Bioorganic & Medicinal Chemistry Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and biological evaluation of novel marine-derived indole-based 1,2,4-oxadiazoles derivatives as multifunctional neuroprotective agents

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ARTICLE INFO

Article history:
Received 10 September 2014
Revised 21 November 2014
Accepted 26 November 2014
Available online xxxx

Keywords:
Phidianidines
1,2,4-Oxadiazole derivatives
Amyloid-β-peptide
Oxygen–glucose deprivation
Neuroprotective activity

ABSTRACT

Phidianidines (**1**), isolated from the marine opisthobranch mollusk *Phidiana militaris*, present the first example of natural products possessing an 1,2,4-oxadiazole ring system and show various bioactivities. However, the structure–activity relationship study related to **1** has not been reported yet. As our ongoing effect toward marine-derived potential neuroprotective agents, a series of phidianidine-based derivatives have been synthesized and evaluated for neuroprotective effects against amyloid-β_{25-35} ($A\beta_{25-35}$)-, hydrogenperoxide (H_2O_2)-, and oxygen–glucose deprivation (OGD)-induced neurotoxicity in SH-SY5Y cells. The bioassay results indicated that some of analogs, especially **2q** and **2r**, exhibited good in vitro neuroprotective effects in the above three screening models. The preliminary SAR study indicated that substituent groups introduced to the benzene ring play a crucial role in their bioactivity. In particular, the linear alkoxy group at 4-position favors the neuroprotective activity, while a bulky group could lead the activity decrease or loss. These findings could provide an alternative strategy for the development of novel indole-based 1,2,4-oxadiazole derivatives for the treatment of Alzheimer's disease.

Alzheimer's disease (AD), the most common form of dementia, is multifaceted neurodegenerative brain disorder featured by loss of memory, progressive deficits in cognitive functions, and severe behavioral abnormalities.[1] Currently, approximate 35 million people worldwide are believed to suffer from AD, and with the aging of the population this number is expected to triple by 2050 if no efficient treatment is developed.[2] To date, although some acetylcholinesterase inhibitors (e.g., donepezil, galantamine) could exert beneficial role in improving AD symptom, no effective treatment has been proved to stop the progress of AD. Therefore, there is an urgent need for developing new anti-AD drugs that are safe and effective with minimal side effects.

Although the histopathogenesis of AD is still unknown, it is hypothesized that the accumulated amyloid-β-peptide (Aβ), triggering critical intracellular signaling pathways that lead to cell stress and apoptosis, is considered as one of the original cause of AD.[3] Moreover, oxidative stress which results from excessive reactive oxygen species (ROS) production and insufficient antioxidant defense systems is commonly observed and may contribute to the progress of AD.[4] Hydrogen peroxide (H_2O_2) produced during the redox process is the main form of ROS, which causes protein and lipid peroxidation and DNA damage and cell death.[5] In addition, cerebral ischemia characterized by insufficient oxygen and glucose supply will result in imbalanced energy metabolism and at last cell death, which is also believed to be a cause of AD.[6,7] As an in vitro model of cerebral ischemia, oxygen–glucose deprivation (OGD) has now been widely used.[8,9] Based on these observations, discovering novel compounds with multi-effects on protecting neurons from toxicity induced by Aβ, H_2O_2, and OGD may be an effective strategy to develop anti-AD drugs.

Marine natural products (MNPs) proved to be a tremendous source for research and development of candidate/clinical drugs.[10] In particular, there is a growing interest from the community of medicinal chemistry in the development of novel marine neuroprotective agents over the last few decades.[11,12] Our group has focused on isolation, synthesis and biological evaluation of MNPs for many years,[13–15] and recently two novel 1,2,4-oxadiazole alkaloids,

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http://dx.doi.org/10.1016/j.bmcl.2014.11.068
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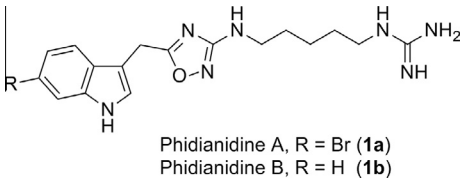


Figure 1. The structures of phidianidines A (**1a**) and B (**1b**).

phidianidines A (**1a**) and B (**1b**) (Fig. 1), had been isolated from the shell-less marine opisthobranch mollusk *Phidiana militaris* by our group in collaboration with Gavagnin's group.[16] These phidianidines are particularly of interest because they present the first example of natural products possessing an 1,2,4-oxadiazole ring system, and meanwhile showed strong antitumor activity against C6 and HeLa cells with the IC_{50} values within nanomolar range. In addition, phidianidine A was found to be a new antagonist of CXCR4, an important pharmacological target for treating HIV infection, rheumatoid arthritis, and cancer development/progression and metastasization.[17] However, both phidianidines showed only 5–30% inhibition on NCI 60 cell lines and no toxicity against HEK293 cell lines at 10 μM.[18,19] Interestingly, they were found to be selective inhibitors of the dopamine transporter and selective agonists of the μ-opioid receptor, indicating that they are useful for developing novel ligands for CNS targets or analgesics due to their unique pharmacological profiles.[19,20]

The bioactivities of phidianidines toward diverse pharmacological targets are not surprising given their interesting structural features: (i) indole fragment is a common but important pharmacophore widely presented in numerous bioactive natural products or drugs for the CNS disorders;[21,22] (ii) the 1,2,4-oxadiazole ring system, known as an ester isostere, is present in various compounds with β-amyloid imaging function in AD and anti-oxidant activity;[23,24] (iii) meanwhile the compounds incorporating guanidine fragment also have potential application in the treatment of neurodegenerative disorders (e.g., AD) and inflammation.[25–27] All the above observations strongly suggested that these phidianidines might have potential value in the treatment of neurodegenerative disorders, such as AD, that stimulated our great interest in the research of their neuroprotective activity.

Since there is no information associated to the SAR study of **1**, at the beginning the aminophenyl- and aminopyrimidine-substituted furan ring moiety were arbitrarily used to replace the alkylguanidinium side chain resulting into the production of phidianidine mimic **2a** and **2b** (Fig. 2). The cytotoxicity of **2a** and **2b** against HL-60 and A549 cell lines were first evaluated. At the concentration of 10 μM, both compounds showed very weak toxicity (26–35% inhibition on HL-60; 2.0–4.2% inhibition on A549). Then, their neuroprotective effects against $Aβ_{25–35}$-, H_2O_2-, and OGD-induced neurotoxicity in human SH-SY5Y neuroblastoma cells were evaluated. The results from the neuroprotective bioassay indicated that compound **2a** was inactive in the abovementioned cell models even at the concentration of 10 μM, but the compound

Table 1
The neuroprotective of compounds against $Aβ_{25–35}$-induced neurotoxicity in SH-SY5Y cells

Compd	Cell viability[a] (%)		Compd	Cell viability (%)	
	1 μM	10 μM		1 μM	10 μM
2a	N.A.[b]	N.A.	**2m**	N.A.	92.1
2b	N.A.	92.4	**2n**	N.A.	92.1
2c	N.A.	N.A.	**2o**	N.A.	N.A.
2d	N.A.	N.A.	**2p**	N.A.	91.5
2e	N.A.	N.A.	**2q**	N.A.	89.1
2f	N.A.	N.A.	**2r**	90	115.5
2g	N.A.	N.A.	**2s**	N.A.	93.3
2h	N.A.	N.A.	**2t**	N.A.	84.8
2i	N.A.	80.3	**2u**	N.A.	83.9
2j	N.A.	100.0	**2v**	N.A.	83.5
2k	89.7	114.2	**11a**	N.A.	N.A.
2l	N.A.	93.3	**11b**	N.A.	106.0
			EGCG	N.T.[c]	96.2

[a] The neuroprotective effect of these compounds on $Aβ_{25-35}$-induced neurotoxicity in SH-SY5Y cells. The cell viability in control was taken as 100%, and the average value of cell viability under $Aβ_{25–35}$ exposure was 69.77% ± 3.14. The positive control is epigallocatechin gallate (EGCG).
[b] N.A. means not active.
[c] N.T. means not tested.

2b displayed significant neuroprotective effect against $Aβ_{25–35}$-induced injuries in SH-SY5Y cells (94.2% of cell viability at 10 μM), similar level with the positive control EGCG at 10 μM (cell viability: 96.2%). These data are shown in Table 1. In addition, compound **2b** also showed neuroprotective activity against OGD-induced injuries in SH-SY5Y cells with 18.96% of increase in cell viability at 1 μM. These positive pharmacological data allowed **2b** to be a potential anti-AD hit compound.

Based on our preliminary result, a series of **2b** derivatives possessing indole-based 1,2,4-oxadiazoles skeleton with different side chain were prepared and evaluated for neuroprotective activities against $Aβ_{25–35}$-, H_2O_2-, and OGD-induced neurotoxicity in SH-SY5Y cells.

The preparation of **2a** and **2b** was accomplished by using the general method outlined in Scheme 1. The commercially available 5-bromo-2-furaldehye **3** was reacted with hydroxylamine hydrochloride in EtOH overnight to afford aldoxime **4** in 90% yield,[24] and the following mild dehydration of **4** catalyzed by $[RuCl_2(p\text{-cymene})]_2$ under refluxing CH_3CN produced nitrile **5** in 70% yield.[28] The intermediate **6** was obtained in 85% yield by the treatment of **5** with hydroxylamine hydrochloride,[29] and then compound **6** was reacted with indole-3-acetic acid **8** to give the key intermediate **7** in two steps with 60% yield.[18,30] Finally, the intermediate **7** was converted into **2a** and **2b** in good yield by reacting with different boronic acid pinacol ester under Suzuki cross-coupling conditions.[31]

Another serieses of target compounds, **11a**, **11b** (possessing thiofuran or benzene instead of furan) and **2c–2v**, were prepared via a similar synthetic route with that of compound **2a** and **2b** (Schemes 2 and 3). Thus, a total of twenty-four new compounds had been prepared.

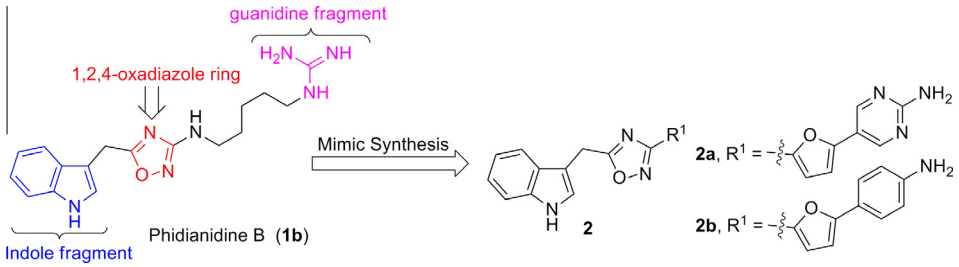
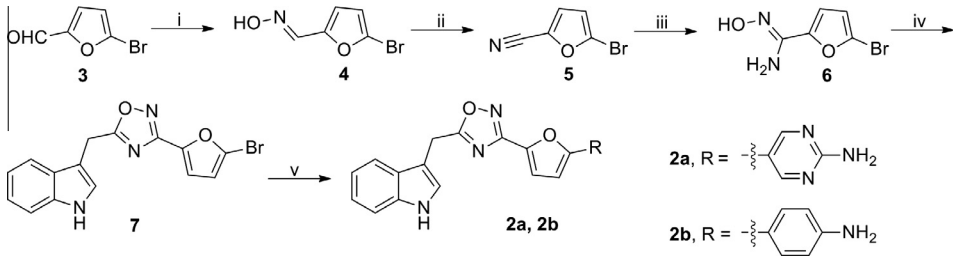
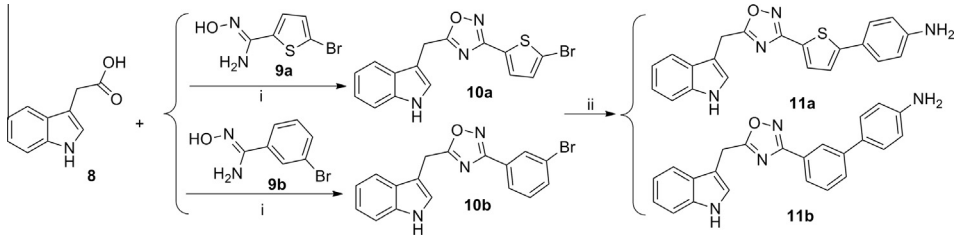


Figure 2. The synthesis of phidianidine B mimic.



Scheme 1. Synthesis of **2a** and **2b**. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, pyridine, EtOH, rt, overnight; (ii) $[Ru_2Cl_2(p\text{-cymene})]_2$, CH_3CN, reflux, 3 h; (iii) $NH_2OH{\cdot}HCl$, K_2CO_3, EtOH, reflux, 2 h; (iv) (1) indole-3-acetic acid (**8**), HATU, DIPEA, CH_2Cl_2, (2) NaOAc, EtOH, reflux, 2 h; (v) $Pd(PPh_3)_4$, 2-aminopyrimidine-5-boronic acid pinacol ester (for **2a**)/4-aminophenylboronic acid pinacol ester (for **2b**), K_2CO_3, dioxane, H_2O, 10 h.



Scheme 2. Synthesis of **11a** and **11b**. Reagents and conditions: (i) (1) HATU, DIPEA, CH_2Cl_2, (2) NaOAc, EtOH; (ii) $Pd(PPh_3)_4$, 4-aminophenylboronic acid pinacol ester, K_2CO_3, dioxane, H_2O.

As mentioned in the introduction section, in the course of our early studies the compound **2b** with the 4-(furan-2-yl)aniline as side chain was found to exhibit promising neuroprotective activity against $A\beta_{25-35}$- and OGD-induced neurotoxicity in SH-SY5Y cells, however compound **2a** with 5-(furan-2-yl)pyrimidin-2-amine as side chain was inactive. The preliminary study indicated that the substituent group attached to the furan played an important role in neuroprotective activity.

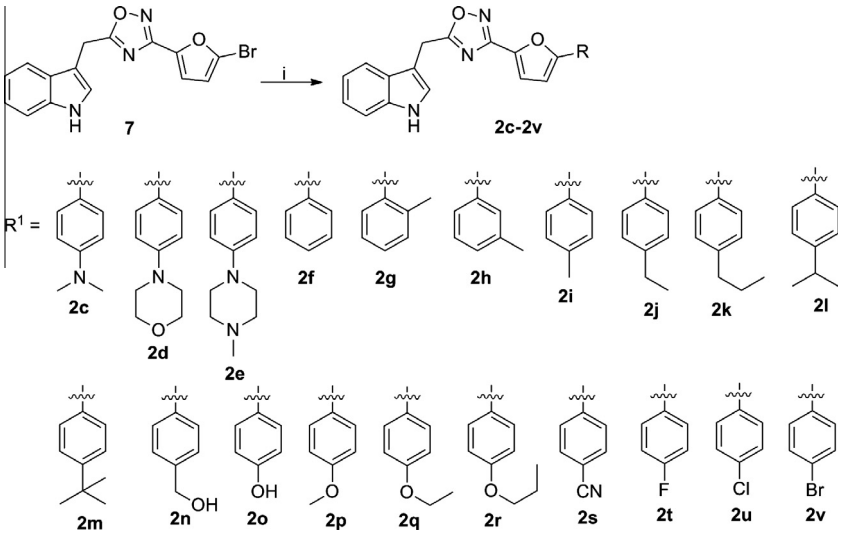
Before a systematic examination of the different substituent groups attached to the furan was undertaken, our initial effort was focused on screening different ring systems to replace the furan ring to optimize the neuroprotective activity. Therefore, the analogs **11a** and **11b** with a thiofuran or benzene ring were synthesized. The result of bioassay indicated that the introduction of thiofuran ring in **11a** completely led to the loss of neuroprotective activity, while the compound **11b** bearing a benzene ring showed good neuroprotective activity against $A\beta_{25-35}$-induced neurotoxicity with cell viability of 106% at 10 μM. However, it was disappointing that compound **11b** did not display neuroprotective activity against OGD-induced neurotoxicity. Consequently, the furan ring was considered to be optimal among the ring systems explored here. Thus, optimization of the substituent groups on the terminal benzene rings attached at 5-position of the furan ring was performed with the series of 1,2,4-oxadiazoles **2c–2v**.

The results of the neuroprotective activity of **2c–2v** against $A\beta_{25-35}$-induced neurotoxicity in SH-SY5Y cells are shown in Table 1. Most of compounds showed bioactivity with the range from 80.3% to 115.5% of cell viability at 10 μM, and two compounds **2k** and **2r** could further significantly increase the cell viability (89.7% and 90%, respectively) at 1 μM. Among all these tested derivatives, compound **2r** bearing propoxy group at the 4-position of the benzene ring showed the highest activity (115.5% at 10 μM), much better than the positive control EGGC. Although MTT reduction activities of compounds **2k**, **2r** and **11b** were over 100%, only **2k** and **2r** are significant as compared with control group, which indicated that these two compounds may promote the cell proliferation. However, it is noticeable that MTT reduction is dependent on NAD(P)H-dependent oxidoreductase enzyme, which is often used to determine the cell viability rather than the cell number, so the result of MTT may reflect either the number of viable cells or the activity of mitochondrion. In order to better determine the changes of cell numbers, we performed SRB assay, which is based on the measurement of protein content. After 24 h of incubation with SH-SY5Y cells, the SRB values of **2k** and **2r** groups were 96% and 94% of control, respectively, which suggested that neither of them promote the cell proliferation.

Compared with 4-amino compound (**2b**), installation of dimethylamino (**2c**), morpholine (**2d**), and 4-methylpiperazino (**2e**) led to the loss of neuroprotective effect due to the increased steric hindrance. Replacement of the 4-amino group with H, or 2-,3-,4-methyl group gave compounds **2f–2i**, of which only compound **2i** with 4-methyl showed activity (cell viability: 80.3% at 10 μM) indicating that the substituent at 4-position in the benzene ring was important for the activity. Among the compounds **2i–2k**, the activity was found to increase with the increase of the alkyl chain. The similar phenomenon was observed when the 4-hydroxyl (**2o**, inactive at 10 μM) was alkylated to give **2p** (91.5% at 10 μM), **2q** (89.1% at 10 μM), and **2r** (115.5%, at 10 μM; 90% at 1 μM). However, the introduction of isopropyl (**2l**), and *tert*-butyl (**2m**) with increased steric hindrance decreased the activity in some degree by comparison with **2j** and **2k**. Interestingly, the replacement of electron-releasing groups (such as methyl and methoxyl groups) with electron-withdrawing groups (nitrile or halogen groups) provided the corresponding **2s**–**2v**, which still showed effective neuroprotective activity (cell viability: 83.5–93.3% at 10 μM), indicating electronic effect of the substituents in 4-position might not be a key factor in their bioactivity against $A\beta_{25-35}$-induced neurotoxicity in SH-SY5Y cells.

All target compounds were further subjected to bioassay to test their in vitro neuroprotective effects against H_2O_2-induced damage in SH-SY5Y cells. The results are shown in Figure 3. Although only four compounds (**2c** and **2p**–**2r**) were active with 98.0–99.7% of cell viability at 10 μM, they still exhibited higher activity compared with the positive control L-NAC (89.2% at 100 μM). Unfortunately, these compounds did not show significant activity at 1 μM.

Further, the above compounds **2c** and **2p**–**2r** were selected to be evaluated for their activity against ODG-induced injury in SH-SY5Y cells (as an in vitro stoke or AD model). Among these compounds, **2q** (76.2%) and **2r** (84.1%) were active at 10 μM (shown in Fig. 4),



Scheme 3. Synthesis of **2c–2v**. Reagents and conditions: (i) $Pd(PPh_3)_4$, boronic acid pinacol ester (for **2d**)/boronic acids, K_2CO_3, dioxane, H_2O.

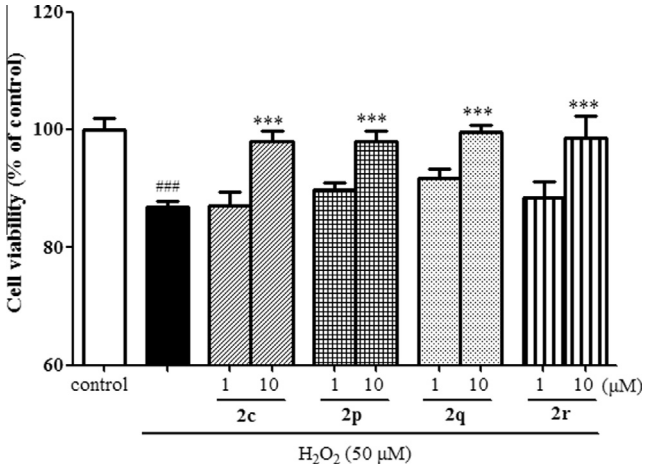


Figure 3. Neuroprotective effects of **2c**, and **2p–2r** on H_2O_2-induced injury in SH-SY5Y cells. Compounds **2c** and **2p–2r** at 10 μM significantly attenuated the reduced cell viability. Data are expressed as mean ± SD (n = 3–6), $^{###}P$ <0.001 versus control, $^{***}P$ <0.001 versus H_2O_2 treated only.

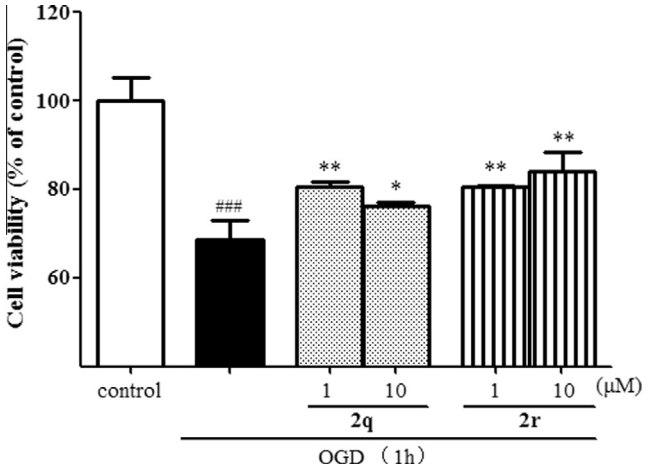


Fig. 4. Neuroprotective effects of **2r** and **2s** on OGD-induced injury in SHSY5Y cells. Compounds **2r** and **2s** showed potent protection against OGD insult. Data are expressed as mean ± SD (n = 3–6), $^{###}P$ <0.001 versus control, $^{*}P$ <0.05, $^{**}P$ <0.01 versus OGD treated only.

and both of them were still significantly active at lower tested concentration (cell viability: 80.6% and 80.4% at 1 μM, respectively). It is worth to note that among all the tested compounds only compounds **2q** and **2r** simultaneously displayed neuroprotective activity in the models of $A\beta_{25-35}$, H_2O_2 and ODG-inducted injury in SH-SY5Y cells. All these results suggested that the linear alkoxy group attached to the 4-position of the benzyl ring in this series have a positive effect on their neuroprotective activity.

In summary, the first mimic synthesis and SAR study of the first example of marine 1,2,4-oxadiazoles, phidianidines, were reported at the present work. A series of derivatives (**2a–2v**, **11a** and **11b**) possessing indole-based 1,2,4-oxadiazoles skeleton were prepared and evaluated for neuroprotective activities against $A\beta_{25-35}$-, H_2O_2-, and OGD-induced neurotoxicity in SH-SY5Y cells. Of these analogs, derivatives **2q** and **2r** showed good in vitro neuroprotective effect in all screening models. The preliminary SAR study indicated that the linear alkoxy group at 4-position of the benzene ring favors the neuroprotective activity, while a bulky group with high degree of steric hindrance could lead to the activity decrease or loss. The present result could provide useful information for the development of novel indole-based 1,2,4-oxadiazole neuroprotective agents for the treatment of AD. Further studies related to optimize the structure and clarify the action mechanism of this group of compounds are in progress.

Acknowledgments

This research work was financially supported by the National Marine '863' Projects (No. 2013AA092902), the Natural Science Foundation of China (Nos. 81302692 and 81273430), and the STCSM Projects (No. 14431901100).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.11.068.

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Please cite this article in press as: Jiang, C.-S.; et al. *Bioorg. Med. Chem. Lett.* (2014), http://dx.doi.org/10.1016/j.bmcl.2014.11.068