P-39

Estimating the Toxic Potential of Entactogens – *In silico* Study

MILENA JADRIJEVIC-MLADAR TAKAC[1]; TIN TAKAC[2]

[1] *Faculty of Pharmacy and Biochemistry, University of Zagreb, A. Kovačića 1, 10000 Zagreb, Croatia*
[2] *Faculty of Chemical Engineering and Technology, University of Zagreb, Trg Marka Marulića 19, 10000 Zagreb, Croatia*

Correspondence: jmtmilenamc@gmail.com

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1. Introduction

Ecstasy (MDMA) and its structural analogs are capable of inducing an "entactogenic syndrome", a reversible controlled alteration of consciousness in humans characterized by emotional relaxation, feelings of happiness, and empathy. This makes MDMA the most popular recreational drug with a high potential for abuse. Recently there has been increasing evidence that MDMA may be used in MDMA-assisted psychotherapy to treat post-traumatic stress disorder (PTSD), autism anxiety, alcoholism, and mood disorders. There is a widespread belief among adolescents and younger adults that ecstasy is a safe drug. However, the "street drugs" that are very commonly sold under this name can vary widely in purity and often contain adulterants or undeclared entactogens with unknown properties. (1–4) Entactogens (***Figure 1***) and reference molecules, the antidepressants paroxetine (SSRI) and venflaxine (SNRI), were studied for their toxic potential and affinity for drug-drug interactions (DDI) *via* membrane transporters.

2. Materials and methods

Entactogens (**1–25**) and references paroxetine and venflaxine were evaluated using ADMET Predictor™ software package (SimulationsPlus Inc., USA, www.simulations-plus.com) and the MetaTox web-application (http://way2drug.com/mg).

3. Results

For the studied entactogens (***Figure 1***), the calculated MlogP ranged from 0.839 to 2.977 and of paroxetine 2.561. ADMET_Risk was calculated in the range from 0.000 (DiFMDA, R^1=R^2=R^4=R^5=H; R^3=CH_3, R^6= R^7=F) to MlogP 3.505 (MDBU, R^1=$CH_2CH_2CH_2CH_3$, R^3=CH_3, R^2=R^4=R^5=R^6=R^7=H).
The main ADMET risks were related to CYP metabolism (CYP1A2, 2C19 and 2D6), volume of distribution (V_d) and mutagenicity (MUT) (Table 1).

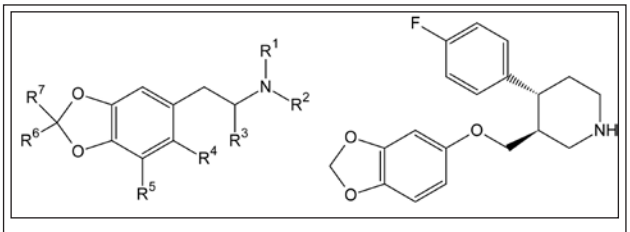

Figure 1 *Entactogens' general formula and structure of paroxetine. R1 = H or CH3; R2 = H, CH3, CH2CH3, CH2CH2CH3, CH2CH2CH2CH3, CH2(CH3)CH3, CH2CH=CH2, CH2C≡CH, CH2C3H5, CH2C6H5, OH, CH2CH2OH, OCH3 or CH2CH2OCH3; R3 = H, CH3, CH2CH3 or CH2CH2CH3; R4 = H or OCH3, R5 = H, CH3, or OCH3; R6 = H, F or CH3; R7 = H or F.*

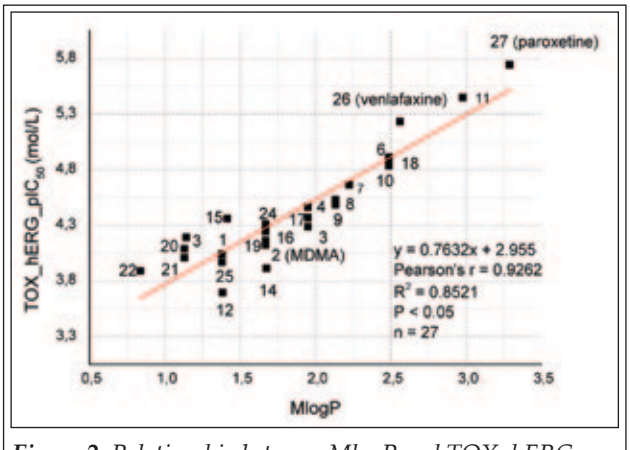

Figure 2 *Relationship between MlogP and TOX_hERG, the affinity for the hERG potassium channel calculated for entactogens and references by ADMET Predictor™*

Lipophilicity (MlogP) was the only physicochemical parameter linearly correlated with cardiotoxicity expressed as hERG_pIC_{50} (mol/L), although TOX_hERG was not predicted to be TOX_risk by ADMET Predictor™ (***Figure 2***). A linear correlation was also observed between MlogP and oral toxicity LD_{50} (mg/mL) predicted by MetaTox software (***Figure 3***). The toxicity between entactogens and their most toxic metabolites is shown in

Table 1 *Predicted ADMET codes for entactogens:1A2, 2C19 or 2D6 – excessive clearance by CYP 1A2, 2C19 or 2D6, respectively; Vd – volume of distribution; MUT – mutagenicity*

1A2	MDA, MDDM, MDOH, EIDA, 2,3-MDA
1A2, 2C19	MDMA, MDHOET, 5-MeMDA, MMDA, MMDPEA
1A2, 2C19, 2D6	MDBZ, MDMOET, BDB, MBDB;
V_d, 1A2, 2C19, 2D6	MDEA, MDPR, MDBU, MDIP, MDAL, MDCPM, paroxetine
MUT, 1A2, 2C19	MDMEO
V_d, MUT, 1A2, 2C19, 2D6	MDPL

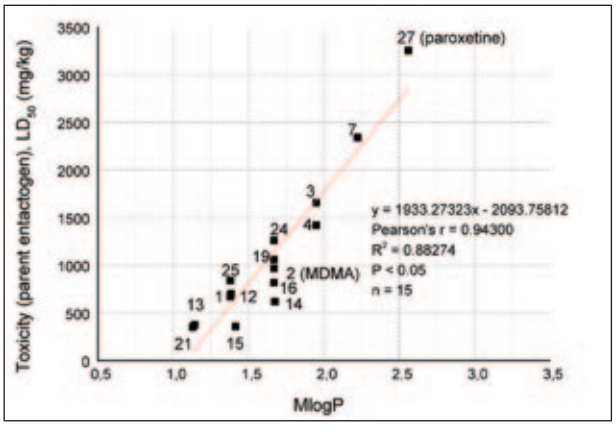

Figure 3 *Figure 3 Relationship between MlogP and oral toxicities (LD50 in mg/kg) of entactogens and paroxetine calculated by the MetaTox*

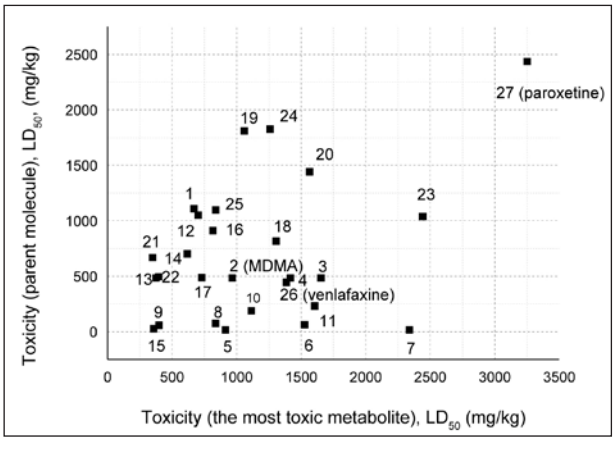

Figure 4 *Relationship between toxicity, calculated by MetaTox for entactogens and their most toxic metabolites primarily catalized by CYP enzymes and references paroxetine and venflaxine*

Figure 4. Toxicity analysis by the MetaTOX web application revealed the following main side effects:

Hepatotoxicity– MDA (1), MDMA (2), MDDM (3), MDEA (4), MDPR (5), MDBU (6), MDIP (7), MDPL (9), MDBZ (11), MDOH (12), MDMEO (14), Ethyl-K (18), MMDA-2 (21), 2,3-MDA (25) and venlafaxine (26); *Cardiac arrhythmia* – paroxetine; *Heart failure* – MDHOET (13) and MDMOET (15); *Myocardial infarction and heart failure* – DiFMDA (23); *No predicted side effect* – MDAL (8), MDCPM (10), BDB (16), MBDB (17), 5-MeMDA (19), MMDA (20), MMDPEA (22) and EIDA (24).

Membrane transporters (MT) can significantly affect the pharmacodynamics (PK) and pharmacokinetics (PD) of drugs, contributing to drug-drug interactions that very often lead to side effects or even serious toxic effects. The study of affinity to membrane transporters of entactogens and references paroxetine and venflaxine by ADMET Predictor™ revealed that they interact *via* transporters Pgp (P-glycoprotein, ABCB1), OCT1 and OCT2 (organic cation transporter 1 and 2), OAT3 (organic anion transporter 3), and BCRP (breast cancer resistance protein) as substrates, while the affinity of inhibitors was predicted mainly for OCT1 and OCT2.

Substrates of *Pgp* (MDPL, MDHOET, MMDPEA and paroxetine); *OCT1* (MDA, MDDM, MDOH, MDMEO, BDB, 5-Me-MDA, MMDA, MMDA-2, MMDPEA, DiFMDA, EIDA and 2,3-MDA); *OCT2* (all except DiFMDA, paroxetine and venflaxine); *OATP1B1* (MDDM); *OAT3* (MDOH and MDMEO); *OAT2* (MDPL); *BCRP* (DiFMDA and venflaxine);

Inhibitors – *Pgp* (venflaxine); *OCT1* (MDDM, MDEA, MDPR, MDBU, MDIP, MDAL, MDPL, MDCPM, MDBZ, MBDB, Ethyl-K, 5-Me-MDA, venflaxine); *OCT2* (the same as for OCT1 except MDMEOET, 5-Me-MDA, plus paroxetine); *OAT3* (MDMEO).

4. Conclusions

There are limited data on the potential toxicity of many of the entactogens abused today. Therefore, the results of this *in silico* study provide useful information on their potential toxic effects as well as their potential for drug-drug-interactions (DDI). QSAR analysis revealed a high linear correlation between MlogP and toxicity parameters (hERG_ pIC_{50} in mol/L, and oral toxicity LD_{50} in mg/kg), and this finding may be useful in predicting these

properties for the new entactogens. Misuse of entactogens in parallel with usual drug therapy may affect the therapeutic outcome due to their affinity for the same membrane transporters.

5. Acknowledgements

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References

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