Jurnal 2020-1.pdf
Jan 21, 2022
3378 words / 17570 characters

Yuji Sumii

Jurnal 2020-1.pdf

Sources Overview

7%

OVERALL SIMILARITY

1	Kentaro Kamiya, Masayoshi Arai, Andi Setiawan, Motomasa Kobayashi. " Anti-dormant Mycobacterial Activity of Viomellein and Xanth... CROSSREF	<1%
2	Arai, Masayoshi, Shunsuke Ishida, Andi Setiawan, and Motomasa Kobayashi. "Haliclonacyclamines, Tetracyclic Alkylpiperidine Alkaloi... CROSSREF	<1%
3	K. C. Nicolaou, Xiao-Shui Peng, Ya-Ping Sun, Damien Polet, Bin Zou, Chek Shik Lim, David Y.-K. Chen. "Total Synthesis and Biological E... CROSSREF	<1%
4	Masayoshi Arai, Kentaro Kamiya, Patamaporn Pruksakorn, Yuji Sumii et al. "Anti-dormant mycobacterial activity and target analysis of ... CROSSREF	<1%
5	El Sahly, H.M.. "Drug-resistant tuberculosis: A disease of target populations in Houston, Texas", Journal of Infection, 200607 CROSSREF	<1%
6	Enrique L. Larghi, María L. Bohn, Teodoro S. Kaufman. "Aaptamine and related products. Their isolation, chemical syntheses, and biol... CROSSREF	<1%
7	Masayoshi Arai, Kentaro Kamiya, Dayoung Shin, Hirokazu Matsumoto et al. "N-Methylniphatyne A, a New 3-Alkylpyridine Alkaloi... CROSSREF	<1%
8	Arai, Masayoshi, Yoshi Yamano, Andi Setiawan, and Motomasa Kobayashi. "Identification of the Target Protein of Agelasine D, a Marin... CROSSREF	<1%
9	Rui Tang, Dongyi Zhou, Atsushi Kimishima, Andi Setiawan, Masayoshi Arai. "Selective cytotoxicity of marine-derived fungal metabolite... CROSSREF	<1%
10	worldwidescience.org INTERNET	<1%
11	JÃ¼rgen Hess, Leander Grode, Jacqueline Hellwig, Peter Conradt et al. " Protection against murine tuberculosis by an attenuated reco... CROSSREF	<1%
12	coek.info INTERNET	<1%
13	link.springer.com INTERNET	<1%

Excluded search repositories:

None

Excluded from document:

Bibliography
Quotes
Citations
Small Matches (less than 10 words)

Excluded sources:

repository.lppm.unila.ac.id, internet, 57%

Yuji Sumii, Naoyuki Kotoku, Chisu Han, Kentaro Kamiya, Andi Setiawan, Catherine Vilchèze, William R. Jacobs, Masayoshi Arai. "3-(Phenethylamino)demethyl(oxy)aaptamine as an anti-dormant mycobacterial substance: Isolation, evaluation and total synthesis", Tetrahedron Letters, 2020, crossref, 57%

Tetrahedron Letters 61 (2020) 151924

Contents lists available at ScienceDirect

Tetrahedron Letters

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

3-(Phenethylamino)demethyl(oxy)aaptamine as an anti-dormant mycobacterial substance: Isolation, evaluation and total synthesis

Yuji Sumii [a,1], Naoyuki Kotoku [a,2,*], Chisu Han [a], Kentaro Kamiya [a], Andi Setiawan [b], Catherine Vilchèze [c], William R. Jacobs Jr. [c], Masayoshi Arai [a,*]

[a] Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan
[b] Department of Chemistry, Faculty of Science, Lampung University, Jl. Prof. Dr. Sumantri Brodjonegoro No. 1, Bandar Lampung 35145, Indonesia
[c] Albert Einstein College of Medicine, 1301 Morris Park Avenue, Bronx, NY 10461, USA

ARTICLE INFO

Article history:
Received 28 February 2020
Revised 2 April 2020
Accepted 7 April 2020
Available online 11 April 2020

Keywords:
Aaptamine derivative
Antimicrobial
Tuberculosis
Dormant

ABSTRACT

3-(Phenethylamino)demethyl(oxy)aaptamine (**1**) was re-discovered from the marine sponge of *Aaptos* sp. as an anti-dormant mycobacterial substance through the bioassay-guided separation. Compound **1** showed potent anti-microbial activity against *Mycobacterium bovis* BCG with a minimum inhibitory concentration of 0.75 μg/mL under both aerobic conditions and hypoxic conditions inducing dormant state. Compound **1** was also effective against pathogenic *M. tuberculosis* strains including clinical multidrug-resistant strains. Furthermore, the successful total syntheses of **1** and its analog 3-aminodemethyl(oxy)aaptamine (**2**) afford sufficient quantities for further biological studies.

© 2020 Elsevier Ltd. All rights reserved.

Tuberculosis (TB) is one of the most common causes of morbidity and mortality in HIV-positive adults living in poverty [1]. There are an estimated 10 million new TB cases and 1.5 million deaths from TB each year [2]. It is now generally accepted that a minimum of 6 months of TB treatment is required owing to the difficulty of eradicating the non-replicating persistent *Mycobacterium tuberculosis*. One of the major reasons for the extended chemotherapeutic regimens and wide epidemicity of TB is the ability of its causative agent, namely *M. tuberculosis*, to become dormant. Therefore, new anti-mycobacterial lead compounds effective against *M. tuberculosis* in both active and dormant states are urgently required. Hypoxic conditions induce the dormant state of *Mycobacterium* sp., which has a drug susceptibility profile resembling that of the latent *M. tuberculosis* infection, although the physiology of the latent *M. tuberculosis* infection remains unclear [3–5]. Based on this background, we previously established a screening system to isolate anti-dormant mycobacterial substances from marine organisms on the basis of a bioassay-guided separation [6–8]. Furthermore, we have also conducted target analyses of the isolated substances to identify novel drug targets against *M. tuberculosis* [9–12].

In the continuous screening from marine organisms and marine-derived microorganisms, 3-(phenethylamino)demethyl(oxy)aaptamine (**1**) [13,14] was re-discovered as a promising anti-dormant mycobacterial substance, from an Indonesian marine sponge of *Aaptos* sp. In this manuscript, we present the isolation, the anti-mycobacterial evaluation against *M. bovis* BCG and pathogenic strains of *M. tuberculosis*, and the total synthesis of 3-(phenethylamino)demethyl(oxy)aaptamine (**1**).

Previously, we isolated a new aaptamine class alkaloid, named 2-methoxy-3-oxoaaptamine (**8**), together with seven known aaptamines (**2**–**7**,**9**), as anti-dormant mycobacterial substances from the marine sponge of *Aaptos* sp. 09C21, which had been collected in 2009 at Kupang, Indonesia (Fig. 1) [8]. Further exploration of the MeOH extract of the same sponge resulted in discovering another active constituent exhibiting potent anti-dormant mycobacterial activity. Bioassay-guided separation using the saprophyte, fast-growing *Mycobacterium smegmatis* provided 3-(phenethylamino)demethyl(oxy)aaptamine (**1**) [13] as a potent anti-microbial substance. Compound **1** was identified by MS and NMR analyses. As shown in Table 1, compound **1** showed a moderate activity against *M. smegmatis* under aerobic and hypoxic

* Corresponding authors.
E-mail addresses: kotoku@fc.ritsumei.ac.jp (N. Kotoku), araim@phs.osaka-u.ac.jp (M. Arai).
[1] Present affiliation: Graduate School of Engineering, Nagoya Institute of Technology, Nagoya 466-8555, Japan.
[2] Present affiliation: College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Noji-higashi, Kusatsu, Shiga, 525-8577, Japan.

https://doi.org/10.1016/j.tetlet.2020.151924
0040-4039/© 2020 Elsevier Ltd. All rights reserved.

1/21/22, 9:58 PM Jurnal 2020-1.pdf - Yuji Sumii

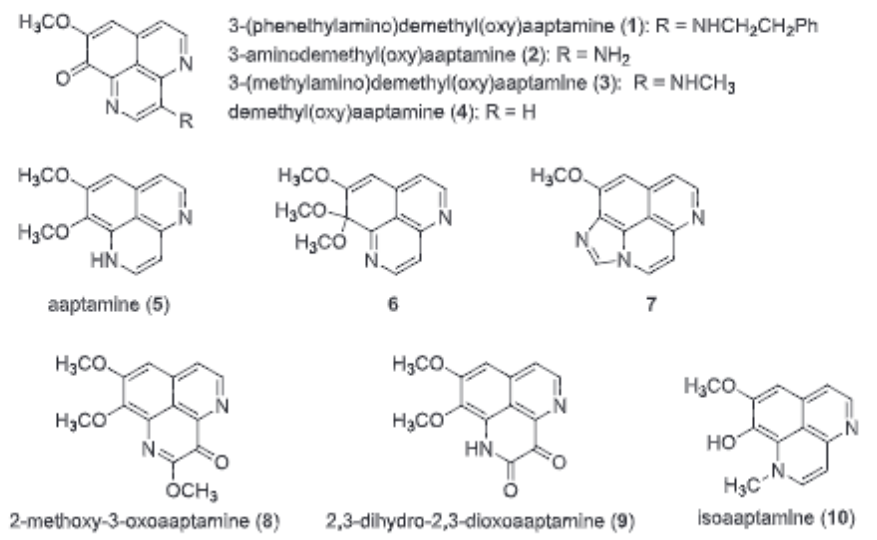


Fig. 1. Chemical structures of 3-(phenethylamino)demethyl(oxy)aaptamine (**1**) and related compounds.

conditions, with minimum inhibitory concentrations (MICs) of 12.5 μg/mL and 6.25 μg/mL, respectively.

We have previously reported that compounds **2–9** showed potent anti-mycobacterial activities against *M. smegmatis* under both actively growing and dormancy-inducing hypoxic conditions, with MIC values of 1.5–25 μg/mL [8]. However, the anti-microbial activity of these compounds on pathogenic mycobacterial species was not investigated. Thus, we examined the anti-mycobacterial activities of compounds **2–9**, together with that of the newly identified compound **1**, against the vaccine strain *M. bovis* BCG, a strain with high homology to *M. tuberculosis*. As a result, compound **9** retained a moderate anti-microbial activity against *M. bovis* BCG under both aerobic and hypoxic conditions with MIC values of 25 μg/mL, whereas the activity of most of the other compounds was markedly reduced against *M. bovis* BCG (Table 1). In contrast, compound **1** showed a potent anti-microbial activity against *M. bovis* BCG with MIC value of 0.75 μg/mL (2 μM) under both aerobic and hypoxic conditions (Table 1). As a comparison, the first-line anti-TB drug isoniazid has an MIC of 0.05 μg/mL (0.4 μM) under both aerobic but is inactive under hypoxic conditions.

The intriguing anti-mycobacterial properties of **1** against *M. bovis* BCG suggested that compound **1** would be a potential novel anti-TB drug lead. However, its scarce supply from natural sources hampered further biological evaluations and mechanistic studies. To address this issue, we engaged in the total synthesis of **1** to supply a sufficient amount of compound for further investigations.

To date, many synthetic approaches to natural aaptamines [15] and the related analogs of isoaaptamine (**10**, Fig. 1) [16–18] have been published due to their interesting fused heterocyclic structures and their biological activities. In general, the third ring of the benzo[*de*][1,6]-naphthyridine ring is constructed using either the isoquinoline (AB) or the quinoline (AC) structure as a starting component (Fig. 2). Although tremendous synthetic studies of aaptaminoids have been conducted, 3-substituted aaptaminoids have yet to be synthesized. To access the synthesis of **1**, the introduction of a nitrogen substituent into the C-3 position and aromatization of the triamine moiety could be considered a potential route. Based on previous synthetic studies and a brief exploration of some of our preliminary studies, we envisioned that adapting the Pelletier and Cava method (AB → C) [19] to the synthesis of **1** would be a scalable synthetic methodology. Next, we disclose a concise synthesis of **1** that allows sufficient amount to be synthesized for further biological studies.

Initially, the tricyclic lactam **19** was prepared from commercially available homoveratrylamine (**14**) according to a previously reported method with some modifications (Scheme 1) [19]. The condensation of **14** with formic acid and the following Bischler – Napieralski cyclization gave 6,7-dimethoxy-3,4-dihydroisoquinoline (**15**) in a quantitative yield [20]. The selective demethylation of **15** by HBr aq. then gave the compound **13** in a moderated yield (46%), and the subsequent nitration by 40% nitric acid and a catalytic amount of $NaNO_2$ gave **16** in 59% yield. Compound **16** was then treated with monoethyl malonate at 125 °C to afford **17** (89% yield), which was subjected to the catalytic hydrogenation in AcOH providing the lactam **12** in a good yield. The secondary amino group of **12** was selectively protected by the Boc group, using Boc_2O in $CHCl_3$ at 75 °C, and then treated with NaOMe in MeOH to give **18**. Finally, **18** was benzylated with BnBr and K_2CO_3 to afford the tricyclic lactam **19**.

With the tricyclic lactam **19** in hand, we then examined the introduction of the amino group at the C-3 position of **19** (Scheme 2). Compound **19** was converted to the bis *N*-Boc derivative **20** in 89% yield using Boc_2O, Et_3N, and DMAP at 75 °C. Fortunately, treatment of **20** with KHMDS and trisyl azide [21] resulted in the successful introduction of the azide moiety to provide **21** in a moderate yield. However, selective reduction of the azide group to the corresponding amine was problematic. Specifically, the catalytic hydrogenation of azide **21** gave a complex mixture, while the Staudinger reaction of **21** gave a stable *N*-ylide compound which could not be hydrolyzed to the corresponding amine under any conditions examined. After screening various reduction conditions, we found that the reduction of **21** was successful when using zinc in an acidic medium. The optimized condition, using zinc powder (2 equiv.) in the presence of HCO_2NH_4 (6 equiv.) as a hydrogen donor [22] in CH_2Cl_2-MeOH (3:1), provided the amine **22** with good reactivity and selectivity, in a moderate yield on the gram scale. The primary amine of **22** was then acylated with phenylacetyl chloride to give the amide **23**. Subsequent

Table 1
MICs of aaptamines against *M. smegmatis* and *M. bovis* BCG under aerobic and hypoxic conditions.

	MICs (μg/mL)			
	M. smegmatis		*M. bovis* BCG	
Compounds	Aerobic	Hypoxic	Aerobic	Hypoxic
1	12.5	6.25	0.75	0.75
2	6.25*	1.5*	200	100
3	6.25*	12.5*	100	100
4	25*	6.25*	200	200
5	100*	200*	200	200
6	25*	6.25*	>200	>200
7	25*	12.5*	100	100
8	6.25*	1.5*	50	25
9	25*	6.25*	25	25
Isoniazid	2.5	25	0.05	>200

*MICs of compounds **2–9** against *M. smegmatis* cited from reference 8.

https://unila.turnitin.com/viewer/submissions/oid:7867:12758122/print?locale=en 4/6

1/21/22, 9:58 PM Jurnal 2020-1.pdf - Yuji Sumii

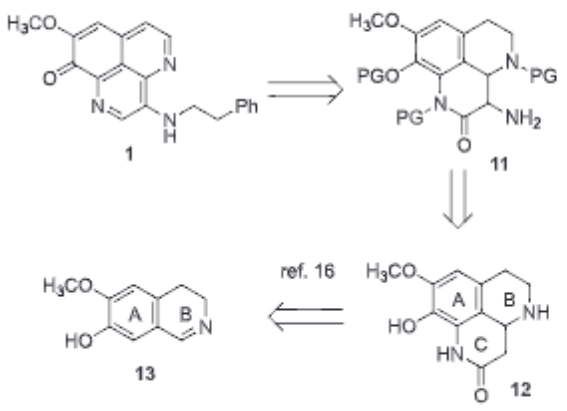
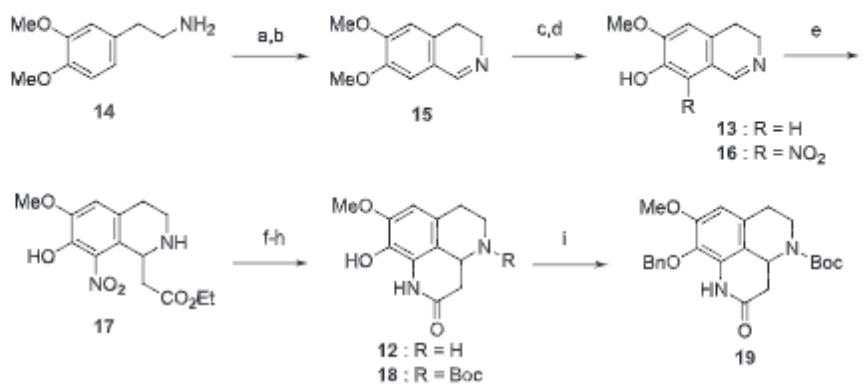
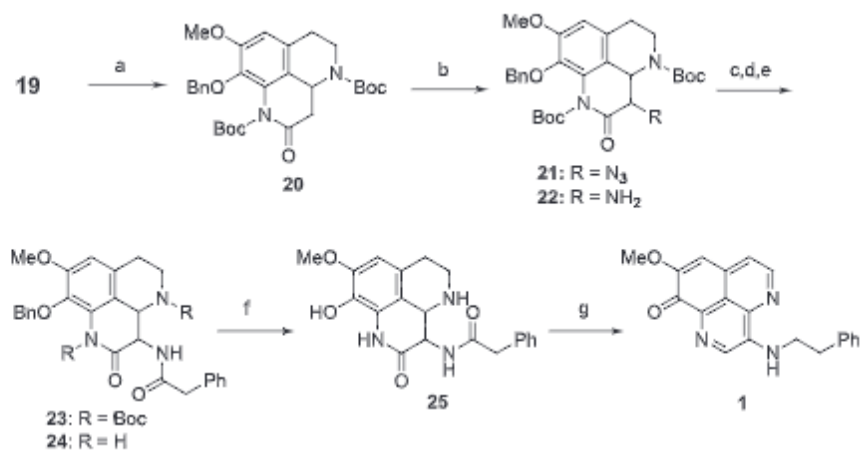


Fig. 2. Retrosynthetic analysis of **1**. PG: protecting groups.

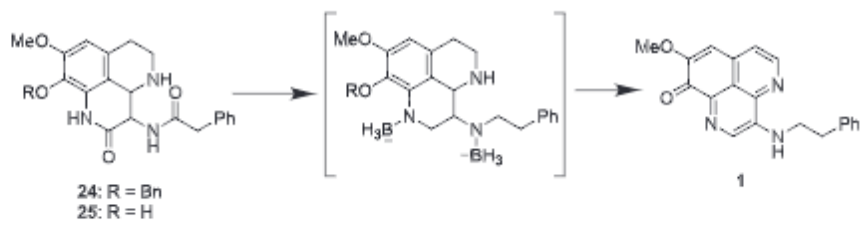


Scheme 1. Reagents and conditions: (a) HCO_2H, 175 °C; (b) $POCl_3$, toluene, 95 °C; (c) 48% HBr, 95 °C, 46% (3 steps); (d) 40% HNO_3, $NaNO_2$, EtOH, −15 °C to 0 °C, 59%; (e) monoethyl malonate, reflux, 89%; (f) H_2, Pd-C, AcOH, 71%; (g) Boc_2O, $CHCl_3$, reflux; (h) NaOMe, MeOH-CH_2Cl_2, 88% (2 steps); (i) BnBr, K_2CO_3, quant.



Scheme 2. Reagents and conditions: (a) Boc_2O, Et_3N, DMAP, $CHCl_3$, reflux, (89%); (b) KHMDS, trisylazide, −78 °C, then AcOH, 0 °C, 70%; (c) Zn, NH_4HCO_2, CH_2Cl_2-MeOH; (d) $PhCH_2COCl$, pyridine; (e) TFA, CH_2Cl_2, 46% (3 steps); (f) H_2, Pd-C, THF-MeOH, 80%; (g) (i) BH_3. THF, THF, 45 °C, (ii) 5% HCl, THF; (iii) O_2, 20% TFA, 85 °C, 45%.

deprotection with TFA provided the amino lactam **24** in 46% yield in three steps. Next, the reduction of the two amide moieties of **24** and the oxidative aromatization to provide the desired compound **1** were examined. Reduction of the diamide proceeded smoothly using BH_3. THF complex (10 equiv) under heating condition (45 °C) to give the amine-borane complex, which was hydrolyzed in a one-pot reaction by 6 N HCl at 80 °C under air to obtain the crude triamine (Scheme 3). Interestingly, we found that another



Scheme 3. Conversion of **24** or **25** to **1**.

product with red color, the desired target compound **1**, was formed during the hydrolysis reaction, albeit in a low yield (~20%). We assumed that this unexpected oxidation might be induced by the presence of oxygen and acid. As expected, a higher yield (~30%) of **1** was obtained when carrying out the hydrolysis-oxidation reaction under an O_2 atmosphere, and no trace of **1** was observed under an argon atmosphere. In addition, longer reaction time (>15 h) or higher temperature (>90 °C) gave **1** in poor yield, and the oxidation did not proceed under lower temperatures (<60 °C) or under basic condition (under O_2, 80 °C).

From these results, we estimated that the phenol **25** might be more reactive in the hydrolysis–oxidation reaction since removal of the Bn group is necessary to the oxidation reaction providing the oxyaaptamine skeleton. Thus, the Bn group of diamide **24** was removed by hydrogenation to give **25** in 80% yield, and the reduction–hydrolysis–oxidation reaction sequence against the phenol **25** was attempted. As expected, phenol **25** was smoothly converted to **1** in moderate yield (42%) under the same reaction condition ((i) BH_3, 45 °C, (ii) O_2, 6 N HCl, 85 °C). Upon further screening of the reaction conditions, we found that using TFA was effective as an acid and aqueous medium could significantly promote the oxidation reaction. Finally, the optimized condition (20% TFA, 85 °C) provided **1** in 69% yield from **25**. Furthermore, this reaction could be scaled up to ≈100 mg to give **1** with slightly lower yield (45%). All physical properties (^{1}H and ^{13}C NMR spectra and MS) of the synthesized **1** were in accordance to those reported for the natural substance. In addition, the prepared **1** exhibited a comparable anti-mycobacterial activity to the natural **1** against *M. smegmatis* and *M. bovis* BCG under both aerobic and hypoxic conditions.

To evaluate the validity of compound **1** as a candidate new lead for an anti-TB drug, we further investigated its anti-microbial activity against various pathogenic strains of *M. tuberculosis* (Table 2). As a result, compound **1** was found to exhibit a potent anti-mycobacterial activity (MIC values ranging from 0.5 to 2.0 μg/mL) against the drug sensitive *M. tuberculosis* H37Rv, Erdman and Beijing strains grown under aerobic conditions. In addition, compound **1** exhibited similar anti-microbial activity against drug-resistant, multidrug-resistant and extensively drug-resistant *M. tuberculosis* strains, with MIC values of 0.5–2.0 μg/mL. These results imply that the mechanism of action of compound **1** differs from those of existing anti-TB drugs. To date, a few semi-synthetic derivatives of aaptamine (**5**) and isoaaptamine (**10**) [16] have been reported to exhibit anti-microbial activity against *M.*

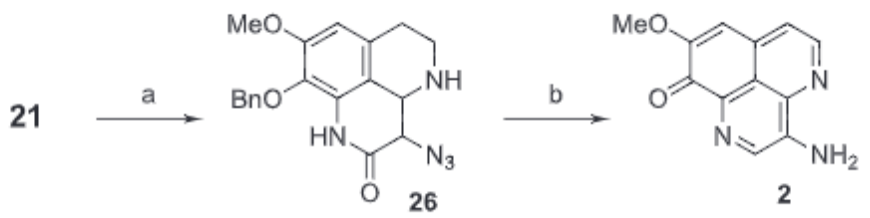
Table 2
MICs of compound **1** against *M. tuberculosis* strains.

Strains	Drug Resistance	MIC (μg/mL)
H37Rv	–	0.5–1.0
Erdman	–	1.0
Beijing	–	2.0
mc^{2}4977	INH[a]	1.0
mc^{2}4986	RIF[b]	1.0
mc^{2}5886	OF[c]	0.5
mc^{2}5858	INH, RIF	1.0
CI5071	INH, SM[d]	2.0
CI5483	EMB[e], SM	0.5–1.0
CI12081	INH, RIF, SM, EMB, ETH[f]	0.5
KZN11	INH, RIF, SM, EMB	0.5
TF275	INH, RIF, SM, EMB, ETH, KM[g], PZA[h]	0.5

[a] : isoniazid,
[b] : rifampicin,
[c] : ofloxacin,
[d] : streptomycin,
[e] : ethambutol,
[f] : ethionamide,
[g] : kanamycin,
[h] : pyrazinamide.

https://unila.turnitin.com/viewer/submissions/oid:7867:12758122/print?locale=en 5/6

1/21/22, 9:58 PM Jurnal 2020-1.pdf - Yuji Sumii



Scheme 4. Reagents and conditions: (a) TFA, CH_2Cl_2, quant.; (b) BH_3. THF, THF, 45 °C, then O_2, 6 N HCl, 85 °C, 33%.

tuberculosis H37Rv or *M. intracellulare* under actively growing conditions, while no anti-microbial activity against pathogenic mycobacterial species has been reported for aaptamine (**5**) and other natural related compounds [17,18]. In addition, the structure-activity relationships and the target molecule of this class of alkaloids as an anti-mycobacterial remain to be investigated.

Considering that the synthesis of 3-(*N*-substituted)demethyl (oxy)aaptamine analogs could lead to potential novel antimycobacterial compounds, we hypothesized that 3-aminodemethyl (oxy)aaptamine (**2**) may be a useful building block and therefore attempted its synthesis. We envisioned that the BH_3-reduction–hydrolysis–aromatization reaction of a 3-azide compound would give **2**. Thus, removal of bis Boc groups of the 3-azide **21** by treatment with TFA in CH_2Cl_2 was carried out to give the 3-azide-amino lactam **26** in a quantitative yield (Scheme 4). We then examined the one-pot BH_3 reduction–hydrolysis–oxidation reaction. After treatment of the azide amino lactam **26** by BH_3, the reaction mixture was hydrolyzed with 6 N HCl and heated at 85 °C under oxygen atmosphere. As expected, removal of Bn group, hydrolysis reaction and aromatization afforded the desired product **2** in a low yield (Scheme 4). All of the spectral data of the synthetic **2** were identical with those of the naturally occurring **2**.

In summary, we re-discovered 3-(phenethylamino)demethyl (oxy)aaptamine (**1**) as a potent anti-dormant mycobacterial substance against *M. bovis* BCG and *M. tuberculosis* under aerobic and hypoxic conditions. We also accomplished the total syntheses of **1** and 3-aminodemethyl(oxy)aaptamine (**2**), through the introduction of nitrogen into the α-position of the lactam, and subsequent oxygen-mediated aromatization. Although the elegant total syntheses of demethyl(oxy)aaptamine and its 3-alkylamino derivatives were reported recently [22], our method provides a more diversified library of analogs with various oxidation states in the core structure and/or substituents. We expect that structure-activity relationship studies of the analogs could lead to the development of more promising anti-dormant mycobacterial drug candidates. Further validation of the feasibility of the above compounds as anti-TB drugs are now underway, along with target identification study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was funded by the Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research [BINDS]) from AMED (grant no. JP19am0101084), the Kobayashi International Scholarship Foundation, and a Grant-in-Aid for Scientific Research B (grant nos. 18H02096 and 17H04645) from JSPS to MA. This work was also supported by the National Institutes of Health Grant AI26170 to WRJ.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151924. These data include MOL files and InChiKeys of the most important compounds described in this article.

References

[1] V. Idemyor, J. Natl. Med. Assoc. 99 (12) (2007) 1414–1419.
[2] Global Tuberculosis report 2019 World Health Organization: Geneva, Switzerland. Available online: http://www.who.int/tb/publications/global_report/en/. (Accessed on 10 February 2020).
[3] L.G. Wayne, C.D. Sohaskey, Annu. Rev. Microbiol. 55 (2001) 139–163.
[4] A. Lim, M. Eleuterio, B. Hutter, B. Murugasu-Oei, T. Dick, J. Bacteriol. 181 (7) (1999) 2252–2256.
[5] T. Dick, B.H. Lee, B. Murugasu-Oei, FEMS Microbiol. Lett. 163 (2) (1998) 159–164.
[6] P. Pruksakorn, M. Arai, N. Kotoku, C. Vilchèze, A.D. Baughn, P. Moodley, W.R. Jacobs Jr., M. Kobayashi, Bioorg. Med. Chem. Lett. 20 (12) (2010) 3658–3663.
[7] Y. Yamano, M. Arai, M. Kobayashi, Bioorg. Med. Chem. Lett. 22 (14) (2012) 4877–4881.
[8] M. Arai, C. Han, Y. Yamano, A. Setiawan, M. Kobayashi, J. Nat. Med. 68 (2) (2014) 372–376.
[9] M. Arai, L. Liu, T. Fujimoto, A. Setiawan, M. Kobayashi, Mar. Drugs 9 (6) (2011) 984–993.
[10] P. Pruksakorn, M. Arai, L. Liu, P. Moodley, W.R. Jacobs Jr., M. Kobayashi, Biol. Pharm. Bull. 34 (8) (2011) 1287–1290.
[11] M. Arai, Y. Yamano, A. Setiawan, M. Kobayashi, ChemBioChem 15 (1) (2014) 117–123.
[12] M. Arai, K. Kamiya, P. Pruksakorn, Y. Sumii, N. Kotoku, J.P. Joubert, P. Moodley, C. Han, D. Shin, M. Kobayashi, Bioorg. Med. Chem. 23 (13) (2015) 3534–3541.
[13] K. Shaari, K.C. Ling, Z.M. Rashid, T.P. Jean, F. Abas, S.M. Raof, Z. Zainal, N.H. Lajis, H. Mohamad, A.M. Ali, Mar. Drugs 7 (1) (2009) 1–8.
[14] H.B. Yu, F. Yang, F. Sun, G.Y. Ma, J.H. Gan, W.Z. Hu, B.N. Han, W.H. Jiao, H.W. Lin, J. Nat. Prod. 77 (9) (2014) 2124–2129.
[15] E.L. Larghi, M.L. Bohn, T.S. Kaufman, Tetrahedron 65 (22) (2009) 4257–4282.
[16] S.A. Fedoreev, N.G. Prokof'eva, V.A. Denisenko, N.M. Rebachuk, Pharm. Chem. J. 22 (8) (1988) 615–618.
[17] W. Gul, N.L. Hammond, M. Yousaf, J.J. Bowling, R.F. Schinazi, S.S. Wirtz, G.C. Andrews, C. Cuevas, M.T. Hamann, Bioorg. Med. Chem. 14 (24) (2006) 8495–84505.
[18] G.R. Pettit, H. Hoffmann, D.L. Herald, P.M. Blumberg, E. Hamel, J.M. Schmidt, Y. Chang, R.K. Pettit, N.E. Lewin, L.V. Pearce, J. Med. Chem. 47 (7) (2004) 1775–1782.
[19] J.C. Pelletier, M.P. Cava, J. Org. Chem. 52 (4) (1987) 616–622.
[20] F. Werner, N. Blank, T. Opatz, Eur. J. Org. Chem. 2007 (23) (2007) 3911–3915.
[21] D.A. Evans, T.C. Britton, J.A. Ellman, R.L. Dorow, J. Am. Chem. Soc. 112 (10) (1990) 4011–4030.
[22] Y. Gao, F. Yang, F. Sun, L. Liu, B. Liu, S.P. Wang, C.W. Cheng, H. Liao, H.W. Lin, Org. Lett. 21 (5) (2019) 1430–1433.

https://unila.turnitin.com/viewer/submissions/oid:7867:12758122/print?locale=en 6/6