



## Review article

## A second life for MAO inhibitors? From CNS diseases to anticancer therapy

Sabina Sblano<sup>a</sup>, Angelina Boccarelli<sup>b,\*</sup>, Francesco Mesiti<sup>a</sup>, Rosa Purgatorio<sup>a</sup>,  
Modesto de Candia<sup>a</sup>, Marco Catto<sup>a,\*</sup>, Cosimo D. Altomare<sup>a</sup>

<sup>a</sup> Department of Pharmacy-Pharmaceutical Sciences, University of Bari Aldo Moro, Via E. Orabona 4, 70125, Bari, Italy

<sup>b</sup> Department of Precision and Regenerative Medicine and Ionian Area, School of Medicine, University of Bari Aldo Moro, Piazza Giulio Cesare 11, 70124, Bari, Italy

## ARTICLE INFO

## Keywords:

Monoamine oxidase  
Inhibitors  
Neuroprotection  
Tumorigenesis  
Antitumor chemotherapy

## ABSTRACT

Monoamine oxidases A and B (MAO A, B) are ubiquitous enzymes responsible for oxidative deamination of amine neurotransmitters and xenobiotics. Despite decades of studies, MAO inhibitors (MAOIs) find today limited therapeutic space as second-line drugs for the treatment of depression and Parkinson's disease. In recent years, a renewed interest in MAOIs has been raised up by several studies investigating the role of MAOs, particularly MAO A, in tumor insurgence and progression, and the efficacy of MAOIs as coadjutants in the therapy of chemoresistant tumors. In this survey, we highlight the implication of MAOs in the biochemical pathways of tumorigenesis and review the state-of-the-art of preclinical and clinical studies of MAOIs as anticancer agents used in monotherapy or in combination with antitumor chemotherapeutics.

## 1. Introduction

Monoamine oxidases (MAOs, EC 1.4.3.4), also known as tyramine oxidases [1], are mammalian enzymes discovered in 1928 by Mary Bernheim [2] who observed for the first time their presence in the liver [3]. Since their discovery, several structural, biochemical, and pharmacological investigations were performed. MAOs catalyze the oxidative deamination of endogenous and dietary monoamines, playing a pivotal role in regulating the levels of monoamine neurotransmitters. MAOs exist in two isoforms, namely MAO A and MAO B (Fig. 1), which are present in all cell types, but mostly expressed in neuronal cells and astrocytes [3]. MAO A prevails in the gastrointestinal tract, lung, liver, and placenta, while platelets present exclusively MAO B [1].

According to their metabolic role, these enzymes have been identified as potential drug targets for the treatment of various diseases, especially neurological disorders [4]. MAO A selective inhibitors (MAOAIs) represent today a secondary option for the treatment of depression, while MAO B selective inhibitors (MAOBIs) are used as monotherapy or as add-on therapy to L-dopa in Parkinson's disease (PD). Recently, new clinical applications have been reported, which support the therapeutic indication of MAOIs for the treatment of prostate cancer, inflammation, vertigo, and diabetes [5].

Our interest toward MAOs began a long time ago, when using a classical quantitative structure-activity relationship (QSAR) approach,

combined with comparative molecular field analysis (CoMFA), some of us modeled the MAO-mediated oxidation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to the parkinsonogenic neurotoxic 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>) [6]. Starting from these studies, novel classes of potent and isoform-selective MAOIs were designed and synthesized, such as annulated indenodiazines [7,8] and substituted coumarins [9,10], some of which showing promise as multitarget-directed ligands (MTDLs) in neurodegeneration and oncology [11,12]. Lastly, we featured new 1*H*-chromeno[3,2-*c*]pyridine-based MAO inhibitors with anticancer activity against some tumor cell lines, including cisplatin-resistant ovarian (SK-OV-3) tumor cells [13].

Due to their neuroprotective effects, MAOIs have been widely investigated but with low success rate in terms of clinical entries, considering that only five MAOIs (rasagiline, moclobemide, clorgyline, selegiline and safinamide; Table 1) have been approved in Europe in the last 50 years for the treatment of neurological disorders. Critical issues due to harmful side effects discourage the setup of new trials, therefore, the mole of studies on selective MAOIs risks getting unused or remaining only speculative.

Herein, we discuss a possible repositioning of MAOIs by resuming their implication in the biochemical pathways of tumorigenesis, namely in epithelial-mesenchymal transition (EMT), inflammation, hypoxia and apoptosis. The choice of these hallmarks, which fall within the pathogenesis of neoplastic transformation, stands on their implication in i) the

\* Corresponding author.

\*\* Corresponding author.

E-mail addresses: [angelina.boccarelli@uniba.it](mailto:angelina.boccarelli@uniba.it) (A. Boccarelli), [marco.catto@uniba.it](mailto:marco.catto@uniba.it) (M. Catto).

<https://doi.org/10.1016/j.ejmech.2024.116180>

Received 11 September 2023; Received in revised form 22 January 2024; Accepted 23 January 2024

Available online 24 January 2024

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modification of the microenvironment (inflammation and hypoxia); ii) the acquisition of a plastic phenotype (EMT) and iii) cellular fate (apoptosis). Understanding the involvement of MAOs in these phases is for sure of great interest, as it could support a role as therapeutic targets. Therefore, in this review we will focus on the preclinical and clinical studies and the patent literature on MAOIs in anticancer chemotherapy over the last ten years.

### 1.1. Structural features of the MAO isoforms

MAOs belong to the flavin protein family. Structurally, MAO A and MAO B are both characterized by a FAD binding domain, similar to other flavoprotein oxidases, a substrate binding domain and a membrane binding domain. Studies with nuclear magnetic resonance (NMR) showed that human and mice MAOs exist as dimers in solution, while only human MAO A crystallizes as a monomer. Both MAO isoforms bind the outer mitochondrial membrane through a C-terminal region of the  $\alpha$ -helix protein, with additional membrane interactions occurring with other hydrophobic residues [14].

MAO A binding site has a cavity of about 400 Å<sup>3</sup>, which in MAO B is accompanied by an accessory site, called entrance cavity (300 Å<sup>3</sup>). In hMAO B, the rotation of Ile199 residue allows the two cavities to merge into a larger one and, depending on the orientation of the side chain of this residue, MAO B can adopt an “open” or “closed” conformation. These cavities remain separate or join depending on the nature of the substrate or inhibitor used. The residues Phe208 and Ile335 (instead of Ile199 and Tyr326 in hMAO B) mainly shape the active site of hMAO A. These residues contribute to the selectivity of the substrate or inhibitor toward the two isoforms. Structural studies initially suggested that differences in substrate specificity were due to the conformation of a residue of six loops (residues 210–216 in MAO A and 201–206 in MAO B), but subsequent studies have shown that loops are in the same conformation in both enzymes [14].

The binding sites of both MAO A and B consist of hydrophobic residues characterized mainly by aromatic and aliphatic residues. An exception is a conserved lysine (Lys296 in MAO B and Lys305 in MAO A) that interacts with a water molecule and binds N5 of the flavin cofactor. Tyr398 and Tyr435 in MAO B, as well as the corresponding Tyr407 and Tyr444 in MAO A, form an aromatic “sandwich” when hosting the substrates [15].

MAOs are encoded by genes placed on the short arm of the X chromosome; in particular, MAO A gene is located on Xp11.23. Both genes are arranged in a tail-to-tail orientation. Moreover, they extend for at

least 60 kb with an identical exon-intron organization. Their promoter regions share 60% sequence homology [15] while transcription organization differs depending on the tissues to which they belong and to specific cellular expressions [17,18].

### 1.2. The MAO-catalyzed reactions

MAOs catalyze the oxidation of primary, secondary and tertiary amines, including several neurotransmitters, into the corresponding imines [1]. MAO A catalyzes the metabolism of serotonin, norepinephrine and dopamine [3], while MAO B preferentially catalyzes the metabolism of benzylamine, phenethylamine and other catecholamines [4]. The oxidized products obtained are hydrolyzed in a non-enzymatic way into the respective aldehydes or ketones [14], with the production of reactive oxygen species (ROS), according to the scheme shown in Fig. 2. The derived aldehydes are rapidly metabolized into the corresponding acid by aldehyde dehydrogenase (ALDH). Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and ammonia (NH<sub>3</sub>) are by-products of the MAOs' catalytic reaction, with H<sub>2</sub>O<sub>2</sub> playing a role in several processes related to aging and chronic diseases, including cancers [3].

## 2. MAOs in cancer pathogenesis

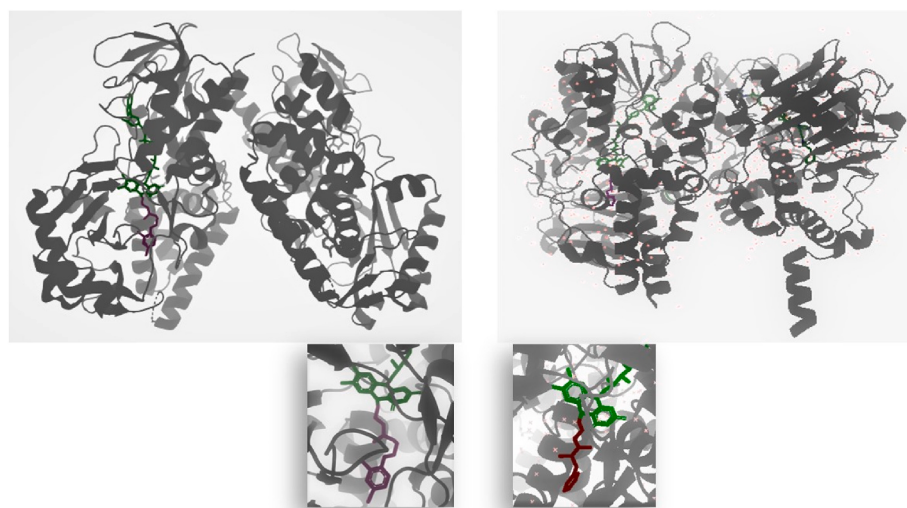
In recent years it has been observed that MAO A and B are constitutively expressed in several human cancers [1,20]. In particular, MAO A is expressed in prostate [20,21], lung [21], kidney [20], and colorectal cancer [20], while MAO B is expressed in gliomas [1] and human glioblastoma [21]. Most of the information provided by the literature is inherent to the prostate and brain tumors, while little is known for other types of tumors such as lung cancer [21].

Several studies hypothesize that especially MAO A may have an important role in growth, migration, and metastasis of different types of cancer, especially in tumors with a high degree of malignancy [21]. Particularly some hallmarks typical of neoplastic transformation (inflammation, hypoxia, EMT, apoptosis) seem to be affected by MAOs. In this light, the identification and validation of MAOs as drug targets could represent a therapeutic approach for the treatment of such malignancies.

### 2.1. MAO A

#### 2.1.1. Role of MAO A in inflammation and hypoxia

MAO A plays a pivotal role in inflammation. It can be considered as a

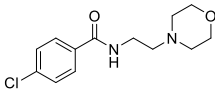
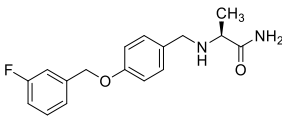
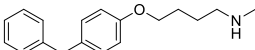
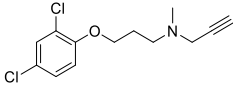
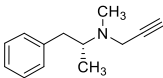
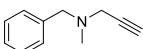
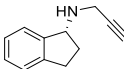
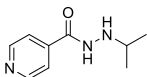
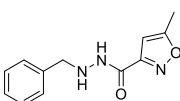
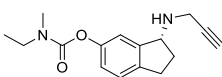
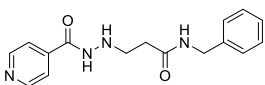
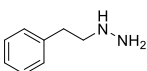
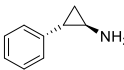


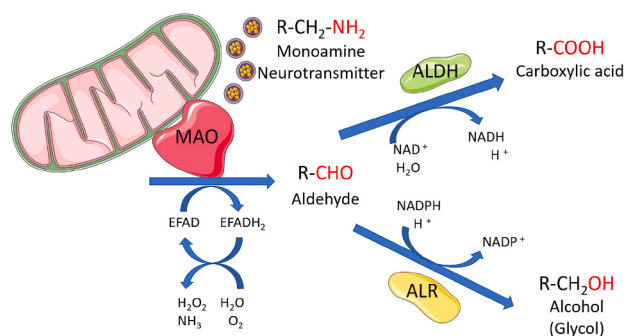
**Fig. 1.** Crystal structures of hMAO isoforms taken from PDB [16]. Left side: complex of hMAO A with clorgyline (PDB 2BXR). Right side: complex of hMAO B with selegiline (PDB 2BYB). For both complexes, magnifications evidence the inhibitors (red) covalently bound to cofactor FAD (green).

marker of activated monocytes/macrophages and could have a role in carcinogenesis due to the production of ROS [21]. In fact, increased levels of ROS promote DNA damage, oxidative lesions of cells, and can mediate tumorigenesis, progression, and metastasis in high-grade tumors [20]. Therefore, MAO A overexpression could be linked to both aggressive cancer cell behavior and advanced cancer status. ROS produced by MAO A can modulate the activation of the hypoxia-inducible

factor 1- $\alpha$  (HIF1 $\alpha$ ) that suppresses the activity of oxygen-dependent prolyl hydroxylase (PHD) [20,22,23]. Shih et al. demonstrated that MAO A improves HIF1 $\alpha$  stability and reduces PHD activities by increasing levels of intracellular ROS [23]. In fact, the treatment of prostate cancer (PCa) cells with a ROS scavenger, such as *N*-acetylcysteine, determines a decrease of HIF1 $\alpha$  expression induced by MAO A, leading to a reduction of cell proliferation. In addition, MAO A

**Table 1**  
Examples of MAOIs used in therapy and preclinical studies.

|                         | Drug                    | Structure                                                                           | MAO selectivity       | Clinical Indication(s)                               | Ref        |
|-------------------------|-------------------------|-------------------------------------------------------------------------------------|-----------------------|------------------------------------------------------|------------|
| Reversible Inhibitors   | Moclobemide             |    | A                     | Depression                                           | [4,19, 51] |
|                         | Safinamide              |    | B                     | Parkinson's Disease                                  | [4,51]     |
|                         | Bifemelane              |    | A/B                   | Depression and dementia                              | [19]       |
| Irreversible Inhibitors | Clorgyline              |    | A                     | Depression                                           | [4,19, 51] |
|                         | Selegiline (L-Deprenyl) |  | B                     | Parkinson's Disease                                  | [4,19, 51] |
|                         | Pargyline               |  | B                     | Hypertension                                         | [19,51]    |
|                         | Rasagiline              |  | B                     | Parkinson's Disease                                  | [4,19, 51] |
|                         | Iproniazid              |  | A/B                   | Depression                                           | [19,51]    |
|                         | Isocarboxazid           |  | A/B                   | Depression                                           | [19,51]    |
|                         | Ladostigil              |  | A/B (brain selective) | Parkinson's Disease, Depression, Alzheimer's Disease | [19]       |
|                         | Nialamide               |  | A/B                   | Depression                                           | [19]       |
|                         | Phenelzine              |  | A/B                   | Depression                                           | [19,51]    |
|                         | Tranylcypromine         |  | A/B                   | Depression                                           | [4,19, 51] |



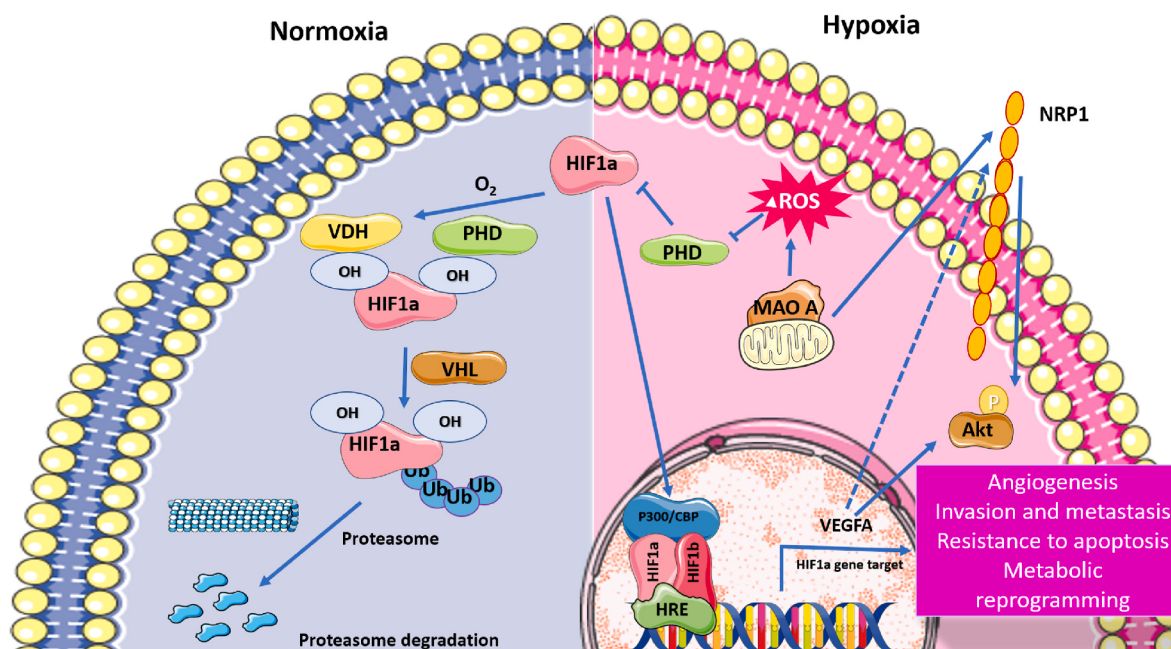
**Fig. 2.** Oxidative deamination reaction of monoamines catalyzed by MAO A and MAO B [4,19]. MAOs are located on the outer membrane of mitochondria and are able to carry out a deamination reaction on endogenous and dietary amines, and neurotransmitters. The catalytic cycle consists in two steps. In the first step, the reduction of the FAD (flavin adenine dinucleotide) to FADH<sub>2</sub> (dihydroflavin adenine dinucleotide) and the oxidation of the amine neurotransmitter (R-CH<sub>2</sub>-NH<sub>2</sub>) with formation of the corresponding imine (not shown). In the second step, oxygen (O<sub>2</sub>) oxidizes the cofactor FAD by with concomitant formation of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). In this step, the imine is hydrolyzed to aldehyde (R-CHO) and ammonia. Subsequently, the aldehyde (R-CHO) is converted to carboxylic acid (R-COOH) or to alcohol (R-CH<sub>2</sub>OH) via the aldehyde dehydrogenase (ALDH) or the aldehyde reductase (ALR), respectively. NAD<sup>+</sup>/NADH: Nicotinamide adenine dinucleotide; NADP<sup>+</sup>/NADPH: Nicotinamide adenine dinucleotide phosphate.

mediates the activation of vascular-endothelial growth factor (VEGF) and its neuropilin-1 receptor (NRP1) in response to hypoxia, which stimulates the signaling pathway Akt/FoxO1 and reduces the activity of forkhead box protein O1 (FoxO1) by promoting phosphorylation with nuclear exports. In turn, FoxO1 acts as a transcriptional repressor of twist-related protein 1 (Twist 1) [20,22]. This mechanism is typical in tumors with a high degree of malignancy that show a significant expression of HIF1 $\alpha$ , VEGF, and Twist1. Therefore, the expression levels of MAO A, HIF1 $\alpha$ , VEGF, and Twist1 should be biomarkers to objectively differentiate malignant grade tumors from low-grade ones [21,23,24].

The increment of ROS under hypoxia conditions leads to the HIF1 $\alpha$  translocation into the nucleus with consequent dimerization of HIF1 $\alpha$  and HIF1 $\beta$ , recruitment of histone acetyltransferase p300 and CREB binding protein (CBP), and the link to hypoxia-response element (HRE). The formation of the dimer and the binding to the promoter, induces the transcription of genes causing cell proliferation, angiogenesis, metastasis formation, resistance to apoptosis, and metabolic reprogramming. Fig. 3 shows the HIF1 $\alpha$  regulatory processes under normoxia and hypoxia conditions. Furthermore, ROS overproduction also promotes epithelial to mesenchymal transition (EMT) in PCa cells [20,21], which results in an increase in migratory, proliferative, invasive, and metastatic potential. Recent evidence also suggests that MAO A expression in high-grade advanced PCa may play a direct role in maintaining a dedifferentiated phenotype and promoting aggressive tumor behavior [20].

#### 2.1.2. Role of MAO A in epithelial to mesenchymal transition (EMT)

EMT is a cellular process characterized by loss of cell adhesion, repression of E-cadherin expression, and increased cell mobility, which relates to increased cell invasiveness, migration, and metastatic



**Fig. 3.** HIF1 $\alpha$  signaling pathways in normoxia and hypoxia. Under normoxia conditions (left) HIF-1 $\alpha$  is hydroxylated by PHD. The hydroxylated enzyme binds to the ubiquitin ligase complex E3. This interaction results in polyubiquitination and degradation of the HIF-1 $\alpha$  proteasome. Under hypoxia conditions (right), lack of oxygen and increased ROS levels inhibit PHD activity, preventing HIF-1 $\alpha$  degradation. Thus, HIF-1 $\alpha$  accumulates in the cytoplasm and subsequently translocates into the nucleus, where it binds to HIF-1 $\beta$ , forming the HIF-1 complex ready to transcription, and promotes the transcription of HIF-1 target genes, including those involved in promoting angiogenesis, invasion and metastasis, metabolic reprogramming, and apoptosis resistance [22,25]. Furthermore, MAO A mediates the activation of VEGF-A/NRP1 signaling to upregulate AKT/FoxO1 pathway, which results in nuclear export of the FoxO1 transcription repressor to activate nuclear expression of Twist 1 (not shown). Together, increased MAO A expression promotes the production of EMT, hypoxia and ROS, which drive tumorigenesis, progression, and PCa metastasis [22-24]. PHD: oxygen-dependent prolyl hydroxylase; HIF1 $\alpha$ : hypoxia-inducible factor 1-alpha; FDH: Formate dehydrogenase; VHL: Von Hippel-Lindau Tumor Suppressor; HRE: Hypoxia-Response Element; P300/CBP: histone acetyltransferase complex p300, CREB binding protein (CBP); ROS: reactive oxygen species; VEGF-A: Vascular-Endothelial Growth Factor-A; NRP1: Neuropilin-1 receptor; AKT: serine/threonine kinase 1; FoxO1: Forkhead box protein O1; Twist 1: Twist Family BHLH Transcription Factor 1.

potential in cancer cells. In studies carried out on human PCa cells, overexpression of MAO A induced loss of E-cadherin, increase of vimentin/N-cadherin migration and cell invasion, while MAO A knockdown prevented EMT [23]. On the other hand, Satram-Marahaj et al. demonstrated that MAO A inhibition triggers an EMT process in the MDA-MB-231 breast cancer cell line, concluding that MAO A inhibition on breast cancer progression depends more on the cellular EMT status than on the estrogen receptor (ER) activation [26]. Further studies, carried out in colorectal cancer (CRC) cells HT29 and SW480, established that interleukin 13 (IL-13), produced by T helper type 2 (Th2) lymphocytes, is a crucial cytokine promoting EMT and aggressiveness, in terms of migration and invasion, by activating IL-13/IL-13R $\alpha$ 1/STAT6/ZEB1 signaling pathway [27] (Fig. 4) and STAT3/ZEB1 [20]. Since MAO A is constitutively expressed or induced by IL-13 in many CRC cells and since STAT6/STAT3 are important regulators of MAO A, the mechanism that could involve MAO A in the EMT process in CRC carcinoma was investigated. These results support that in the HCT116 cells (constitutive MAO A cellular model), the MAO A-mediated generation of ROS is related to an advanced level of migration and invasion (Fig. 4) [20,27].

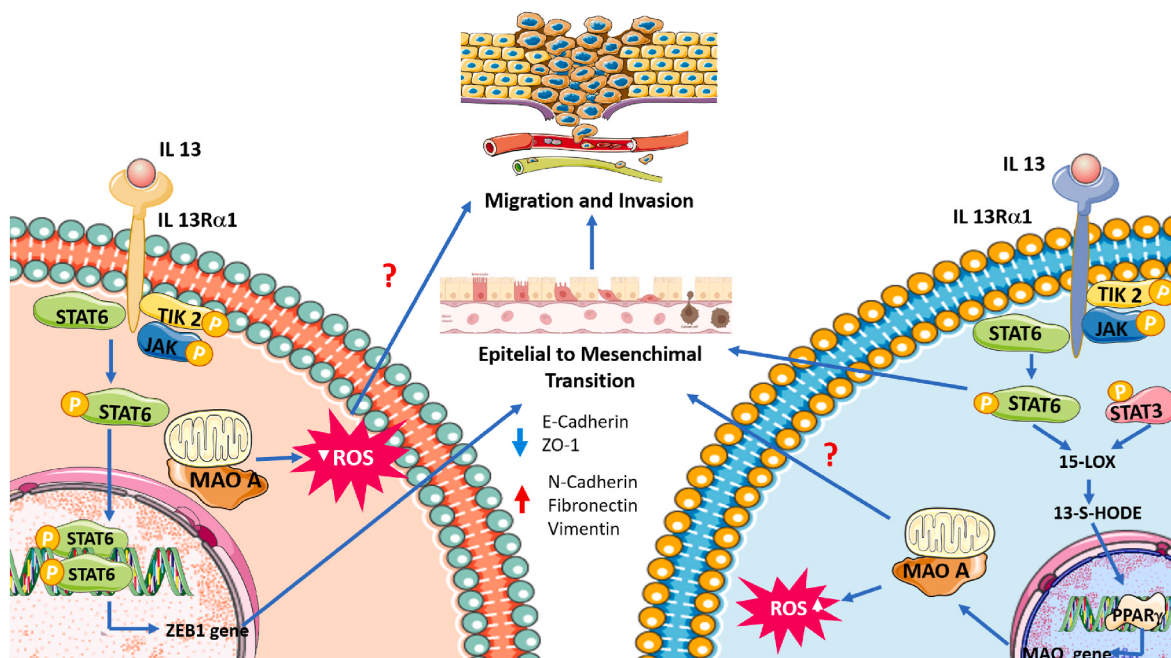
Besides, Bhattacharjee et al. [20] demonstrated that the IL-13/IL-13R $\alpha$ 1/STAT 6 signaling pathway is involved in the regulation of MAO A expression/activity in the epithelial lung cancer A549 cell model through a 15-lipoxygenase (15-LOX)-dependent process involving peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ , Fig. 4), causing EMT promotion in these specific cancer cells after IL-13 stimulation [28]. In addition, the high level of MAO A constitutively present in HCT116 colon cancer cells and in H1299 lung cancer cells may promote the generation of ROS, which in turn sets in migration and invasion of H1299 cells (Fig. 4) [20,21].

Other studies revealed the implication of MAO A in metastatization. Increased MAO A expression is associated with poor clinical outcomes in patients with PCa. Furthermore, MAO A has also been reported as an

important mediator of bone and visceral PCa metastases by stimulating the release of IL-6 from osteoblasts resulting in activation of Shh-IL6-RANKL paracrine signaling [20]. However, conflicting results have been reported in hepatocellular carcinoma (HCC) and cholangiocarcinoma [21]. In this context, MAO A suppression is observed in cholangiocarcinoma where the hypermethylation of the MAO A promoter and IL-6 signaling improve cancer invasiveness. Furthermore, MAO A expression is silenced in HCC by histone methylation and acetylation processes identifying MAO A as a negative regulator of HCC malignancy. To investigate the mechanism behind MAO A-dependent HCC invasion and metastasis, studies were conducted whose results indicate that MAO-A reduces HCC cell invasion and metastasis by inhibiting canonical adrenergic signaling norepinephrine/epinephrine-dependent, along with transactivation of adrenergic receptors mediated by epithelial growth factor (EGFR) signaling. These results indicate that MAO A plays a key role in the adrenergic system controlling invasion and metastasis in HCC [20].

### 2.1.3. Role of MAO A in apoptosis

Another noteworthy biological aspect is the relationship between autophagy and apoptosis, in which MAO A is involved. Apoptosis and autophagy share common regulatory signals and mechanisms, including activation of ROS, ceramide, and tumor protein 53 (p53). It has been hypothesized that MAO A has a key role in orienting the cell towards autophagy or apoptosis by shifting the balance between the two events in relation to the amount of ROS that are produced by MAO A. In fact, ROS present in the cell induce the reduction of p53 transactivation, thus inhibiting apoptosis. In addition to identifying MAO A as responsible for autophagy and apoptosis events, a further role was the identification of MAO as a target of RE1 silencing transcription factor (REST). Recent studies have revealed that REST performs important functions in hypoxia and pathways responsible for tumor resilience [29,30]. In fact, it has been observed that REST expression is significantly reduced in



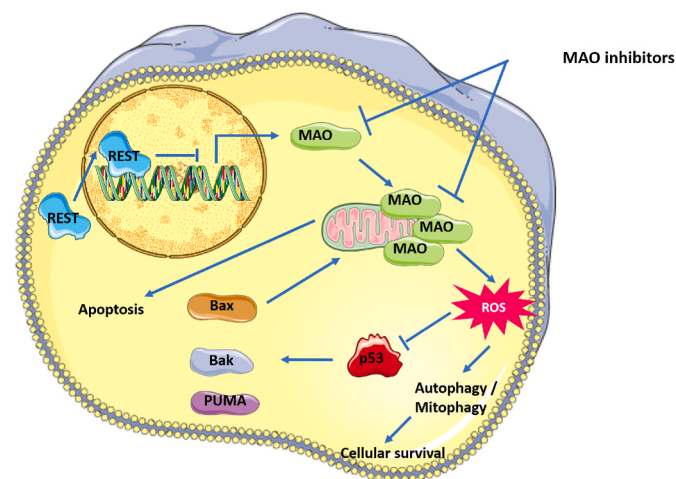
**Fig. 4.** Overview of signaling events associated with EMT and aggressiveness in colorectal cancer cells (left) and model of regulation of the aggressiveness of lung cancer regulated by MAO A (right). IL-13 may induce an aggressive tumor phenotype showing EMT induced by the expression of ZEB1. Activated STAT6 binds directly to the ZEB1 promoter, which first activates EMT, then cell migration and invasion; the IL-13/IL-13R $\alpha$ 1/STAT6/ZEB1 pathway plays a key role in promoting EMT and CRC aggressiveness [27]. On the other hand, IL-13-mediated activation of MAO A expression and activity is linked to activation of the IL-13/STAT6/STAT3/15-LOX/PPAR $\gamma$  signaling axis [20,21,28], while ROS-mediated MAO A expression and activity induces EMT, tumor cell migration and invasion. IL-13: Interleukin 13, ZEB1: Zinc Finger E-Box Binding Homeobox 1, STAT6 and STAT3: Signal transducer and transcription activator 6 and 3, 15-LOX: 15 lipoxygenase, 13-S-HODE: 13-hydroxyoctadecadienoic acid; TYK2: Tyrosine Kinase 2; JAK: Jak janus kinase; ZO-1: Zonula occludens-1 (Tight junction protein-1); IL13R $\alpha$ 1: receptor for interleukin 13 alpha subunit 1.

recurrent PCa. The mechanisms underlying the activation of autophagy by REST are still largely unknown, although it is evident that MAO A is a REST target in PCa cells. Fig. 5 graphically illustrates such a reasonable mechanistic hypothesis [31].

According to numerous literature data, MAO A is expressed in different types of breast cancer. Normally, breast cancer is classified according to the expression of hormone receptors present in tumor tissue (estrogen, progesterone, epithelial growth factor receptor) and can be divided into luminal A, luminal B, HER-2, and triple-negative breast cancer (TNBC) [33]. MAO A is expressed in luminal type A and luminal type B, while MAO B is highly expressed in TNBC [32]. Accordingly, it is clear that in breast cancer the action of MAO A seems to be much more complex and is addicted to the tumor histotype [3]. Therefore, cancer progression, angiogenesis, and metastasis require deeper investigation, especially at the molecular level.

#### 2.1.4. Role of MAO A in the formation of tumorspheres

A tumorsphere is a solid, spherical formation developed by the proliferation of a cancer stem/progenitor cell. The role of MAO A in the formation of tumorspheres in cancer stem cells is debated [32]. In recent years, numerous experimental data have been obtained using tumorspheres, in particular studies on breast cancer cells overexpressing MAO A. Studies conducted on murine or human breast cancer cells showed that serotonin produced in cancer cells promotes tumorigenesis through a cascade of signals mediated by serotonin itself and its receptors [34, 35], as well as MAO A-derived metabolites [17]. Recently, Rybaczuk et al. [36] analyzed a subset of cancer datasets, focusing on genes involved in the serotonergic pathway. They proved that MAO A suppression could be linked to an increased risk of cancer. In fact, MAO A expression was reduced in 95.4% of human cancer patients and in 94.2 % of animal cancer cases compared to non-cancerous controls [21]. The major expression of MAO A in high-grade tumors in renal carcinoma cell samples was confirmed in a study of Hodorová et al., also reported by Bhattacharjee et al., which further proved that MAO A expression in high-grade tumors may have a direct role in maintaining a dedifferentiated phenotype and promoting aggressive behavior [20,37]. These evidences led to the hypothesis that MAO A could act as a diagnostic biomarker and could be a therapeutic target in the cancer chemotherapy [1].



**Fig. 5.** Decision mechanism between apoptosis and autophagy in the prostate cancer cell with neuroendocrine differentiation. The gene expressing MAO A has been identified as a new target gene repressed by REST. In particular, H<sub>2</sub>O<sub>2</sub>, produced by MAO A, inhibits p53-mediated apoptosis. REST: RE1 Silencing Transcription Factor; BAX: Bcl-2-associated X (cytosolic protein); BAK: Bcl-2-associated X (membrane protein); PUMA: p53 upregulated modulator of apoptosis also known as Bcl-2-binding component 3 (BBC3); P53: tumor protein 53 [31].

## 2.2. MAO B

Although scientific interest has been mostly focused on MAO A, MAO B expression has also been studied in tumor tissues. In biopsy samples of human glioma, not only an increase in MAO A expression but also an important correlation with MAO B has been demonstrated. It has been reported that MAO B is overexpressed in glioma associated with HIF-1 $\alpha$  factor expression [3]. Therefore, MAO B could be considered a therapeutic target for the treatment of gliomas, although the role of MAO B in this context needs further investigation [35]. The resistance of gliomas to radiation therapy is believed to be mainly due to the presence of the nuclear factor kappa B subunit 1 (NF- $\kappa$ B) [38]. In this respect, it has been reported that NF- $\kappa$ B is activated by a series of signals induced by H<sub>2</sub>O<sub>2</sub> produced by MAO B metabolism. This observation seems confirmed by the presence of MAO B also in lung cancer cells [38], identifying this enzyme as a tumor biomarker [39]. Similarly, Ho et al. [40] investigated MAO B as a potential biomarker for early detection of oral squamous cell carcinoma (OSCC), while Yang et al. [41] showed that MAO B expression is strongly up-regulated in CRC and that it is related to EMT and to a higher incidence of relapse and poor prognosis [42].

## 2.3. MAO inhibitors and drug resistance in cancer

The problem of resistance to therapy in cancer is multifaceted. The key determinants are multiple: tumor burden and growth kinetics, tumor heterogeneity, physical barriers, role of the immune system, microenvironment, and the consequences of therapeutic pressure.

Currently, three main strategies are recognized for modifying the initial therapeutic scheme when drug resistance occurs [43]. The most used therapy in cancer patients is the sequential therapy, in which the onset of drug-resistant cell clones are treated with a new drug better suited to control newly acquired tumor characteristics. The second method is based on the combination of several drugs (combined treatment), while the third is based on adaptive therapy. The latter is a method still in the experimental phase, as it partly contradicts the conventional therapeutic guidelines [43]. Among these methods, the most promising is the combined treatment whose purpose is to prevent the onset of drug resistance and overcome the blockade of the response to tumor therapy [20]. This therapeutic solution aims to target intra-tumor colonists with different pathological characteristics, delaying the evolution of phenotypes resistant to chemotherapy treatment [43].

In the last few years, reducing resistance to chemotherapy has been gaining ground. Therefore, it is necessary to consider new “key nodes” of cancer cells. A promising strategy could be the multi-drug therapy able to recognize several cancer targets to improve the long-term therapeutic regimen [44]. The drug repurposing approach has also shown good potential in preclinical studies, particularly when MAOIs are involved [45].

Overall, the data we discussed highlighted that MAOs are important mediators of metastatic evolution and that their regulation may vary in different cancer types, making them potential therapeutic targets, particularly for drug-resistant tumors [20,28,46]. Further studies are needed to better understand the multiple mechanisms underlying treatment of resistance. There are many ways in which an initially therapy-sensitive tumor can evade treatments [46], thus, their identification would facilitate the development of new therapies [44,47].

## 3. Clinical use of MAO inhibitors

Over the years, a large number of MAOIs have been identified. First generation MAOIs were the first antidepressants introduced into clinical practice, but nowadays they are no longer the first choice treatment of mental disorders due to their numerous side effects and drug-food interactions [48,49]. Therefore, they represent only a therapeutic option when all other drugs are unsuccessful [50]. MAOIs can be classified according to their mechanism of action, either reversible or irreversible

[49], as well as based on the A/B selectivity [48,49]. Reversible inhibitors interact with the enzymes by establishing weak, non-covalent interactions. The irreversible inhibitors act by the formation of a covalent bond with the cofactor FAD, then, the biosynthesis of new enzymes is required to restore the enzymatic activity. Reversible and irreversible MAOIs are listed in Table 1.

In recent decades, the use of MAOIs has been also associated with other diseases, such as metabolic disorders, diabetes, obesity, skin damage, alopecia, cardiovascular diseases [52]. Recently, according to numerous studies reported in the literature, it has been observed that these molecules also possess antitumor activity [50–53], leading to their possible therapeutic repositioning [54]. Preclinical studies showed that MAOIs may potentiate the antineoplastic activity of other classical anticancer agents when associated with them, by playing a synergistic activity [55]. In this case, their role seems to determine an increment of antitumor activity and reduce drug resistance, interfering with several pathways implicated in tumor processes whose mechanisms are becoming clearer [56].

From this background, studies on several types of cancer have been conducted highlighting the role and the mechanism of action of MAOIs in tumorigenesis. A literature survey evidenced the registration of several clinical trials in which the use of MAOIs is proposed for the treatment of cancer. The molecules mainly studied are phenelzine, selegiline, and tranylcypromine [55]. These molecules are irreversible inhibitors with variable A or B selectivity [54]. Other examples of drugs, used for studies conducted on cellular or animal models, are clorgyline, CX-157, pargyline and rasagiline [57], as well as drugs not yet approved in clinical practice. The most investigated tumors, for which drug resistance mechanisms have been proposed, are prostate, brain, breast, and lung cancer. Tables 2 and 3 summarize information about patents of the last decade and clinical trials, respectively, examined in this review.

### 3.1. Phenelzine

Phenelzine sulfate (Nardil, Table 1), a non-selective and irreversible MAOI, is still used as an antidepressant and acts by restoring the balance of neurotransmitters in the brain [54]. Phenelzine sulfate has been considered in some clinical trials either alone [66] or in combination with other anticancer drugs used in the treatment of PCa [67] or metastatic breast cancer [68]. Phenelzine is most frequently associated with drugs belonging to the family of taxans. Among the proposed studies for the treatment of PCa, only the combination of phenelzine with docetaxel has now been completed [66]. This combination achieved antitumor activity in patients and was well tolerated without significant toxicity effects.

Phenelzine sulfate can stop the growth of cancer cells by blocking some enzymes necessary for cell growth. To support these observations, several hypotheses on the mechanism of action were considered.

Phenelzine sulfate acts synergistically with docetaxel making cancer cells more sensitive to the anticancer drug, overcoming drug resistance. Such feature did not clearly identify the mechanism of action, but the intervention of other enzymes such as lysine specific demethylase 1 (LSD-1) was hypothesized. It has been observed that tumor cells with metastatic potential overexpress MAO A, while the expression of MAO A in circulating tumor cells (CTCs) has not been demonstrated compared to other potential biomarkers such as LSD-1 [67]. In fact, LSD-1 is believed to facilitate the generation of stem cells with metastatic potential [68]. Considering the coadjuvant antiproliferative activity of phenelzine sulfate, it has been proposed for the treatment of bone metastases in prostate cancer, in combination with the tyrosine kinase inhibitor 4-aminoquinoline [58].

In a further study, phenelzine sulfate was combined with the next-generation antiandrogen enzalutamide (Enz) for the treatment of castration-resistant prostate cancer [63,72]. Often, the patients treated with Enz show a reduction of the therapeutic response after 1–2 years of treatment due to the development of a severe form of castration resistance. The onset of resistance remains unclear, although it has recently been observed that Enz could induce the expression of androgen receptor splice variant 7 (ARv7) responsible for the development of resistance. Moreover, it has been observed that enzalutamide resistant (EnzR) prostate cancer cells overexpress MAO A, therefore, the coadministration of phenelzine sulfate sensitized EnzR cells and interfered with Enz/ARv7/MAO A signaling [63].

### 3.2. Selegiline

Selegiline (Zelapar, Table 1) belongs to the class of propargylamines acting as irreversible MAO B-selective inhibitor, used in clinical practice for the treatment of depression as well as second line drug for PD. In previous studies, this molecule has been shown to possess an antitumor effect by preventing p53-dependent apoptosis and loss of mitochondrial function [54]. Selegiline has been proposed for the treatment of prostate cancer as an alternative to MAOIs. In previous studies, it has been shown that a minimal amount of MAO B is present in the stroma of tumor tissue and this could represent a target in the treatment of prostate cancer [23]. Starting from this observation, it was possible to demonstrate that selegiline is able to exert its action either alone or in association with MAOIs such as clorgyline. Selegiline, in fact, significantly reduces the viability of cancer cells both on human androgen-sensitive prostate adenocarcinoma (LNCaP) cells and on human prostate cancer cells with a high degree of metastasis (PC3), considered hormone-sensitive and resistant to hormones in in-vitro models and human xenotransplantation on SCID NSG mice.

It should be noted, however, that MAOBIs should generally be associated with an antitumor agent for the treatment of PCa in clinical practice such as cabazitaxel, abiraterone, enzalutamide or docetaxel

**Table 2**

List of cited patents regarding preclinical studies on MAO inhibitors in cancer therapy (2012–2022).

| Patent Number  | Filing year | Drug                         | Aims of the study                                                                                         | Status                       | Ref  |
|----------------|-------------|------------------------------|-----------------------------------------------------------------------------------------------------------|------------------------------|------|
| US2012065166A1 | 2012        | Phenelzine, 4-aminoquinoline | Treatment of bone metastases and other bone diseases                                                      | In vivo studies              | [58] |
| WO2012018761A2 | 2012        | MAO-A Is                     | Treatment of androgen-mediated tumors, and PCa in particular, using MAOIs                                 | In vitro studies             | [59] |
| WO2013016580A2 | 2013        | Clorgyline derivatives       | Treatment of PCa using MAOIs, such as fluorescent clorgyline derivatives                                  | In vitro and in vivo studies | [23] |
| US8524717B2    | 2013        | TCP derivatives              | Synthesis and in vitro evaluation of some TCP derivatives on cancer cell lines                            | In vitro studies             | [60] |
| WO2014018563A2 | 2014        | Pargyline, Selegiline        | Use of various antidepressants, including some MAOIs in the treatment of cancer                           | In vitro studies             | [61] |
| US10125099B2   | 2018        | Clorgyline derivatives       | Treatment of brain cancer using MAOIs, such as fluorescent clorgyline derivatives                         | In vitro and in vivo studies | [62] |
| WO2020146845A1 | 2020        | ENZ, Phenelzine              | Treating cancer using ENZ and phenelzine as MAO A inhibitor                                               | In vitro studies             | [63] |
| WO2021/024005  | 2021        | Selegiline, Rasagiline       | Use of MAOBIs selegiline and rasagiline in PCa                                                            | In vitro studies             | [64] |
| EP3815685A2    | 2021        | SN38, MP-MUS                 | Treatment of glioma through the use of new prodrugs of MAOBIs that can alter the function of mitochondria | In vitro studies             | [65] |

ENZ: Enzalutamide; TCP: tranylcypromine.

**Table 3**

List of cited clinical trials, their progression, and therapeutic indications.

| NCT Number  | Cancer   | Drug                          | Aims of the study                                                                                                                                                               | Stage      | Status                      | Ref  |
|-------------|----------|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------------------------|------|
| NCT02217709 | PCa      | Phenelzine Sulfate            | Treatment of recurrent and non-metastatic PCa                                                                                                                                   | Phase II   | Complete                    | [66] |
| NCT01253642 | PCa      | Phenelzine Sulfate; Docetaxel | Treatment of PCa that is growing, spreading, or getting worse after first-line therapy with only docetaxel                                                                      | Phase II   | Terminated (low enrollment) | [67] |
| NCT03505528 | BCa      | Phenelzine Sulfate; Abraxane  | Treatment of metastatic or advanced BCa                                                                                                                                         | Phase Ib   | Complete                    | [68] |
| NCT04586543 | PAd      | Selegiline; Docetaxel         | Evaluating the effectiveness and safety of selegiline plus docetaxel therapy compared to the standard of care among patients diagnosed with metastatic, castrate-resistant PAd. | Phase II   | Recruiting                  | [69] |
| NCT02261779 | AML      | ATRA; TCP                     | Evaluating safety and efficacy of ATRA/TCP treatment in patients with relapsed or refractory AML or in patients with AML who are not eligible for intensive treatment           | Phase I/II | Unknown                     | [70] |
| NCT02273102 | AML; MSL | ATRA; TCP                     | Evaluating safety and efficacy of ATRA/TCP treatment in patients suffering from AML or MSI                                                                                      | Phase I    | Completed                   | [71] |

BCa: Breast cancer; PAd: Prostate adenocarcinoma; AML: Acute myeloid leukemia; MSL: Myelodysplastic syndromes leukemia; ATRA: All-Trans Retinoic Acid; TCP: tranlylcypromine.

[64,69]. Experimental evidence has shown that selegiline combined with cabazitaxel, abiraterone or enzalutamide reduces the viability of human and animal cancer cells in a dose-dependent manner, leading to a general improvement of the clinical outcome [64]. The results of the combination of selegiline with docetaxel will be available by 2025 [69].

### 3.3. Tranlylcypromine

Tranlylcypromine (TCP, Parnate; Table 1) was first discovered in the 1940s as an analogue of amphetamine to relieve symptoms of nasal congestion. TCP belongs to the class of irreversible, non-selective cyclopropylamine-based MAOIs. It increases neurotransmitter levels in the brain by inhibiting the catabolism of serotonin and norepinephrine. Because of this ability, TCP was approved as an antidepressant drug by the Food and Drug Administration (FDA) in 1961 for patients with major depressive disorder [54].

Following the repurposing strategy of antidepressant drugs in the treatment of cancer, TCP has also been the focus of research and several clinical trials have been registered. From the studies conducted, it emerges that the antitumor activity of TCP is linked to the action on LSD-1. Several studies have shown that LSD-1 overexpression is associated with the development of blood and breast cancers, then LSD-1 has been proposed as a new and promising target of anticancer drugs [54]. In this light, Guibort et al. patented a series of 60 TCP-related molecules for their use as potential anticancer agents with inhibitory activity in-vitro against both MAOs and LSD-1 [60].

In 2012, Schenk et al. showed that combination therapy of TCP and all *trans*-retinoic acid (ATRA) or tretinoin has a superior antileukemic effect compared to ATRA single treatment. It was observed that by inhibiting the normal pro-differentiation role of ATRA, combination therapy opened a new avenue for the treatment of acute myeloid leukemia (AML). In fact, two clinical trials were initiated in 2014 to evaluate the safety and efficacy of TCP in combination with ATRA in patients with myelodysplastic syndrome (MDS) and relapsed or refractory AML [70,71]. The latter study was concluded and demonstrated that the ATRA-TCP association synergistically increases differentiation capacity and cell death by regulating the expression of key gene sets that segregate patients with MDS and AML. In addition, ATRA-TCP shows an acceptable security profile [73]. In the literature there are other pre-clinical studies in which TCP showed efficacy against glioblastoma and squamous cell carcinoma of the head and neck (HNSCC) [54].

### 3.4. Clorgyline, clorgyline conjugates, and CX-157

Clorgyline (Table 1) is an irreversible MAO A selective inhibitor used for research purposes. The use of clorgyline in the xenograft mouse model of prostate cancer showed a reduction in cell proliferation,

migration and invasiveness of cancer cells [20]. As noticed, overexpression of MAO A in prostate cancer is associated with increased aggressiveness; therefore, the inhibition of MAO A by clorgyline reverses the trend of high-grade prostate cancer. In fact, treatment with clorgyline shows an inhibition of the growth of tumor cells determining the downregulation of several oncogenic pathways. These results were observed both on mouse models with xenotransplantation and vertebral cancer of the prostate (VCaP) cells of advanced prostate cancer [23].

In 2015 Shih et al. suggested that a clorgyline conjugate (NMI, Fig. 6) selectively inhibited MAO A at concentrations in the low micromolar range (IC<sub>50</sub> between 5.1 and 6.1  $\mu$ M) [74], although three orders of magnitude higher than clorgyline. Experimental evidence indicated that this molecule can reduce proliferation, migration, and invasion of prostate cancer cells. These studies pointed out NMI as an effective anticancer agent with high tumor targeting specificity [23,74]. The same authors also reported a congener of NMI, the fluorescent clorgyline conjugate MHI 148-clorgyline (Fig. 6), which reduced the progression of temozolomide (TMZ)-resistant glioma, by increasing cytotoxicity and reducing the invasion of tumor cells in recurrent tumor forms [62].

However, the use of clorgyline and its derivatives requires special attention, due to some known cardiovascular side effects. For this reason, it was proposed the use of a MAOAI with the same biological properties as clorgyline, the phenoxathiine CX-157 (TriRIMA™), already approved by FDA (Fig. 6), whose therapeutic activity is observable especially in adenocarcinomas [59].

### 3.5. Pargyline

Pargyline (Table 1) is a propargylamine derivative with fair B/A selectivity. The effects of pargyline as anticancer compound have been evaluated in a cellular model of PCa. In particular, the effects observed on the survival of PCa cells LNCaP-LN3 suggest that pargyline may be a potential drug for the treatment of prostate cancer. Pargyline inhibits cell proliferation by blocking the cell cycle in the G1 phase in a dose-dependent manner and promotes the apoptosis process by increasing the rate of cell death [20].

Pargyline, as well as TCP, has been proposed for the treatment of neuroendocrine tumors, such as small cell lung cancer (SCLC). However, neither pargyline nor TCP significantly inhibit the growth of mouse and human SCLC cells, nor they are effective in inducing cell death. Both molecules were also inactive for non-small cell lung cancer cells (NSCLC) and did not antagonize G-protein coupled receptors (GPCRs). These results suggested that these molecules, unlike other antipsychotics considered in other studies, do not possess a good intrinsic antitumor capacity [61].

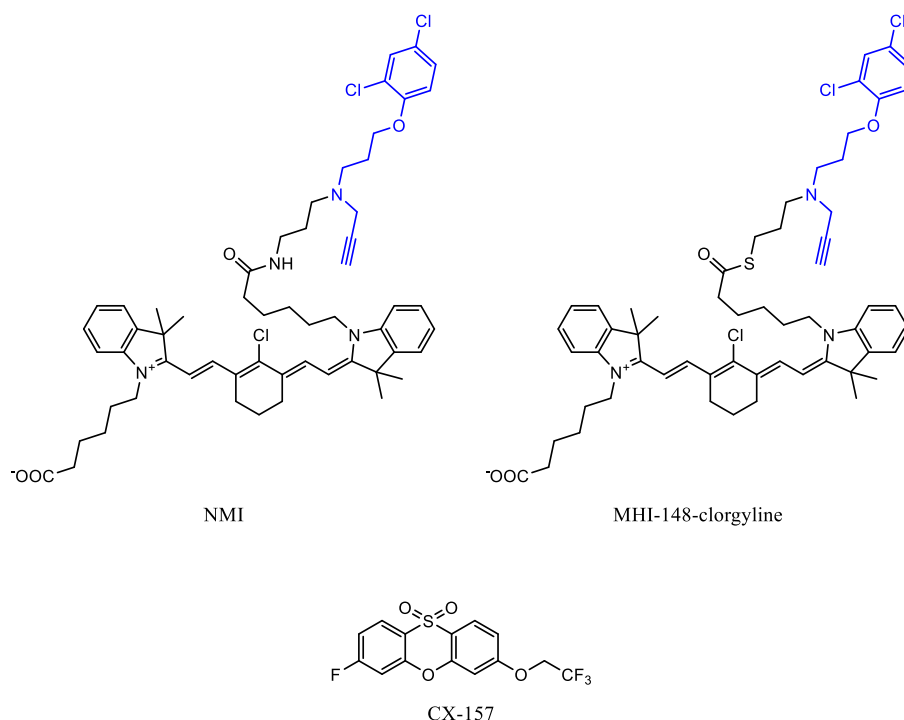


Fig. 6. Chemical structures of the clorgyline derivatives NMI and MHI-148-clorgyline and CX-157.

### 3.6. MP-MUS and SN38

MP-MUS and SN38 express their therapeutic potential interfering with mitochondrial cell activity (Fig. 7). These molecules have been specifically designed as prodrugs of selective MAOIs to be active on glioma cancer cells. This assumes that MP-MUS and SN38, for being activated, must have at least 10-fold B/A selectivity. Once activated, these drugs cross the mitochondrial membrane of cancer cells reaching concentrations even 1000 times higher than those into the environment outside the mitochondria. The active molecules can acylate mitochondrial DNA and ribosomal RNA, and thus act on cancer cells by disrupting the normal mitochondrial function, resulting in a 50 % reduction in tumor mass in a short time after administration [65].

## 4. Conclusions and perspectives

Cancer is the second leading cause of death in the world, with 19 million diagnoses and more than 10 million deaths worldwide in 2020 [75,76]. Although clinical practice in oncology has achieved considerable success, there is still room for improvement, especially in terms of efficacy and safety of the enrolled chemotherapy regimens. The anti-cancer drug resistance is a complex process and appear as a serious problem [43]. One of the first solutions to overcome the drug resistance

to single chemotherapeutic agents was the polytherapy strategy, i.e., the combined administration of agents with diverse mechanisms of action. This empirical approach provides positive feedbacks in different forms of cancers, such as lymphomas, breast cancer and testicular cancer. Therefore, the polytherapy strategy becomes a new promising paradigm for cancer therapy [77].

The development of new, more complex therapeutic regimens has consequently led to the evaluation of new aspects and key mechanisms in tumorigenesis, marking a new starting point for overcoming drug resistance. In the recent years, the understanding of certain biological mechanisms of tumorigenesis has led to the identification of new molecular targets, including MAOs [52]. Albeit the association between MAOs and cancer has been observed, the molecular mechanism underlying the cancer progression due to MAOs' overexpression in some tumor cells is still poorly understood.

In this review we focused on hallmarks falling within the pathogenesis of neoplastic transformation, namely the acquisition of the plastic phenotype (EMT), inflammation, hypoxia and apoptosis, in the attempt of clarifying the role of MAOs in the altered functional pathways of various tumors. Several studies pointed out the relationship between the expression of MAO A and the progression of some types of cancer, in particular prostate cancer. The silencing or knockdown of this enzyme are able to regulate essential events for the growth and development of tumors, such as EMT or production of ROS, leading to a significant reduction in tumor mass and formation of metastases. From a therapeutic point of view, the use of MAOIs could lead to an increase in survival, overcoming the phenomenon of drug resistance. Experimental evidence has shown that the above reported molecules, with few serious side effects at the tested doses, could modulate antitumor activity through several potential mechanisms including the inhibition of cell proliferation and reduction of metastases, interruption of the cell cycle, induction of apoptosis and autophagy [54].

The landscape depicted above assesses a possible second life for MAOIs, a class of biologically active substances primarily studied for their use in the treatment of neurologic disorders. Despite such huge efforts, very few molecules have passed the preclinical filters in the last

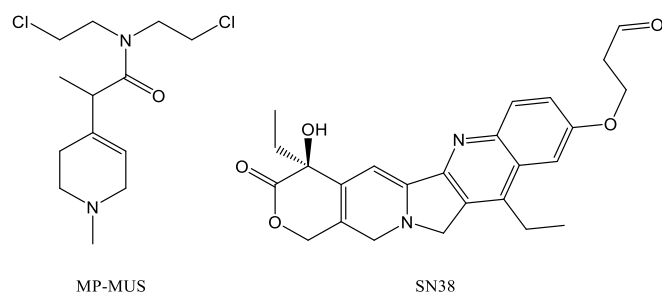


Fig. 7. Chemical structures of MP-MUS and SN38.

decade, and only safinamide, a selective and reversible MAO-B inhibitor, has been approved for the treatment of PD [50]. In front of such a low success rate, it is legitimate to ask if there is still reason to pursue the research for potent, selective, and safe MAOIs. This data survey, focused especially on patents and clinical trials of the last ten years, suggests that MAOIs may be repositioned from CNS pathologies to cancer therapy, and particularly MAOIs would benefit from their coadjuvant effects in some drug-resistant tumors.

Surprisingly, almost all drugs herein investigated belong to the first generation of MAOIs (with the valuable exception of clorgyline), being irreversible and unselective with relevant side effects at therapeutic doses. Little attention has been devoted to these crucial aspects of MAO inhibition in cancer therapy, which could be overcome by investigating in-depth selective and reversible MAOIs. Nevertheless, the use of MAOIs for cancer therapy would always take into consideration the occurrence of off-target effects at the CNS level, for which an accurate dosage (or a smart delivery system) of the inhibitor should be defined at the (pre) clinical stages.

As a general remark, greater evidence is needed to assess whether MAOIs act only as coadjuvant drugs, for overcoming drug resistance to chemotherapeutics, or may display an intrinsic antitumor activity. An increased investigative focus on drug design and repurposing in individual or combination regimens at the preclinical level, as well as new suitably designed clinical trials, will be necessary to better assess the potential of MAOIs in cancer therapy.

## Note

Figs. 2–5 were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (<https://creativecommons.org/licenses/by/3.0/>) [78].

## Funding

The Authors acknowledge the financial support of the Italian Ministry of Education, Universities and Research (PRIN, Grant 201744BNST\_004).

## CRediT authorship contribution statement

**Sabina Sblano:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **Angelina Boccarelli:** Conceptualization, Data curation, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Francesco Mesiti:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **Rosa Purgatorio:** Writing – original draft, Writing – review & editing. **Modesto de Candia:** Writing – original draft, Writing – review & editing. **Marco Catto:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Cosimo D. Altomare:** Funding acquisition, Supervision, Writing – original draft, 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

No data was used for the research described in the article.

## Acknowledgements

The authors gratefully acknowledge the support of equipment and

supplies provided by University of Bari Aldo Moro. R.P. acknowledges financial support from Apulian Region “Research for Innovation (REFIN)” – POR PUGLIA FESR-FSE 2014/2020 (Project F88A1A13).

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