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Calcium Channel Blocking and Anti-arrhythmic Activities of Some Thienopyrimidine with Benzoxazine, Quinazoline and Azole Moieties

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In our previous work, some of thienopyrimidine, benzoxazine, quinazoline and azole moieties 1-18 were synthesized before. We herein report the calcium channel blocking and anti-arrhythmic activities. Nineteen of these compounds were screened for their calcium channel blocking and anti-arrhythmic activities using of Nifedipine as the reference drug. The newly synthesized compounds showed potent calcium channel blocking and anti-arrhythmic activities with low toxicity (LD_{50}) comparable to Nifedipine as reference drug.

Key words: Thienopyrimidinoyl chloride, Thienopyrimidine, Benzamidazole, Calcium channel blocking, Anti-arrhythmic activities.

In our previous work, we have reported that certain of our newly substituted heterocyclic sulfure compounds exhibited antiandrogenic[1], anti-inflammatory[2], anticancer[3], anticonvulsant[4], antiarrhythmic[5] and antiparkinsonian, anti-inflammatory, serotonin antagonist and antianexiety activities [6-8]. Calcium ions play an essential role in regulating skeletal and smooth muscle contractility and in the performance of the normal and diseased heart[9,10]. In classifying agents that inhibit the movement and binding of calcium, the World Health Organization has identified two types of calcium channel blocker that are used in clinical situations: those that are selective for L-type (long-lasting, large-current, or slow), voltage-dependent calcium channels, and those that are nonselective[11]. Recently, some new steroidal derivatives fused with heterocyclic moieties have been synthesized and used as 5α-reductase and aromatase inhibitors, anti-inflammatory, anti-alzheimer, anti-arthritic and immunosuppressive[12-18] agents. In view of these observations and as continuation of our previous works in heterocyclic chemistry, we have herein screened some of pyrimidine derivatives fused with thiophene ring as calcium channel blocking and anti-arrhythmic agents.

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EXPERIMENTAL

All melting points are uncorrected and were recorded on Buchi 510 apparatus. IR spectra were recorded as KBr disks on a perkin- Elmer 383-Spectrometer and FTIR spectrometer Nicollet, impact 400. 1H NMR was obtained a Bruker Ac 200f and Ac 250, DRX400 instrument at room

temperature using TMS as internal standard. Microanalyses were carried out at micro analytical center, Cairo University, Egypt, National Research Center and Friedrich–Schiller University, Jena, Germany.

Pharmacological screening

Calcium Channel Blocking Activity

In vitro method ^{3}H-nitrendipine binding in vitro

Radiolabeled dihydropyridine calcium channel antagonists such as 3H-nitrendipine are selective ligands for a drug receptor site associated with the voltage-dependent calcium channel. A constant concentration of the radioligand ^{3}H-nitrendipine (0.3-0.4 nM) is incubated with increasing concentrations of a non-labeled test drug (0.1 nM–1 mM) in the presence of plasma membranes from bovine cerebral cortices. If the test drug exhibits any affinity to calcium channels, it is able to compete with the radioligand for channel binding sites. Thus, the lower the concentration range of the test drug, two freshly-slaughtered bovine brains are obtained from the slaughter house and placed in ice-cold preparation buffer. In the laboratory, approx. 5 g wet weights of the two frontal cerebral cortices are separated from the brains.

Materials and solutions

- Preparation buffer Tris-HCl 50 mM pH 7.4
- Incubation buffer Tris-HCl 50 mM
- Genapol 0.001% pH 7.4
- Radioligand ^{3}H-nitrendipine Specific activity 2.59–3.22 TBq/mmol (70–87 Ci/mmol) (NEN)

For inhibition of 3H-ni-trendipine binding in non-specific binding experiments Nifedipine (Sigma)

Membrane preparation

The tissue is homogenized (glass Teflon potter) in icecold preparation buffer, corresponding to 1 g cerebral wet weight/50 ml buffer, and centrifuged at 48 000 g(4 °C) for 10 min. The resulting pellets are resuspended in approx. 270 ml preparation buffer, and the homogenate is centrifuged as before. The final pellets are dissolved in preparation buffer, corresponding to 1 g cerebral cortex wet weight/30 ml buffer. The membrane suspension is immediately stored in aliquots of 5–10 ml at –77 °C. Protein content of the membrane suspension is determined according to the method of Lowry *et al*.,[19] with bovine serum albumin as a standard.

At the day of the experiment, the required volume of the membrane suspension is slowly thawed and centrifuged at 48 000 g (4 °C) for 10 min. The resulting pellets are re-suspended in a volume of ice-cold incubation buffer, yielding a membrane suspension with a protein content of 0.6-0.8 mg/ml. After homogenization (glass Teflon potter), the membrane suspension is stirred under cooling for 20–30 min until the start of the experiment[20].

Experimental course

As 1,4-dihydropyridines tend to bind to plastic material, all dilution steps are done in glass tubes.

For each concentration samples are prepared in triplicate. The total volume of each incubation sample is 200 µl (micro titer plates).

Saturation experiments

Total binding

- 50 µl ^{3}H-nitrendipine (12 concentrations, $5x10^{-11}$–$4\ x10^{-9}$ M).
- 50 µl incubation buffer.

Non Specific Binding

- 50 µl ^{3}H-nitrendipine (4 concentrations, $5x10^{-11}$–$4x10^{-9}$ M).
- 50 µl nifedipine ($5\ X10^{-7}$ M).

Competition experiments

- 50 µl ^{3}H-nitrendipine (1 constant concentration, 3–4 $x10^{-10}$ M)
- 50 µl incubation buffer without or with non-labeled test drug (15 concentrations, 10^{-10}–10^{-3} M)

The binding reaction is started by adding 100 µl membrane suspension per incubation sample (0.6–0.8 mg protein/ml). The samples are incubated for 60 min in a bath shaker at 25 °C. The reaction is stopped by subjecting the total incubation volume to rapid vacuum filtration over glass fiber filters. Thereby the membrane bound is separated from the free radioactivity. Filters are washed immediately with approx. 20 ml ice-cold rinse buffer per sample. The retained membrane-bound radioactivity on the filter is measured after addition of 2 ml liquid scintillation cocktail per sample in a Packard liquid scintillation counter[21].

The following parameters are calculated:

- Total binding
- Non-specific binding
- Specific binding = total binding – non-specific binding

The dissociation constant (Ki) of the test drug is determined from the competition experiment of ^{3}H-nitrendipine versus non-labeled drug by a computer- supported analysis of the binding data. The Ki-value of the test drug is the concentration, at which 50% of the receptors are occupied by the test drug.The affinity constant Ki [mol/l] is recorded and serves as a parameter to assess the efficacy of the test drug. Standard data: nifedipine Ki= 2.4×10^{-9} mol/L [22].

In vivo method Evaluation of calcium blockers in the pithed rat

Using the cardio accelerator response in pithed rats, calcium entry blockers can be distinguished from other agents which have modes of action not involving direct blockade of calcium entry. Male Sprague-Dawley rats (250–350 g) are anaesthetized with methohexitone sodium (50 mg/kg i.p.). Following cannulation of the trachea, the rats are pithed through one orbit with a stainless steel rod and immediately artificially respired with room air (78 strokes/min,1 ml/100 g body weight) via a Palmer small animal respiration pump. A jugular vein is cannulated for administration of drugs. Arterial blood pressure is recorded from a carotid artery using a pressure transducer. Heart rate is derived from the phasic arterial pressure signal with a phase lock loop ratemeter (BRL Instrument Services). Both parameters are displayed on a recorder. The animals are kept warm by an incandescent lamp positioned about 25 cm above them. The pithing rod is withdrawn so that the tip lays in the thoracic portion of the spinal cord. All rats then receive (+) tubocurarine (1.5 mg/kg i.v.) and are bilaterally vagotomized.

The cardio accelerator response is obtained by continuous electrical stimulation of the thoracic spinal cord with square wave pulses of 0.5 ms duration, at supramaximal voltage at a frequency of 0.5 Hz using the pithing rod as a stimulating electrode. An indifferent electrode is inserted subcutaneously in the femoral region. Only rats with a resulting tachycardia of more than 100 beats/min are included into the experiments.

When the cardio accelerator response has stabilized for about 3–5 min, cumulative intravenous doses of drug or corresponding vehicle are administered. Succeeding doses are given when the response to the previous dose has stabilized.

Calcium antagonists and β-blockers inhibit dose dependent the tachycardia elicited by electrical stimulation of the spinal cord, whereas lignocaine and nicorandil are not effective.

Doses of β-blockers or calcium-antagonists, which reduce the tachycardia to 50% are tested again. Three min after administration of the drug, calcium gluconate (1 mg/min) or water (0.1 ml/min) are infused using a Harvard apparatus compact infusion pump. The effects of calcium entry blockers, but not of β-adrenoreceptor blockers, are antagonized[23].

The level of tachycardia immediately prior to drug administration is taken as 100% and responses to drugs are expressed as a percentage of this predose tachycardia. If an inhibitory effect >50% is seen, then an ID_{50} (with 95% confidence limits) is interpolated from linear regression analysis. Significance of differences between the groups receiving calcium gluconate and their parallel vehicle controls is calculated by Student's t-test.

Anti-arrhythmic activity

The plant alkaloid aconitine persistently activates sodium channel. Infusion of aconitine in the anesthetized rat causes ventricular arrhythmias. Drugs considered having anti-arrhythmic properties can be tested in aconitine-intoxicated rats[24]. Male Ivanovas rats weighing 300–350 g are used. The animals are anesthetized by intra peritoneal injection of 1.25 g = kg urethane: 5 mg = kg aconitine dissolved in 0.1N HNO_3 is administered by continuous infusion into the saphenous vein of 0.1 cm^3 = min and the ECG (Electro cardio graph) in lead II is recorded every 30 sec. The test compound is injected IV at a screening dose of 3 mg = kg 5 min before the start of the aconitine infusion, 24 animals are used per compound.

The anti-arrhythmic effect of a test compound is measured by the amount of aconitine=100 g animal (Duration of infusion) which induces[25].

– Ventricular extra systoles.
– Ventricular tachycardia.
- Ventricular fibrillation.

Higher doses of aconitine in the treated group as compared to an untreated control group are an indication of anti-arrhythmic activity[26-28]. Statistical significance between the groups is

assessed by the Student's T-test.

Measurement of drug levels in plasma and in different organ samples

Drug levels in plasma and in different organ samples were measured by liquid chromatography as previously described[29]. Briefly, samples were prepared by adding 300µl acetonitrile and 40µl phosphoric acid 40% to 100µl plasma or organ homogenate and placing the mixture in a vortex for 5 s. plasma and brain samples were then centrifuged at 14,000 rpm for 5 min and the supernatants (15 and 50 µl, respectively) were injected into the HPLC system. Equipment system with mass spectrometry (API2000, Applied Biosystems, Foster City, CA, USA with MassLynx Showroom) detector were used. The chromatographic conditions were adapted to each compound to obtain good peak separation and detection sensitivity. Temperature was maintained at 25 °C by a thermo stated cell holder. Measurements with the flow rate 0.22 ml/min. A mixture of ammonium formate (20 µM) buffer-acetonitrile-methanol was used as mobile phase. For drugs s in Mass the assay was liner between 400 and 20,000 ng g^{-1} in the organand 100-8500 ng ml^{-1} in plasma[29].

RESULTS AND DISCUSSION

In continuation of our previous work, a series of thienopyrimidine, benzoxazine and quinazoline candidates **1–18** (Fig. 1) were synthesized in advance[30]. Herein, we used these compounds for evaluation as calcium channel blocking and anti-arrhythmic activities agents.

Pharmacological activities

Calcium Channel Blocking and Anti-arrhythmic Activities

From the previous we test the calcium channel blocker activity of the tested compounds due to their structural similarity with many clinical used ones especially benzothiazepines type, where the author aim to discuss the effect replacing the dihydropyridine with quinazoline on the calcium

Table 1. The affinity constant Ki [mol/l] for the tested compounds using vitro method ^{3}H-nitrendipine binding

Comp. No	The affinity constant Ki mol/l ±S.E %Main Value
1	*Inactive*
2	*Inactive*
3	*Inactive*
4	*Inactive*
5	*Inactive*
6	1.2×10^{-12} ±0.13%
7	3.2×10^{-9}±0.41%
8	5.4×10^{-10}±0.21%
9	5.7×10^{-11}±0.12%
10	5.6×10^{-12}±0.17%
12	*Inactive*
13	*Inactive*
14a	6.7×10^{-13}±0.14%
14b	$8.7 \times 10^{-}$14±0.22%
14c	5.4×10^{-15}±0.34%
15	*Inactive*
16	4.3×10^{-16}±0.21%
17	2.3×10^{-17}±0.25%
18	2.3×10^{-18}±0.21%
Nifedipine	2.4×10^{-9}±0.61%

All the results are statistical valid at P<0.005
The data are expressed as the mean of three separate experiments

Table 2. ID_{50} [µM] for the tested compounds using in vivo method (Evaluation of calcium blockers in the pithed rat)

Comp. No	ID_{50} [µM] ±S.E % of main value
1	Inactive
2	Inactive
3	Inactive
4	Inactive
5	Inactive
6	98.16 ±0.1%
7	96.78±0.2%
8	95.48±0.4%
9	94.58±0.2%
10	92.18±0.3%
12	*Inactive*
13	*Inactive*
14a	90.13±0.6%
14b	87.89±0.7%
14c	81.29±0.8%
15	*Inactive*
16	78.65±0.9%
17	71.77±0.21%
18	66.67±0.2%
Nifedipine	112.34±0.1%

All the results are statistical valid at P<0.005
The data are expressed as the mean of three separate experiments.

channel blocker activity. In the same time calcium channel blockers that affect calcium influx play an important role in treating arrhythmia via alter membrane ion conductance's (i.e. both affecting ion influx). So the authors aiming to discuss the anti-arrhythmic activity of the tested compounds aiming to reach to agent combined both calcium channel blocker and anti-arrhythmic activities. It was found that compounds **6, 7, 8, 9, 10, 14a, 14b, 14c, 16, 17** and **18** showed potent calcium channel blocking and anti-arrhythmic activities and it discussed as follow.

Table 3. Anti-arrhythmic activities of the tested compounds

Comp. No	LD_{100} µM /100mg± S.E %of main value
1	Inactive
2	Inactive
3	Inactive
4	Inactive
5	Inactive
6	8.5×10^{-3}±0.23%
7	6.5×10^{-3}±0.45%
8	5.7×10^{-3}±0.26%
9	5.4×10^{-3}±0.29%
10	5.2×10^{-3}±0.37%
12	Inactive
13	Inactive
14a	4.9×10^{-3}±0.37%
14b	4.4×10^{-3}±0.48%
14c	3.2×10^{-3}±0.36%
15	Inactive
16	2.3×10^{-3}±0.37%
17	2.2×10^{-3}±0.36%
18	2.1×10^{-15}±0.38%

All the results are statistical valid at P<0.005
The data are expressed as the mean of three separate experiments.

Table 4. Pharmacokinetic data for the tested compounds

Comp. No.	Plasma Drug Conc in Male Sprague-Dawley rats nM.	Plasma Drug Conc in Male Ivanovas rats nM.
6	12.34	43.33
7	2.46	5.56
8	4.55	4.54
9	5.64	3.34
10	6.55	4.67
14a	5.46	5.54
14b	4.37	6.34
14c	5.49	7.33
16	6.58	8.26
17	7.67	7.57
18	6.77	2.67
Nifedipine	11.99	12.66

All the results are statistical valid at P<0.005
The data are expressed as the mean of three separate experiments.

Reaction of thienopyrimidinoyl chloride **3** with 2-aminocyclohexanothiophene-3-carboxamide **4** yielded thienopyrimidine derivative **5.** All the previous compounds have neither calcium channel blocking activity nor anti-arrhythmic activity. Thienopyrimidine derivative **5** that undergoes cyclodehydration to afford thienopyrimidine **6** that have calcium channel blocking activity and anti-arrhythmic activity. The synthesis of benzamidazole **8** and benzoxazole **10** derivatives was achieved by condensation of thienopyrimidinoyl chloride **3** and *o*-phenylenediamine or *o*-aminophenol giving compounds **7** and **9** followed by cyclization of the later compounds. It's worth to mention that the both the calcium channel blocking activity and anti-arrhythmic activity increases and the activities of the cyclic derivatives **8** and **10** are higher than the non cyclic **7** and **9.** This findings suggest that the cyclic form have such configuration that permit it to approach and binding to the receptor, while this phenomenon is higher of the isooxazole heterocycle than for pyrazoline ones due to the higher electronegativity of the oxygen atom more than the nitrogen one. Reaction of 4-thio-6-methyl-2-(*p*-methoxyphenyl)-5-acetylpyrimidine **1** and *N*(o-carboxyphenyl) chloroacetamide **11** yielded pyrimidine derivative **12** that cyclized to benzoxazine **13** which were completely devoid from any calcium channel blocking activity and anti-arrhythmic activity. Compound **13** was transformed to quinazoline derivatives **14a-c** and **16** that have higher calcium channel blocking activity and anti-arrhythmic activity due to the quinazoline bind in a strong manner to the calcium receptors and causing such receptor structural deformations lead to block calcium micro tubules influx pathways. This assumption was supported by the high increase of the calcium channel blocking activity and anti-arrhythmic activity of compounds **17** and **18** that prepared by the reaction of **13** with semicarbazide yielded compound **17** that converted

to triazoloquinazoline **18.** The urea part allow high of degree of hydrophilic characters that increase the incidence of stricken the calcium receptor and consequently blocking calcium influx, while this increases in case of derivative **18.**

The affinity constant Ki [mol/l] is recorded and serves as a parameter to assess the efficacy of the test drug. Standard data: nifedipine Ki= 2.4×10^{-9} mol/l

Procaine amide, 5 mg = kg iv, and lidocaine, 5 mg/kg iv, led to an increase in LD_{100} by 65%, which corresponds to a LD_{100} of approximately 9.8×10^{-15} µM /100 mg ID_{50} doses of β-blockers or calcium-antagonists, which reduce the tachycardia to 50% LD_{100} the level of tachycardia immediately prior to drug administration is taken as 100% and responses to drugs are expressed as a percentage of this predose tachycardia. If an inhibitory effect >50% is seen, then an ID_{50} (with 95% confidence limits) is interpolated from linear regression analysis. Significance of differences between the groups receiving calcium gluconate and their parallel vehicle controls is calculated by Student's t-test.

LD_{100} the anti-arrhythmic effect of a test compound is measured by the amount of aconitine=100 g animal (Duration of infusion) which induces Ventricular extra systoles, tachycardia and fibrillation.

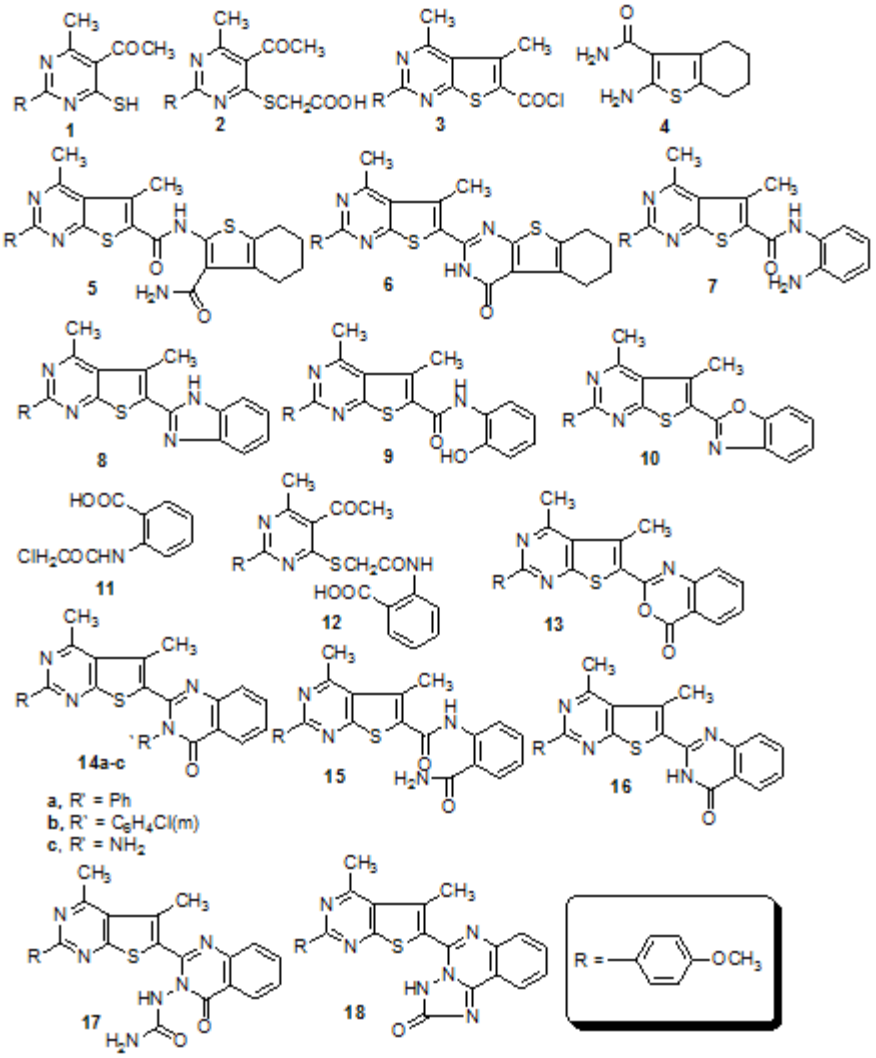

Fig. 1. Chemical structure for tested compounds 1-18

CONCLUSION

It was found that compounds **6, 7, 8, 9, 10, 14a, 14b, 14c, 16, 17** and **18** showed potent calcium channel blocking and anti-arrhythmic activities. It's worth to mentioned that all the active compounds showed good pharmacokinetics and pharmacodynamics profiles. From the obtained data we can go to the following structural features about the structural requirements needed fo the agents to combine both calcium channel blocking and anti-arrhythmic activities that could summarized in the following SAR points.

Structure activity relationship (SAR)

- Thienopyrimidine derivative 5 are inactive while the cyclodehydration thienopyrimidine 6 are more active so we got to the conclsion that cyclodehydration increases activity.
- The cyclized benzamidazole **8** is more active than its non-cyclized start **7**.
- The enzoxazole **10** is more active than more active than its non-cyclized start **9.**
- Quinazoline derivatives **14a-c** and **16** are highly active but derivatives **16** are more potent than **14** to the NH free that increase receptor binding.
- The triazoloquinazoline **18** are the most active ones (also it more active than then-urea derivatives **17**.
- Regarding to the aromatic substitute for derivatives **14** the descending order of activity is NH_2>Cl>H

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