Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 43 (2008) 2116–2121
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Facile synthesis of dithiatetraaza-macrocycles of potential anti-inflammatory activity

Adel S. Girgis*

Pesticide Chemistry Department, National Research Centre, El-Behoos Street, Dokki, 12622 Cairo, Egypt

Received 28 June 2007; received in revised form 5 November 2007; accepted 6 December 2007
Available online 23 December 2007

Abstract

A facile synthetic approach towards dithiatetraaza-macrocycles **4a** and **b** was achieved through reaction of 2,2′-[alkanediylbis(thio)]bisbenzenamines **1a** and **b** with 1,4-phenylenediisocyanate. However, reaction of **1a** and **b** with a variety of aryl-, alkylisocyanates or isothiocyanates **2a–f** afforded the corresponding bisurea and their thio-analogues **3a–l**. Anti-inflammatory activity of the prepared compounds (in a dose of 50 mg/kg body weight) using in vivo acute carrageenan-induced paw oedema in rats is studied. Compounds **3e** and **4b** reveal the best anti-inflammatory properties among all the tested compounds with potency (% oedema inhibition of the tested compounds regarding % oedema inhibition of indomethacin "which was used as a reference standard in a dose of 10 mg/kg body weight") 0.90 and 0.85, respectively.

Keywords: Bisbenzenamines; Bisureas; Bisthioureas; Macrocycles; Anti-inflammatory

1. Introduction

N,*N*′-Disubstituted ureas represent an important class of organic compounds attracting great attention of many researchers due to their wide applications in various fields especially as biological and pharmacological active agents. Many *N*,*N*′-disubstituted urea derivatives were reported to possess anticancer properties against human skin melanoma (M21), colon carcinoma (HT-29), breast carcinoma (MCF-7), breast hormone-independent adenocarcinoma (MDA-MB-231) and bladder cancer (T-24) cell lines [1–5]. *N*-Aryl-*N*′-benzylureas were reported to be transient receptor potential vanilloid 1 (TRPV1) antagonists with good pharmacokinetic properties and great potency in animal model of inflammatory pain [6]. On the other hand, *N*,*N*′-disubstituted ureas as well as their thio-analogues were reported to be nitric oxide production inhibitors in lipopolysaccharide-activited macrophages [7], antibacterial [8,9], insecticidal and acaricidal [10–12] active agents. Many trisubstituted urea analogues were achieved to be MCH-R1 antagonists (G-protein-coupled receptor bind to melanin concentrating hormone) for treatment of obesity [13]. Other trisubstituted analogues were reported as glucogen receptor antagonists which were efficacious in correcting hyperglycemia conditions [14].

In the present work, it is intended to investigate synthesis of bisurea containing-compounds as well as their thio-analogues (i.e. compounds possessing two biologically active centers) utilizing easily accessible starting chemicals and facile synthetic approaches. The cyclic form structures will be also considered in an attempt to construct dithiatetraaza-macrocyclic derivatives. The anti-inflammatory properties of the prepared compounds will be screened not only to develop a promising pharmacological active agent but also to determine the structure–activity relationships of the adopted compounds. The recent research reports concerning biological as well as pharmacological properties of macrocyclic analogues also prompted the present study. Many macrocyclic derivatives have been achieved to be inhibitors of hepatitis C virus (HCV) NS3 [15,16], FIV and HIV proteases [17], besides potent activity against human cytomegalovirus (HCMV) [18]. Other analogues were reported to be inhibitors of β-secretase

* Tel.: +202 2235 2405; fax: +202 3337 0931.
E-mail address: girgisas10@yahoo.com

0223-5234/$ - see front matter © 2007 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2007.12.010

(BACE-1, β-site amyloid precursor protein cleaving enzyme) which is widely recognized as one of the most promising therapeutic approaches for the treatment and prevention of Alzheimer's disease [19]. Moreover, macrocyclic amides were exhibited to be anti-inflammatory [20], antibacterial [21] and inhibitors of malarial aspartic proteases plasmepsin I, II and IV with considerable selectivity over the human aspartic protease cathepsin D [22].

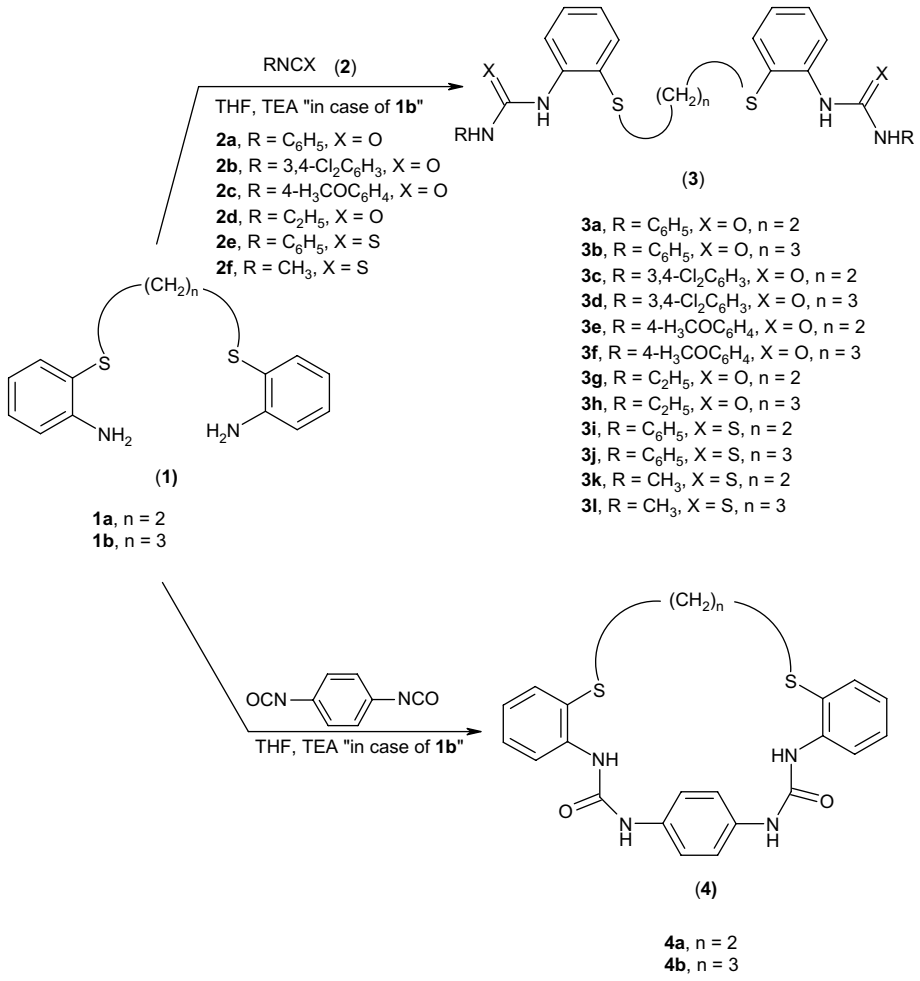
Non-steroidal anti-inflammatory drugs (NSAIDs) have been recognized as important class of therapeutic agents for the alleviation of pain and inflammation associated with a number of pathological conditions especially for treatment of rheumatoid disorders, osteoarthritis and also in many other inflammatory diseases and injuries [23,24]. However, long term use of NSAIDs has been associated with several side effects such as gastrointestinal mucosal damage, bleeding, intolerance and renal toxicity [25–28]. Consequently, extensive research has been directed towards improving their pharmacological profiles.

The most widely accepted mode of action of NSAIDs is the inhibition of the cyclooxygenase enzyme involved in arachidonic acid conversion to prostaglandin. With the identification of another isoform of constitutive COX-1, namely COX-2 (inducible) and inhibition of COX-2 proving beneficial in clinical situations had led to the introduction of many potent anti-inflammatory agents called COX-2 inhibitors [29–32].

2. Results and discussion

2.1. Chemistry

Reaction of 2,2′-[1,2-ethanediylbis(thio)]bisbenzenamine **1a** and 2,2′-[1,3-propanediylbis(thio)]bisbenzenamine dihydrochloride **1b** with a variety of arylisocyanates (namely, phenyl-, 3,4-dichlorophenyl-, 4-methoxyphenylisocyanate) **2a–c** as 1:2 molar ratio in dry tetrahydrofuran "in presence of triethylamine in case of **1b**, where the dihydrochloride salt was used" at room temperature, afforded the corresponding bisurea derivatives **3a–f** in good yields. The structure of **3a–f** was inferred through spectroscopic (IR, ^{1}H NMR) and elemental analyses data. The IR spectra of **3a–f** reveal the presence of imino and carbonyl stretching vibration bands at $\nu = 3336-3284$, $1662-1638\ cm^{-1}$, respectively. ^{1}H NMR spectra exhibit the alkylsulfanyl function (singlet at $\delta = 2.95-2.98$ in case of **3a**, **c** and **e** assignable to 2 SCH_2



Scheme 1.

residue, quintet and triplet signals at $\delta = 1.72-1.74$, 2.93–2.94 in case of **3b**, **d** and **f** corresponding to the SCH_2CH_2 and 2 SCH_2, respectively), besides two sets of singlet signals at $\delta = 8.17-8.37$, 9.27–9.74 each integrated to 2 NH functions (Scheme 1, Tables 1 and 2).

Similarly, reaction of **1a** and **b** with ethylisocyanate **2d** ''as a representative example of alkylisocyanate'' afforded the corresponding bisurea analogues **3g** and **h**. Moreover, bisthiourea derivatives **3i–l** were obtained through reaction of **1a** and **b** with phenyl- and methylisothiocyanate (as representative examples of aryl- and alkylisothiocyanate).

On the other hand, reaction of **1a** and **b** with 1,4-phenylenediisocyanate as 1:1 molar ratio under similar reaction conditions gave dithiatetraaza-macrocycles **4a** and **b** in 46–49% yield. IR spectra of **4a** and **b** reveal the imino and carbonyl functions at $\nu = 3295-3293$, 1642–1637 cm^{-1}, respectively. In addition, ^1H NMR spectra add good support for the deduced structure exhibiting the alkylsulfanyl residues (singlet at $\delta = 2.95$ in case of **4a**, quintet and triplet signals at $\delta = 1.70$, 2.91 in case of **4b**, respectively) besides the imino groups ($\delta = 8.23-8.24$, 9.36–9.38) and other expected aromatic protons ($\delta = 6.91-8.10$). Mass spectra (CI) of **4a** and **b** add sharp evidence for the established structure which show the parent ion peaks with considerable relative intensities (3–7%).

2.2. Anti-inflammatory activity

Anti-inflammatory activity of the synthesized compounds **3a–j**, **4a** and **b** (in a dose of 50 mg/kg body weight) was determined in vivo by the acute carrageenan-induced paw oedema standard method in rats [33–35]. The anti-inflammatory properties were compared with that of indomethacin (in a dose of 10 mg/kg body weight) which was used as a reference standard. From the obtained results (Table 3), it has been noticed that most of the tested compounds exhibit considerable anti-inflammatory properties, especially compounds **3e** and **4b** which reveal remarkable activities with potency (% oedema inhibition of the tested compounds regarding % oedema inhibition of indomethacin) 0.90 and 0.85, respectively.

Structure–activity relationships based on the obtained results indicated that, substitution of the phenyl group in diarylurea analogues **3a–f** with an electron-donating moiety (e.g. methoxy function) **3e** and **f** is associated with enhancement in pharmacological properties than the case of unsubstituted phenyl derivatives **3a** and **b**. However, attachment of the phenyl group with a deactivating function (e.g. chlorine atom) **3c** and **d** led to decreasing pharmacological activity. This makes the sequence of ruling anti-inflammatory properties regarding

Table 1
Physical data of the prepared compounds

Compd.	Mp (°C)	Yield (%), Reaction time (h)	Mol. formula (Mol. wt.)	Analysis (%) Calcd/Found		
				C	H	N
3a	238–240[a]	86, 10	$C_{28}H_{26}N_4O_2S_2$	65.34	5.09	10.89
			(514.64)	65.53	5.17	11.05
3b	211–213[a]	80, 12	$C_{29}H_{28}N_4O_2S_2$	65.88	5.34	10.60
			(528.66)	66.10	5.48	10.73
3c	248–250[b]	92, 2	$C_{28}H_{22}Cl_4N_4O_2S_2$	51.54	3.40	8.59
			(652.44)	51.41	3.29	8.80
3d	228–230[a]	75, 10	$C_{29}H_{24}Cl_4N_4O_2S_2$	52.26	3.63	8.41
			(666.46)	52.43	3.82	8.59
3e	236–238[b]	80, 5	$C_{30}H_{30}N_4O_4S_2$	62.69	5.26	9.75
			(574.69)	62.49	5.15	9.66
3f	202–204[b]	78, 10	$C_{31}H_{32}N_4O_4S_2$	63.24	5.48	9.52
			(588.72)	63.15	5.40	9.69
3g	248–250 (Dioxane)	72, 72	$C_{20}H_{26}N_4O_2S_2$	57.39	6.26	13.39
			(418.56)	57.25	6.10	13.19
3h	192–194[c]	65, 72	$C_{21}H_{28}N_4O_2S_2$	58.30	6.52	12.95
			(432.58)	58.09	6.38	13.14
3i	176–177 (Dioxane)	77, 72	$C_{28}H_{26}N_4S_4$	61.50	4.79	10.25
			(546.78)	61.64	4.90	10.19
3j	165–167[c]	86, 72	$C_{29}H_{28}N_4S_4$	62.11	5.03	9.99
			(560.80)	62.27	5.11	9.75
3k	148–150 (*n*-Butanol)	76, 95	$C_{18}H_{22}N_4S_4$	51.15	5.25	13.26
			(422.65)	51.21	5.29	13.37
3l	170–172[c]	69, 95	$C_{19}H_{24}N_4S_4$	52.26	5.54	12.83
			(436.67)	52.14	5.44	12.62
4a	>300[d]	46, 95	$C_{22}H_{20}N_4O_2S_2$	60.53	4.62	12.84
			(436.53)	60.76	4.78	13.02
4b	>300[d]	49, 95	$C_{23}H_{22}N_4O_2S_2$	61.31	4.92	12.44
			(450.56)	61.44	5.03	12.24

[a] Solvent: *N*,*N*-Dimethylformamide–water mixture as 5:1 v/v.
[b] Solvent: *N*,*N*-Dimethylformamide–water mixture as 9:1 v/v.
[c] Solvent: *N*,*N*-Dimethylformamide–water mixture as 1:1 v/v.
[d] Solvent: Dimethyl sulfoxide–water mixture as 3:1 v/v.

substitution of phenyl group in diarylurea derivatives as, methoxyphenyl > phenyl > dichlorophenyl as exhibited in compounds **3e** > **3a** > **3c** (potency, 0.90, 0.57, 0.12, respectively) and compounds **3f** > **3b** > **3d** (potency, 0.61, 0.51, 0.49, respectively).

Moreover, substitution of the urea derivatives with an alkyl function (e.g. ethyl group) may afford a better pharmacological active agent comparable with the case of using phenyl moiety as observed in pairs **3h** and **b** (potency, 0.73, 0.51, respectively). On the other hand, diarylthioureas seem to be more effective anti-inflammatory active agents than the corresponding urea analogues as observed in pairs **3i**, **a** (potency, 0.75, 0.57, respectively) and **3j**, **b** (potency, 0.66, 0.51, respectively).

Table 4, demonstrates the anti-inflammatory properties of compounds **3e** and **4b** ''the most effective prepared analogues'' at successive time intervals (1, 2, 3 and 4 h). From the observed data, it has been noticed that compound **4b** reveals its anti-inflammatory behaviour more or less stable among all the detected time intervals, in contrast to compound **3e**, where its pharmacological effect increases with time.

Toxicological studies of the most promising prepared anti-inflammatory active agents (**3e** and **4b**) were performed using LD_{50} standard method in mice [36] in 500, 750 and 1000 mg/kg (body weight) ''i.e. 10–20 folds of the used anti-inflammatory effective dose''. However, no toxic symptoms or mortality rates were observed after 24 h postadministrations explaining the safe behaviour of the used doses.

3. Experimental

Melting points are uncorrected and recorded on an Electrothermal 9100 digital melting point apparatus. IR spectra (KBr) were recorded on a Nexus 670 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian MERCURY 300 MHz spectrometer in DMSO-d_6. Mass spectra (CI) were recorded on a Finnigan SSQ 7000 spectrometer. The starting compounds **1a** and **b** [37,38] were prepared according to the previously reported procedures.

3.1. Reaction of *1a* and *b* with *2a–f*

A mixture of **1a** and **b** (5 mmol) and the corresponding **2a–f** (10 mmol) in dry tetrahydrofuran (25 ml) ''containing triethylamine (10 mmol) in case of **1b** where the dihydrochloride salt was used'', was stirred at room temperature (20–25 °C) for the appropriate time. The separated solid was collected, washed with water and crystallized from a suitable solvent affording **3a–l** as colourless crystals. In case of **3d** and **k**, the reaction mixture was evaporated till dryness under reduced pressure and the remaining residue was triturated with methanol and diethyl ether giving **3d** and **k**, respectively.

3.2. Synthesis of dithiatetraaza-macrocycles *4a* and *b*

A solution of 1,4-phenylenediisocyanate (5 mmol) in dry tetrahydrofuran (40 ml) was added dropwise to a solution of

Table 2
Spectroscopic data of the prepared compounds

Compd.	IR (ν_{max}/cm^{-1})	^{1}H NMR (DMSO-d_6), δ
3a	3300 (NH), 1651 (C=O), 1599, 1579 (C=C)	2.96 (s, 4H, 2 SCH_2), 6.93–8.08 (m, 18H, arom. H), 8.28 (s, 2H, 2 NH), 9.43 (s, 2H, 2 NH)
3b	3303 (NH), 1638 (C=O), 1597, 1554 (C=C)	1.74 (quintet, 2H, SCH_2CH_2, J = 7.5 Hz), 2.94 (t, 4H, 2 SCH_2, J = 7.2 Hz), 6.92–8.08 (m, 18H, arom. H), 8.26 (s, 2H, 2 NH), 9.44 (s, 2H, 2 NH)
3c	3336, 3284 (NH), 1662 (C=O), 1577, 1537 (C=C)	2.98 (s, 4H, 2 SCH_2), 6.98–8.10 (m, 14H, arom. H), 8.37 (s, 2H, 2 NH), 9.74 (s, 2H, 2 NH)
3d	3291 (NH), 1647 (C=O), 1574, 1537 (C=C)	1.72 (quintet, 2H, SCH_2CH_2, J = 7.2 Hz), 2.93 (t, 4H, 2 SCH_2, J = 7.2 Hz), 6.95–8.02 (m, 14H, arom. H), 8.30 (s, 2H, 2 NH), 9.72 (s, 2H, 2 NH)
3e	3294 (NH), 1643 (C=O), 1581, 1552 (C=C)	2.95 (s, 4H, 2 SCH_2), 3.73 (s, 6H, 2 OCH_3), 6.86–8.11 (m, 16H, arom. H), 8.21 (s, 2H, 2 NH), 9.27 (s, 2H, 2 NH)
3f	3311 (NH), 1652 (C=O), 1578, 1549 (C=C)	1.72 (quintet, 2H, SCH_2CH_2, J = 7.5 Hz), 2.93 (t, 4H, 2 SCH_2, J = 7.5 Hz), 3.72 (s, 6H, 2 OCH_3), 6.84–8.08 (m, 16H, arom. H), 8.17 (s, 2H, 2 NH), 9.27 (s, 2H, 2 NH)
3g	3325 (NH), 1645 (C=O), 1561, 1526 (C=C)	1.06 (t, 6H, 2 CH_3CH_2, J = 6.9 Hz), 2.87 (s, 4H, 2 SCH_2), 3.09 (q, 2H, NCH_2CH_3, J = 6.9 Hz), 3.11 (q, 2H, NCH_2CH_3, J = 6.9 Hz), 6.87–8.06 (m, 12H, 8 arom. H + 4 NH)
3h	3332, 3297 (NH), 1641 (C=O), 1578, 1560 (C=C)	1.05 (t, 6H, 2 CH_3CH_2, J = 7.2 Hz), 1.66 (quintet, 2H, SCH_2CH_2, J = 7.2 Hz), 2.86 (t, 4H, 2 SCH_2, J = 7.2 Hz), 3.09 (q, 2H, NCH_2CH_3, J = 7.2 Hz), 3.10 (q, 2H, NCH_2CH_3, J = 7.2 Hz), 6.86–8.00 (m, 12H, 8 arom. H + 4 NH)
3i	3238, 3160 (NH), 1533, 1498, 1473 (C=C, C=S)	3.14 (s, 4H, 2 SCH_2), 7.21–7.62 (m, 18H, arom. H), 9.32 (s, 2H, 2 NH), 10.00 (s, 2H, 2 NH)
3j	3256, 3167 (NH), 1537, 1498, 1474 (C=C, C=S)	1.79 (quintet, 2H, SCH_2CH_2, J = 6.9 Hz), 2.99 (t, 4H, 2 SCH_2, J = 7.2 Hz), 7.11–7.54 (m, 18H, arom. H), 9.14 (s, 2H, 2 NH), 9.87 (s, 2H, 2 NH)
3k	3240, 3163 (NH), 1541, 1510, 1468 (C=C, C=S)	2.98 (s, 6H, 2 NCH_3), 3.11 (s, 4H, 2 SCH_2), 7.23–7.54 (m, 8H, arom. H), 7.74 (br s, 2H, 2 NH), 9.01 (s, 2H, 2 NH)
3l	3318, 3242, 3168 (NH), 1541, 1511, 1466 (C=C, C=S)	1.80 (quintet, 2H, SCH_2CH_2, J = 7.2 Hz), 2.91 (s, 6H, 2 NCH_3), 2.98 (t, 4H, 2 SCH_2, J = 7.2 Hz), 7.18–7.43 (m, 8H, arom. H), 7.65 (br s, 2H, 2 NH), 8.89 (s, 2H, 2 NH)
4a[a]	3295 (NH), 1642 (C=O), 1557, 1506 (C=C)	2.95 (s, 4H, 2 SCH_2), 6.91–8.10 (m, 12H, arom. H), 8.24 (s, 2H, 2 NH), 9.36 (s, 2H, 2 NH)
4b[b]	3293 (NH), 1637 (C=O), 1560, 1508 (C=C)	1.70 (quintet, 2H, SCH_2CH_2, J = 6.9 Hz), 2.91 (t, 4H, 2 SCH_2, J = 6.9 Hz), 6.91–8.09 (m, 12H, arom. H), 8.23 (s, 2H, 2 NH), 9.38 (br s, 2H, 2 NH)

[a] MS (CI): *m/z* (%) 436 (3).
[b] MS (CI): *m/z* (%) 450 (7).

Table 3
Anti-inflammatory activity of the tested compounds using acute carrageenan-induced paw oedema in rats

Compound	Mean swelling volume (ml)	% Inhibition of oedema	Potency[c]
Control	0.665 ± 0.038[b]	00.0	–
Indomethacin	0.282 ± 0.023[a]	57.6	1.00
3a	0.447 ± 0.035[a]	32.8	0.57
3b	0.468 ± 0.012[a,b]	29.6	0.51
3c	0.618 ± 0.053[a,b]	7.1	0.12
3d	0.477 ± 0.043[a,b]	28.3	0.49
3e	0.320 ± 0.017[a]	51.9	0.90
3f	0.432 ± 0.044[a]	35.0	0.61
3g	0.445 ± 0.024[a]	33.1	0.57
3h	0.385 ± 0.020[a,b]	42.1	0.73
3i	0.377 ± 0.036[a]	43.3	0.75
3j	0.412 ± 0.018[a]	38.0	0.66
4a	0.433 ± 0.032[a,b]	34.9	0.61
4b	0.340 ± 0.033[a]	48.9	0.85

[a] Statistically significant from the control at $p < 0.05$.
[b] Statistically significant from indomethacin at $p < 0.05$.
[c] Potency was expressed as % oedema inhibition of the tested compounds regarding % oedema inhibition of indomethacin ''reference standard''.

1a and **b** (5 mmol) in dry tetrahydrofuran (20 ml) ''containing triethylamine (10 mmol) in case of **1b**, where the dihydrochloride salt was used'', within a period of half an hour, while stirring at room temperature (20–25 °C). After complete addition, the reaction mixture was continued stirring at room temperature for the appropriate time. Then, the separated solid was collected, washed with water and crystallized from a suitable solvent giving **4a** and **b** as colourless crystals.

3.3. Anti-inflammatory activity screening

The anti-inflammatory activity screening for the prepared compounds was determined in vivo by the acute carrageenan-induced paw oedema standard method in rats [33–35]. Wister albino rats of either sex (pregnant female animals were excluded) weighing 160–190 g were divided into 14 groups of 6 animals each ''the animals had free access to standard commercial diet and water adlibitum and were kept in rooms maintained at 22 ± 1 °C with 12 h light dark cycle, taking into account international principles and local regulations concerning the care and use of laboratory animals''. Administration of indomethacin (reference standard in a dose of 10 mg/kg body weight) and the tested compounds (**3a–j**, **4a** and **b**) dissolved in DMSO, in a dose of 50 mg/kg (body weight) was given intraperitoneally 1 h before induction of inflammation. The control group was given DMSO only. Carrageenan paw oedema was induced by subcutaneous injection of 1% solution of carrageenan in saline (0.1 ml/rat) into the right hind paw of rats. Paw volumes were measured volumetrically after 4 h with plethysmometer 7150 (UGO BASILE, Italy) and compared with the initial hind paw volume of each rat for determining the oedema volume. Data were collected, checked, revised and analyzed. Quantitative variables from normal distribution were expressed as means ± SE ''standard error''. The significant difference between groups was tested by using one-way ANOVA followed by LSD test at $p < 0.05$.

The anti-inflammatory activity was expressed as percentage inhibition of oedema volume in treated animals in comparison with the control group (Tables 3 and 4).

$$\%\ \text{Inhibition of oedema} = \frac{V_c - V_t}{V_c} \times 100$$

where, V_c and V_t are the volumes of oedema for the control and drug-treated animal groups, respectively, while potency of the tested compounds was calculated regarding indomethacin ''reference standard'' treated group according to the following equation:

$$\text{Potency} = \frac{\%\ \text{Oedema inhibition of tested compound treated group}}{\%\ \text{Oedema inhibition of indomethacin treated group}}$$

3.4. LD_{50} determination

The toxicological studies of the most promising prepared anti-inflammatory active agents (**3e** and **4b**) were determined using standard known LD_{50} method in mice [36]. Albino mice weighing 20–25 g were divided in 9 groups of 6 mice each. Administrations of the tested compounds (**3e** and **4b**) dissolved in DMSO in 500, 750 and 1000 mg/kg (body weight) were given intraperitoneally. The control groups were given DMSO only. The toxic symptoms, mortality rates

Table 4
Anti-inflammatory activity of compounds **3e** and **4b** at successive time intervals using acute carrageenan-induced paw oedema in rats

Compd.	Mean swelling volume (ml) (% inhibition of oedema)			
	1 h	2 h	3 h	4 h
Control	0.293 ± 0.013[b] (00.0)	0.425 ± 0.021[b] (00.0)	0.515 ± 0.027[b] (00.0)	0.665 ± 0.038[b] (00.0)
Indomethacin	0.145 ± 0.009[a] (50.5)	0.220 ± 0.021[a] (48.2)	0.257 ± 0.028[a] (50.1)	0.282 ± 0.023[a] (57.6)
3e	0.190 ± 0.009[a,b] (35.2)	0.262 ± 0.018[a] (38.4)	0.313 ± 0.033[a] (39.2)	0.320 ± 0.017[a] (51.9)
4b	0.160 ± 0.010[a] (45.4)	0.238 ± 0.024[a] (44.0)	0.275 ± 0.029[a] (46.6)	0.340 ± 0.033[a] (48.9)

[a] Statistically significant from the control at $p < 0.05$.
[b] Statistically significant from indomethacin at $p < 0.05$.

and postmortem findings in each group were recorded 24 h postadministration.

LD_{50} of the tested compounds were calculated according to the following formula:

$$LD_{50} = D_m - \frac{\sum (zxd)}{n}$$

Where, D_m = the largest dose which kill all animals, z = mean of dead animals between two successive groups, d = the constant factor between two successive doses, n = number of animals in each group, $\sum$ = the sum of $(z \times d)$.

Acknowledgment

The author is grateful to the (i) U.S.–Egypt Science and Technology Joint Fund under Project No. MAN10-007-002, (ii) Pharmacology Department, NRC, Cairo, Egypt, for allowing performance of pharmacological activity screening.

References

[1] J.S. Fortin, J. Lacroix, M. Desjardins, A. Patenaude, É. Petitclerc, R. C.-Gaudreault, Bioorg. Med. Chem. 15 (2007) 4456–4469.
[2] S. Fortin, E. Moreau, J. Lacroix, J.-C. Teulade, A. Patenaude, R. C.-Gaudreault, Bioorg. Med. Chem. Lett. 17 (2007) 2000–2004.
[3] S. Fortin, E. Moreau, A. Patenaude, M. Desjardins, J. Lacroix, J.L.C. Rousseau, R. C.-Gaudreault, Bioorg. Med. Chem. 15 (2007) 1430–1438.
[4] E. Moreau, S. Fortin, M. Desjardins, J.L.C. Rousseau, É. Petitclerc, R. C.-Gaudreault, Bioorg. Med. Chem. 13 (2005) 6703–6712.
[5] C. Sanmartin, M. Echeverria, B. Mendivil, L. Cordeu, E. Cubedo, J. Garcia-Foncillas, M. Font, J.A. Palop, Bioorg. Med. Chem. 13 (2005) 2031–2044.
[6] A. Gomtsyan, E.K. Bayburt, R. Keddy, S.C. Turner, T.K. Jinkerson, S. Didomenico, R.J. Perner, J.R. Koenig, I. Drizin, H.A. McDonald, C.S. Surowy, P. Honore, J. Mikusa, K.C. Marsh, J.M. Wetter, C.R. Faltynek, C.-H. Lee, Bioorg. Med. Chem. Lett. 17 (2007) 3894–3899.
[7] Y.J. Kim, J.-H. Ryu, Y.J. Cheon, H.J. Lim, R. Jeon, Bioorg. Med. Chem. Lett. 17 (2007) 3317–3321.
[8] S. Nag, R. Pathak, M. Kumar, P.K. Shukla, S. Batra, Bioorg. Med. Chem. Lett. 16 (2006) 3824–3828.
[9] P.P. Seth, R. Ranken, D.E. Robinson, S.A. Osgood, L.M. Risen, E.L. Rodgers, M.T. Migawa, E.A. Jefferson, E.E. Swayze, Bioorg. Med. Chem. Lett. 14 (2004) 5569–5572.
[10] L. Chen, X.-M. Ou, C.-H. Mao, J. Shang, R.-Q. Huang, F.-C. Bi, Q.-M. Wang, Bioorg. Med. Chem. 15 (2007) 3678–3683.
[11] M.S. Brouwer, A.C. Grosscurt, U.S. Patent 4609676, 1986.
[12] B. Daniele, M. Pietro, M. Giovanni, R. Franco, C. Vincenzo, EP 0211665, 1986.
[13] S. Galiano, J. Ceras, N. Cirauqui, S. Pérez, L. Juanenea, G. Rivera, I. Aldana, A. Monge, Bioorg. Med. Chem. 15 (2007) 3896–3911.
[14] R. Liang, L. Abrardo, E.J. Brady, M.R. Candelore, V. Ding, R. Saperstein, L.M. Tota, M. Wright, S. Mock, C. Tamvakopolous, S. Tong, S. Zheng, B.B. Zhang, J.R. Tata, E.R. Parmee, Bioorg. Med. Chem. Lett. 17 (2007) 587–592.
[15] A. Arasappan, F.G. Njoroge, K.X. Chen, S. Venkatraman, T.N. Parekh, H. Gu, J. Pichardo, N. Butkiewicz, A. Prongay, V. Madison, V. Girijavallabhan, Bioorg. Med. Chem. Lett. 16 (2006) 3960–3965.
[16] K.X. Chen, F.G. Njoroge, A. Prongay, J. Pichardo, V. Madison, V. Girijavallabhan, Bioorg. Med. Chem. Lett. 15 (2005) 4475–4478.
[17] C.C. Mak, A. Brik, D.L. Lerner, J.H. Elder, G.M. Morris, A.J. Olson, C.-H. Wong, Bioorg. Med. Chem. 11 (2003) 2025–2040.
[18] G. Falardeau, H. Lachance, A. St-Pierre, C.G. Yannopoulos, M. Drouin, J. Bédard, L. Chan, Bioorg. Med. Chem. Lett. 15 (2005) 1693–1695.
[19] S.R. Lindsley, K.P. Moore, H.A. Rajapakse, H.G. Selnick, M.B. Young, H. Zhu, S. Munshi, L. Kuo, G.B. McGaughey, D. Colussi, M.-C. Crouthamel, M.-T. Lai, B. Pietrak, E.A. Price, S. Sankaranarayanan, A.J. Simon, G.R. Seabrook, D.J. Hazuda, N.T. Pudvah, J.H. Hochman, S.L. Graham, J.P. Vacca, P.G. Nantermet, Bioorg. Med. Chem. Lett. 17 (2007) 4057–4061.
[20] P. Rajakumar, A.M. Abdul Rasheed, A.I. Rabia, D. Chamundeeswari, Bioorg. Med. Chem. Lett. 16 (2006) 6019–6023.
[21] E.A. Jefferson, E.E. Swayze, S.A. Osgood, A. Miyaji, L.M. Risen, L.B. Blyn, Bioorg. Med. Chem. Lett. 13 (2003) 1635–1638.
[22] K. Ersmark, M. Nervall, H. Gutiérrez-de-Terán, E. Hamelink, L.K. Janka, J.C. Clemente, B.M. Dunn, A. Gogoll, B. Samuelsson, J. Aqvist, A. Hallberg, Bioorg. Med. Chem. 14 (2006) 2197–2208.
[23] Y. Harrak, G. Rosell, G. Daidone, S. Plescia, D. Schillaci, M.D. Pujol, Bioorg. Med. Chem. 15 (2007) 4876–4890.
[24] A. Palomer, J.J. Pérez, S. Naveo, O. Llorens, J. Pascual, M.L. Garcia, D. Mauleón, J. Med. Chem. 43 (2000) 2280–2286.
[25] S.J. Sontag, Drugs 32 (1986) 445–447.
[26] M.C. Allison, A.G. Howatson, C.J. Torrance, F.D. Lee, R.I. Russell, N. Engl. J. Med. 327 (1992) 749–754.
[27] R.J. Flower, Nature Rev. Drug Discov. 2 (2003) 179–191.
[28] D.M. Clive, J.S. Stoff, N. Engl. J. Med. 310 (1984) 563–570.
[29] N. Futaki, K. Yoshikawa, Y. Hamasaka, I. Aria, S. Higuchi, Gen. Pharmacol. 24 (1993) 105.
[30] K. Seibert, Y. Zhang, K. Leahy, S. Hauser, J. Masferrer, W. Perkins, L. Lee, P. Isakson, Proc. Natl. Acad. Sci. U.S.A. 91 (1994) 12013–12017.
[31] C.C. Chan, S. Boyce, C. Brideau, A.W. Ford-Hutchinson, R. Gordon, D. Guay, R.G. Hill, C.S. Li, J. Mancini, M. Penneton, J. Pharmacol. Exp. Ther. 274 (1995) 1531–1537.
[32] D.W. Gilroy, P.R. Colville-Nash, J. Mol. Med. (Berlin) 78 (2000) 121.
[33] A.S. Girgis, M. Ellithey, Bioorg. Med. Chem. 14 (2006) 8527–8532.
[34] A.S. Girgis, N. Mishriky, M. Ellithey, H.M. Hosni, H. Farag, Bioorg. Med. Chem. 15 (2007) 2403–2413.
[35] C.A. Winter, E.A. Fisley, G.W. Nuss, Proc. Soc. Exp. Biol. Med. 111 (1962) 544.
[36] C. Kärber, Naunyn-Schmiedebergs Archiv für experimentelle pathologie und pharmakologie 162 (1931) 480.
[37] R.D. Cannon, B. Chiswell, L.M. Venanzi, J. Chem. Soc. A (1967) 1277–1281.
[38] A.A. Abbas, A.S. Girgis, Heteroat. Chem. 18 (2007) 249–254.