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# SAR-studies of γ-secretase modulators with PPARγ-agonistic and 5-lipoxygenase-inhibitory activity for Alzheimer's disease

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ABSTRACT

We present the design, synthesis and biological evaluation of compounds containing a 2-(benzylidene)hexanoic acid scaffold as multi-target directed γ-secretase-modulators. Broad structural variations were undertaken to elucidate the structure–activity-relationships at the 5-position of the aromatic core. Compound **13** showed the most potent activity profile with $IC_{50}$ values of 0.79 μM (Aβ42), 0.3 μM (5-lipoxygenase) and an $EC_{50}$ value of 4.64 μM for PPARγ-activation. This derivative is the first compound exhibiting low micromolar to nanomolar activities for these three targets. Combining γ-secretase-modulation, PPARγ-agonism and inhibition of 5-lipoxygenase in one compound could be a novel disease-modifying multi-target-strategy for Alzheimer's disease to concurrently address the causative amyloid pathology and secondary pathologies like chronic brain inflammation.



Alzheimer's disease (AD) is the most prevalent form of dementia, with an estimated 24 million affected individuals worldwide and projected 81 million patients in 2040.[1] AD is a progressive neurodegenerative disease, resulting in loss of memory and cognitive functions in the elderly, ultimately leading to death. According to the amyloid hypothesis, the accumulation of Aβ peptides in the brain, in particular the longer and more hydrophobic Aβ42 species, leads to the formation of soluble, neurotoxic oligomers and the characteristic extracellular amyloid plaques. These soluble and insoluble Aβ aggregates are believed to initiate pathological changes in the AD brain like synaptotoxicity, neuronal death, and chronic brain inflammation.[2,3]

Aβ-Peptides are formed by sequential cleavage of the amyloid precursor protein (APP) by β- and γ-secretase.[2] Based on this process, approaches to modulate the proteolytic processing of APP and the generation of Aβ peptides include targeting of the aspartic proteases β- and γ-secretase.[4] For γ-secretase, γ-secretase-inhibitors (GSIs) and γ-secretase-modulators (GSMs) have been developed. GSIs reduce the overall enzymatic activity of γ-secretase. In contrast, GSMs shift the Aβ product spectrum from Aβ42 towards shorter and less aggregation-prone peptides like Aβ38. Importantly, GSMs do not affect NOTCH receptor cleavage and signalling.[5,6] Impairment of NOTCH signaling was likely at least in part responsible for the reported clinical side-effects of GSIs.[7] Thus, modulation of γ-secretase could be a safe approach to selectively target Aβ42 production and aggregation, and downstream pathological changes.

The first GSMs were discovered among non-steroidal anti-inflammatory drugs (NSAIDs) and included sulindac sulfide, ibuprofen or flurbiprofen.[6,8] The drug candidate R-flurbiprofen (tarenflurbil), which lacks undesired cyclooxygenase-(COX)-inhibition but exerts equivalent GSM activity compared to racemic flurbiprofen, failed to show efficacy in a phase III clinical trial, possibly due to substance specific limitations such as low penetration of the blood brain barrier and weak GSM activity ($IC_{50}$Aβ42 = 307 μM).[9,10] Despite the failure of tarenflurbil, novel GSMs have been developed that can be structurally divided in acidic, NSAID-like GSMs (e.g., the Cellzome GSM series)[5] and non-acidic tetracyclic GSMs. Potential future drug candidates have shown activity in the low nanomolar range and are evaluated in early clinical trials (for review see Ref. 11).

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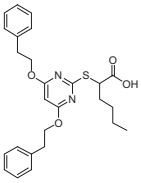
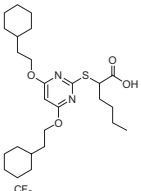
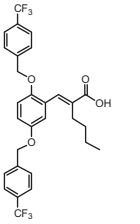
0960-894X/

**Table 1**
Previously published compounds that act as dual γ-secretase-modulators/PPARγ-agonists[12,13]

| Compound | γ-Secretase modulation | | PPARγ activation | | 5-LO-inhibition |
|---|---|---|---|---|---|
| | $IC_{50}$ Aβ42 | $EC_{50}$ Aβ38 | $EC_{50}$ | Max. activation | $IC_{50}$ |
| **1**  | 22.8 | 11.3 | 8.3 | 61% | 0.6 |
| **2**  | 5.1 | 4.6 | 6.6 | 71% | 0.8 |
| **3**  | 1.2 | 1.1 | 28% @10 μM | | 0.2 |

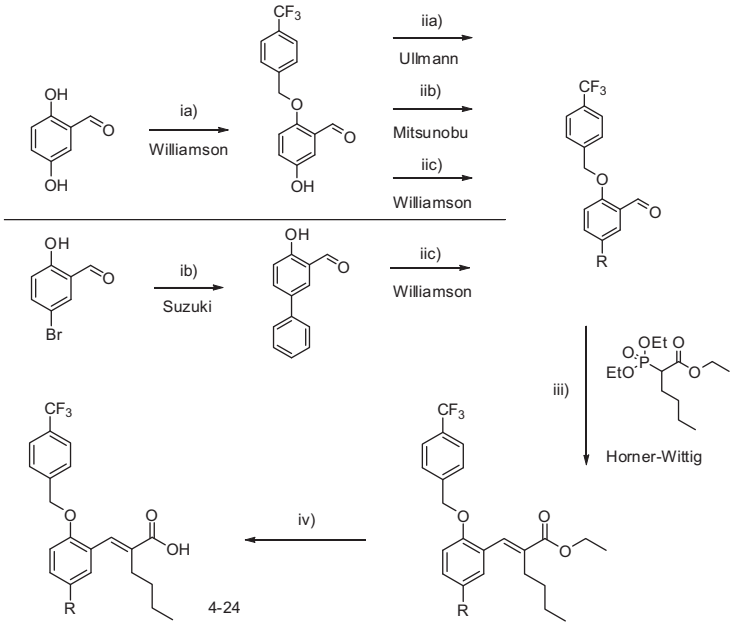
Values in μM; 100% maximal activation normalized to 1 μM pioglitazone.

We have contributed to the field with an approach to combine modulation of γ-secretase and of the peroxisome-proliferator-activated-receptor-γ (PPARγ).[12,13] PPARγ is a nuclear receptor involved in the lipid-metabolism and the response of peripheral tissues to glucose- and fatty acid uptake. PPARγ agonists were widely used as antidiabetic drugs, due to their insulin-sensitizing mode of action. Epidemiological studies have suggested a positive correlation between type 2 diabetes and the incidence of AD.[14] In addition, in vitro and in vivo investigations have demonstrated other activities of PPARγ agonists that might be beneficial in AD including down-regulation of β-secretase-(BACE1) expression, activation of insulin-degrading enzyme (IDE, which also degrades Aβ) and apolipoprotein E expression, enhancement of Aβ phagocytosis by microglia cells, improvement of hippocampus-dependent cognition, anti-inflammatory actions as well as improved glucose utilization of cerebral tissues.[15–20] Interestingly, an unbiased screen for suppressors of Aβ-induced neuronal degeneration recently identified the PPARγ agonist 5-deoxy-Δ12,14-prostaglandin J2, indicating that Aβ toxicity might, at least in part, be mediated by inhibition of PPARγ signaling.[21] Common safety liabilities of PPARγ agonists in the clinic are edema, weight gain and changes in lipid parameters. Rosiglitazone and Pioglitazone also showed substance-specific toxicity and their use was restricted.[22]

In addition to the potentially beneficial effects of modulating γ-secretase and PPARγ, 5-lipoxygenase (5-LO) could be another attractive target with implications for Aβ generation and brain inflammation.[23] Leukotrienes are products of the 5-LO-pathway, are well known mediators of inflammatory reactions and 5-LO expression appears to be upregulated in patients with AD.[24] A recently published study also showed that 5-LO and leukotrienes could promote Aβ generation, likely by transcriptional upregulation of γ-secretase subunits.[25] In other reports, the potent and selective 5-LO inhibitor zileuton reduced the amyloid and tau pathology as well as memory impairments in different mouse models of AD.[26,27] However 5-LO inhibition as a novel approach for the treatment of AD is still subject to further investigations evaluating its in vivo efficacy.

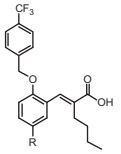
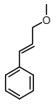
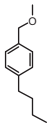
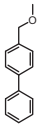
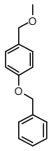
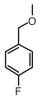
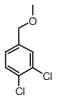
In summary, it could be a promising approach to combine GSM, PPARγ agonistic and 5-LO inhibitor activities in one compound to obtain a broad and potentially synergistic range of beneficial actions.

Our previous studies were based on the pirinixic acid derivative **1** (see Table 1), which is a moderately potent GSM with PPARγ ago-




**Scheme 1.** Synthesis of cinnamic acid derivatives: Reagents and conditions: (ia) 4-(Trifluoromethyl) benzyl bromide (1.0 equiv), $Cs_2CO_3$ (1.0 equiv), DMF, 60 °C, 2 h. (ib) Arylboronic acid (1 equiv), $Cs_2CO_3$ (2.5 equiv), $Pd(PPh_3)_4$ (0.1 equiv), toluene/EtOH 5:1, 80 °C, 2–3 h. (iia) Aryliodide (1.5 equiv), CuI (0.1 equiv), *N*,*N*-dimethylglycine (0.3 equiv), $Cs_2CO_3$ (2 equiv), DMF, 110 °C, 24 h. (iib) R-alcohol (1.3 equiv), TPP (1.3 equiv), DIAD or ADDP (1.3 equiv), THF, rt, 3–17 h. (iic) R-benzylhalide (1.3 equiv), $Cs_2CO_3$ (1.3 equiv), DMF, 60 °C, 2 h. (iii) Ethyl-2-diethoxy phosphorylhexanoate (1.3 equiv), NaH (1.3 equiv), THF, rt, 3–17 h. (iv) LiOH (10 equiv), THF, $H_2O$, MeOH, 40–60 °C, 17–72 h.

**Table 2**
In vitro pharmacological characterization I

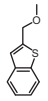
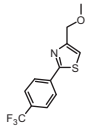
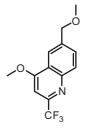
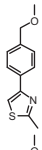
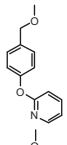
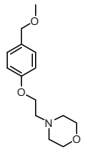
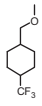
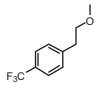
| Compound |  | γ-Secretase modulation | | PPARγ activation | | 5-LO-inhibition |
|---|---|---|---|---|---|---|
| | | $IC_{50}$ Aβ42 | $EC_{50}$ Aβ38 | $EC_{50}$ | Max. activation | $IC_{50}$ |
| Hydrophobic residues and different linkers | | | | | | |
| **4** |  | 11.9 | 12.0 | 26% @ 10 μM | | 5.7 |
| **5** |  | 14.9 | 15.6 | 0.72 | 76% | 2.1 |
| **6** |  | 19.3 | 14.1 | 11.7 | 108% | 0.55 |
| **7** |  | 4.1 | 2.5 | 12.9 | 56% | 0.75 |
| **8** |  | 4.9 | 4.4 | ia. | ia. | ia. |
| **9** |  | 11.9 | 3.2 | ia. | ia. | ia. |
| **10** |  | 8.5 | 1.8 | ia. | ia. | ia. |
| Haloaromatic substitution pattern | | | | | | |
| **11** |  | 7.0 | 13.8 | 5.17 | 76% | 0.5 |
| **12** |  | 2.0 | 3.2 | 2.11 | 56% | 0.3 |
| **13** |  | 0.79 | 1.0 | 4.64 | 103% | 0.3 |

ia. = inactive; values in μM; 100% maximal activation standardized to 1 μM pioglitazone.

nistic activity.[12] Improvement of activity was achieved through different substituents at the central pyrimidine core, with compound **2** being the most potent of this set. In addition to their function as GSMs and PPARγ-agonists, these structures are also known inhibitors of 5-LO and microsomal prostaglandin E2 synthase-1 (mPGES-1).[28] Through additional structural optimization,[13] we were able to establish a 2-[2,5-(phenalkoxy)benzylidene] hexanoic acid scaffold for further investigations in structure–activity-relationships (SAR). Compound **3** was the most potent GSM of this class, but activity toward PPARγ was nearly absent. In previous studies, we showed an important influence of the lipophilic backbone on the pharmacological activity profile of this class of compounds.[12,13] As the most potent GSM, compound **3** served as a structural template for all the presented derivatives. The 2-[(4-trifluoromethyl)benzyl]oxy-substituent was kept constant and the 5-position was varied to investigate the SAR of this part of the molecule. Based on 2,5-dihydroxybenzaldehyde, a four-step-synthesis incorporating mono-benzylation at position 2, derivatization of position 5 and formation of the conjugated acidic headgroup with subsequent hydrolysis was carried out to yield the compounds of this study (Scheme 1). Structural modifications of the 5-substituents were focused on hydrophobic moieties, different linkers, several haloaromatics and heteroaromatic mono- and multicyclic systems.

The synthetic procedures used in this work are described in Hieke et al. 2011.[13] In the first step, mono-benzylation of 2,5-dihydroxybenzaldehyde was done under Williamson-like conditions (step ia). Derivatization of position 5 resulted from a consecutive Williamson ether-synthesis, Mitsunobu-reaction or Ullmann ether-synthesis of the respective phenalkoxy halo gens, -alcohols and aryliodides (steps iia/b/c). Formation of the 2-(benzylidene)hexanoic acid derivatives was carried out in a Horner–Wittig

**Table 3**
In vitro pharmacological characterization II

| Compound | | γ-Secretase modulation | | PPARγ activation | | 5-LO-inhibition |
|---|---|---|---|---|---|---|
| | | $IC_{50}$ Aβ42 | $EC_{50}$ Aβ38 | $EC_{50}$ | Max. activation | $IC_{50}$ |
| Heterocyclic residues | | | | | | |
| **14** |  | 32.1 | 23.2 | 2.56 | 120% | 2.3 |
| **15** |  | 4.6 | 2.1 | ia. | ia. | 0.7 |
| **16** |  | 2.3 | 10.7 | ia. | ia. | 0.9 |
| **17** |  | 0.63 | 1.17 | 17% @ 10 μM | | 0.2 |
| **18** |  | 20.2 | 2.2 | ia. | ia. | 6.7 |
| **19** |  | 5.0 | 4.5 | ia. | ia. | 0.2 |
| **20** |  | 2.2 | 0.97 | 3.77 | 66% | 0.9 |
| Miscellaneous | | | | | | |
| **21** |  | >40 | >40 | 48% @ 10 μM | | ia. |
| **22** |  | 11.4 | 11.2 | 1.26 | 97% | 0.25 |
| **23*** |  | 1.0 | 1.1 | 2.16 | 158% | 1.7 |
| **24** |  | 1.5 | 1.3 | 21% @ 3 μM<br>72% @ 6 μM | | 0.5 |

ia. = inactive; values in μM; 100% maximal activation standardized to 1 μM pioglitazone.
* Mixture of *cis* and *trans*.

reaction to the ester intermediate (step iii) with subsequent hydrolysis (step iv). It has been successfully established to merge steps iii and iv into a one-pot-synthesis, without isolation of the ester intermediate. Synthesis of the biphenyl-derivative started with a Suzuki-coupling of 5-bromosalicyl aldehyde to introduce the biphenyl-backbone (step ib). The phosphonate-precursor for step iii) was prepared in an arbuzov reaction of the α-bromo-ester and triethylphosphite.

The methods for the biological characterization are described in previous reports.[12,13,28] To determine the GSM activity of novel derivatives, changes in the amounts of secreted Aβ38, Aβ40 and Aβ42 peptides were measured by ELISA in a previously described cell-based assay.[12] Transactivation of all PPAR subtypes was assessed with a cell-based luciferase assay. 5-LO inhibition was tested in a cell-based assay using polymorphonuclear leukocytes, and 5-LO enzymatic activity was measured by HPLC analysis of formed 5-LO products. Detailed procedures and conditions of synthesis and biological evaluation are provided in the Supporting information.

First, we varied the aliphatic spacer between the aromatic core and the phenyl residue in compounds **4** to **7** (see Table 2) compared to the parental compound **3**. Compound **6** showed the

weakest $IC_{50}$Aβ42 activity in this subgroup, and shorter and longer residues improved the GSM activity. Shortening to the biphenyl derivative (**4**) increased activity almost two-fold. Elongation (compound **7**) led to even higher potency with respect to GSM activity. There seemed to be a trend for higher GSM activity of less rigid structures when comparing $IC_{50}$Aβ42 data of the biphenylmethoxy-substituent (**9**) to hydrophobic residues of corresponding length (compound **8**). With regard to PPARγ activation and 5-LO inhibition, optimal activity was obtained for the diarylether (**5**, PPARγ) and benzyl derivative (**6**, 5-LO). The biphenyl analogue **4** showed a decreased activity for both targets. For longer residues, the PPARγ agonism and 5-LO inhibition was completely lost (**8** to **10**).

The haloaromatically substituted compounds showed a clearly higher potency at all three targets than compound **6**. A gradual increase of potency was observed with substituents providing a higher negative inductive effect at the aromatic system (**11** to **13**). Based on its activity profile at all three targets, compound **13** showed the best overall pharmacological profile with considerably increased activities (Aβ42: 0.79 μM, PPARγ: 4.64 μM, 5-LO: 0.3 μM) and a potent triple-target effect in the submicromolar to low-micromolar range.

In the heteroaromatic subset (see Table 3), the most potent GSMs were found with electron-poor terminal heterocycles (compounds **16**, **17** and **20** with 2.3, 0.63 and 2.2 μM for $IC_{50}$Aβ42). The most potent GSM of this study (compound **17**) showed the combination of an electron-deficient heterocycle with an attached trifluoromethyl group. The most potent GSM of this study (compound **17**) showed the combination of an electron-deficient heterocycle with an attached trifluoromethyl group. Furthermore, it exhibited the highest inhibition of 5-LO, but lacked potent PPARγ agonism. 5-LO inhibition was not exceptionally high throughout the heterocyclic-residue-subset, but in contrast to compounds **8** to **10** with large residues, the bulkier heterocyclic moieties were not detrimental. PPARγ activation, in contrast, was considerably lower, except for compound **14** and **20**. Only the latter showed a balanced but not remarkably potent activity profile.

In the miscellaneous fourth subset, the 5-hydroxy-derivative (**21**) showed no GSM activity, weak PPARγ agonism and a lack of 5-LO inhibition. In comparison to the benzyl derivative **6** the branched diphenylethoxy-derivative (compound **22**) showed a nearly two-fold higher GSM activity and 5-LO inhibition as well as a ten-fold increase in PPARγ agonism. The cyclohexyl analogue **23** displayed an interesting pharmacological profile with its potent and balanced activity at all three targets (Aβ42: 1.0 μM, PPARγ: 2.16 μM, 5-LO: 0.9 μM). The maximal PPARγ activation was exceptionally high with 158%. In comparison with the structural template of this study (compound **3**), derivative **24** showed a slightly weaker GSM activity and 5-LO inhibition, but higher potency for PPARγ agonism.

Previous studies had shown that 5-LO inhibitors often also affect mPGES-1 and/or COX enzymes, in particular pirinixic acid derivatives and derivatives of compound **3**,[29,30] and recent data suggested a role of $PGE_2$ and mPGES-1 in AD.[31] Therefore, we analyzed the ability of selected compounds that inhibited 5-LO (with $IC_{50}$ <2 μM) to suppress mPGES-1 and COX-1 and -2 (see Table 4). Whereas the parental compound **3** was a moderate mPGES-1 inhibitor ($IC_{50}$ > 10 μM), several compounds (i.e., **7**, **11**, **12**, **17**, **23**, **24**) efficiently inhibited mPGES-1 with $IC_{50}$ values in the range of 1.6 to 5.0 μM, being equally potent as the well-recognized mPGES-1 inhibitor MK-886 ($IC_{50}$ = 2.4 μM).[32] Interestingly, the compounds were much less active in inhibiting COX-1 and COX-2 ($IC_{50}$ >10 μM) suggesting that these compounds might preferentially suppress the synthesis of pro-inflammatory $PGE_2$ rather than blocking formation of all COX-derived prostanoids.

A cell-based NOTCH-1 reporter assay was used to investigate potential adverse effects of compounds **17** and **23** on NOTCH processing and signaling. Reporter activity was not affected in a concentration range of 5–50 μM. In contrast, treatment of cells with 0.5 μM of the γ-secretase inhibitor LY-411575 reduced reporter activity by >75%. The evaluation of cell viability of the compounds in Jurkat cells showed low overall toxicity at concentrations up to 30 μM for most compounds of this study. Only compounds **15** and **24** reduced cell viability at 30 μM by more than 50%. Further investigation of toxicity in CHO cells for compounds **13**, **17** and **23** showed at least 50% cell viability up to 30 μM (data in Supporting information).

In summary, the substitution at position 5 of the aromatic core contributed significantly to the potency and selectivity of the presented compounds. Shortening of the benzyl-motif to diarylether- and biphenyl-derivatives (compounds **4** to **6**) resulted in enhanced GSM activity, a decline in 5-LO inhibition and remarkably higher potency of PPARγ agonism for the diarylether derivative. There was an overall benefit of activity for electron-deficient aromatic systems, especially halogen-substituted (compounds **11** to **13**), as well as branched moieties at the 5-position (**22**). With the exception of compound **20**, structural elongation of the residues through para-substitution with additional aromatic and aliphatic systems resulted in a loss of PPARγ activity. With introduction of more polar heterocyclic structures we were in part able to decrease the high lipophilicity of the compounds and to maintain or enhance activity at the targets of this study (**17**, **20**).

In conclusion, this study describes the first series of triple-target-directed γ-secretase-modulators and gives valuable insights into the SAR of the 5-position of the aromatic core. Compound **13** was the first derivative that displayed activities at low micromolar to nanomolar levels at the desired targets, with substantial increases in activity compared to the lead structure of this study (compound **3**), particularly with regard to PPARγ activation. Compound **17** showed even higher activity for Aβ42 and 5-LO

**Table 4**
Effects of test compounds on mPGES-1 and COX1/2 in cell-free assays

| Compound | mPGES-1 | COX-1 | COX-2 |
|---|---|---|---|
| | $IC_{50}$ (or remaining activity at 10 μM) | $IC_{50}$ (or remaining activity at 10 μM) | $IC_{50}$ (or remaining activity at 10 μM) |
| **3** | >10<br>55.1 ± 5.4% | >10<br>82.6 ± 4.7% | >10<br>102.0 ± 5.5% |
| **6** | 5.6 | >10<br>86.6 ± 8.5% | >10<br>84.8 ± 2.6% |
| **7** | 5.0 | >10<br>69.5 ± 6.9% | >10<br>77.7 ± 8.8% |
| **11** | 4.9 | >10<br>78.4 ± 3.0% | >10<br>84.2 ± 4.2% |
| **12** | 1.6 | >10<br>59.4±6.3% | >10<br>73.3±0.5% |
| **13** | >10 | >10<br>62.4 ± 5.5% | >10<br>77.3 ± 4.1% |
| **15** | 9.2 | >10<br>67.4 ± 3.3% | >10<br>91.7 ± 4.3% |
| **16** | >10 | >10<br>73.5 ± 3.1% | >10<br>84.4 ± 3.3% |
| **17** | 3.0 | >10<br>69.0 ± 5.1% | >10<br>84.2 ± 2.3% |
| **19** | 10.0 | >10<br>75.7 ± 4.2% | >10<br>91.1±2.8% |
| **20** | 8.7 | >10<br>91.3 ± 1.8% | >10<br>95.0 ± 2.6% |
| **22** | >10 | >10<br>61.1 ± 1.3% | >10<br>79.5 ± 1.9% |
| **23** | 2.5 | >10<br>58.0 ± 4.3% | >10<br>75.3 ± 1.7% |
| **24** | 3.1 | >10<br>66.3 ± 2.9% | >10<br>72.2 ± 3.0% |

Values in μM, remaining activity in%.

inhibition, but PPARγ agonism was rather weak and therefore can be considered as a selective GSM/5-LO inhibitor. Compound **23** showed an overall balanced and potent pharmacological profile with high maximal activation of PPARγ. The lead compounds of this study are promising as a platform for optimization and preclinical investigations in AD animal models. The presented multitarget directed approach could be efficacious in AD by targeting different stages of the amyloid cascade and secondary pathological events like chronic brain inflammation.

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## Supplementary data

Supplementary data (including synthetic procedures, analytical data and assay descriptions) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.12.073.

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