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Quinazolindione derivatives as potent 5-HT$_{3A}$ receptor antagonists

Byung-Hwan Lee [a], Min Jung Choi [b], Mi Na Jo [b], Hee Jeong Seo [b], Seung-Yeol Nah [a], Yong Seo Cho [b], Ghilsoo Nam [b], Ae Nim Pae [b], Hyewhon Rhim [b,*,†], Hyunah Choo [b,*,†]

[a] Department of Physiology, College of Veterinary Medicine and Bio/Molecular Informatics Center, Konkuk University, Seoul 110-460, Republic of Korea
[b] Center for Chemoinformatics Research, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, Republic of Korea

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ABSTRACT

5-HT$_{3A}$ receptor antagonists have been used mainly for the treatment of nausea and vomiting. These days, the antagonists are of special interest due to their therapeutic potential to treat other diseases such as depression, psychotic disorder, drug abuse, and irritable bowel syndrome. To discover novel 5-HT$_{3A}$ receptor antagonists, we screened our in-house small molecule library, resulting in identifying the quinazolindione derivatives as potent 5-HT$_{3A}$ receptor antagonists. For the purpose of structure–activity relationship study, 24 quinazolindione analogues were biologically evaluated against 5-HT$_{3A}$ receptor. Among those, KKHT10612 shows the best antagonistic effect against 5-HT$_{3A}$ receptor with an IC$_{50}$ value of 0.8 μM which is comparable with that of the reference compound, MDL72222, and selectivity over T-type calcium channel as well.

1. Introduction

The 5-hydroxytryptamine (5-HT) receptors are divided into seven distinct subfamilies (5-HT$_1$ to 5-HT$_7$) by their structure and operational system. Among the subfamilies of 5-HT receptors, the 5-HT$_3$ receptor is the only ligand-gated ion channel (LGIC), and all other 5-HT receptors are G-protein-coupled receptors (GPCRs).[1] 5-HT$_3$ Receptors are cationic ion channels that produce a transient inward current upon activation by serotonin or its agonists and share structural similarity with other LGICs such as GABA$_A$, glycine, and nicotinic acetylcholine receptors.[2,3]

After the 5-HT$_{3A}$ subunit was first cloned,[4] four additional subunits (5-HT$_{3B}$, 5-HT$_{3C}$, 5-HT$_{3D}$, and 5-HT$_{3E}$) have been added to the 5-HT$_3$ receptor family.[5,6] 5-HT$_{3A}$, 5-HT$_{3B}$, and 5-HT$_{3C}$ subunits exist in both the central nervous system (CNS) and peripheral nervous system (PNS), whereas 5-HT$_{3D}$ and 5-HT$_{3E}$ subunits exist only in peripheral tissue.[6] The 5-HT$_3$ receptor consists of a pentamer, and each subunit includes a large N-terminal extracellular domain, four hydrophobic transmembrane domains (M1–M4) and a short C-terminal domain. The 5-HT$_3$ receptor exists either as a 5-HT$_{3A}$ homomer or a heteromer of 5-HT$_{3A}$ and 5-HT$_{3B}$, and in both cases the functional activity of the 5-HT$_3$ receptor is provided by the common 5-HT$_{3A}$ subtype. All other subunit subtypes must heteropentamerize with 5-HT$_{3A}$ subunits to form functional channels.[4,7]

The physiological and pathological roles of 5-HT$_3$ receptors have been suggested to be involved in pain transmission, vomiting, mood disorders, drug abuse, anxiety, and alcohol dependence.[7,8] Specific 5-HT$_3$ receptor antagonists (ondansetron, granisetron, tropisetron, and bemesetron) are effective in control of chemotherapy related nausea and vomiting (Fig. 1). Although these drugs are the first-line treatment choice as antiemetic agents for many cancer patients, they can cause adverse effects such as headache, constipation, diarrhea, asthenia, and somnolence.[9,10] Therefore, the investigation of new 5-HT$_3$ receptor antagonists is still needed to provide a wide selection range of long-term usable antiemetic agents.

There have been a lot of efforts to search for new scaffolds active against the 5-HT$_3$ receptor, especially 5-HT$_{3A}$ receptor, which is a basic component of homomeric or heteromeric pentamers. To discover a new 5-HT$_3$ receptor antagonist, an in-house small molecule library was screened against the 5-HT$_{3A}$ receptor, which was previously designed and synthesized to discover T-type calcium channel blockers.[11] Some quinazolindione derivatives show potent antagonistic activities against 5-HT$_{3A}$ receptor. Herein, we report the biological evaluation of novel 5-HT$_3$ receptor antagonists.

2. Results and discussion

2.1. Chemistry

The quinazolindione analogues were synthesized starting from dimethyl 2-aminoterephthlate **1** in total 4 or 5 steps in previously reported method (Schemes 1 and 2).[11] The compound **1** was

* Corresponding authors. Tel.: +82 2 958 5923; fax: +82 2 958 5189 (H.R.); tel.: +82 2 958 5157; fax: +82 2 958 5189 (H.C.)
E-mail addresses: hrhim@kist.re.kr (H. Rhim), hchoo@kist.re.kr (H. Choo).
† These co-corresponding authors contributed equally to this work.

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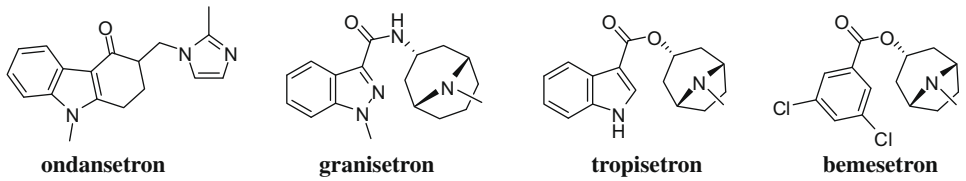
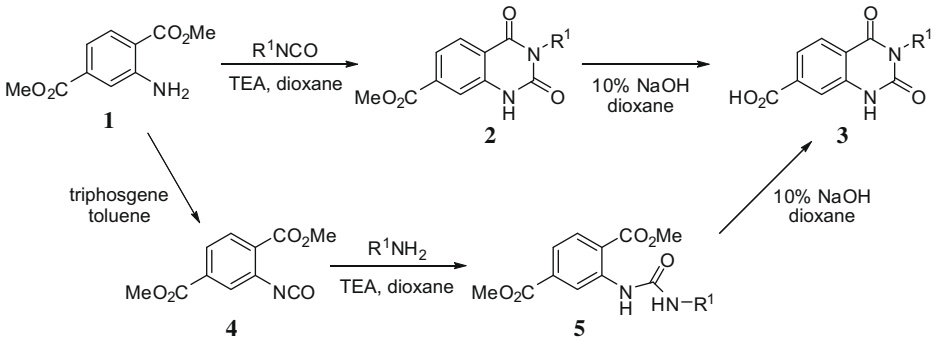


Figure 1. Specific 5-HT_3 receptor antagonists.



Scheme 1. Synthesis of the key intermediate **3**.[11]

treated with R^1-substituted isocyanates and TEA in 1,4-dioxane to give the corresponding quinazolindiones **2** in 41–90% yields. Compounds **2**, thus obtained, were hydrolyzed to the corresponding key intermediates **3** in 90–99% yields. When R^1 was an alkyl group, on the other hand, the compound **1** was converted to the isocyanate **4**, which was treated with alkyl amines and TEA in 1,4-dioxane to give the corresponding ureas **5** in 37–61% yields. The compounds **5** underwent cyclization to afford the key intermediates **3** in 53–98% yields (Scheme 1).

The key intermediate **3** was converted to the corresponding acyl chloride, which was treated with various R^2-substituted alkyl amines in DCM to give the desired products in 13–60% yields (Scheme 2).

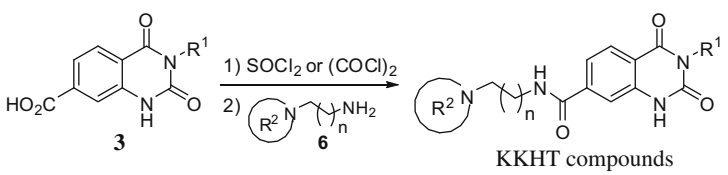
Thus, 24 quinazolindione analogues (KKHT compounds) which have three variants such as R^1 (morpholinyl, pyrrolidinyl, piperidinyl, 2-methylpiperidinyl or 2-ethylpiperidinyl), R^2 (*p*-methoxyphenyl, *p*-fluorophenyl, *o*-fluorobenzyl, *m*-fluorobenzyl, *p*-fluorobenzyl, *o*-chlorobenzyl, *p*-chlorobenzyl, cyclohexyl, propyl or methyl), and *n* (1 or 2) were prepared.

2.2. Biological activities

The biological activities of the synthesized quinazolindione analogues were evaluated against 5-HT_{3A} receptor which is stably expressed in *Xenopus* oocytes containing cRNA of 5-HT_{3A} receptor. As a positive control, MDL72222 (bemesetron) was used, which is currently in phase II clinical trial for treatment of nausea, vomiting and migraine.[12] The biological activities are summarized in Table 1. The range of IC_{50} values and hill coefficients are 0.8–57.0 μM and 0.8–5.3, respectively. Most synthesized compounds exhibit potent antagonistic activities against the 5-HT_{3A} receptor, and 18 out of 24 compounds show high efficacies with maximum% inhibition (V_{max}) values of over 96%. Among those, the most active compound is KKHT10612 (Table 1, entry 12) with an IC_{50} value of 0.8 μM and a hill coefficient (n_H) of 1.7 which are comparable with those of MDL72222 (bemesetron).

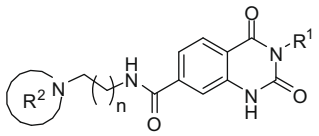
2.3. Discussion

5-HT_{3A} Receptor antagonists have been used mainly for the treatment of nausea and vomiting. These days, the antagonists are of special interest due to their therapeutic potential to treat other diseases such as depression, psychotic disorder, drug abuse, irritable bowel syndrome and so on. Therefore, there has been much attention paid to discover novel 5-HT_{3A} receptor antagonists. The quinazolindiones, which were obtained during screening of our in-house small molecule library against 5-HT_{3A} receptor, are a novel scaffold among the 5-HT_{3A} receptor antagonists. The structure–activity relationship study of the quinazolindione derivatives has been done with three variants such as R^1, R^2 and *n* (Table 1). When *n* was fixed as 1 (entries 1–19), the compounds with a piperidinyl group as R^1 (entries 5–17) show more potent activities against 5-HT_{3A} receptor than the compounds with a morpholinyl group or pyrrolidinyl group (entries 1–4). Thus, with R^1 fixed with piperidinyl group (entries 5–17), various R^2 substituents gave almost similar IC_{50} values. Among those, KKHT10612 (entry 12) with *p*-methoxybenzyl group at R^2 shows the best inhibition against 5-HT_{3A} receptor with an IC_{50} value of 0.8 μM, which is comparable with that of the reference compound, MDL72222. A methyl subsituent on the piperidine has no effect on the activity (entry 19), but an ethyl group affects it negatively (entry 18). On the other hand, when *n* = 2 (entries



Scheme 2. Synthesis of the final products, KKHT compounds.[11]

Table 1
Antagonistic activities against 5-HT_{3A} receptor



KKHT compounds

Entry	Sample code	n	R^1	R^2	V_{max}	IC_{50} (n = 6–7)	n_H
1	KKHT10103	1	Morpholinyl	*p*-Fluorophenyl	34.5 ± 37.1	57.0 ± 21.9	0.8 ± 0.3
2	KKHT10109	1	Morpholinyl	*p*-Fluorobenzyl	80.0 ± 2.7	19.8 ± 1.6	1.2 ± 0.1
3	KKHT10118	1	Morpholinyl	*p*-Chlorobenzyl	78.5 ± 6.2	15.8 ± 2.8	1.6 ± 0.4
4	KKHT10318	1	Pyrrolidinyl	*p*-Chlorobenzyl	103.2 ± 12.8	7.5 ± 2.5	0.9 ± 0.1
5	KKHT10603	1	Piperidinyl	*p*-Fluorophenyl	107.9 ± 6.0	1.9 ± 0.4	0.9 ± 0.1
6	KKHT10606	1	Piperidinyl	*p*-Methoxyphenyl	100.6 ± 3.6	1.6 ± 0.2	1.4 ± 0.2
7	KKHT10607	1	Piperidinyl	*o*-Fluorobenzyl	100.2 ± 9.6	2.1 ± 0.6	1.4 ± 0.4
8	KKHT10608	1	Piperidinyl	*m*-Fluorobenzyl	107.5 ± 11.5	2.4 ± 0.8	1.0 ± 0.2
9	KKHT10609	1	Piperidinyl	*p*-Fluorobenzyl	104.6 ± 7.5	1.9 ± 0.4	1.0 ± 0.2
10	KKHT10610	1	Piperidinyl	*o*-Methoxybenzyl	103.1 ± 5.1	1.4 ± 0.2	1.1 ± 0.2
11	KKHT10611	1	Piperidinyl	*m*-Methoxybenzyl	107.4 ± 8.5	2.7 ± 0.6	1.3 ± 0.3
12	KKHT10612	1	Piperidinyl	*p*-Methoxybenzyl	96.4 ± 2.9	0.8 ± 0.1	1.7 ± 0.2
13	KKHT10613	1	Piperidinyl	Cyclohexyl	98.8 ± 4.2	2.0 ± 0.3	1.1 ± 0.1
14	KKHT10614	1	Piperidinyl	Propyl	103.7 ± 3.6	2.2 ± 0.2	1.3 ± 0.1
15	KKHT10615	1	Piperidinyl	Methyl	103.2 ± 3.3	2.2 ± 0.2	1.4 ± 0.1
16	KKHT10617	1	Piperidinyl	*o*-Chlorobenzyl	96.0 ± 3.9	2.1 ± 0.2	1.8 ± 0.3
17	KKHT10618	1	Piperidinyl	*p*-Chlorobenzyl	106.4 ± 2.5	3.3 ± 0.5	1.2 ± 0.2
18	KKHT11018	1	2-Ethylpiperidinyl	*p*-Chlorobenzyl	104.0 ± 2.5	13.6 ± 2.9	1.4 ± 0.3
19	KKHT11118	1	2-Methylpiperidinyl	*p*-Chlorobenzyl	104.0 ± 2.5	2.8 ± 0.2	1.2 ± 0.1
20	KKHT20218	2	Morpholinyl	*p*-Chlorobenzyl	52.5 ± 0.6	1.3 ± 0.1	5.3 ± 1.5
21	KKHT20713	2	2-Methylpiperidinyl	Cyclohexyl	86.5 ± 11.5	5.9 ± 2.5	1.1 ± 0.4
22	KKHT20718	2	2-Methylpiperidinyl	*p*-Chlorobenzyl	85.7 ± 4.3	11.6 ± 1.4	1.5 ± 0.2
23	KKHT20818	2	2-Ethylpiperidinyl	*p*-Chlorobenzyl	99.5 ± 1.6	4.8 ± 0.2	1.4 ± 0.1
24	KKHT20918	2	Piperidinyl	*p*-Chlorobenzyl	98.2 ± 4.5	5.7 ± 0.6	1.5 ± 0.2
Positive control	MDL72222 (bemesetron)	—	—	—	99.6 ± 7.7	0.77 ± 0.16	1.25 ± 0.2

20–24), the compounds with a morpholinyl group as R^1 (entry 20) show very potent activity with an IC_{50} value of 1.3 μM, but low efficacy with a V_{max} value of 52.5%. In other cases with n = 2 (entries 21–24), the activities were decreased compared with the congeners with n = 1.

The antagonistic activities of KKHT compounds against 5-HT_{3A} receptor were compared with those against T-type calcium channel (Table 2). It is worth to note that selectivity between 5-HT_{3A} receptor and T-type calcium channel is achieved depending on the substituents such as R^1, R^2 and n. Thus, while all 24 compounds investigated in this study show moderately to potent antagonistic activities against 5-HT_{3A} receptor, only 6 compounds are moderate active against T-type calcium channel with α_{1G} subunit and other 18 compounds show no significant activities. Among the 6 compounds active against both 5-HT_{3A} receptor and T-type calcium channel, KKHT10608 and KKHT10609 show selective antagonistic activity against 5-HT_{3A} receptor whereas KKHT10318, 11018 and 20918 are more active against T-type calcium channel. KKHT10618 is the only compound which shows similar activities against 5-HT_{3A} receptor and T-type calcium channel with IC_{50} values of 3.3 and 2.08 μM, respectively. Importantly, the most active compound against 5-HT_{3A} receptor, KKHT10612, shows no significant activity against T-type calcium channel.

3. Conclusion

A focused small molecule library of quinazolindione derivatives was biologically evaluated to develop novel 5-HT_{3A} receptor antagonists. Among 24 compounds, KKHT10612 shows the most potent antagonistic activity against 5-HT_{3A} receptor and selectivity over T-type calcium channel. We discovered the quinazolindione compounds as novel 5-HT_{3A} receptor antagonists with a new scaffold. Further evaluations of KKHT10612 such as selectivity for other ion channels, pharmacokinetics and therapeutic effect are in progress.

Table 2
Comparison with activities of KKHT compounds against 5-HT_{3A} receptor and T-type calcium channel

Entry	Sample code	5-HT_{3A} IC_{50} in μM	T-type calcium channel (α_{1G})[11] IC_{50} in μM
1	KKHT10103	57.0 ± 21.9	—[a]
2	KKHT10109	19.8 ± 1.6	—[a]
3	KKHT10118	15.8 ± 2.8	—[a]
4	KKHT10318	7.5 ± 2.5	2.46 ± 0.22
5	KKHT10603	1.9 ± 0.4	—[a]
6	KKHT10606	1.6 ± 0.2	—[a]
7	KKHT10607	2.1 ± 0.6	—[a]
8	KKHT10608	2.4 ± 0.8	16.87 ± 2.38
9	KKHT10609	1.9 ± 0.4	9.23 ± 0.68
10	KKHT10610	1.4 ± 0.2	—[a]
11	KKHT10611	2.7 ± 0.6	—[a]
12	KKHT10612	0.8 ± 0.1	—[a]
13	KKHT10613	2.0 ± 0.3	—[a]
14	KKHT10614	2.2 ± 0.2	—[a]
15	KKHT10615	2.2 ± 0.2	—[a]
16	KKHT10617	2.1 ± 0.2	—[a]
17	KKHT10618	3.3 ± 0.5	2.08 ± 0.36
18	KKHT11018	13.6 ± 2.9	3.38 ± 0.36
19	KKHT11118	2.8 ± 0.2	—[a]
20	KKHT20218	1.3 ± 0.1	—[a]
21	KKHT20713	5.9 ± 2.5	—[a]
22	KKHT20718	11.6 ± 1.4	—[a]
23	KKHT20818	4.8 ± 0.2	—[a]
24	KKHT20918	5.7 ± 0.6	1.95 ± 0.25
Positive control	MDL72222 (bemesetron)	0.77 ± 0.16	ND[b]

[a] Not active enough to be tested for IC_{50} against T-type calcium channel.
[b] Not determined.

4. Materials and methods

4.1. Synthetic experimental

All the compounds were synthesized in previously reported method.[11]

4.1.1. Spectroscopic data of 3-(4-methoxybenzyl)-N-(3-(2-piperidin-1-yl)ethyl)-2,4-dioxoquinazoline-7-carboxamide (KKHT10612)

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.57 (s, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 10.1 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.01 (s, 2H), 3.70 (s, 3H), 3.37-3.34 (m, 2H), 2.44–2.36 (m, 6H), 1.48–1.36 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.5, 162.0, 158.9, 150.7, 141.2, 139.8, 129.8, 128.1, 121.0, 115.8, 115.1, 114.2, 57.9, 55.5, 54.5, 43.2, 37.6, 26.1, 24.5; IR (KBr) 3264, 3195, 1712, 1662 cm^{-1}.

4.2. Biological assay

4.2.1. Materials

The mouse 5-HT$_{3A}$ receptor cDNA was kindly provided by Dr. D. Julius (University of California San Francisco, CA, USA).

4.2.2. Preparation of *Xenopus* oocytes

Xenopus laevis frogs were purchased from Xenopus I (Ann Arbor, MI, USA). Their care and handling were in accordance with the highest standards of institutional guidelines. For isolation of oocytes, frogs were anesthetized with an aerated solution of 3-amino benzoic acid ethyl ester. Oocytes were surgically removed and separated by collagenase treatment followed by agitation for 2 h in a Ca^{2+}-free medium containing 82.5 mM NaCl, 2 mM KCl, 1 mM $MgCl_2$, 5 mM HEPES, 2.5 mM sodium pyruvate, 100 units/ml penicillin and 100 μg/ml streptomycin. Stage V–VI oocytes were collected and stored in ND96 (96 mM NaCl, 2 mM KCl, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$, and 5 mM HEPES, pH 7.5) supplemented with 0.5 mM theophylline and 50 μg/ml gentamicin. This oocyte-containing solution was maintained at 18 °C with continuous gentle shaking and changed daily. Electrophysiological experiments with oocytes were performed within 5–6 days of their isolation.

4.2.3. cRNA preparation of 5-HT$_{3A}$ receptor and microinjection

The 5-HT$_{3A}$ DNA constructs were linearized at the 3′ end by *Sal*I digestion, and run-off transcripts were prepared using the methylated cap analog, m^{7}G(50)ppp(50)G. For generation of wild-type cRNAs, recombinant plasmids containing the wild-type 5-HT$_{3A}$ receptor cDNA were linearized by digestion with appropriate restriction enzymes. All cRNAs were prepared using T3 RNA polymerase and the mMessage mMachine transcription kit (Ambion, Austin, TX, USA). The final cRNA products were resuspended at 1 μg/μl with RNase-free water and stored at –80 °C until use.[13] The absence of degraded RNA was confirmed by denaturing agarose gel electrophoresis followed by ethidium bromide staining. 40 nl of cRNAs were injected into the animal or vegetal pole of each oocyte using a 10 μl VWR microdispenser (VWR Scientific, San Francisco, CA, USA) fitted with a tapered glass pipette tip that was 15-20 μm in diameter (Neuropharm).[14]

4.2.4. Data recording

A custom-made Plexiglas net chamber was used for two-electrode voltage-clamp recordings. The chamber was constructed by milling two concentric wells into the chamber bottom (diameter/height: upper well, 8/3 mm; lower well, 6/5 mm) and gluing plastic mesh (~0.4 mm grid diameter) onto the bottom of the upper well. The perfusion inlet (~1 mm in diameter) was formed through the wall of the lower well, and a suction tube was placed on the edge of the upper well. The oocyte was placed on the net that separated the upper and lower wells, with the net grids serving to keep the oocyte in place during the electrophysiological recordings. Oocytes were impaled with two microelectrodes filled with 3 M KCl (0.2–0.7 MΩ). Recordings were performed in ND96 solution. The electrophysiological experiments were performed at room temperature using an Oocyte Clamp (OC-725C; Warner Instruments, Hamden, CT, USA) and stimulation and data acquisition were controlled by pClamp 8 (Axon Instruments, Union City, CA, USA). Membrane currents were recorded at a holding potential of −80 mV.

4.2.5. Data analysis

To obtain concentration–response curves of the effect of drugs on $I_{5\text{-}HT}$, the peak amplitudes at different concentrations of drugs were plotted and then fitted to the following Hill equation using the Origin software (OriginLab Corp, Northampton, MA, USA): Response = $V_{max} - V_{min}/1 + (IC_{50}/[A]^{nH}) + V_{min}$, where V_{max} and V_{min} are maximal and minimal responses, respectively. [A] is concentration of drugs and n_H is the Hill coefficient. IC_{50} is the concentration of drugs required to decrease the response by 50%. All values are presented as means ± S.E.M.

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