International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

International Journal of Pharmacology 11 (5): 502-507, 2015
ISSN 1811-7775

ansinet
Asian Network for Scientific Information

RESEARCH ARTICLE OPEN ACCESS

DOI: 10.3923/ijp.2015.502.507

Synthesized of Some Heterocyclic Systems and their Nucleoside of Potent Anti-inflammatory Activities

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ARTICLE INFO
Article History:
Received: January 06, 2015
Accepted: April 24, 2015

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ABSTRACT
Some of synthesized heterocyclic pyrimidine, pyrimidine, furopyridine derivatives and their nucleoside candidates (2-14) were previously prepared and were founded to have some aspects of structural similarity with many anti-inflammatory agents. Therefore, these agents were screened for this property. The evaluation of the anti-inflammatory activities was based on evaluation of the abilities of these compounds in protection against carrageenan-induced edema. The anti-inflammatory activities of the tested compounds further confirmed based on evaluation of the abilities of these compounds to inhibit plasma PGE2. These compounds showed potent anti-inflammatory activity with low toxicity (LD_{50}) comparable to Valdicoxib® as reference anti-inflammatory drugs.

Key words: Pyrimidine, furopyridine, thioglycoside, nucleoside, anti-inflammatory activities

INTRODUCTION

In a previous work we reported that certain of our newly substituted heterocyclic compounds exhibited anti-parkinsonian (Amr *et al*., 2005), antitumor (Abo-Ghalia and Amr, 2004; Hammam *et al*., 2003; Amr *et al*., 2006), antimicrobial (Amr *et al*., 2003; Al-Salahi *et al*., 2010) and anti-inflammatory (Said *et al*., 2009; Fakhr *et al*., 2008) activities. Furopyridines and heterocycles derived from them are found to be associated with diverse pharmacological activities (Rapoport and VanSickle, 1990; Scriba *et al*., 1995a). They are also reported to possess significant antipsychotic (New *et al*., 1989), antianaphylactic (Wagner and Prantz, 1993), antiproliferative (Bukoski *et al*., 1993), anticonvulsant (Scriba *et al*., 1995b) and anthelmintic (Jeschke *et al*., 2005) activities. On the other hand, glycosylsulfanyl heterocycles have attracted much attention because of their biological activity as antitumor (El-Sayed *et al*., 2009), antimicrobial (El-Sayed *et al*., 2008; Moustafa *et al*., 2009), antiviral (Abdel-Mageed *et al*., 2014) and in particular because of their inhibition of the activity of enzymes (Awad *et al*., 2004; El Ashry *et al*., 2000). Recently, it was reported that certain of our newly substituted heterocyclic compounds exhibited anti-inflammatory (Hussain *et al*., 2014, 2015), antiviral (Al-Salahi *et al*., 2015), antimicrobial (Hossan and Amr, 2014) and androgen receptor antagonists and anti-prostate cancer activities (Bahashwan *et al*., 2014). In view of these reports and in continuation of our previous works in heterocyclic chemistry, the tested compounds have two basic centers separated by two carbon atoms which is the common essential feature present in all anti-inflammatory agents prompted the authors to examine the anti-inflammatory activities of these compound. This beside the presence of glycone moiety that believed it improve pharmacokinetics and pharmacodynamics properties of these entities. Some compounds containing pyridine, pyrimidine and nucleoside derivatives have been screened here for their evaluation as anti-inflammatory agents.

MATERIAL AND METHODS

Chemistry: All the tested compounds were confirmed by physical and spectroscopic evidences according to the previously reported procedures (El-Sayed *et al*., 2014).

Pharmacological screening

Experimental animals: Adult male albino rats (150-180 g), were obtained from National Research Center, Cairo, Egypt, Giza, Egypt and were acclimatized for 10 days under standard housing conditions (24±1°C; 45-55% RH with 12:12 h light/dark cycle). The animals had free access to rat food (Lipton Gold Mohr, India) and water. The animals were habituated to laboratory conditions for 48 h prior to the experimental protocol to minimize any nonspecific stress. The experimental protocol was approved by the Institutional Animal Ethics Committee by Government College of Pharmacy, Karad, India and animals were maintained under standard conditions in the animal house approved by Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA).

Determination of acute toxicity (LD_{50}): The LD_{50} for compounds were determined by injected different gradual increased doses of the tested compounds to adult male albino rats, then calculating the dose that caused 50% animal death, according to Austen and Brocklehurst (1961) OPPTS test guideline are 40 CFR 797.140.

Anti-inflammatory activity

Procedure: Groups of adult male albino rats (150-180 g), each of 8 animals (To permit high significance limits in statistics) were orally dosed with tested compounds at a dose level of 25-50 mg kg^{-1} 1 h before Carrageenan® challenge where the anti-inflammatory profiles of the tested compounds below a dose of 25 mg kg^{-1} were of low fluctuated response with no significant margins of statistics. Foot paw edema was induced by subplantar injection of 0.05 mL of 1% suspension of Carrageenan® in saline into the planter tissue of one hind paw. An equal volume of saline was Subcutaneous injected to the other hind paw and served as control. Four hour after drug administration, the animals were decapitated, blood was collected and the paws were rapidly excised.

The average weight of edema was examined for the treated as well as the control group and the percentage inhibition of weight of edema was also evaluated. Valdicoxib® (5 mg kg^{-1}) was employed as standard reference, against which the tested compounds were compared.

Calculation and evaluation: Thirty minutes after the rats are challenged by subcutaneous injection of 0.05 mL of 1% solution of carrageenan into the planter side of the lift hind paw. The paw is marked with ink at the level of the lateral malleolus; the paw volume was measured by a sensitive method developed by Webb and Griswold (1984) that calculated by interfacing a Mettler DeltaRange top-loading balance with a micro computer.

$$\text{Protection (\%)} = (A-B)\times 100/A \quad (1)$$

where, A is the paw volume of non-treated group and B is the paw volume of treated group.

Estimation of plasma prostaglandin E2 (PGE2)

Procedure: Heparinized blood samples were collected from rats obtained from the previous anti-inflammatory examined groups (n = 8), plasma was separated by centrifugation at 12,000 g for 2 min at 40°C and immediately stored frozen -2°C until use. The design correlate EIA prostaglandin E2 (PGE2) kit (Merck, Darmstadt, Germany) is a competitive immunoassay for the quantitative determination of PGE2 in biological fluids. The kit uses a monoclonal antibody to PGE2 to bind, in a competitive manner, the PGE2 in the sample after a simultaneous incubation at room temperature. The excess reagents were washed away and the substrate was added, after a short incubation time the enzyme reaction was stopped and the yellow color generated was read on a micro plate reader (DYNATCh, MR 5000) at 405 nm. The intensity of the bound yellow color is inversely proportional to the concentration of PGE2 in either standard or samples.

Calculation and evaluation: The PGE2 was calculated for the treated and control groups, then the PGE2 percentage inhibition is downloaded by University of York at: 21:37 21 January 2009 some novel S-Pyridyl glycosides derivatives 3055 determined by the following equation:

$$\text{Inhibition (\%)} = (A-B)\times 100/A \quad (2)$$

where, A is PGE2 in the control group and B is PGE2 in the treated group.

RESULTS AND DISCUSSION

Chemistry: In continuation of our previous work, a series of heterocyclic pyrimidine, pyrimidine, furopyridine derivatives and their nucleoside candidates (1-14) (Fig. 1 and 2) were synthesized and illustrated by physical, chemical and spectroscopic evidences before (El-Sayed *et al*., 2014). Herein, the activities of compounds for evaluation as anti-inflammatory agents were reported.

Pharmacological screening

Acute toxicity: Initially the acute toxicity of the compounds was assayed via the determination of their LD_{50}. All the compounds except 7 were interestingly less toxic than Valdecoxib® as the reference drug (Table 1).

Anti-inflammatory potency: The tested compounds were then pharmacologically screened on male albino rats for their anti-inflammatory potency (Table 2 and 3). The evaluation of the anti-inflammatory activities was based on evaluation of the abilities of these compounds in protection against carrageenan-induced edema.

The anti-inflammatory activities of the tested compounds further confirmed based on evaluation of the abilities of these compounds to inhibit plasma PGE2.

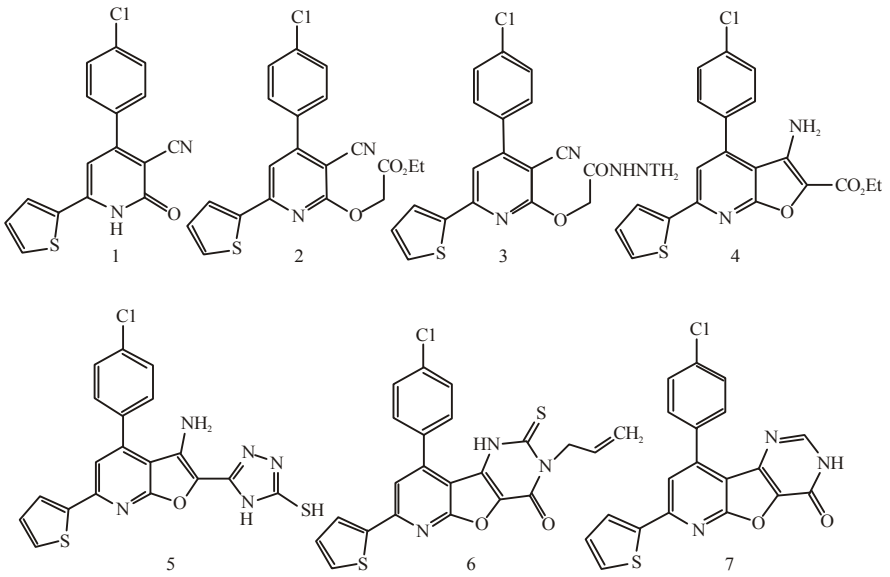

Fig. 1: Chemical structure of compounds 1-7

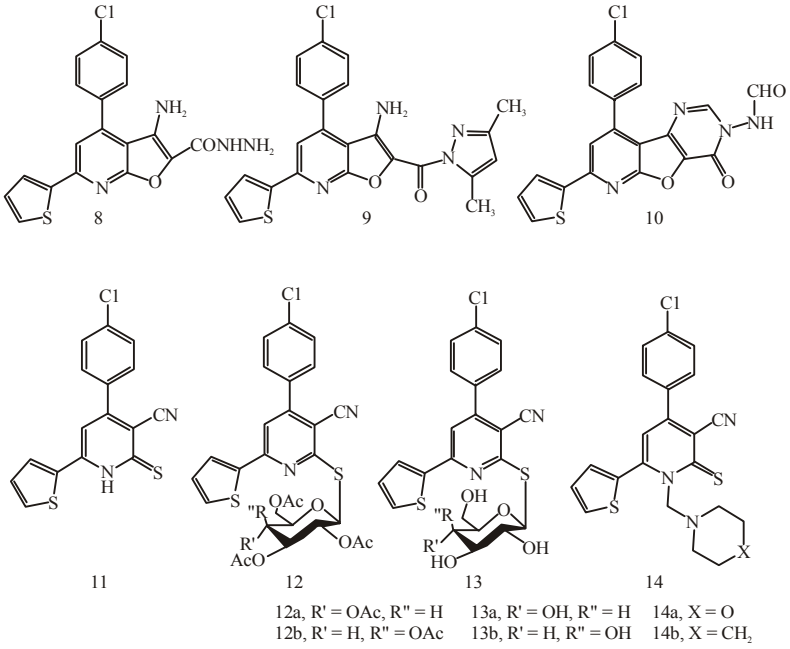

Fig. 2: Chemical structure of compounds 8-14

The anti-inflammatory potency of the tested compounds were determined at two dose levels 25 and 50 mg kg^{-1} rat body weight using the protection against Carrageenan® induced edema animal model according to Winter *et al*. (1962).

The values for the percentage protection against carrageenan-induced edema for the compounds at the two dose levels 25 and 50 mg kg^{-1} rat body weight were as follows: 1 (55.22/76.14), 2 (88.86/95.81), 3 (48.18/64.11), 4 (89.84/98.95), 5 (90.66/96.95), 6 (94.15/97.10), 7 (55.75/75.13), 8 (90.18/97.12), 9 (93.60/98.56), 10 (55.22/66.15), 11 (54.22/73.14), 12a (91.85/98.82), 12b (53.16/65.18), 13a (88.86/97.97), 13b (93.18/96.75), 14a (89.26/98.31), 14b (56.16/68.18), Valdicoxib® (80.95/92.98).

The inhibition of plasma PGE of the tested compounds were determined at two dose levels 25 and 50 mg kg^{-1} rat body weight (Herrmann *et al*., 1990).

The values for the percentage inhibition of plasma PGE for the compounds at the two dose levels 25 and 50 mg kg^{-1} rat body weight were as follows: 1 (48.18/64.13),

Table 1: Acute toxicity (LD_{50}) of starting material (1) and the synthesized compounds (2-14)

Comp. No.	LD_{50} (mg kg^{-1})
1	3.615±0.011
2	2.722±0.012
3	3.705±0.010
4	2.420±0.012
5	2.662±0.010
6	2.110±0.010
7	1.501±0.011
8	2.480±0.010
9	1.660±0.011
10	3.100±0.010
11	2.812±0.014
12a	1.790±0.011
12b	3.070±0.012
13a	3.612±0.014
13b	4.176±0.013
14a	1.810±0.013
14b	2.105±0.014
Valdicoxib®	1.635±0.014

Table 2: Anti-inflammatory potencies of starting material (1) and the synthesized compounds (2-14) (protection against carrageenan-induced edema)

Comp. No.	Dose (mg kg^{-1})	Protection against carrageenan-induced edema (%)[a]
1	25	55.22±0.068
	50	76.14±0.052
2	25	88.86±0.066
	50	95.81±0.071
3	25	48.18±0.080
	50	64.11±0.058
4	25	89.84±0.076
	50	98.95±0.066
5	25	90.66±0.084
	50	96.95±0.082
6	25	94.15±0.081
	50	97.10±0.076
7	25	55.75±0.067
	50	75.13±0.072
8	25	90.18±0.081
	50	97.12±0.077
9	25	93.60±0.088
	50	98.56±0.085
10	25	55.22±0.055
	50	66.15±0.068
11	25	54.22±0.067
	50	73.14±0.050
12a	25	91.85±0.074
	50	98.82±0.075
12b	25	53.16±0.078
	50	65.18±0.065
13a	25	88.86±0.076
	50	97.97±0.068
13b	25	93.18±0.068
	50	96.75±0.076
14a	25	89.26±0.060
	50	98.31±0.074
14b	25	56.16±0.075
	50	68.18±0.060
Valdicoxib®	25	80.95±0.990
	50	92.98±0.080

[a]Doses tested were 25, 50 mg and carry out three determinations for each dose

2 (79.18/83.15), 3 (44.17/55.15), 4 (45.36/62.42), 5 (93.56/99.84), 6 (78.62/82.66), 7 (52.99/70.88), 8 (44.31/60.38), 9 (96.75/91.98), 10 (45.18/62.13), 11 (83.76/94.98), 12a (81.16/92.62), 12b (45.31/60.38), 13a (93.84/99.56), 13b (78.41/94.56), 14a (84.76/95.98), 14b (42.16/56.17), Valdicoxib® (77.00/91.00).

Table 3: Anti-inflammatory potencies of starting material (1) and the synthesized compounds (2-14) (Inhibition of Plasma PGE2)

Comp. No.	Dose (mg kg^{-1})	Inhibition of plasma PGE2 (%)*
1	25	48.18±0.085
	50	64.13±0.076
2	25	79.18±0.075
	50	83.15±0.077
3	25	44.17±0.077
	50	55.15±0.091
4	25	45.36±0.090
	50	62.42±0.110
5	25	93.56±0.085
	50	99.84±0.092
6	25	78.62±0.110
	50	82.66±0.088
7	25	52.99±0.101
	50	70.88±0.096
8	25	44.31±0.090
	50	60.38±0.110
9	25	96.75±0.105
	50	91.98±0.088
10	25	45.18±0.096
	50	62.13±0.078
11	25	83.76±0.109
	50	94.98±0.110
12a	25	81.16±0.088
	50	92.62±0.100
12b	25	45.31±0.088
	50	60.38±0.112
13a	25	93.84±0.085
	50	99.56±0.092
13b	25	78.41±0.088
	50	94.56±0.086
14a	25	84.76±0.110
	50	95.98±0.112
14b	25	42.16±0.075
	50	56.17±0.090
Valdicoxib®	25	77.00±0.084
	50	91.00±0.087

*Doses tested were 25, 50 mg and carry out three determinations for each dose

CONCLUSION

All the tested compounds showed excellent inhibition on plasma PGE2 profiles and the descending order of anti-inflammatory potency was as follow 9, 13a, 5, 14a, 11, 12a, 2, 6, 13b, Valdicoxib, 7, 1, 4, 12b, 10, 3, 8 and 14b.

Structure Activity Relationship (SAR): Carefully studying the relation between the structural features of the tested compounds and their activities revealed on the following structural activities relationship assumptions:

- The pyrazoline moiety sharply increases the anti-inflammatory activities as in compound 9 but appending triazole moiety provides less anti-inflammatory activities as in compound 5
- Appending alicyclic methane to the N-atom of pyridine nucleus provided moderate anti-inflammatory activities as in compounds 14

- Fusing extra polyheterocyclic ring system nucleus provided moderate anti-inflammatory activities as in compounds 6, 7 and 10
- Generally the nucleoside increasing the anti-inflammatory activities except the case of compound 12b and the deacetylated nucleoside (13a and b) were more active than the acylated ones (12a and b) due to their high hydrophilic characters and their abilities to undergoes hydrogen bond formations
- Open chain as in compounds 2, 3 and 8 decreases anti-inflammatory activities

ACKNOWLEDGMENT

The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through the research group project No. RGP-0172.

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