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The monoamine oxidase inhibition properties of selected structural analogues of methylene blue

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ABSTRACT

The thionine dye, methylene blue (MB), is a potent inhibitor of monoamine oxidase (MAO) A, a property that may, at least in part, mediate its antidepressant effects in humans and animals. The central inhibition of MAO-A by MB has also been linked to serotonin toxicity (ST) which may arise when MB is used in combination with serotonergic drugs. Structural analogues and the principal metabolite of MB, azure B, have also been reported to inhibit the MAO enzymes, with all compounds exhibiting specificity for the MAO-A isoform. To expand on the structure-activity relationships (SARs) of MAO inhibition by MB analogues, the present study investigates the human MAO inhibition properties of five MB analogues: neutral red, Nile blue, new methylene blue, cresyl violet and 1,9-dimethyl methylene blue. Similar to MB, these analogues also are specific MAO-A inhibitors with cresyl violet (IC_{50} = 0.0037 μM), Nile blue (IC_{50} = 0.0077 μM) and 1,9-dimethyl methylene blue (IC_{50} = 0.018 μM) exhibiting higher potency inhibition compared to MB (IC_{50} = 0.07 μM). Nile blue also represents a potent MAO-B inhibitor with an IC_{50} value of 0.012 μM. From the results it may be concluded that non-thionine MB analogues (e.g. cresyl violet and Nile blue) also may exhibit potent MAO inhibition, a property which should be considered when using these compounds in pharmacological studies. Benzophenoxazines such as cresyl violet and Nile blue are, similar to phenothiazines (e.g. MB), representative of high potency MAO-A inhibitors with a potential risk of ST.

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1. Introduction

During the late 19th century a great need to artificially colour fabrics resulted in the development of synthetic dyes. In 1876, Heinrich Caro synthesised methylene blue (MB) for the first time as a cotton dye (Fig. 1) (Oz et al., 2009; Schirmer et al., 2011). Nile blue (NB) and Nile red were synthesised in 1896 by Möhlau and Uhlmann, (1896) and were also used to dye clothing. MB was the first synthetic drug used in medicine and was used for the treatment of malaria as early as 1891 (Guttmann and Ehrlich, 1891). MB has since been employed as an antibacterial against tuberculosis (Wainwright and Crossley, 2002), and is currently used as an injectable therapeutic for methemoglobinemia (Wright et al., 1999) and as prophylaxis and treatment of ifosfamide-induced encephalopathy (Küpfer et al., 1994). Clinically MB has shown promise in the prevention of the progression of Alzheimer's disease (Wischik et al., 2008) and is being investigated as a possible treatment for distributive shock (Jang et al., 2013). MB also has been shown to possess anxiolytic and antidepressant effects in pre-clinical models as well as in clinical trials (Eroglu and Caglayan, 1997; Harvey et al., 2010; Narsapur and Naylor, 1983; Naylor et al., 1986; Naylor et al., 1987; Alda et al., 2011). The antidepressant properties of MB are linked to its ability to non-selectively inhibit nitric oxide synthase (NOS) and guanylate cyclase (Luo et al., 1995; Mayer et al., 1993; Moore and Handy, 1997; Volke et al., 1999) as well as by acting as a potent inhibitor of monoamine oxidase (MAO) A (Aeschlimann et al., 1996; Harvey et al., 2010; Ramsay et al., 2007), both mechanisms being implicated in antidepressant response (Brand et al., 2015). MB exhibits an IC_{50} value of 0.07 μM for the in vitro inhibition of human MAO-A (Harvey et al., 2010). The central inhibition of MAO-A by MB is also linked to the occurrence of serotonin toxicity (ST), which arises when MB is used in conjunction with other serotonergic agents (Gillman, 2006a, 2006b; Isbister et al., 2003; Ramsay et al., 2007; Stanford et al., 2010). Cases of MB-induced ST usually occur following intravenous administration of MB, and presents as mild toxicity. Recently a case of fatal ST was described in a patient who had received 1 g MB prior to surgery. It was concluded that an interaction with venlafaxine

Abbreviations: CV, cresyl violet; DMMB, 1,9-dimethyl methylene blue; ETC, etylthioninium chloride; FAD, flavin adenine dinucleotide; MAO, monoamine oxidase; MB, methylene blue; NB, Nile blue; NMB, new methylene blue; NOS, nitric oxide synthase; NR, neutral red; SAR, structure-activity relationship; SD, standard deviation; SI, selectivity index; ST, serotonin toxicity.

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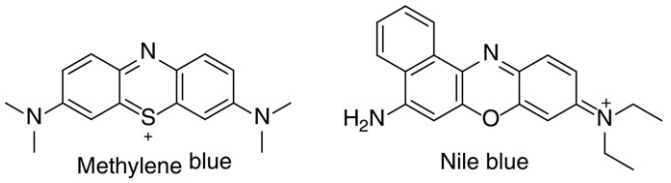

Fig. 1. The structures of methylene blue (MB; CAS 61-73-4) and Nile blue (NB; CAS 2381-85-3). MB is a phenothiazine derivative and NM is a benzophenoxazine.

(a serotonin-norepinephrine reuptake inhibitor) precipitated the syndrome, and that ST could have been prevented if the serotonin reuptake inhibitors have been discontinued at least five half-lives before administration of MB (Top et al., 2014). It was also noted that low doses (0.7–1 mg/kg) of MB, given intravenously may already give rise to clinically relevant MAO inhibition (Top et al., 2014; Schwiebert et al., 2009). This suggests that although no cases of ST has been reported following oral MB administration, the possibility of a clinical significant interaction cannot be ruled out, particularly when considering that oral MB (100 mg twice or three times daily) does lead to psychoactive responses (Narsapur and Naylor, 1983). In addition, ST also occurs with MAO-A inhibitors following oral administration (Lawrence et al., 2006; Go et al., 2010; Mason et al., 2008).

Recently it was reported that, besides MB, other redox dyes such as toluidine blue O, thionine, brilliant cresyl blue and toluylene blue also act as reversible inhibitors of the MAO enzymes, with all compounds exhibiting specificity for the MAO-A isoform over MAO-B (Fig. 2) (Oxenkrug et al., 2007). The dyes also exhibited antidepressant-like activity in melatonin-primed frogs in that they suppress the righting reflex (Oxenkrug et al., 2007). A subsequent study investigated the human MAO inhibition properties of additional structural analogues of MB, and included methylene green, methylene violet, thionine, acriflavine and tacrine (Fig. 3). Among these methylene green and acriflavine proved to be potent and specific MAO-A inhibitors with IC_{50} values of 0.25 μM and 0.43 μM, respectively (Harvey et al., 2010), although similar to MB, only methylene green was shown to possess an antidepressant-like effect in rodents (Harvey et al., 2010). The monodemethylated metabolite of MB, azure B (Fig. 4), also is a potent and reversible inhibitor of human MAO-A with an IC_{50} value of 0.01 μM. Azure B inhibits the MAO-B isoform with an IC_{50} of 0.97 μM (Petzer et al., 2012). Recently, our laboratory synthesised a structural analogue of MB, ethylthioninium chloride (ETC), and found that it too is a reversible non-selective inhibitor of MAO-A and MAO-B with IC_{50} values of 0.51 μM and 0.59 μM, respectively (Delport et al., 2014). Moreover, both azure B and ETC exhibit antidepressant-like effects in an animal model (Delport et al., 2014). Based on the reported MAO inhibition of MB and some of its analogues as well as

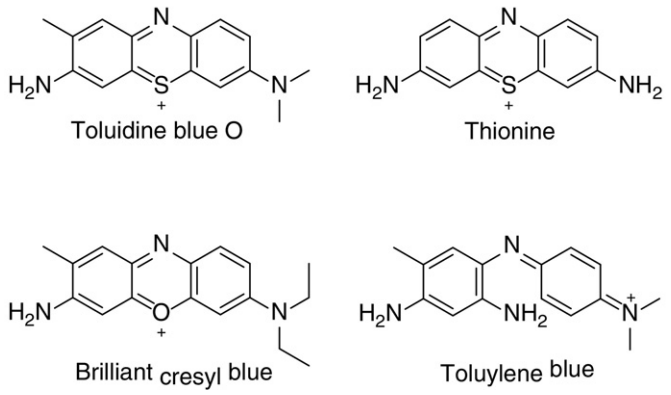

Fig. 2. The structures of toluidine blue O (CAS 92-31-9), thionine (CAS 78338-22-4), brilliant cresyl blue (CAS 81029-05-2) and toluylene blue (CAS 97-26-7). Toluidine blue O and thionine are phenothiazine derivatives, brilliant cresyl blue is a phenoxazine derivative and toluylene blue may be viewed as an open ring phenazine.

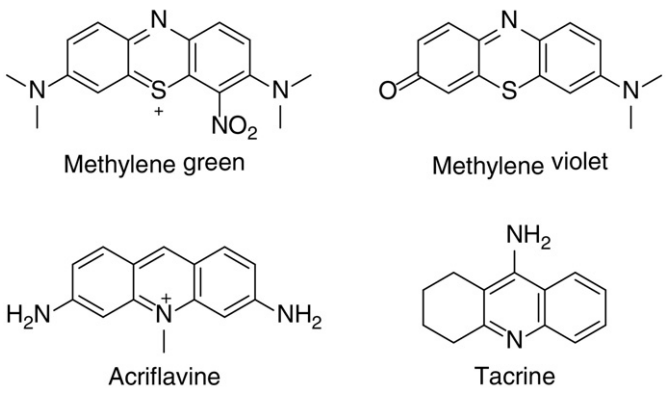

Fig. 3. The structures of methylene green (CAS 224967-52-6), methylene violet (CAS 2516-05-4), acriflavine (CAS 8048-52-0) and tacrine (CAS 1684-40-8). Methylene green and methylene violet are phenothiazine derivatives, while acriflavine and tacrine are acridine derivatives.

their apparent in vivo efficacies, the present study selected five redox dyes and structural analogues of MB and evaluated their ability to inhibit human MAO. These dyes are neutral red (NR), NB, new methylene blue (NMB), cresyl violet (CV) and 1,9-dimethyl methylene blue (DMMB) (Fig. 5). These analogues were selected based on planarity, aromaticity and the potential for redox chemistry similar to MB. A further consideration in the selection was commercial availability and the presence of a fused tricyclic heteroaromatic system that is similar to phenothiazine. With this study, the aim was to expand on the structure-activity relationships (SARs) of MAO inhibition by MB analogues and to discover new compounds with high potency MAO inhibition (Harvey et al., 2010). Secondarily, this study aims to alert to possible toxicological issues (e.g. ST) that may arise as a result of the use of some of these dyes.

NR has been used as a histological and vital stain since the early twentieth century (Koehring, 1930), but is mostly used in the NR-release assay (Reader et al., 1989) and the NR-uptake assay (Repetto et al., 2008; Borenfreund and Puerner, 1985) used to test the short-term cytotoxic effects of chemicals. NB was first synthesised as a clothing dye and histological stain (Möhlau and Uhlmann, 1896). During the 1940's it was discovered that NB has the ability to stain and hinder the growth of transplantable mouse carcinomas and sarcomas (Riley, 1948; Bates and Kershman, 1949). NB has also been investigated as a photosensitiser (Wainwright, 1996) and as an agent for photodynamic therapy in human bladder carcinoma cells (Lin et al., 1991). Interestingly, NB has been shown to be a potent butyrylcholinesterase inhibitor (Kucukkilinc and Ozer, 2007; Yücel et al., 2008). NMB is used as a supravital stain for reticulocytes (Brecher, 1949), and is bactericidal against Gram-positive and Gram-negative organisms (Wainwright et al., 1998; Wainwright et al., 2006) in photodynamic therapy. Indeed, several studies have shown that NMB is an effective photodynamic therapy agent against *Candida albicans* (Dai et al., 2011; Rodrigues et al., 2013; Fekrazad et al., 2015; Freire et al., 2016) and to be highly photocytotoxic in melanoma cell lines (Rice et al., 2000). As a result of its lipophilic nature, DMMB can cross membranes allowing it to not only stain erythrocytes at the membrane site but to stain the entire erythrocyte blue-

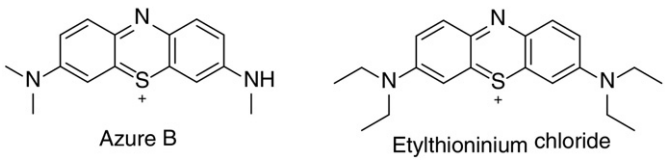

Fig. 4. The structures of azure B (CAS 531-55-5) and etylthioninium chloride (ETC). Both azure B and ETC are phenothiazines.

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