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Synthetic cannabinoids: In silico prediction of the cannabinoid receptor 1 affinity by a quantitative structure-activity relationship model

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HIGHLIGHTS

- QSAR prediction is a simple, fast and cheap tool to get a first hint of the biological activity of new synthetic cannabinoids.
- The Pearson ratio (R^2) of the presented QSAR model was 0.78 (maximum performance: $R^2 = 0.81$).
- Not every new synthetic cannabinoid, which is used by consumers, provide higher CB1 affinity than THC.

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ABSTRACT

The number of new synthetic psychoactive compounds increase steadily. Among the group of these psychoactive compounds, the synthetic cannabinoids (SCBs) are most popular and serve as a substitute of herbal cannabis. More than 600 of these substances already exist. For some SCBs the *in vitro* cannabinoid receptor 1 (CB1) affinity is known, but for the majority it is unknown.

A quantitative structure-activity relationship (QSAR) model was developed, which allows the determination of the SCBs affinity to CB1 (expressed as binding constant (Ki)) without reference substances. The *chemically advance template search* descriptor was used for vector representation of the compound structures. The similarity between two molecules was calculated using the *Feature-Pair Distribution Similarity*. The Ki values were calculated using the *Inverse Distance Weighting* method. The prediction model was validated using a cross validation procedure.

The predicted Ki values of some new SCBs were in a range between 20 (considerably higher affinity to CB1 than THC) to 468 (considerably lower affinity to CB1 than THC).

The present QSAR model can serve as a simple, fast and cheap tool to get a first hint of the biological activity of new synthetic cannabinoids or of other new psychoactive compounds.

1. Introduction

Since the first synthetic cannabinoids hit the market in the late 2000s, the abuse of new synthetic psychoactive compounds have become a worldwide trend. These compounds are marketed as so called "legal highs" and can be easily and legally purchased *via* the internet or in local shops in most countries. The synthetic "legal highs" are predominantly derivatives and analogues of existing drugs, pharmaceutical products, previously developed lead compounds, or naturally occurring compounds (Elliott and Evans, 2014). They can be roughly divided into groups such as cannabinoids ("Spice"), drug mimetics, and phenethylamines ("Research Chemicals") like amphetamine derivatives or cathinones ("Bath Salts"). Among those, the synthetic cannabinoids (SCBs) are the most popular and serve as a substitute of herbal cannabis (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2014).

Abbreviations: SCBs, synthetic cannabinoids; CB1, cannabinoid receptor 1; QSAR, quantitative structure-activity relationship; Ki, binding constant; CATS, chemically advance template search; PPP, potential pharmacophore points; FPDSim, feature-pair distribution similarity; IDW, inverse distance weighting.

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SCBs were originally developed to modulate the cannabinoid receptor 2 (CB2) (Huffman, 2000, 2005; Anand et al., 2009), which is mainly located on immune cells (*e.g.* T cells, macrophages, monocytes, B cells) and plays an important role in the modulation of the immune system. Cannabinoids may provide beneficial effects in several diseases and disorders like Alzheimer's (Aso and Ferrer, 2014; Aso et al., 2015), anxiety disorders (Blessing et al., 2015), multiple sclerosis (Notcutt, 2015), epilepsy (Rosenberg et al., 2015), chemotherapy induce nausea and vomiting (Smith et al., 2015), or neuropathic and cancer pain (Jensen et al., 2015), but the medical use of cannabinoids is still under discussion (Whiting et al., 2015). As side effect, the SCBs exhibit some activity on the cannabinoid receptor 1 (CB1), which is mainly located in the central nervous system (*e.g.* cortical and subcortical regions, cerebellar cortex, brain stem). CB1 mediates, among others, psychoactive effects and very likely leads to euphoria, talkactiveness, altered visual and acoustical perception, and changes in sense of time after cannabinoid consumption. Nowadays, for abuse SCBs are intentionally created as modulators of CB1. The lead structures of the most common SCBs are well known from studies of *e.g.* Huffman (2000) (c.f. Fig. 1). Recently, several review and research papers appeared dealing with these substances (Elsohly et al., 2014; Lewin et al., 2014; Wiley et al., 2014). The number of synthesised SCBs worldwide is still unknown, official statistics are missing. Since 2008 the number of new SCBs in the EU is constantly increasing. In 2010 a prevalence of SCB use of 2.8% among drivers was found (Jaenicke et al., 2014). In 2013, 81 new psychoactive compounds were noted by the member states of the EU for the first time through the EU Early Warning System (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2014). Twenty-nine (36%) of these substances are SCBs (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2014).

At present, the total number of existing SCBs is estimated to be more than 600 substances, as one of the biggest suppliers for forensic reference substances, the Cayman Chemicals Company, offered about 630 reference substances in the category cannabinoids in June 2014 (Cayman Chemicals Company, 2014). For few SCBs the *in vivo* activity has been studied (Marshell et al., 2014) and for some the *in vitro* CB1 affinity is known (Wiley et al., 2014), but for the majority – especially for the totally new synthesised SCBs – the pharmacological activity or the *in vitro* CB1 affinity is unknown. To perform *in vivo* pharmacological studies for all SCBs seems impossible due to their high number. Thus, *in vitro* pharmacological assays are helpful to get a first idea of the pharmacological potential of these compounds. However, *in vitro* assays are time consuming and costly and depend on the availability of appropriate reference substances. On the other hand, it seems likely that new SCBs will appear in ever shorter time intervals in future due to the dynamic of the illicit drug market.

Under these aspects it is desirable to have a method available, which is useful to determine the CB1 affinity of SCBs within a short time, with low costs and without any reference substances. In order to meet these criteria, a computer aided *in silico* method was developed to predict the CB1 affinities, expressed as binding constant (Ki), of different SCBs based on their molecular structure and CB1 affinity data from the free ChEMBL database (European Bioinformatics Institute, 2012; Gaulton et al., 2012). Similar approaches for the prediction of CB1 and CB2 receptor affinities have been developed by other researchers (Myint, 2012; Chen et al., 2013; Mella-Raipán et al., 2014; Myint and Xie, 2015). However, these methods are more complex and may involve longer development time. The advantage of the present method is the short development time, the robustness and low costs.

2. Theory and calculations

2.1. In silico *prediction model*

It is generally assumed that molecules with similar structure exhibit similar biological activity (Johnson et al., 1989). Thus, the comparison of the structure of well known molecules and of a novel compound may provide a first idea of the biological activity,

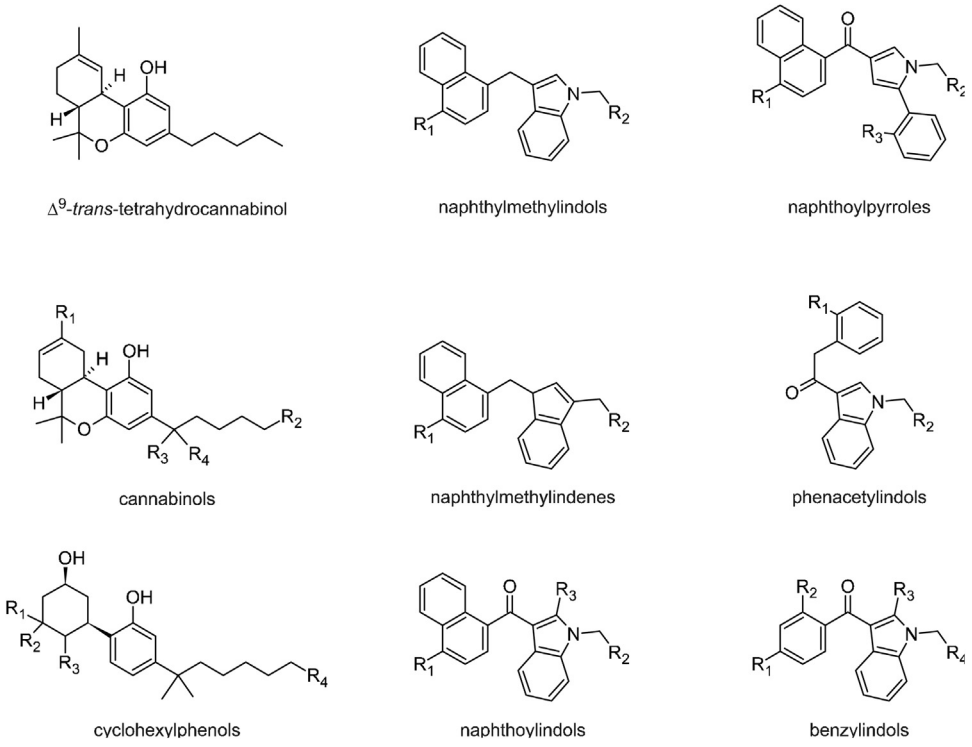

Fig. 1. Structure of Δ^9-trans-tetrahydrocannabinol (THC) and lead structures of SCBs used in "Spice" (Huffman, 2000).