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A Brief History of the Minor Groove Binders (MGBs)

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ABSTRACT

The two naturally occurring polyamide heterocycles Distamycin and Netropsin belong to a group of heterocyclic compounds called Lexitropsins. These compounds exhibit their activity by binding to the minor groove of the DNA. These minor groove binders MGBs have several biological activities such as anticancer, antibiotics, and anti-parasitic qualities. Over the years several research groups have modified these compounds by replacing the pyrrole groups by other heterocyclic compounds and many other modifications have been employed to both the tail group and the head group. These gave rise to compounds with different biological activities.

الملخص

ديستامايسين ونيتروبسين هي مواد تكونت طبيعياً من البولي أميد الغير متجانسة والتي تنتمي الى طائفة من المركبات تسمى ليكسيتروبسينات، هذه المركبات استمدت نشاطها البيولوجي من قدرتها العالية على الأرتباط بمنطقة الأخدود الصغير للحمض النووي DNA، الأمر الذي زاد من أهمية هذه المركبات وأتساع الأنشطة البيولوجية المختلفة كأستخدامها كمضادات للسرطان، والمضادات الحيوية، وكذلك مضادات للطفيليات. لذلك قامت العديد من الدراسات و الابحاث العلمية بالأهتمام بدراسة هذه المركبات من خلال تعديلها واستبدال مجموعة البيرول بمركب حلقي غير متجانس أخراضافة الى الكثير من التعديلات الأخرى التي تمت على مجموعتي الرأس و الذيل في المركب. هذه التعديلات أعطت زيادة كبيرة في النشاطات البيولوجية لهذه المركبات.

INTRODUCTION

Minor Groove Binders (MGBs) are now vast group of compounds generally called Lexitropsins. These polyamide heterocycles bind to the minor groove of the DNA (deoxyribonucleic acid) and therefore they are DNA binding ligands (Kennedy *et al*.,1999 ; Khalaf.,2009). The binding of these molecules

differs from one molecule to another depending on the different changes created to the MGBs. The very first two compounds discovered were Distamycin A (Di Marco *et al*.,1962 ; Arcamone *et al*.,1964) and Netropsin (Martin *et al* 1957; Finlay *et al*.,1951). Distamycin A is now a well-known naturally occurring antibiotic which was isolated back in 1962 from the cultures of *Streptomyces distallicus* (DiMarco *et al*.,1962).

Netropsin (also named as congocidine or sinanomycin(Weiss *et al*.,1957) was discovered, who first isolated this material from the actinobacterium *Streptomyces netropsis* (Finlay *et al*.,1951). Netropsin belongs to a class of pyrrole-amidine antibiotics.

These two naturally occurring polyamides were found to be active against a variety of viruses, Gram-positive bacteria and protozoa (Khalaf *et al*.,2016). The structure of Distamycin A and Netropsin (Scheme1) shows the presence of an oligopeptidic pyrrolecarbamoyl frame ending with an amidino moiety. It was found that Distamycin A reversibly binds to the minor groove of DNA by hydrogen bonds, van der Waals contacts and electrostatic interactions. The binding has a strong preference for adenine-thymine (AT) rich sequences containing at least four AT base pairs (Pelton & Wemmer,1990). It was also found that when the number of pyrrole rings in a minor groove binder increases to four, the activity will increase also to almost 20-fold relative to the Distamycin A. The increase in the sequence specificity for longer tracts of AT-rich DNA is the result of the enhanced availability of hydrogen bonding and van der Waals forces. The domain of the MGBs was studied by several researchers incorporating organic compounds, such as mitomycin C and anthramycin, and inorganic compounds, for example cisplatin (Aleksi, Kapetanovi.,2014; Vafazadeh *et al*., 2015; Khan *et al*.,2016) published their research on alcohol containing Netropsin-type symmetrical compounds which they successfully synthesised. Those researchers also managed to construct various unsymmetrical triaryl compounds and further explored the activity of these r of small indole derivatives for their DNA binding capability using fluorescence quenching experiments in addition to molecular docking methods.

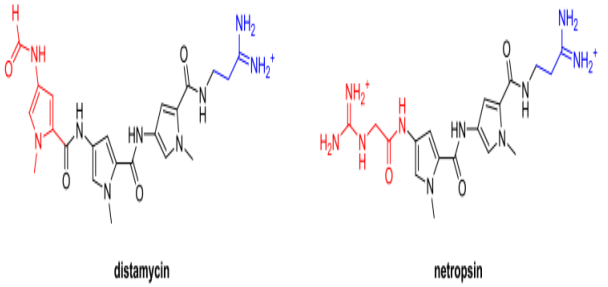


Figure 1: Schematic representation of Distamycin A and Netropsin.

Modification of Distamycin A and Netropsin

There are many methods for the modification of Distamycin A and Netropsin (Khalaf,2009). Changes can be made to the head group, tail group or the heterocyclic rings. This involved changing the heterocyclic rings, for example the N-methylpyrroles to rings such as thiazole, imidazole, oxazole, furan and thiophene. Other modifications can also be made to the amide linkages. These can be replaced with olefinic double bonds or in some cases with an azo group. The synthesis of a large number of modified Lexitropsins containing a variety of changes to the head groups, tail groups and the heterocyclic rings were reported from our laboratory at the University of Strathclyde (Nahoum et.al.,2007).

Minor Groove Binders as anti-fungal and anti - mycobacterial therapeutics:

There are several known classes of microbes which cause infections to humans. These microbes developed resistance to the drugs which used to be a good tool as anti-infective treatment. These drug resistant infections are causing a startling increase in patient mortality, as well as the associated effects (Heymann, 2006). Also, from our laboratory at the University of Strathclyde (Scott *et al*.,2017) reported in 2017 the discovery of a number of MGB compounds which showed considerable activities against Cryptococcus neoformans and Mycobacterium tuberculosis. These two organisms are causing problems for the

scientists working on drug discovery programmes due to the challenges of piercing the cell wall (Brown *et al*., 2015). The fungal pathogen Cryptococcus neoformans has the capability of striking serious threat on patients who are in an immunocompromised state by introducing life-threatening cryptococcal meningitis. It is also noteworthy that in patients with advanced AIDS it caused 15%-20% of AIDS-associated deaths (Smith *et al*.,2015). The authors concentrated their study on a collection of structurally similar MGBs that were designed to target mycobacteria and fungi. The examination was also extended to include the biological activity profiles against a number of infectious organisms, such as bacteria, fungi and parasites. The compound collection they investigated encompassed three series that differ in the heterocyclic rings attached to the tail group, which were represented by N-methylpyrrole, N-isopentylpyrrole, or isopentylthiazole (Fig. 2). The head group position was varied, within each series, as shown in the structures indicated in (Fig. 2). However, the isopentylthiazole series also included four additional head groups in an effort to expand the research further since these compounds showed interesting activity during the course of the study. The amidine linked head group used in their studies had been explored in isolated cases in some of their previous work. The authors expected the amidine head group link to have advantages in terms of solubility and intrinsic activity with pathogens which have difficult cell walls because it produces dicationic MGBs. The study inspected the methodical structural changes including the addition of lipophilic moieties, such as thiazoles and alkyl side chains, and their importance for penetration of the waxy cell wall of the mycobacteria. The researchers also investigated the insertion of amidine-linked head groups and their importance in providing an extra source of hydrogen bonding to donate in penetrating the polyglycan cell wall of fungi (Brown *et al*., 2015). These structural modifications could assist the cellular accumulation and it could also be important for the activity and selectivity of MGBs.

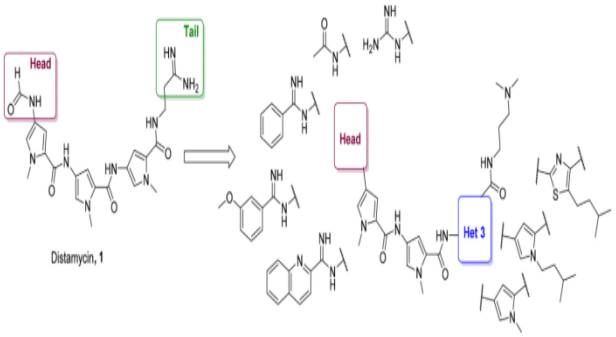
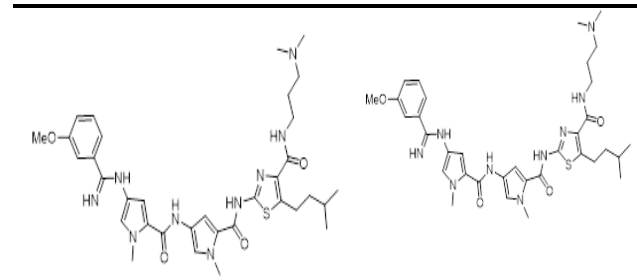
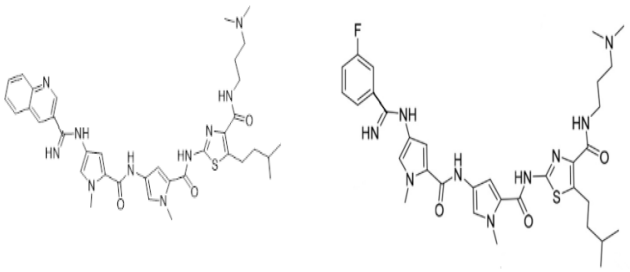


Figure 2: Structure of Distamycin and examples of modified MGBs.

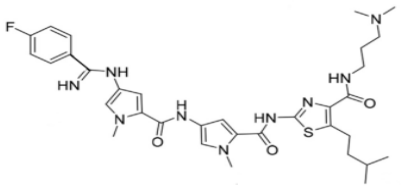
The conclusions from this study are: the authors investigated 19 structurally related MGBs and found several important compounds suitable for further investigation. For example: compounds MGB-4 and MGB-317 showed promising MIC80s of 2 and 4 mg/mL, respectively, against C. neoformans and good selectivity indices. While MGB-325 has a lower MIC80 of 0.25 mg/mL than any of the other active compounds, the researchers found the toxicity of this compound was too high. They found two important compounds MGB-353 and MGB-354, which have MIC99s of 2.4 mg/L against M. tuberculosis. However, they have modest mammalian cell toxicity. Moreover, SAR studies revelled that the addition of the thiazole ring was involved in enhancing the anti-infective activity to this group of MGBs (Fig. 3). This could be the effect of the increased lipophilicity brought about by the substitution of a pyrrole by a thiazole. In general, the authors have found many compounds of this class of minor groove binders were worth the investigation to further optimise the activity for both antifungal and antimycobacterial. The researchers also found that individual structural modifications that were possibly to be crucial in enhancing selectivity of uptake through cell walls were: charge and lipophilicity both were important in determining the penetration of an MGB into living organisms such as bacteria and fungi.



MGB4 MGB317



MGB353 MGB325



MGB354

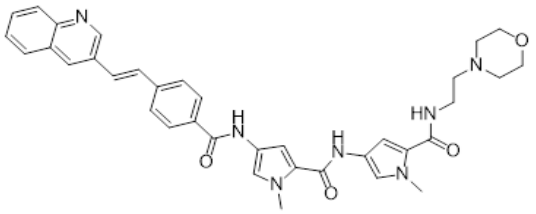
Figure 3: Selection of MGBs.

Selective Toxicity of MGBs.

The central point of the MGB class of antibacterial compounds is their selectivity for Gram-positive bacteria and they should not have any adverse activity against mammalian cells. This important issue became obvious from the information acquired using one of our synthesised compounds namely [AIK-20/25/1]. This specific compound is almost as active as MGB-BP-3 (Fig. 4) which is one of the most active compounds from a library of compounds synthesised at our laboratories. University of Strathclyde had licenced a small pharmaceutical company, MGB Biopharma, to develop this new drug (MGB-BP-3), as a novel class of anti-infective to tackle the main global issue of antibiotic resistance. This drug has passed its phase I and phase IIa clinical trials which were conducted in America and Canada. MGB-BP-3 was invented at the University of Strathclyde and it is a very powerful bactericidal antibiotic with a totally innovative mode of action. The oral formulation has been established by MGB Biopharma specifically for the treatment of Clostridium difficile-associated disease (CDAD). Phase IIa clinical trial was conducted to assess the safety, tolerability and efficacy of MGB-BP-3 in patients with CDAD and it was found to be very successful.

To date, MGB-BP-3 is the only powerful antibiotic that kill bacteria and specifically C. difficile very fast and within a few hours. It is worth mentioning that MGB-BP-3 has a very strong bactericidal activity against the BI/NAP1/027 strain, which is the most infectious strain of C. difficile, which is resistant to current treatment. Also, important to mention that CDAD is a serious and life-threatening infection of the large intestine and is the most recurrent cause of diarrhoea in infirmaries and care homes around the world. It is projected that in the US alone there are nearly half a million cases every year leading to about 30,000 deaths yearly (Giordani *et al*.,2016; Khalaf *et al*.,2016).

(Fig.5) Shows the result on cellular viability for this compound comparing a mammalian cell line (HS27 murine fibroblast) with *Staphylococcus aureus*. The two graphs are displaying clearly that there was no evidence of toxicity to be found with the HS27 cells but catastrophic death was found for the bacteria. The bactericidal death has been attributed to the minor groove binders interfering with a number of biochemical pathways that lead to cell death (Suckling,2015).



MGB-BP-3

Figure 4: Schematic representation of MGB-BP-3

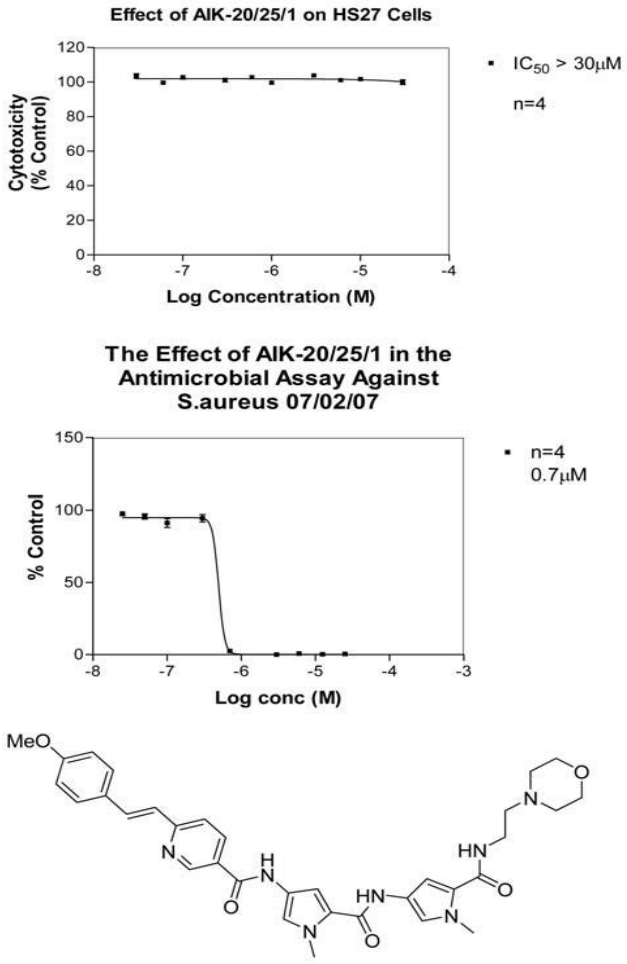


Figure 5:The effect of AIK-20/25/1 in the antimicrobial assay against S. aureus as compared to HS2.

MGBs as drugs to combat the Mycobacterium tuberculosis (Mtb) disease (Hlaka *et al.*,2017**):**

Mycobacterium tuberculosis (Mtb), is a vital topic as it is among the top infectious illnesses around the world. The world health organisation in 2016 (G.T.Report.,2016) reported that TB killed around 1.8 million people in 2015, that is an increase from 1.5 million deaths in the previous year (G.T.Report.,2015). Now adays there is a six-month treatment for drug-susceptible Mtb, though it is active in the majority of cases, but it is slowly becoming less effective as result of increasing resistance against the drugs prescribed for the treatment (Zumla *et al.*, 2012). There are several advances have been made in the area of TB drug research, accomplished by collaboration around the world. The Global Alliance for TB Drug Development these days conducts large scale screening programme on all newly prepared anti-TB drug compounds for the multi drug resistance and extensive drug resistance TB (Mwaba, *et al.*,2011). There are many organisations working on a variety of projects to eliminate TB and one of them is "the STOP TB partnership", which involves a worldwide working group to advance new TB drugs (Mwaba, *et al.*,2011). It is known that drugs administered orally have a number of limitations, among them drug inefficiency as a result of drug poor solubility as a result of low gastric pH, and another reason could be the poor absorbance in the gastrointestinal tract. The use of effective drug delivery system may enhance drug retention at the site where it is needed. Building on the idea of the capability to deliver the medication to the site of action could provide a continued drug concentration, enhancing the efficiency of the drug against its planned target. If we take the case of pulmonary TB treatment, for example, oral drug administration leads to high systemic concentrations of the drugs which have associated and unwanted side effects such as liver toxicity and cytotoxicity (Gulbay *et al.*,2006). Also, there are disadvantages connected with the oral administration of antibiotics led to the development of ground-breaking drug delivery methods. Liposomes was used as a drug delivery system. This has previously been reported to reduce microbial drug resistance through faster drug delivery as well as increasing the antimicrobial drug concentration. This has led to the prevention of microbial drug efflux pump activity **(**Pelgrift & Friedman, 2013). It was reported that liposome-encapsulated drugs can kill microbes faster, before microbial mutations can develop. Also, It has been reported (Gaidukevich *et al.*,2016) that, the incorporation of the antibiotic drug levofloxacin into liposomes enhanced the antimycobacterial activity to kill Mtb strains resistant to the drug levofloxacin. Several drug delivery systems, among them the non-ionic surfactant vesicles (NIVs), have the capability to encapsulate both hydrophobic and

hydrophilic drugs for direct delivery to the site of infection **(**Kumar & Rajeshwarrao, 2011**).** NIVs has been described as small colloidal particles which are consisted of a non-aqueous, non-ionic surfactant bilayer that surrounds a central aqueous compartment. These NIVs are thermodynamically robust and can be fairly easily made and do not require distinctive storage conditions. The main benefit of NIVs is that they are capable to entrap various types of drugs and their size can be modified. Anyway, the most important aspect of the NIVs is their ability of enhancing the delivery of the drug small to the precise target and deposition of these small molecules within the respiratory tract. There are several reports showing NIVs to be a promising inhalable drug delivery system for the treatment of pulmonary aspergillosis with aerosolized amphotericin . B/NIV administration lowered fungal lung infection when it was compared with amphotericin B solution alone (Alsaadi *et al*.,2012 ; Mehta & Jindal, 2015).

There are various drug delivery systems have been used to entrap first-line TB drugs **(**Hari *et al*.,2010**),** However, there were only a small number which have been studied for their anti-mycobacterial activity against Mtb and intracellular Mtb in infected primary macrophages. And, for that reason, the use of NIVs as a drug delivery system to enhance the delivery and efficacy of novel MGB compounds active against Mtb-infected macrophages was explored.

MIC_{99} of MGB compounds for H37Rv-GFP

South African researchers **(**Lerato *et al*.,2017) screened 96 MGBs (supplied to them by the Department of Pure and Applied Chemistry at the University of Strathclyde, Glasgow) for their anti-mycobacterial activity against GFP-labelled H37Rv Mtb in liquid broth culture using a 96-well plate assay. Relative fluorescence was measured at 0, 4, 8, 10 and 12 days in broth culture of MGBs (these were serially diluted from 25 to 0.19 µm) to determine the MIC_{99} of MGBs required to eradicate 99% of Mtb. HIT compounds, defined as previously reported, **(**Hughes *et al*.,2011) were identified as drugs that were active at or below the threshold concentration of 3.12µM. A hit-list of seven compounds with an MIC_{99} of 1.56 µM or less was identified. The drug Rifampicin, which possess an MIC of 0.0977µm, was used as a positive control. These compounds which were selected as HIT compounds were MGBs 362, 368, 361, 365, 359, 364 and 367 with an MIC_{99} range of 0.391–1.56 µm, and were chosen for further intracellular anti-mycobactericidal activity screening, (Fig 7).

A study of the intracellular drug activity against clinical Mtb and macrophage cell viability:

The study of the capability of anti-TB compounds to penetrate macrophages as well as induce mycobactericidal activity, in spite that they are non-toxic to the macrophages, is an important issue required in TB drug development. Therefore, BMDMs were subjected to serial MGB drug concentrations from 1.56 to 12.5 µm to determine their anti-mycobacterial activity against the clinical Mtb strain HN878, after 5 days of infection. Several compounds were screened for the concentration that eradicated 50% of bacilli MIC_{50}. Two of the seven hit compounds found from the screening studies against Mtb had good intracellular mycobacterial killing efficacy against Mtb-infected macrophages, with MIC_{50} values of 4.09 µm (MGB 362) and 4.19µM (MGB 364). The drug Rifampicin, was chosen as a positive control, had an MIC50 of 1.7 µm. CellTiter-Blue cell viability assay was conducted to examine the macrophage cell viability in MGBs-treated BMDMs after 5 days of exposure. MGB 362 and 364 and the drug rifampicin were found to have no significant effect on macrophage viability at the particular intracellular drug activity MIC_{50} concentrations (Fig 6). The researchers have found that the data they have obtained propose that MGB 362 and 364 have an effective intracellular anti-mycobacterial activity against Mtb and in the same time they were non-toxic to the host cells.

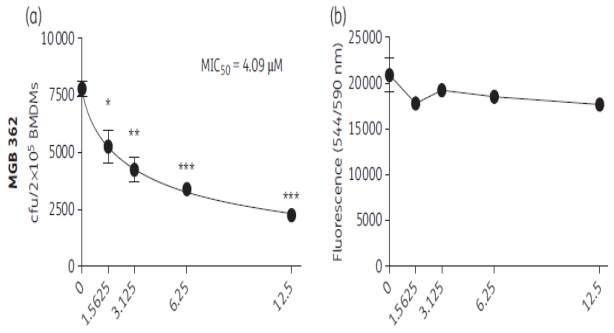
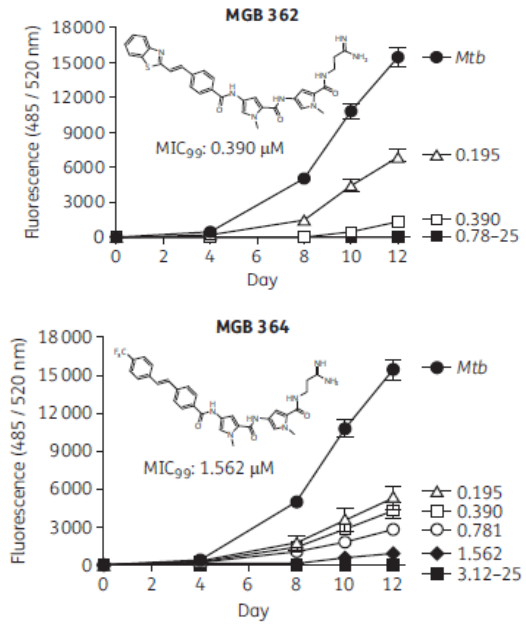


Figure 6 : MIC_{50}s of MGB compounds for HN878 Mtb-infected BMDMs and cell viability.

(a) The intracellular anti-mycobacterial activities of MGBs (1.5625–12.5 µm) and the drug rifampicin (0.3906–3.125 µm) were assessed by counting cfu at the respective concentration at five days post-Mtb HN878 infection. MIC_{50} values of each drug compound were identified in GraphPad Prism by non-linear regression analysis. (b) Macrophage cell viability was determined at five days of MGB compound exposure and determined by CellTiter-Blue assay with fluorescence detection at 544ex/590em nm. Data were corrected for background culture medium fluorescence and are shown as mean+SEM, representative of triplicates.



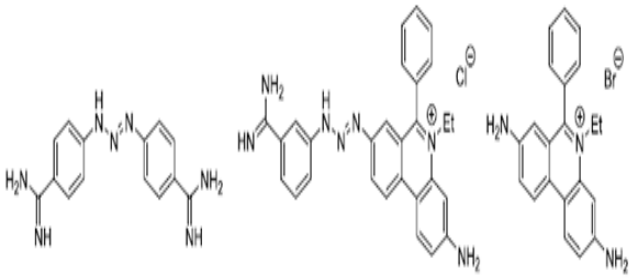
Figures 7: The study of anti-mycobacterial activity of MGB compounds against H37Rv-GFP.

These are the results of the direct antimicrobial activity of MGB compounds at the drug concentration range of 0.195–25 µm which were tested against H37Rv-GFP (1% 105 cfu/well) in 7H9 liquid broth culture using a microplate assay. The antimycobacterial activity of MGB compounds against H37Rv-GFP was determined in a concentration-dependent manner by measuring fluorescence (485ex/520em nm) on days 0, 4, 8, 10 and 12. Data were corrected for background 7H9 fluorescence. Data are shown as mean+SEM of duplicates.

The conclusion from this research work: The authors of this research had discussed the ability of NIVs to trap the drug within their hydrophilic/hydrophobic compartment which allows the drug to be taken up by phagocytosis of the infected macrophage, which lead to transportation of the drug to the site of infection. They have found that using NIV drug formulations resulted in higher drug levels compared with similar treatment with drug solution at the site of infection after treatment by the pulmonary or intravenous routes for water-soluble (Carter *et al*.,2001; Williams *et al*.,1998) and lipid soluble drugs (Alsaadi *et al*.,2012). There are studies in dogs treated by the intravenous route with a sodium stibogluconate (SSG)/dextran/NIV formulation increased the elimination half-life and the volume of distribution at a steady state compared with SSG/dextran solution (Nieto *et al*.,2003). This is suggesting that MGB/NIV formulations can be a possible pulmonary treatment for Mtb. This study showed that MGBs constitute an important new class of drug/chemical entity with favourable antimycobacterial activity and could have some benefit in future anti-TB therapy. The authors also demonstrated that NIVs (a) contribute to better delivery of drugs for an intracellular infection, (b) act as a delivery device for entrapped MGB compounds and (c) serve as the initial step into future research of targeted delivery of entrapped drugs to Mtb-infected cells.

New MGBs as drugs to Cure Animal African Trypanosomiasis in an in Vivo Mouse Model:

The disease "*Animal African Trypanosomiasis*" (AAT) is a problem to cattle production and, consequently, to the development of rural parts of sub-Saharan Africa. AAT is a complex of diseases mostly caused by three tsetse-transmissible trypanosome species: Trypanosoma congolense, Trypanosoma vivax and, to a lesser extent, Trypanosoma brucei spp. While all domesticated animals can be infected by trypanosomes, cattle are the foremost economically and clinically relevant host [58]. Most AAT cases are chronic, with animals suffering from anaemia, weight loss, weakness, immunosuppression, sterility, and lower milk production. Eventually, these animals would perish from these diseases. Consequently, AAT effects agricultural development significantly and in the same time effects food production and, socioeconomic growth. It is therefore, a well-known factor and a significant cause of poverty in African countryside communities, with an estimated loss at US$ 4.75 billion every year (Grady *et al*.,2011). Therefore, control the AAT relies heavily on chemotherapy or chemoprophylaxis (Giordani *et al*.,2016). There are two drugs in use at the moment regardless of the type of parasite. These are diminazene diaceturate (a diamidine and DNA minor groove binder) and isometamidium chloride (a hybrid molecule of ethidium and diminazene) used for both cure and prophylaxis. In addition to these drugs, the DNA intercalator ethidiumbromide, is available for treatment and also gives some short-term prophylaxis. All of these drugs are well known to have toxic effects on animals, and their efficacy is weakened by increasing levels of the resistance. In spite of the high usage levels (at least 35 million doses/year), pharmaceutical companies are not willing to participate in any research in this area because of the lack of commercial benefit. Consequently, since the introduction of diminazene and isometamidium more than fifty years ago, no new drugs have come to the market for the treatment of AAT. In recent years, a renewed interest in variety of animal trypanocides has appeared because of the disease's effect on the availability of food, and the arrangement of a product development partnership, and the Global Alliance for Livestock Veterinary.



Diminazene Isometamidium chloride Ethidium bromide

CONCLUSION

The two naturally occurring polyamide heterocycles Distamycin and Netropsin belong to a group of heterocyclic compounds called Lexitropsins. These compounds exhibit their activity by binding to the minor groove of the DNA. These minor groove binders MGBs have several biological activities such as anticancer, antibiotics, and anti-parasitic qualities. Over the years several research groups have modified these compounds by replacing the pyrrole groups by other heterocyclic compounds and many other modifications have been employed to both the tail group and the head group. These gave rise to compounds with different biological activities.

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