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Review article

The potential of MAO inhibitors as chemotherapeutics in cancer: A literature survey

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ABSTRACT

Drug resistance in cancer is determined by genetic mutations and adaptations of tumor cells to drug treatments, raising a challenge in the treatment of cancer. Factors such as prolonged drug exposure, genetic variability among patients, and tumor heterogeneity have been established as contributors to rising incidence of drug resistance, prompting ongoing research into alternative therapies and combination treatments to overcome this challenge.

Monoamine oxidases (MAOs), including both isoforms MAO-A and MAO-B, are mitochondrial enzymes responsible for the catabolism of monoamine neurotransmitters such as dopamine, norepinephrine, and serotonin. While these enzymes play a pivotal role in the nervous system, their role in tumorigenesis has garnered increasing attention in the last years. Recent studies, in fact, have highlighted the potential of MAO inhibitors (MAOIs) as antitumor agents, emphasizing their use as standalone treatments or in synergy with traditional anticancer therapies, focusing on pathways involved in tumorigenesis. This review aims to provide a comprehensive overview of MAOIs currently under study for their potential antitumor activity, focusing on their structural characteristics, mechanisms of action, and efficacy in preclinical and clinical settings, referencing key articles in the field.

1. Cancer: biological mechanisms of drug resistance

Cancer is a multifactorial disease [1] caused by both environmental and genetic factors that spreads within the body to create metastases [2]. It is estimated to be the second leading cause of death in the world [1]. In fact, there were almost 20 million cases and 10 million deaths in 2022 [3]. For men, the most frequent types of cancer are prostate, lung, stomach and liver cancer, while for women, they are breast, cervix uteri, colon, lung and thyroid cancer [3]. Traditional therapies for the treatment of cancer comprise surgery, radiotherapy and chemotherapy, while immunotherapy [4] and stem cell therapy [5] represent the newest and most promising treatments. At the moment, there are lots of possible therapies, but their success depend upon several factors, including immune surveillance and drug resistance [6]. The latter occurs when the cancer cells develop a tolerance to drug therapy [7] and this is a major cause of failure of a given therapeutic treatment (Fig. 1) [8].

In drug-resistant tumor cells, in fact, there are a number of drug efflux transport proteins involved in pumping low molecular weight drugs out of the cell, thus preventing the critical concentration of drug accumulation within the cells themselves. Among the family of the so-called ATP binding cassette (ABC) transporter proteins, *P*-glycoprotein (*P*-gp), encoded by the MDR1 gene, is considered as one of the main obstacles in the anticancer therapy of several cancers as it is characterized by a wide spectrum of activity. Other known MDR proteins are the multi-drug resistance protein-1 (MRP-1, ABCC1), the breast cancer resistance protein (BCRP, ABCG1), the mitoxantrone resistance protein (MXR1/BCRP, ABCG2) and the ABCB4 (MDR3) protein [6]. It should be noted that several drug efflux transporters, including *P*-gp, MRP and BCRP, have been identified in particular cell populations, defined as cancer stem cells (CSCs) [9].

DNA repair mechanisms are another method by which cancer cells show drug resistance [10]. They consist of a complex network of proteins (e.g. ATM, ATR, Chk1/2, BRCA1 or p53) capable of identifying DNA damage and repairing it, allowing the cell to survive.

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Another aspect to take into account is the gene amplification of receptors that can very often compromise the success of drug treatment. Furthermore, the alteration of the balance between pro-apoptotic and anti-apoptotic activation pathways contributes to the establishment of biochemical phenomena of resistance to cytotoxic xenobiotics [9].

Cytochrome P450 and glucuronyl transferases are enzymes that are most involved in drug metabolism. They are responsible for the biotransformation of many anticancer drugs. Alterations in their functioning cause a lowering of intracellular levels of drugs, thus determining a low availability of active drug [10].

In addition to the factors described above, other processes responsible for chemoresistance involve epigenetic alterations due to acetylation or methylation of microRNAs (miRNAs) [6], variations in the tumor microenvironment (TME) and oxidative stress [11], the presence of hypoxia regions [9] and alternative mechanisms to aerobic glycolysis, which stimulate the activation of the epithelial to mesenchymal transition (EMT) [10], heterogeneity and plasticity of cancer cells [12]. All these mechanisms can act independently or in combination by promoting multi-resistance in cancer.

Hypoxia is a main characteristic aspect of the tumor microenvironment in senescence, in which there is a low supply of oxygen [6]. It promotes chemoresistance through interference with cellular plasticity, leading to tumor heterogeneity and progression [13]. In fact, several scientific evidences indicate that the hypoxic condition in the tumor is able to control the phenotypic plasticity of cells of different types of cancer by selecting metastatic phenotypes. In the case of melanoma, for example, cellular plasticity leads to the formation of new blood capillaries [9].

Human cells are very plastic and under physiological conditions can generate new tissues or reprogram into other types of cells through finely regulated mechanisms [12]. In pathological conditions, however, these mechanisms are lost by generating multiple cell populations and giving cells new functional properties [6]. For example, a growing number of studies have shown that activation of the EMT process can generate cells with greater motility, greater invasive potential and stem properties [11]. The stem cells that can be derived from that process, on the other hand, have greater plasticity when they are not found within their tissues of origin [12]. This observation has led to the most recent idea that the origin of cancer is to be found in these pluripotent stem cells, which despite being aberrant cells [14] maintain several properties common with normal stem cells, including the ability to self-renew by cell division, generating a cell population with tumor phenotype [6].

According to the cancer stem cell (CSC) model, these cells survive even after completion of primary therapy, contributing to the onset of drug resistance and causing recurrence and metastasis [15]. CSCs expressing the transmembrane protein CD133 ($CD133^{+}$), in fact, are characterized by a therapeutic refractoriness and are able to evade apoptosis mechanisms and develop multi-drug resistance mechanisms [16] creating a particular metastatic niche that contributes to determining the overall growth of the tumor, its survival, angiogenesis, invasion and the formation of the same metastases.

However, the existence of CSCs may not be the only way by which cancer cells acquire plasticity. There is, in fact, a more traditional theory of cancer that proposes an alternative process that takes into account epigenetic instability and the tumor microenvironment. Recent studies have suggested that the tumor microenvironment and the resulting tumor heterogeneity are fundamental aspects in drug resistance and that resistance to a wide range of anticancer drugs is indicative of the dynamism of the tumor tissue itself [9]. The tumor microenvironment includes the extracellular matrix, interstitial tissues, stromal cells (such as cancer-associated fibroblasts, mesenchymal cells, tumor-associated macrophages, endothelial cells, and CSCs) [14] and some paracrine signals [9], (such as those mediated by serotonin and its metabolites) [17] which all stimulate tumor growth, development, evolution and tumor invasiveness besides the drug resistance factors [17]. Some of the pathways that are activated are Wnt/B-catenin, Notch and Hedgehog, all typical of cancer stem cells. For example, Wnt/b-catenin promotes the activation and expression of some stem cell markers such as ALDH and CD44 [18]. The Notch and Hedgehog pathways, on the other hand, if altered, in breast cancer, lead to the onset of the phenomenon of self-renewal of CSCs [16].

Moreover, a number of markers have also been used for the isolation of CSCs subsets and their presence is indicative to distinguish different types of cancer including breast cancer, colorectal cancer, chronic and acute myeloid leukemia, pancreatic cancer, head and neck neoplasms [9]. In this case an important role is played by monoamine oxidases MAO-A^{11} and MAO-B [19]. Their presence in biological fluids and tissues, in fact, is quantified to evaluate the disease status and its degree of

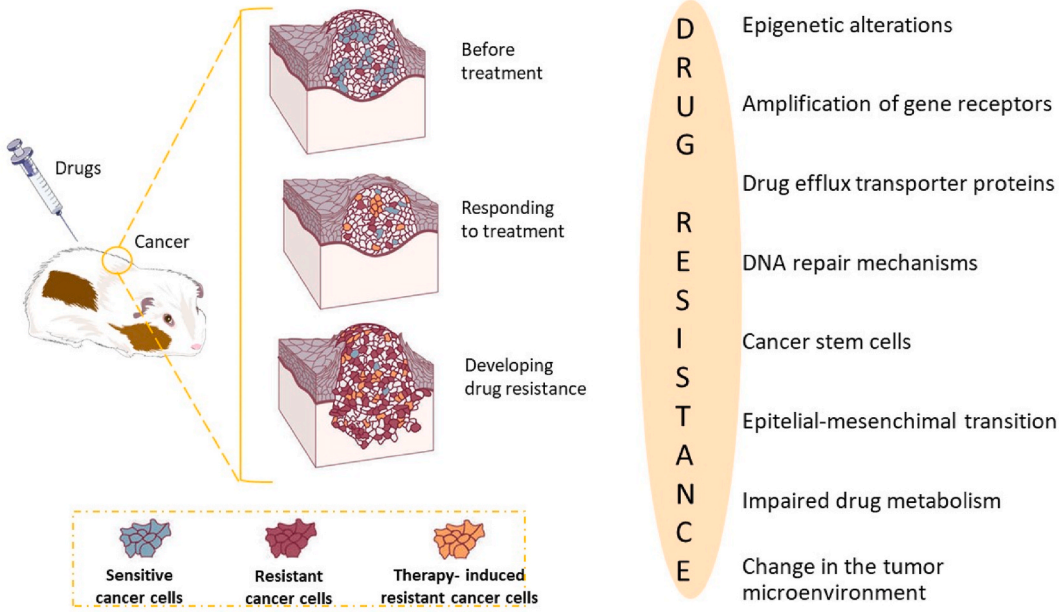

Fig. 1. Mechanisms of drug resistance in cancer. These mechanisms can act directly or indirectly, through different signal transduction. Image has been adapted from ref. 7.

malignancy. It is assumed that the activity of amine oxidases is present both in tumor tissues and in the biological fluids of cancer patients and that the increase in their expression would seem to be associated to the increase in intracellular amines [13]. In addition, some correlation between the activity of MAO (both MAO-A and MAO-B) and the occurrence of a malignant tumor has been demonstrated [20]. On the other hand, MAOs, and in particular MAO-A, may be targeted with inhibitors in combination with chemotherapeutics for the treatment of cancer [21].

Recently, the presence of MAO-A in tumor tissues has been identified as one of the main causes of tumorsphere formation by CSCs [15]. Interestingly, the same author also found that breast cancer cells from both mouse and human synthesize serotonin (5-HT) which promotes tumorigenesis through pathway-mediated signaling with 5-HT receptor [22]. Therefore, as MAO-A regulation varies in different types of cancer, it is likely that 5-HT receptors may also play a distinct role in the progression of tumorigenesis or metastasis [19]. In 2019, Gwynne et al. also demonstrated that tumorspheres derived from various human breast cancer cell lines exhibit significantly higher expression of MAO-A transcripts. Furthermore, elevated MAO-A levels are commonly observed in breast cancer cell lines that have developed resistance to anticancer drugs and are associated with poor recurrence-free survival in patients with high-grade, ER-negative breast tumors. These findings suggest that MAO-A is crucial for tumorsphere formation and that the discovery of selective MAO-A inhibitors provides initial evidence of their anticancer potential [23].

2. Monoamine oxidases: general characteristics, structure and pharmacophoric model

MAOs are mitochondrial enzymes responsible for the catabolism of biogenic amines [24]. MAO exists in two isoforms, namely MAO-A and MAO-B (Fig. 2), both of which are necessary for the metabolism of monoamines, such as serotonin, melatonin, norepinephrine, epinephrine, dopamine, tyramine, tryptamine, etc. [25] Moreover, considering their crucial role in neurotransmitter metabolism, malfunctioning MAOs could be responsible for a whole range of neurodegenerative diseases [26] and various psychiatric problems [27]. It is well known that abnormal levels of those enzymes underlie diseases such as schizophrenia, migraine, attention deficit disorder, addictions, including alcoholism [27]. In addition, MAOs have been shown to play an equally significant role in other diseases not directly related to the nervous system, such as cardiovascular diseases, metabolic diseases, sexual dysfunction, diseases of ageing and, last but not least, cancer [27].

In 2002 and 2005, the crystal structures of the human MAO-B in complex with isatin (PDB ID: 2BK5) [28] and of the MAO-A complex with clorgyline (PDB ID: 2BXS) [29] were identified. MAOs are flavoproteins which contain a covalently bound flavin adenine dinucleotide (FAD) cofactor [30]. Both MAO isoenzymes have a substrate binding cavity and an inlet cavity in which the substrate binding sites are hydrophobic and surrounded by aromatic and aliphatic residues (Fig. 3) [29]. In human MAO-A, the substrate binding site is a 400 $Å^3$ cavity, while in MAO-B, a smaller lipophilic cavity, called an “entrance cavity," lies between the main substrate binding site and the protein surface [31]. Depending upon the substrate or inhibitor, cavities remain separate or interconnected. Four critical amino acid residues were identified in the structure of MAO-A, Lys305, Trp397, Tyr407 and Tyr444 and their residue equivalents in MAO-B, Lys296, Trp388, Tyr398 and Tyr435, amino acids playing an important role in the catalytic activity of both MAOs. Furthermore, according to the 3D crystal structure of polyamine oxidase, non-covalent binding to FAD can be mediated by Lys305, Trp397 and Tyr407 for MAO-A and Lys296, Ile199, Trp388 and Tyr398 for MAO-B. On the other hand, in the structure of enzymes there may be Tyr residues forming aromatic sandwiches that are able to stabilize the binding of the substrate [32]. In human MAO-B, moreover, the presence of an Ile199, which may exist in two distinct conformations, acts as a gate, because of its conformation, which can be closed and separate the substrate and the inlet or open joining the two cavities [28]. Ile 335 in MAO-A and Tyr326 in MAO-B are two further differences in substrate binding regions of the two enzymes, contributing to their selectivity [33,34].

The elucidation of the two MAO crystal structures had great importance for the rational design of new isoform-selective MAO inhibitors (MAOIs). Pharmacophore modeling can also explain biological/chemical complementarity with the target. One of the common challenges facing this type of modeling is building the final model, especially when there are large structural differences in the compounds [21].

3. Scaffold of MAO inhibitors

Several chemical classes were first identified, exhibiting MAO inhibition, including hydrazines, propargylamines, cyclopropylamines, pyridine-containing derivatives (Fig. 4) [34]. The first generation of MAOIs used in therapy belong to these main classes. The selectivity of these compounds for MAO-A or MAO-B is determined by their interaction with the distinct substrate-binding pockets of each MAO isoform.

MAOIs, in fact, can be classified based upon their selectivity in MAO-A (MAOAIs) and MAO-B inhibitors (MAOBIs). MAOAIs, such as

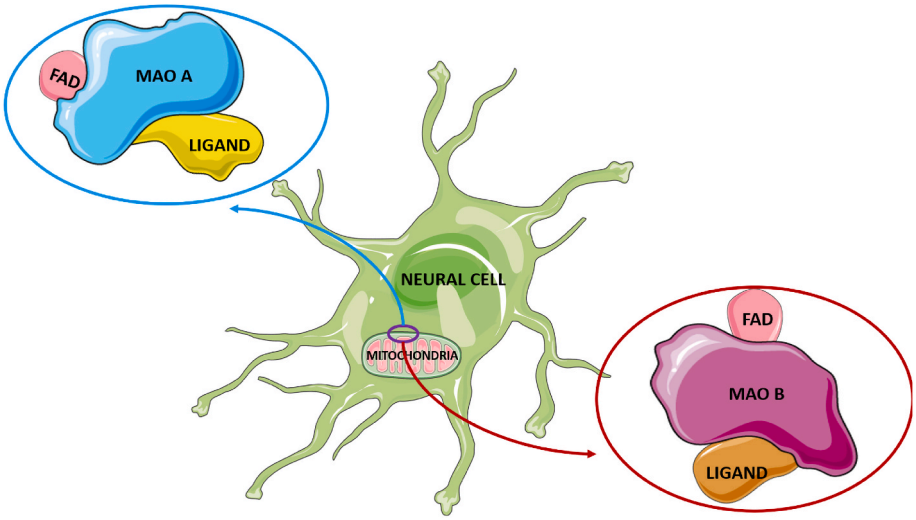

Fig. 2. Location of MAO-A and MAO-B.

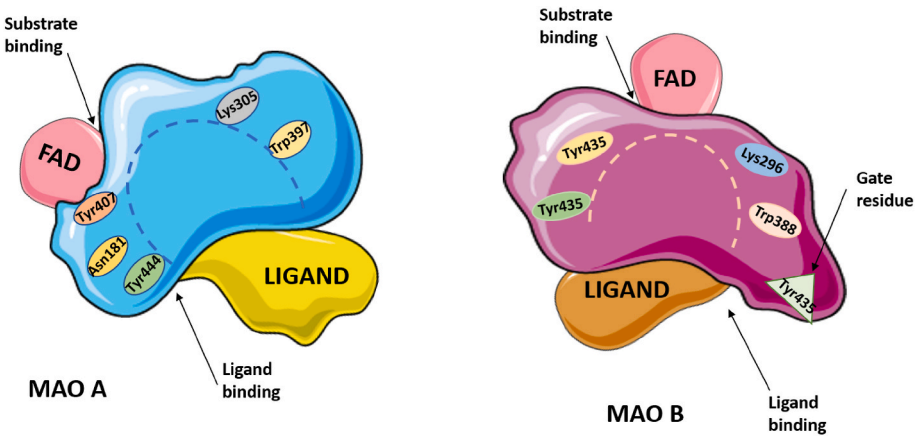

Fig. 3. Ligand binding active site of MAO enzymes. Adapted from ref. 24.

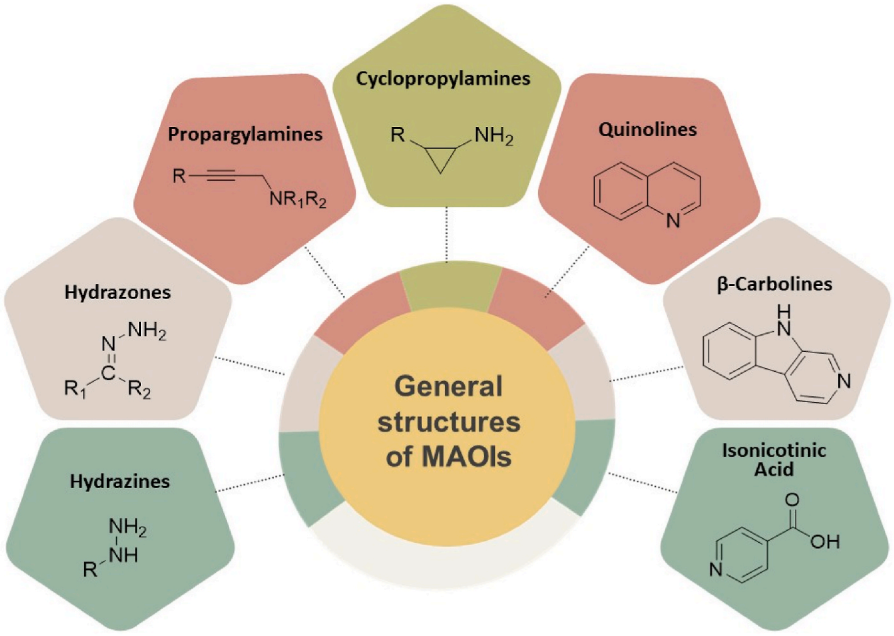

Fig. 4. General structures of MAOI scaffolds.

clorgyline, typically feature a propargylamine scaffold that covalently binds to the FAD cofactor, while MAOBIs, like selegiline, contain a similar propargylamine group but are modified to enhance binding to the MAO-B active site. The chemical structure of these inhibitors is quite diverse, but there are some common scaffolds that have been identified in the research; they generally contain a core structure that allows for the binding to the FAD cofactor or the active site of the enzyme.

1 Hydrazine scaffold

Hydrazines and hydrazones are among the first MAOIs developed and include compounds like iproniazid and phenelzine. Hydrazones act by forming a covalent bond with the flavin cofactor, leading to irreversible inhibition of both MAO-A and MAO-B, permanently inactivating the enzyme [35].

2 Propargylamine scaffold

Propargylamines are characterized by the presence of a propargyl group attached to a tertiary amine and include inhibitors like selegiline and rasagiline, which are specific inhibitors for MAO-B and form covalent adducts with the flavin cofactor. Their selectivity for MAO-B over MAO-A makes them useful for treating diseases as Parkinson's disease (PD) [36] but also highlights their potential in targeting MAO-B-expressing tumors.

3 Cyclic scaffolds

Cyclopropylamines compounds like tranylcypromine inhibit both MAO-A and MAO-B. Their unique three-membered ring structure facilitates the nucleophilic attack of the N5 of FAD, leading to an irreversible binding to the active site, with low A/B selectivity [35].

4 Pyridine-containing scaffolds

Quinolines and beta-carbolines include reversible inhibitors with different selectivity [37]. Isonicotinic acid-based inhibitors, such as iproniazid, are known for having a pseudo-irreversible binding to the enzyme, modifying the active structure in such a way as to prevent the normal functioning of MAO.[35 38]

4. Identification of new active scaffolds as MAOIs

Kumar et al. identified some frequent fragments such as chromenone, benzoquinone, pyrrole, indenone, naphthalenedione, morpholinone, thiophene, benzodioxol, imine-methyleneazolidinone, cyclopropane, cyclobutanedione, furan, azetidine, indole and piperidine, which represent scaffolds or fragments useful for the creation of libraries of potential MAO inhibitors (Fig. 5) [39].

The same authors, using the method of Murcko for scaffolding structure and comparing the bioactivity associated with these molecules in silico, were able to identify scaffolds with better biological activity, particularly the 2*H*-chromen-2-one scaffold (coumarin, Fig. 5). This analysis confirmed the observation of the MAO inhibitory activity reported by some of us for coumarin-based compounds, often showing a multitarget activity profile [40,41].

5. MAOIs: current therapeutic uses

Given their therapeutic use, several MAOIs have been approved by the US Food and Drug Administration (FDA) and marketed for the treatment of many neurodegenerative disorders, although due to the possibility of drug interactions with both food (cheese effect) and other drugs, they do not represent the therapy of choice [39]. MAOIs can be classified into irreversible and reversible inhibitors. Irreversible inhibitors, such as tranylcypromine and selegiline, form a covalent bond with the enzyme, leading to prolonged inhibition. Reversible inhibitors, on the other hand, bind non-covalently and can be displaced by substrate molecules [36]. Phenelzine, isocarboxazid and tranylcypromine are non-selective MAOIs approved by the FDA. Because the use of first-generation MAOIs, such as phenelzine and tranylcypromine, caused several unwanted side effects, several second-generation MAOIs were identified: being again irreversible inhibitors, they led to the onset of important side effects such as tyramine-induced hypertensive crises [19]. Subsequently, a keen interest was devoted to the development of selective MAOIs, like moclobemide (MAOAI) and selegiline (MAOBI), which have demonstrated greater potency and lower toxicity. In addition, reversible inhibitors currently approved by the FDA and used in clinical practice only block the MAO-B enzyme. From literature, it can be deduced how many scaffolds have been brought to research, but none of them are marketed due to failure in phase 2 studies [39].

In addition to the known therapeutic uses, recent studies have highlighted the potential use of MAOIs in oncology, repurposing some of them for cancer therapy [42]. The therapeutic potential of MAOIs in cancer involves multiple mechanisms critical for tumor growth and metastasis [43,44]. The chemical structures of MAOIs that exhibit anticancer properties are characterized by their ability to interact with the flavin cofactor and active site residues of MAOs. Key structural features include propargylamine group, essential for covalent binding and irreversible inhibition of MAO and aromatic ring systems that enhance binding affinity and selectivity by fitting into the hydrophobic pockets of the MAO active sites [38].

6. MAOIs with potential antitumor activity: case studies from the literature

During the last decade, several studies have been published that identify MAO-A, not only as a tumor marker, but also as ROS source ultimately associated with tumor development [11,45]. Wang and collaborators recently proposed the “MAO-A-ROS axis" model, wherein MAO-A not only regulates ROS levels in neurons, but also plays a pivotal role in modulating tumor-associated macrophage (TAM) polarization within the tumor microenvironment (TME). This, in turn, modulates their immunosuppressive polarization through the IL-4/IL-13-induced JAK-Stat 6 signaling pathway. Their findings suggest that MAO-A promotes the immunosuppressive phenotype of TAMs by enhancing oxidative stress. By targeting MAO-A, it is possible to reprogram TAMs into an immunostimulatory state, thereby enhancing antitumor immune responses. This may represent an opportunity to repurpose MAO-A inhibitors, traditionally used in neurological disorders, as new agents in cancer immunotherapy [46].

Also MAO-B could be involved in increased ROS levels. In fact, literature reports that MAOIs can mitigate this effect by reducing ROS levels, thereby preventing cancer cell proliferation. Marconi et al. showed that MAO-B inhibitors upregulate oxidative stress, leading to

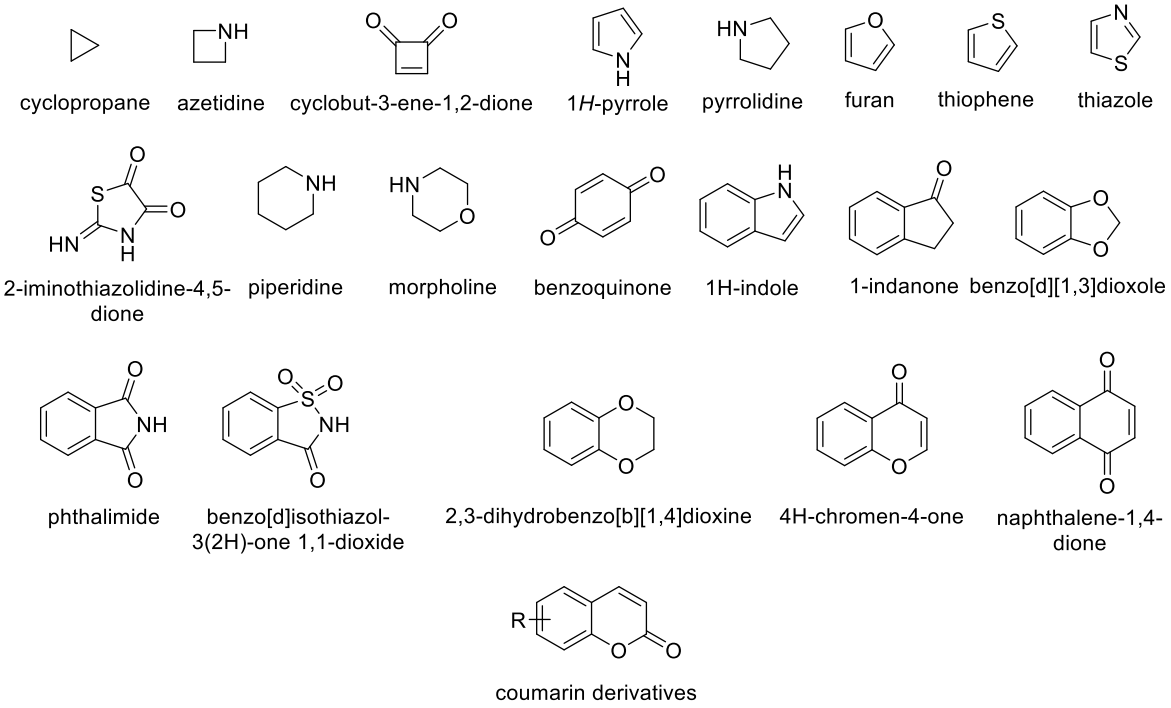

Fig. 5. Molecular scaffolds retrieved in libraries of MAOIs [39].

glioblastoma cell death [45].

Already in 2004, Pierangeli and Mondovì reported that MAOs and other amine oxidases are involved in the processes of cell growth and differentiation [47] and may be related to the degree of malignancy of the tumor [19]. MAOs are involved in the apoptosis process and the production of hydrogen peroxide by MAO-A, a crucial element for this process, is responsible for influencing the activity of MAP kinases, enzymes sensitive to the redox state of the cytosol [30]. However, the products of oxidative deamination exert a contrasting and opposite effect; if on one hand a cytotoxic action is observed, leading to consider their activity as inhibiting cell growth, on the other hand, they lead to carcinogenesis. In fact, amine oxidases are key enzymes in the growth and differentiation of cancer cells, and promote carcinogenesis due to reduced antioxidant enzyme activity [47].

In other recent studies it was demonstrated that MAOs influence the PI3K/AKT/mTOR pathway and the epigenetic regulation, both key pathways in cancer development and progression [44]. To this regard, Wang et al. demonstrated that MAO-A suppresses gastric cancer growth by interacting with NDRG1 and regulating the Warburg effect through the PI3K/AKT/mTOR pathway. This pathway is crucial for cell growth, proliferation, and survival, and its modulation by MAOIs represents a promising therapeutic strategy [44]. Interestingly, the previously unexplored role of MAOs in bladder cancer was evidenced by Resta et al. They observed that human urothelial tumor explants and the bladder cancer cell line AY27 expressed both MAO-A and MAO-B isoforms. Interestingly, they observed that AY27 cells were highly dependent on glucose metabolism for growth, and the inhibition of MAOs led to a marked reduction in glycolysis and oxidative phosphorylation, primarily due to pyruvate depletion. Furthermore, MAO inhibition downregulated key proteins involved in glucose transport and metabolism, such as GLUT1 and HK2. These findings suggest that bladder cancer cells undergo a metabolic shift towards glucose dependency, driven in part by MAO-generated oxidative stress, highlighting a potential therapeutic target in urothelial cancer [48].

Epigenetic regulation also becomes important in cancer progression. LSD1, a histone demethylase belonging to the MAO family, plays a significant role in epigenetic regulation. Inhibitors of LSD1, such as those studied by Zheng et al. (2016), can alter gene expression patterns and inhibit cancer cell growth, offering a novel approach to cancer therapy [49]. To date, nine LSD1 inhibitors have entered clinical trials, for hematological and/or solid cancers. Among them, ORY-1001 (Iadademstat), developed by Oryzon Genomics, is a highly potent LSD1 inhibitor currently undergoing clinical trials for the treatment of acute myeloid leukemia (AML) and solid tumors. It binds irreversibly to the FAD cofactor of LSD1 and has demonstrated robust antitumor effects, including a reduction in colony formation in AML cells. Additionally, phenelzine (Fig. 6), a non-selective irreversible inhibitor of MAO, has also been found to inhibit LSD1. It recently entered Phase I clinical trial in combination of Abraxane, a nanoparticle formulation of Paclitaxel bound to albumin, for the treatment of advanced or metastatic breast cancer [50].

Subsequently, the anticancer activity of MAOs has also been investigated in preclinical studies, using both cells and animal models. Selegiline (L-deprenyl; Fig. 6), one of the first selective MAO-B inhibitors with an enhanced pharmacological profile, used for almost 40 years to treat PD, was used for these studies conducted on prostate cancer and showed good antitumor activity [51]. In other studies, the same compound and its desmethyl derivative have shown efficacy in modulating neuroendocrine-immune signaling in aging and mammary cancer models, illustrating their potential in cancer therapy by influencing hormonal and immune responses [43].

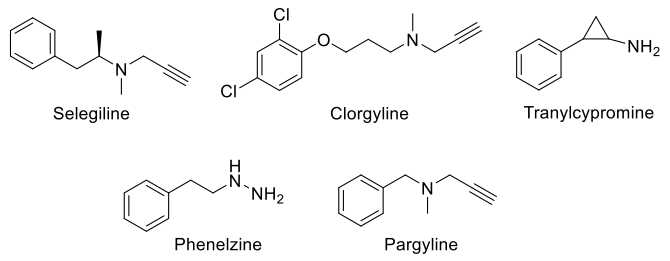

Fig. 6. Chemical structures of MAOIs for which a repositioning in the field of oncology has been proposed.

More recent studies, however, have evaluated the expression of MAO in tumor tissue biopsies. It has been observed that there are frequent changes in the expression levels of the enzyme and in particular, the expression of MAO-A increases in several types of cancer [19] including lung cancer [52], breast cancer [53–55], prostate cancer [56], gastric cancer [44], adrenal cortical adenoma [57], pheochromocytoma [57] or in the case of glioma [58]. Studies have shown that overexpression of MAO-A is associated with an increased risk of cancer [21] and poor prognosis in patients suffering from prostate cancer [59].

In recent decades, research has also been focused on the roles and mechanisms of action of MAO-A in tumorigenesis and metastasis formation in different types of cancer [24], while the role of MAO-B in cancers has not been studied extensively [60], although interest has increased in recent years as it is believed to be directly linked to different types of cancer [21]. It seems that patients suffering from prostate cancer in whose biopsies high MAO-B values were detected have a different fate marked by a better prognosis if compared to those whom a high MAO-A expression is present in tumor microenvironment [61,62].

According to some literature patents and/or clinical trials, some MAOIs already approved by FDA for the treatment of neurodegenerative diseases or depression, have been repurposed in oncology for the treatment of prostate cancer or, more generally, solid tumors. In most cases, these molecules have been tested as adjuvants of classic antitumor drugs [63,64]. The molecules most used for these studies (clorgyline and its fluorescence-tagged derivatives, phenelzine, pargyline and tranylcypromine; Fig. 6), have been discussed in our previous review [64], underlining their potential in oncology and describing some of the probable mechanisms of action involved in overcoming drug resistance.

Clorgyline, traditionally known as a selective MAOAI, has gained attention for its potential antitumor properties. Recent studies have highlighted its ability to target various cancer cell lines. Its antitumor potential is multifaceted, involving the inhibition of MAO-A activity, reduction of oxidative stress, suppression of EMT, and modulation of apoptosis pathways [65,66].

Recently, it has been evidenced that MAOAIs and heat shock protein 90 (HSP90) inhibitors induce a decrease in the progression of several tumors, including glioblastoma. For this reason, molecules were synthesized to display dual activity towards both MAO-A and HSP90. These molecules present the pharmacophore of the HSP90 inhibitors (isopropylresorcinol) linked by an amide spacer to the phenyl group of clorgyline (**1**, Fig. 7) [67].

Other studies have been driven on clorgyline derivatives. In 2023, Jacobs et al. revisited the structure of clorgyline to reduce the adverse effects of the drug related to activity on the central nervous system and to increase its selectivity towards MAO-A. Furthermore, the set of synthesized compounds was tested on Caco-2 cells to evaluate their absorption. Structurally, hydrogen bond donor groups such as NH_2 or OH have been introduced in position 5 on the aromatic ring of clorgyline (**2**, Fig. 7). It was seen that these substituents led to a greater inhibition of MAO-A (about three-fold increase in potency), an increase in selectivity towards MAO-B, while the cytotoxicity towards prostate cancer cell lines remained comparable. However, by introducing larger substituents in the same position, a potency decrease was observed [68].

Several molecules derived from clorgyline [69] and L-deprenyl [70] were prepared as fluorescent probes or radiolabeled compounds, to study the progress and development of prostate tumors and glioblastomas, respectively. Furthermore, in the case of glioblastomas and solid

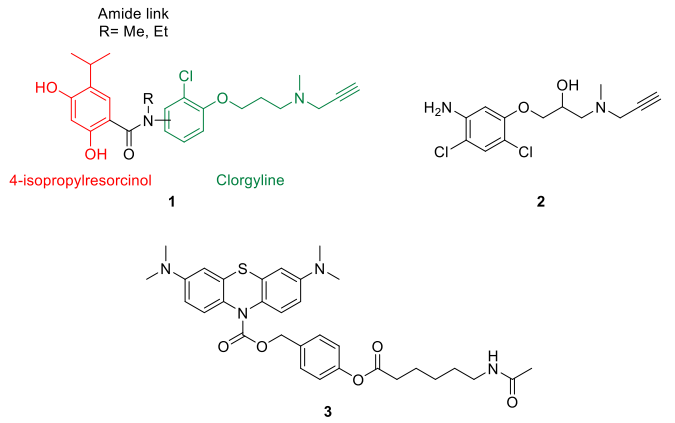

Fig. 7. Chemical structures of clorgyline (**1**, **2**) and methylene blue (**3**) derivatives. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

brain tumors, a small hybrid molecule, called HDAC-MB (**3**, Fig. 7), was also studied as a dual prodrug, whose hydrolytic cleavage liberates a HDAC6 inhibitor and methylene blue, a known MAOAI [71].

Literature reports other molecules, either from natural or semi-synthetic origin, achieving inhibitory activity against MAO-A and MAO-B which have been tested in the treatment of some forms of cancer refractory to normal drug therapy. Among the first ones, the β-carbolines harmine (**4**) and norharman (**5**) and the isoquinoline berberine (**6**) have been studied in the prevention and treatment of neurodegenerative diseases (Fig. 8). These molecules not only act as MAOAIs, with IC_{50} values between 0.002 and 4.29 μM, thus representing new leads for neuroprotection in neurological disorders, but have also been proposed for the treatment of neuroblastoma [72]. *In vitro* studies on neuroblastoma cell lines proved that harmine inhibits cell proliferation and induces apoptosis by activating caspases 3, 7 and 9. Norharman also induces cell death by apoptosis, most likely with the same mechanisms of harmine. Finally, the studies conducted on berberine demonstrated that this molecule is able to induce cell differentiation in neuronal cells and to interfere in the G_0 and G_1 phases of the cell cycle of neuroblastoma cells. In addition, it is able to inhibit signals of the β-adrenergic pathway, which is important for the growth of cancer cells. Harmine has also been proposed as a radiolabeled probe to study the evolution of the tumor mass in animal models of aggressive prostate cancer. This observation would confirm that this molecule could find an application in the personalized therapy of patients suffering from prostate cancers in which MAO-A is expressed [69].

Doxorubicin is one of the most used drugs in the treatment of cancer, including breast cancer [63]. It has always been used in polytherapy because of its toxic cardiac effects. Isoniazid, one of the first MAOI discovered, showed additive effects to doxorubicin in breast cancer cells resistant to doxorubicin [63]. Based on this evidence, Jin et al. synthesized a hybrid molecule DOX-INH (**7**, Fig. 9) merging the structures of doxorubicin and isoniazid. Biological tests showed that this molecule displayed an effective dual activity, acting as MAOAI affecting most of

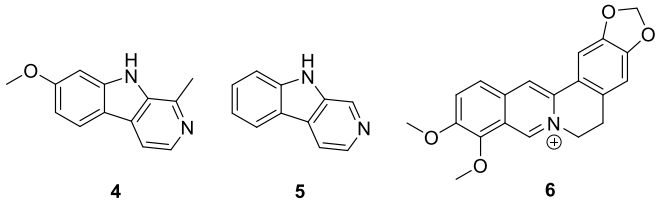

Fig. 8. Structures of harmine **4**, norharman **5** and berberine **6**, natural molecules with MAOI activity.

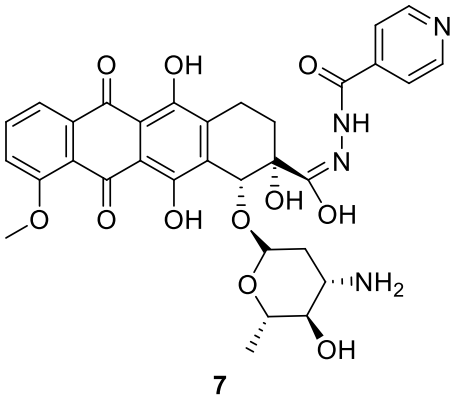

Fig. 9. Structure of DOX-INH hybrid **7**.

the checkpoints controlled by MAO-A in the processes of tumorigenesis, and warranting the antitumor activity of doxorubicin [63].

Flavonoids also appear to have good activity as MAOIs. Therefore, they were considered in a 2020 study in which derivatives (called KKR) were synthesized, initially aimed at preventing and treating depressive disorders in patients with prostate cancer. For these molecules, in fact, a multitarget action was postulated since oncologic patients often suffer from associated depression. In fact, new reversible MAOAIs (often reported with the acronym RIMA) with anticancer activity were found [73]. To evaluate the activity of these molecules, authors carried out enzymatic tests and, using three prostate cancer cell lines (LNCaP, DU145 and PC3) they evaluated the cytotoxic and antiproliferative effects of the most promising molecules. From the results obtained, molecules KKR7 (**8**), KKR11 (**9**) and KKR20 (**10**; Fig. 10), achieving IC_{50} values between 0.02 and 16 μM, also had antiproliferative activity against LNCaP ($IC_{50} \sim 10$ μM), while the most potent MAOAI KKR21 (**11**; K_i 7.4 nM) was ineffective against the tumor cells.

Molecular docking studies allowed to explain how KKR molecules form hydrophobic interactions with amino acid residues in the structure of MAO-A, and that the presence of some functional groups such as chlorine and carboxyl play a fundamental role in determining anticancer activity. It appears, therefore, that there is a correlation between the inhibition of MAO-A by these molecules and their antitumor capacity. Starting from these assumptions it was possible to identify chalcone **9** as a lead compound, which also showed antimetastatic properties in vitro assays on DU145 cell line.

There are also molecules of synthetic origin for which the enzymatic activity on MAOs has been evaluated and for which the use in the treatment of prostate cancer, glioma or lung cancer has been envisaged. Among these molecules, particular importance has been attributed to polyamines, hydrazothiazoles, hydrazoles, imidazolins, quinolines, indoles, pyrrole, pyrazoles and cromenopyridines.

In recent years, it has been demonstrated that polyamines can play a role as MAOIs. In 2023 Nordio et al. taking into account that MAO-A are overexpressed in some types of tumors such as glioblastoma or prostate cancer, demonstrated how some MAO-inhibiting polyamines could also be good antiproliferative agents. They identified an in-house library of molecules, two of which (Fig. 11) endowed with good antiproliferative activity. These compounds, characterized by a dianiline (**12**) or dianilide (**13**) moiety, were the most potent competitive MAOIs ($K_i < 1$ μM), with high antiproliferative activity in the LN-229 cell line ($GI_{50} < 1$ μM) [74].

Hydrazones (Fig. 12) are another class of molecules with MAOI activity. The hydrazotiazoles **14** and **15**, having IC_{50} values against MAO-B of 6.8 and 2.5 nM, respectively, have been studied for the treatment of glioma. Their biological activity was evaluated on the C6 cell line in terms of cell proliferation, apoptosis, inflammatory response and cell migration. The results showed that both compounds are able to block the

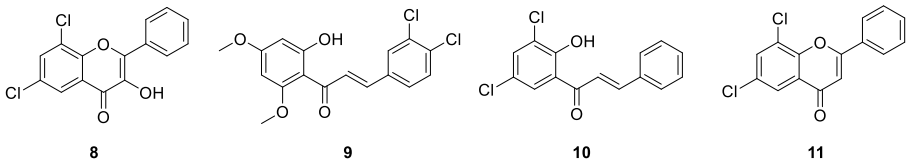

Fig. 10. Semisynthetic derivatives of flavonoids with dual MAOI/antitumor activity.

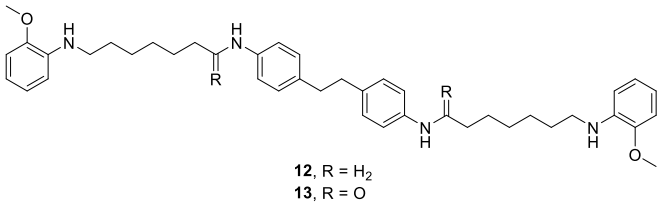

Fig. 11. Polyamines with MAOI and antiproliferative activity.

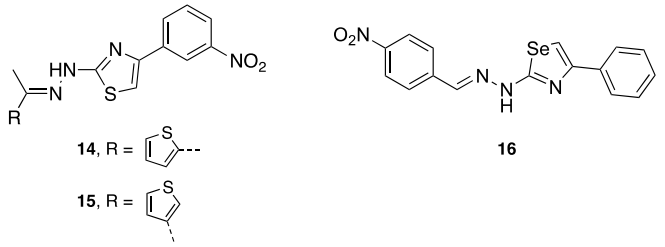

Fig. 12. Chemical structure of hydrazones **14–16**.

proliferation of the tumor cell, sparing normal astrocytes and inducing the production of ROS. In contrast, only **15** is able to interfere with the cell cycle of C6 cells in the G_1 and S phase [45].

Helshaflu et al. reported in 2018 the activity of some derivatives of selenozoyl hydrazones as MAOIs with antioxidant and antiproliferative activity. A panel of four sets of molecules were tested on a set of six different cell lines: lung cancer (A549, SW1573), breast cancer (HBL-100, T-47D), uterine cervix (HeLa) and colorectal cancer (WiDr), leading to the identification of the lead molecule **16** (Fig. 12), which had an IC_{50} of about 7.2 μM for MAO-A and a good antiproliferative response on T-47D and WiDr cell lines. Antioxidant activity, on the other hand, was assessed by radical scavenging activity (DPPH), measurement of radical oxygen absorption capacity (ORAC) and measurement of reduction capacity [75].

Imidazolines (Fig. 13) are known MAOBIs. The imidazole ring, in fact, is recognized by a portion of the binding site known as binding site I2 and typical of MAO-B. In 2019, Shetnev et al. proposed the synthesis of 33 molecules derived from 2-imidazoline, and 13 of them showed IC_{50} in the nM range. The frontrunner molecules **17** and **18** reported values of IC_{50} equal to 0.012 μM for MAO-B (selective MAOBI) for **17** and 0.75 and 0.41, respectively for MAO-A and MAO-B, for **18**; notably, these values are comparable with the MAOIs used in clinics. This promising aspect led the authors to propose these two new molecules derived from 2-imidazoline as possible candidates for a biological evaluation on PCa cell lines [76].

In 2018, Chirkova et al. based on molecular docking studies, suggested that molecules with structures attributable to indole-5,6-dicarbonitrile **19** and pyrrole [3,4-*f*]-indole-5,7-dione **20** (Fig. 13) bind the active site of MAO-A with similar orientations, while both structures do not bind the MAO-B due to a steric clash with Tyr326, Ile199, Leu 171 and Phe 168 which define the boundary at the entrance cavity of MAO-B [77]. Enzymatic assays showed that the most active scaffold is the indole-5,6-dicarbonitrile, while the latter has a higher selectivity for MAO-A [78]. These molecules, given their inhibitory potential against MAOs, could represent new lead compounds with multitarget action in the treatment of carcinomas such as prostate cancer, cardiomyopathies, neurodegenerative diseases and depression [78].

In 2022, Bardaweel et al. reported the activity of some derivatives of 1*H*-indol-2-carboxamide **21** (Fig. 13), a scaffold already known as MAOI, as potential anticancer agents against three cell lines of lung cancer, by evaluating the effect of molecules at 24, 48 and 72 h. Worthy of note, the best in class molecule displayed an antiproliferative effect in the order H661 > H1299 > A549 [79].

In 2023, some of us evaluated 1*H*-chromeno [3,2-*c*]pyridine derivatives (THCP) as dual inhibitors of MAOs and cholinesterases. For the most active MAOIs, assays were carried out to evaluate their antiproliferative activity on several cell lines of breast cancer (MCF-7), colorectal cancer (HCT116) and ovarian cancer (SKOV-3 and SKOV-3 naturally resistant to cisplatin). Assays revealed that the 10-indolyl-bearing 2,3,4,10-THCP analog **22** (Fig. 14) exerted antitumor activity with IC_{50}s in the range between 4.83 and 11.3 μM in all the different cell lines used [80].

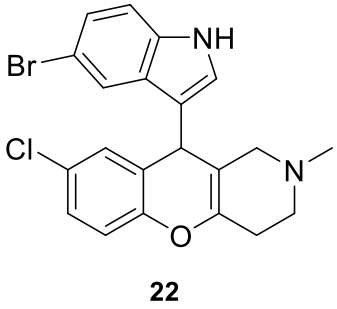

Fig. 14. Structure of 10-indolyl-2,3,4,10-THCP analog studied by Kulikova and coll.

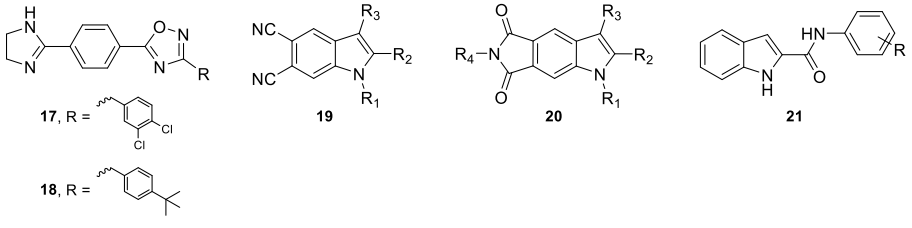

Fig. 13. Chemical structures of imidazolines **17** and **18** and indole derivatives **19–21**.

In 2021 Ayoup et al. synthesized a new series of quinoxaline-based dual matrix metalloproteinase-9 (MMP-9)/MAO-A inhibitors, in the light of the fact that MMP-9 and MAO-A are key signaling molecules in colorectal cancer (CRC), promoting metastasis and contributing to high mortality rates. These compounds were designed to combine the pharmacophoric features of both MMP-9 and MAO-A inhibitors in a hybrid molecular structure. After being tested for safety and cytotoxicity on normal colonocytes, the most promising derivatives **23–26** (Fig. 15) displayed potent anticancer activity on CRC cells, particularly HCT116, with nanomolar IC_{50} values. Compound **26** emerged as the most potent and balanced dual inhibitor, showing strong selectivity for MAO-A over MAO-B. Additionally, these compounds significantly inhibited HCT116 cell migration and downregulated hypoxia-inducible factor 1-alpha (HIF-1α), a key driver of metastasis. Docking simulations supported their binding modes with MMP-9 and MAO-A, and in silico assessments confirmed their drug-like properties [81].

In 2024, the same authors investigated the combined roles of MAO and VEGFR-2, as these are key promoters of CRC progression and play a role in EMT via hypoxia-inducible factors. A novel series of quinoxaline-based compounds linked to triazole were synthesized, integrating features of both VEGFR-2 and MAOI. These compounds were tested for cytotoxicity and anticancer activity, specifically against HCT-116 CRC cells overexpressing MAOs. Two compounds, **27** and **28**, demonstrated significant anticancer effects against HCT-116 cells, with IC_{50} values of 18.04 μM and 7.85 μM, respectively, while remaining within safe EC_{100} doses for normal colonocytes. A wound healing assay revealed that both compounds effectively reduced HCT-116 cell migration by over 75 %, indicating strong antimetastatic potential. *In vitro* enzymatic assays further showed that both **27** and **28** inhibited VEGFR-2 with IC_{50} values in the nanomolar range, as well as MAO-A and MAO-B, with greater selectivity for MAO-B [82].

7. Conclusion

According to literature reports, MAO-A and MAO-B are highly expressed in several human cancers. MAO-A is expressed in prostate and lung cancer, while MAO-B is found in gliomas and renal cancer. Since the last decade, several papers have been published associating MAO-A activity with tumor development and progression. Increased ROS production mediated by the oxidative deamination activity of MAO-A could aggravate tumorigenesis and metastasis in high-grade tumors. In addition, the ability of cancer cells to migrate from their primary location to another tissue appears to be linked to signaling pathways involving MAO-A activity. Interestingly, several MAO-A inhibitors have been reported to affect cell proliferation, resulting in cell cycle arrest with a dose-dependent trend. It has also been reported that cancer cell death induced by apoptosis pathways is the main effect of some MAO-A inhibitors on prostate cancer cells [21].

Studies focused on molecules potentially acting as MAOIs have led to the identification of particularly interesting nuclei such as chromenone, isoindoline dione, benzoquinone, pyrrole, indenone, naphthalene dione, morpholine, thiophene, benzodioxol, imine-methyleneazolidinone, cyclopropane, cyclobutanedione, furan, azetidine, indole and piperidine, which represent scaffolds or fragments useful for the creation of libraries of small molecules with MAOI activity [39]. In addition, some of these core structures have been tested as antitumor agents against different forms of cancer, thus showing potential multitarget activity.

According to the current state of the art, MAOIs, generally used in the treatment of CNS disorders, could present a valid therapeutic approach for the treatment of cancer, used in association with traditional anticancer drugs to synergistically improve their activity. Their use as standalone treatments or in synergy with traditional therapies led us to consider MAOIs as valuable additions to the anticancer drugs.

CRediT authorship contribution statement

Sabina Sblano: Data curation, Writing – original draft, Writing – review & editing. **Angelina Boccarelli:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Caterina Deruvo:** Data curation, Writing – original draft, Writing –

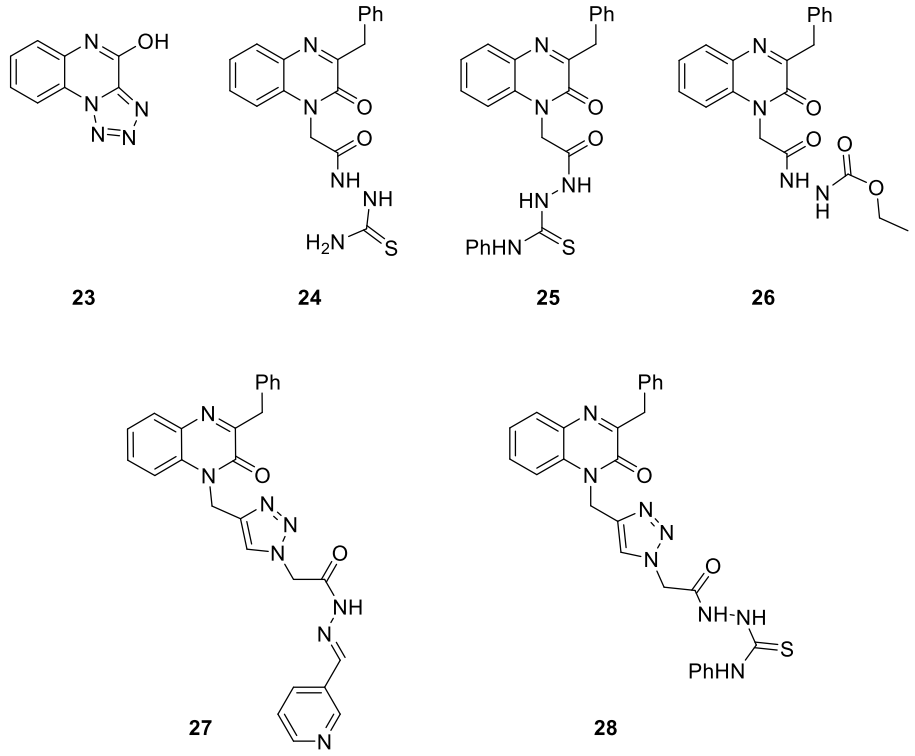

Fig. 15. Chemical structures of quinoxalines **23–28**.

review & editing. **Gabriella La Spada:** Data curation, Writing – original draft, Writing – review & editing. **Modesto de Candia:** Data curation, Writing – original draft, Writing – review & editing. **Rosa Purgatorio:** Data curation, Writing – original draft, Writing – review & editing. **Cosimo Damiano Altomare:** Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. **Marco Catto:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data were collected from cited references

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