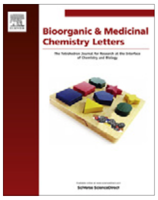
Bioorganic & Medicinal Chemistry Letters 22 (2012) 4926–4929

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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



Synthesis and evaluation of aplysinopsin analogs as inhibitors of human monoamine oxidase A and B

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ARTICLE INFO

Article history:
Received 8 May 2012
Revised 13 June 2012
Accepted 18 June 2012
Available online 23 June 2012

Keywords:
Monoamine oxidase inhibitors
Aplysinopsin analogs
Neurotransmitters
Natural product
Indole alkaloids

ABSTRACT

Aplysinopsins are tryptophan-derived natural products that have been isolated from a variety of marine organisms. Previous studies have shown aplysinopsin analogs to possess a variety of biological activities, including modulation of neurotransmissions. A series of fifty aplysinopsin analogs was synthesized and assayed for monoamine oxidase A and B inhibitory activity. Three compounds displayed significant MAO inhibitory activity and selectivity. The compound (*E*)-5-[(6-bromo-1*H*-indol-3-yl)methylene]-2-imino-1,3-dimethylimidazolidin-4-one (**3x**) possessed an IC_{50} of 5.6 nM at MAO-A and had a selectivity index of 80.24. An SAR study revealed that multiple N-methylations, one of which should be at position N-2′, and bromination at C-5 or C-6 are important factors for MAO-A potency and selectivity.

Depression effects nearly 1 in 10 adults in the US according to a study by the CDC.[1] The WHO estimates that by 2020 depression will be the second most disabling condition in the world.[2] Based on these statistics it is obvious that there is a need for new drug candidates in the treatment of depression.[3] Monoamine oxidase inhibitors (MAOIs) initially were first line medications in the treatment of depressive illness, however, due to serious side effects, the interest in these drugs diminished.[4] When the two isoforms, MAO-A and MAO-B, were discovered, interest was renewed in their potential therapeutic use and several new generations of selective MAO inhibitors have been developed.[5] Today, much more is known about the use of selective MAO inhibitors to treat various mental disorders such as depression, anxiety, Parkinson's, and Alzheimer's disease.[6] Due to this increased understanding of neurological disease states, there is an increased interest in development of potent and selective MAOIs.

Aplysinopsins (Fig. 1) are tryptophan-derived natural products isolated from a variety of marine organisms and found to have various biological activities.[7] Natural analogs differ in the bromination pattern of the indole ring as well as in the number and position of N-methylations of the imidazolidinone ring. Aplysinopsins have received considerable attention as promising neuromodulators with significant affinity to serotonin receptors[8] and the potential to inhibit MAO activity.[9] Since these two mechanisms account for antidepressant action, aplysinopsins represent potentially useful candidates in antidepressant drug development.

Structurally, aplysinopsins are made up of two distinct moieties: an indole and an imidazolidinone ring. The indole scaffold is known to contribute to MAO inhibitory activities, and many analogs have been prepared using it.[10] Furthermore, a recent study has shown that imidazolines possess potent and selective activity at both MAO isoforms.[11] Based on this information, we sought to design a series of aplysinopsin analogs with potent and selective MAOI activity. In the current work, the synthesis and structure–activity relationship (SAR) study of this series of aplysinopsin analogs are described.

A series of aplysinopsin analogs, **3a–ii**, were synthesized utilizing the condensation of indole-3-carboxyaldehydes and the appropriate imidazolidinones.[12a,b] (Scheme 1) The indole aldehydes **1a–e** were commercially available and the imidazolidinones **2a–h** have been obtained according to the published procedures.[13–15] Our attempts to obtain the imidazolidinone **2c** following the published procedure[14] and the condensation of glyoxal with *N*-methylguanidine[16] failed (Scheme 2). Eventually, the analogs with methylamine substitution, **7a–e**, were synthesized by condensation of corresponding indole-3-carboxyaldehydes **1a–e** with thiohydantoin (**4**), methylation of intermediate thiones **5a–e**, followed by substitution of thioethers **6a–e** with methylamine (Scheme 3).[12c–e]

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http://dx.doi.org/10.1016/j.bmcl.2012.06.058

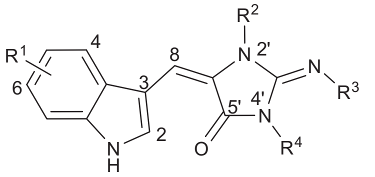
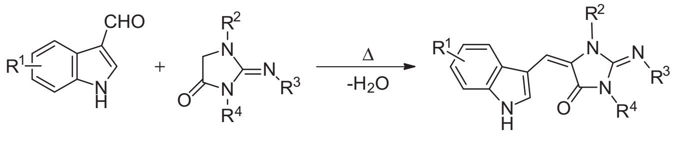


Figure 1. General structure of aplysinopsin analogs.

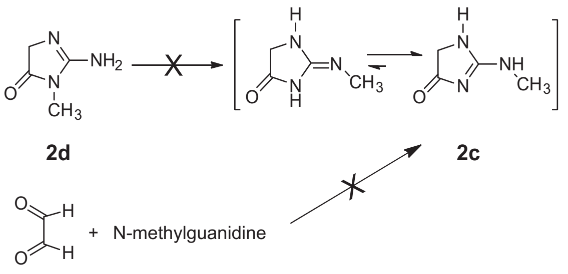


1a-e **2a-h** **3a-ii**

Compd	R^1	Compd	R^2	R^3	R^4
1a	-	**2a**	H	H	H
1b	4-Br	**2b**	Me	H	H
1c	5-Br	**2c**	H	Me	H
1d	6-Br	**2d**	H	H	Me
1e	7-Br	**2e**	Me	Me	H
		2f	Me	H	Me
		2g	H	Me	Me
		2h	Me	Me	Me

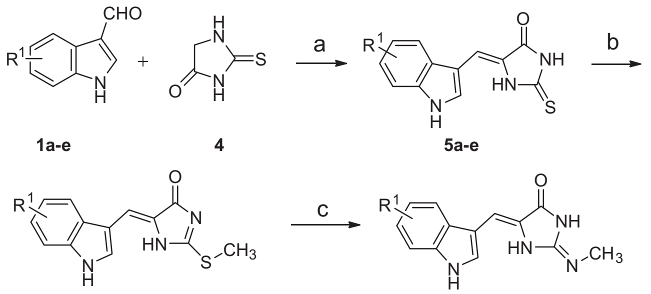
Compd	R^1	R^2	R^3	R^4	Compd	R^1	R^2	R^3	R^4
3a	-	H	H	H	**3r**	5-Br	Me	Me	H
3b	4-Br	H	H	H	**3s**	6-Br	Me	Me	H
3c	5-Br	H	H	H	**3t**	7-Br	Me	Me	H
3d	6-Br	H	H	H	**3u**	-	Me	H	Me
3e	7-Br	H	H	H	**3v**	4-Br	Me	H	Me
3f	-	Me	H	H	**3w**	5-Br	Me	H	Me
3g	4-Br	Me	H	H	**3x**	6-Br	Me	H	Me
3h	5-Br	Me	H	H	**3y**	7-Br	Me	H	Me
3i	6-Br	Me	H	H	**3z**	-	H	Me	Me
3j	7-Br	Me	H	H	**3aa**	4-Br	H	Me	Me
3k	-	H	H	Me	**3bb**	5-Br	H	Me	Me
3l	4-Br	H	H	Me	**3cc**	6-Br	H	Me	Me
3m	5-Br	H	H	Me	**3dd**	7-Br	H	Me	Me
3n	6-Br	H	H	Me	**3ee**	-	Me	Me	Me
3o	7-Br	H	H	Me	**3ff**	4-Br	Me	Me	Me
3p	-	Me	Me	H	**3gg**	5-Br	Me	Me	Me
3q	4-Br	Me	Me	H	**3hh**	6-Br	Me	Me	Me
					3ii	7-Br	Me	Me	Me

Scheme 1. Synthetic route to aplysinopsin analogs (**3a–ii**).



2d **2c**

Scheme 2. Synthetic scheme to obtain imidazolidinone **2c**.



1a-e **4** **5a-e** **6a-e** **7a-e**

Compound	R^1
5a, 6a, 7a	-
5b, 6b, 7b	4-Br
5c, 6c, 7c	5-Br
5d, 6d, 7d	6-Br
5e, 6e, 7e	7-Br

Scheme 3. The synthesis of C-3′ N-methylamine aplysinopsin analogs (**7a–e**). Reagents and conditions: (a) ETA, EtOH, reflux, 1 h; (b) CH_3I, NaOH, MeOH, rt, 18 h; (c) CH_3NH_2, EtOH, sealed vessel, 70 °C, 24h

The 50 new aplysinopsin analogs (**3a–ii**, **5a–e**, **6a–e**, **7a–e**) were evaluated for their MAO-A and MAO-B inhibitory activity.[21,22] (Table 1) In addition, clorgyline and deprenyl were evaluated as reference compounds. The results, expressed as IC_{50} and SI (selectivity index given by the MAO B IC_{50}/MAO A IC_{50} ratio) values are summarized in Table 1. In general we found that most aplysinopsin analogs showed greater inhibitory activity at MAO-A compared to MAO-B, with IC_{50} values ranging from 0.0056 to 26.12 μM for MAO-A and 0.207 to 100 μM for MAO-B. In particular, compound **3x** displayed excellent MAO-A inhibitory activity, with an IC_{50} value of 0.0056 μM and an SI of 80.24. It possesses a lower MAO-A IC_{50} than reference compound clorgyline (0.0067 μM).

To understand the SAR of the 50 aplysinopsin analogs, we prepared eight groups of analogs, based on the substitution pattern of their imidazolidinone moiety. In each of those eight groups there are five analogs, one non-brominated and four analogs brominated at positions 4, 5, 6, and 7 of the indole ring. In general, we found that analogs which did not have *N*-methyl groups on the imidazolidinone moiety displayed less inhibitory activity at both MAO-A and MAO-B, indicating that N-methylation of the imidazolidinone moiety is important for MAO inhibitory activity. Furthermore, mono-N-methylated compounds (**3f–o**, **7a–e**) did not possess significant activity at MAO-A or MAO-B. As we advanced to di-N-methylated analogs (**3p–dd**), we saw an overall increase in MAO inhibitory activity. The aforementioned **3x** as well as **3s** and **3u**, all displayed potent inhibition of MAO A with IC_{50} values of 0.0056, 0.029, and 0.035 μM, respectively. Compounds **3u** and **3x** are identical in their N-methylation pattern on the imidazolidinone, with positions N-2′ and N-4′ methylated, but differ in their indole bromination pattern. All three (**3s**, **3u**, **3x**) are di-N-methylated, with one of the N-methylations occurring at N-2′, which appears to play a large role in activity, as similar di-N-methylated compounds **3z–dd**, which are un-substituted at N-2′, are significantly less active. All three of the aforementioned compounds also possess a high SI, especially **3u**, which has an SI of 290.34.

The series of five tri-N-methylated analogs (**3ee–ii**) yielded the two lowest MAO-B IC_{50} values in compounds **3gg** and **3hh** (0.370 and 0.207 μM, respectively). These compounds lacked selectivity though, as they were both quite active at MAO-A as well.

Concerning the bromination pattern, we found that bromination at C-5 and C-6 resulted in the lowering of IC_{50} values across all eight groups of analogs. This is not surprising considering that most naturally occurring halogenated aplysinopsin analogs are