國立臺灣大學技術行銷表

臺大案號: 10A-101228

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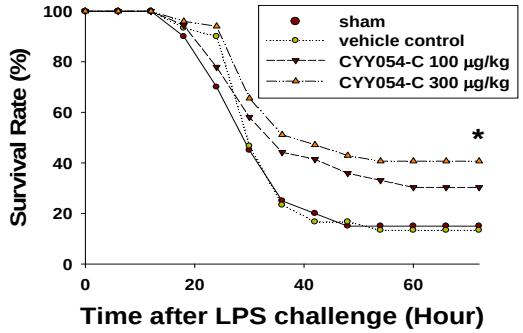
技術名稱	藥物 CYY 系列化合物用於敗血症之治療
發明人/單位	蘇銘嘉/醫學院藥理學科、忻凌偉/藥學系
技術內容	以香草醛（vanillin）為起使原料，經由比許勒－內皮勞斯基合環反應（Bischler-Napieralsky reaction）、親電子的芳香環取代反應（electrophilic aromatic substitution reaction）以及鈴木反應（Suzuki reaction）等關鍵步驟，成功合成得到一系列具有八苯基異喹林（8-phenylisoquinoline）核心骨架的新穎化合物。這些八苯基異喹林衍生物在不同的生物體外及體內試驗中，都展現了良好的生物活性，具有進一步開發應用的潛力。此系列中化合物 CYY054-C 對於 5-HT_{2A} receptor 之 Ki 值為 3.47 nM，其親和力及專一性大於目前市面上 5-HT_{2A} receptor antagonist-sarpogrelate(對 5-HT_{2A} receptor 之 Ki 值為 8.39 nM)，並接近於另一種 antagonist – ketanserin(對 5-HT_{2A} 之 Ki 值約為 3.5 nM)，然而 CYY054C 對於 α_1-adrenoceptor 之親和力明顯小於 ketanserin (α_1-adrenoceptor Ki 值分別為 521 nM 及 40 nM)，因此 CYY054C 具有更佳的專一性；對於 5-HT 增強 collagen 引發之血小板凝集，CYY054C 有明顯抑制作用，也可抑制 5-HT 所引發之血管平滑肌收縮，並於小鼠腹腔注射內毒素 (lipopolysaccharide) 誘發毒血症 (endotoxaemia)之敗血症模式中，可明顯減低小鼠死亡率。此外，此一系列之另二個化合物，CYY415 及 KSS041 對於 5-HT_{2A} receptor 之親和力(Ki 值分別為 0.119 nM 及 2.21 nM)更勝於 CYY054C，同樣極具發展潛力。
應用方式及預期產品說明	敗血症臨床治療用藥
技術創新度/優點	1. 本系列化合物為全新的化合物，從未被任何文獻報導，亦未被任何化合物專利所涵蓋，故具有新穎性及獲得專利之潛力。 2. 採用的合成方法具有步驟少、總產率高、可量產的優勢。可快速生產足夠的目標化合物，提供進一步的藥物開發所需。 3. 本案實施例涵蓋結構範圍廣，可提供較完整的專利保護。 4. CYY054C、CYY415，以及 KSS041 對與血清素受器 5-HT_{2A} 亞型之親和力高於現行藥物 sarpogrelate 及 ketanserin，且相對於 α_1-adrenoceptor 之選擇性更佳。 5. 於小鼠治療腹腔注射內毒素(Lipopolysaccharide) 引發血毒症(endotoxaemia)之敗血症模式，於誘發之後 12 小時開始投與本藥物治療可有效使存活率由 15%提高至 40.66%。具申請人知識所及，本藥物是唯一在誘發敗血症 12 小時候開始給予仍能有效提高存活率之藥物。
智慧財產權	專利申請中

圖片

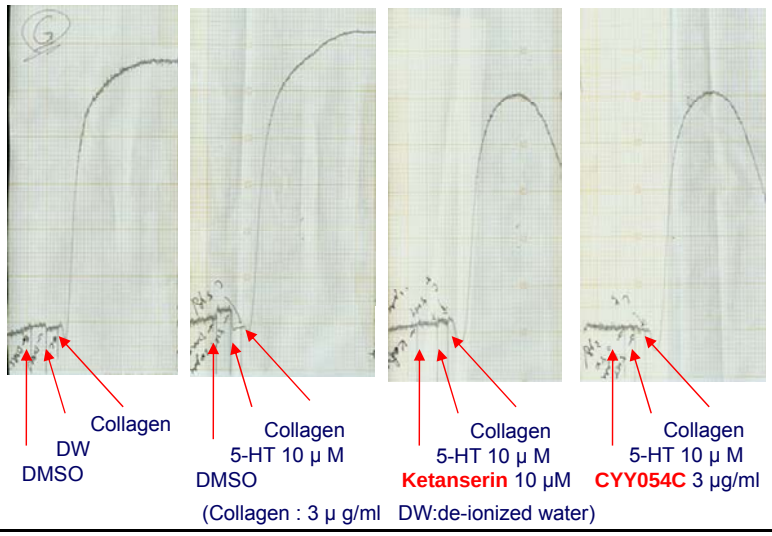
(已公開之成果可提供圖片)

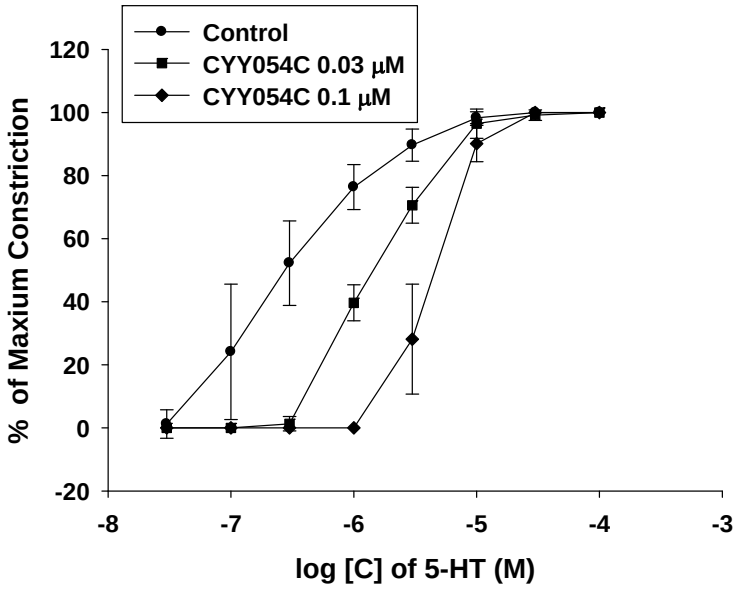
Protective effects of post-treatment of multiple doses of CYY054-C on LPS induced endotoxaemia in mice model.



12 hours after intraperitoneal injection of LPS 100 mg/kg, CYY 054-C 100 μg/kg or 300 μg/kg were administrated intraperitoneally or subcutaneously every 6 hour till 48 hours after LPS insults. Both CYY054-C 100 μg/kg and 300 μg/kg treatment shifted survive curve rightward significantly compared to vehicle control group ($p<0.01$.).Survival curves were compared by Log rank test, and 3 days survival rate were compared by chi square test.

CYY 054-C did not exert platelet activation, but inhibited 5-HT induced amplification of platelet aggregation





Marketing Abstract of NTU's Invention Disclosure

NTU's docket no: 10A-101228

CIAC contact：Wei-Chen Lou　　Tel：02-33669948　　e-mail：weichenlou@ntu.edu.tw

Title	CYY054-C and related compounds as new therapeutic agents for severe sepsis
Inventor (s)	Ming-Jai Su/Institute of pharmacology, Ling-Wei Hsin/School of pharmacy
Brief Description	A library of novel derivatives of 8-phenylisoquinoline are synthesized from vanillin by utilizing Bischler-Napieralsky reaction, electrophilic aromatic substitution reaction, and Suzuki reaction. Some of these derivatives exhibit high affinity and specificity to serotonin receptor subtype 5-HT_{2A} in *in vitro* and organ bath tests. CYY054-C, one of these derivatives, is a novel compound and has high affinity and selectivity to serotonin receptor subtype 5-HT_{2A}. CYY054-C can inhibit the amplification effects of serotonin in collagen induced platelets aggregation, and also it can antagonist the constriction effects of serotonin on rat de-endothelial descending aorta smooth muscle. On endotoxaemic mice induced by intra-peritoneal injection of lipopolysaccharide (LPS), intra-peritoneal administration of CYY054-C every 6 hour since 12 hours to 48 hours after LPS injection can increase survival rate.
Fields of Application	Clinical application for severe sepsis.
Advantages	1. These novel compounds are original and hopeful for take patents because these compounds have never been reported and the structures of these compounds are still open for patent. 2. The procedure of synthesizing these compounds is advantageous with less steps and high yield, hence the target compound is mass producible, which is beneficial for further medical development. 3. This application includes a wide range of structural derivatives, which can provide integrated protection of the patent. 4. The affinity of CYY054C, CYY415, and KSS041 to 5-HT_{2A} receptor (Ki value 3.47 nM, 0.119 nM, and 2.21 nM, respectively) is higher than 5-HT_{2A} antagonist Sarpogrelate and ketanserin. CYY054C has low affinity to α1-adrenoceptor while ketanserin acts as potent α1-adrenoceptor antagonist. 5. In mouse intra-peritoneal injection of LPS induced endotoxaemia model, administration of CYY054 300 μg/kg intrperitoneally 12 hr after LPS insult and then serially administration of CYY054C ever 6 hour till 48 hr after LPS insult can increase 3 days survival rate (40.66% compared to control group, 15.79%). To the best of our knowledge, CYY054C is the only one therapeutic agent which is administrated 12 hrs after LPS insult can reduce mortality.
IP Right(s)	Patent pending

Picture

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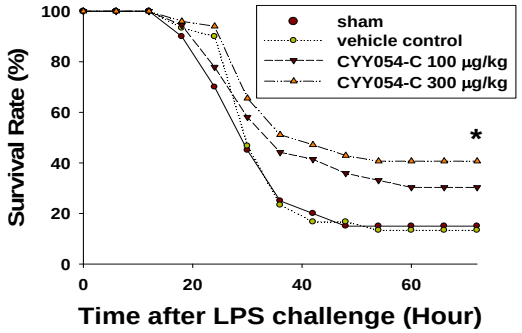

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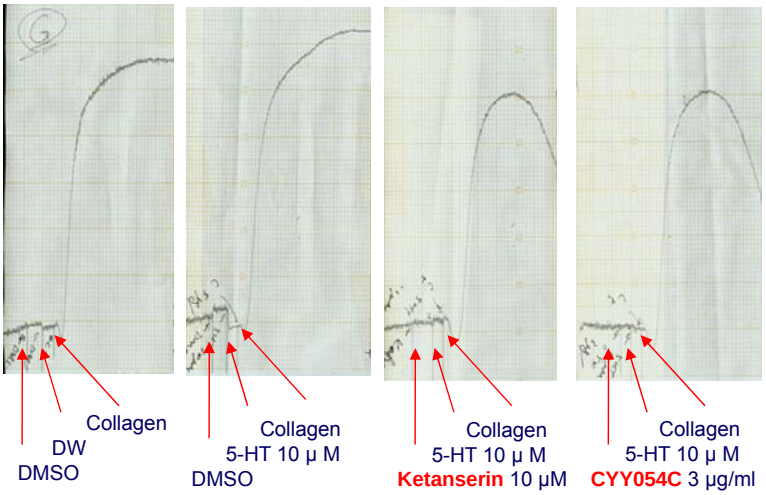

(Collagen : 3 μ g/ml DW:de-ionized water)

Effects of the CYY054-C on 5-HT induced vasoconstriction of de-endothelium rat thoracic descending aorta