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Extraction & Transport Studies Using Synthetic Ionophores (Chromogenic Ionophores)

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ABSTRACT: Novel fluorogenic and chromogenic three-dimensional ionophores are provided which selectively bond ions such as potassium, sodium, and lithium, even in neutral aqueous or alcohol media. The novel ionophores comprise an "ion-recognizing system" fused to a "signal-moiety" through one or more heteroatoms having a non-bonded electron pair. The signal-moieties are selected from the group consisting of fused ring heterocyclics, fused aromatics, and substituted aromatics having at least one nitro or azo moiety. The ion-recognizing system is a three-dimensional cryptand. The ionophores are ideal for the selective and direct termination of ions in biological or environmental samples and the like. Chromogenic ionophores (or ionophore dyes) are a class of color-responsive reagents for detecting alkali and alkaline earth metal ions. In these reagents, a size-specific ionophore group (the ion recognizing ionophore) is fused to an aromatic ring which in turn is functionalized with a chromophore such as an azo, or picrylamino group. Chromogenic ionophores have been extensively . There are two classes of chromogenic ionophores, those that show a pH-dependent response and those that function at neutral pH. The former class of ionophores shows dramatic changes in color. However, the colored form is usually detected in organic solvents and hence an extraction step is essential in addition to adjustment of the pH of the system. Chromoionophores presently known to the art, that function at neutral pH, have yet to demonstrate a sufficient change in color. Without an easily detectable change in color, these chromoionophores cannot be useful as analytical reagents and the like.

KEYWORDS: chromogenic ionophores, signal moiety, aromatics, ion recognizing, extraction, transport

I. INTRODUCTION

The present invention provides a novel ionophore comprising an "ion-recognizing system" fused to a "signal moiety" through one or more heteroatoms having a non-bonded electron pair said ionophore having the General Structural Formula: ##STR1##

wherein said "signal moiety" is selected from the group consisting of fused ring heterocyclics, fused aromatics, and substituted aromatics having at least one nitro or azo moiety; and wherein said "ion recognizing system"[1] is a three-dimensional cryptand wherein X_1 and X_2 of said three dimensional cryptand are the same or different and are heteroatoms selected from the group consisting of oxygen (O) nitrogen (N), sulfur (S), phosphorous (P), and selenium (Se); and the repeating units m and n are the same or different and are integers from about 0-12.

In the preferred embodiments, the signal moiety is selected from the group consisting of coumarins, anthracenes, azo aromatics,[2] nitro aromatics, particularly nitroaniline dyes; and said cryptand contains heteroatoms selected from the group consisting of O, N, S and P.

The preferred heteroatoms in the cryptand moiety as depicted in General Structure 1 are nitrogen (N) and oxygen (O); and the repeating units n and m are the same or different and are preferably integers from about 1-3. Further, these ionophores function at neutral pH in aqueous or alcoholic media.

A second type of ionophore is the "fluoroionophore." The measurement of fluorescence quenching or enhanced fluorescence emission when metal ions are bound to these fluorogenic ionophores is more accurate than measurements based on chromogenic phenomena. This is because fluorescence measurements are made against a dark background, whereas chromogenic methods require detection of absorption maxima or charges in absorption coefficients. Among the fluorogenic ionophores[3] reported in the literature are those described by scientists .[4] However, all the above ionophores suffer from a disadvantage in that they are pH dependent, and can function only at a pH much higher than that of normal body fluid, and hence cannot be used for in vivo applications. The change in optical properties is evidenced fluorometrically when binding of the metal ion causes quenching or enhancement of fluorescence. Fluorescence measurements are preferred to absorption measurements since light intensities are measured against a dark background.[5] Additionally, between fluorescence quenching and fluorescence emission, the latter is preferred, since in this measurement, signal to noise ratio is minimized, particularly at higher concentrations of metal ions. Thus, the signal moiety in the fluorogenic three-dimensional cryptands of the invention is designed to absorb light, preferably

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above 300 nm. and re-emit the absorbed light energy as fluorescence. The signal moiety contains a chromophoric group or several chromophoric groups, capable of efficient absorption of light energy. Of the preferred chromophores for fluorescent emission are those having carbonyl groups, carbon-carbon double bonds, and aromatic rings.[6] In the preferred embodiments of the reagent ionophores of the invention, fused rings such as naphthalenes, anthracenes, benzofurans, benzodiazines, benztrioxazines, benzotriazepines, pyrenes, coumarins (or 1,2-benzopyrones) and the like are used as the fluorescent signal moiety. In the particularly preferred embodiments, a coumarin is the signal moiety, a typical structure being depicted below. ##STR3## Of the preferred coumarins are those having one or more substitutions at positions 3 4 5, 6 or 8. Illustrative substituents may be hydrogen, hydrocarbons, esters acids, fluorinated hydrocarbons, aromatic groups. ethers, thiols, thioethers or various combinations of these groups, and the like. Structure 9 (a) and (b) is representative (substituents indicated by R_1 -R_4): ##STR4## wherein R_1, R_2, R_3, R_4 are the same or different and are H. hydroxy, amine, alky, aryl, fluorocarbon, ester, acid, ether, thiol, or thioether (and 3DC=three-dimensional cryptand).[7]

In the more preferred embodiments, substituting the hydrogen at position 7 in the coumarin ring with a heteroatom with lone pairs of electrons has been discovered to enhance the quantum yield of fluorescence. While the present inventors do not wish to be bound by theory, this may be due to the stabilization of the dipolar form, as illustrated in Structures 10 and 11 for oxygen atom which increases the transition moment of the lowest energy electronic excitation of the molecule: ##STR5##

A particularly preferred reagent ionophore[8] of the invention comprises 4-methylcoumarin fused to a three-dimensional cryptand through positions 6 and 7 or 7 and 8. The fusion may be through two heteroatoms such as P, S, N, O or Se, which may be the same or different at these positions. However, it is particularly preferred that O be the heteroatom at both of the positions. Structures 12 and 13 depict certain preferred embodiments. ##STR6##

Although the present inventors do not wish to be bound by scientific theory, or in any other way be limited thereby, they have discovered that when irradiated, compounds such as those shown in Structures 12 and 13 may be excited to polar states.[9] It has been postulated that when the metal ion binds to the ionophore, it drains the electrons from the heteroatoms of the ionophore and thus causes electronic perturbations in these heteroatoms, i.e.: the electrons flow from the heteroatoms to the newly complexed metal ion. In the compounds of the present invention, one of the heteroatoms is a source of electrons transferred to the remote carbonyl oxygen in the process of optical excitation. The molecule as a whole responds to the presence of a selectively bound metal ion causing a change in fluorescence emission.[10] This change is used to deduce the presence of and, if desired, to quantitate the amount of the target metal ion that has been drawn from its surrounding medium to bind to the ionophore. Thus, the signal moiety serves as an optical transducer for measuring the ion-recognizing capability of the ionophore.

The ion-recognizing moiety of the novel compounds of the invention is a three-dimensional cryptand, that can vary widely with respect to its cavity dimensions. By the term cavity is meant the three-dimensional spherical space available for metal ion binding within the cryptand. In general, cavity dimensions should be approximately the size of the ionic diameter of the ion it is desired to accomodate. It is thus preferred that the cavity dimensions not be substantially larger or smaller than the ionic diameter.[11] In this sense, it is preferred that the cavity dimensions not vary from the ionic diameter of the ion by more than about ±0.8Å, preferably not more than about ±0.5Å, and most preferably not more than about ±0.2Å. It should be appreciated that the cryptands are selected according to their cavity measurements for detection of particular ions. For example, lithium ion has an ionic diameter of 1.2Å, sodium ion, approximately 1.9Å, and potassium ion approximately 2.66Å. Thus,. the cavity diameter can be varied from about 1.3Å to about 3.0Å in order to selectively accommodate these particular ions. One skilled in the art will understand that the cavity size can be progressively increased by increasing the number of bridging ethoxy groups (for example increase the number of repeating units n and m in Structures 12 and 13 from 0 to 12).[12]

In the preparation of the compounds of the invention, the signal group is attached to two pendant reactive groups. Of these pendant reactive groups may be mentioned 2-hydroxyethoxy, 2-chloroethoxy, 2-iodoethoxy, 3-hydroxypropoxy, and the corresponding chloro and iodo analogues of these compounds, and the like. This reaction may be carried out by conventional methods such as nucleophilic substitution reactions.[13]

For example, these two pendant groups may be attached simultaneously to the two nitrogens of a two-dimensional diazacrown ether to produce the three-dimensional cryptand. Of the two-dimensional diazacrown ethers useful in this synthesis may be mentioned 1.10-diaza-18-crown-6. 1.7-diaza-15-crown-5, 1,7-diaza-12-crown-4, 1.10-diaza-21-crown-7, 1,13-diaza-24-crown-6, 1,13-diaza-27-crown-7, 1.16-diaza-30-crown-8, and 1,4-diaza-9-crown-3. Such crown ethers may be obtained commercially or first synthesized de novo according to procedures set forth in published literature. It should be appreciated that the size of the two dimensional diaza-crown ether will, to a great extent, govern the cavity size of the resulting three-dimensional cryptand.[14]

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II. DISCUSSION

In its broadest aspect, the method of using the compounds of the invention as reagent ionophores to detect ions may be carried out by simply contacting the ionophore with the sample, which may contain the target ions. Detection of ions using the ionophores of the invention may take place in liquid media varying widely in composition. For example, a pure alcohol medium, a pure aqueous medium, or a mixture of both is suitable. However, if the reagent ionophore is used in a liquid form, it is preferably in a solution medium that is compatible with the sample under analysis.[15]

It should be appreciated that the present reagent ionophores, especially the fluorogenic ionophores, do function quite well in neutral or basic pH media. Thus, monitoring of crude biological systems is possible with these reagents. Crude biological, physiological, environmental samples and the like may be assayed in their natural states for ion content, preferably after minimum sample preparation is performed, such as freeing the sample of suspended impurities and the like. The latter may be accomplished by filtration, sedimentation, centrifigation, or any other suitable conventional technique. However, it should be appreciated that the acidity of the medium should preferably be above about a pH of about 6.0. Thus, if it is desired to analyze a highly acidic sample, such as for example, stomach contents or the like, the sample should be neutralized prior to analysis. The pH of the medium assayed preferably ranges between about 7 to about 12.[16]

The chromogenic ionophores of the invention may be used in neutral or basic media to an extent, and demonstrate a measurable change in absorption maximum or reflectivity upon binding to ion. However, the fluorogenic reagent ionophores of the invention offer the greatest advantage for operating in neutral or basic media, and thus are preferred for use in such systems, especially when in vivo monitoring is desired.

The compounds of the invention may be used as reagent ionophores in solution for use in the detection of ions. Concentrations of reagent ionophores may vary widely according to the ionophore utilized and the medium in which ion detection is to take place. Hence, any concentration that serves to complex with an ion in a given medium may be utilized, and one skilled in the art will readily appreciate that concentrations of ionophore may be optimized. However, the present inventors have discovered that when reagent ionophores are used in a water/ethanol solution system, a preferred concentration of reagent ionophore is about 2.10^{-5} M to about 3.10^{-4} M.[17] These preferred ranges help to avoid self-quenching by the ionophores.

The maximum fluorescence efficiency for fluorogenic ionophores (such as the one described above) is expected to be about 10^{-4} M concentration of the ionophore (See Example 7). Above this concentration, the fluorescence emission may be expected to decrease due to self-quenching.

The compounds may also be immobilized by conventional techniques for use as a reagent ionophore, such as by dispersing the compound in a matrix, such as a polymer matrix. Other possibilities include chemical attachment of the compound to matrix components or conventional solid supports. When so immobilized, the concentration of ionophore may then vary widely and can be increased beyond 3.10^{-4} M.[18] Self-quenching is not a factor in this situation.

Matrices are particularly suited for use with the chromogenic ionophores of the invention. Suitable matrix components in this regard are any materials that can serve to disperse the chromogenic reagent ionophore in a substantially homogeneous manner. Homogeneity will facilitate provision of a uniform surface for contact with a sample that possibly contains a metal ion under investigation. The matrix component should be a dispersant medium that is appreciably inert, in that it is not inhibitory of desired color development. Further, it is preferred that the matrix be translucent or transparent so that optical properties, such as UV absorption, reflectance, fluoroescence, and the like may be accurately measured. Other forms of immobilization include depositing the reagent onto optic fibers and the like, by conventional techniques.[19]

The detectability range of the reagent ionophores of the present invention for ions varies widely according to the ion it is desired to detect and the medium in which detection takes place. One skilled in the art will appreciate that the concentration of the analyte ion over which it may be detected by a given fluorogenic ionophore may be established by dissolving known amounts of the ion in a solution of the ionophore, and plotting fluorescence emission values against ion concentration. It is generally preferred that about a 10^{-4} M solution of the ionophore be utilized for this purpose. Plots such as these are conventionally used as standards against which emission values from a sample containing an unknown concentration of ion may be compared, to thus determine the unknown concentration of ion in the sample. Similar ranges of detection capability may be determined for the chromogenic ionophores, by measuring and plotting changes in absorption values. Visual color changes may also be standardized for certain concentrations to develop standard color charts.[20]

With respect to the detection of lithium ion, the present inventors have discovered that in the case of 6,7-(4-methyl)coumaro cryptand, the fluorescence emission increases on adding lithium ion in amounts of up to about 5 mmol/L and attains a limiting value at about 6 mmol/L . Thus, the detection capability of this reagent ionophore for lithium ion appears to be about 0 to about 6 mmol/L lithium ion. Sodium also shows an increase in fluorescence

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emission until a concentration of about 6 mmol/L. However, the maximum fluorescence enhancement is less than about 25% of that observed for lithium ion, and thus, lithium ion may be detected in the presence of sodium ion.[21]

Interference in fluorescence caused by sodium ion in a system such as this can also be selectively suppressed by altering the medium in which detection takes place. This may be accomplished by adding a known excess of a commercially available sodium ion selective non-photoresponsive ionophore, as for example, about 120 to about 180 mmol/L of Kryptofix® 221. In this manner the detectability range for lithium ion can thus be modified to range from about 0-20 mmol/L lithium ion, while sodium ion does not interfere Other examples of possible modifications would be to attach a cryptand to a polymer backbone This construct is capable of sequestering sodium ion by precipitation and is preferred in some cases over the use of Kryptofix in improving both the selectivity and the sensitivity of the 6,7-(4-methyl)coumaro cryptand for lithium ion.

With respect to detection of potassium ion, a plot of fluorescence emission of a 10^{-4} M solution of 6,7(4-methyl)coumaro cryptand against potassium ion concentration shows a selective limiting value at about 15 mmol/L potassium ion. Therefore, it is believed that the preferred range for detecting potassium ion using this ionophore is from about 0 to about 15 mmol/L potassium ion, which is well above the anticipated level of this ion in biological samples such as human blood serum. Similar ranges for detection of sodium ion with 6,7-(4-methyl)coumaro cryptand are also preferred.[22]

In addition to selective sequestering of interfering ions as noted above, the range of detection and quantitation capabilities of the reagent ionophores of the invention can be increased by other means. For example, one of skill in the art will appreciate that a sample containing a high concentration of the ion under investigation may be diluted so that the concentration of the ion will fall within the optimum range of its detectability. As alluded to previously, a second approach may be to immobilize the ionophore to a solid surface by conventional techniques. Immobilization will prevent self-quenching and the detectability range can be extended by increasing the loading levels of the immobilized ionophore, so that there is more reagent ionophore available for complexing.[23]

The ionophores of the present invention may be used in many diverse applications wherein it is desired to detect specific ions ionophores selective for potassium ion are of interest in the fast and accurate determination of these ions in body fluids and the like. Fluorogenic ionophores selective for potassium can be used in reagent kits, and conventional protocols may be easily developed for mixing a solution, preferably an alcoholic solution of the ionophore with blood serum samples, and then to measure potassium using fluorescence spectrophotometers. The present inventors have discovered that representative ionophores of the present invention are stable for a long period of time in aqueous and alcoholic solutions, and thus, these are the preferred solutions. Chromogenic ionophores may also be used in reagent kits. For example, they may be coated onto plastic strips or filter paper and used as dip sticks for serum analysis. Ion concentration can be determined by matching a color change with a standard color charts by visual or reflectance measurement techniques as detailed previously.

The fluorogenic ionophores can also be incorporated in fiber optic-based automatic analytical instruments, especially bifurcated fiber optics. For example, the fluorogenic ionophore may be immobilized at the terminal end of conventional optic fibers, or a solution of the ionophore may be contacted with the optic fiber using a sensor cap provided with a permeable membrane for the transport of ions into the sensor cap. One branch of the bifurcated fiber optic may thus carry the light for excitation, while the other branch may carry the fluorescence emission. Optical sensors using fiber optics have a number of advantages over electrochemical sensors. First, they do not require reference signals, and second, because the primary signal is optical, it is not subject to electrical disturbances such as those arising from surface potentials. Optical sensors can measure concentrations of the target ions without significantly disturbing the sample, and can thus be used for continuous monitoring, an example of which is the in vivo monitoring of potassium ion in the human blood during surgery. Fiber optic-based sensors also offer the advantage that the signal can be transmitted over long distances (about 2-100 meters) thus facilitating remote sensing. Further, they are amenable to miniaturization.

Certain ionophores of this invention preferentially complex with sodium ion, resulting in enhanced fluorescence or color change. These can be used to develop test kits or fiber optic-based sensors for detecting sodium ion. One example of this is in the detection of leakage of sea water into electronic instruments in towed arrays for sonar sensing or in reusable booster rockets used in launching vehicles into outer space.[24]

Chemical analogues of certain of the preferred fluorogenic reagents may also be used for developing ion-selective Field Effect Transistors (FETs). In one such embodiment, FETs are electronic switching devices which can be used in turning on an alarm when sea water leaks occur. The ionophore is covalently bound to the surface oxygens of an inorganic insulator such as silica, alumina, thoria and the like. Since the fluorogenic ionophores of the invention are especially efficient in transmitting electronic perturbations, one may expect that modulation of the electric potentials "seen" by the FETs will occur when targeted ions are bound to the ionophores. An example of this is a sea water leakage warning system. When contacted with sea water, the sodium ion complexes with the ionophore-based FET, thus affecting the output voltage of the FET amplifier. Such voltage changes can set off an alarm.

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Ionophores selective for lithium ion are useful in the detection of therapeutic levels of lithium in blood serum. Lithium has an important role in the management of a number of psychiatric disorders. Lithium is administered orally in the form of tablets, capsules, or liquid. Because lithium has the potential for having adverse effects on the kidneys and thyroid, it is important to carefully control the lithium dosage. Heretofore, the blood (serum) lithium level has been monitored through time-consuming and expensive procedures of flame photometry or atomic absorption spectrophotometry .

In one embodiment of the present invention, there is provided a fluorogenic reagent and analytical system for the monitoring of lithium content of blood. This indicator system will aid the clinician in the rapid and inexpensive control of lithium dosage, to provide a dosage regime that is likely to be therapeutic without running the risk of toxicity. The present reagent is particularly suited for this analysis of blood serum, for the detection of lithium used for medical treatment even in the presence of substantial amounts of naturally occurring sodium and potassium ions. Lithium has a relatively narrow therapeutic range. Doses of 0.7-1.7 mmol/L can alleviate acute manic symptoms in some cases, while doses of about 2.0 mmol/L or above can be toxic. The sensitivity of the present fluorogenic indicator is within this critical range. In general, concentrations as low as 0.1 mmol/L may be detected.[25]

In another preferred embodiment, chromophoric ionophores are coated onto a suitable substrate to prepare a test strip or disk or the like. The resulting solid indicator may then be dipped into a liquid sample under analysis, or a drop of sample placed onto it. Various concentrations of sample under analysis may be tested and the development of color hue may be visually compared against that produced by a known concentration of lithium. Alternatively, the presence of lithium may be detected by a change in reflectivity utilizing conventional analytical devices for this purpose, such as those described for a reflectance spectrum.

The following are more specific embodiments of the present invention, and are not to be considered limitative thereof.

III. RESULTS

Several life-threatening diseases, also known as ‘Channelopathies’ are linked to irregularities in ion transport proteins. Significant research efforts have fostered the development of artificial transport systems that facilitates to restore the functions of impaired natural transport proteins. Indeed, a few of these artificial ionophores demonstrate the rare combination of transmembrane ion transport and important biological activity, offering early promises of suitability in ‘channel replacement therapy’. In this review, structural facets and functions of both cationophores and anionophores are discussed. Ionophores that are toxic to various bacteria and yeast, could be exploited as antimicrobial agent. Nevertheless, few non-toxic ionophores offer the likelihood of treating a wide range of genetic diseases caused by the gene mutations. In addition, their ability to disrupt cellular homeostasis and to alter lysosomal pH endow ionophores as promising candidates for cancer treatment. Overall, critically outlining the advances in artificial ionophores in terms of in vitro ion transport, possible modes of action and biological activities enables us to propose possible future roadmaps in this research area.[26]Exchange of Na^+, K^+, Ca^{2+} and Cl^- ions across cell membranes is indispensable for sustaining cellular life as it controls diverse biological processes including metabolism, maintenance of osmotic pressure and cell volume, regulation of cellular pH and signalling pathways. In biological systems, the plasma membrane of a cell is a hydrophobic barrier, which separates the interior of the cells from the environment outside. It allows small neutral molecules such as CO_2 and H_2O to easily pass through the hydrophobic bilayer but exchange of charged solutes across the membrane needs assistance of natural channel proteins. These channel proteins are not only extraordinarily selective gatekeepers for specific ions but also maintain several physiological processes. For instance, Ca^{2+} channels are vital in regulating the cardiovascular system, Na^+ and K^+ channels form the basis of neuronal signal transduction. In addition, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel is associated with cystic fibrosis disease. Consequently, dysfunction of these ion transport systems lead to ‘Channelopathies’ such as cystic fibrosis (CF), epilepsy, Long QT syndrome, Bartter syndrome, myotonia, nephrolithiasis, osteoporosis, and other ailments.

Of late, development of synthetic ionophores has attracted considerable interest because they are structurally robust and offer adjustable ion transport behaviour relying upon simple structural fine-tuning as compared to the complex structured natural ion channels. The transmembrane ion transport could be attained either via ion channels or ion carriers by exploiting various non-covalent interactions, e.g. electrostatic interactions, H-bonding, halogen bonding, chalcogen interactions, pnictogen interactions, cation/anion-π interactions, hydrophobic interactions, etc. Such transport machineries might potentially mimic the function of their natural congeners and have immense therapeutic potential in ‘channel replacement therapies’ that address ‘Channelopathies’. Despite the current state of underexplored research knowledge, quite a few ion channels/carriers have delivered record-high biological activities. For example, some artificial ion channels were identified with noteworthy antibacterial activity against Gram-negative and Gram-positive bacteria. A few studies also showed potential applications including DNA sequencing, sensors and delivery systems. In

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some cases, ion channels were found to kill cancer cells via the necrotic pathway. Recent studies have established the advantages of apoptotic pathway over the necrotic cell pathway concerning cell death based therapeutic applications. This is linked to the latter's toxic nature, far from ideal considering the living organs. In fact, of late, quite a few ion channels/carriers demonstrated the ability to alter the intracellular pH gradient in the cellular acidic components (e.g. lysosomes, endosomes and Golgi apparatus) or to destroy the ionic homeostasis of cells, thereby triggering the apoptosis-inducing pathway. However, for the treatment of 'channelopathies' e.g. CF, the transport systems must be non-toxic so that they can be delivered in sufficient quantities (same order of magnitude as endogenous ion channels) to the targeted cell lines for producing considerable effects. Recently, a few exciting results have been published in this direction by developing anionophores with minimum or no toxicity towards epithelial cell lines.[27]Simply put, focus of this review is to highlight the biological activities of artificial channels/carriers and recent advances towards achieving the diverse functions of natural ion channels.

IV. CONCLUSIONS

In the past two decades, arguably there has been a rapid development in the area of synthetic ionophores. These structurally simple and robust molecules offer remarkable ion transport activity, selectivity and promising bioactivity. In the context of transporting molecules of biological relevance, quite a few ionophores have been recently discovered with potential biological activities. In fact, few of these membrane-active synthetic molecules are taking the leap from model bilayer membrane to cells. In this review, we have comprehensively summarised the progress on biological activity of the synthetic ionophores. A few studies have demonstrated their potential applications as antimicrobial agent. However, some of the non-toxic ionophores promoted Cl^- transport in epithelial cells and they could indeed be promising candidates for 'Channel replacement Therapy'.

Another significant therapeutic application of these systems could be observed in antitumour treatment. Recent reports show that the active transport systems trigger cell death by apoptosis in a wide range of human cancer cell lines and often they are identified with selective toxicity towards specific cell lines. Also another possible mechanism for cell death could be by the disruption of autophagy process and this function might be entirely independent of apoptosis. We hope that the examples discussed herein will stimulate future research across the existing and hitherto unreported generations of new ionophore families. Such intensive fundamental research in this area is highly likely to catalyse the discovery of novel modes of functions. Potential biological properties will evolve in the synthetic ionophores of the future, to mimic the natural ion transport protein, in essence.[27]

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