption, BBB-permeant, and no evidence of P-gp substrate) allows us to outline several of the most realistic clinical scenarios and development strategies.

Importantly, the present findings should not be interpreted as evidence that the investigated compounds are safe drug candidates. The predicted gastrointestinal absorption and possible BBB exposure may be pharmacokinetically favorable, but the same properties could also increase systemic or CNS exposure to undesirable biological effects. For organophosphate derivatives, a critical safety question is whether the compounds inhibit AChE or BChE or interact with other essential neuronal proteins. The potential for neurotoxicity, delayed neuropathy, cardiovascular effects, hepatotoxicity, metabolic liabilities, and adverse drug–drug interactions should therefore be evaluated before any therapeutic claims are made [21–24].

The predicted permeability across the blood-brain barrier, combined with moderate lipophilicity, forms the prerequisites for studying compounds as candidates for diseases where central exposure is required, such as neurodegenerative disorders, neuroinflammation, cognitive impairment, and some forms of neuropathic pain. As primary biotargets requiring prioritization, it is advisable to consider enzymes and receptor systems that are sensitive to small lipophilic molecules and where pharmacological modulation is possible without irreversible toxicity.

If further experimental validation confirms interactions with hydrolases/oxidoreductases, potential clinical niches may include metabolic and inflammatory pathologies and infectious/antitumor programs (as adjuvant or targeted approaches). This direction is especially relevant for compounds with predominantly peripheral distribution or limited CNS exposure will be shown against the background of transporter effects that are not fully reflected in silico.

The oral route is considered a priority because high intestinal absorption and acceptable drug-like "geometry" (limited molecular weight, drug-likeness compliance) are predicted for all compounds.

Simultaneously, moderate aqueous solubility (LogS of the order of -2.5 3.1) may lead to bioavailability variability for the more lipophilic members of the series.

At the early stages of development, it is advisable to consider formulation and physicochemical optimization strategies, including the application of solubilizing delivery systems (e.g., microemulsions or lipid-based carriers), the selection of appropriate salt or co-crystal forms where structurally feasible, and the optimization of crystal morphology and particle size to enhance dissolution rate and bioavailability.

If necessary, mild structural modifications are made to increase solubility without loss of permeability.

For organophosphate structures, it is essential to exclude undesirable inhibitory activity against vital enzymes, primarily acetylcholinesterase/butyrylcholinesterase, as well as potential off-target covalent binding mechanisms (if possible for a particular chemical motif).

Given the predicted central nervous system exposure, comprehensive safety evaluation should prioritize the assessment of neurotoxicity and potential behavioral effects, early cardiotoxicity screening including evaluation of hERG channel interaction risk, investigation of hepatic safety and metabolic stability (with particular attention to cytochrome P450 profiles and the formation of reactive metabolites), as well as the analysis of potential drug–drug interactions during concomitant therapy.

It is important to emphasize that the "non-P-gp substrate" prediction reduces the risk of active efflux on BBB but does not negate the need for experimental confirmation in cell models of transporters (e.g., MDR1-expressing lines) prior to transition to in vivo.

Based on the obtained profile, the strategy of developing small oral molecules with potential CNS exposure seems to be the most justified, provided that cholinesterase and other critical off-target risks are strictly excluded from the study. Compounds 2 and 3 (which have the most balanced lipophilicity/solubility) can be considered primary leads for an in-depth pilot program.

IV. CONCLUSION

In silico analysis demonstrated that the organophosphate derivatives under study possess several favorable physicochemical and pharmacokinetic characteristics and meet commonly used drug-likeness criteria. However, these findings should be interpreted as preliminary and do not, by themselves, establish therapeutic potential or safety. Because organophosphorus compounds include both useful pharmaceutical structures and highly toxic pesticides and nerve agents, a balanced assessment must consider both potential beneficial activities and possible adverse or off-target effects.

The results obtained substantiate the feasibility of conducting further in-depth studies of these compounds using molecular modeling methods and biological tests.

The identified spectrum of targets indicates a predominant targeting of compounds on enzyme systems and neurotransmitter receptors, which is consistent with the calculated ADME profile and the predicted ability to penetrate the blood-brain barrier.

At the same time, it is necessary to take into account the probabilistic nature of the forecast and the need for subsequent experimental validation (molecular docking, biochemical tests in vitro and in vivo) to confirm the selectivity and pharmacological significance of the identified interactions.

CRedit authorship contribution statement

Asadov Khammed Asad: supervision, writing- review, editing, methodology, investigation;
Asgarova Aytan Rafiq: writing - original draft, data curation, investigation, visualization, software;
All authors have discussed the results, read the manuscript and agreed with its content.

Disclosure statement

No potential conflict of interest was reported by the author(s)

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