Divergent Syntheses and Biological Evaluations of New Artificial Glutamate Analogs

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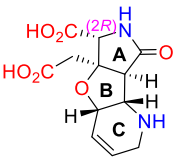
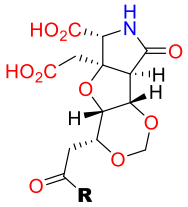
(2*R*)–IKM–159, a hybrid of two neuroactive natural products (dysiherbaine and kainic acid), was designed and synthesized in our laboratory.[1] Reasonably, IKM–159 was later identified as an antagonist selective to subtypes of AMPA-type ionotropic glutamate receptor. To study the structure–activity relationships, and to develop probes for the receptor, we synthesized new analogs (TKM–50, TKM–86, TKM–99) bearing dioxane ring for the C–ring by the novel three-component oxa–Michael reaction.

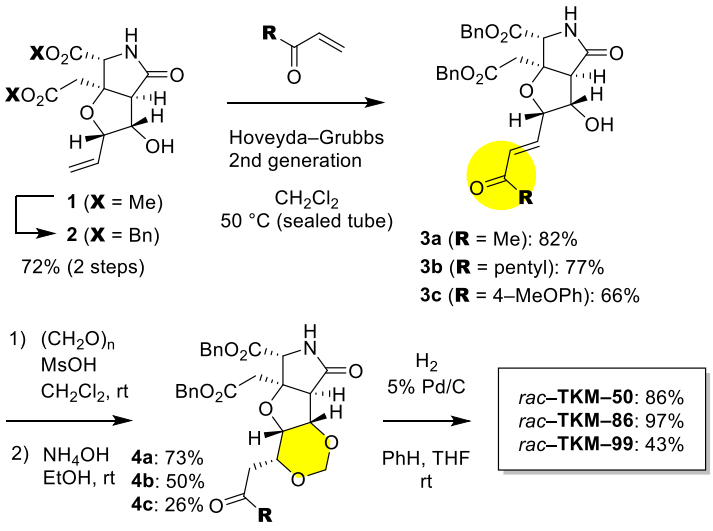


(2*R*)–**IKM–159**
AMPA receptor antagonist



rac–**TKM–50** (**R** = Me)
rac–**TKM–86** (**R** = pentyl)
rac–**TKM–99** (**R** = 4–MeOPh)

The known dimethyl ester **1**,[2] prepared over 8 steps starting with four-component coupling reaction, was converted to dibenzyl ester **2** by acidic hydrolysis (6M HCl) followed by esterification with BnBr. As a common intermediate in the present study, **2** was subjected to cross metathesis mediated by Hoveyda–Grubbs 2nd generation catalyst with three vinyl ketones to furnish enones **3a**–**3c**. Upon exposure to paraformaldehyde in the presence of MsOH, dioxane ring formed smoothly by oxa–Michael reaction to give rise to heterotricycles **4a**–**4c** in reasonable yields after alkaline hydrolysis of the *N*–hydroxymethyl group generated. Finally, dibenzyl ester groups were removed by hydrogenolysis to provide glutamate analogs TKM–50, TKM–86, and TKM–99. The syntheses and *in vivo* activities will be presented.



1) M. B. Gill, S. Frausto, M. Ikoma, M. Sasaki, M. Oikawa, R. Sakai and G. T. Swanson, *Br. J. Pharmacol.*, **2010**, *160*, 1417-1429. 2) M. Chiba, C. Fujimoto, R. Sakai and M. Oikawa, *Bioorg. Med. Chem. Lett.*, **2015**, *25*, 1869-1871.