

A Review of Heterocyclic Compounds for Anti-Diabetic Activity

Laliteshwar Pratap Singh*

Department of Pharmacy, Narayan Institute of Pharmacy, Gopal Narayan Singh University, Bihar, India

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ABSTRACT

The heterocyclic compounds, which include phytochemical components, offer medicinal and food characteristics that are crucial in the drug business. They are commonly used in folk medicine to heal conditions such as chilly, asthma, constipation, headache, tobacco, fever and skin issues. Most prescription medicinal products also induce other side effects, such as gastrointestinal issues. There is therefore high need for the development of new and efficient anti-diabetic medicines with fewer side effects. New forms of anti-diabetic drugs are needed continuously as diabetes is a pandemic worldwide. The heterocyclic

manufactured derivatives data have comparable characteristics than natural alkaloids. More and more heterocyclic derivatives were created and synthesized to investigate their bioactivities in the previous two decades. This study enables researchers to investigate further the potential for numerous medicinal uses of these heterocyclic multilateral derivatives.

Keywords: Heterocyclic compounds, Anti-diabetic, Derivatives, Diabetic complications, Synthesis

***Correspondence:** Laliteshwar Pratap Singh, Department of Pharmacy, Narayan Institute of Pharmacy, Gopal Narayan Singh University, Bihar, India, E-mail: lalitpharma@gmail.com

INTRODUCTION

Medicinal chemistry is the discipline of science exploration that creates prescriptions through one or the other revelation or plan. Aside from that, therapeutic science involves the recognizable proof, characterization, and blend of particles that can be utilized in medication for sickness avoidance, therapy, and fix (Davis A and Ward SE, 2014). Organic therapeutic substances, regardless of whether normal or incorporated, are the focal point of clinical science. Numerous alkaloids, glycosides, nutrients, chemicals, and anti-toxins are gotten from regular sources. Sure of them are integrated, like nutrients and chemicals, while others, like alkaloids, glycosides, numerous anti-infection agents, and a few chemicals like insulin, are gotten monetarily from normal sources. Semi-engineered drugs, like semi-manufactured penicillin, can be made by altering the construction of normal drugs in essential or more confounded ways. Numerous original analgesics, neighborhood sedatives, sympathomimetics, and different prescriptions have been created by recognizing changes in the designs of regular and made drugs (Barret R, 2018; Roughley SD and Jordan AM, 2011).

Diabetes

Diabetes mellitus is an assortment of metabolic diseases characterized by hyperglycemia. Hyperglycemia happens when the body doesn't make sufficient insulin or when cells don't react to the insulin created because of irregularities in insulin creation, insulin flagging, or both. 1/3 Diabetes mellitus is viewed as one of the most genuine dangers to human wellbeing in the twenty-first century (Krishnasamy S and Abell TL, 2018).

Insulin inadequacy causes diligent hyperglycemia, creating some issues with starch, fat, and protein metabolism. Diabetes mellitus has now turned into a worldwide pandemic, with India being named the "diabetes capital" (Kitabchi AE, *et al.*, 2009).

Type 1 diabetes: Because of the deficiency of beta cells in the pancreas, the pancreas can't produce sufficient insulin. Beforehand, this condition was known as "Insulin-Dependent Diabetes Mellitus" (IDDM) or "adolescent diabetes". An immune system response causes the passing of beta cells. This immune system reaction's etiology is hazy.

Type 2 diabetes: Insulin opposition is a condition wherein cells don't respond fittingly to insulin. A lack of insulin might happen as the condition progresses. Already, this condition was known as "Non-Insulin-Dependent Diabetes Mellitus" (NIDDM) or "grown-up beginning diabetes". A mix of high body weight and deficient exercise is the most commonplace reason.

Gestational diabetes: The third most common kind happens when pregnant ladies who have never had diabetes foster high glucose levels.

We detail the disengagement, combination, and against diabetic properties of these heterocyclic compounds in this survey, which centers around heterocyclic mixtures and composite courses, just as manufactured heterocyclic subsidiaries dependent on underlying arrangement.

LITERATURE REVIEW

Heterocyclic compounds

Heterocyclic chemistry is concerned uniquely with the amalgamation, qualities, and employments of heterocyclic mixtures, which are especially significant in medicine improvement. A carbocyclic compound is a cyclic natural particle with all carbon molecules organized in a ring design. A heterocyclic compound is one in which something like one component other than carbon is a part of the ring structure. The most incessant hetero molecules are nitrogen, oxygen, and sulfur, but heterocyclic rings containing extra hetero components are additionally well-known. There are countless heterocyclic mixtures known, and the number is constantly developing. Contingent upon their electronic cosmetics, the science of heterocyclic particles is really that consistent of aliphatic or fragrant mixtures. Their exploration is intriguing from both a hypothetical and a functional viewpoint. Heterocyclic mixtures are plentiful in nature and are important for life in an assortment of ways. Heterocyclic ring frameworks are found in a wide scope of mixtures, including alkaloids, anti-microbial, imperative amino acids, nutrients, hemoglobin, chemicals, and a huge assortment of manufactured prescriptions and colors (Rees CW, 1992). Biosynthesis and medication digestion both advantage from a comprehension of heterocyclic chemistry (Vitaku E, *et al.*, 2014) (Figure 1).

Images of rings with one Heteroatom

| Heteroatom | Saturated | | | Unsaturated | | |
|-------------|-----------------|-------------|--------------|--------------|-------------|---------------|
| | Nitrogen | Oxygen | Sulfur | Nitrogen | Oxygen | Sulfur |
| 3-Atom Ring | Aziridine | Oxirane | Thiirane | Azirine | Oxirene | Thiirene |
| 4-Atom Ring | Azetidine | Oxetane | Thietane | Azete | Oxete | Thiete |
| 5-Atom Ring | Pyrrolidine | Oxolane | Thiolane | Pyrrole | Furan | Thiophene |
| 6-Atom Ring | Piperidine | Oxane | Thiane | Pyridine | Pyran | Thiopyran |
| 7-Atom Ring | Azepane | Oxepane | Thiepane | Azepine | Oxepine | Thiepine |
| 8-Atom Ring | Azocane | Oxocane | Thiocane | Azocine | Oxocine | Thiocine |
| 9-Atom Ring | Azonane | Oxonane | Thionane | Azonine | Oxonine | Thionine |

Figure 1: It shows about the recent progress made over the last years on new heterocyclic compounds and their anti-diabetic actions

In this study, we summarize the recent progress made over the last years on new heterocyclic compounds and their anti-diabetic actions.

Indole compounds with potential anti-diabetic activity

Zhu Y, *et al.* established that the attributes of engineered indole subordinates are equivalent to those of normal indole alkaloids. More indole subsidiaries have been made and integrated over the most recent twenty years to research their bioactivities. In light of the anti-diabetic effects and instruments of activity of indole compounds with potential anti-diabetic movement, including regular indole alkaloids and engineered indole subordinates, his article summarizes methodologies disconnected from natural sources or by manufactured strategies, and investigates the anti-diabetic impacts and instruments of activity of indole compounds with potential anti-diabetic movement, including regular indole alkaloids and engineered indole subordinates. Likewise, his outline momentarily portrays the amalgamation methods for various huge indole subordinates (Zhu Y, *et al.*, 2021).

Srividya L and Reddy AR demonstrated that diabetes was set up in chicks by managing alloxan monohydrate at a portion of 0.9 mg/egg on the fourteenth day of agonizing, as proven by the conveyance of chicks with raised blood glucose levels when contrasted with chicks that didn't get alloxan treatment. One-way Analysis of Variance (ANOVA) was utilized to assess the information in one manner. Following the association of the test substance, it was found that portions of 10 and 30 mg kg⁻¹ sections brought about a huge drop in glucose levels. Chosen indole was subordinate thio-carbohydrazone (Srividya L and Reddy AR, 2017).

Kanwal K, *et al.* within the sight of the coupling reagent 1,1-carbonyldiimidazole, indole-3-acetamides (124) were delivered by joining indole-3-acidic corrosive with various subbed anilines. Distinctive spectroscopic strategies, for example, electron ionization-mass spectroscopy were utilized to

find the designs of manufactured mixtures (High-Resolution Electron Ionization Mass Spectrometry (HREI-MS)). The anti-hyperglycemic and cell reinforcement properties of these substances were examined. Compound 15 (IC₅₀=1.09 0.11 M) was the most dynamic of the gathering, with IC₅₀ (Half-maximal Inhibitory Concentration) upsides of 0.35 0.1 and 0.81 0.25 M in DPPH (2,2-diphenyl-1-picrylhydrazyl). *In silico* tests affirmed the restricted interchanges of created particles with the compound's powerful site. Different lead particles were distinguished as potential anti-hyperglycemic and cell support experts in the flow research (Kanwal K, *et al.*, 2021).

Fattaheian-Dehkordi S, *et al.* found that restorative plants, including extricates and cleansed dynamic parts, have a significant capacity in blood glucose guideline. In view of the great to-brilliant results depicted in the writing, they've turned into a significant hotspot for making and delivering against Diabetes mellitus prescriptions and enhancements. The positive outcomes incited us to return to their viability to prepare for the making of home grown enemy of diabetic drugs (Fattaheian-Dehkordi S, *et al.*, 2021).

Novel triazole compounds have anti-diabetic action

Mohamed MA, *et al.* under green science conditions, a progression of new sulfonamide and Thiazolidinedione (TZD) 5a-c, 7a-c subsidiaries were delivered from amino acids connected triazole subordinates 1a-h. The previously mentioned substances had solid enemy of diabetic activity *in vitro* and *in vivo*. The range and natural information were utilized to portray the constructions of the newfound mixtures (Mohamed MA, *et al.*, 2020).

Scope of nitrogen-based compounds in medicine

Kerru N, *et al.* found the broadness of nitrogen-based atoms in medication is developing an everyday schedule, and their various analogs give a possible and vital pathway for the revelation of prescriptions with an assortment of natural employments. His survey paper is useful in advancing the underlying model and advancement of durable and successful nitrogen-based prescriptions for an assortment of illnesses with few unfriendly impacts (Kerru N, *et al.*, 2020).

Flefel EM, *et al.* found the production of novel spirothiazolidine subsidiaries and their melded analogs, which were created and explained using range and essential investigations, was uncovered in their paper. As a general rule, the anticancer and anti-diabetic adequacy of these mixtures was affected by the heterocyclic structure type. The anticancer movement of the blended mixtures was tried on human bosom and liver cell lines. Besides, it was shown that intensifies, which incorporate amino spirothiazolopyridine-carbonitrile and pyrazolo spirothiazolidine gatherings, had huge movement against alpha-amylase and alpha-glucosidase proteins at all portions (Flefel EM, *et al.*, 2019).

Gutiérrez-Hernández A, *et al.* and according to the researchers, three cross varieties containing benzimidazole and thiazolidine-2,4-dione has been combined, with the following advantages over current anti-diabetic glitazone drugs (Gutiérrez-Hernández A, *et al.*, 2019).

Manoharan D, *et al.* found the counter diabetic impact of indoline subordinates was shown in this review utilizing-amylase restraint movement. The forerunner N-(4-aminophenyl) indoline-1-carbothiamide was utilized to make a progression of indoline subordinates. Fourier-Transform Infrared Spectroscopy (FT-IR) was utilized to affirm the created compounds. The norm-amylase restraint test was utilized to test the anti-diabetic adequacy of created indoline subsidiaries *in vitro* (Manoharan D, *et al.*, 2017).

Diabetic complications

Sun L, *et al.* these are one more gathering of tyrosine kinase inhibitors that show selectivity for indisputable Receptor Tyrosine Kinases (RTKs) and have been made and conveyed. For bioisosteric substitution, oxindole is orchestrated (Sun L, *et al.*, 1998). Few studies itemized the improvement of metabolic issues in genetically weighty rodents by M16209 (1-(3-bro-

mobenzofuran-2-ylsulfonyl) hydantoin), an anti-diabetic trained professional, in innately chubby rodents and mice is a result of upgrade of insulin deterrent in periphery tissues. Castro A, *et al.* uncovered study of basic necessities for thiadiazolidinone subordinates as non-ATP genuine Glycogen Synthase Kinase 3 (GSK-3) inhibitors. The fundamental development of 1,2,4-thiadiazole, similarly as one of the carbonyl get-togethers, are held, yet changes in positions 3 and 5 are added, independently. The GSK-3 development of the novel thiadiazole auxiliaries made here showed IC50 regards in the micro molar range for a long while the mixtures (Castro A, *et al.*, 2008). A gathering of new tetrahydroquinoline-inferred spirohydantoin compounds has been found to be helpful in the therapy of some persistent diabetes problems.

Licht-Murava A, *et al.* explaining Substrate and Inhibitor Binding Sites on the Surface of GSK-3, similarly as the refinement of a competitive inhibitor, was disseminated. Adding joint efforts with Phe93 or extending the hydrophobic formation of the peptide might fabricate deterrent, as shown by computational exhibiting of novel L803 variations (Licht-Murava A, *et al.*, 2011). Gaisina IN, *et al.* found the Glycogen Synthase Kinase 3 (GSK-3) is overexpressed in human colon and pancreatic carcinomas, provoking harmful development cell augmentation and perseverance, according to continuous assessment. The arrangement, association, and natural evaluation of one more drug are portrayed as benzofuran-3-yl-(indol-3-yl) maleimides, serious GSK-3 β inhibitors (Gaisina IN, *et al.*, 2009). Engler TA, *et al.* definite Glycogen Synthase Kinase-3 (GSK3) is a protein associated with insulin receptor hailing. GSK3 inhibitors are expected to equivalently influence plasma glucose decline as insulin, making GSK3 a promising target for the treatment of type 2 diabetes (Engler TA, *et al.*, 2004; Osborne A, *et al.*, 2003). Patel S, *et al.* in diabetes, GSK-3 protein verbalization and kinase activity are extended, and specific GSK-3 inhibitors have showed ensure as glucose assimilation and insulin affectability modulators. An unexpected quality zeroing in on methodology was used to take a gander at the possible relationship of GSK-3 in insulin work, in which mice with GSK-3 verbalization unequivocally eliminated inside insulin-fragile tissues were created (Patel S, *et al.*, 2008; Knies T, *et al.*, 2009). Pinto A, *et al.* a three-section palladium-catalyzed blend of 3-(diarylmethylene) indolin-2-ones has been made, as demonstrated by the experts. A three-section oxindole combination catalyzed by palladium for bioisosteric replacement (Pinto A, *et al.*, 2009). Peat AJ, *et al.* focuses upon expansive plan activity affiliations and basic cognizance of the GSK-3 confining site, achieving further developed force above before analogs. Additionally, these blends have a low nanomolar sufficiency for propelling glycogen creation *in vitro*, recommending that they might be important in the treatment of type-2 diabetes (Peat AJ, *et al.*, 2004). O'Neill DJ, *et al.* following that, elective chain lengths and practical gatherings were utilized to supplant hydroxy propyl. A large number of the mixtures created were displayed to show high GSK 3 strength, solid GS movement in Human Embryonic Kidney (HEK) 293 cells, and great to remarkable metabolic security in human liver microsomes (O'Neill DJ, *et al.*, 2004). They examined the wipe *Hemimycale arabica* as a part of their constant undertakings to uncover bioactive assistant metabolites from Red Sea marine yellow animals. As per the review, an assortment of hydantoin subsidiaries were created and integrated with in general yields of 25%-30%. Synthetic substances 3 and 5 are two of the six recently incorporated mixtures that have never been accounted for. The Aldol interaction was utilized to make intensifies 2-6, and the designs of these mixtures were confirmed utilizing 1H and 13C Nuclear Magnetic Resonance (NMR). The cytotoxic attributes of all newly blended subsidiaries were tried against HepG2 human cancer cell lines. Mixtures 2 and 4 showed solid enemy of growth action against liver disease, as per the discoveries.

CONCLUSION

The current review showed that diabetes is the most continuous endocrine

illness and by 2021 more than 200 million individuals internationally are expected to have Diabetes mellitus and 300 million will then, at that point, have Diabetes mellitus by 2025. Diabetes is a significant wellspring of illness and mortality in the globe, regardless of each progress in treatments. In the current survey, we have seen that endeavors to incorporate heterocyclic subordinates accepted to be anti-diabetic. The audit information uncovers the drug local area interest in the advancement of compelling, amazing inhibitors for diabetic mellitus treatment with a low aftereffect. The work may likewise be additionally evolved on by the physical and synthetic attributes important to assemble all the more impressive particles for the treatment and treatment of diabetes mellitus liberated from antagonistic impacts demonstrated by customary enemy of diabetic meds.

FUTURE PROSPECTS

New advancement with manufactured techniques permitting speedy admittance to a huge scope of utilitarian heterocyclic mixtures is fundamental for the therapeutic physicist as it permits the compound space available as a medication to be extended and the conveyance of medication research projects to be more proficient. Also, creating solid engineered pathways, which can undoubtedly deliver mass measures of an ideal compound, assists with accelerating the medication advancement process. While the production of exceptional heterocyclical blends that grant assorted restricting techniques are frequently utilized all through a medications revelation program, the improvement of various restricting procedures impacts hostile to diabetic viability.

The future would be better ready to give individualized strategies to protection diabetology by utilizing biotechnology procedures. A future-situated specialist work area reference would remember data for each hereditary profile that would be matched to exact phytochemical treatments. Simultaneously, harmfulness to specific parts is immaterial, as proposals depend on the hereditary profiles and affectability information of an individual. Preventive diabetology is outfitted with a cell of photo constituents and splendid hereditary information to follow the hints of old information. Such prescriptions are additionally totally normal and exceptionally reasonable and might be utilized to the general population overall. In addition, some heterocyclic synthetic substances now being used have not been cautiously experimentally surveyed and some are possibly prompting serious unfavorable impacts and significant collaborations with drugs.

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REFERENCES

1. Davis A, Ward SE. The handbook of medicinal chemistry: Principles and practice. Royal Society of Chemistry. 2014.
2. Barret R. Medicinal Chemistry: Fundamentals. Elsevier. 2018. [Google Scholar]
3. Roughley SD, Jordan AM. The medicinal chemist's toolbox: An analysis of reactions used in the pursuit of drug candidates. *J Med Chem.* 2011; 54(10): 3451-3479.
4. Krishnasamy S, Abell TL. Diabetic gastroparesis: Principles and current trends in management. *Diabetes Ther.* 2018; 9(1): 1-42.
5. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care.* 2009; 32(7): 1335-43.
6. Rees CW. Polysulfur-nitrogen heterocyclic chemistry. *J Heterocycl Chem.* 1992; 29(3): 639-651.

- Vitaku E, Smith DT, Njardarson JT. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: Miniperspective. *J Med Chem.* 2014; 57(24): 10257-10274.
- Zhu Y, Zhao J, Luo L, Gao Y, Bao H, Li P, *et al.* Research progress of indole compounds with potential antidiabetic activity. *Eur J Med Chem.* 2021; 223: 113665.
- Srividya L, Reddy AR. Antidiabetic activity of 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) Thiocarbohydrazone in chick model. *Asian J Biol Sci.* 2017; 10: 126-129.
- Kanwal K, Khan KM, Chigurupati S, Ali F, Younus M, Aldubayan M, *et al.* Indole-3-acetamides: As potential antihyperglycemic and antioxidant agents; Synthesis, *in vitro* α -amylase inhibitory activity, structure-activity relationship, and *in silico* studies. *ACS Omega.* 2021; 6(3): 2264-2275.
- Fattaheian-Dehkordi S, Hojjatifard R, Saeedi M, Khanavi M. A review on antidiabetic activity of *Centaurea* sp.: A new approach for developing herbal remedies. *Evid Based Complement Alternat Med.* 2021.
- Mohamed MA, Abd Allah OA, Bekhit AA, Kadry AM, El-Saghier AM. Synthesis and antidiabetic activity of novel triazole derivatives containing amino acids. *J Heterocycl Chem.* 2020; 57(6): 2365-2378.
- Kerru N, Gummidi L, Maddila S, Gangu KK, Jonnalagadda SB. A review on recent advances in nitrogen-containing molecules and their biological applications. *Molecules.* 2020; 25(8): 1909.
- Flefel EM, El-Sofany WI, Al-Harbi RA, El-Shahat M. Development of a novel series of anticancer and antidiabetic: Spirothiazolidines analogs. *Molecules.* 2019; 24(13): 2511.
- Gutiérrez-Hernández A, Galván-Ciprés Y, Domínguez-Mendoza EA, Aguirre-Vidal Y, Estrada-Soto S, Almanza-Pérez JC, *et al.* Design, synthesis, antihyperglycemic studies, and docking simulations of benzimidazole-thiazolidinedione hybrids. *J Chem.* 2019.
- Manoharan D, Kulanthai K, Sadhasivam G, Raji V, Thayumanavan P. Synthesis, characterization and evaluation of antidiabetic activity of novel indoline derivatives. *Bangladesh J Pharmacol.* 2017; 12(2): 167-172.
- Sun L, Tran N, Tang F, App H, Hirth P, McMahon G, *et al.* Synthesis and biological evaluations of 3-substituted indolin-2-ones: A novel class of tyrosine kinase inhibitors that exhibit selectivity toward particular receptor tyrosine kinases. *J Med Chem.* 1998; 41(14): 2588-2603.
- Castro A, Encinas A, Gil C, Bräse S, Porcal W, Pérez C, *et al.* Non-ATP competitive glycogen synthase kinase 3 β (GSK-3 β) inhibitors: Study of structural requirements for thiadiazolidinone derivatives. *Bioorganic Med Chem.* 2008; 16(1): 495-510.
- Licht-Murava A, Plotkin B, Eisenstein M, Eldar-Finkelman H. Elucidating substrate and inhibitor binding sites on the surface of GSK-3 β and the refinement of a competitive inhibitor. *J Mol Biol.* 2011; 408(2): 366-378.
- Gaisina IN, Gallier F, Ougolkov AV, Kim KH, Kurome T, Guo S, *et al.* From a natural product lead to the identification of potent and selective benzofuran-3-yl-(indol-3-yl) maleimides as glycogen synthase kinase 3 β inhibitors that suppress proliferation and survival of pancreatic cancer cells. *J Med Chem.* 2009; 52(7): 1853-1863.
- Engler TA, Henry JR, Malhotra S, Cunningham B, Furness K, Brozinick J, *et al.* Substituted 3-imidazo [1, 2-a] pyridin-3-yl-4-(1, 2, 3, 4-tetrahydro-[1, 4] diazepino-[6, 7, 1-hi] indol-7-yl) pyrrole-2, 5-diones as highly selective and potent inhibitors of glycogen synthase kinase-3. *J Med Chem.* 2004; 47(16): 3934-3937.
- Osborne A, Teng Q, Miles EW, Phillips RS. Detection of open and closed conformations of tryptophan synthase by 15N-heteronuclear single-quantum coherence nuclear magnetic resonance of bound 1-15N-L-tryptophan. *J Biol Chem.* 2003; 278(45): 44083-44090.
- Patel S, Doble BW, MacAulay K, Sinclair EM, Drucker DJ, Woodgett JR. Tissue-specific role of glycogen synthase kinase 3 β in glucose homeostasis and insulin action. *Mol Cell Biol.* 2008; 28(20): 6314-6328.
- Kniess T, Bergmann R, Kuchar M, Steinbach J, Wuest F. Synthesis and radiopharmacological investigation of 3-[4'-[18F] fluorobenzylidene] indolin-2-one as possible tyrosine kinase inhibitor. *Bioorg Med Chem.* 2009; 17(22): 7732-7742.
- Pinto A, Neuville L, Zhu J. Palladium-catalyzed domino N-arylation/carbopalladation/C-H functionalization: Three-component synthesis of 3-(diarylmethylene) oxindoles. *Tetrahedron Lett.* 2009; 50(26): 3602-3605.
- Peat AJ, Garrido D, Boucheron JA, Schweiker SL, Dickerson SH, Wilson JR, *et al.* Novel GSK-3 inhibitors with improved cellular activity. *Bioorganic Med Chem Lett.* 2004; 14(9): 2127-2130.
- O'Neill DJ, Shen L, Prouty C, Conway BR, Westover L, Xu JZ, *et al.* Design, synthesis, and biological evaluation of novel 7-azaindoly-heteroaryl-maleimides as potent and selective glycogen synthase kinase-3 β (GSK-3 β) inhibitors. *Bioorganic Med Chem.* 2004; 12(12): 3167-3185.