Journal of the Korean Chemical Society
2020, *Vol. 64, No. 2*
Printed in the Republic of Korea
https://doi.org/10.5012/jkcs.2020.64.2.79

Discovery of Epinastine-NSAID Hybrids as Potential Anti-inflammatory Agents: Synthesis and *In Vitro* Nitric Oxide Production Inhibitory Activity Study

Hyeong Ryeol Woo, Kongara Damodar, Yeontaek Lee[†], Soon-sung Lim[‡], Sung Ho Jeon[†,*], and Jeong Tae Lee*

Department of Chemistry and Institute of Applied Chemistry, Hallym University, Chuncheon 24252, Korea.
**E-mail: jtshl@hallym.ac.kr*
[†]*Department of Life Science and Multidisciplinary Genome Institute, Hallym University, Chuncheon 24252, Korea.*
**E-mail: sjeon@hallym.ac.kr*
[‡]*Department of Food Science and Nutrition and Institute of Korean Nutrition, Hallym University, Chuncheon 24252, Korea.*
(Received December 30, 2019; Accepted February 7, 2020)

ABSTRACT. A novel pharmacophore with epinastine (**1**) and NSAID moieties (**2**–**5**) was designed by molecular hybridization approach. The hybrid compounds **6**–**9** were synthesized by EDCI/HOBt or HATU-mediated coupling of **1** with salicylic acid (**2**), mefenamic acid (**3**), indomethacin (**4**) and naproxen (**5**), respectively, and were assessed for their inhibitory effect against NO production in LPS-induced RAW-264.7 macrophages in vitro. The Hybrids were found to exhibit significant NO production inhibitory effects with half-maximal inhibitory concentration (IC_{50}) values ranging in between 15.96 ± 1.32 and 36.68 ± 2.53 μM and were non-cytotoxic to macrophages. Comparing the inhibition concentration (IC_{50}), cytotoxicity concentration (CC_{50}) and in vitro efficacy index (*i*EI), **6** (IC_{50} = 17.97 ± 1.92 μM; *i*EI = 11.13) and **9** (IC_{50} = 15.96 ± 1.32 μM; *i*EI = 12.53) were better suited than other hybrids as well as their parent compound. Our findings signify that hybrids **6** and **9** may serve as platforms for continued investigations for the development of more efficient anti-inflammatory agents.

Key words: Epinastine, NSAIDs, Hybrid molecules, Nitric oxide, Anti-inflammatory

Inflammation is an early biological response that helps our body heal and defends itself from harm, such as infections, injuries, and toxins.[1] This process involves the release of diverse pro-inflammatory cytokines and mediators, such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), IL-6, prostaglandins (PGs), and nitric oxide (NO), mainly by activated macrophages and increased blood flow to the damaged area.[2] It usually turns off after a few hours or days and goes back to normal in the case of acute inflammation. However, uncontrolled or misdirected inflammation underlies chronic diseases, such as Parkinson's disease, Alzheimer's disease, cancer and asthma.[3] Hence, inflammation can be considered as a double-edged sword. On this ground, the above-stated mediators have a vital role in inducing inflammatory-related disorders and may have the potential as therapeutic targets.[4]

Non-steroidal anti-inflammatory drugs (NSAIDs), steroids and antihistamines are the most frequently prescribed medicines for analgesia in primary health care. The major therapeutic effects as well as unwanted actions of NSAIDs are observed due to the inhibition of cyclo-oxygenase (COX) enzymes.[5] Hence, beyond a certain limit, their usage is restricted because they are well known to affect the gastrointestinal tract, kidneys, liver, and cardiovascular system adversely.[6] As a result, some NSAIDs were withdrawn from the global market. This has urged pharmaceutical companies and research institutions to continuously explore new pharmacophores with improved anti-inflammatory activity and low toxic profiles.

The ophthalmic second-generation antihistamine, epinastine hydrochloride (EH) (**1**) is used to treat allergic conjunctivitis without any CNS or cardiac complications compared to oral antihistamines.[7] Its anti-inflammatory properties are also reported.[8] During the last two decades, there has been increasing interest for hybrid molecular technique in the new drug discovery.[9–12] As part of our ongoing investigations on the development of novel anti-inflammatory agents,[13] herein, we describe the synthesis of new anti-inflammatory agents **6**–**9** designed as hybrids of EH and NSAIDs such as salicylic acid (**2**), mefenamic acid (**3**), indomethacin (**4**) and (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (naproxen) (**5**) (*Fig*. 1) and evaluation of their in vitro NO production inhibition potential.

EXPERIMENTAL

General Information

All starting materials and reagents were purchased

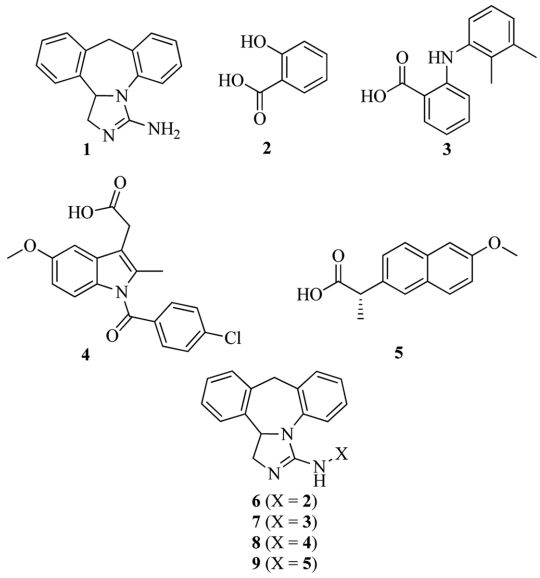


***Figure* 1.** Structures of epinastine (**1**), salicylic acid (**2**), mefenamic acid (**3**), indomethacin (**4**), naproxen (**5**) and epinastine-NSAID hybrid compounds (**6**–**9**).

commercially and were used without any additional purification. Solvents used for reactions were purchased Sigma-Aldrich and Alfa Aesar in sure seal bottles and used as received. Proton nuclear magnetic resonance (^{1}H-NMR 400 MHz) spectra and proton decoupled carbon ^{13}C (^{13}C{^{1}H}) NMR (100 MHz) spectra were recorded at 300 K on a JNM-ECZRS FT-NMR (JEOL Ltd., Tokyo, Japan) and deuterated chloroform was used as a solvent. Chemical shifts were expressed in δ parts per million (ppm) relative to tetramethylsilane (TMS, δ 0.00 ppm) or the solvent resonance (chloroform-d, δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR). The following pattern was employed for 1H-NMR data: chemical shift (multiplicity (singlet = s), (doublet = d), (triplet = t), (quartet = q), (doublet of doublet = dd) and (multiplet = m), integration, coupling constants (*J*) quoted in Hz). Low-resolution electron impact mass spectra [MS (EI)] and high-resolution electron impact mass spectra [HRMS (EI)] analyses were acquired on a JMS-700 (JEOL Ltd., Tokyo, Japan) spectrometer at the central laboratory of Kangwon National University. Routine monitoring of reactions was conducted by thin-layer chromatography using Merck silica gel plates 60 F_{254}. The spots were visualized by UV light (λ = 254 nm) or an appropriate reagent (7% ethanolic phosphomolybdic acid, *p*-anisaldehyde solution in H_2SO_4 followed by heating). For open column chromatographic purifications, silica gel 60 (230−400 mesh size, Merck, Darmstadt, Germany) was utilized.

Synthesis

***N*-(9,13*b*-Dihydro-1*H*-dibenzo[*c*,*f*]imidazo[1,5-*a*]azepin-3-yl)-2-hydroxybenzamide (6).** The product was prepared according to our previously reported method and the characterization data (1H and ^{13}C-NMR and HRMS) of **6** were also in accordance with the reported values.[13]

***N*-(9,13*b*-Dihydro-1*H*-dibenzo[*c*,*f*]imidazo[1,5-*a*]azepin-3-yl)-2-((2,3-dimethylphenyl)amino)benzamide (7).**[14] Cooled solution of **3** (0.13 g, 0.52 mmol) in tetrahydrofuran (3 mL) was treated with EDCI (0.09 mL, 0.52 mmol) followed by HOBt (0.07 g, 0.52 mmol) under argon atmosphere and stirred for 20 min. In another round bottom flask, **1** (0.10 g, 0.35 mmol) in tetrahydrofuran (3 mL) was treated with DIPEA (0.24 mL, 1.40 mmol), stirred for 20 min at ambient temperature and added to **3** containing reaction mixture. The resultant mixture was stirred at ambient temperature for 6 h. The reaction solution was quenched by adding deionized water (10 mL) and the whole was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with deionized water (2 × 20 mL) and saturated aqueous sodium chloride solution (20 mL) successively, dried over sodium sulfate, and concentrated under reduced pressure. Purification of the resulting residue by column chromatography (petroleum ether/ethyl acetate, v/v, 2:1) gave 0.09 g of **7** (57%) as pale yellow solid. R_f = 0.58 (petroleum ether/ethyl acetate = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 3H), 2.26 (s, 3H), 3.51 (d, 1H, *J* = 14.4 Hz), 3.75 (t, 1H, *J* = 9.6 Hz), 4.29 (t, 1H, *J* = 9.4 Hz), 4.64 (d, 1H, *J* = 14.1 Hz), 5.21 (t, 1H, *J* = 10.1 Hz), 6.55 (d, 1H, *J* = 8.4 Hz), 6.59 (t, 1H, *J* = 7.7 Hz), 6.79 (t, 1H, *J* = 7.7 Hz), 6.92-7.04 (m, 5H), 7.10 (t, 1H, *J* = 8.6 Hz), 7.21 (t, 2H, *J* = 5.2 Hz), 7.25-7.27 (m, 2H), 7.46 (dd, 1H, *J* = 7.9 Hz, *J* = 1.0 Hz), 8.13 (dd, 1H, *J* = 8.0 Hz, *J* = 1.7 Hz), 9.29 (s, 1H), 10.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 20.7, 39.0, 50.6, 61.1, 115.7, 119.1, 124.0, 125.7, 126.2, 127.3, 127.5, 127.6, 127.8, 127.9, 128.0, 128.3, 130.6, 132.4, 132.8, 133.3, 135.9, 136.0, 136.6, 113.6, 137.6, 139.3, 140.0, 149.3, 162.6, 179.1; EI-MS *m/z* 472 ([M]$^+$, base), 352, 194, 118; HRMS (EI) *m/z* calcd for $C_{31}H_{28}N_4O$: 472.2263 ([M]$^+$), found: 472.2262.

2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-*N*-(9,13*b*-dihydro-1*H*-dibenzo[*c*,*f*]imidazo[1,5-*a*]azepin-3-yl)acetamide (8). DIPEA (0.12 mL, 0.70 mmol) was added to a stirred suspension of **1** (0.1 g, 0.35 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (2 mL) at ambient temperature and stirred for 20 min under argon atmosphere. (1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-

triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.16 g, 0.42 mmol) followed by DIPEA (0.12 mL, 0.70 mmol) were added to another round bottom flask containing a solution of indomethacin **4** (0.15 g, 0.42 mmol) in anhydrous DMF (2 mL), stirred for 10 min. and this solution was transferred to **1** containing mixture via syringe. The resultant reaction mixture was stirred for 2 h. After this period, deionized water (10 mL) was added and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were washed with deionized water (3 × 20 mL) and saturated aqueous sodium chloride solution (20 mL), dried over sodium sulfate, and concentrated under reduced pressure. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, v/v, 3:1) gave 0.03 g of **8** (16%) as pale yellow liquid. R_f = 0.24 (petroleum ether/ethyl acetate = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.50 (d, 1H, *J* = 14.3 Hz), 3.64 (m, 3H), 3.76 (s, 3H), 4.14 (t, 1H, *J* = 9.4 Hz), 4.58 (d, 1H, *J* = 14.2 Hz), 5.07 (t, 1H, *J* = 9.4 Hz), 6.64 (dd, 1H, *J* = 9.4, 2.4 Hz), 6.93 (d, 1H, *J* = 8.8 Hz) 6.96 (m, 1H), 7.03 (d, 1H, *J* = 2.4 Hz), 7.18–7.25 (m, 5H), 7.28–7.33 (m, 2H), 7.44 (d, 2H, *J* = 8.4 Hz), 7.62 (d, 2H, *J* = 8.4 Hz), 8.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 36.7, 39.1, 49.9, 55.8, 61.3, 102.1, 111.4, 114.9, 116.1, 127.3, 127.4, 127.5, 127.7, 127.8, 128.0, 128.3, 129.1, 130.4, 131.0, 131.2, 131.7, 134.5, 135.4, 135.6, 135.8, 136.7, 138.8, 138.9, 156.0, 162.9, 168.4, 184.8; EI-MS *m/z* 588 ($[M]^+$), 341, 249, 139 (base); HRMS (EI) *m/z* calcd for $C_{35}H_{29}ClN_4O_3$ 588.1928 ($[M]^+$), found: 588.1926.

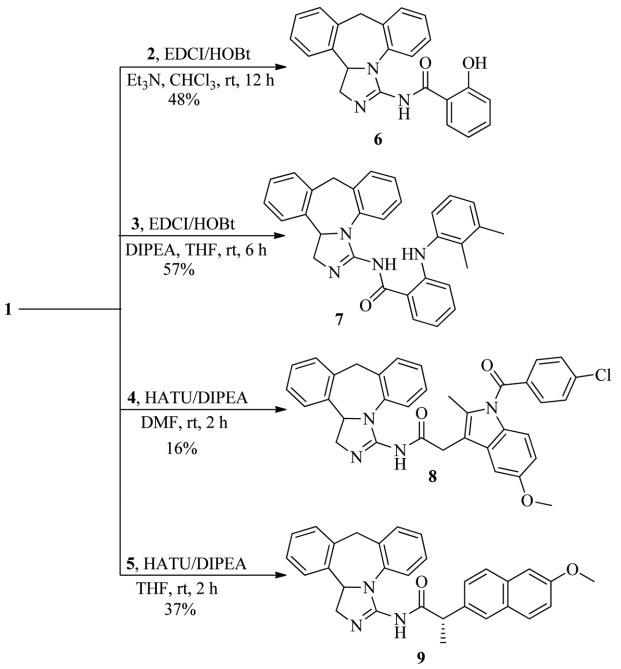
(2*S*)-*N*-(9,13*b*-Dihydro-1*H*-dibenzo[*c*,*f*]imidazo[1,5-*a*]azepin-3-yl)-2-(6-methoxynaphthalen-2-yl)propaamide (9). DIPEA (0.25 mL, 1.4 mmol) was added to a stirred suspension of **1** (0.1 g, 0.35 mmol) in anhydrous tetrahydrofuran (2 mL) at ambient temperature and stirred for 20 min under argon atmosphere. HATU (0.19 g, 0.49 mmol) was added to another round bottom flask containing a solution of **5** (0.1 g, 0.42 mmol) in anhydrous tetrahydrofuran (2 mL), stirred for 10 min. and this solution was transferred to **1** containing mixture via syringe. The resultant reaction mixture was stirred for 2 h. After this period, deionized water (10 mL) was added and extracted with ethyl acetate (2 × 25 mL). The combined organic phases were washed with deionized water (2 × 20 mL) and saturated aqueous sodium chloride solution (20 mL), dried over sodium sulfate, and concentrated under reduced pressure. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, v/v, 3:1 to 1:1) gave 0.06 g of **9** (37%) as white solid. R_f = 0.62 (petroleum ether/ethyl acetate = 1:1). Major diastereomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, 3H, *J* = 7.2 Hz), 3.47 (d, 1H, *J* = 14.4 Hz), 3.62 (dd, 1H, *J* = 12.8, 3.2 Hz), 3.88 (q, 1H, *J* = 7.0 Hz), 3.91 (s, 3H), 4.11 (t, 1H, *J* = 8.8 Hz), 4.52 (d, 1H, *J* = 14.4 Hz), 5.06 (dd, 1H, *J* = 11.6, 9.2 Hz), 6.93–6.96 (m, 1H), 7.08–7.11 (3H, m), 7.17–7.19 (m, 2H), 7.20–7.22 (m, 2H), 7.29 ((dd, 2H, *J* = 7.6, 1.6 Hz), 7.47 (dd, 1H, *J* = 8.4, 1.6 Hz), 7.63–7.67 (m, 3H), 8.89 (br s, 1H); Minor diastereomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (d, 3H, *J* = 7.2 Hz), 3.50 (d, 1H, *J* = 14.4 Hz), 3.59 (dd, 1H, *J* = 12.8, 3.2 Hz), 3.82 (q, 1H, *J* = 7.2 Hz), 3.92 (s, 3H), 4.09 (t, 1H, *J* = 8.8 Hz), 4.60 (d, 1H, *J* = 14.4 Hz), 4.97 (dd, 1H, *J* = 11.6, 9.2 Hz), 6.91–6.94 (m, 1H), 7.12–7.14 (m, 3H), 7.15–7.16 (m, 2H), 7.22–7.24 (m, 2H), 7.38 (2H, dd, *J* = 7.6, 1.6 Hz), 7.48 (dd, 1H, *J* = 8.4, 1.6 Hz), 7.66–7.71 (m, 3H), 8.93 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 19.0, 39.0, 39.1, 49.6, 49.8, 50.2, 50.7, 55.2, 55.3, 61.2, 61.3, 105.5, 105.6, 118.3, 118.4, 126.1, 126.2, 126.4, 127.1, 127.2, 127.3, 127.4, 127.5, 127.6, 127.8, 127.9, 128.1, 128.2, 129.0, 129.1, 129.3, 130.2, 130.3, 133.3, 133.4, 135.5, 135.6, 135.7, 136.0, 136.9, 138.3, 138.4, 138.7, 138.8, 157.1, 157.2, 162.7, 162.9, 188.2, 188.8; EI-MS *m/z* 461($[M]^+$), 277 (base), 234; HRMS (EI) *m/z* calcd for $C_{30}H_{27}N_3O_2$ 461.2103 (M^+), found: 461.2102.

Biology

Cell Culture and Cell Viability Assay. The murine macrophage cell line, RAW 264.7 was acquired from the Korea Cell Line Bank (Seoul, South Korea) and cultivated in Dulbecco's modified Eagle's medium (DMEM; Gibco, Carlsbad, CA, USA) containing 10% fetal bovine serum (FBS, Gibco) added with 2 mM glutamine and 100 units/mL penicillin-streptomycin.

Cell viability assay was carried out by using CellTiter 96® AQueous One solution cell proliferation assay kit (Promega, Fitchburg, WI, USA). To the cultured cells (5 × 10^4 cells/well) on 96-well plates was added a series of dilutions of the samples. After 24 h incubation, MTS (tetrazolium salt) reagents were applied to the plates and incubated at 37 ºC for 1 h. Absorbance at 490 nm was recorded using a Microplate reader (Thermo Scientific, Waltham, MA, USA).

NO Assay. RAW264.7 cells (5 × 10^4 cells/well on 96-well plates) were treated with various amounts of sample (approximately 0.78–100 μM) and prompted with LPS (100 ng/mL) for 24 h at 37 ºC. After incubation, the amount of nitrite (NO_2^-) in the culture supernatant was quantified through the Griess Reagent System (Promega Corporation).



***Scheme* 1.** Synthesis of epinastine-NSAID hybrids **6**–**9**.

RESULTS AND DISCUSSION

The synthetic pathway for the requisite epinastine-NSAID hybrids **6**–**9** is outlined in *Scheme* 1. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI)/1-hydroxy-benzotriazole (HOBt) or (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluoro-phosphate (HATU) mediated amide coupling reaction was employed to synthesize the target hybrids. The initial reaction was conducted by the direct coupling of **1** with **2** in the presence of EDCI/HOBt and triethylamine in chloroform at ambient temperature for 12 h to obtain the hybrid **6** in 48% yield.[13] Whereas, HATU-mediated coupling using *N*,*N*-diisopropylethylamine (DIPEA) in *N*,*N*-dimethylformamide offered **6** in 38% only. Next, EDCI/HOBt-promoted coupling of **1** with **3** in tetrahydrofuran proceeded smoothly to furnish **7** in 57% yield.[14] Coupling of **1** with the NSAIDs **4** and **5** in the presence of HATU and DIPEA afforded the desired hybrids **8** and **9** in 16% and 37% yields, respectively. Compound **9** was obtained as an inseparable diastereomeric mixture. Structures of these novel hybrids **6**–**9** were well characterized by their nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) and mass (MS) spectral data. ^{1}H-NMR of all the hybrids showed a singlet/broad singlet peak with downfield chemical shift δ in the range of 8.89–9.29 ppm, which designate that the amide bond was formed and in case of hybrid **6** the phenolic (-OH) proton and an additional amide (-CO-NH) proton of **7** were observed at δ 13.20 and 10.19 ppm, respectively. The high resolution mass spectrometry (HRMS) data of all hybrids were also in good agreement with the expected chemical structures.

Bioactivity

The novel epinastine-NSAID hybrids **6**–**9** were screened for their *in vitro* inhibitory activities against NO production in LPS-stimulated macrophages by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (*Table* 1). The preliminary biological evaluation showed that the hybrids exhibited moderate to potent inhibitory potential with the half maximal inhibitory concentration (IC_{50}) values in the range of 15.96 ± 1.32 and 36.68 ± 2.53 μM. It is apparent from the IC_{50} values of the synthesized hybrids that hybrid **6** (IC_{50} = 17.97 ± 1.92 μM) and **9** (IC_{50} = 15.96 ± 1.32 μM) were more potent than the parent control compound **1** (IC_{50} = 53.17 ± 2.21 μM). Toxicity levels were evaluated through MTT assay which indicated that none of the hybrids exhibited any significant toxicity against macrophages ($CC_{50} \geq$ 200 μM). It is worth mentioning that the *in vitro* efficacy index (*i*EI),[15] the ratio of toxicity (CC_{50})/anti-inflammatory potency (IC_{50}), values are significant for **6** (*i*EI = 11.13) and **9** (*i*EI = 12.53), when compare to the control (*i*EI = 2.29). Therefore, the present preliminary results provide a platform to consider hybrids **6** and **9**, having salicylic acid and naproxen as NSAID units respectively, for further investigations and may shed light in exploring newer NSAID hybrids toward the development of new anti-inflammatory drugs with fewer toxicities.

***Table* 1.** NO production inhibitory effects of epinastine-NSAID hybrids **6**–**9**

Compound	NO assay IC_{50} (μM)[a]	Cell viability CC_{50} (μM)[a]	*i*EI (CC_{50}/IC_{50})
1	53.17 ± 2.21	121.92 ± 3.58	2.29
6	**17.97 ± 1.92**	≥ 200.00	**11.13**
7	28.86 ± 0.98	≥ 200.00	6.93
8	36.68 ± 2.53	≥ 200.00	5.45
9	**15.96 ± 1.32**	≥ 200.00	**12.53**

[a]The results are reported as mean value ± SEM for n=3.

CONCLUSION

In this work, we designed and synthesized a series of hybrid compounds (**6**–**9**) of epinastine (**1**)-NSAID (**2**–**5**) as novel anti-inflammatory agents. The hybrid compounds were procured by direct linkage of **1** and the NSAID via an amide bond. The *in vitro* screening results indicated that some hybrid compounds showed better inhibitory effect against NO production without serious cytotoxicity towards macrophages. A notable observation from the results and *in vitro* efficacy index (*i*EI) values was that two hybrid compounds **6** (IC_{50} = 17.97 ± 1.92 μM, *i*EI = 11.13) and **9** (IC_{50} = 15.96 ± 1.32 μM, *i*EI = 12.53) significantly inhibited NO production compared to positive control **1** (IC_{50} = 53.17 ± 2.21 μM, *i*EI = 2.29), and they are worthy of further exploitation.

Acknowledgments. This work was supported by the Hallym University Leading Research Group Support Program of 2017 (HRF-LGR-2017-0004).

Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

REFERENCES

1. Medzhitov, R. *Nature* **2008**, *454*, 428.
2. Hamidzadeh, K.; Christensen S. M.; Dalby, E.; Chandrasekaran, P.; Mosser, D. M. *Annu. Rev. Physiol.* **2017**, *79*, 567.
3. Chen, L.; Deng, H.; Cui, H.; Fang, J.; Zuo, Z.; Deng, J.; Li, Y.; Wang, X.; Zhao, L. *Oncotarget* **2017**, *9*, 7204.
4. Kopf, M.; Bachmann, M. F.; Marsland, B. J. *Nat. Rev. Drug Discov.* **2010**, *9*, 703.
5. Wongrakpanich, S.; Wongrakpanich, A.; Melhado, K.; Rangaswami J. *Aging Dis.* **2018**, *9*, 143.
6. Waller D.; Sampson, A. *Medical Pharmacology and Therapeutics*; Elsevier: Oxford, U. K., 2017; p 363.
7. Mizoguchi, T.; Ozaki, M.; Ogino, N. *Clin. Ophthalmol.* **2017**, *11*, 1747.
8. Pradhan, S.; Abhishek, K.; Mah F. *Expert Opin. Drug Metab. Toxicol.* **2009**, *5*, 1135.
9. Meunier, B. *Acc. Chem. Res.* **2008**, *41*, 69.
10. Bosquesi, P. L.; Melo, T. R.; Vizioli, E.O.; Santos, J. L.; Chung, M. C. *Pharmaceuticals* **2011**, *4*, 1450.
11. Shaveta; Mishra, S.; Singh P. *Eur. J. Med. Chem.* **2016**, *124*, 500.
12. Mohsin, N. A.; Ahmad, M. *Turk. J. Chem.* **2018**, *42*, 1.
13. Lee, J. M.; Damodar, K.; Lee, Y.; Lee, J. Y.; Jeon, S. H.; Lee, J. T. *Bull. Korean Chem. Soc.* **2019**, *40*, 761.
14. Lee, J. M.; Damodar, K.; Lee, Y.; Woo, H. R.; Suh, H. W.; Jeon, S. H.; Lee, J. T. *Bull. Korean Chem. Soc.* **2020**, In press. https://doi.org/10.1002/bkcs.11990.
15. Mazzio, E. A.; Bauer, D.; Mendonca, P.; Taka, E.; Soliman, K. F. *J. Neuroimmunol.* **2017**, *302*, 10.