Review

Unsubstituted Oximes as Potential Therapeutic Agents

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Abstract: Oximes, which are highly bioactive molecules, have versatile uses in the medical sector and have been indicated to possess biological activity. Certain oximes exist in nature in plants and animals, but they are also obtained by chemical synthesis. Oximes are known for their anti-inflammatory, antimicrobial, antioxidant and anticancer activities. Moreover, they are therapeutic agents against organophosphate (OP) poisoning. Two oximes are already commonly used in therapy. Due to these abilities, new oxime compounds have been synthesized, and their biological activity has been verified. Often, modification of carbonyl compounds into oximes leads to increased activity. Nevertheless, in some cases, oxime activity is connected to the activity of the substrate. Recent works have revealed that new oxime compounds can demonstrate such functions and thus are considered to be potential drugs for pathogenic diseases, as adjuvant therapy in various types of cancer and inflammation and as potential next-generation drugs against OP poisoning.

Keywords: oximes; OP poisoning; antimicrobial; biological activity

1. Introduction

The progressive and rampant development of the world, technological advances, overpopulation and environmental issues may cause many threats to human health. We are facing serious problems with a growing number of cancer-related and pathogenic diseases that cannot be effectively treated in traditional ways. Other detrimental factors are dangers from the development of agriculture, especially fertilization and the use of pesticides. The exposure to organophosphates (OPs) results in poisoning, and untreated OPs can lead to death. Obviously, the grand developments in medicine in recent years are undeniable, but drug alternatives have yet to be sought. Research is largely inspired by substances that occur in nature. Since 1960s plant oximes are known as one of the precursors of secondary metabolites in plants both aliphatic and aromatic forms. The majority of oximes are produced by one of the CYP79 family member—cytochrome P450. All flowering plants possessing CYP79 blueprint are, theoretically, able to produce oximes. These metabolites are often elements of the protective systems of plants that act in their defense against herbivores and pests in particular as intermediates in cyanogenic glycosides formation. Most of plant oximes are excreted as volatiles, only those that are converted into glycosides are stored in the plant. Oximes of natural origin often possess biological activities. Their presence in the biological sample might be omitted: oximes are intermediates for biosynthesis of other metabolites and their concentration is often low. [1]. Oximes in animals are, among other things, part of the olfactory communication between the animals. Oximes occur in nature as elements of metabolic pathways and are part of the enzymatic oxidation of amino acids and products of its decarboxylation. Two isomers are possible due to specificity of the C=N double bond; there are two
stereoisomeric forms according to the $E/Z$ configuration [2]. $E$ isomers of oximes are more biologically active than $Z$ isomers. Moreover in metabolic processes, certain isomers and a mixture of both forms are obtained. It is possible that chemical conversion $E$-isomer to $Z$-isomer in enzyme catalyzed reaction takes place [1]. During chemical synthesis, both stereoisomers are obtained, most of which can be separated completely [3]. The oxime moiety can be biotransformed, for example, during oxidation or reduction. The most important property of oximes is their ability to complex with metals, which makes them suitable for the role of potential therapeutic agents as inhibitors of metalloenzymes [4]. Another aspect is the poor water solubility of oximes, but a property that is obligatory to mark a compound as a potential drug. Therefore, many researchers have modified existing oximes to improve their water solubility. One such modification has been presented by Okolotowicz et al., who obtained one amidine-oxime with excellent water solubility (300 mg/mL). Oximes can be formed through a fusion strategy. Implementing reactive C=O groups and electron pair donor into biomolecules is also one of oximes features [5]. Moreover, they assume a second- and next generation catalyst role in bioconjugation [6]. The aspect that should be taken under consideration for the application of oximes as drugs is its cytotoxicity. On the one side cytotoxicity of oximes might cause side effects of certain therapies, on the other side cytotoxic activity allows one to consider oximes as potential anticancer agents [4]. Many oximes are already known as therapeutic agents. This is why we have decided to review the recent information about unsubstituted oximes, their anti-inflammatory, antimicrobial, antioxidant and anticancer activities, and their role against OP poisoning.

2. The Anti-Inflammatory Activity

Anti-inflammatory activity has been indicated for various oximes with diverse skeletons. The Park group reported that steroidal antidrugs with the C-16,17-isoxazoline ring system—oxime derivatives (Figure 1) had a high binding affinity with no suppressive effects. Moreover, nitric oxide (NO) production was blocked. Many pathophysiological events are associated with production of NO. It is also a response to proinflammatory cytokines. Moreover both oxime derivatives presented the ability to bind to the glucocorticoid receptor of liver cytosol, which might indicate ability to exert biological activity [7].

![Figure 1](image.png)

**Figure 1.** Fluorinated oxime derivatives with the C-16,17-isoxazoline ring system. (a) with methoxy group and (b) with hydroxyl group.

Additionally, one oxime synthetized by Li was found to be a potent compound in blocking NO ($IC_{50} = 6.66 \mu M$) and interleukina 6 (IL-6; $IC_{50} = 5.07 \mu M$) production. IL-6 is one of the proinflammatory cytokines. [8]. The results of the Tharini and Sangeetha study indicate that 3,3-dimethyl-2,6-dimethylpiperidine-4-one oxime (Figure 2) has severe general anti-inflammatory activity in contrast to the typical drug dexamethasone [9].
Zeferino-Diaz and coworkers recently presented research on oxocholestan oxide diosgenin derivatives (Figure 3) as potential anti-inflammatory drugs. In in vivo studies their compounds have been indicated to reduce inflammation and edema triggered in mice ear. The expression of proinflammatory genes such as tumor necrosis factor (TNF-α), prostaglandin-endoperoxide synthase 2 (COX-2) and IL-6, with macrophage migration inhibitory factor (MIF) was repressed by the three most active oximes [10].

In their research Liu and colleagues presented in vivo activity of 6-bromoindirubin-3′-oxime (Figure 4) on the inflammatory reaction. They analyzed response to mastitis induced by lipopolysaccharide and signals of inflammation in mouse mammary epithelial cells (MMECs). Pretreatment with tested oxime led to downregulation of the expression of the proinflammatory factors and reduced inflammatory lesions [11].

Kasare et al. presented studies involving protein denaturation inhibition bioassay of bovine serum albumin to examine if protein is protected from denaturation. Both tested ligands (Figure 5) acquire remarkable anti-inflammatory activity in comparison to diclofenac sodium, achieving values of IC₅₀ 46.76 µM/mL and 55.77 µM/mL respectively [12].
Three of compounds (Figure 6) possessing oxime moiety presented excellent general anti-inflammatory activity in in vivo studies, using paw edema in rats induced by carrageenan injection, compared to indomethacin. Observed percentage of edema inhibition were 100%, 101% and 111% respectively [13].

Hassan et al. presented results of anti-inflammatory activity of various novel quinoline hybrids. Modification of already existing antibiotics into oximes is a subject that has appeared in research over the years. Good examples of such modifications are those in cephalosporin antibiotics.

Cytotoxicity is one property of oximes; thus, oximes are therapeutic agents for bacterial, fungal and viral infections. Nocardicin A (Figure 7) is the first β-lactam antibiotic isolated from *Nocardia uniformis* [15]. The presence of the oxime moiety in this antibiotic makes it less stable to β-lactamases [16].

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**Figure 5.** Azo-azomethine based oxime derivatives: (a) with methyl group and (b) with methoxy group.

**Figure 6.** Quinoline 1,2,4-triazole/oxime derivatives: (a,b) with phenyl group linked to triazole ring; (c) with allyl group linked to triazole ring (c).

With the same method Abd-Ellah and coworkers tested 1,3,4-oxadiazole/oxime derivatives as a result on of the hybrids obtained 96.67% reduction in edema [14].

3. The Antimicrobial Activity

Modification of already existing antibiotics into oximes is a subject that has appeared in research over the years. Good examples of such modifications are those in cephalosporin antibiotics.
Improvement of water solubility of oximes can be achieved by a modification of oxime moiety by attaining their ether and ester derivatives. Ceftobiprole medocaril (Figure 8b) is a fifth-generation cephalosporin antibiotic [17]. Prodrug of ceftobiprole with satisfactory water solubility is shown in (Figure 8a). It is a β-lactam antibacterial agent from one of the cephem series of cephalosporins. Its antibacterial activity is connected with the ability to bind to penicillin-binding proteins (PBPs) [18].

Figure 8. (a) Prodrug of ceftobiprole and (b) ceftobiprole medocaril.

Paulsen and colleagues synthetized (+)-N-6-hydroxyagelasine D, the enantiomer of a well-known secondary metabolite from marine sponges—(−)-ageloxime D, [19]. The authors revealed that the previously proposed structures of (−)-ageloxime D extracted from a natural product [20] are in fact not an oxime, as the spectral data did not match. However, (−)-ageloxime can be obtained by a basic hydrolysis of agelasine D. (−)-Ageloxime D inhibits biofilm formation from Gram-positive bacteria Staphylococcus epidermis [19] but is unable to inhibit the growth of planktonic bacteria (MIC > 45 µM) [20]. Proposed (+)-N-6-hydroxyagelasine D bromide also possesses the ability to reduce biofilm formation of Staphylococcus epidermidis by 90% at 63 µM [19].

Many antimicrobial active compounds are modified to resemble oximes to increase their activity. The compound 5,7-dimethoxyflavone carbonyl was modified into an oxime, and this modification amplified its antifungal functions [21]. In their research, Min et al. synthesized new oxime esters that had antifungal activity. In addition, they also considered the E, Z stereoisomer substrates of 3-caren-5-one oxime (Figure 9a,b), which were separated for the first time. Both stereoisomers had relative inhibition rates above 50% against Physalospora piricola [22].
Synthetic naringenin, a flavonoid that naturally occurs in grapefruits, was modified to contain oximes by Kozłowska et al. Four derivatives have indicated to have antibacterial activity. The minimal inhibitory concentration (MIC) against *Staphylococcus aureus* was below 100 µg/mL. Two oximes (Figure 10) showed MIC values against *Staphylococcus aureus* and *Bacillus subtilis* below 12.5 µg/mL [23]. In comparison to naringenin itself, which had no antimicrobial activity, the results obtained were satisfactory [24].

Additionally, Xu observed that in chalcone derivatives oxime moiety enhances antimicrobial activity [25]. The presence of oxime moiety in compound (Figure 11b) resulted with a MIC value of ≤128 µg/mL [26] whereas compound (Figure 11a) had a MIC value of 150 µg/mL [27] against *B. subtilis*. Similar difference was observed for both of compounds against *A. niger* obtained MIC values was 300 µg/mL [27] and ≤256 µg/mL (oxime) [26].
Kozioł et al. presented the results (MIC values) of experiments performed on synthesized oximes on bacteria. Among nine oximes, three (Figure 12) presented satisfactory antibacterial activity. Oximes (a) and (c) had the best antibacterial activity against *Staphylococcus aureus*, whereas oxime (b) presented the best antibacterial activity. Their MIC values were 100 µg/mL [28].

The antiviral activity of *E,Z* isomers of Janus-type nucleoside against *Herpes simplex virus-I* (HSV-1) were tested by Liu et al. Most oximes demonstrated improved anti-HSV-1 activity compared to the Janus-type nucleosides. Among the oximes, exquisite anti-HSV-1 activity was displayed by two compounds (Figure 13), both had low IC_{50} values of 0.05 and 0.04 µg/mL. Moreover the compounds shown in Figure 13 also presented antiviral activity against distinct viruses as *Herpes simplex virus-II* (HSV-2), influenza viruses (H3N2), coxsackievirus B3 (CVB3), *Hepatitis B virus* (HBV), *Hepatitis B virus* (HCV) and Human papillomaviruses (HPV) [29].

Chan et al. tested antiviral activity of indirubin-3′-oxime (Figure 14) by the assessment of the infectious virus titers in epithelial cells and human macrophages. Viral replication was inhibited by about 10-fold in H5N1 virus–infected macrophages and ATIs by oxime compared to untreated cells. In the H1N1 treatment of virus–infected macrophages at 24 h post-infection, as well as in infected ATIs at 48 h post-infection similar results were observed. Additionally, viral matrix 1 protein expression in...
H5N1 virus-infected macrophages was effectively suppressed. In vivo studies on mice have proven that indirubin-3’-oxime does not have a positive effect on survival and does not promote weight loss, despite that the reduction of expression and secretion of cytokine and chemokine is observed [30].

![Indirubin-3’-oxime](image)

**Figure 14.** Indirubin-3’-oxime.

**4. The Antioxidant Activity**

In addition to having anti-inflammatory activity, naringenin also revealed antioxidant properties. The modification of this compound into an oxime increased its antioxidant activity. The oxime is considered a radioprotector or an anticancer agent [31]. Another example of an oxime with a high antioxidant activity is an isoxanthohumol oxime (Figure 15). This compound has a 200 times higher activity than isoxanthohumol, which is comparable to ascorbic acid [32].

![Isoxanthohumol oxime](image)

**Figure 15.** Isoxanthohumol oxime.

Kaur et al. evaluated the content of *Anethum graveolens* L. essential oil and its relationship to its antioxidant activity. Five parameters were tested. The carvone oxime has indicated to have good radical scavenging activity. For the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical the *IC*$_{50}$ reached 0.31 mg/mL, for the hydroxyl radical the *IC*$_{50}$ was 0.23 mg/mL and for the nitric oxide (NO) radical the *IC*$_{50}$ was 0.31 mg/mL. The ferric reducing antioxidant power (FRAP) mean value was 196.88 mg/mL. The mean superoxide radical scavenging activity was 44.57 with an *IC*$_{50}$ value of 0.31 mg/mL [33]. Bandeira et al. proved that organotellurium oximes have promising radical scavenging activity. Against the DPPH radical both compounds presented in Figure 16 had *IC*$_{50}$ values of 5.12 ± 0.71 mg/mL and 7.79 ± 0.33 mg/mL, respectively. Both oximes have also been examined for their ability to reduce the 1-n-propyl-tetrazole complex with Fe$^{3+}$ (PTZ-Fe$^{3+}$) complex in 2,2’-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radicals and FRAP. The results showed an antioxidant activity similar to that demonstrated by trolox. The first oxime had a capacity of approximately 8 mM TE/g (ABTS) and 11 mM TE/g (FRAP). The second oxime had a capacity of approximately 7 mM TE/g (ABTS) and 14 mM TE/g (FRAP), which were similar to the control quercetin [34].
Bensegueni et al. presented original work on antioxidant activity of aromatic oximes. Outstanding results were obtained by one of the oximes (Figure 17). Percentage of DPPH inhibition was 34.50 ± 1.56. Additionally, in Cupric reducing antioxidant capacity assay (CUPRAC) with an \( A_{50} \) of 2.60 ± 0.16 µg/mL [35].

Siddiqui and colleagues have tested 2,6-diphenylpiperidine-4-one oxime derivatives (Figure 18). The DPPH activity was tested. Both oximes presented antioxidant activity. Compound (Figure 18b) presented better activity (IC\(_{50}\) + SEM = 4.53 ± 0.41 µg/mL) than other oxime (IC\(_{50}\) + SEM = 11.13 ± 0.17 µg/mL) [36].

5. The Anticancer Activity

Pregnenolone is an endogenic steroid and a precursor in the biosynthesis of steroid hormones. Pregnenolone was modified to a benzylidene oxime and two other. The derivatives were tested for against cancerous cells: colon (HT-29, HCT-15), central nervous system (SF-295), lungs (HOP-62, A-549) and breast (MCF-7). All of the derivatives showed promising anticancer properties [37]. The oxime presented in Figure 19 has a specific function as an inhibitor of kinases during the cell cycle and it also suppresses tumor growth. It was tested in liver cells (Hep G2) [38].
Other oximes that display anticancer activity are alkannin and shikonin derivatives. These modified compounds (Figure 20) show no activity in healthy cells, but they are active in K562 leukemia cells [39].

Qin et al. prepared oxime derivatives of $\alpha,\beta$-unsaturated tetralone. All synthetized compounds were tested on its antiproliferative activity on human cancer cells: PC-3, HT-29, MCF-7, H-460, A-549, PaCa-2 and PANC-1. The most active compounds were then assessed for their mechanistic effects on the EGF receptor (EGFR) tyrosine kinase (TK), BRAF$^{V600E}$ gene mutation and tubulin polymerization. In vitro studies were carried out in order to determine the potential of reversion of the efflux-mediated resistance of cancer cells. Three of the oxime derivatives (Figure 21) were extremely active.

Significant antiproliferative activity was presented by one of the oxime compounds (Figure 21c) against the PANC-1, A-549, PaCa-2 and PC-3 cell lines, achieving $IC_{50}$ value of 0.02 $\mu$M. Another compound (Figure 21a) inhibited the BRAF$^{V600E}$ gene mutation with an $IC_{50}$ value of 0.9 $\mu$M. One of the oxime analogs (Figure 21c) presented excellent inhibitory activity to EGFR TK ($IC_{50}$ of 0.07 $\mu$M). Moreover, all three compounds have been indicated to have dual roles as anticancer agents and MDR (multidrug resistance) reversal agents [40]. Additionally, Kozłowska et al. evaluated the cytotoxicity of naringenin derivatives in the human colon adenocarcinoma HT-29 cell line. The incorporation of the oxime group into one of the compounds allowed this compound to become a highly potent antiproliferative agent from a nonactive substrate. The oxime (Figure 10b) had an $IC_{50} = 4.59 \pm 0.56 \mu$g/mL. Further, three other oximes revealed decreased $IC_{50}$ value compared to the positive control,
cisplatin and were a bit weaker than the cytostatic antibiotic, doxorubicin [23]. Zha et al. synthesized α,β-unsaturated carbonyl-based oximes containing ligustrazine moiety. Those compounds strongly inhibited growth of five cancer cell types, A-549, PC-3, MCF-7, PaCa-2 and HT-29. The best activity, as an inhibitor of tubulin polymerization, BRAF\textsuperscript{V600E}, focal adhesion kinase (FAK) and EGFR-TK, was displayed by the oxime shown in Figure 22 [41].

![Oxime Structure](image)

**Figure 22.** α,β-unsaturated carbonyl based oxime with ligustrazine moiety.

Often, oximes are more polar than their baseline molecules [42]. Griseofulvin oxime derivatives proved to have improved anticancer activity than the baseline molecule. Presence of the oxime moiety at the 4′ position improved the potency 2-fold to 12 µM [43].

### 6. A Counteractive Agent to Organophosphorus Compound Poisoning

Poisoning from organophosphorus (OP) compounds is a very large therapeutic problem, especially from pesticides and substances that pose serious danger to the nervous system. Treating of OP-poisoning depends on the type of nerve agent, which can distinguish the G-type and V-type according to volatility [44]. Additionally it is proven that the location of the oxime moiety is the most important for the capacity of reversing different OP inhibitors effect [45]. There are two therapeutic agents used in OP poisoning: pralidoxime and obidoxime (Figure 23a,b), which are applied as reactivators of OP-inhibited acetylcholinesterase (AChE) in the presence of reversible antagonists of a muscarinic receptor, such as, for example, atropine [44]. Recently, pralidoxime was tested in vivo for its tissue and blood distribution profiles in nonintoxicated rats. The considerable uptake was observed in the kidney and quite lower rates were observed in the liver, lung and heart, with lesser amounts in the brain and blood [46]. Another three promising oxime drugs are asoxime dichloride, trimedoxime dibromide and methoximedichloride, which were synthesized in the previous century [44]. Wilhelm et al. tested reactivators on OP-poisoned guinea pigs. Methoximedichloride is efficacious against broad spectrum of OP (soman, tabun, cyclosarin, sarin and VX, and the chlorpyrifos oxon, pesticides paraoxon and phorate oxon) in case of 24-h survivability in equimolar dose (146 µmol/kg). Asoxime dichloride was also active but on the second tier, trimedoxime dibromide as the toxic compound was tested in a dose of 35 µmol/kg and offered survival protection between the second and third tier [47]. Costa et al. proposed two new oximes (Figure 23c,d) to reactivate human AChE and butyrylcholinesterase (BChE) that has been inhibited by organophosphate compounds, mainly the inhibitory activity of three OPs: chlorpyrifos, diazinon and malathion [48]. Unfortunately, oximes are mostly useless against soman poisoning [49].
The oxime presented in Figure 23c reached a percent (%) reactivation ± SEM at a concentration of 1 µM of 10 ± 0.016, and in Figure 23d showed a value of 7 ± 0.009 against chloropyrifos. The oxime presented in Figure 23b had a percent (%) reactivation ± SEM at a concentration of 1 µM of 20 ± 0.010, and shown in Figure 23d oxime 2 showed a value of 12 ± 0.025 against the second OP. The oxime presented in Figure 23d had percent (%) reactivation ± SEM at a concentration of 1 µM of 5 ± 0.012, and the oxime shown in Figure 23d showed a value of 12 ± 0.019 against the third OP. The oximes shown in Figure 23c,d had similar activity to pralidoxime: oxime (Figure 23c) had the same percent reactivation against diazinon poisoning as obidoxime [48]. Žunec et al. presented their in vivo research on new therapeutic agents against paraoxon poisoning. Two oximes presented in Figure 24, stood out for their low acute toxicities and excellent antidotal effects.

Oximes have been applied in male mice in the amount of 5% of their lethal dose (LD50) and combined with atropine, resulting in a protection index (PI) of 74.1 and 100, respectively. Moreover, the use of these combinations increased the survival of all animals up to 63.0 of the LD50 of paraoxon. Both oximes might be good antidotes for OP poisoning. Moreover, both monoximes are the least toxic among all tested. The LD50 of oxime presented in Figure 24a was 672.8 mg/kg [50]. Kuca et al. presented their research results on trisquarternary bisoxime as a potential drug against OP poisoning. Unfortunately, it cannot be considered an AChE reactivator because the rate of reactivation of AChE was worse than for standard reactivators. The oxime shown in Figure 25 has indicated to reactivate AChE after inhibition by sarin and agent VX with a percent reactivation above 20% at high concentrations (10-3 M). Moreover, this compound will not penetrate the blood–brain barrier due to three positive charges. However, the high hydrophilicity and relatively large size of the studied bisoxime reactivator makes it an interesting candidate for BChE pseudocatalytic reactivation [51].
Another approach was presented by Santoni and colleagues. They synthesized a tetrahydroacridine linked to the non-quaternary oxime reactivator presented in Figure 26 and a chlorinated derivative. Both molecules proved to have excellent nerve agent antidote efficacy (kr2 reactivation), better than the well-known drug obidoxime against three OPs: agent VX, sarin and paraoxon [52].

![Figure 26. Tetrahydroacridine based oxime.](image)

Zorbaz et al. presented two oximes (Figure 27a,b) that proved to have notable potential in cyclosarin poisoning especially in reversing hBChE blockage. Moreover, both oximes have been predicted to cross the blood-brain barrier at satisfactory levels. [53].

![Figure 27. Hydroxypiridine oxime derivatives: with pentyl (a) and heptyl (b) linker.](image)

An active compound able to reverse OP poisoning was presented by Kovarik et al. The best results in the in vivo study were obtained against agent VX and paraoxon. The compound shown in Figure 28 proved to have the greatest antidotal potential with a PI above 10 and ensured mouse survival against 10× the LD<sub>50</sub>. Moreover, this oxime proved to have a better PI against tabun poisoning than the other commonly known drug, trimedoxime bromide. No significant cytotoxicity was observed [54].
7. Conclusions

In conclusion, oximes were indicated to have a therapeutic potential. Some have already been used as drugs for OP poisoning and antibiotics. Many newly synthesized oximes have shown promising properties, such as antimicrobial, anti-inflammatory, antioxidant, anticancer and against OP poisoning. Consequently, further studies on oximes and their biological activities should be undertaken to determine more active agents that might be considered as effective drugs.

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