Supplementary Information

Expeditious synthesis of isolated steroids-fluorine prodrugs, their single crystal X-ray crystallography, DFT studies and mathematical modeling

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Mathematical modelling

Appendix A

To prove Lemma (4.3.1.1)

Proof. Let (R, S, P) be solution with positive initial values (R_0, S_0, P_0). From system (4.3.1), we get

$$\frac{dR}{dt} \leq A_1 - h_c - \mu R. \tag{A.1}$$

According to comparison principle, it follows that

$$R_m = \frac{A_1 - h_{1c}}{\mu}. \tag{A.2}$$

R_m is always positive if $A_1 > h_{1c}$.

Now from the system (4.3.1), we get

$$\frac{dS}{dt} \le A_2 - h_c - \mu_1 S. \qquad \text{(A.3)}$$

According to comparison principle again, we get

$$S_m = \frac{A_2 - h_{1c}}{\mu_1}. \qquad \text{(A.4)}$$

S_m is always positive if $A_2 > h_{1c}$

Again from the system (4.3.1),we have

$$\frac{dP}{dt} \le \frac{\beta R_m S_m}{a} + h_c - \beta_0 P. \qquad \text{(A.5)}$$

According to comparison principle again, we get

$$P_m = \frac{\beta R_m S_m + a h_c}{a \beta_0}. \qquad \text{(A.6)}$$

This completes the proof of lemma.

Appendix B

For finding the condition of global stability at $E(R^*, S^*, P^*)$ in region Ω we construct the Lyapunov function

$$H = \frac{1}{2}(R - R^*)^2 + \frac{1}{2}(S - S^*)^2 + \frac{1}{2}(P - P^*)^2. \qquad \text{(B.1)}$$

Differentiating H with respect to time t along the solutions of the system (4.3.1), we get

$$\frac{dH}{dt} = (R - R^*)\frac{dR}{dt} + (S - S^*)\frac{dS}{dt} + (P - P^*)\frac{dP}{dt}. \qquad \text{(B.2)}$$

Using system of equations (4.3.1), we get after some algebraic manipulations as

$$\begin{aligned}\frac{dH}{dt} = & -\frac{a\alpha S^*}{(a+R^*)(a+R)}(R-R^*)^2 - \frac{\alpha R^*}{(a+R^*)}(S-S^*)^2 - \beta_0 (P-P^*)^2 \\ & + \left(-\frac{aR}{a+R} - \frac{a\alpha S}{(a+R)(a+R^*)}\right)(R\text{-}R^*)(S-S^*) \qquad \text{(B.3)} \\ & + \frac{a\beta S}{(a+R)(a+R^*)}(R\text{-}R^*)(P-P^*) + \frac{\beta R^*}{a+R^*}(S\text{-}S^*)(P\text{-}P^*).\end{aligned}$$

Then $\frac{dH}{dt}$ to be negative definite, the following inequality must hold.

$$\left(R_m + \frac{\alpha S_m}{(a+R^*)}\right)^2 < 2\frac{a\alpha^2 R^* S^*}{(a+R^*)(a+R_m)}, \qquad \text{(B.4)}$$

$$\left(\frac{\beta S_m}{(a+R^*)}\right)^2 < \frac{a\alpha\beta_0 S^*}{(a+R^*)(a+R_m)}, \text{(B.5)}$$

$$\left(\frac{\beta R^*}{a+R^*}\right)^2 < 2\frac{\alpha R^* \beta_0}{(a+R^*)}. \qquad \text{(B.6)}$$

This shows that equilibrium point $E(R^*, S^*, P^*)$ is globally stable in the region Ω.

Appendix C

From first equation of the system (4.3.1), we have

$$\frac{dR}{dt} \geq A_1 - h_c - (\alpha S_m + \mu)R, \qquad \text{(C.1)}$$

According to lemma 4.3.1.1 and comparison principle, it follows that

$$R_{\min} = \frac{A_1 - h_1}{\alpha S_m + \mu}. \qquad \text{(C.2)}$$

With condition $A_1 > h_{1c}$, $R_{\min}$ remains always positive. From second equation of the system (4.3.1) , we have

$$\frac{dS}{dt} \geq A_2 - h_c - (\alpha\, R_m + \mu_1)S, \qquad \text{(C.3)}$$

According to lemma 4.3.1.1 and comparison principle, it follows that

$$S_{\min} = \frac{A_2 - h_c}{\alpha\, R_m + \mu_1}. \qquad \text{(C.4)}$$

With condition $A_2 > h_{1c}$, $S_{\min}$ remains always positive.

From the second last equation of the system (4.3.1) , we have

$$\frac{dP}{dt} \geq \frac{\beta R_{\min} S_{\min}}{a + R_m} + h_c - \beta_0 P. \qquad \text{(C.5)}$$

Using comparison principle, it follows that

$$P_{\min} = \frac{\beta\, R_{\min} S_{\min} + (a + R_m)h_c}{(a + R_m)\beta_0}. \qquad \text{(C.6)}$$

This completes the proof of the theorem. Thus, system (4.3.1) persists if $A_1 > h_{1c}$ and $A_2 > h_{1c}$

4.3.1 Boundedness of the System

In the following lemma, we state the bounds of the various variables which would be needed in our study.

Lemma(4.3.1.1) The set $\Omega = \{(R,S,P): 0 \leq R \leq R_m, 0 \leq S \leq S_m \text{ and } 0 \leq P \leq P_m\}$, is the region of attraction for all solutions initiating in the interior of the positive octant,

where $R_m = \dfrac{A_1 - h_c}{\mu}, S_m = \dfrac{A_2 - h_c}{\mu_1}$ *and* $P_m = \dfrac{\beta\, R_m S_m + h_c a}{a\, \beta_0}$ with conditions $A_1 > h_{1c}, A_2 > h_{1c}$..For proof, see Appendix A.

4.3.2 Equilibrium Analysis:

The system (4.3.1) has only one nonnegative equilibrium point $E\left(R^*, S^*, P^*\right)$.

Here R^*, S^* and P^* are the positive solutions of the following equations:

$$A_1 - \frac{\alpha\, R^*\, S^*}{a + R^*} - \mu\, R^* - h_c = 0, \qquad (4.3.2.1)$$

$$A_2 - \frac{\alpha\, R^*\, S^*}{a + R^*} - \mu_1\, S^* - h_c = 0, \qquad (4.3.2.2)$$

$$\frac{\beta\, R^*\, S^*}{a + R^*} + h_c - \beta_0 P^* = 0, \qquad (4.3.2.3)$$

From equations (4.3.2.2) and (4.3.2.3), we get

$$P^* = \frac{\beta\, R^* S^* + h_c\left(a + R^*\right)}{\left(a + R^*\right)\beta_0}, S^* = \frac{\left(A_2 - h_c\right)\left(a + R^*\right)}{\alpha\, R^* + \mu_1\left(a + R^*\right)}. \qquad (4.3.2.4)$$

Putting the value of P^* and S^* from the equation (4.3.2.4) in the equation (4.3.2.1), we get following equation

$$F\left(R^*\right) = p_1 R^{*3} + p_2 R^{*2} + p_3 R^* + p_4 = 0. \qquad (4.3.2.5)$$

Where $p_1 = \mu\left(\alpha + \mu_1\right)$,

$$p_2 = \left(A_2 - h_c\right)\alpha + \mu\mu_1 a + \mu\, a\left(\alpha + \mu_1\right) - \left(A_1 - h_c\right)\left(\alpha + \mu_1\right),$$

$$p_3 = \left(A_2 - h_c\right)\alpha\, a + \mu\mu_1 a^2 - \left(A_1 - h_c\right)\mu_1 a - \left(A_1 - h_c\right)\left(\alpha + \mu_1\right)a,$$

$$p_4 = -\left(A_1 - h_c\right)\mu_1 a^2.$$

From (4.3.2.5), we have

$$F(0) = -\left(A_1 - h_c\right)\mu_1 a^2 < 0\ . \qquad (4.3.2.6)$$

$$F\left(R_m\right) = p_1 R_m^3 + p_2 R_m^2 + p_3 R_m + p_4 > 0. \qquad (4.3.2.7)$$

Thus there exists a R^*, $0 < R^* < R_m$, such that $F(R^*) = 0$.

Now, the sufficient condition for the uniqueness of E is $F^{'}(R^{*})>0$ .For this we find $F^{'}(R^{*})>0$ from (4.3.2.5) as follows.

$F^{'}(R_m)=3p_1R_m^2+2p_2R_m+p_3>0.$(4.9.2.8)

This completes the existence of E.

4.3.3.1 Local Stability

To discuss the local stability of system (4.3.1) as follows,

$$V(E)=\begin{bmatrix} e_{11} & e_{12} & 0 \\ e_{21} & e_{22} & 0 \\ e_{31} & e_{32} & e_{33} \end{bmatrix}.$$

Where the entries in the matrix are

$$e_{11}=-\frac{a\alpha S^{*}}{(a+R^{*})^2}-\mu, e_{12}=-\frac{\alpha R^{*}}{a+R^{*}}, e_{21}=-\frac{a\alpha \mathrm{S}^{*}}{(a+R^{*})^2}, e_{22}=-\frac{\alpha R^{*}}{a+R^{*}}-\mu_1,$$
$$e_{31}=\frac{a\beta S^{*}}{(a+R^{*})^2}, e_{32}=\frac{\beta R^{*}}{a+R^{*}}, e_{33}=-\beta_0.$$

The characteristic polynomial corresponding to equilibrium point $E(R^{*},S^{*},P^{*})$ is given by

$$\lambda^3+q_1\lambda^2+q_2\lambda+q_3=0,$$

where $q_1=-e_{11}-e_{22}-e_{33}, q_2=e_{11}e_{22}+e_{11}e_{33}+e_{22}e_{33}-e_{12}e_{21}, q_3=e_{12}e_{21}e_{33}-e_{11}e_{22}e_{33}$.

Then by Routh-Hurwitz criteria equilibrium point $E(R^{*},S^{*},P^{*})$ is locally asymptotically stable if $q_1>0, q_2>0$ and $q_1q_2>q_3$ and unstable if either of these conditions is not satisfied.

4.3.3.2 Global Stability

The following theorem characterizes the global stability behaviour of equilibrium point $E(R^*, S^*, P^*)$.

Theorem 4.3.3, Let the following inequalites hold:

$$\left(R_m + \frac{\alpha S_m}{(a+R^*)}\right)^2 < 2\frac{a\alpha^2 R^* S^*}{(a+R^*)(a+R_m)},$$

$$\left(\frac{\beta S_m}{(a+R^*)}\right)^2 < \frac{a\alpha\beta_0 S^*}{(a+R^*)(a+R_m)},$$

$$\left(\frac{\beta R^*}{a+R^*}\right)^2 < 2\frac{\alpha R^* \beta_0}{(a+R^*)}.$$

Then equilibrium point $E(R^*, S^*, P^*)$ is globally stable in the region Ω. For proof, see Appendix B.

4.3.4 Persistence

Theorem 4.9.4 Assume that $A_1 > h_c$ and $A_2 > h_c$. Then system (4.3.1) persists. For proof, see Appendix C.

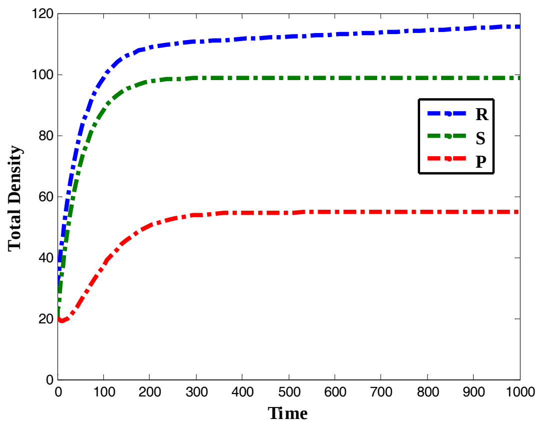

Figure S1. Stable behavior of R, S and P with time and other parameter values are same as (4.9.1).

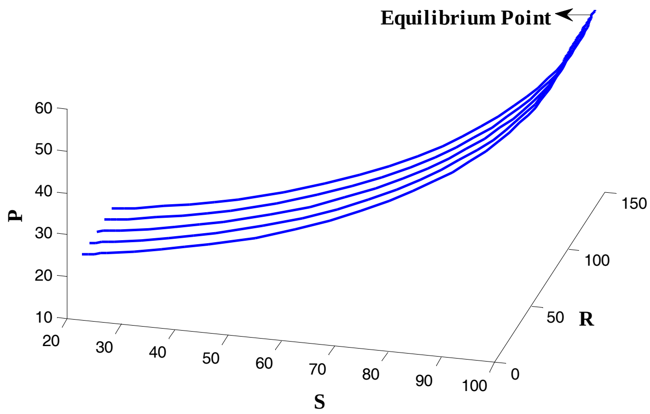

Figure S2. Global behavior of the System.

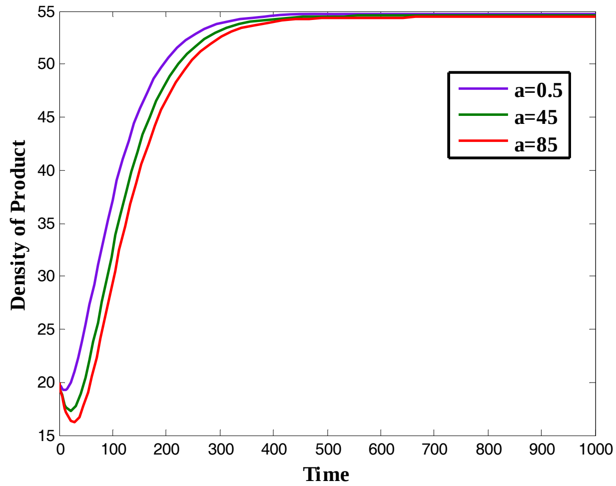

Figure S3. Effect of moisture on the reaction.

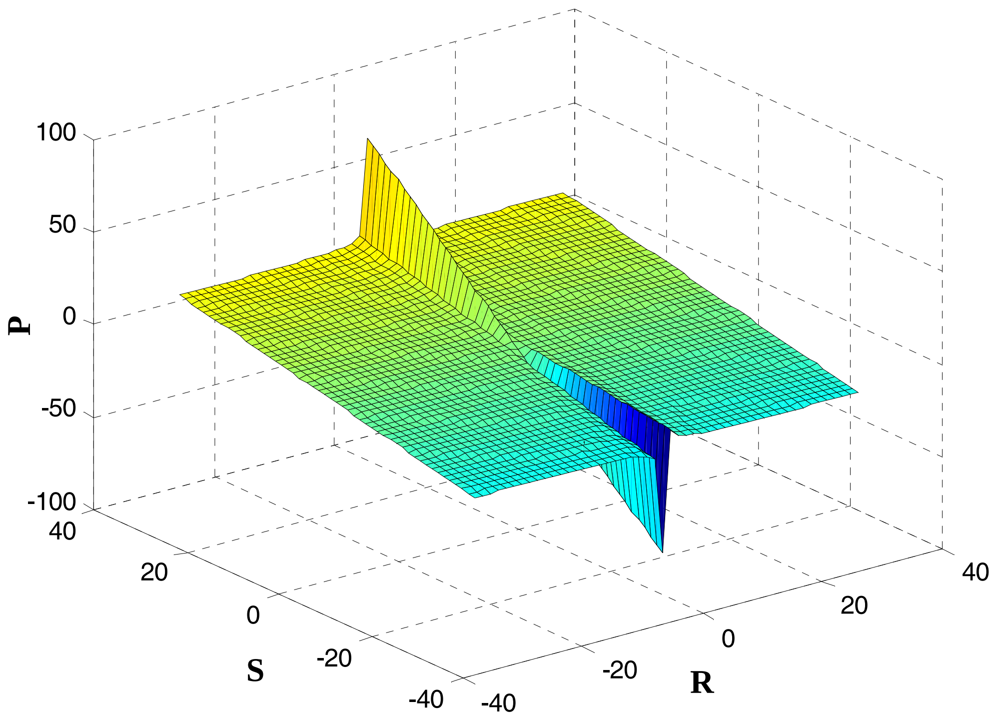

Figure S4. Stability behavior of the system in 3D view.