Quantitative structure activity relationships—Part V. Release and uptake of norepinephrine in murine heart by phenethylamines

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Abstract. Quantitative structure activity studies have been carried out on a series of hydroxyphenethylamines. The calculated Fujita-Ban group contributions indicate that the $m$ and $p$-hydroxyphenethylamines have high affinity for uptake and efflux of radioactive norepinephrine. The highly negative contribution of the $-\text{OH}$ group at the second ortho position indicates that the derivatives with hydroxyl groups at both the ortho positions should have no activity or extremely low activity as inhibitors of uptake and as releasing agents.

Keywords. Fujita-Ban calculations; norepinephrine; phenethylamines.

1. Introduction


The present paper embodies quantitative structure-activity studies concerning the effects of hydroxyl groups from various positions in phenethylamine on in vivo inhibition of uptake of $[^3\text{H}]$ norepinephrine into, and its release from, murine heart.

2. Method and data set

For phenethylamine(I) and its hydroxy derivatives Rotman et al (1975) have assayed inhibition of uptake and release of radioactive norepinephrine by measurement of
tritium content of the cardiac tissue. Inhibition of uptake has been assayed 20 minutes after intravenous administration of the test compound and \[^{[H]}\]-DL-norepinephrine whereas the affinity to release norepinephrine has been assayed three hours after intravenous administration of the test compound and double the amount of \[^{[H]}\]-DL-norepinephrine. Both these activities have been expressed in terms of \(ED_{50}\) (mol/kg).

In the present work the observed activity, however, refers to \(- \log ED_{50}\) where \(ED_{50}\) is taken in mol/kg units. The present quantitative structure-activity studies are carried out in the light of the Fujita-Ban de novo model (Fujita and Ban 1971) because the purpose of this study is to quantify the effect of hydroxyl group at different positions in the aromatic ring of phenethylamine. The group contributions have been calculated as per Kubinyi’s algorithm of converting the Fujita-Ban matrix into normal equations matrix followed by simultaneous equations’ solution by any of the standard methods (Kubinyi 1977). A computer program FUKUB, fully incorporating this algorithm was developed by the author and used for the present work. All data were processed on the DECsystem-2050 at the Regional Computer Centre (North), Chandigarh, India.

3. Results

The structures, observed activities and Fujita-Ban matrix for phenethylamines exhibiting inhibition for uptake of norepinephrine are given in table 1. This information about phenethylamines eliciting release of norepinephrine is collected in table 2. Both these sample sets are statistically unbiased as the observed activity is found to vary about two log units which corresponds to 100-fold difference in activity. Tables 3 and 4 respectively contain the normal equations matrices corresponding to the Fujita-Ban matrices in tables 1 and 2. In tables 3 and 4 \(\mu_0\) represents contribution by the unsubstituted arbitrary reference (phenethylamine) and \(\lambda_X\) represents the contribution by the group \(X\). The group contributions calculated in the two cases (figure 1) lead to the following correlations.

\[- \log ED_{50} \text{ (uptake)} = 5.80 - 0.40 \times [2-OH] + 0.36 \times [3-OH] + 0.27 \times [4-OH] + 0.003 \times [5-OH] - 1.10 \times [6-OH]\]

\[n = 15; \quad r = 0.806; \quad s = 0.416\]  

(1)

\[- \log ED_{50} \text{ (release)} = 3.87 - 0.39 \times [2-OH] + 0.36 \times [3-OH] + 0.50 \times [4-OH] + 0.42 \times [5-OH]\]

\[n = 14; \quad r = 0.755; \quad s = 0.468\]  

(2)

It is observed that these correlations are significant almost at 95% level.

4. Discussion

4.1. Inhibition of uptake of norepinephrine

It is evident from the contributions of hydroxyl group at different positions (figure 1a) that phenethylamines with \(-OH\) substituent at \(m\) or/and \(p\)-positions