OPEN ACCESS Freely available online

Journal of Clinical Chemistry and Laboratory Medicine

Research Article

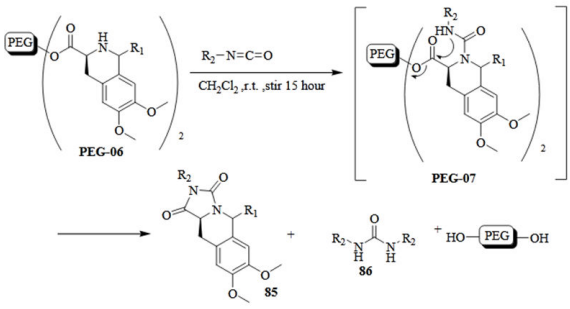
Synthesis and Pharmacological Evaluation of 1-Oxo-2-(3-Piperidyl)-1, 2, 3, 4-Tetrahydroisoquinolines as a New Class of Specific Bradycardic Agents Possessing I (F) Channel Inhibitory Activity: N-Methyl-D-Aspartate Receptor Modulators that Potentiates Glun2b-Containing N-Methyl-D-Aspartate Receptors

Suman Thummanagoti[1], Chih-Hau Chen[1], Zhan-Hui Xu[1], Chung-Ming Sun[1*]

[1]Department of Applied Chemistry, Laboratory of Combinatorial Drug Discovery, National Chiao Tung University, Hsinchu 300-10, Taiwan

ABSTRACT

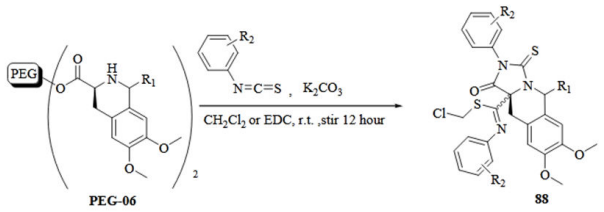
The test strategy is to use soluble polymer carrier polyethylene glycol (Poly ethylene glycol will be referred to as PEG for short) quantity 6000 or leave liquid carrier (Ionic-liquid support), coupled with the protected compound 80, for use with analogy Under acidic conditions, enter the row Pictet-Spengler reaction to obtain the desired heterocyclic compound tetrahydroiso-quinolines, profit use different cyanate (ioscyanate) and different cyanate (iosthiocyanate) under alkaline conditions to enter row cyclization cut to remove the carrier to obtain the second heterocycle , Such as Scheme 2-1. Several novel multicomponent assembly processes have been developed for the rapid and efficient assembly of various heterocyclic scaffolds bearing a tetrahydroisoquinoline core, each of which allows for facile derivatization to access a diverse array of compounds. This work led to the serendipitous discovery of a new method for the synthesis of a fused ring system.



***Correspondence to:** Chung-Ming Sun, *Department of Applied Chemistry, Laboratory of Combinatorial Drug Discovery, National Chiao Tung University, Hsinchu 300-10, Taiwan* , E-mail: cmsun@mail.nctu.edu.tw

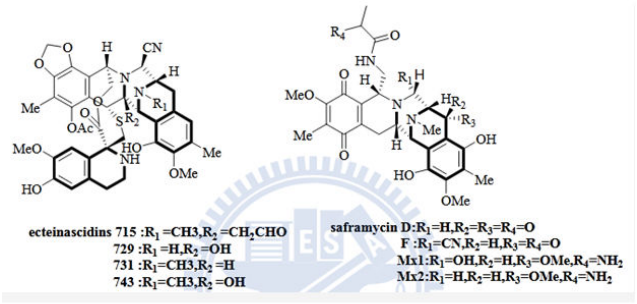
Received Date: June 11, 2021; **Accepted Date:** October 25, 2021; **Published Date:** November 05, 2021

Citation: Thummanagoti S, Chen CH, Xu ZH, Sun CM (2021) Synthesis and Pharmacological Evaluation of 1-Oxo-2-(3-Piperidyl)-1, 2, 3, 4-Tetrahydroisoquinolines as A New Class of Specific Bradycardic Agents Possessing I(F) Channel Inhibitory Activity: N-Methyl-D-Aspartate Receptor Modulators that Potentiates Glun2b-Containing N-Methyl-D-Aspartate Receptors. J Clin Chem Lab Med 4:p371.



INTRODUCTION

A series of 1-oxo-2-(3-piperidyl)-1, 2, 3, 4-tetrahydroisoquinolines and related analogues were prepared and evaluated for their bradycardic activities in isolated right atrium and in anesthetized rats. (+/) 6, 7 Dimethoxy 2 [1 [3 (3,4 methylenedioxyphenoxy)propyl] 3 piperidyl] 1,2,3,4 tetrahydroisoquinoline (4) was chosen as a lead, and structural modifications were performed on the tetrahydro isoquinoline ring and the terminal aromatic ring. The modifications on the tetrahydroiso uinoline ring revealed that the 1-oxo-1, 2, 3, 4-tetrahydroisoquinoline ring system was optimum structure for both in vitro potency and in vivo efficacy. Furthermore, methoxy, ethoxy, and methoxycarbonyl groups were identified as preferable substituents on the terminal aromatic ring. One of the 1-oxo-1, 2, 3, 4-tetrahydroisoquinoline derivatives, (R)-10a, was further evaluated for its bradycardic activity and inhibitory activity against I(f) currents. Compound (R) 10a demonstrated potent bradycardic activity in rats with minimal influence on blood pressure after oral administration. The compound also showed inhibition of I(f) currents (IC(50) = 0.32 muM) in guinea pig pacemaker cells. We have identified a series of positive allosteric NMDA receptor (NMDAR) modulators derived from a known class of GluN2C/D-selective tetrahydro isoquinoline analogues that includes CIQ. The prototypical compound of this series contains a single isopropoxy moiety in place of the two methoxy substituents present in CIQ. Modifications of this isopropoxy-containing scaffold led to the identification of analogues with enhanced activity at the GluN2B subunit. We identified molecules that potentiate the response of GluN2B/GluN2C/GluN2D, GluN2B/GluN2C, and GluN2C/GluN2D-containing NMDARs to maximally effective concentrations of agonist. Multiple compounds potentiate the response of NMDARs with sub micromolar EC50 values. Analysis of enantiomeric pairs revealed that the S-(−) enantiomer is active at the GluN2B, GluN2C, and/or GluN2D subunits, whereas the R-(+) enantiomer is only active at GluN2C/D subunits. These results provide a starting point for the development of selective positive allosteric modulators for GluN2B-containing receptors [1-10].



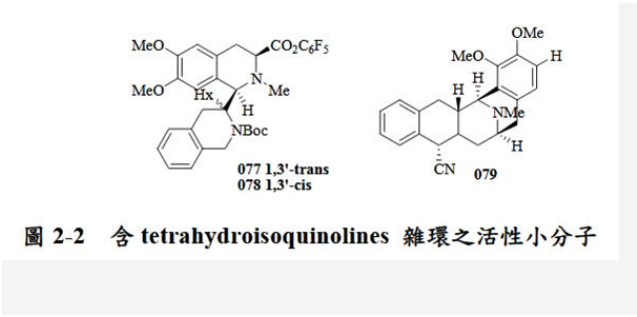


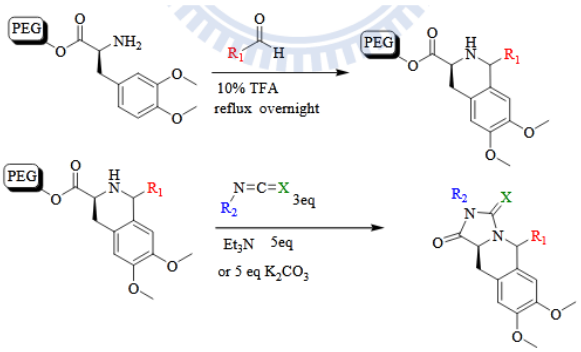
圖 2-2 含 tetrahydroisoquinolines 雜環之活性小分子

The addictiveness of a new synthetic isoquinolinc analgesic (I-K-1) has been compared with that of morphine, codeine, and D-propoxyphene in former opiate addicts. Single oral doses of 600 and 1,200 mg. of I-K-1 (ten to seventeen times the recommended anolgesic dose) did not induce subjective or objective patterns of morphine like effects. Intramuscularly and intravenously, I-K-1 was identified as an opiate, but it was not possible to give repeated doses of the drug by these routes because of its water insolubility and tissue irritant properties. When I-K-1 was substituted for morphine in patients addicted to morphine, it partially prevented development of withdrawal symptoms, but it was only one-seventh as potent as codeine in this respect. In a direct addiction test that lasted 60 days, using maximally tolerated doses (750 to 1,500 mg. orally daily), I-K-1 was disliked by former addicts and when it was discontinued abruptly withdrawal signs were insignificant. It is concluded that I-K-1 has substantially less addiction liability than morphine and codeine and even less addictiveness than D-propoxyphene. Nitrogen-containing heterocyclic compounds are an important class of molecules that are commonly used for the synthesis of candidate drugs. Phosphatidylinositol-4-phosphate 5-kinase-α (PIP5Kα) is a lipid kinase, similar to PI3K. However, the role of PIP5K1α in oncogenic processes and the development of inhibitors that selectively target PIP5K1α have not been

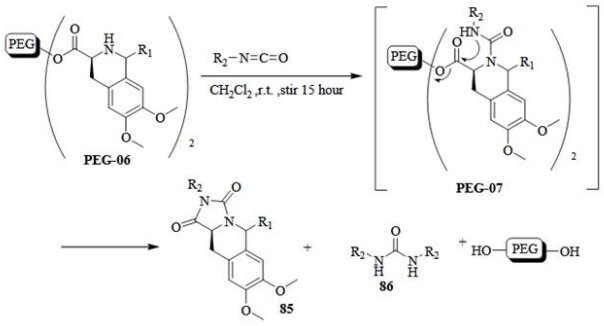
reported. In the present study we report that overexpression of PIP5K1α is associated with poor prognosis in prostate cancer and correlates with an elevated level of the androgen receptor. Overexpression of PIP5K1α in PNT1A nonmalignant cells results in an increased AKT activity and an increased survival, as well as invasive malignant phenotype, whereas siRNA-mediated knockdown of PIP5K1α in aggressive PC-3 cells leads to a reduced AKT activity and an inhibition in tumor growth in xeno graft mice. We further report a previously unidentified role for PIP5K1α as a druggable target for our newly developed compound ISA-2011B using a high-throughput KINOME scan platform. ISA-2011B was discovered during our synthetic studies of C-1 indol-3-yl substituted 1, 2, 3, 4-tetrahydroisoquinolines via a Pictet-Spengler approach. ISA-2011B significantly inhibits growth of tumor cells in xenograft mice, and we show that this is mediated by targeting PIP5K1α-associated PI3K/AKT and the downstream survival, proliferation, and invasion pathways. Further, siRNA-mediated knockdown of PIP5K1α exerts similar effects on PC3 cells as ISA-2011B treatment, significantly inhibiting AKT activity, increasing apoptosis and reducing invasion. Thus, PIP5K1α has high potential as a drug target, and compound ISA-2011B is interesting for further development of targeted cancer therapy [11-20].

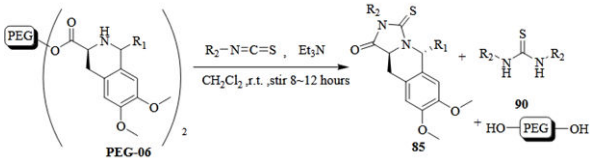
RESULTS AND DISCUSSIONS

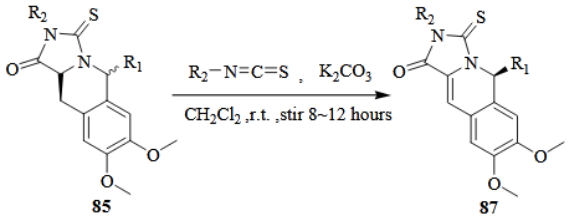
First profit L-3-(3, 4-Dihydroxyphenyl)alnine compound 80, reacted with Di-tert-butyl di carbonate (1.2eq), mixed with 1 N sodium hydroxide and 1,4 dioxane as a solvent in the lower chamber Warm reaction for six hours to obtain compound 81 (L)-2-(tert-butoxy-carbonylamino)-3-(3,4-di-hydroxyphenyl)propanoic acid. The initial product after the reaction is first converted to 1, 4 by a concentrator Dioxane was removed and the product was extracted with ethyl acetate. Then, compound 81 was added to 3.5 angst of dimethyl sulfone, and 5 angst of potassium carbonate (K2CO3) was returned under acetone as solvent for 48 hours to obtain compound 82 (L) methyl 2 (tert butoxycarbonylamino) 3 (3,4 dimethoxyphenyl) propanoate, purified by column chromatography with ethyl acetate and n-hexane 1:4 as a flushing solution to obtain pure compound 82; finally use compound 82, and use 1N NaOH: MeOH: THF = 1: The 1:1 mixed solvent was stirred at room temperature for 8 hours to convert the ester group to the acid group compound 83 before it could be coupled with the subsequent polymer carrier [21-25].

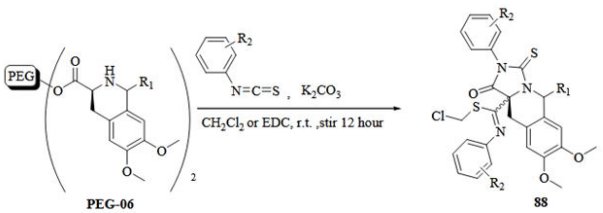


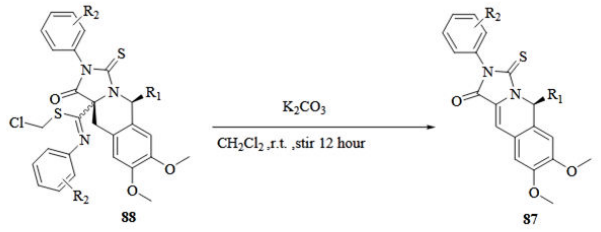
Scheme 2-1 預期之合成策略

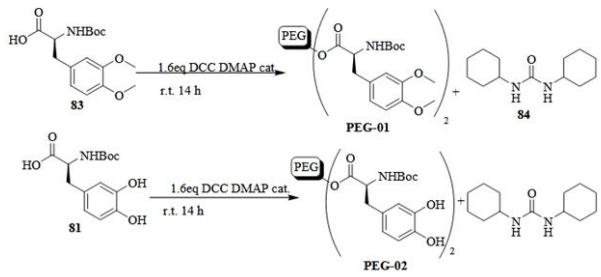


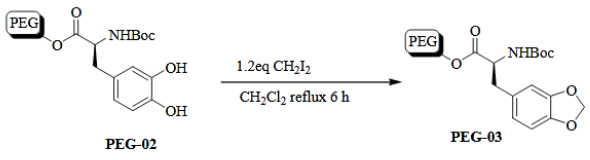


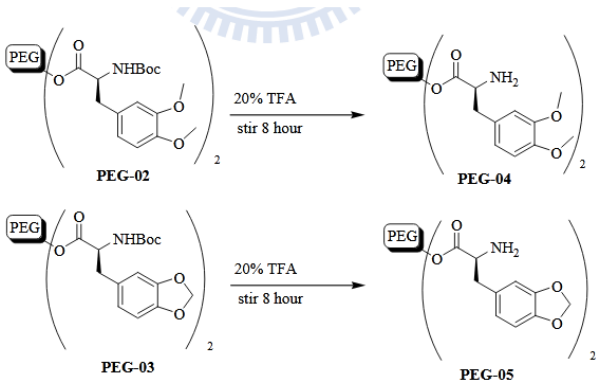












Using soluble polymer resin polyethylene glycol (Polyethylene glycol, PEG) as a carrier and the compound 81 and compound 83 synthesized in the previous step, using dichloromethane as a solvent in the coupling reagent carbonized cycloheximide (N, N' dicyclohexylcarbodimide (DCC) and catalyst N,N' dimethylanilinepyridine (DMAP) under the esterification reaction to produce compounds PEG-01 (such as Scheme 2-3) and PEG- 02. The reaction mechanism is mechanism 2-1. After the reaction is over, the by-product 84 dicyclohexylurea (DCU) is first weighed off, and the DCU is removed. The DCU is removed, and then the product is completely precipitated with large ice ice ether, and then the air is passed through the air. Method and ice ether to remove by-products and impurities, and finally dichloromethane to dissolve the precipitate and collect it, you can get the product compound PEG-01 and compound PEG-02. This step requires stirring for more than one day at room temperature. Jolie reaction with household microwave or focused microwave furnace can shorten the reaction time to number minutes [26-30].

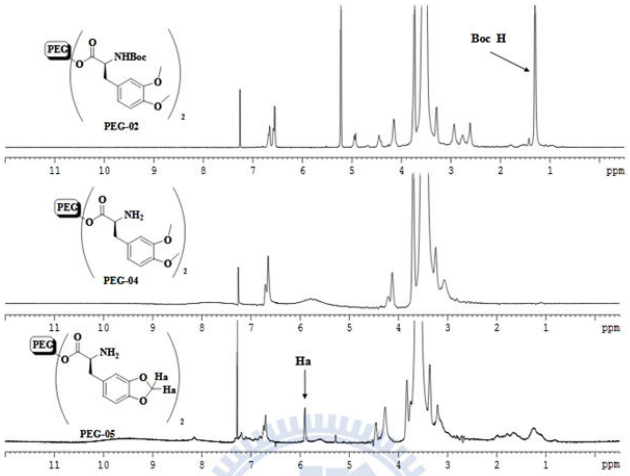
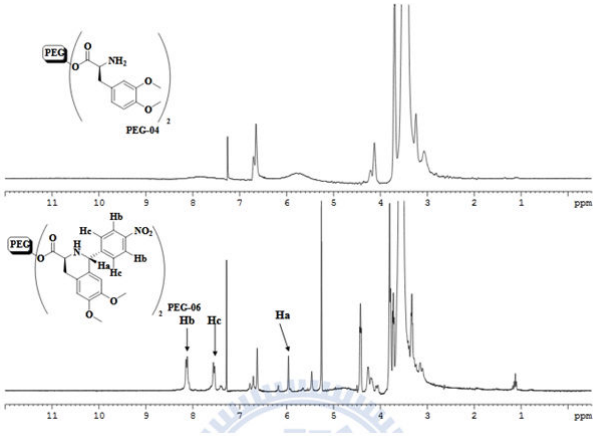
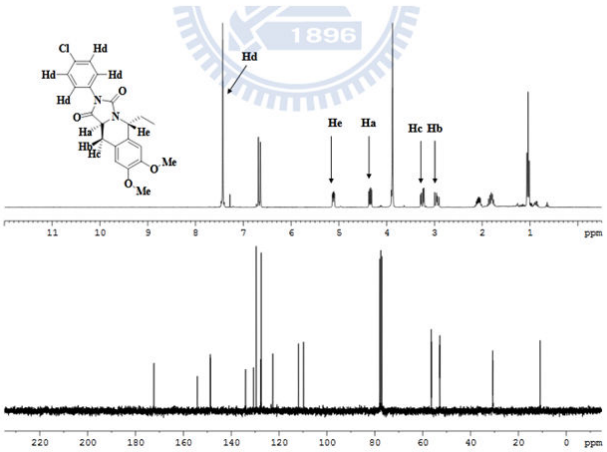
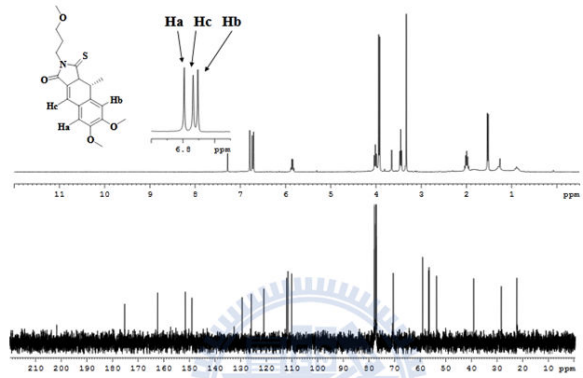
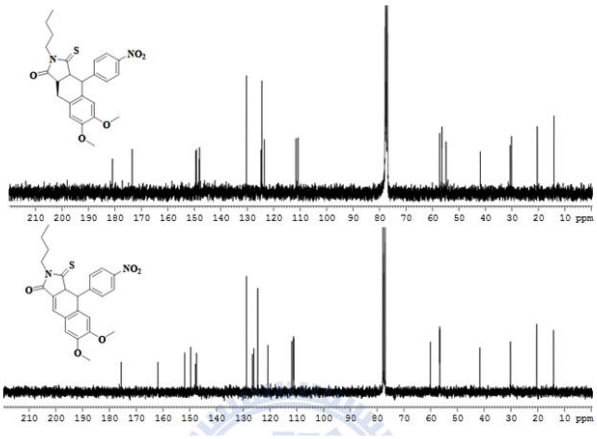


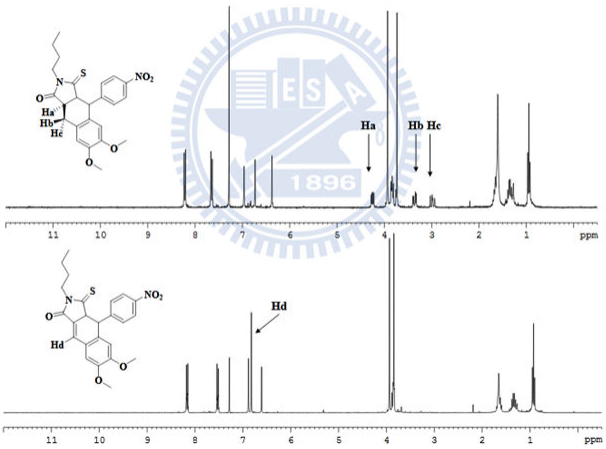
圖 2-3 高分子載體 PEG 上之去保護之氫譜。

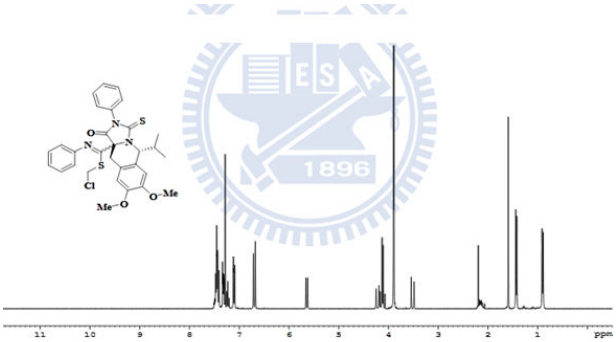




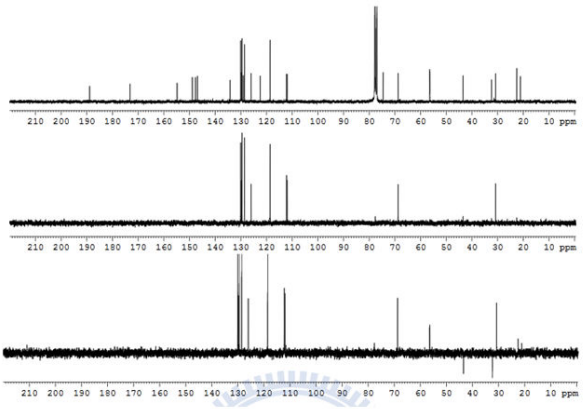


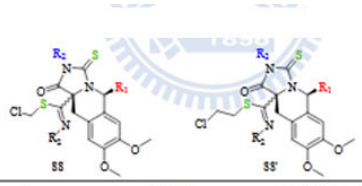


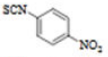
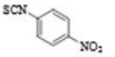




Combining all the above steps, the current derivation of the reaction mechanism is that the base first grabs the hydrogen on the PEG-06 tetrahydro isoquinolines nitrogen, and then reacts with the first Amount of difference cyanate ester to produce the compound PEG-08 At this time, another secondary amine of the PEG-08 intermediate compound PEG-08 will attack the ester group on the polymer carrier product according to even to obtain compound 085. The hydrogen on the alpha carbon of compound 085 tetrahydroisoquinolines will be captured by potassium carbonate. Then it reacts with the second iso cyanate (iso thiocyanate) to produce compound 88. Finally, the hydrogen on the tetrahydro isoquinolines β carbon of compound 088 is captured by the third inspection agent, and enters into an E1 leave to react [31-34].

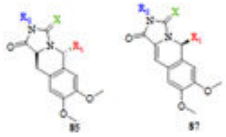




entry[a]	R_1	XCN−R_2	LRMS(M+1)	Isolated yield (%)[b]
5S a			580	65%
5S b			670	54%
5S' a			608	69%
5S' b			695	66%

a compond number for traceless product

b isothiocyanate were lower than isocyanate because isothiocyanate easy formed both single bond and double bond



entry[a]	R_1	XCN−R_2	LRMS(M+1)	Isolated yield (%)[b]
8Sa			459	85%
8Sb			439	88%
8Sc			487	82%
8Sd			438	78%
8Se			380	76%
8Sf			434	90%
8Sg			467	89%
8S'a			398	81%
8Sh			308	69%
8Si			455	70%

S7a	Me		362	86%
S7b			437	87%
S7c			453	82%
S7d			395	75%
S7e			426	74%
S7f			438	79%
S7g			473	78%
S7h			453	86%
S7'a			453	86%

a compond number for traceless product

b isothiocyanate were lower than isocyanate because isothiocyanate easy formed both single bond and double bond

Add compound PEG-02 to 1.2 as quantity diode methane, and use dichloromethane as the solvent to return to flow six hours to obtain the five rings protected by 2 hydroxyl, namely compound PEG 03, PEG L methyl 3 (benzo[d][1,3]dioxol 5 yl) 2 (terta but oxycarbonyl amino)propanoate, profit purify by the aforementioned method.

Compounds PEG-02 and PEG-03 were added to dichloromethane containing 20% trifloro acetic acid, and stirred at room temperature for 6-8 hours, and the de protected product compounds PEG-04 and PEG- 05 Pictet-Spengler cyclization reaction (such as Scheme 2-5 in 12 to 15 hours) (Shown), the reaction mechanism is that the compound PEG-04 reacts with the acid-activated hydrazone to form an imine (intermediate product) PEG-08, and then the electron on the benzene ring of the compound PEG-08 will be provided to the carbon atom of the imine Forming the intermediate PEG-09, and finally entering row proton transfer, the product PEG-06 (as shown in Mechanism 2-2) can be obtained, and the obtained product is purified in profit using the aforementioned method.Compound PEG-04 and compound PEG-05 are mixed with various do not in the same conditions in 10% tri fluoro acetic acid with chloroform as solvent to return them to first, the compound PEG-06, profit using 5 times quantity triethyl amine (triethyl amine) and 3 times Amount of difference cyanate dichloromethane as a solvent to form compound 85 and by-product 86, this reaction is the first compound with different cyanate (Or different cyanate sulfur ester) reaction to form pee element intermediate product PEG-07, and then triethyl amine to remove hydrogen from tetra hydro iso quinolines. At this time, pee element intermediate product PEG-07 another secondary amine will attack even the ester group on the polymer carrier product, directly The product is cut off from the leave liquid cut to obtain the initial product (compounds 85 and 86) and the polymer carrier of the starting material (as shown in Mechanism 2-3).

CONCLUSION

The mechanism underlying the interactions between AR andPI3K/AKT still remains poorly understood. In the present study we uncover several unrecognized interlinks among PIP5K1α, PI3K/AKT, AR, and CDK1 in PCa. Previous studies show that thePI3K/AKT and AR pathways negatively regulate each otherduring castration resistance (38, 39). Our proposed model suggests that ISA2011B inhibits PIP5K1α, which leads to a subsequent inhibition in PI3K/AKT levels and sustained P27 and down-reg-ulation of CDK1 and other cell cycle regulators. Down-regulation of CDK1 may lead to an inhibition in AR signaling pathways. This model is supported by our data that CDK1 and AR form protein–protein complexes predominantly in the nuclear compartment ofcells. The complexes of CDK1–AR are persistent in PNT1A cells overexpressing PIP5K1α. In agreement with our findings, a pre-viously reported study showed that CDK1 phosphorylates ARand thereby activates AR activity during progression of castra tion resistant PCa (40). This indicates that ISA 2011B targetsCDK1associated pathways that regulate AR activity. One of the most significant preclinical extensions of this work is todetermine the therapeutic benefit of ISA-2011B in PCa growth. Treatment of xenograft mice with ISA-2011B results in tumor re-gression. Similarly, PC-3 cells in which PIP5K1αis inhibited through knockdown only formed a small tumor in one out of seven mice, incontrast to control PC-3 cells, which formed large tumors in all seven xenograft mice. These in vivo data are in agreement with the data obtained in cell line studies in which ISA-2011B treatment inhibits tumor growth by inhibiting levels of PIP5K1αand pAKT S473.However, because of the small size of tumors at the end of the ex-periment, it is difficult to measure the levels of pAKT S473 in vivo. In the present study we also observed that treatment withISA2011B in combination with docetaxel completely blocked the progression of invasive PCa locally and profoundly inhibited tumor growth. Docetaxel inhibits mitosis and induces apoptosisin cancer cells as well as normal proliferating cells and is highly toxic. We found that ISA-2011B together with docetaxel showedless toxic effects in mice compared with docetaxel alone. Becausethe interaction between two drugs often results in changes inmetabolic pathways and binding of drugs to cellular membranes, our data suggest that the interaction between ISA-2011B anddocetaxel via unknown mechanisms may lead to reduced off-target effects in mice bearing tumors. Taken together, our findings in the present study provide valuable information on novel targets and anticancer drugs, which hold a great potential for further development of ad-vanced PCa treatment. It will be interesting to further system-atically investigate the on-target effect of ISA-2011B treatment on pAKT S473 in vivo by using several well-designed in vivo mouse models in our future studies.

ACKNOWLEDGEMENT

We gratefully acknowledge National Science Council, Taiwan; for the financially support and the authorities of National Chiao Tung University.

REFERENCES

1. Erica S. Burnell, Mark Irvine, Guangyu Fang, Kiran Sapkota, David E. Jane, Daniel T. Monaghan. Positive and Negative Allosteric Modulators of N-Methyl-d-aspartate (NMDA) Receptors: Structure–Activity Relationships and Mechanisms of Action. J Med Chem. 2019; 62 (1), 3-23.
2. Barbora Krausova, Barbora Slavikova, Michaela Nekardova, Pavla Hubalkova, Vojtech Vyklicky, Hana Chodounska, Ladislav Vyklicky, Eva Kudova. Positive Modulators of the N-Methyl-d-aspartate Receptor: Structure–Activity Relationship Study of Steroidal 3-Hemiesters. J Med Chem. 2018; 61 (10), 4505-4516.
3. Vankudoth Jayaram, Tailor Sridhar, Gangavaram V. M. Sharma, Fabienne Berrée, and Bertrand Carboni. Synthesis of Polysubstituted Isoquinolines and Related Fused Pyridines from Alkenyl Boronic Esters via a Copper-Catalyzed Azidation/Aza-Wittig Condensation Sequence. J Org Chem. 2018; 83 (2), 843-853.
4. Zongjian Zhu, Feng Yi, Matthew P. Epplin, Ding Liu, Samantha L. Summer, Ruth Mizu, Gil Shaulsky, Wenshu XiangWei, Weiting Tang, Pieter B. Burger, David S. Menaldino, Scott J. Myers, Dennis C. Liotta, Kasper B. Hansen, Hongjie Yuan, Stephen F. Traynelis. Negative allosteric modulation of GluN1/GluN3 NMDA receptors. Neuropharmacol. 2020; 108117.
5. Riley E. Perszyk, Sharon A. Swanger, Chris Shelley, Alpa Khatri, Gabriela Fernandez-Cuervo, Matthew P. Epplin, Jing Zhang, Phuong

Le, Pernille Bülow, Ethel Garnier-Amblard, Pavan Kumar Reddy Gangireddy, Gary J. Bassell, Hongjie Yuan, David S. Menaldino, Dennis C. Liotta, Lanny S. Liebeskind, Stephen F. Traynelis. Biased modulators of NMDA receptors control channel opening and ion selectivity. Nat Chem Biol. 2020; 16 (2), 188-196.

6. Paul J. Goldsmith. NMDAR PAMs: Multiple Chemotypes for Multiple Binding Sites. Curr Topics Med Chem. 2019; 19 (24), 2239-2253.
7. Alasdair J. Gibb, Kevin K. Ogden, Miranda J. McDaniel, Katie M. Vance, Steven A. Kell, Chris Butch, Pieter Burger, Dennis C. Liotta, Stephen F. Traynelis. A structurally derived model of subunit-dependent NMDA receptor function. J Physiol. 2018; 596 (17), 4057-4089.
8. Thomas M. Kaiser, Steven A. Kell, Hirofumi Kusumoto, Gil Shaulsky, Subhrajit Bhattacharya, Matthew P. Epplin, Katie L. Strong, Eric J. Miller, Bryan D. Cox, David S. Menaldino, Dennis C. Liotta, Stephen F. Traynelis, Pieter B. Burger. The Bioactive Protein-Ligand Conformation of GluN2C-Selective Positive Allosteric Modulators Bound to the NMDA Receptor. Mol Pharmacol. 2018; 93 (2), 141-156.
9. Jianchun Wang, Guangbin Dong. Palladium/Norbornene Cooperative Catalysis. Chem Rev. 2019; 119 (12), 7478-7528.
10. Akhilesh K. Verma, Siva K. Reddy Kotla, Trapti Aggarwal, Sonu Kumar, Hemlata Nimesh, and Rakesh K. Tiwari . Tandem Synthesis of Pyrroloacridones via [3 + 2] Alkyne Annulation/Ring-Opening with Concomitant Intramolecular Aldol Condensation. J Org Chem. 2013; 78 (11), 5372-5384.
11. Olaia Nieto García and Ricardo Alonso. IMDAF/ Aromatization Path of Halogenated Furylacrylamides and Furylpr opiolamides to Dihydroisoquinolin 1(2H) ones. J Org Chem. 2013; 78 (6), 2564-2570.
12. Satya Prakash Shukla, Rakesh K. Tiwari, and Akhilesh K. Verma. Palladium-Catalyzed Sonogashira-Coupling Conjoined C–H Activation: A Regioselective Tandem Strategy to Access Indolo- and Pyrrolo[1,2-a]quinolines. J Org Chem. 2012; 77 (22), 10382-10392.
13. Roland E. Dolle, Bertrand Le Bourdonnec, Karin Worm, Guillermo A. Morales, Craig J. Thomas, and Wei Zhang . Comprehensive Survey of Chemical Libraries for Drug Discovery and Chemical Biology: 2009. J Combinat Chem. 2010; 12 (6), 765-806.
14. Zhiyao Lu, Chunmei Hu, Jiajie Guo, Jing Li, Yuxin Cui and Yanxing Jia. Water-Controlled Regioselectivity of Pd-Catalyzed Domino Reaction Involving a C−H Activation Process: Rapid Synthesis of Diverse Carbo- and Heterocyclic Skeletons. Org Lett. 2010; 12 (3), 480-483.
15. Ze-Shui Liu, Qianwen Gao, Hong-Gang Cheng, Qianghui Zhou. Alkylating Reagents Employed in Catellani-Type Reactions. Chemistry - A European Journal. 2018; 24 (58), 15461-15476.
16. Tetrahydroisoquinolines. 2018; 356-413.
17. Jeffrey S. Quesnel, Bruce A. Arndtsen. Metal-Catalyzed Multicomponent Reactions. 2017; 1195-1220.
18. Hai-Yu He, Wei Wang, Xiao-Jun Yu, Jin Huang, Lei Jian, Hai-Yan Fu, Xue-Li Zheng, Hua Chen, Rui-Xiang Li. Palladium-Catalyzed Domino Reaction of Two Aryl Iodides involving C-H Activation Processes: Efficient Synthesis of Fused Polycycles. Eur J Org Chem. 2016; 2016 (34), 5616-5619.
19. Ping-Xin Zhou, Lan Zheng, Jun-Wei Ma, Yu-Ying Ye, Xue-Yuan Liu, Peng-Fei Xu, Yong-Min Liang. Palladium-Catalyzed/ Norbornene-Mediated C□H Activation/ N -Tosylhydrazone Insertion Reaction: A Route to Highly Functionalized Vinylarenes. Chemistry - A European Journal. 2014; 20 (22), 6745-6751.
20. Avanashiappan Nandakumar, Selvarangam E. Kiruthika, Kanagaraj Naveen, Paramasivan Thirumalai Perumal. Pd(0)-catalyzed regio- and stereoselective cyclization of alkynes: selective synthesis of (E)-4-(isobenzofuran-1(3H)-ylidene)-1,2,3,4-tetrahydroisoquinolines and aze/oxepinoindoles. Org Biomol Chem. 2014; 12 (6), 876-880.
21. Stefan Bräse, Armin de Meijere. Cross-Coupling of Organyl Halides with Alkenes - The Heck Reaction. 2013; 533-663.
22. Jacques Muzart. Three to seven C–C or C–heteroatom bonds from domino reactions involving a Heck process. Tetrahedron. 2013; 69 (33), 6735-6785.
23. Bin Li, Pierre H. Dixneuf. Metal-Catalyzed C-H Bond Activation and C-C Bond Formation in Water. 2013; 47-86.
24. Christoph Sämann, Benjamin Haag, Paul Knochel. Highly Regioselective Preparation of Heteroaryl-Magnesium Reagents by Using a Br/Mg Exchange. Chemistry - A European Journal. 2012; 18 (50), 16145-16152.
25. Farnaz Jafarpour, Nafiseh Jalalimanesh. Palladium/norbornene catalysis: a versatile aryl C–H hydroxyalkylation, alkyl cinnamate formation. Tetrahedron. 2012; 68 (50), 10286-10292.
26. Po-Yuan Chen, Hsing-Ming Chen, Michael Y. Chiang, You-Feng Wang, Sie-Rong Li, Tzu-Pin Wang, Eng-Chi Wang. A novel and chemoselective synthesis of substituted 3,4-1(2H) ones from o oxiranylmethylbenzonitrile intermediates a nd TBAB/NaCN. Tetrahedron 2012; 68 (14), 3030-3036.
27. Tim C. Efthymiou, Jean-Paul Desaulniers. Synthesis and properties of oligonucleotides that contain a triazole-linked nucleic acid dimer. J Heterocyclic Chem. 2011; 48 (3), 533-539.
28. Jason A. Smith, Peter P. Molesworth, Christopher J.T. Hyland, John H. Ryan. Seven-Membered Rings. 2011; 491-536.
29. Madeleine Livendahl, Antonio M. Echavarren. Palladium-Catalyzed Arylation Reactions: A Mechanistic Perspective. Isr J Chem. 2010; 50 (5-6), 630-651.
30. David A. Candito, Mark Lautens. Palladium-Catalyzed Domino Direct Arylation/N-Arylation: Convenient Synthesis of Phenanthridines. Angewandte Chemie. 2009; 121 (36), 6841-6844.
31. David A. Candito, Mark Lautens. Palladium-Catalyzed Domino Direct Arylation/N-Arylation: Domino Direct Arylation/N-Arylation:
Convenient Synthesis of Phenanthridines. Angewandte Chemie I nt Edition. 2009; 48 (36), 6713-6716.
32. Timothy C. Gallagher. New reactivity realized. Nat Chem. 2009; 1 (5), 343-345.
33. Praew Thansandote, Christina Gouliaras, Marc-Olivier Turcotte-Savard, Mark Lautens. ChemInform Abstract: A Rapid Approach to the Synthesis of Highly Functionalized Tetrahydroisoquinolines. ChemInform. 2009; 40 (27)
34. Praew Thansandote, Mark Lautens. Construction of Nitrogen-Containing Heterocycles by C□H Bond Functionalization. Chemistry - A European Journal. 2009; 15 (24), 5874-5883.