

Novel 2D MBenes—Synthesis, Structure, and Biotechnological Potential

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2D transition metal borides (MBenes) have emerged as promising post-MXene materials with potential application in various biotechnological fields. Although they possess prospective bioactive properties due to boron in their structure, the experience gained from MXenes shows that an in-depth understanding of their biological recognition and response as well as the exploration of their biological applications are highly challenging. This makes the identification of the most promising 2D MBenes for future biological research and final industrial applications rather complicated. Herein, MBenes are differentiated from MXenes and further untangled for their bioactivity-generating features. It is expected that MBenes' positive or negative biological impact on living organisms and different types of cells connect with their morphological, structural and physicochemical features in the context of relevant environments. Necessary toxicological data are also highlighted, which are key aspects to enable MBenes' safe application in biotechnology and nanomedicine. Furthermore, a perspective for the rational development and design of novel biotechnological solutions based on MBenes is provided, which will meet the legal safety requirements for nanomaterials. In this regard, this work is an unprecedented contribution toward strategies for regulatory development for MBene/MXene-type nanomaterials. It provides an inspiration for future biotechnological and nanotoxicological approaches using MBenes.

interaction with living organisms based on their shape and surface chemistry, the development of easier methods to control material parameters regarding an efficient functionalization with bioactive agents as well as the improvement of targeting, delivery and extravasation through heterogeneous, extremely complex tumour micro-environments.^[1] Most recent innovations are based on the next generation of nano-therapeutics involving various 2D materials beyond graphene^[2] such as 2D early transition metal carbides/nitrides (2D MXenes^[3,4]) and their most recent counterpart—2D transition metal borides (2D MBenes).^[5] These 2D materials hold great potential since they combine basic functions of standard delivery agents with new features that may enable overcoming the mentioned key barriers in their biotechnological applications.

2D MBenes,^[5] although being relatively new and rather underexplored, are a highly promising family of nanomaterials. First reports on MBenes by Ade and Hillebrecht^[6] date back to 2015, which considered them analogously to early transition

metal carbides, nitrides, and carbonitrides (MXenes). Very recently, both MAB phases and bulk precursor powders were used for 2D borides synthesis.^[5,7] MoAlB^[5] with double Al layers and Mo₂AlB₂^[8] were partially etched into MoB^[5] and 2D CrB was obtained from its parental Cr₂AlB₂ MAB phase.^[9] Also Ti₂InB₂ was thermally dealloyed into TiB.^[10] In case of bulk powders, MgB₂,^[11] MnB,^[7] ZrB₂^[12] and GdB₆^[13,14] phases were disassembled into their corresponding 2D nano-sheets with the assistance of microwaves or ultrasounds. It can be thus expected that the development of new synthesis routes will enlarge the MBene family.

At first glance, MBenes seem to expand the family of MXenes by a new group of structures with boron 'B' simply replacing carbon "C" and/or nitrogen "N." However, when considering their structural and chemical features,^[15] it becomes evident that the MAB-MBene pairs cannot be just simply compared to and linked with the corresponding MAX-MXenes systems due to different stoichiometries, variable modes of 2D layer sandwiching, and variable types of structural transformations.^[6]

These differences and the presence of boron make MBenes particularly interesting for their application in biotechnology. The outstanding results of the corresponding 2D structures

1. Introduction

Nanomaterials-based healthcare has gained significant attention in recent years due to its outstanding flexibility in designing advanced drug delivery and theranostic systems. However, several key barriers persist that hinder their widespread use in clinical practice. These barriers correspond to the elucidation of molecular mechanisms of nanomaterials'

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DOI: 10.1002/adfm.202103048

are related to optical adsorption and emission,^[14] photothermal effects,^[7] presence of surface borate-rich features,^[12] and hydrolytic hydrogen generation.^[11] Therefore, we nimbly expect 2D MBenes to pursue their facile counterparts—2D MXenes in upcoming years.^[16,17]

This perspective aims at summarizing the existing knowledge about MBenes' synthesis, structures and properties. We also assess their biological potential and possible impact on living organisms compared to the knowledge gained for their MXene counterparts. We thoroughly describe the expected positive and/or negative biological effects in the context of 2D MBenes' structural, morphological, and other physicochemical properties under relevant conditions and testing environments. Structural transformations of 2D MBenes, such as their susceptibility to surface oxidation and related biodegradation in ambient or physiological conditions are also essential to discuss in this context.

Consequently, this work contributes toward a detailed understanding of 2D MBenes' biological recognition, response, and potential impact to living organisms by connecting their biological properties with structural and chemical features. Finally, we highlight the need to provide necessary and comparable toxicological data to enable MBenes' safe applications that will be consistent with the assumed regulatory strategies and future legislation in the field of environmental protection.

2. Structure of 2D MBenes

MBenes have been introduced for the first time in 2015 by Ade and Hillebrecht.^[6] Since then, they have gained considerable attention due to numerous potential applications. MBenes appear to be fairly similar to MXenes by solely replacing carbon and/or nitrogen sites with boron.^[4] However, due to differences in the resulting stoichiometries, modes of 2D layer sandwiching and structural transformations, MAB-MBene pairs cannot be just straightforwardly linked with the corresponding MAX-MXenes combinations.^[15]

The parental phases for MBenes' synthesis are thermodynamically stable MAB nanolaminates (atomically laminated ternary transition metal borides^[6]). It is worth mentioning that they were discovered before the 1990s as ternary boride phases.^[18,19] MAB phases possess variable chemical formulas with the relevant compositions being MAB, M_2AB_2 , M_3AB_4 , and M_4AB_6 , for which M represents an early transition metal and A stands for an IIIA and IVA group element.^[6] When assuming A = Al for the sake of simplicity, MALB phases exhibit an orthorhombic crystal structure with space groups varying from $Cmcm$ (for MALB) over $Cmmm$ (for M_2AlB_2 and M_4AlB_6) to $Pmmm$ (for M_3AlB_4).^[6] The M-A bond is metallic, while M-B bonds have a mixed covalent/metallic/ionic character, being fairly similar to M-X in MAX phases.^[20] The metal boride (M-B) layers of variable thickness, composed of face-sharing BM_6 trigonal prisms, are interleaved by layers of A atoms (mostly aluminum). The B atoms are then separated by short distances and form covalently bonded "zig-zag" chains.

In contrast, 2D MXenes (early transition metal carbides and/or nitrides) are rather simply structured.^[16] MXenes exhibit long-range order due to the presence of diverse chemical

bonding accompanied by Van-der-Waals forces.^[4] The name "MXene" evolved from their parental "MAX" phase,^[21,22] reflecting their stoichiometry and composition. In this regard, $M_{n+1}AX_n$, for which M represents an early transition metal (e.g., Ti), A stands for an element of group 13 or 14 of the periodic table and X reflects carbon and/or nitrogen, while $n = 1, 2, 3, 4$,^[4] or even 5.^[23] In case of solid solutions containing C and N, carbonitrides have been also produced.^[24]

It can be noticed that the stoichiometric descriptions of MXenes and MBenes only reflect the relative proportion of different elements, but they do not match with the actual stoichiometry of the unit cell. MBenes and MXenes with different stoichiometries were envisioned based on theoretical first principle calculations,^[25] while around 30 different MXenes have already been successfully synthesized.^[4] Due to the fast progress on MXenes coupled with their chemical and structural diversity,^[26] we hypothesize that MBenes can be also synthesized with different chemical compositions.

For MBenes, it is important to emphasize that the M-B layers are separated by either mono- and bi-layers of Al. In case of Cr_2AlB_2 , Mn_2AlB_2 , Fe_2AlB_2 , Cr_3AlB_4 , Cr_4AlB_6 , and the recently synthesized Cr_4AlB_4 phase,^[27] mono-layers of Al can be found, while $MoAlB$ or $WAIB$ phases are separated by Al bi-layers. Moreover, Cr_2AlB_2 , Cr_3AlB_4 , and Cr_4AlB_6 form the $(CrB_2)_nCrAl$ series with 2, 3, and 4 M-atom planes with M-B layers, respectively. The ability to alloy the M sites was also verified for $(Fe_{1-x}M_x)_2AlB_2$ ($M = Mn, Co$)^[28] and $(Mo_{1-x}M_x)AlB$ ($M = Cr, W$).^[29] Consequently, it can be deduced that MBenes are a rather diverse group of 2D nanomaterials regarding their resulting structure and are not simply a mirror reflection of MXenes.

Layered MBenes can be obtained from their parental MAB-phases using top-down approaches. However, this field is rather underexplored and only a couple of MABs have already been utilized for MBenes' synthesis. Nevertheless, the first attempts of MBenes' preparation suggest that they are highly promising and possess significant potential for further development due to their unique boron-containing structure and much greener synthesis routes. Recently, Mo-B, Cr-B, and Fe-B derived from their MAB-phase were selected from a large group of MBenes as promising candidates for scalable exfoliation-based synthesis methods.^[30] These results are based on mapping the relative formation enthalpies (ΔH) of various MAB phases (see Figure 1) with $\Delta H = 0.036$ eV per atom as a cut-out. Most of the already experimentally synthesized MABs lay well below the respective line (marked by arrows). In this context, MALB, M_2AlB_2 , M_3AlB_4 , and M_4AlB_6 have been identified as those with large potential for further etching and further delamination. Based on theoretical studies, it is also well accepted that various M elements can extend the family of MAB phases.^[30] In recent computational studies, it has been demonstrated that the synthesis of ordered MAB phases with double transition metals such as $M_2M'AlB_4$ ($M = Mn, Fe, Co$, $M' = Cr, Mo, W$) is possible.^[31]

To differentiate MAB/MBenes from MAX/MXenes, their structures as illustrated in Figure 2 need to be taken into consideration. When comparing the structure of both nanomaterials, significant changes and structural variations become evident. The crystal structures of various MAB phases

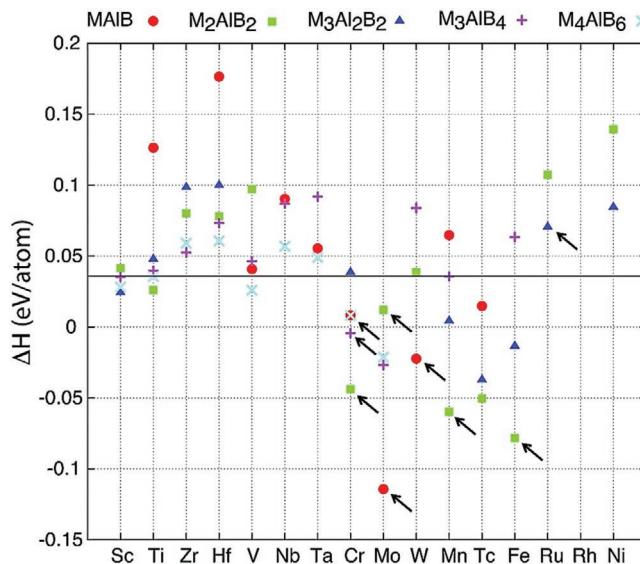


Figure 1. Relative formation enthalpies (ΔH) of various MAB phases with different stoichiometries. The ΔH value of 0.036 eV per atom indicates the cut-off between non-stable (above) and stable (below) phases. The arrows highlight compounds, which have already been experimentally synthesized (Reproduced with permission.^[30] Copyright 2019, Elsevier).

and related MBenes (Figure 2a) can be classified in the following manner. The first group of compounds are “212” phases with *Cmmm* crystal symmetry, “414” phases with *Immmm* symmetry, and “222” with *Cmcm* symmetry.^[3] The second group consists of “314” structures with *Pmmm* symmetry, whereas the third group is formed by “416” structures with *Cmmm* symmetry. MBene phases can be generated from these groups with the corresponding CrB/ β -MoB-type MBenes having a *Cmcm* symmetry, Ta₃B₄/Cr₃B₄-type MBenes with *Immmm* symmetry and V₂B₃/Cr₄B₆-type MBenes with *Cmcm* symmetry.^[3] Consequently, mainly orthorhombic crystal symmetries can be identified for MAB, M₂AB₂, M₃AB₄, and M₄AB₆ phases.

In contrast, only hexagonal *P6₃/mmc* symmetries are known for MAX/MXene pairs (M₂AC, M₃AC₂, and M₄AC₃).^[32] For instance, a hexagonal structure has been recently verified for Ti₂InB₂ MAB phase with *P6₃/mmc* space group.^[10] For these pairs, M, A, and X atoms are parallelly packed in a hexagonal manner as depicted in Figure 2b. In case of MAB phases, M and A atoms are stacked in an orthorhombic manner. In these structures, the B-coordinated M atoms are bonded in trigonal prisms, perpendicular to the A layers. Moreover, the boron atoms form zig-zag chains in the structure that are also perpendicular to the A layers. Due to these significant differences, these ternary B-containing compounds were excluded from the MAX group and were named MAB phases.

Recent research related to MAB phases has primarily focused on fundamental physical properties such as magnetic properties.^[33] The breakthrough material is a lightweight AlFe₂B₂ ferromagnetic phase with a Curie temperature of 300 K without any rare-earth element. There is still a lot of space for further improvements in this field due to existing impurities in the obtained MBene phases, which downgrade the resulting physical properties.^[34] Other experimentally synthesized MAB

phases, which have been analyzed regarding their purity, include MAIB (M = Mo and W), M₂AlB₂ (M = Cr, Mn, and Fe), Ru₃Al₂B₂, Cr₃AlB₄, and Cr₄AlB₆.^[3]

3. Synthesis of 2D MBenes

Compared to MXenes, it is well accepted that MBenes can be synthesized under milder conditions,^[9] which paves the way for basic and applied research and opens up the possibility to use them for industrial applications. Just for comparison, the synthesis of MXenes generally makes use of concentrated HF or its *in-situ* formation when utilizing fluoride salts with HCl for etching. It can be traced back to pronounced differences in the bonding strength between the M-A and M-X bonds. While M-X bonds have a covalent-metallic-ionic character with a relatively high bonding strength, metallic M-A bonds are considerably weaker.^[4] Therefore, MXenes can be obtained by the selective etching of the A-layers from MAX phases^[35] using rather harsh etching routes such as concentrated hydrofluoric acid (HF).^[4] The search for milder and more sustainable etching routes for MXenes finally came up with more practical approach using a mixture of lithium fluoride (LiF) and hydrofluoric acid (HCl). Due to the existing surface terminations, the compromised chemical formula of MXenes is generally given as Ti₃C₂T_x or, more specifically, as Ti₃C₂(OH)_xO_yF_z.

Most recent studies on 2D MBenes follow the outstanding quest for obtaining delaminated, atomically thin 2D MXene flakes. Researchers have used two different approaches with respect to the starting materials and the etchant's composition. The first group is based on using MAB phases as starting materials altogether with an acidic or basic treatment. The second group relates to the use of bulk powders and their solvothermal defragmentation into certain nanostructures. Moreover, dealloying has been also used for this purpose. **Table 1** summarizes recently obtained 2D boride structures and their functional properties.

In the first case, the use of MoAlB, Cr₂AlB₂, and Ti₂InB₂ resulted in partial and complete etching thus obtaining 2D CrB,^[9] MoB,^[5] TiB,^[10] respectively. In case of CrAlB, MAB grains can be etched into CrB multilayers using diluted (about 1 mol L⁻¹) basic (NaOH) or acidic (HCl) aqueous solutions.^[36] However, for MoAlB, the Al layers were observed to etch into large MoAlB stacks with thicknesses ranging between 50 and 300 nm.^[5,37] Notably, it is not straightforward to fully etch MAB phases into MBenes in contrast to MAX phases. The complete removal of Al layers can be achieved after about 24 h, thus forming MXene multilayers.^[32] Another study described layered Mo₂AlB₂ and Mo₂AlB₂-AlO_x heterostructures, which can be obtained from MoAlB via low-temperature, stepwise topotactic etching^[8] (Figure 3b). The first step involves the chemical deintercalation of Al layers from microscale MoAlB to destabilize MoAl_{1-x}B powder. Afterward, the powder is subjected to recrystallization into submicron powder, which is subsequently annealed to further deintercalated Al to finally obtain layered crystalline Mo₂AlB₂ powder. Longer annealing times result in Mo₂AlB₂-AlO_x, which represent 2D Mo₂AlB₂ layers interleaved with amorphous nanometric-sized aluminum oxide layers (please refer to Figure 4a–c).

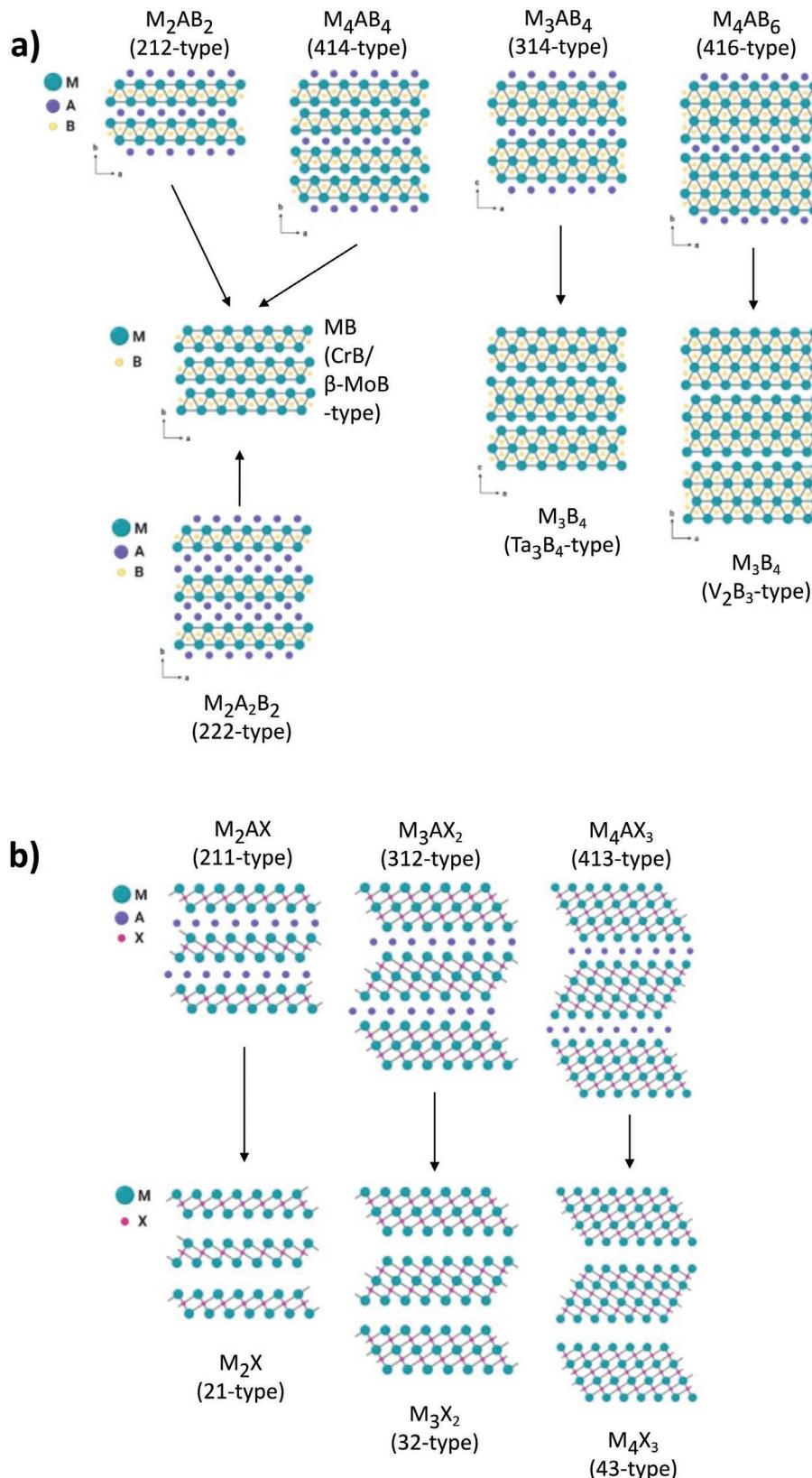


Figure 2. a) Structure and classification of MAB and related MBene phases by their crystal structures including 212-, 222-, 414-, 314-, 416-, CrB/ β -MoB-, Ta_3B_4 / Cr_3B_4 -, and V_2B_3 / Cr_4B_6 -type structures. (Adapted with permission.^[3] Copyright 2019, Taylor & Francis Group). b) Structure and classification of MAX and related MXene structures such as 211-, 312-, 413-type structures. The M, A, B, and X atoms are shown in blue, purple, light yellow, and pink in individual unit cells, respectively.

Table 1. Summary of the most recent findings regarding the experimental synthesis of 2D boride phases and their properties.

| Chemical composition | Synthesis method | Synthesis effects | Phase composition | Surface chemistry | Key findings | Ref. |
|--|---|--|--|---|--|------|
| MoB (thickness of 1.0–1.5 nm) | MoAlB etching with NaOH or LiF/HCl | Al removed partially in a stepwise manner with growing stacking faults, possible MoB monolayers forming etched cavities | Mostly partially etched MoAlB MAB phase with MoB layer slowly dissolves in the presence of HF at room temperature, which makes LiF/HCl not suitable for deintercalation of Al from MoAlB MAB phase | Some residues from the etching process could be present | This study aimed at synthesis of 2D MBene. MoB layer slowly dissolves in the presence of HF at room temperature, which makes LiF/HCl not suitable for deintercalation of Al from MoAlB MAB phase | [5] |
| MgB ₂ (lateral sizes of 30 nm) | Ultrasound-assisted chemical etching with CH ₃ COOH, H ₂ O ₂ , and PEG4000 | Obtaining of 2D nanosheets | Major MgB ₂ with minor MgB ₄ | Boric acid ester borate (B-O-PEG) with HO-B on the surface of MgB ₂ | High acid-responsiveness for decomposition into H ₂ , after combining with polyvinylpyrrolidone (PVP) and doxorubicin (DOX) facile agent for hydrogen chemotherapy | [11] |
| TiB (thickness of 10–20 nm) | Dealloying strategy adopted to exfoliate In layers from Ti ₂ InB ₂ MAB phase | In layers were gradually extracted with increasing heating temperature, layered boride as a product | TiB with almost no In residue | Calculations describing surface functional groups (F, Cl, OH, and O) which attributes to metal-to-semimetal transition | Analysis of possible Li ⁺ or Na ⁺ ions intercalation between TiB sheets to make it a promising material for Li- or Na-ion batteries confirmed by calculations | [10] |
| CrB (thickness of several to tens nanometer) | Etching out Al atomic layers from Cr ₂ AlB ₂ MAB phase using diluted HCl | Investigated MAB was successfully etched into single nanosheets with high purity | A high content of 2D CrB with Cr ₂ B ₂ as a transition phase | Functional groups rather not present due to the high purity of product confirmed by EDS analysis | This work aimed at verification of a precursor for the synthesis of 2D CrB | [9] |
| MoB/Mo ₂ B ₂ | NaOH Etching of MoAlB/Mo ₂ AlB ₂ MAB phase with etching temperature optimization | Al was partially deintercalated with phase transformations of MoAlB/Mo ₂ AlB ₂ into a stable nanosheet heterostructure containing 2D Mo ₂ AlB ₂ layers and amorphous aluminum oxide layers. MoAlB was etched only near the surface | Depending on the stage of synthesis/etching process, different contents of MoAlB/Mo ₂ AlB ₂ MAB phases and amorphous aluminum oxide | The formation of aluminum oxide surface coating | This work aimed at studying multi-step topochemical pathway for 2D materials synthesis | [8] |
| MnB/MnB ₂ (1.04±0.34 nm thickness, 150 nm lateral size) | Microwave-assisted chemical etching of MnB powder using CH ₃ COOH and H ₂ O ₂ , assisted by PVP. | Successful exfoliation of a precursor powder into a flower-like structure consisted of nanosheets | A mixture of two phases (MnB and MnB ₂) due to the presence of two crystal phases in a precursor powder | Shortly after synthesis, Bi-anchored manganese boride nanosheet | shown supreme NIR-photothermal conversion efficiency and high photothermal stability, as well as comprehensive imaging functionality | [7] |
| ZrB (7.4 nm thickness, 150 nm lateral size) | Microwave-assisted chemical etching of ZrB ₂ powder | Successful etching into single nanosheets, which maintained the crystal structure of the pristine ZrB ₂ starting powder | No significant amount of any additional functional groups | Formation of borate ester between nanosheets after modification with HA. This allowed to prevent ZrB HA detachment and aggregation of ZrB ₂ , nanosheets aggregation and therefore NIR-controlled intratumoral retention to achieve high intratumoral accumulation | A broad absorption peak in the range of UV to NIR for HA-modified flakes, beneficial for NIR-photothermal effect. Photopyrolysis of borate ester allowed in comparison to non-modified flakes | [12] |
| GdB ₆ (180 nm lateral size) | Microwave-assisted chemical etching of GdB ₆ powder, using CH ₃ COOH and H ₂ O ₂ , assisted by PVP55000 | The 2D flakes remained their initial stoichiometry and proved to be GdB ₆ | Pure GdB ₆ | The product was surface-modified with PVP | Fluorescence imaging and near-infrared (NIR) photothermal conversion capability. The fluorescence with bright greenish-yellow emission | [13] |
| CrB (10–100 nm in height) | Etching in diluted HCl solution at room temperature from Cr ₂ AlB ₂ MAB phase | After 6 h of etching in diluted HCl, exfoliation of MAB phase, similar to exfoliated graphite and MAX phases was observed | Almost pure CrB with 0.52 wt% of Al | Speculations about the existence of OH or Cl groups on the surface of nanosheets | The authors concluded that the purity and thickness of 2D CrB may be controlled by adjusting the concentration of etchant, etching time, and temperature. As observed on SEM images, obtained nanosheets can roll up to form irregular tubes with different shapes and dimensions. | [9] |

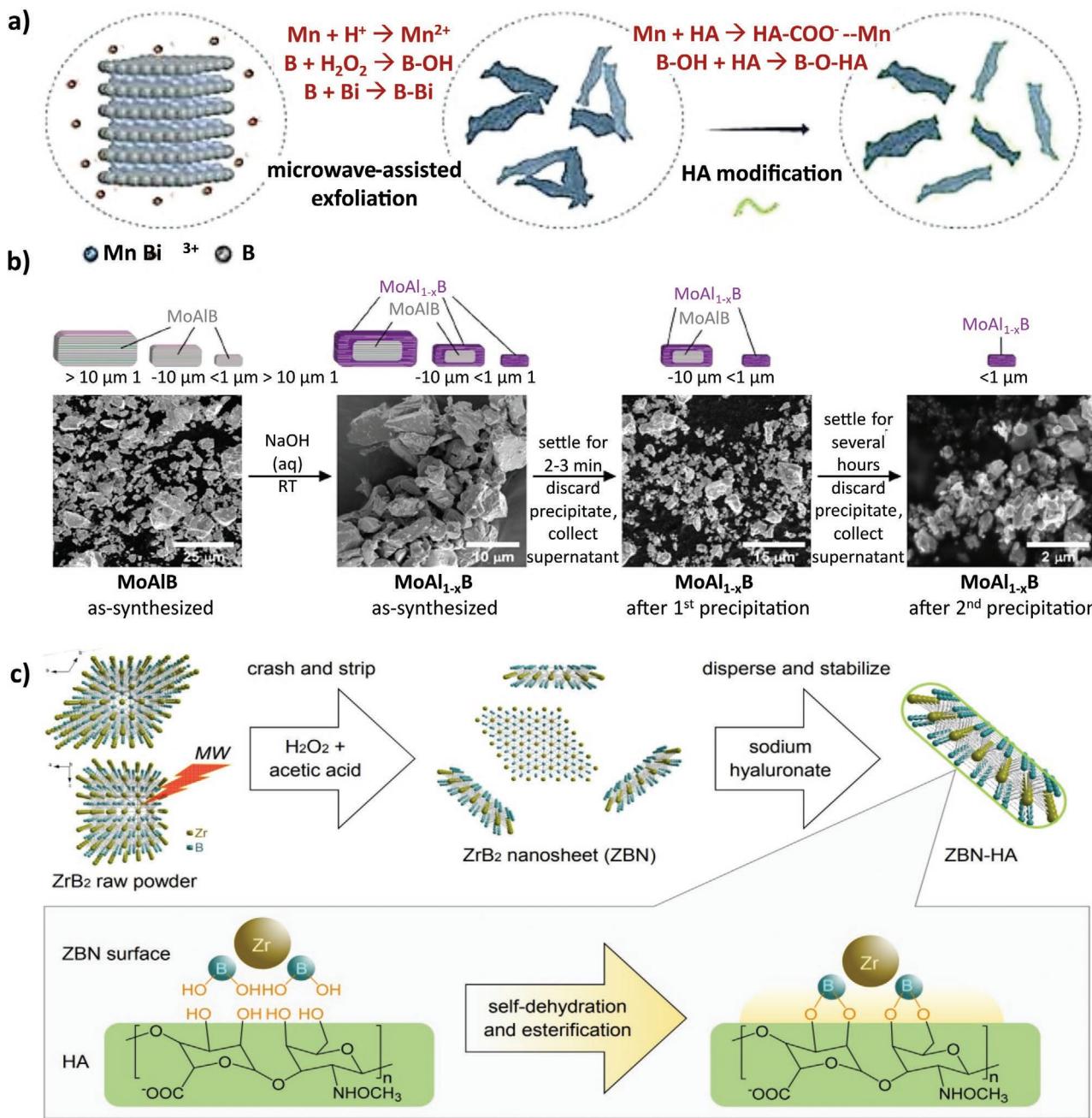


Figure 3. a) Schematic illustration of coordination-induced microwave-assisted chemical exfoliation of MAB phase to obtain MnB₂/MnB nano-sheets (Reproduced under the terms of the CC-BY license.^[7] Copyright 2020, Ivspring International Publisher). A schematic stepwise topotactic approach developed to obtain b) Mo₂AlB₂ and Mo₂AlB₂-AlO_x heterostructures, which can be obtained from MoAlB MAB phases (Reproduced with permission.^[8] Copyright 2019, ACS Publications) as well as c) ZrB₂ nano-sheets surface-modified with hyaluronic acid (Reproduced with permission.^[12] Copyright 2021, Wiley-VCH).

To overcome the problem of partial etching of MAB phase, Wang et al. thermally dealloyed Ti₂InB₂ (space group $P\bar{6}m2$) into 2D TiB.^[10] It is worth noting that diluted HCl (2 mol L⁻¹) was applied for 10 h to remove any impurities (e.g., Ti₃In, Ti₃In₄, Ti_{2.2}In_{1.8}). After this post-treatment, the MAB phase contained 93.7 wt% of Ti₂InB₂ and 6.3 wt% of TiB₂, which could not be removed due to its stability. Additionally, when nitric acid was used as an etchant, TiO_x was formed as an impurity. In general, the synthesis involved placing the Ti₂InB₂ sample into a

dynamically evacuated quartz tube. A heat treatment at about 1050 °C for 6 days under $\approx 10^{-4}$ Pa allowed for dealloying of In from the MAB phase.

In terms of using bulk powders for defragmentation into 2D flakes of MgB₂,^[11] MnB,^[7] ZrB₂,^[12] and GdB₃^[13,14] phases were successfully disassembled into their corresponding 2D nano-sheets.

The 2D MgB₂ nanosheets were synthesized using an ultrasound-assisted chemical etching.^[11] The starting bulk MgB₂

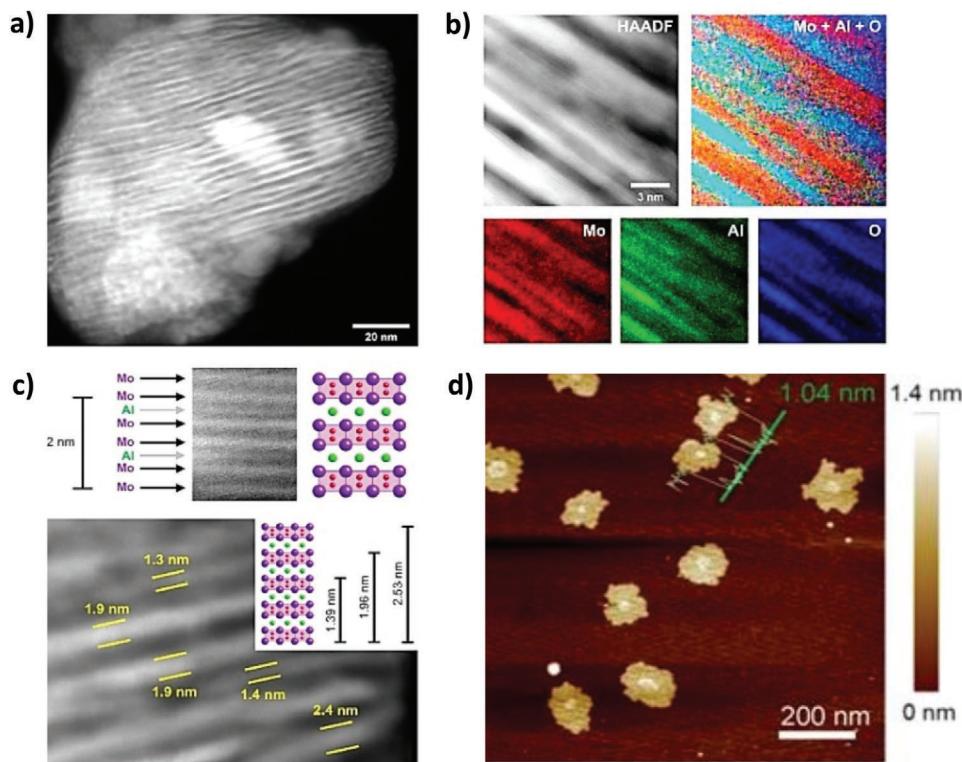


Figure 4. a) Representative edge-viewed $\text{Mo}_2\text{AlB}_2\text{-AlO}_x$ particle, b) STEM-EDS mapping, and c) simulations of Mo_2AlB_2 crystal structure (Reproduced with permission.^[8] Copyright 2019, ACS Publications). d) Representative AFM image of the Bi-anchored MnB_2/MnB nano-sheets, where the green line represents the distribution of flakes' height with an average value of 1.04 nm (Reproduced under the terms of the CC-BY license.^[7] Copyright 2020, Ivspring International Publisher).

powder was mixed with large-weight polyethylene glycol PEG4000 in 120 mL of deionized water. Subsequently, 9 mL of hydrogen peroxide (H_2O_2 , 30%) and 540 μL of acetic acid (CH_3COOH) were added to the mixture. An ultrasonic treatment with a power density of 425 W cm^{-2} was then applied for 60 min with a pulsed sonicator mode (2.2 s on / 6.6 s off).^[11]

An approach developed by Jin et al.^[7] allowed to obtain MnB nano-sheets (MBN) being a mixture of MnB_2 and MnB phases. This method (see Figure 3a), motivated by previous difficulties in MAB etching, was based upon oxidative acidic etching of manganese boride under microwave assistance.^[32] herein, also two etching agents were used (CH_3COOH and 30% H_2O_2). The mixture was heated up to 160 °C in a microwave reactor for 2 h, washed, surface-modified by hyaluronic acid (HA) and sonicated for 1 h. The addition of Bi^{3+} during etching into the reaction system most probably allowed to form a bonding between boron and bismuth, thus generating Bi-anchored MnB_2/MnB nano-sheets (MBBN)^[7] (see also Figure 4d).

A similar method was used by Chen et al.^[12] to produce ZrB_2 nano-sheets (see Figure 3c). The microwave-assisted chemical etching of bulk ZrB_2 powder involved the modification of 2D ZrB_2 by HA. They dispersed 170 mg of raw powder in 50 mL of ethylene glycol (EG), and 385 mg of CH_3COOH . They further added 3 mL of H_2O_2 (30%) and transferred the mixture to a 400 W autoclave, heated up to 160 °C for 2 h. The HA surface modification involved dispersing 2D flakes with HA, treated with ultrasounds, and washing.^[12]

Chen et al.^[14] also used microwave-assisted chemical etching to develop 2D GdB_6 flakes. They also made use of CH_3COOH and H_2O_2 as etching agents in EG, with the assistance of PVP as a dispersing agent. After cooling, the reaction mixture was centrifuged at 12 000 rpm and further washed with deionized water and ethanol. The remaining bulk GdB_6 was collected by centrifugation at 4000 rpm. A comprehensive analysis showed that 180 nm-sized 2D flakes remained their parent structure with a GdB_6 stoichiometry.^[14]

The abovementioned attempts to synthesize 2D MBenes clearly show that an effective method for separating 2D MBene flakes from partially delaminated MAB-based mixtures is yet to be developed. Detailed studies on the effect of the delamination method (the type of etching and intercalating agent used) on the resulting surface chemistry by advanced, high-resolution materials characterization techniques are urgently needed and highly recommended. Furthermore, the impact of the delamination method on materials' structure, physicochemical properties, and colloidal behavior needs to be studied in detail for 2D MBenes, especially for their application in biotechnology.

4. Morphological, Structural, Physicochemical Features and Transformations of MBenes

Until now, only theoretical studies addressed structural and physicochemical changes in 2D MBenes.^[30] These suggested transforming 2D MBenes with cubic or orthorhombic lattices

to a hexagonal one that occurred only at elevated temperatures. Moreover, it has been experimentally confirmed that 2D MXenes transform into a cubic phase, nanocrystals of transition metal oxides, and disordered graphitic carbon structures upon heating.^[38] Therefore, new approaches to precisely transform MBenes' structure are expected to be revealed soon.

The orthorhombic MAB phases with M = Cr, Mn, Tc, Fe, Ru, and Ni seem to be more stable,^[30] since Sc, Ti, Zr, Hf, V, Nb, Ta, Mo, and W tend to form hexagonal binary boride phases. These MAB phases are good candidates for applications that require long-term stability under relevant working conditions.

Moreover, it is well accepted that structural transformations of 2D MBenes due to oxidation cannot be omitted. Recently, we have quantitatively investigated the impact of some ambient post-treatments on the degree of physicochemical degradation of MXenes' surface.^[39] The importance of the verification of MXenes' properties in close-to-real working environments has been highlighted.^[39,40] This aligns well with the existing literature indicating that, in case of Ti_3C_2 , the delamination process should be carried out in an inert and dark environment.^[41] Moreover, the as-produced flakes are advised to be stored in the same way due to the potential surface oxidation of titanium to TiO_2 .^[41] Other studies also confirmed MXenes' surface oxidation at elevated temperatures.^[38,42] It has been verified that MXenes transform to TiO_2 together with the desorption of H_2O and CO_2 reaction products under oxygen exposure.^[43] All these aspects emphasize the verification of the time-dependent stability of MBenes' fundamental properties, which is still in its infancy.

MBenes' structural and chemical properties are expected to be closely connected with their biological properties. In 2017, we showed for the first time that the surface chemistry^[44,45] and the stability of delaminated 2D Ti_3C_2 flakes influence the *in-vitro* response of human cancer cells.^[46] Further studies of Chen et al.^[47] showed that the adsorption of amino acids such as glycine or leucine prevents restacking of 2D sheets in charge storage systems. Wu et al.^[48] used -OH surface terminations to immobilize enzymes to maintain MXenes' bioactivity and stability in mediator-free phenol biosensor platforms. Our studies revealed that the electrostatic adsorption of lysozyme^[49] and collagen^[50] on the surface of Ti_2C and Ti_3C_2 leads to changes of MXenes' physicochemical and biological properties. Liu et al.^[51] obtained similar results while modifying the surface of Ti_3C_2 with hyaluronic acid to achieve an active tumor targeting and accumulation together with enhanced stability of the multifunctional nanoplatform. It is noted that polyethylene glycol (PEG) can be also used to modify Ti_2C to stabilize the photothermal ablation of cancer cells and minimize negative effects on non-malignant ones.^[52] Other studies used soybean phospholipid-stabilized Ta_4C_3 MXene^[53] or polyvinylpyrrolidone (PVP)-stabilized Nb_2Cl ^[54] for dual-mode photoacoustic/CT imaging and photothermal therapy of cancer with no appreciable *in-vitro* and *in-vivo* toxicity. Furthermore, we have revealed that changes in the surface charge of Ti_3C_2 flakes during adsorption of poly-L-lysine (PLL) affect MXenes' colloidal, antibacterial and cytotoxic properties.^[55]

Additionally, it is likely that the surface functionalization of 2D MBenes with various biomacromolecules, if properly used/anchored, can tune their biocompatibility and stability

thus adding biocidal properties to an impressive list of their advanced functionalities. It is essential to point out that most of MXenes' surface modifications were possible due to the presence of -OH surface terminations. Although there is no direct evidence of surface terminations for 2D MBenes yet, we hypothesize that MBenes' highly reactive surface chemistry will also be available for interactions with various chemical moieties. This assumption will be strongly supported by future development of a water-based delamination procedure,^[36] which induced hydrophilic and oxygen-enriched surface chemistry for MXenes.^[32,4]

In case of 2D nanomaterials, other mechanisms like chemical reactions or preferential surface sites for bio-action also need to be considered due to their chemical reactivity and high specific surface area.^[56,57] Another important aspect is the possibility of their functionalization, which can be induced intentionally or occur spontaneously. For instance, it has been proven that the oxidation of Ti_3C_2 MXenes noticeably increased the bioactivity against *E. coli* and *B. subtilis* bacteria.^[58] The decoration of graphene oxide sheets with silver or copper nanoparticles significantly boosted their *E. coli* and *S. aureus* bacteria activity.^[59] When different structures like graphene or MXenes and metallic nanoparticles are merged into a composite-type material, other mechanisms, possibly working together and caused by various factors, need to be considered. For instance, titanium oxide nanocrystals are an effective photocatalyst and their effectiveness can be improved by preparing nanocomposites, thus changing process parameters or the light wavelength.^[60,61]

It is widely known that controlling material properties is an important step toward biotechnological applications. The first aspect that can be described as potentially problematic in controlling MBenes and MXenes properties is their structural inhomogeneity. The second one, probably also being connected to the first aspect, is the variable surface chemistry. The first aspect greatly depends on the starting materials (MAB- and MAX-phases in MBenes and MXenes, respectively). At the same time, the latter is undoubtedly more problematic if it comes to interactions with susceptible biological systems. The surface chemistry of MBenes is closely related to the early transition metal and a M_xO_y passivation layer resulting from the reaction of M with oxygen and/or water. In fact, every MBene surface exposed to air can naturally react with oxygen. The formation of M-O bonds is likely to occur since the freshly exposed metallic surface is energetically unsaturated and possesses high reactivity. This can happen immediately after delamination and depends on MBene's stability. Moreover, the freshly exposed surface of MBenes also acquires bonding with products of chemical reactions that occur during acidic etching of the "A" element from the MAB phase.

Given the abovementioned issues, we speculate about MBenes' features defining their biological impact on living organisms. There is no doubt that the presence of surface terminations, materials' structure, physicochemical characteristics and many more (see Figure 5 cannot be omitted considering MBenes' potential impact on biological matter. All these aspects greatly influence the material itself and result in many incoherencies and variations when biological systems with high sensitivity to such changes are intended to be studied.

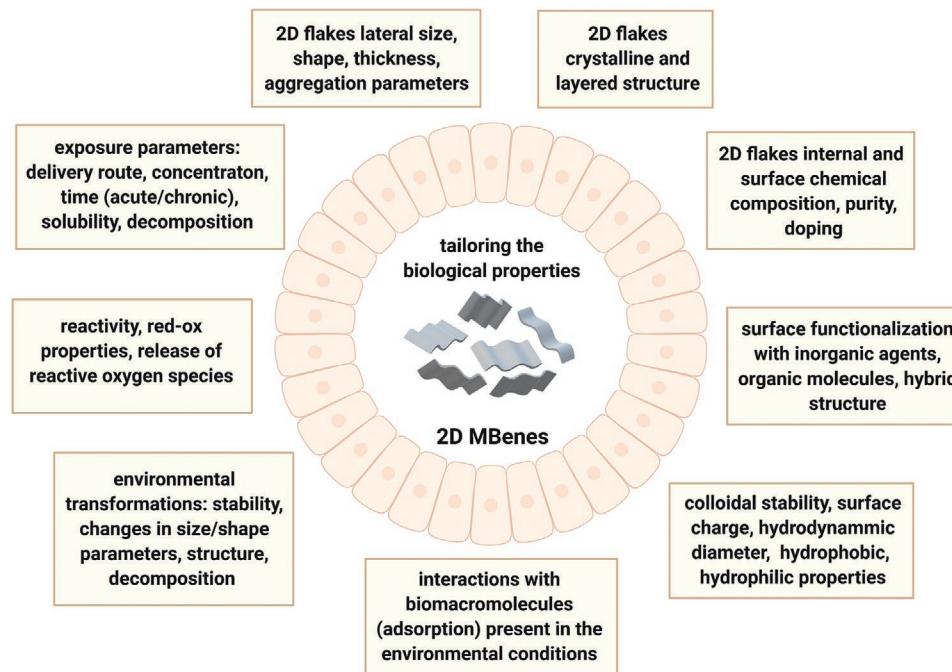


Figure 5. Expected features defining the MBenes' biological impact on living organisms (created using BioRender.com).

5. Potential Impact of MBenes in Modern Biotechnology

Compared to other carbon- and nitrogen-based 2D materials, MBenes' potential in modern biotechnology is still subject to speculation and ongoing discussions.^[7] The envisioned biotechnological potential of MBenes is summarized in Figure 6. It is reasonable that the observed bioeffects will result from combining the unique nanostructural architecture and chemical composition of MBenes.^[7] In contrast to MXenes, MBenes may offer remarkable bioactivity due to the presence of non-toxic boron. It is one of the vital trace elements essential for the proper functioning of living organisms. Boron is responsible for the regulation of metabolic processes^[62] and shows an anti-inflammatory effect.^[63] The latter bases on inhibiting the pro-inflammatory cyclic nucleotide phosphodiesterase 4 (PDE4), which corresponds to the release of inflammation-related cytokines. This effect can be potentially utilized in drug-delivery systems against inflammatory-related diseases.

Another function of boron in the human body is the activation of hormones, including estrogen.^[64,65] This aspect is involved in regulating the metabolism of numerous essential substances, such as vitamin D, calcium, magnesium, phosphorus and fluorine^[66] thus helping to prevent osteoporosis and rheumatic diseases.^[67] Additionally, boron is responsible for the maintenance of the stability of cellular membranes and the proper functioning of the digestive and nervous systems.^[68] Therefore, the delivery of boron into targeted areas using MBenes may be an efficient way to develop innovative combinatory treatment methods that can simultaneously enable healing, regeneration and local nutrition of growing cells. This can be used for designing self-assembly systems for regenerative medicine. These multi-purpose organoids or scaffolds can

be prepared via different techniques such as, for instance, 3D bioprinting, which are expected to decompose in the treated body into non-toxic, easily removable counterparts.

It is reasonable to assume that MBenes may show biological properties similar to other types of boron-based substances. The preliminary *in-vitro* cytotoxicity studies considered Cr₂AlB₂ and MoAlB toward different cell lines using increasing concentrations of MAB phases for 24 h.^[69] This study used four human cell lines such as lung carcinoma (A549), kidney cells (HEK 293), breast carcinoma cells (MCF-7), and liver carcinoma cells (HepG2) (see Figure 7a,b,e,f). The *in-vitro* results showed low toxicity on the cells within low exposure (80 % viability remained). However, higher concentrations of MABs caused noticeable differences in cell viability. Upon exposure of over 125 µg mL⁻¹, the cell viabilities were reduced below 80%. Furthermore, a sudden drop in cell viability to 39% was observed, when exposing MCF-7 cells to 150 µg mL⁻¹ of MoAlB. In contrast, the cytotoxicological effects for Cr₂AlB₂ were not that pronounced.

MBenes may also exhibit antibacterial or biostatic properties and can be utilized as biocidal agents in various applications. Their synthesis can involve *in-situ* reactions on the surface of flakes to form biologically active surface terminations. In a natural environment, boron occurs only in the form of B-containing compounds. A family of boron heterocycle-based synthetic structures, called diazaborines^[70,71] and benzoxaboroles,^[72] are known for over 20 years for their biocidal performance against a variety of microorganisms. Diazaborines are efficient against gram-negative bacteria^[70,71] and their molecular mechanism was described to be essential as a carrier for protein reductase, an enzyme involved in the process of fatty acid synthesis.^[70,71] In case of benzoxaborole^[72] functionalization, it is possible to obtain both excellent antifungal^[73]

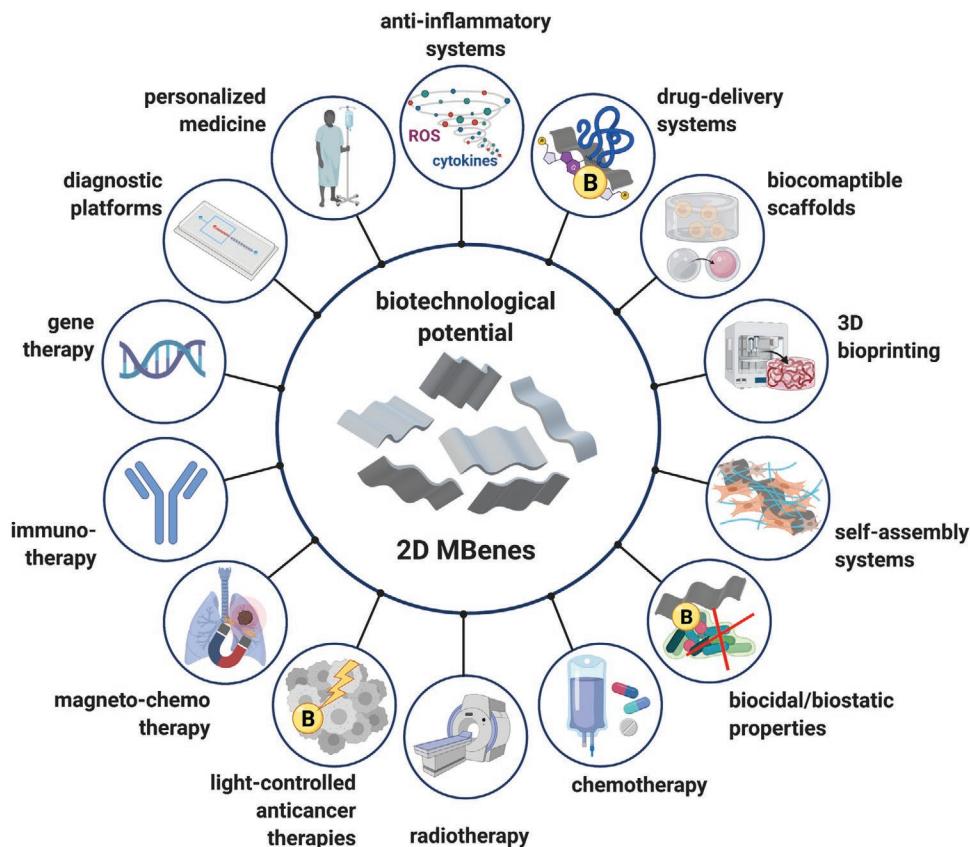


Figure 6. Envisioned biotechnological potential of 2D MBenes (Created with BioRender.com).

and antibacterial^[74] properties, including bacteria showing resistance to conventional, β -lactam antibiotics. It is worth mentioning that the onychomycosis treatment using a tavaborole-based formulation was recently approved for use in clinical practice by the US Food and Drug Administration.^[75]

The mechanism of biocidal action of benzoxaborole is associated with the presence of free hydroxyl group and boron atom, which is a relatively strong Lewis acid.^[76] Therefore, the unique 2D structure of MBenes may result in an affinity to biological matter, which is crucial for their selectivity of B-containing headgroups.^[73,75,76] The development of benzoxaborole-related headgroups on the surface of MBenes may enable inhibition of β -lactamases.^[74] These are bacterial enzymes involved in the development of antibiotic resistance via breaking the β -lactam bonds present in antibiotic molecules. The involved mechanism is β -lactamase enzyme blocking by the specific interaction between the free hydroxyl group of serine residuals present in the enzyme's catalytic site and the empty p orbital of B atoms.^[74] Furthermore, we recognize that the specific inhibition of a variety of enzymes such as amino-acyl tRNA synthetase, phosphodiesterase or serine protease of bovine viral diarrhoea virus NS3, has been identified as the most possible mechanism of action of boron-based compounds against various types of pathogens.^[77–79]

The potential cytotoxicity of each material can be preliminarily linked to the observed interactions with microorganisms. However, to the best of our knowledge, no study sheds light

on the mechanisms of MBenes' antibacterial properties. Some ideas about their antibacterial properties can be only gained by considering the antibacterial performance of other 2D materials such as MXenes or graphene-based materials. In this context, researchers extensively explored MXenes as well as graphene and its derivatives.

Since the discovery of MXenes, only few studies elucidated biocidal properties of Ti_3C_2 and Ti_2C MXenes. Rasool et al.^[56] speculated that the antibacterial properties of Ti_3C_2 may be due to sharp edges of the 2D flakes, which cause their direct death by damaging the bacteria's cell membrane. Additionally, smaller nanoflakes can potentially penetrate the microorganisms through endocytosis. Moreover, we verified no biocidal activity of Ti_2C .^[80] In a follow-up study comparing the antibacterial properties of Ti_3C_2 and Ti_2C against *E. coli*,^[57] we confirmed that Ti_2C did not affect the viability of bacteria, while Ti_3C_2 showed antibacterial properties. Shamsabadi et al.^[81] investigated the mode of action of 2D Ti_3C_2 flakes with lateral dimensions of 0.09, 0.35, 0.57, and 4.40 μm against *E. coli* and *Bacillus subtilis* for exposure times of 3 and 8 h. These studies demonstrated that the antibacterial activity of Ti_3C_2 depended on the nanoflakes' size and duration of exposure, which is also a mirror reflection of *in-vitro* cytotoxicological results. Moreover, these experiments confirmed the direct physical damage of the bacterial cells, leading to the release of bacterial DNA from the cytosol followed by bacterial cell dispersion.

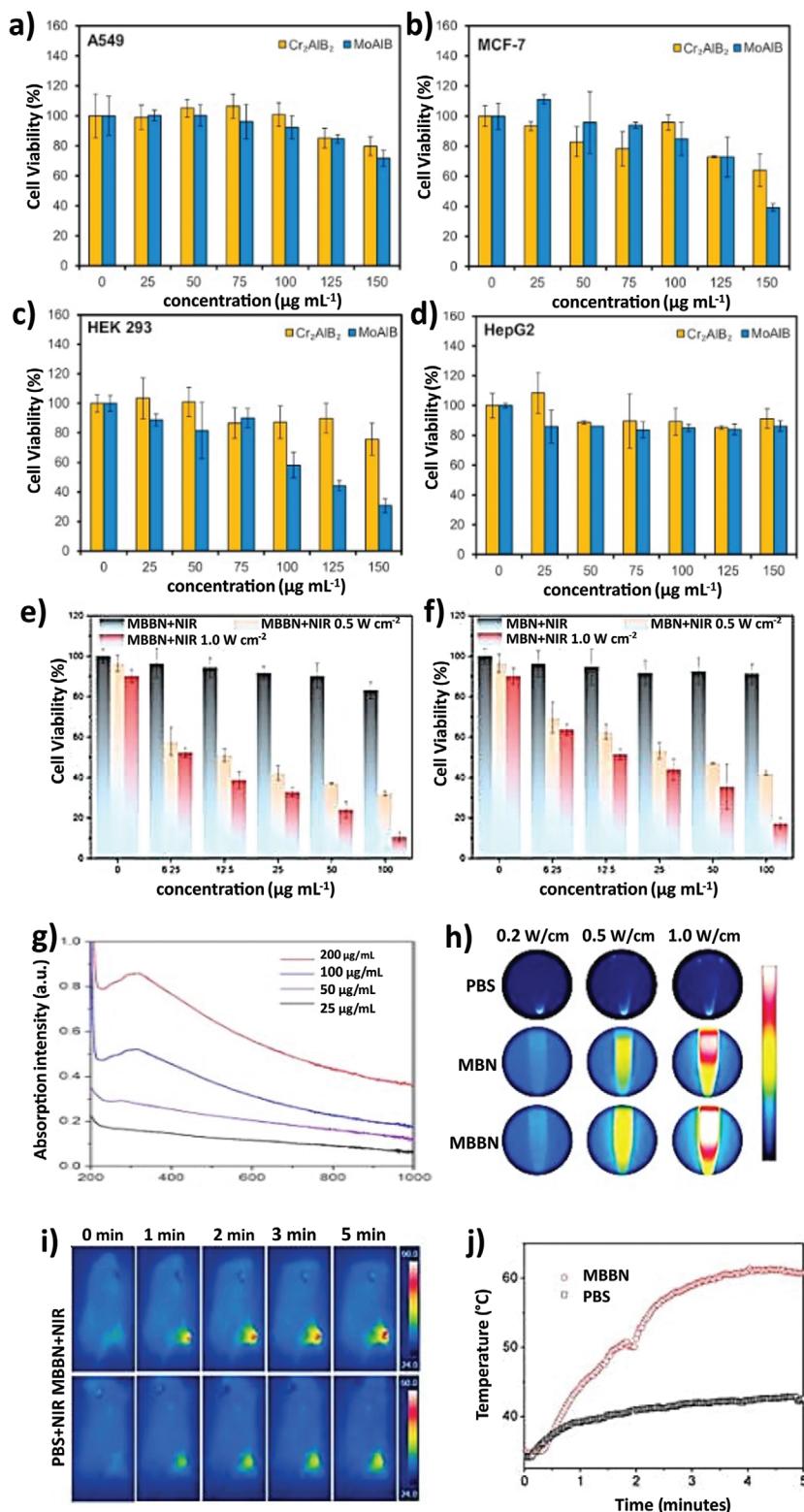


Figure 7. Percentage of cell viabilities for a) A549, b) MCF-7, c) HEK 293, and d) HepG2 cells after 24 h exposure to increasing concentrations of Cr₂AlB₂ and MoAlB phases (Reproduced with permission.^[69] Copyright 2019, American Chemical Society). e,f) Percentage of 4T1 cancerous cells' viabilities during *in-vitro* photothermal therapy (PTT) with Bi-anchored MnB₂/MnB phase (marked originally as MBBN) (Reproduced under the terms of the CC-BY license.^[7] Copyright 2020, Ivspring International Publisher). g) UV-VIS-NIR absorbance spectra of MBBN for variable concentrations (25, 50, 100, 200 µg mL⁻¹). h) Thermal images of MBN and MBBN (100 µg mL⁻¹) after 5 min 808 nm laser irradiation (0.2, 0.5, and 1.0 W cm⁻²). i) Infrared thermographic images of 4T1-tumor-bearing mice in groups of PBS (100 µL) and MBBN (20 mg kg⁻¹) at different times during laser irradiation. j) Time-dependent temperature changes at the tumor sites of 4T1-tumor-bearing mice during laser irradiation. (Reproduced under the terms of the CC-BY license.^[7] Copyright 2020, Ivspring International Publisher).

Considering the mechanisms of the antibacterial activities of other 2D nanomaterials, Zou et al.^[82] deduced the following aspects: destruction via physical contact, oxidative stress, drug or metal ions release or synergic, multi-mode antibacterial effects. These mechanisms also seem to occur for 2D nanomaterials beyond graphene.^[83] Nanomaterials containing graphene and its derivatives and post-graphene structures such as MXenes, MoS₂ or BP are linked together by their relatively sharp edges. Consequently, it seems imperative to make the direct contact mechanism responsible for the observed effects.^[84,85] The sharp edges of reduced graphene oxide (rGO) played a major role in the studies conducted by Sengupta et al.^[86] as they induced mechanical stresses by piercing and rupturing the cell membrane of *P. aeruginosa*, causing nucleic acid leakage. This effect has not been observed for graphene oxide (GO), since the bacterial cells were mainly damaged via chemical reactions. In both cases, the shape and type of bacteria cells were key factors, which greatly affected the bioactivity of GO and rGO.

Although having a similar 2D layered structure, MBenes may exhibit different physical, chemical and biological properties. Therefore, the “nano-blade” action may not be the only antibacterial mechanism.^[87] MBenes may be capable of attaching to bacteria effectively due to their inherent hydrophilicity and/or specific boron reactivity thus intensifying the direct contact mechanism. This has been confirmed for Ti₃C₂, which showed higher antibacterial abilities due to the presence of Ti compared to GO in studies presented by Rasool et al.,^[88] who additionally observed membrane disruption, cytoplasm leakage and cell lysis.

Other examples of B-containing nanomaterials are borophenes—nanomaterials composed of boron atoms forming ultrathin 2D layers with the hexagonal arrangement.^[89] The unique biological properties and potential biocompatibility of borophenes have been thoroughly investigated in recent years.^[90] It is accepted that the presence of boron enables the development of novel anticancer nanomedicines with multimodal imaging-guided drug delivery features. Recently, PEGylated 2D borophene showed a lack of cytotoxicity in both *in-vitro* and *in-vivo* cancer models together with a PTT performance. Unfortunately, the optical transparent of borophenes offers a relatively low absorption with an extinction coefficient of $\approx 2.5 \text{ L g}^{-1} \text{ cm}^{-1}$, which is considered as a potential limitation for further development of a pristine borophene as PTT agent.^[91] Nevertheless, various possibilities of borophenes’ surface modification with drug molecules, for instance doxorubicin,^[90,91] offer great possibilities in designing new anticancer modalities. In this regard, the application of MBenes can enable new synergistic effects and further utilization of boron-based compounds in theranostic applications, involving imaging-guided radio-, magneto-, chemo-therapy systems combined with immunotherapy and gene delivery.

Due to their unique light-to-heat transition properties,^[6] MBenes are likely to find their application as a novel agent for light-controlled anti-cancer modalities as described by Jin et al.^[7] The authors proposed a photothermal therapeutic (PTT) procedure using mono-layer Bi-anchored manganese boride nano-sheets (MBBN) and flower-like manganese boride

nano-sheets (MBN) as materials with a highly efficient “light-to-heat” NIR transition ($\eta = 59.4\%$ for MBBN and $\eta = 41.6\%$ for MBN, respectively) as well as properties suitable for photoacoustic and MRI imaging.

Similarly to a wide variety of 2D post-graphene nano-materials, the Bi-anchored MnB₂/MnB (MBBN) exhibited a broad absorption in the UV-vis and NIR range^[52] (Figure 7c). The NIR-photothermal conversion efficiency (η) was calculated after a series of irradiation experiments using a laser with a wavelength of 808 nm and a power density of 1.0 W cm⁻² (see Figure 7d). The calculated values were similar or even higher than values reported for MXenes (such as Ti₃C₂ and Nb₂C).^[92,54] Both structures also demonstrated satisfying photothermal stability.

MBenes’ ability to efficiently convert light into heat was further confirmed via monitoring the temperature of aqueous MBene suspensions with variable concentrations (0–200 µg mL⁻¹) after the exposition to an 808 nm laser with different power densities (0.5–1 W cm⁻²). In contrast to reference samples without MBenes, the suspension with a concentration of 50 µg mL⁻¹ caused a remarkable temperature increase, which was dose- and laser power-related. Additionally, the obtained data proved that the NIR-photothermal effect was more significant for MBBN than MBN because of its higher photothermal conversion efficiency.

The *in-vitro* PTT procedure was performed on three cancerous cell lines derived from different tissues (HEK-293T, 4T1, and BGC-823 lines). The results of standard CCK8 assays allowed to select a non-toxic solution range of 0–100 µg mL⁻¹ (so-called “dark cytotoxicity”).^[7] The samples’ irradiation resulted in a highly efficient dose-dependent ablation of malignant models, while the proposed treatment’s efficacy was also related to the applied laser power density.

In the next step, the treatment was applied under *in-vivo* conditions. An excellent tumor-targeting and accumulation of MBBN were proven via *in-vivo* and *ex-vivo* imaging by MRI and PA techniques.^[7] The results indicated a long blood circulation and an efficient intratumoral accumulation of MBBN, which is highly desirable to fight cancers. The *in-vivo* therapy was evaluated after intravenous injection of MBBN (PBS suspension with a concentration of 20 mg kg⁻¹) for 4 h. The animal model (tumor-bearing mice) was anesthetized and then exposed to an 808 nm laser with a power density of 1.0 W cm⁻². Analogous to *in-vitro* studies, a rapid temperature increase (33–60 °C after 5 min of NIR irradiation) was observed (see Figure 7d,g,h), which enabled efficient cancer therapy. Afterward, the procedure was evaluated on BGC-823 tumor-bearing nude mice with inoculated tumors reaching around 100 mm³. The nude mice were then selected to different groups—blank controls and groups exposed to nanomaterials only or a combination of nanomaterial coupled with irradiation. The laser irradiation using a wavelength of 808 nm and a power density of 0.6 or 1.0 W cm⁻² was carried out for 5 min after 1 and 25 h post-injection. After 3 weeks, all treated mice survived, implying good biocompatibilities of the used nanomedicines and high efficacy of the proposed PTT modality.^[7]

2D MgB₂ was recently proposed to apply in combined hydrogenochemotherapy of gastric cancer (4T1) as a hydrogen-generating prodrug.^[11] The prodrug was administered orally to

mice after being encapsulated with PVP. Similarly, doxorubicin (DOX) was routinely administered via intravenous injections. The novel therapeutic synergy with hydrogencochemotherapy prolonged the survival time of mice by the reduction of toxic side effects. Also, 2D GdB₆ was used as a multifunctional theranostic nano-agent.^[13] The unique optical properties referred to bright greenish-yellow fluorescence. After the intracellular localization, fluorescence imaging and near-infrared (NIR) photothermal conversion were applied for efficient photothermal therapy (PTT). The conversion efficiency was 24%, and 2D flakes showed a good stability after four cycles of PTT. The temperature increase was 19.3 °C after irradiating 400 µg mL⁻¹ 2D flakes with 1 W cm⁻² NIR light for 5 min. Notably, they also showed a high NIR-photoacoustic effect. Therefore, the obtained results show superior antitumor performance and imaging with high biocompatibility of GdB₆.

We note that the further application of MBenes in diagnostic systems may design new platforms for anchoring various biomolecules with extraordinary specificity and sensitivity.^[93] The organoboron derivatives can be also used as receptors for critical biological molecules such as neurotransmitters in an ion-selective electrode.^[94]

6. The Influence of MBenes' Chemistry

It seems reasonable that all experience acquired during MXenes' research and development can be further used and considered as preliminary with the potential extension toward more advanced mechanistic analyses planned for MBenes. Although the effect of surface chemistry is considered to be of minor importance for most macroscopic materials, it plays an essential role for 2D nano-materials due to their large lateral sizes and specific surface areas, which dominate their colloidal behavior.^[95]

It needs to be stressed that MBenes' surface chemistry will inherently determine the interface for interactions with biological species and cells. This issue appeared to be valid for MXenes, which showed the appearance of hydroxide (–OH), oxygen (=O), fluorine (=F) and chlorine (=Cl) functional groups on MXenes' outer surfaces resulting from chemical reactions during acidic etching.^[96,25] More detailed investigations showed that one removed "A" atom is replaced by at least two –OH groups and one –F group.^[97] Thus, it is reasonable to assume that etching and delamination will result in specific surface chemistry for MBenes. Also, intercalating and stabilizing agents will contribute to the development of MBenes' surface chemistry, such as in the case of MXenes.^[80]

Also, the presence of boron in MBenes' structure may significantly change the interactions with biological matter, which needs careful attention and verification. Revealing these aspects is considered the key to understanding the influence of their surface chemistry on the resulting bioactivity.^[98]

Another aspect closely related to MXenes/MBenes' surface chemistry, which needs to be considered when studying the interaction with biological matter, is their ability to generate reactive oxygen species (ROS). Notably, ROS are molecules consisting of oxygen atoms with unsaturated electron pairs with high reactivity and a considerably short lifetime.^[99–101]

Four critical species, namely superoxide anion radicals ($\cdot\text{O}_2^-$), hydrogen peroxide (H₂O₂), singlet oxygen ($\cdot\text{O}_2$) and hydroxyl radical ($\cdot\text{OH}$) need to be distinguished. ROS are generated in oxygen- and/or water-containing environments by complex redox reactions when exceeding the respective activation energy, which is typically achieved by the absorption of light. In this context, superoxide anion radicals and hydrogen peroxide are obtained by step-wise reduction processes or the addition of an additional electron to the π^* orbitals with subsequent protonation processes.^[99] When further reducing hydrogen peroxide, the dissociation of the oxygen bond induces the generates of the hydroxyl radical.^[99] It is essential to mention that, in aqueous environments, the oxidation of water causes ROS formation in the following order hydroxyl radicals, hydrogen peroxide, superoxide anion radicals, and singlet oxygen. In contrast, complex reduction processes of O₂ generate ROS in the respective order of superoxide anion radicals, hydrogen peroxide and hydroxyl radicals.^[99]

The research community agrees that ROS plays a decisive role when considering photo-catalytic degradation processes.^[99,102,103] In this regard, titanium dioxide (TiO₂)—certainly having a great connection to Ti-based MXenes and MBenes—offers an outstanding photocatalytic performance coupled with low cost and low toxicity. When irradiating TiO₂ for photocatalytic processes, the absorbed energy induces electron-hole pairs due to the transfer of an electron from the valence to the conduction band.^[100,104] Their interaction with the surrounding water or oxygen induces the formation of ROS. Apart from the important impact of TiO₂ particle size, dimensionality, surface area and crystallinity, it has been shown that the photocatalytic activity is fairly sensitive to the amount of generated ROS.^[105,106] It has been also verified that materials properties such as crystalline phases and dimensionality as well as defect densities of TiO₂ notably affect the ROS formation and, therefore, the photocatalytic activity.^[106,107]

The important influence of ROS regarding photocatalytic properties has been also recently demonstrated for few- and multi-layer MXenes nano-sheets.^[103,108] Rosales et al.^[109] showed that active TiO₂ sites on the surface of few-layer Ti₃C₂ nano-sheets, which were verified by XPS, are capable to form electron/hole pairs under UVA irradiation. As aforementioned, the electrons experience a transfer from the conduction band of TiO₂ to the nano-sheets surface thus helping to separate the photogenerated carriers. The existing surface terminations and MXenes' outstanding electrical conductivity reduce the probability for recombination thus notably boosting photocatalytic processes. It can be assumed that complex redox reactions (–OH surface terminations and oxygen or water) are likely to induce ROS generation. Few-layered Ti₃C₂ nano-sheets have shown a higher capability to generate ROS due to an increased amount of superficial TiO₂ compared to multi-layer nano-sheets.^[110]

Irrespective of the material considered, biological matter is known to be very sensitive regarding chemical activity of the surface (related to chemical composition) and the presence of ROS.^[99,111] For instance, it has been demonstrated that proteins or DNA tend to be damaged by ROS.^[112] Moreover, ROS are capable of disturbing physiological functions.^[113] Very important for 2D nano-materials is the existence and formation of ROS is typically connected to topics including cyto- and

ecotoxicity.^[114] For TiO₂/rGO catalysts, superoxide radicals are the driving force regarding disinfection of *E. coli* bacteria.^[115] For doped TiO₂, ROS were made responsible for the degradation of cyanotoxin.^[116] Furthermore, TiO₂ present on Ti-based MXenes has been beneficial in inducing photo-oxidation of As(III) to As(V) for water purification purposes.^[110]

Consequently, it becomes evident that ROS are essential for photo-catalytic and photo-oxidative processes, which has a significant connection to biological systems and processes, including toxicity aspects. Since TiO₂ is the material of choice due to an outstanding photocatalytic activity and the potential presence of TiO₂ on, at least, Ti-based MXenes/MBenes. A lot of knowledge gained for TiO₂ is potentially transferrable to MXenes and MBenes. This implies that it is essential to identify and quantify ROS in the systems and connect their kinetics to biological species-involved interaction.

To the best of our knowledge, no in-depth studies assessing the mechanism of MBenes' cytotoxicity are published yet. Only the work of Jin et al.^[7] showed—based upon microscopic images after differential staining—MBenes' potential as apoptosis agent, which is a highly desirable strategy for cancer treatment. Therefore, we can learn a lot from the first representatives of this novel family—2D MXenes. Numerous studies on MXenes considered 2D flakes after delamination. The state-of-the-art is focused on *in-vitro* toxicity testing and the verification of modes of action^[46] thus correlating these properties to the respective material properties of Ti₃C₂T_x and Ti₂CT_x.^[57] Recently, we verified for 2D Ti₂NT_x MXene the importance of the number of layers on the material's stability and toxicity.^[117] We also carried out toxicological studies toward micro-organisms^[80] and

elucidated the influence of surface oxidation on cytotoxicity of 2D Ti₃C₂T_x^[39] as well as V₂CT_x^[118] MXenes together with potential mechanisms of action. It has been noted that surface oxidation can be intentionally manipulated to achieve a desired anticancer effect.^[39] Furthermore, we compared 2D Nb₂CT_x with Nb₄C₃T_x MXenes thus implementing surface properties management to reveal the effect of ROS scavenging and effective targeting of the malignant melanoma cell cycle into programmed cell death.^[119] These results suggest that this effect is greatly connected to the early transition metal presence. It is reasonable to assume that the mode of MBenes' action could also be related to their chemical composition.

The 2D structure of MBenes suggests that expected bioeffects could be similar to other 2D nanomaterials such as graphene and its derivatives and MXenes. In previous works on the biological activity of 2D materials, surface chemistry was identified as a primary factor responsible for the observed affinity of the nanomaterial to cellular membranes and, consequently, physical membrane damage further associated with cytoplasm leakage. If the cellular uptake occurs, 2D material further accumulates in the organelle. Herein, a wide range of adverse effects can be induced including protein oxidation, mitochondria, DNA, and cytoplasmic reticulum damage. Notably, most of them are likely to be caused by the generated ROS and/or the presence of metal oxide (M_xO_y) nanoparticles (NPs) released from the oxidizing material's surface. Given the above, we attempt to propose the potential mechanisms of action between 2D MBenes and the cells *in-vitro* (see Figure 8).

The proposed surface modification strategies enhance the colloidal stability of tested nanoplates and impose increased

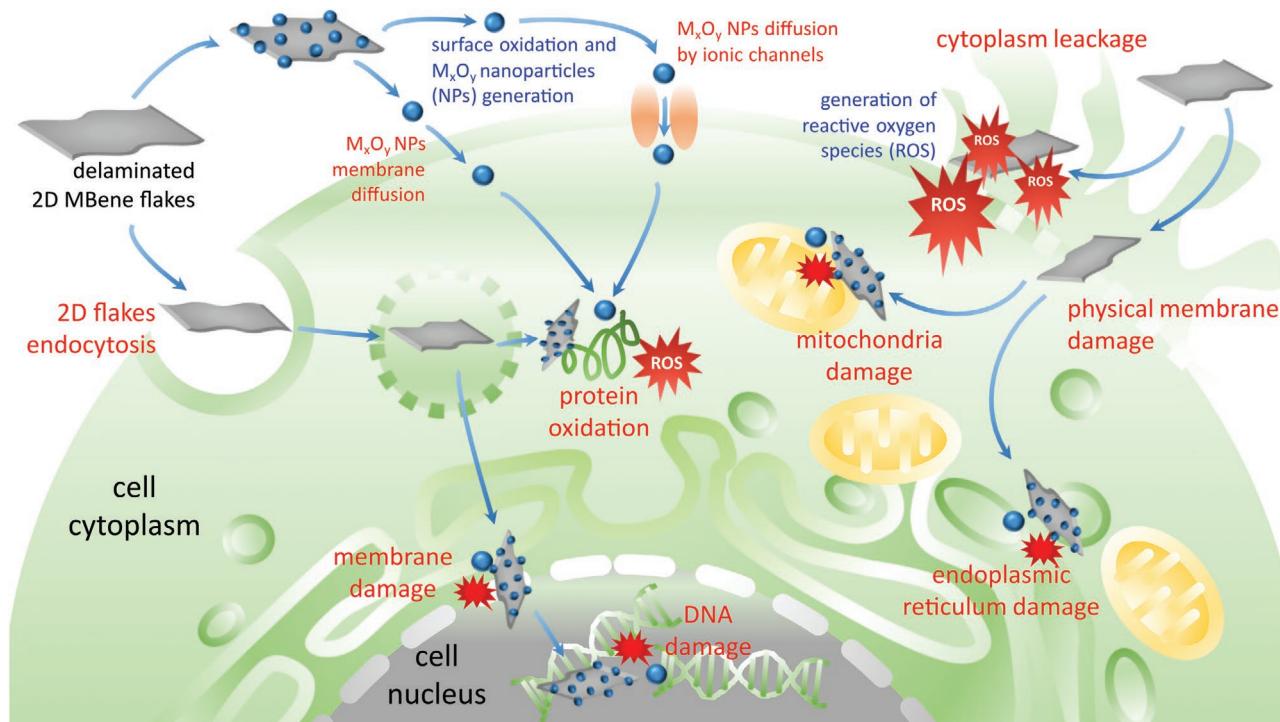


Figure 8. Schematic representation of mechanisms of action to be considered in the context of potential cytotoxicity of 2D MBenes related to living cells including physical membrane damage and cytoplasm leakage, generation of ROS, protein oxidation, mitochondria, DNA, and cytoplasmic reticulum damage.

accumulation in malignant cells.^[120,50] At a relevant concentration, they can also influence the cellular cycle.^[50] Our works showed that the exposition to MXenes disturbs the malignant cell cycle and their abnormal proliferative potential, which suggests the occurrence of specific interaction between the nano-material and the DNA. The role of graphene in the abnormal reproduction of genetic material has been also addressed.^[121] Consequently, similar effects are likely to occur for MBenes, as they also partially include Ti in their structure.

Many studies proposed the induction of oxidative stress as a common mechanism explaining partially, if not fully, nano-materials' bioactivity, including carbon-based 2D nanostructures.^[122-125] As proven by Rasool et al.,^[56] the role of Ti_3C_2 in superoxide anion production was negligible. Moreover, they observed glutathione depletion, which could relate to ROS generation and MXene working as an oxidant for glutathione. It needs to be highlighted that MBenes, similarly to MXenes or graphene derivatives, possess good conductivity, affecting their bioactivity as it disrupts the electron transfer from the cells to the external environment by building up a conductive bridge thus resulting in bacteria's death.^[56,126,127]

7. Does the Use of 2D MBenes Causes Any Environmental Concern?

The family of MBenes expands quickly since the experimental appearance of their first representative MoB phase. Many phases for the application in biotechnology and nanomedicine are yet to be obtained from solution processing. After the development of industrial synthesis and processing methods, there is no doubt that they can be released into the natural environment and could end up distributed over a wide area persisting there for a considerable amount of time. The extent to which MBenes can be released into the environment is largely unknown at present. However, researchers are expected to make scientific and commercial use of MBenes soon, making their release into aquatic, terrestrial, and atmospheric environments highly probable. This situation appeared several years ago for MXenes, for which applications such as water desalination and environmental filtration developed rapidly.^[128] Consequently, there is an urgent need to understand how 2D MBenes interact with living organisms since the rational reduction of their toxicity can be only realized by revealing their modes of bio-action.

MBenes exhibit attractive physical properties, making them promising candidates for filtration membranes, adsorbents, photocatalysts, and antimicrobials.^[129] However, it is essential to emphasize that the potential toxicity of MXenes toward the natural environment has been practically unexplored for a long time. Nasrallah et al.,^[130] reported on the lack of significant toxicity of pristine Ti_3C_2 on *Daphnia magna*. Our ecotoxicological studies considered green algae (*Desmodesmus quadricauda*) as well as two seed plants such as sorghum (*Sorghum saccharatum*) and charlock (*Sinapis alba*).^[131] Ecotoxicological data available for MXenes are still scarce and should be taken with care with the need for more in-depth studies that will support requirements in terms of contribution to strategies for regulatory development ensuring the safety of

2D nanomaterials. In this context, it is worth mentioning that ecotoxicological studies of MAB-MBenes largely fall behind MAX-MXenes.

The lack of complete ecotoxicological studies on MBenes does not imply that this aspect is unnoticed. As MXene-enriched materials/composites can be widely used, it is essential to investigate their potential impact on organisms of different groups of the trophic chain.^[132] The toxicity of other nanomaterials including nanocarbons or ceramic oxide nanoparticles has already been studied not only for different cells, including human ones (cytotoxicity),^[133] but also different biological systems (ecotoxicity) including organisms like bacteria (*V. fisheri*,^[134] *E. coli*,^[135] *S. typhimurium*,^[136] *B. subtilis*,^[137]), algae (*R. subcapitata*,^[138] *Chlamydomonas sp.*,^[135] *D. subspicatus*,^[136] *C. minutissima*,^[139] crustaceans (*D. magna*,^[140] *H. azteca*,^[141] copepods,^[141] worms (*E. fetida*,^[135] *L. variegatus*,^[135] *E. andrei*,^[142]), larvae (*R. arenarium*,^[134] fishes (*D. rerio*,^[136] *F. minnows*,^[143] *O. latipes*,^[143]), plants (*R. sativus*,^[135] *L. multiflorum*,^[135] *L. sativa*, *A. sativa*, *L. lycopersicum*, and *Z. mays*,^[142]). Consequently, the field of ecotoxicity studies on 2D MBenes is mainly underexplored and it seems reasonable to look into recent studies performed on other nanomaterials to speculate about their ecotoxic properties.

The ecotoxicity of GO has been investigated by Evariste et al.^[144] toward different food chain organisms such as producers (algae and bacteria), consumers and decomposers (chironomid larvae), and larvae of the amphibian *Pleurodeles waltl* as secondary consumers. Their studies showed that biofilm communities were more vulnerable to GO through direct contact mechanism, which also primarily contributes to the MXenes' bioactivity.^[58] Moreover, they observed that microorganisms could oxidize rGO into GO.^[144] Bearing in mind that MXenes contain titanium, the bioactivity can be increased due to the potential surface oxidation into TiO_2 nanocrystals.^[58] It is worth pointing out that potential ecosystem risks in case of graphene, its derivatives and morphologically graphene-like materials also depend on the environment in which they are located and deposited. Their behavior, transport, and fate may vary as they are found in water, sediments, or soil.^[145] For instance, GO can diffuse through the soil, which also acts as a contaminant's carrier due to its strong adsorption affinities.^[146] It tends to become less stable and settles in hard soils containing less natural organic matter and groundwater. Surface waters with a greater amount of natural organic matter and divalent ions become more stable and can be transported more easily and migrate through food chain levels.^[147]

Both MXenes and MBenes are made of layers of early transition metals. The presence of metals in natural environments must not negatively influence the growth of different groups of organisms. It may be beneficial or even crucial, in conjunction with other factors such as sunlight, affecting the redox potential in the distribution of chromium among surface seawater organisms.^[148,149] Metals are necessary in small concentrations for standard ecotoxicological testing organisms such as algae, as they participate in performing the cell functions, e.g. photosynthesis, and are also constituents of vitamins.^[149] Another vital aspect is bioaccumulation—marine phytoplankton like *D. salina* can accumulate chemicals and metallic compounds in their cell structures and tissues. At first glance,

it may increase biomass, but after a closer look, the accumulated nanomaterials can migrate through the whole aquatic trophic chain.^[150] As they accumulated in the liver and other reticuloendothelial organs, this effect has been observed for iron nanoparticles.^[151,152]

As can be seen, a significant package of ecotoxicological data of other types of 2D materials also considers graphene and its derivatives^[153] showing their toxicity for bacteria, animals, and human cells.^[154] Furthermore, 2D structures were shown to exert growth-inhibiting effects via nutrient absorption, shading,^[155] and the so-called “nano-blade” action causing mechanical damage to cell membranes.^[156]

Our studies on the MXenes’ toxicity have shown that the most important features responsible for the toxicological properties are surface oxides and the adsorption of biological moieties from relevant exposure environments.^[131,157] These results align well with experimental findings and the biological knowledge of the cellular death mechanisms.

It is also known that highly oxidized systems do not cause physical damage since -OH species prevent physical interaction with cell membranes.^[156] It has been demonstrated that algae can dynamically protect themselves against toxic effects of 2D materials by secreting extracellular proteins and carbohydrates into the culture media.^[156] These results show that the chemical composition of every 2D material, and particularly its degree of oxidation, must be precisely characterized when considering their potential toxicological effects in given environments. This holds especially true since it can be expected that methodologies, assumptions, and conclusions derived for spherical nanoparticles may not be applicable for 2D nano-sheets.

According to the conclusions of the report “Nanosafety in Europe 2015–2025: Towards Safe and Sustainable Nanomaterials and Nanotechnology Innovations”^[158] as well as the conclusions of the “2019 Global Summit on Regulatory Science” (GSRS19, 2019, Sept. 24–26), hosted by the European Commission’s Joint Research Center (JRC) and the U.S. National Nanotechnology Initiative (NNI), the current nanosafety activities for the upcoming new Horizon Europe will concentrate on specific research priorities. Just to name a few, these include environmental and human-related hazards, emerging nanomaterials and potential risks thereof, social and natural science research to support balanced risk governance of emerging nanomaterials, nanoinformatics, extended exposure assessments, as well as standardization of the methodologies. Following the mentioned provisions, numerous studies on bioactivity and toxicity of spherical nanomaterials are currently underway^[159] and much more is already known about their mechanisms of action toward living organisms. For instance, it has been suggested that some of the features of nanomaterials such as the total surface area can be used as a reasonable measure of their ecotoxicological effects in biological systems.^[160] However, it is unclear if these assumptions also hold true for 2D materials, including MXenes and MBenes.

8. Discussion

This perspective contributes to a detailed understanding of the potential biological recognition, response, and impact of 2D

MBenes regarding living organisms before their application in biotechnological fields. We also highlight current challenges and future research directions for both basic research and 2D MBene-based biotechnological applications.

The *in-vitro* biological and anticancer properties of MXenes are well known^[161] and their potential ecotoxicological effects are also being extensively investigated.^[131,130] Although the MBene family is rather diverse with great potential for further development, the poor availability of high-quality MAB phases and the lack of a universal synthesis methods will slow the development of new MBenes down. By comparison, Ti₃C₂ is the most studied MXene so far due to its well-developed processing route.

Recently, we have presented first-principle *in-vitro* studies on the toxicity of delaminated Ti₃C₂ flakes for human cancer cells.^[46] The development of knowledge regarding this topic finally rushed into the possibility to modify MXenes’ surface with enzymes^[44] and different approaches for toxicity mitigation. Research on the adsorption of biological macromolecules has been successfully carried out for other 2D nanomaterials such as MoS₂^[162] graphene^[163] and its derivatives.^[164] In case of MXenes, we studied the adsorption behavior of bacterial cells on the surface of HF-etched Ti₂C by zeta potential.^[80] Our work showed that electrostatic interactions and the pH of the environment are of great importance for adsorption.^[49] The similar conclusions may be also valid for MBenes.

To date, there are only a few reports on the possibility to manipulate the surface of Ti-based MXenes with biomacromolecules^[50] and no reports on MBenes’ stabilities in different environments, i.e., natural waters, extracellular matrices, and various close-to-real environments. Colloidal stabilization and verification methods are needed to allow for their further application in biotechnology, which requires the analysis of the colloidal properties using zeta potential,^[50] and the monitoring of the dispersion’s stability in real-time. It is also an effective analytical tool to study adsorption of various species coming from surrounding biological environments^[80] and structural changes of the surface such as the appearance of various types of oxides.^[165,166] Therefore, the current need is a verification of colloidal stabilities^[49,167] and biological studies based upon more pronounced mechanistic approaches,^[117] advanced in-depth studies linking biological properties to material characteristics,^[57] and the development of simpler and low-cost methods for their surface functionalization and stabilization.^[50]

Considering these aspects and the available knowledge on metal borides, we envision that the expected biological impact of 2D MBenes on living organisms will depend on their:

- 1) morphological and physical features including 2D flake size and shape, specific surface area, surface porosity etc.,
- 2) structural features including stoichiometry, number of M-B layers, their positioning, nature and number of interleaving heterolayers,
- 3) chemical features including the chemical composition of the layered structure and surface chemistry including the presence of boron and terminal functional groups,
- 4) colloidal features and stabilities in the investigated relevant environments and biological media,

- 5) oxidative and structural transformations, i.e., the susceptibility of the 2D MBenes to generate ROS, surface oxidation and/or biodegradation, causing changes in structure and appearance of different types of superficial metal oxides in relevant environments.

It becomes evident that ROS are essential for the assessment of MBenes' bioactivity, also in terms of surface oxidation/reduction and presence of ROS-generating surface metal oxides. It is essential to identify and quantify ROS in these systems and connect their appearance and kinetics with the involved interactions with biological species. ROS/ M_xO_y -assisted photo-catalytic and photo-oxidative processes will inherently affect interacting biological systems. Therefore, the knowledge gained about MXenes' surface chemistry, redox potential, and structural transformations are potentially transferrable to MBenes.

Regarding MBenes' environmental impact, it is reasonable to use knowledge achieved for other 2D materials. The choice of borophene as reference material in biological studies is adequate since testing solutions developed for spherical nanoparticles are not fully compatible.

Variations in these features are of particular interest since they significantly change the biological properties of 2D materials. Consequently, identifying the most promising package of 2D MBenes and the most non-toxic candidates for future biotechnological research and industrial application is highly challenging. Preliminary studies on starting MAB phases and corresponding attempts for delamination into 2D flakes indicate that the Cr-B, Mo-B, and Mn-B phases hold great potential for further development in the biotechnological field. It is noted that only non-toxic concentrations are valid, which should be much below $100 \mu\text{g mL}^{-1}$ (note, that this is only 0.01 wt%) for direct nano-drug delivery to the body (e.g., intravenous administration) and mostly below 1 wt% in case of nano-formulations/materials designed for direct or indirect contact with human body.

We also highlight that tremendous progress in nanotechnology is usually accompanied by much slower progress regarding the detailed knowledge of the material impact on living organisms, which holds also true for 2D MBenes. Consequently, (eco)-toxicological knowledge and studies greatly lack behind the fast progress of their synthesis and exploration of their physical properties, which leads to a scarce knowledge on MBenes' properties and their potential interactions with target organisms in relevant environments. Although being highly interesting due to non-obvious modes or biocidal actions, this results in an inability to balance the opportunities versus risks associated with their industrial use.

Due to the lack of fundamental knowledge regarding the material and its interaction with biological systems, major doubts about its safe use emerge. The general lack of standardized assessment methods for 2D nanomaterials further complicates the analysis of 2D MBenes' safety and their potential impact on human beings and the environment. More advanced cyto- and ecotoxicological studies are needed to tackle these problems together with a comprehensive modeling and comparative study of their chemical and structural properties.

9. Conclusion and Outlook

2D MBenes currently emerge as highly prospective nanomaterials with intriguing biological properties. They are being developed in parallel to 2D MXenes and to a certain extent in their shadow. Due to the presence of boron in their layered structure, MBenes are expected to cut the edge of bioactivity limitations of 2D nanomaterials. Therefore, we define signposts for a future paradigm shifts that will enable science-to-nanotechnology breakthroughs in the field of biotechnological applications of 2D nanomaterials based on throughout, standardized, and systemic research.

2D MBenes have certain advantages over 2D MXenes. They exhibit structural differences regarding the resulting stoichiometries and layer sandwiching. Also, milder synthesis methods are a valuable improvement in terms of sustainability over harsh approaches used for 2D MXenes. However, due to many difficulties in separating MBene flakes from its partially delaminated mixture, an effective method for 2D MBene synthesis is yet to be developed.

MBenes' potential in modern biotechnology results from their unique structure combined with their specific chemical composition. Therefore, morphological, structural, and physicochemical transformations of MBenes in relevant bio environments are essential to be studied. Experience gained for MXenes can guide researchers to rationally explore MBenes biological and biotechnological properties aiming at more advanced mechanistic analyses.

It is reasonable to assume that unique features of 2D materials such as the high degree of morphological anisotropy, specific chemical functionalities, and even local surface charges define their biological properties. Since these properties are more pronounced for 2D materials than spherical nanoparticles, we expect this knowledge to revolutionize current approaches to develop bioactive, safe nano-systems.

We envision that MBenes bear tremendous biotechnological potential. We expect that the presence of boron in MBenes' structure significantly changes the interactions with biological matter, which needs careful attention and verification. We expect that the increasing number of practical biological applications will rapidly develop for 2D MBenes. In upcoming years, MBenes will pursue their counterparts—2D MXenes. Their interesting bioactive and functional features such as light-to-heat transition properties, which are highly relevant for PTT procedures with near-infrared (NIR) transition, photoacoustic and magnetic resonance imaging (MRI) of tumor sites as well as multimodal imaging-guided photothermal therapy, are expected to boost more fundamental research toward the exploration of MBenes' bioactive features in the next decade.

To summarize, it is worth mentioning that the experimental pursuit on development of experimental approaches and standardization for 2D MBenes is currently far from the theoretical peloton, and the chronic verification of their safety is also far from satisfactory. It is highly desirable to recognize the most promising MBene representatives with the highest biotechnological potential and the lowest cyto-and ecotoxicological threats. Altogether, the research efforts will enable answering the outstanding question on the safety of 2D MBenes.

Acknowledgements

A.M.J. is grateful to her Ph.D. and graduate students, as well as all valuable collaborators from Warsaw University of Technology (Faculties of Chemistry; Building Services, Hydro- and Environmental Engineering; and Physics), University of Warsaw (Poland), Tulane University (USA), Drexel University (USA), Palacký University (Czech Republic), and elsewhere, who accompanied through this exciting journey toward uncovering MXenes' biological properties that are now concentrated also on MBenes. The biological-related research on MXenes and MBenes was and is currently widely supported by The National Science Centre, Ministry of Science and Higher Education, and internal funds allotted by Dean of the Faculty of Materials Science and Engineering, Warsaw University of Technology. This particular research was funded by The National Science Centre, grant "OPUS 18" number UMO-2019/35/B/ST5/02538. A.M.J. also acknowledges funding from the BIOTECHMED-1 project granted by Warsaw University of Technology under the program Excellence Initiative: Research University (ID-UB). A.R. gratefully acknowledges the financial support given by ANID-Chile within the project Fondecyt 11180121 as well as the VID of the University of Chile in the framework of "U-Inicia UI013/2018." A.R. furthermore acknowledges the financial support of Chinese Academy of Sciences President's International Fellowship Initiative (2020VEC0006). Funding sources are from UMO-2019/35/B/ST5/02538. The authors approve ethics in publishing and consent to participate thereof. The authors declare consent for publication. The authors declare no competing interests.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

M.J. analyzed the ecotoxicological data and provided the insight into expected ecotoxicity of 2D MBenes, possible mechanisms of action, and MBenes' advantages; A.S. analyzed the cytotoxicological data and provided the insight into expected cytotoxicity of 2D MBenes and possible mechanisms of action; A.R.-W. analyzed potential morphological and physicochemical changes of 2D MBenes including colloidal features and stabilities in the investigated relevant environments and biological media; A.R. analyzed the involvement of reactive oxygen species in biological matter and edited the manuscript; A.M.J. developed the concept of the review study, designed the structure of the manuscript, collected and analyzed the obtained data, provided the insight into material features, biological recognition, response, and potential impact of 2D MBenes toward living organisms, and supervised the research as a project leader and coordinated the preparation of the manuscript. All authors helped to prepare, correct, and proofread the manuscript.

Keywords

2D materials, biotechnology, MBenes, safety, structure–property relationship

Received: March 30, 2021

Revised: May 24, 2021

Published online:

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