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RESEARCH ARTICLE

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Antilipolytic effects of 1,8-naphthyridine derivatives β-adrenoceptor antagonists in rat white adipocytes

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The rat fat cell β-adrenoceptors were investigated by studying the effects of new 1,8-naphthyridine derivatives synthesized starting from 7-amino-2-chloro-3-phenyl-1,8-naphthyridine on lipolysis induced by isoprenaline, and alprenolol. Lipolysis induced by isoprenaline agonist was competitively antagonized by the 1,8-naphthyridine analogue with a 7-hydroxy-2-(4′-methoxybenzylamine)-6-nitro-3-phenyl substituent designated as **3**. In contrast, 10, 50, and 100 μM of 7-methoxy and 7-ethoxy derivatives did not modify the concentration–response curve of isoprenaline. A rightward shift of the curve was, however, observed with 50 μM of a 7-methoxy-2-(4′-methoxybenzylamine)-6-amino-3-phenyl substituent designated as **10**. The selective β_1-AR antagonist, 7-hydroxy-4-morpholinomethyl-2-piperazino-1,8-naphthyridine slightly reduced isoprenaline-induced lipolysis only at high doses. Alprenolol-mediated lipolytic effect was antagonized by derivative **3**, **10** and the selective β_3-AR antagonist SR 59,230A, but resistant to the selective β_1-AR antagonist 7-hydroxy-4-morpholinomethyl-2-piperazino-1,8-naphthyridine. The results provide preliminary pharmacological evidence for the antilipolytic effect of the newly synthesized 1,8-naphthyridine derivatives on rat fat cells. The analogues designated as **3** and **10** were the most potent antagonists of this series.

KEYWORDS
1,8 naphthyridine, lipolysis, rat white adipocytes, β-adrenergic receptors

1 | INTRODUCTION

β-adrenergic receptors (β-ARs) are thought to transmit the thermogenic signal to peripheral target tissues as pharmacologic treatment with β-AR-selective agonists potently stimulates thermogenesis.[1,2] There are three β-ARs which could mediate sympathetically driven thermogenesis, one of these receptors, the β_3-AR, appears to be the main functional subtype in rodent adipocytes,[3,4] and humans brown adipocytes.[5]

The presence of a β_3-AR in white and brown fat cells was established by the pharmacological analysis of the β-AR-mediated metabolic responses (i.e., lipolysis, and cyclic AMP accumulation).[6,7] Excessive fatty acid production in white adipocytes inhibits cAMP production,[8] thereby matching lipase activation with extracellular fatty acid clearance. From a pharmacological point of view, receptors of the β_3-adrenergic type differ from β_1- or β_2-receptors in that they are not subjected to ligand-induced desensitization, and they have lower binding affinities of the endogenous catecholamines.[9–11] A marked thermogenic response to selective β_3-adrenergic receptor agonists was found in rodents.[1,12,13] Furthermore, in addition to their thermogenic effects, β_3 agonists may promote fat loss by stimulating fatty acid mobilization and β-oxidation. When administered over a relatively long period of time, these agonists induce weight loss and have antidiabetic effects.[14] This effect was not inhibited by the non-selective β_1 and β_2 antagonist propranolol, and it was suggested that the β_3-adrenergic receptor

may be responsible for a large part of the lipolytic response to norepinephrine in humans and in rodents.[15,16]

In previous studies,[17–19] we used 1,8-naphthyridine as the starting compound, variously modified its molecule and obtained several compounds that showed β-AR blocking activity to various extents. Taking into account, some observations of the structure–activity relationship, a series 1,8-naphthyridine analogues that are closely related to the previously studied compounds were designed and synthesized and evaluated for their β-adrenergic activities on fat cells isolated from rat. Therefore, the aim of the current study was to elucidate how the structure of modified 1,8-naphthyridine analogues affects β-AR blocking activity.

2 | MATERIALS AND METHODS

The pharmacological agents used to study β-adrenoceptor activation of lipolysis were the non-selective β-AR agonist, isoprenaline, the partial β_3-adrenoceptor agonist alprenolol, and the selective β_3-AR antagonist, SR 59,230A, were obtained from Sigma. The selective β_1-AR antagonist, 7-hydroxy-4-morpholinomethyl-2-piperazino-1,8-naphthyridine (HMMPN), was synthesized in our laboratory.[19] Collagenase, bovine serum albumin, and enzymes for glycerol assays were obtained from Boehringer. All other chemicals and organic solvents were of the highest purity grade commercially available.

All drugs were solubilized in normal saline except for 1, 8-naphthyridine derivatives, which were dissolved in dimethyl sulfoxide (DMSO).

2.1 | Adipocyte preparation and lipolysis measurements

The animal experiments were performed in accordance with the recommendations of the internationally accepted principles concerning care and use of laboratory animals. Rat white adipocytes were prepared from the epididymal pads of male Wistar rats weighing approximately 200–320 g. Adipocytes were isolated according to a previously described method.[20] In brief, adipose tissue fragments (0.5–1.0 g) were incubated with 1 mg/ml collagenase in Krebs-Ringer bicarbonate buffer containing 4% bovine serum albumin and 5 mM glucose (pH 7.4) for 50 min at 37°C in a shaking water bath. At the end of the incubation, fat cells were filtered and washed three times with 10 ml of the same buffer to eliminate collagenase. The isolated cells were brought to a suitable dilution, in order to obtain a final concentration of approximately 1,000 cells per 50 μl.

Pharmacological agents for lipolysis stimulation or inhibition at suitable dilutions were added to the cell suspension (~1,000 cells/assay) just before the beginning of the assay in a final volume of 100 μl. After 90 min of incubation at 37°C in a shaking water bath, the tubes were placed on ice and 50 μl aliquots were taken for enzymatic determination of the glycerol released in the incubation medium which was used as the index of fat cell lipolysis using the free glycerol determination kit (Sigma).

2.2 | Instrumental analysis

The ^{1}H NMR spectra were determined in DMSO-d_6 or $CDCl_3$ with TMS as the internal standard, on a Varian CFT-20 NMR spectrometer. Analytical TLC was carried out on E. Merch 0.20 mm precoated silica-gel glass plate (60 F254), and the location of spots was detected by illumination with an UV lamp.

Elemental analysis of all compounds synthesized for C, H, N, and Cl was within ±0.4% of theoretical value and was performed in our analytical laboratory.

2.3 | Synthesis of the key intermediates

2.3.1 | Preparation of 7-amino-2-(4′-methoxybenzylamine)-3-phenyl-1,8-naphthyridine (1)

To a mixture of 7-amino-2-chloro-3-phenyl-derivative (**X**) (4.0 g, 15.64 mmol) and 4-methoxybenzylamine (7.1 ml, 54 mmol) was added pyridine (70 ml) under N_2. The mixture was heated to reflux for 48 hr and then cooled to room temperature, the pyridine was removed, and the compound was obtained by column chromatography followed by recrystallization (Tables 1 and 2).

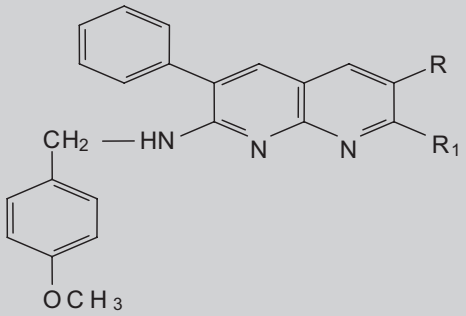
2.3.2 | Preparation of 7-hydroxy-2-(4′-methoxybenzylamine)-3-phenyl-1,8-naphthyridine (2) and 7-hydroxy-2-(4′-methoxybenzylamine)-6-nitro-3-phenyl-1,8-naphthyridine (3)

To a solution of 2.0 mmol of 7-amino-2-(4′-methoxybenzyl amine)-3-phenyl-derivative (**1**) in 6 ml of concentrated sulfuric acid, sodium nitrite was added drop wise at −3°C, after standing at room temperature for 1 hr crushed ice was added and then concentrated NH_4OH until pH 4–5, the solid was collected by filtration and purified to give compound **2** and **3** (Tables 1 and 2).

2.3.3 | Preparation of the 7-chloro-2-(4′-methoxybenzylamine)-3-phenyl-1,8-naphthyridine (4) and 7-chloro-2-(4′-methoxybenzylamine)-6-nitro-3-phenyl-1,8-naphthyridine (5)

A mixture of the appropriate 7-hydroxyl-1,8-naphthyridine (**2**) or (**3**) (5 mmol) and $POCl_3$ (10 ml) was heated at 90°C

TABLE 1 Physical data of 1,8-naphthyridine derivatives



Comp.	R	R1	Yield %	M.P. [a]	Mol. formula	Analysis (calcd/found %) C	H	N	Cl
1	H	NH_2	83	182–184[b]	$C_{23}H_{22}N_4O$	74.57	5.99	15.12	–
						74.51	6.02	15.11	–
2	H	OH	42	166–168[c]	$C_{23}H_{21}N_3O_2$	74.37	5.70	11.31	–
						74.35	5.68	11.28	
3	NO_2	OH	31	132–134[c]	$C_{23}H_{20}N_4O_4$	66.34	4.84	13.45	–
						66.28	4.83	13.47	–
4	H	Cl	85	180–182[b]	$C_{23}H_{20}N_3ClO$	70.85	5.17	10.78	9.09
						70.93	5.19	10.81	9.07
5	NO_2	Cl	77	158–160[b]	$C_{23}H_{19}N_4ClO_3$	63.52	4.40	12.88	8.15
						63.45	4.39	12.92	8.17
6	H	OCH_3	82	143–145[b]	$C_{24}H_{23}N_3O_2$	74.78	6.01	10.90	–
						74.72	5.98	10.92	–
7	NO_2	OCH_3	72	138–140[b]	$C_{24}H_{22}N_4O_4$	66.97	5.15	13.03	–
						66.94	5.17	13.00	
8	H	OCH_2CH_3	76	132–134[d]	$C_{25}H_{25}N_3O_2$	75.16	6.31	10.52	–
						75.21	6.28	10.55	–
9	NO_2	OCH_2CH_3	59	126–128[d]	$C_{25}H_{24}N_4O_4$	67.55	5.44	12.60	–
						67.48	5.41	12.58	–
10	NH_2	OCH_3	88	143–145[d]	$C_{24}H_{24}N_4O_2$	71.98	6.04	13.99	–
						72.01	6.01	14.02	–
11	NH_2	OCH_2CH_3	81	134–136[b]	$C_{25}H_{26}N_4O_2$	72.44	6.32	13.52	–
						72.47	6.35	13.49	–

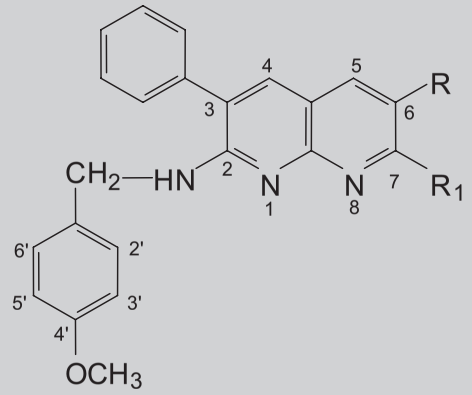
[a]Recrystallization solvent.
[b]Toluene.
[c]Separated by flash chromatography with EtOAc.
[d]Petroleum ether 100–140°C.

for 45 min. The resulting solution was cooled to room temperature, and excess $POCl_3$ was removed by high vacuum equipped with a double trap. The flask containing the crude product was placed in an ice-water bath, and the solution was, carefully and slowly, made basic with concentrated NH_4OH and ice water. The solid obtained (compound **4** or **5**) was washed with H_2O and purified by crystallization (Tables 1 and 2).

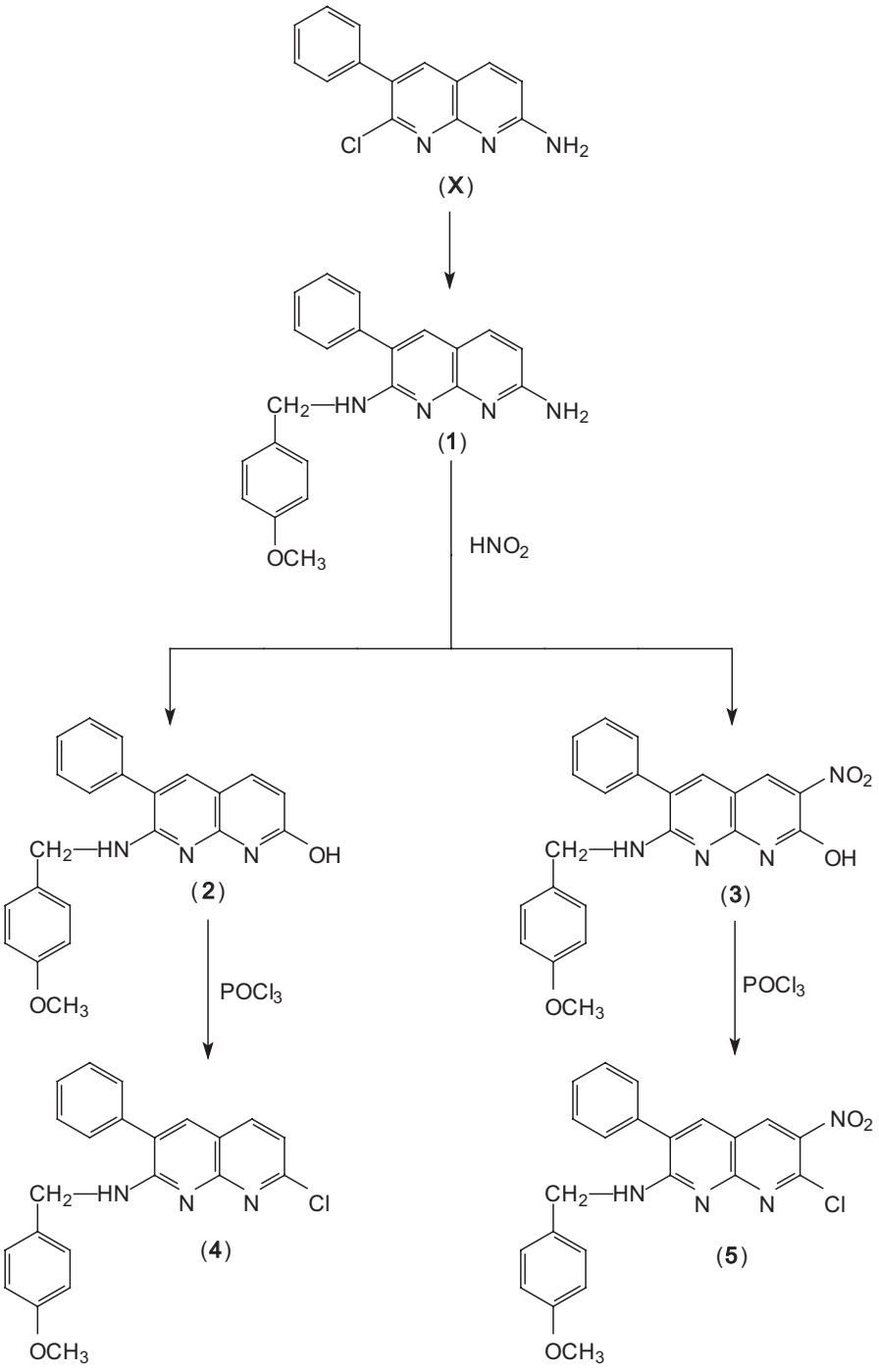
2.3.4 | Preparation of 7-methoxy and 7-ethoxy derivatives 6-9

A solution of 10 mmol of freshly prepared sodium methoxide (in the case of 7-methoxy derivatives **6** and **7**) or sodium ethoxide (in the case of 7-ethoxy derivatives **8** and **9**) and 1.0 mmol of the 7-chloro-derivatives **4** or **5** in 10 ml of anhydrous methanol was refluxed for 2.5 hr.

TABLE 2 ^{1}H NMR Chemical shifts (δ PPM/TMS)



Comp	H4 (s)	H5	H6 (d)	C_6H_5 (m)	NH- (t)	-CH_2 (t)	4′-OCH_3 (s)	OCH_3 (s)	-OCH_2CH_3	Others (d)			
										H2′	H3′	H5′	H6′
1	7.58	6.32 (d)	7.55	7.55	7.32	3.22	3.58	–	–	7.79	7.67	7.26	6.83
2	7.61	6.43 (d)	7.81	7.38	7.28	3.35	3.62	–	–	7.72	7.72	7.18	6.91
3	7.83	8.18 (s)	–	7.61	7.29	3.28	3.47	–	–	7.81	7.78	7.08	6.95
4	8.01	6.21 (d)	7.71	7.53	7.41	3.31	3.38	–	–	7.68	7.65	7.24	6.78
5	7.91	8.01 (s)	–	7.61	7.48	3.38	3.49	–	–	7.56	7.82	7.17	7.02
6	7.55	6.08 (d)	7.38	7.65	7.33	3.38	3.48	3.72	–	7.85	7.68	7.06	6.88
7	6.98	8.63 (s)	–	7.48	7.29	3.43	3.53	3.64	–	7.74	7.65	7.27	6.92
8	7.76	5.90 (d)	7.91	7.55	7.44	3.51	3.51	–	3.96 (t), 1.37 (q)	7.88	7.55	7.34	6.87
9	7.81	8.21 (s)	–	7.62	7.52	3.28	3.54	–	3.84 (t), 1.41 (q)	7.76	7.78	7.25	6.97
10	7.39	8.51 (s)	–	7.67	7.50	3.37	3.61	3.54	–	7.55	7.65	7.26	6.78
11	7.35	8.58 (s)	–	7.33	7.38	3.24	3.53	–	3.91 (t), 1.44 (q)	7.68	7.72	7.35	6.94



SCHEME 1 Synthetic pathways of intermediates 1–3 and target compounds 4, 5

The reaction mixture was evaporated to dryness in vacuo, and the crude residue was treated with water, neutralized with 10% hydrochloric acid and the solid precipitate collected by filtration and purified by crystallization to obtain **6**, **7** or **8**, and **9** (Tables 1 and 2).

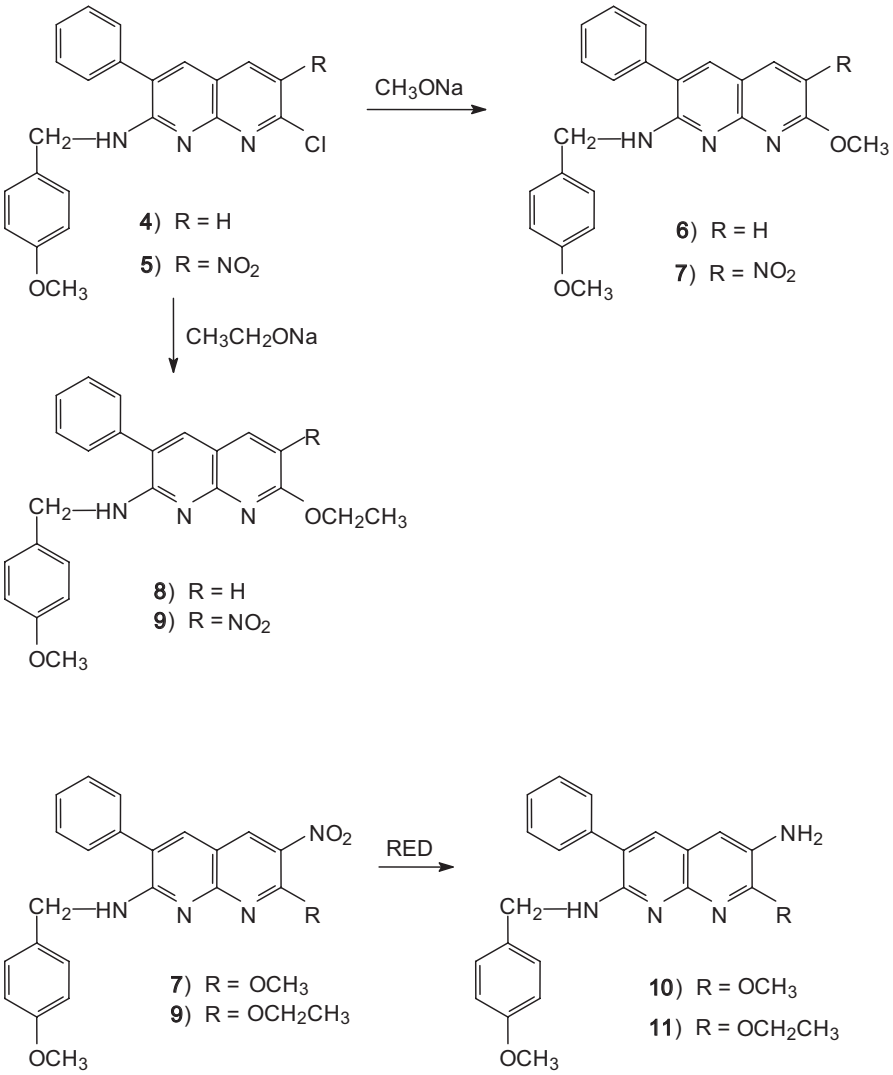
2.3.5 | Preparation of 6-amino derivatives 10 and 11

A solution of 1.1 mmol of 6-nitro derivatives **7** or **9** in glacial acetic acid was hydrogenated in the presence of 30 mg of 10% palladium on charcoal at room temperature and at atmospheric pressure for 3 hr. The catalyst was filtered and the solvent evaporated to dryness in vacuo to give compound **10** or **11**, which was purified by crystallization (Tables 1 and 2).

3 | RESULTS

3.1 | Chemistry

As a key intermediate of our designed compounds, compound **1** was synthesized utilizing Park et al., reaction.[21]



SCHEME 2 Synthetic pathways of intermediates 7, 9 and target compounds 6, 8, 10, 11

The 7-amino-2-chloro-3-phenyl-1,8-naphthyridine[22] designated as (**X**) was treated with 4-methoxybenzylamine, to obtain 7-amino-2-(4′-methoxybenzylamine)-3-phenyl -1,8-naphthyridine (**1**), Scheme 1. Diazotization of the 7-amino-2-(4′-methoxybenzylamine)-3-phenyl- (**1**) was effected with nitrous acid at −3°C to get the 7-hydroxy-2-(4′-methoxybenzylamine)-3-phenyl-1,8-naphthyridine (**2**) and 7-hydroxy-6-nitro-2-(4′-methoxybenzylamine)-3-ph enyl-1,8-naphthyridine (**3**), Scheme 1. Introduction of lipophilic groups, such as methoxy or ethoxy in position 7 of the 1,8-naphthyridine nucleus, was then obtained by the treatment of 7-hydroxy derivative **2** and **3** with phosphoryl chloride to obtain the relative 7-chloro derivatives **4** and **5**, Scheme 1, which were subsequently reacted with sodium methoxide to obtain the relative 7-methoxy compounds **6** and **7**, Scheme 2. The 7-chloro derivatives **4** and **5** were reacted with sodium ethoxide to obtain the relative 7-ethoxy derivatives **8** and **9**, Scheme 2. The 6-nitro derivatives **7** and **9** were reduced with palladium to 6-amino derivatives **10** and **11**, Scheme 2.

3.2 | Biological activity

The adipocytes were incubated with different concentrations of β-AR agonists, and glycerol release was measured as index of lipolysis. Isoprenaline and alprenolol treatment of isolated white adipocytes showed a dose-dependent increase in lipolysis, as reflected in glycerol production. A comparison between isoprenaline and alprenolol lipolytic effects is shown in Figure 1. Spontaneous glycerol release (basal lipolysis) was 0.24 ± 0.06 μmol/100 mg lipids. As shown in Figure 1, treatment of isolated rat adipocytes with 1 μM isoprenaline caused a sevenfold increase in glycerol release above basal levels. Alprenolol at concentration of 10 μM increased basal lipolysis from 0.24 ± 0.06 to 1.25 ± 0.26 μmol/100 mg lipids. At the concentration of 10 and 50 μM, basal lipolysis did not change by new 1,8-naphthyridine derivatives (not shown). However, it significantly decreased isoprenaline-induced lipolysis from 1.65 to 0.74 μmol/100 mg lipids. As shown in Figure 2, incubation of isoprenaline-stimulated adipocytes with 10 μM of 7-hydroxy-2-(4′-methoxybenzylamin

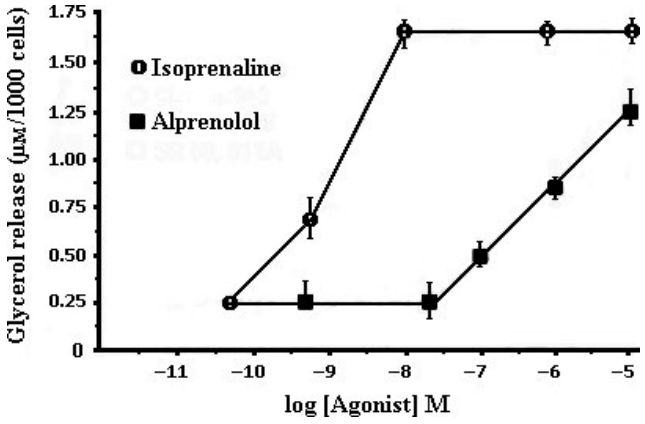


FIGURE 1 β agonists-mediated lipolysis in isolated white adipocytes. Dose–response curves for isoprenaline and alprenolol. Adipocytes were isolated from epididymal fat pads. Fat cells (~1,000 cells/assay) were incubated with the indicated concentration of lipolytic agents at 37°C for 90 min, and lipolytic activity was determined by the amount of glycerol released. Values are the mean of 2–3 experiments; vertical lines show standard errors mean

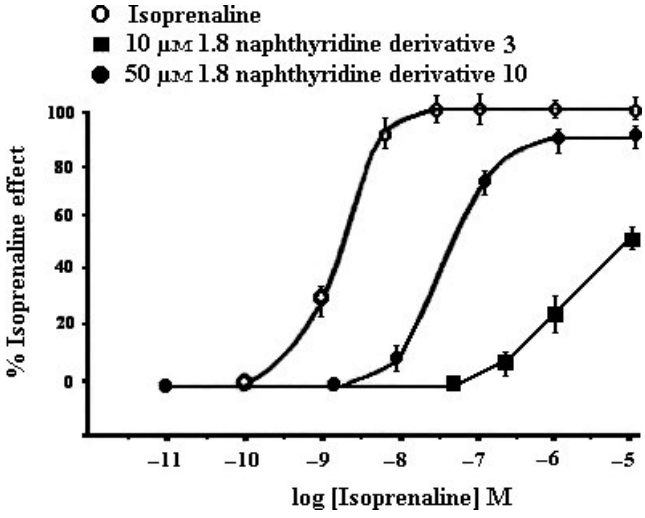


FIGURE 2 Antagonism of isoprenaline-induced lipolysis by the analogues **3** and **10** in rat adipocytes. Lipolysis induced by isoprenaline in the presence and absence of 10 μM of 7-hydroxy-2-(4′-methoxybenzylamine)-6-nitro-3-phenyl substituent, derivative **3** and 50 μM of 7-methoxy-2-(4′-methoxybenzylamine)-6-amino-3-phenyl substituent, derivative **10.** Values are means of 2–3 experiments expressed as % maximal stimulation observed in the presence and absence of antagonist; vertical lines show standard errors mean

e)-6-nitro-3-phenyl substituents designated as **3** and 50 μM of 7-methoxy-2-(4′-methoxybenzylamine)-6-amino-3-phen yl substituent designated as **10** significantly antagonized the lipolytic effect induced by isoprenaline.

Figure 3 shows the concentration–response curves of isoprenaline in the presence of increasing concentrations of the new 1,8 naphthyridine derivatives **3**, **10**. For both compounds, a clear inhibition was observed, whereas the selective β_1-AR

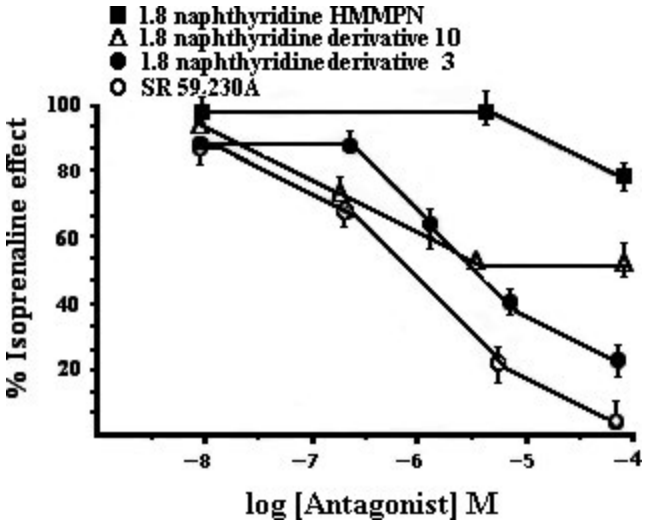


FIGURE 3 Dose–response curves for stimulatory effects of isoprenaline on white adipocyte lipolysis measured in the presence of increasing concentrations of the selective β_3-AR antagonist SR 59,230A, the analogues **3** and **10** with a 7-hydroxy-2-(4′-methoxybenzylamine)-6-nitro-3-phenyl and 7-methoxy-2-(4′-methoxybenzylamine)-6-amino-3-phenyl substituent, the selective β_1-antagonist 7-hydroxy-4-morpholinomethyl-2-piperazino-1,8-naphthyridine (HMMPN). Values are means of 2–3 experiments expressed as % maximal stimulation observed in the presence of antagonist; vertical lines show standard errors mean

antagonist, HMMPN inhibited this release only at high doses. The lower concentrations of HMMPN did not affect the release of glycerol in response to isoprenaline. Incubation of isoprenaline-stimulated adipocytes with 10 μM of the selective β_3-AR antagonist SR 59,230A also abolished the stimulatory effect of isoprenaline on glycerol release.

These results provide good evidence that more than one β-adrenoceptor subtype mediating the metabolic effects of isoprenaline, and derivative **3** almost completely antagonized the lipolytic effect induced by the β_3-AR agonist isoprenaline.

The subtype selectivity of the new 1,8-naphthyridine derivatives effect was measured, by use of alprenolol (a β_1- and β_2-adrenoceptor antagonist/β_3-AR partial agonist), SR 59,230A, and HMMPN. The inhibitory effects of the antagonists were studied on 10 μM alprenolol-mediated lipolytic effects. Alprenolol has been shown to induce lipolysis in rat adipose tissue, putatively through β_3-adrenoceptor activation.[23–25] As shown in Figure 4, the concentration–response curves of alprenolol were displaced by increasing concentrations of the selective β_3-AR antagonist, SR 59,230A and 1,8-naphthyridine derivatives **3** and **10**. The data clearly demonstrate that the lipolytic effects of 10 μM alprenolol can be almost totally inhibited by the derivative **3** at 100 μM.

The inhibitory effects of derivative **10** were much smaller than that of derivative **3** and SR 59,230A on the release of glycerol by alprenolol. The selective β_1-antagonist HMMPN was ineffective.

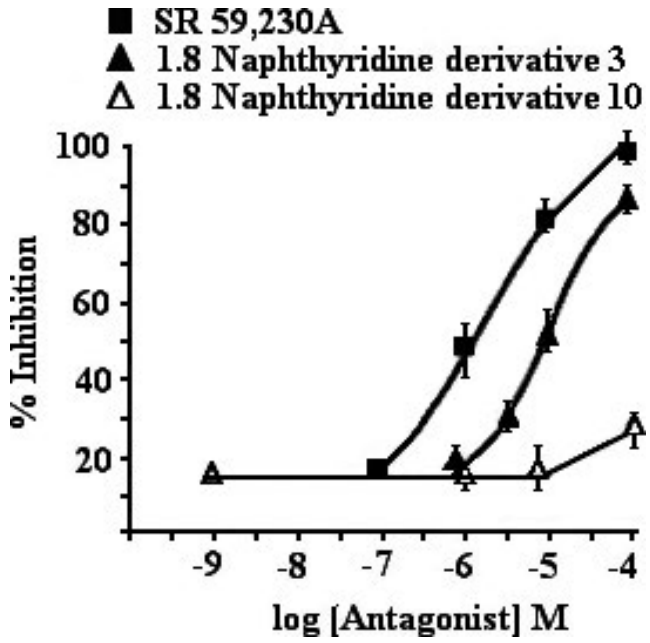


FIGURE 4 Antagonism of alprenolol-induced lipolysis by increasing concentrations of the selective β_3-AR antagonist SR 59,230A, the analogues **3** and **10** with a 7-hydroxy-2-(4′-methoxybenzylamine)-6-nitro-3-phenyl and 7-methoxy-2-(4′-methoxybenzylamine)-6-amino-3-phenyl substituent. The antilipolytic effect of increasing concentrations of antagonists was expressed in % inhibition of stimulated lipolysis. Values are the mean of 3 experiments; vertical lines show standard errors mean

4 | DISCUSSION

The primary function of adipose tissue in rodents is to maintain body temperature during exposure to cold by generating heat. The amount of triglycerides stored in the adipocytes depends on the balance between lipogenesis and free fatty acids release. The main fate of fatty acids in white adipose tissue is extracellular efflux, whereas fatty acids in brown fat function to balance production with oxidation.[26]

Antilipolytic agents reduce or prevent the thermogenic activity of β_3-adrenoceptor agonists in white adipose tissue.[27,28] The present study investigated the antilipolytic effects of 1,8-naphthyridine derivatives in rats white adipocytes. Standard approach has been used to assess the involvement of a β_3-antagonist-like response of the newly synthesized 1,8-naphthyridine derivatives in the β_3-adrenoceptor-mediated lipolysis induced by isoprenaline and alprenolol. We compared the effects of newly synthesized 1,8-naphthyridine derivatives on the lipolysis induced by the non-selective β_3 agonists, with that of the selective β_3 antagonist SR 59,230A and the selective β_1 antagonist HMMPN, to isolate any effect caused by β_3 agonist stimulation.

Using the β_3-AR agonists isoprenaline and alprenolol in the presence or absence of newly synthesized 1,8-naphthyridine derivatives, the selective β_1-AR antagonist, 7-hydroxy-4-morpholinomethyl-2-piperazino-1,8-naphthyridine (HMMPN) that specifically targets β_1 receptor[19] (to rule out confounding effects of β_1 stimulation), and the selective β_3-AR antagonist, SR 59,230A, showed that 1,8-naphthyridine derivatives do not increase lipolysis and even have antilipolytic effect in a dose-dependent manner.

The lipolytic effect of isoprenaline was significantly antagonized by 1,8-naphthyridine derivatives **3**, **10** and the selective β_3-AR antagonist SR 59,230A. However, the β_1-antagonist HMMPN failed to inhibit the stimulatory effects of isoprenaline (Figure 3), particularly at isoprenaline concentrations that maximally stimulate lipolysis. This effect may be interpreted as indicating that lipolysis is more controlled by the low-affinity β_3-ARs.

Blockade of the effect of alprenolol was different, derivative **10** partially inhibited alprenolol-induced lipolysis, whereas the selective β_3-AR antagonist, SR 59,230A and 1,8-naphthyridine derivative **3** completely blocked the effect (Figure 4) and HMMPN had no influence on the release of glycerol at the lower concentrations of alprenolol (not shown).

A clear antagonism was observed between 1,8-naphthyridine derivatives **3**, **10** and the β_3-AR agonist isoprenaline-induced lipolytic effects (Figure 3). Conversely, competition studies on alprenolol effects showed that elevated concentrations of derivative **10** were necessary to antagonize alprenolol-induced lipolysis. This effect is completely blocked by SR 59,230A and significantly blocked by derivative **3** and resistant to HMMPN blockade. Collectively, data obtained with isoprenaline, alprenolol, SR 59,230A, and 7-hydroxy-4-morpholinomethyl-2-piperazino-1,8-naphthyridine (HMMPN) suggest that the new 1,8-naphthyridine analogues **3** and **10** act in the same way as SR 59,230A and may bind to a β_3-AR which is responsible for a substantial proportion of the lipolytic response in white adipose tissue.

5 | CONCLUSION

A series of novel 1,8-naphthyridine derivatives variously modified were synthesized and their β-AR blocking activities were determined. Preliminary evidence suggests that the inhibitory effects of the newly synthesized 1,8-naphthyridine analogues **3** and **10** on either alprenolol or isoprenaline-induced lipolysis in rat fat cells may result from inhibition of the low-affinity β_3-adrenoceptor.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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