Full Paper

Synthesis of New Pyrroles of Potential Anti-Inflammatory Activity

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We herein disclose a series of novel pyrrole derivatives **1–4** and pyrrolo[2,3-*d*]pyrimidine derivatives **6–11** as novel potent anti-inflammatory compounds. The structures were confirmed by IR, ^{1}H-NMR, and MS. Some newly synthesized compounds were examined for their *in-vivo* anti-inflammatory activity. Several derivatives showed a promising anti-inflammatory activity compared to ibuprofen. In this paper, we examine and discuss the structure–activity relationships and anti-inflammatory activities of these compounds.

Keywords: Anti-inflammatory activity / Pyrrole / Pyrrolo[2,3-*d*]pyrimidine / Structure–activity-relationship

Received: February 14, 2011; Revised: June 8, 2011; Accepted: June 20, 2011

DOI 10.1002/ardp.201100056

Introduction

In the past decade, efforts aimed at the discovery of therapeutically useful inhibitors of cyclooxygenase-2 (COX-2) have intensified. These efforts have resulted [1, 2] in the identification of a variety of templates, which depend on the nature of the attached substituent that provides a selective inhibition. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed and effective therapy for decreasing pain and inflammation, whereas, one of its privileged scaffolds is the pyrrole nucleus, which has served [3] as the core template for a variety of potential selective COX-2 inhibitors.

The favorable presence of pyrrole derivatives provoked an interest in the search for new active NSAIDs in generalized classes: analogs of effective COX-2 inhibitors [4–7]. Pyrrole compounds are a promising starting point in drug research in view of their various pharmacological activities [8]. Derivatives of pyrrolylacetic acid proved as NSAIDs are: tolmetin (CAS 64490-92-2), ketorolac (CAS 74103-06-3), indomethacin (CAS 53-86-1), and zomepirac (CAS 64092-48-4) (Fig. 1).

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Recently, other pyrrole compounds have been reported [9–12] as potent selective COX-2 inhibitors. PNU-142731A [13] (Fig. 1) is a potent and efficient pyrrolopyrimidine inhibitor of eosinophilic lung inflammation that is currently in Phase II clinical evaluation for the potential treatment of asthma.

Motivated by these aforementioned findings, and in continuance of our research efforts [14–17], we decided to prepare certain novel pyrrole and pyrrolopyrimidine derivatives and evaluate them for anti-inflammatory activity.

Results and discussion

Chemistry

Compound **1** was prepared as reported in [14–17, 23]. This compound was utilized for the preparation of pyrrole derivatives **2** and **3** using appropriate reagents and reaction conditions. Diazotization of the 2-amino-pyrrole was reported [18] many times in the literature. This reaction is considered as the key route to prepare a series of 2-triazenopyrroles, deaza analogues of dacarbazine, a famous anti-tumor drug. Diazotization [19] of **1** using a mixture of sodium nitrite and HCl (without acetic acid) at 0–5°C, without separation, adding an active methylene compounds, namely malononitrile in ethanol in the presence of sodium acetate afforded the corresponding hydrazono derivatives **2**. This reaction could be explained *via* formation of the diazonium chlorides at

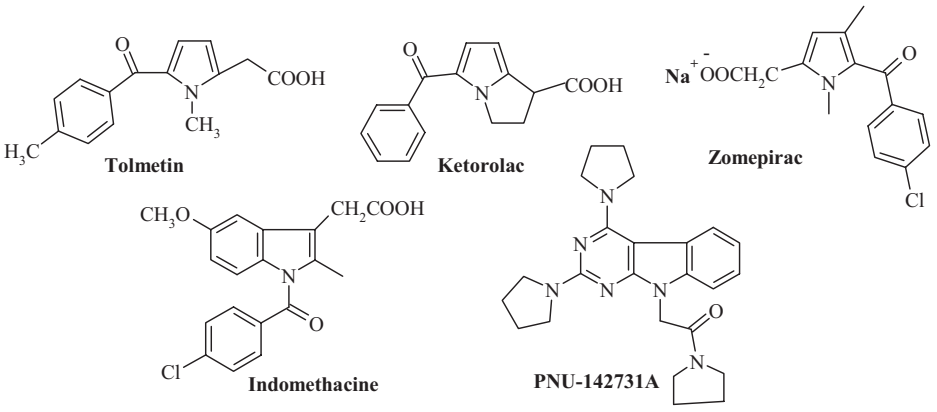


Figure 1. Anti-inflammatory drugs (NSAIDs).

first, which in addition to malononitrile afforded **2**. Cyclization of hydrazono derivatives **2** using hydrazine hydrate in boiling ethanol leads to the formation of the corresponding pyrazolin-5-one derivatives **3**.

On the other hand, diazotization [20] of **1** using sodium nitrite in a mixture of acetic acid and HCl (2:1) at 0–5°C afforded compound **4** the carboxamide derivatives. The spectral data of compounds **4a,b** assigned their structure (cf. Experimental). Many reports [18, 20–22] stated that diazotization of compounds analogous to **1** gave the corresponding triazine derivatives; however, our attempts to cyclize compound **1** to **5** by stirring with nitrous acid gave the unexpected carboxamide derivatives **4**. The formation of compounds **4** was explained by the hydrolysis of cyano group on acidic medium to amide group without formation of the unstable diazonium salt on the amino group. In addition, this could be established chemically through hydrolysis of compound **1c**, same compound **4c** was obtained; **4c** prepared by this method gave the same data as reported [23].

The pyrrole derivatives **4** were converted to the corresponding pyrrolo[2,3-*d*]pyrimidine-2-thione **6** via refluxing [24] with thiourea in ethanol. Alkylation [25–27] of pyrrolopyrimidin-2-thiones **6** with halo compounds gave the corresponding *S*-alkylated pyrimidine derivatives **7**. The reaction [28, 29] of *S*-alkylated compounds **7** with hydrazine hydrate yielded the 2-hydrazine derivative **8**. The reaction [27–30] of compound **8** with acetyl acetone in ethanol containing catalytic amount of glacial acetic acid yielded the corresponding pyrazolyl derivatives **9** in good yield. Refluxing [27] **4** with ethyl acetoacetate in sodium ethoxide solution afforded the pyrazolone derivatives **10**. Reactions of 4-hydrazinopyrimidines with one carbon donor moiety produce the respective isomeric triazolopyrimidines [21, 22, 31]. Compound **8** was used to prepare some pyrrolotriazolo[4,3-*a*]pyrimidines **11** acetic anhydride/acetic anhydride (Scheme 1).

Biological results and discussion

Synthesized compounds were assessed for their anti-inflammatory activity. Compounds **2c**, **3a**, **4a**, **6a**, **6b**, **7a**, and **9c** induced significant anti-inflammatory activity, comparable with that of ibuprofen (Fig. 2).

In addition, compounds **1c**, **4c**, **8a** and **11a** exerted moderate activities compared to ibuprofen at the 3rd and 4th h post-carrageenan. Their activity profile was the same as ibuprofen (response increasing by time).

Compounds **2c**, **3a**, **6a** and **7a** showed a stronger anti-inflammatory effect than ibuprofen, from 1st to 4th h post-carrageenan. Yet, compound **4a** showed the opposite profile compared to ibuprofen: It showed 79.6% inhibition at 1-h post-carrageenan and 68.5% inhibition at 2-h post-carrageenan and then decreased to 66% inhibition at 3-h and 4-h post-carrageenan.

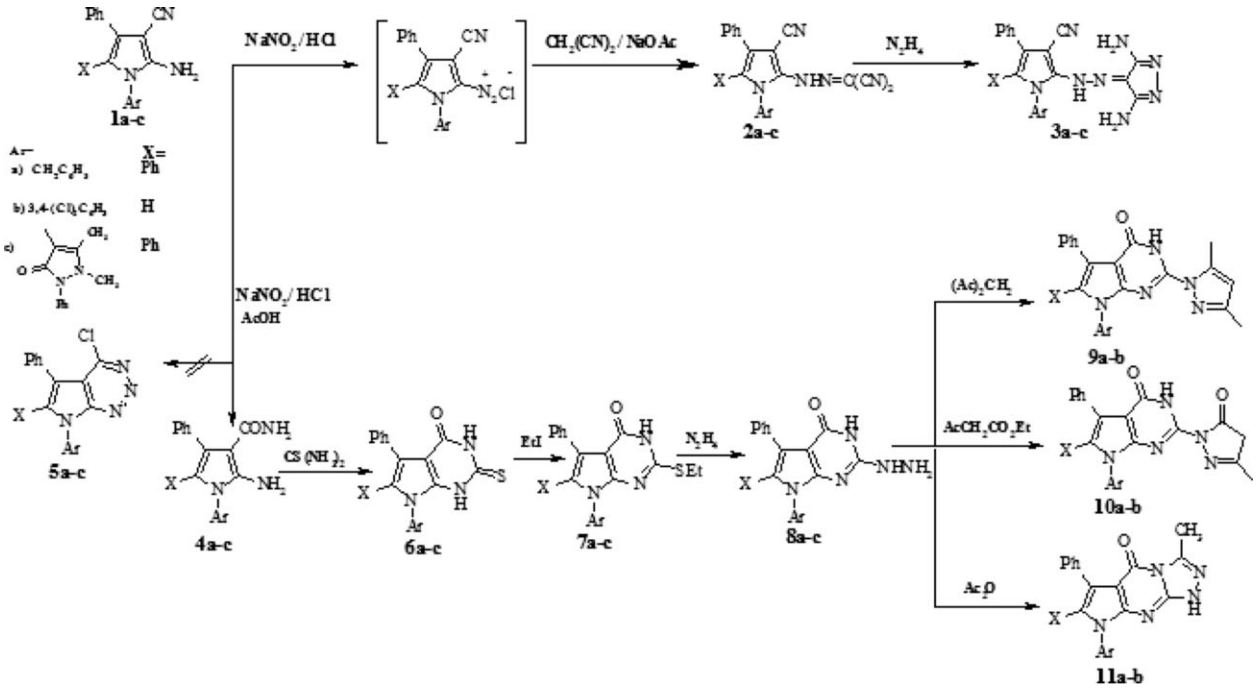
Compound **6b** exerted a stronger anti-inflammatory effect than ibuprofen (95% and 96% inhibition at 2-h and 3-h interval post-carrageenan). Likewise, compounds **8b** showed a significant higher inhibitory action at the 3-h interval; 95% inhibition.

Compound **9c** showed no activity at 1st and 2nd h intervals post-carrageenan injection. Yet, they exerted significantly higher activity compared to ibuprofen at the 3rd and 4th h post-carrageenan; (63.5% at 3rd h and 79% at 4th h post-carrageenan).

Compounds **1c**, **4c**, **8a** and **11a** exerted markedly but not significantly higher activity compared to ibuprofen at the 4th h post-carrageenan. Compound **1c** showed 68% inhibition, **4c** showed 62% inhibition, **8a** showed 70% inhibition and **11a** showed 66% inhibition.

Compounds **1a** and **1b** showed weak activities 4 h after carrageenan injection.

To analyze structure–activity relationships, three structural components were considered: The nature of the hetero-



Scheme 1. Synthesis of compounds **1–11**.

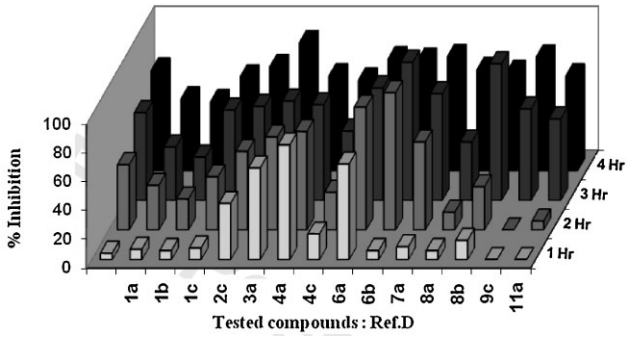


Figure 2. Anti-inflammatory effect (% inhibition) of tested compounds compared to the drug (Ibuprofen).

cycle nucleus, the type of the side chain, and the position of the side chain.

First, the influence of the nature of the aromatic heterocyclic system; pyrrolopyrimidine **6a**, **6b**, **7a**, **8a** and **8b** condensed ring showed the highest activity over pyrrole **1c** and pyrrolotriazolopyrimidine **11a**.

Regarding the side chain type, adding bulky group (as hydrazonoyl dicyanide and pyrazolyl) in compounds **2c** and **3a** confers greater activity over the net amino groups in compound **1c**: While compound **2c** (hydrazonoyl dicyanide) showed 72.3% inhibition at 4th h post-carrageenan injection, increased to 89% inhibition at 4th h post-carrageenan injection in compound **3a** (pyrazolyl), the amino group in **1c** presented only 68% inhibition at 4th h post-carrageenan injection.

Also, hydrolysis of cyano group in **1a** to carboxamide group in **4a** increased the activity during all time intervals: While amide **4a** showed 79–66% inhibition at 1st h to 4th h post-carrageenan, the cyano **1a** exerted 7% inhibition at 1st h then increased to 50% inhibition at 4th h.

Alkylation of thione group at compound **7a** decreased the activity at 1st to 3rd h, yet increased at 4th h than the free thione in compound **6a**. While **6a** showed 66–78.1% inhibition at 1st h to 3rd h post-carrageenan and decreased to 77% inhibition at 4th h, **7a** exerted 8–74% inhibition at 1st h to 3rd h then increased to 79.5% inhibition at 4th h.

Replacing the antipyrine moity in compound **4c** with benzyl group in compound **4a** confers significantly higher activity during all time intervals than antipyrine moiety at **4c**; while **4a** showed 79–66% inhibition at 1st h to 4th h post-carrageenan, **4c** exerted 19% inhibition at 1st h then increased to 62% inhibition at 4th h.

Regarding the side chain position, addition of bulky group on position 2 decreased the activity; compounds **8b** and **9c** over free thione in **6a** and **6b**. Also, triazolo ring as fused ring with pyrrolopyrimidine at position 2 in compounds **11a** decreased the activity (6.5% and 66% inhibition) at 3rd h and 4th h post-carrageenan injection over pyrrolopyrimidine system.

Conclusion

We have synthesized and evaluated a series of heterocyclic compounds as potential anti-inflammatory agents. Based on their structure, we conclude that the best aromatic nucleus is the pyrrole with an *N*-benzyl substituent and a pyrazolyl subunit on the C-2 such as in compound **3a**. In the pyrrolopyrimidine derivatives, the anti-inflammatory activity also depends on the nature of the side group on the C-2 at the heterocyclic system (compound **6a,b** is more active than **8a,b** or **11a**).

Experimental

General methods

All melting points were uncorrected and measured using Electrothermal IA 9100 apparatus (Shimadzu, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (USA), Faculty of Science, Cairo University, Cairo, Egypt. ^{1}H-NMR spectra were determined on a Varian Mercury (300 MHz) spectrometer (Varian, UK) and chemical shifts were expressed as ppm against TMS as internal reference (Faculty of Science, Cairo University, Cairo, Egypt). Mass spectra were recorded on 70 eV EI Ms-QP 1000 EX (Shimadzu, Japan), Faculty of Science, Cairo University, Cairo, Egypt. Microanalyses were operated using Vario, Elmentar apparatus (Shimadzu, Japan), Organic Microanalysis Unit, Faculty of Science, Cairo University, Cairo, Egypt. Column chromatography was performed on (Merck) Silica gel 60 (particle size 0.06–0.20 mm). Compounds **1a–c** and **4c** were prepared as reported in [14–17, 23]. All new compounds yielded spectral data consistent with the proposed structure and microanalysis within ±0.4% of the theoretical values.

*General procedure for the preparation of compound **2***

A mixture of **1** (0.01 mol) in concentrated HCl (10 mL) was cooled with stirring to 0–5°C under ice, and cooled sodium nitrite solution (2.5 g in 10 mL of water) added to it dropwise during 30 min. The reaction mixture was then stirred for 30 min. Without separation an ice-cold mixture of malononitrile (0.015 mol) and sodium acetate (4.10 g; 0.05 mol) in ethanol (50 mL) was added dropwise with stirring over 15 min. The stirring was continued for 30 min under ice and the reaction mixture then left for 12 h at room temperature. The precipitate was filtered off, recrystallized from ethanol/H_2O to give **2**.

*(1-Benzyl-3-cyano-4,5-diphenyl-1H-pyrrol-2-yl)-carbonohydrazonoyl dicyanide (**2a**)*

Yield 58 %, m.p. 115–120°C. IR (KBr) ν (cm^{-1}): 3280 (NH), 2330 (C≡N), 1585 (C=N). MS (EI) *m/z* (%): 426 (M$^+$, 18%), 427 (M$^+$+1, 5.5%), 428 (M$^+$+2, 1.5%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 5.62 (s, 2H, CH_2), 6.9 (s, 1H, NH, hydrazone), 7.2–7.8 (m, 15H, Ar-H). Anal. calcd. for $C_{27}H_{18}N_6$ (426.47): C, 76.04; H, 4.25; N, 19.71. Found: C, 76.25; H, 4.41; N, 19.86.

*(3-Cyano-1-(3,4-dichlorophenyl)-4-phenyl-1H-pyrrol-2-yl)-carbono hydrazonoyl dicyanide (**2b**)*

Yield 45 %, m.p. 218–222°C. IR (KBr) ν (cm^{-1}): 3300 (NH), 2310 (C≡N), 1565 (C=N). MS (EI) *m/z* (%): 405 (M$^+$, ^{35}Cl, 19%), 407 (M$^+$+2, ^{37}Cl, 12.2%), 409 (M$^+$+4, 2 (^{37}Cl), 2.1%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.9 (s, 1H, NH, hydrazone), 7.0 (s, 1H, C_6-H), 7.2–7.8 (m, 8H, Ar–H). Anal. calcd. for $C_{20}H_{10}Cl_2N_6$ (405.24): C, 59.28; H, 2.49; Cl, 17.50; N, 20.74. Found: C, 59.41; H, 2.62; Cl, 17.65; N, 20.86.

*(3-Cyano-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-4,5-diphenyl-1H-pyrrol-2-yl)-carbonohydrazonoyl dicyanide (**2c**)*

Yield 48 %, m.p. 153–157°C. IR (KBr) ν (cm^{-1}): 3290 (NH), 2320 (C≡N), 1695 (C=O), 1585 (C=N). MS (EI) *m/z* (%): 522 (M$^+$, 18%), 523 (M$^+$+1, 8.5%), 524 (M$^+$+2, 0.8%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.2 (s, 2H, CH_2–C=O), 2.33 (s, 3H, CH_3), 3.12 (s, 3H, N–CH_3), 6.9 (s, 1H, NH, hydrazone), 7.3–7.9 (m, 15H, Ar–H). Anal. calcd. for $C_{31}H_{22}N_8O$ (522.559): C, 71.25; H, 4.24; N, 21.44; O, 3.06. Found: C, 71.48; H, 4.62; N, 21.55; O, 3.17.

*General procedure for the preparation of compound **3***

A mixture of compound **2** (0.01 mol) and hydrazine hydrate (0.64 mL, 0.02 mol) in ethanol (30 mL) was heated under reflux for 8 h controlled by TLC. The solvent was concentrated and the reaction product was allowed to cool then poured on acidified ice/H_2O. The product was filtered off, washed with water, dried and recrystallized from ethanol to give **3**.

*1-Benzyl-2-(2-(3,5-diamino-4H-pyrazol-4-ylidene)-hydrazinyl)-4,5-diphenyl-1H-pyrrole-3-carbonitrile (**3a**)*

Yield 60%, m.p. 112–117°C. IR (KBr) ν (cm^{-1}): 3340–3290 (broad NH and NH_2), 1560 (C=N). MS (EI) *m/z* (%): 458 (M$^+$, 21%), 459 (M$^+$+1, 6.5%), 460 (M$^+$+2, 1.3%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 5.62 (s, 2H, CH_2), 6.5 (s, 4H, 2 NH_2), 6.8 (s, 1H, NH, hydrazone), 7.2–7.9 (m, 15H, Ar-H). Anal. calcd. for $C_{27}H_{22}N_8$ (458.517): C, 70.73; H, 4.84; N, 24.44. Found: C, 70.54; H, 4.91; N, 24.65.

*2-(2-(3,5-Diamino-4H-pyrazol-4-ylidene)hydrazinyl)-1-(3,4-dichloro phenyl)-4-phenyl-1H-pyrrole-3-carbonitrile (**3b**)*

Yield 51%, m.p. 178–181°C. IR (KBr) ν (cm^{-1}): 3330–3270 (broad NH and NH_2), 1580 (C=N). MS (EI) *m/z* (%): 436 (M$^+$, ^{35}Cl, 20%), 438 (M$^+$+2, ^{37}Cl, 13.5%), 440 (M$^+$+4, 2 (^{37}Cl), 2.5%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.6 (s, 4H, 2 NH_2), 6.9 (s, 1H, NH, hydrazone), 7.0 (s, 1H, C_6-H), 7.3–7.8 (m, 8H, Ar–H). Anal. calcd. for $C_{20}H_{14}Cl_2N_8$ (437.285): C, 54.93; H, 3.23; Cl, 16.22; N, 25.62. Found: C, 54.69; H, 3.42; Cl, 16.51; N, 25.47.

*2-(2-(3,5-Diamino-4H-pyrazol-4-ylidene)hydrazinyl)-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-4,5-diphenyl-1H-pyrrole-3-carbonitrile (**3c**)*

Yield 48%, m.p. 178–181°C. IR (KBr) ν (cm^{-1}): 3340–3290 (broad NH and NH_2), 1690 (C=O), 1565 (C=N). MS (EI) *m/z* (%): 554 (M$^+$, 22%), 555 (M$^+$+1, 9.1%), 556 (M$^+$+2, 2.1%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.2 (s, 2H, CH_2–C=O), 2.3 (s, 3H, CH_3), 3.14 (s, 3H, N–CH_3), 6.58 (s, 4H, 2 NH_2), 6.9 (s, 1H, NH, hydrazone), 7.3–7.9 (m, 15H, Ar–H). Anal. calcd. for $C_{31}H_{26}N_{10}O$ (554.605): C, 67.13; H, 4.73; N, 25.26; O, 2.88. Found: C, 67.36; H, 4.95; N, 25.48; O, 2.96.

*2-Amino-1-(aryl)-4-phenyl-5-substituted -1H-pyrrole-3-carboxamide (**4**)*

To a suspended solution of compound **1** (0.01 mol) in a mixture of hydrochloric acid (5 mL, 34%) and glacial acetic acid (10 mL) at 0–5°C, a solution of sodium nitrite (4 g in 10 mL water) was added dropwise with continuous stirring over 30 min. After 8 h of stirring at room temperature the foamy mixture was diluted with water, neutralized with ammonia, filtered off, and recrystallized from (EtOH/H_2O) to give compound **4.** Compound **4c** prepared with this method is identical in all respects (physical and spectral data) as reported.

*2-Amino-1-benzyl-4,5-diphenyl-1H-pyrrole-3-carboxamide (**4a**)*

Yield 60%, m.p. 98–102°C. IR (KBr) ν (cm^{-1}): 3350–3300 (NH_2), 1680 (C=O). MS (EI) *m/z* (%): 367 (M^+, 27%), 368 (M^++1, 8.5%), 369 (M^++2, 1.3%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 5.62 (s, 2H, CH_2), 6.5 (s, 2H, NH_2), 7.2–8 (m, 15H, Ar–H and 2H, $CONH_2$). Anal. calcd. for $C_{24}H_{21}N_3O$ (367.443): C, 78.45; H, 5.76; N, 11.44; O, 4.35. Found: C, 78.26; H, 5.59; N, 11.32; O, 4.61.

*2-Amino-1-(3,4-dichlorophenyl)-4-phenyl-1H-pyrrole-3-carboxamide (**4b**)*

Yield 58%, m.p. 178–181°C. IR (KBr) ν (cm^{-1}): 3330–3280 (NH_2), 1670 (C=O). MS (EI) *m/z* (%): 346 (M^+, ^{35}Cl, 32%), 348 (M^++2, ^{37}Cl, 19%), 350 (M^++4, 2*(^{37}Cl), 5.6%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.6 (s, 2H, NH_2), 7.0 (s, 1H, C_6-H), 7.3–8 (m, 8H, Ar–H and 2H, $CONH_2$). Anal. calcd. for $C_{17}H_{13}Cl_2N_3O$ (346.211): C, 58.98; H, 3.78; Cl, 20.48; N, 12.14; O, 4.62. Found: C, 59.04; H, 3.96; Cl, 20.71; N, 12.47; O, 4.85.

*7-Aryl-5,6-disubstituted-2-thioxo-2,3-dihydro-1H-pyrrolo[2,3-d] pyrimidin-4(7H)-one (**6**)*

A mixture of compound **4** (0.01 mol) and thiourea (1.2 g, 0.02 mol) was refluxed in dry ethanol (20 mL) for 10 h. The reaction mixture was evaporated under reduced pressure and the residues were recrystallized from methanol to give **6**.

*7-Benzyl-5,6-diphenyl-2-thioxo-2,3-dihydro-1H-pyrrolo[2,3-d] pyrimidin-4(7H)-one (**6a**)*

Yield: 80%, m.p. 92–94°C. IR (KBr) ν (cm^{-1}): 3350 (NH), 1680 (C=O), 1615 (C=S). MS (EI) *m/z* (%): 409 (M^+, 45%), 410 (M^++1, 13.5%), 411 (M^++2, 1.1%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 5.56 (s, 2H, CH_2), 7.1–7.8 (m, 15H, Ar-H), 12.20 (s, 1H, NH), 13.30 (s, 1H, NH). Anal. calcd. for $C_{25}H_{19}N_3OS$ (409.503): C, 73.32; H, 4.68; N, 10.26; O, 3.91; S, 7.83. Found: C, 73.49; H, 4.90; N, 10.42; O, 3.63; S, 7.86.

*7-(3,4-Dichlorophenyl)-5-phenyl-2-thioxo-2,3-dihydro-1H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**6b**)*

Yield 75%, m.p. 138–140°C. IR (KBr) ν (cm^{-1}): 3360 (NH), 1690 (C=O), 1605 (C=S). MS (EI) *m/z*: 387 (M^+, ^{35}Cl, 20%), 389 (M^++2, ^{37}Cl, 8.3%), 391 (M^++4, 2 (^{37}Cl), 7.5%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 7.0 (s, 1H, C_6-H), 7.3–8 (m, 8H, Ar–H), 12.20 (s, 1H, NH), 13.30 (s, 1H, NH). Anal. calcd. for $C_{18}H_{11}Cl_2N_3OS$ (388.270): C, 55.68; H, 2.86; Cl, 18.26; N, 10.82; O, 4.12; S, 8.26. Found: C, 55.89; H, 2.97; Cl, 18.58; N, 10.99; O, 4.23; S, 8.49.

*7-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-5,6-diphenyl-2-thioxo-2,3-dihydro-1H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**6c**)*

Yield 74%, m.p. 132–137°C. IR (KBr) ν (cm^{-1}): 3390 (NH), 1690 (C=O), 1630 (C=S). MS (EI) *m/z* (%): 505 (M^+, 70.0%), 506 (M^++1, 22.17%), 507 (M^++2, 3.73%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.43 (s, 3H, CH_3), 3.12 (s, 3H, N–CH_3), 7.2–7.8 (m, 15H, Ar–H), 12.32 (s, 1H, NH), 13.14 (s, 1H, NH). Anal. calcd. for $C_{29}H_{23}N_5O_2S$ (505.590): C, 68.89; H, 4.59; N, 13.85; O, 6.33; S, 6.34. Found: C, 68.89; H, 4.59; N, 13.85; O, 6.33; S, 6.34.

*7-Aryl-5,6-disubstituted-2-(ethylthio)-3H-pyrrolo[2,3-d]-pyrimidin-4(7H)-one (**7**)*

To a warmed sodium ethoxide solution (prepared by dissolving 0.56 g, 0.01 mol of sodium in 50 mL of ethanol) compound **6** (0.01 mol) was added, and heating was continued for 20 min. The mixture was allowed to cool to r.t., and alkyl halide (0.02 mol) was added dropwise with continuous stirring over 30 min. The mixture was stirred under reflux for 5 h controlled by TLC, allowed to cool to r.t., and finally poured into cold water. The solid product was filtered off and washed with water; residue was dried and recrystallized from methanol to give **7**.

*7-Benzyl-2-(ethylthio)-5,6-diphenyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**7a**)*

Yield 80%, m.p. 84–86°C. IR (KBr) ν (cm^{-1}): 3330 (NH), 1680 (C=O). MS (EI) *m/z* (%): 437 (M^+, 34%), 438 (M^++1, 10.28%), 439 (M^++2, 1.4%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.32 (t, 3H, J = 7.2 Hz, CH_3), 3.53 (q, 2H, J = 7.2 Hz, CH_2), 5.98 (s, 2H, CH_2), 7.1–7.8 (m, 15H, Ar–H), 12.59 (s, 1H, NH). Anal. calcd. for $C_{27}H_{23}N_3OS$ (437.556): C, 74.11; H, 5.30; N, 9.60; O, 3.66; S, 7.33. Found: C, 74.41; H, 5.63; N, 9.80; O, 3.79; S, 7.56.

*7-(3,4-Dichlorophenyl)-2-(ethylthio)-5-phenyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**7b**)*

Yield 76%, m.p. 125–128°C. IR (KBr) ν (cm^{-1}): 3410 (NH), 1680 (C=O). MS (EI) *m/z* (%): 416 (M^+, ^{35}Cl, 43.2%), 418 (M^++2, ^{37}Cl, 8.9%), 420 (M^++4, 2 (^{37}Cl), 2.1%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.43 (t, 3H, J = 6.8 Hz, CH_3), 3.23 (q, 3H, J = 6.8 Hz, CH_3), 6.9 (s, 1H, C_6-H), 7.2–7.8 (m, 8H, Ar–H), 12.61 (s, 1H, NH). Anal. calcd. for $C_{20}H_{15}Cl_2N_3OS$ (416.324): C, 57.70; H, 3.63; Cl, 17.03; N, 10.09; O, 3.84; S, 7.70. Found: C, 57.93; H, 3.89; Cl, 17.26; N, 10.18; O, 3.96; S, 7.75.

*7-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(ethylthio)-5,6-diphenyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**7b**)*

Yield 64%, m.p. 145–147°C. IR (KBr) ν (cm^{-1}): 3450 (NH), 1700 (C=O), 1675 (C=O). MS (EI) *m/z* (%): 533 (M^+, 31.15%), 534 (M^++1, 11.2%), 535 (M^++2, 2.3%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): ^{1}H-NMR (DMSO, 300 MHz) δ (ppm): 1.46 (t, 3H, J = 7.5 Hz, CH_3), 2.43 (s, 3H, CH_3), 3.01 (q, 3H, J = 7.5 Hz, CH_3), 3.21 (s, 3H, N–CH_3), 7.0–7.8 (m, 15H, Ar–H), 12.49 (s, 1H, NH). Anal. calcd. for $C_{31}H_{27}N_5O_2S$ (533.643): C, 69.77; H, 5.10; N, 13.12; O, 6.00; S, 6.01. Found: C, 70.01; H, 5.38; N, 16.01; O, 6.25; S, 6.35.

*7-Aryl-5,6-disubstituted-2-(hydrazinyl)-3H-pyrrolo[2,3-d]-pyrimidin-4(7H)-one (**8**)*

A mixture of **7** (0.01 mol) and hydrazine hydrate (99%, 0.03 mol) in absolute ethanol (20 mL) was refluxed for 10 h. The reaction mixture was poured onto ice. The solid product was filtered off and washed with water; residue was dried and recrystallized from methanol to give **8**.

*7-Benzyl-2-hydrazinyl-5,6-diphenyl-3H-pyrrolo[2,3-d]-pyrimidin-4(7H)-one (**8a**)*

Yield 60%, m.p. 100–102°C. IR (KBr) ν (cm^{-1}): 3460–3380 (NH_2), 3350 (NH), 1680 (C=O). MS (EI) *m/z* (%): 407 (M^+, 20%), 408 (M^++1, 8.2%), 409 (M^++2, 1.3%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 5.92 (s, 2H, CH_2), 6.70 (s, 2H, NH_2), 7.1–7.8 (m, 15H, Ar–H), 8.1 (s, 1H, NH, D_2O exchangeable), 8.2 (s, 1H, $NHNH_2$), 11.21 (s, 1H, NH). Anal. calcd. for $C_{25}H_{21}N_5O$ (407.467): C, 73.69; H, 5.19; N, 17.19; O, 3.93. Found: C, 73.47; H, 5.28; N, 17.42; O, 3.65.

*7-(3,4-Dichlorophenyl)-2-hydrazinyl-5-phenyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**8b**)*

Yield 68%, m.p. 142–146°C. IR (KBr) ν (cm^{-1}): 3480–3400 (NH_2), 3380 (NH), 1670 (C=O). MS (EI) *m/z* (%): 386 (M^+, ^{35}Cl, 29%), 388 (M^++2, ^{37}Cl, 12.5%), 390 (M^++4, 2(^{37}Cl), 1.7%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.48 (s, 2H, NH_2), 6.9 (s, 1H, C_6-H), 7.1–7.8 (m, 8H, Ar–H), 8.23 (s, 1H, $NHNH_2$), 11.21 (s, 1H, NH). Anal. calcd. for $C_{18}H_{13}Cl_2N_5O$ (386.235): C, 55.97; H, 3.39; Cl, 18.36; N, 18.13; O, 4.14. Found: C, 56.09; H, 3.64; Cl, 18.57; N, 18.41; O, 4.28.

*7-(1,5-Dimethyl-3-oxo-1-phenyl-2,5-dihydro-1H-pyrazol-3-yl)-2-hydrazinyl-5,6-diphenyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**8c**)*

Yield 56%, m.p. 153–158°C. IR (KBr) ν (cm^{-1}): 3420, 3390 (NH_2), 3340 (NH), 1710 (C=O), 1640 (C=C). MS (EI) *m/z* (%): 502 (M^+, 65%), 503 (M^++1, 20.1%), ^{1}H-NMR (DMSO, 300 MHz) δ (ppm): 2.42 (s, 3H, CH_3), 3.23 (s, 3H, N–CH_3), 6.62 (s, 2H, NH_2), 7.2–7.9 (m, 15H, Ar–H), 8.30 (s, 1H, NH NH_2). Anal. calcd. for $C_{29}H_{25}N_7O_2$ (503.555): C, 69.17; H, 5.00; N, 19.47; O, 6.35. Found: C, 69.04; H, 5.13; N, 19.24; O, 6.61.

*7-(Aryl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)-5,6-disubstituted-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**9**)*

A mixture of compound **8a,c** (0.01 mol) and acetylacetone (0.02 mol) in absolute ethanol (30 mL, containing a catalytic amount of glacial acetic acid (2mL)) was heated under reflux for 10 h. The precipitate was filtered while hot, washed with water several times and recrystallized from ethanol to give **9a,b**.

*7-Benzyl-2-(3,5-dimethyl-1H-pyrazol-1-yl)-5,6-diphenyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**9a**)*

Yield 55%, m.p. 162–164°C. IR (KBr) ν (cm^{-1}): 1680 (C=O), 1640 (C=N). MS (EI) *m/z* (%): 471 (M^+, 15%), 472 (M^++1, 3.6%), 473 (M^++2, 1.1%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.0 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 6.8 (s, 1H, pyrazole), 7.3–7.8 (m, 15H, Ar-H), 10.3 (s, 1H, NH, pyrimidine). Anal. calcd. for $C_{30}H_{25}N_5O$ (471.552): C, 76.41; H, 5.34; N, 14.85; O, 3.39. Found: C, 76.25; H, 5.62; N, 14.53; O, 3.21.

*2-(3,5-Dimethyl-1H-pyrazol-1-yl)-7-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-5,6-diphenyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**9b**)*

Yield 58%, m.p. 125–127°C. IR (KBr) ν (cm^{-1}): 1695 (C=O), 1680 (C=O). MS (EI) *m/z* (%): 551 (M^+, 65%), 552 (M^++1, 21%), 553 (M^++2, 3.1%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.2 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.12 (s, 3H, N–CH_3), 6.8 (s, 1H, pyrazole), 7.2–7.7 (m, 15H, Ar–H), 10.6 (s, 1H, NH, pyrimidine). Anal. calcd. for $C_{34}H_{29}N_7O_2$ (567.640): C, 71.94; H, 5.15; N, 17.27; O, 5.64. Found: C, 72.05; H, 5.39; N, 17.51; O, 5.74.

*7-(Aryl)-2-(5-methyl-3-oxo-2,3-dihydro-1H-pyrazol-1-yl)-5,6-disubstituted-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**10**)*

A mixture of compound **8b,c** (0.01 mol) and ethylacetoacetate (0.05 mol) in sodium ethoxide solution (prepared by dissolving 0.23 g of sodium metal in absolute ethanol (30 mL)) was heated under reflux with stirring for 10 h. The reaction mixture was allowed to cool, poured into cold water and neutralized by HCl. The solid product was filtered off and recrystallized from ethanol to give **10a,b**.

*7-(3,4-Dichlorophenyl)-2-(5-methyl-3-oxo-2,3-dihydro-1H-pyrazol-1-yl)-5-phenyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (**10a**)*

Yield 45%, m.p. 132–135°C. IR (KBr) ν (cm^{-1}): 1695 (C=O), 1680 (C=O). MS (EI) *m/z* (%): 452 (M^+, ^{35}Cl, 32.1%), 454 (M^++2, ^{37}Cl, 9.2%), 456 (M^++4, 2 (^{37}Cl), 3.1%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.5 (s, 3H, CH_3), 6.42 (s, 1H, pyrazole), 6.8 (s, 1H, C_6-H), 7.0–7.9 (m, 8H, Ar–H), 9.05 (s, 1H, NH, pyrazole), 10.8 (s, 1H, NH, pyrimidine). Anal. calcd. for $C_{22}H_{15}Cl_2N_5O_2$ (452.293): C, 58.42; H, 3.34; Cl, 15.68; N, 15.48; O, 7.07. Found: C, 58.42; H, 3.34; Cl, 15.68; N, 15.48; O, 7.27.

*7-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(5-methyl-3-oxo-2,3-dihydro-1H-pyrazol-1-yl)-5,6-diphenyl-3H-pyrrolo [2,3-d]pyrimidin-4(7H)-one (**10b**)*

Yield 49%, m.p. 118–120°C. IR (KBr) ν (cm^{-1}): 1695 (C=O), 1680 (C=O). MS (EI) *m/z* (%): 569 (M^+, 16.2%), 570 (M^++1, 2.6%), 571 (M^++2, 1.2%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.32 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.15 (s, 3H, N–CH_3), 6.58 (s, 1H, pyrazole), 7.2–7.8 (m, 15H, Ar–H), 9.15 (s, 1H, NH, pyrazole), 10.58 (s, 1H, NH, pyrimidine). Anal. calcd. for $C_{33}H_{27}N_7O_3$ (569.613): C, 69.58; H, 4.78; N, 17.21; O, 8.43. Found: C, 69.73; H, 4.92; N, 17.42; O, 8.65.

*8-(Aryl)-3-methyl-6,7-disubstituted-1H-pyrrolo[2,3-d][1,2,4]triazolo [4,3-a]pyrimidin-5(8H)-one (**11**)*

A mixture of compound **8a,b** (0.01 mol), acetic anhydride (20 mL), and acetic acid (10 mL) was refluxed for 8 h. The reaction mixture was cooled, poured onto ice-water, filtered, dried, and recrystallized from ethanol to afford **11a,b**.

*8-Benzyl-3-methyl-6,7-diphenyl-1H-pyrrolo[2,3-d]-[1,2,4]triazolo[4,3-a]pyrimidin-5(8H)-one (**11a**)*

Yield 53%, m.p. 110–112°C. IR (KBr) ν (cm^{-1}): 1670 (C=O), 1590 (C=N). MS (EI) *m/z* (%): 431 (M^+, 18%), 432 (M^++1, 6.2%), 433

Table 1. In vivo anti-inflammatory activity.

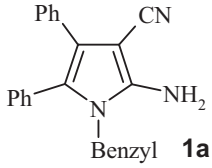
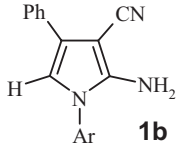
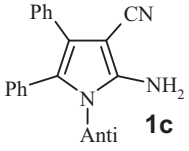
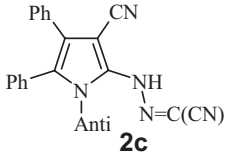
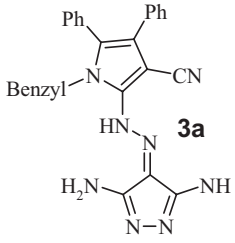
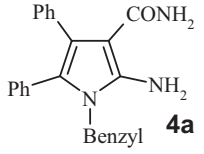
Compounds	Edema induced by carrageenan (% edema inhibition relative to control)							
	1 h		2 h		3 h		4 h	
	Swel ± SE	% inh.	Swel ± SE	% inh.	Swel ± SE	% inh.	Swel ± SE	% inh.
 **1a**	0.21 ± 0.025	0.71	0.18 ± 0.063	31	0.35 ± 0.056	37	0.32 ± 0.032[a]	50
 **1b**	0.212 ± 0.078	6.19	0.20 ± 0.032	21.5	0.384 ± 0.044	30	0.33 ± 0.031a	48.1
 **1c**	0.212 ± 0.034	6.2	0.165 ± 0.048	36.35	0.18 ± 0.04a	66.7	0.2 ± 0.076a	68
 **2c**	0.138 ± 0.058	39	0.118 ± 0.055	54.6	0.19 ± 0.042a	65.3	0.177 ± 0.065a	72.3
 **3a**	0.082 ± 0.032	63.7	0.092 ± 0.032	64.6	0.17 ± 0.029a	69	0.07 ± 0.03a	89
 **4a**	0.046 ± 0.004	79.6	0.082 ± 0.007	68.4	0.184 ± 0.003a	66.41	0.218 ± 0.02	66

Table 1. (*continued*)

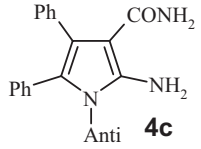
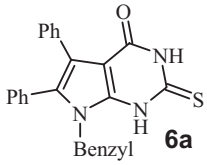
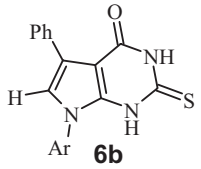
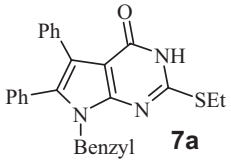
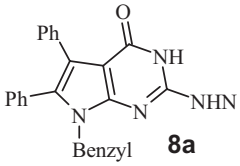
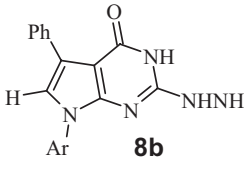
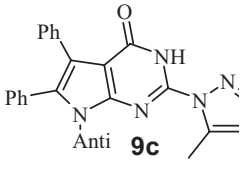
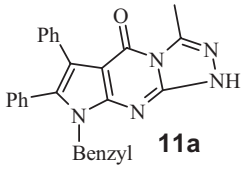
Compounds	Edema induced by carrageenan (% edema inhibition relative to control)							
	1 h		2 h		3 h		4 h	
	Swel ± SE	% inh.	Swel ± SE	% inh.	Swel ± SE	% inh.	Swel ± SE	% inh.
 **4c**	0.182 ± 0.044	19.13	0.192 ± 0.0403	26.15	0.28 ± 0.08	47.8	0.23 ± 0.062a	62.55
 **6a**	0.13 ± 0.043	66.37	0.038 ± 0.01a	85.4	0.12 ± 0.035a	78.1	0.142 ± 0.025a	77.8
 **6b**	0.212 ± 0.09	6.19	0.012 ± 0.002a	95.3	0.022 ± 0.0058a	96	0.148 ± 0.046a	76.87
 **7a**	0.206 ± 0.021	8.8	0.101 ± 0.023	61	0.142 ± 0.006a	74	0.132 ± 0.004a	79.3
 **8a**	0.212 ± 0.048	6.2	0.228 ± 0.025	12.3	0.326 ± 0.032	40.5	0.19 ± 0.039a	70.3
 **8b**	0.19 ± 0.052	13.2	0.182 ± 0.018	30	0.028 ± 0.0048a	95	0.202 ± 0.02a	68.4
 **9c**	0.23 ± 0.031	0	0.26 ± 0.024	0	0.2 ± 0.047a	63.5	0.134 ± 0.027a	79

Table 1. (*continued*)

Compounds	Edema induced by carrageenan (% edema inhibition relative to control)							
	1 h		2 h		3 h		4 h	
	Swel ± SE	% inh.	Swel ± SE	% inh.	Swel ± SE	% inh.	Swel ± SE	% inh.
 **11a**	0.229 ± 0.018	0	0.244 ± 0.08	6.1	0.238 ± 0.028	6.5	0.218 ± 0.082a	66
Ibuprofen	0.216 ± 0.034	6.08	0.1425 ± 0.031	45	0.214 ± 0.024a	60.66	0.192 ± 0.012a	69.52
Control	0.23 ± 0.033		0.26 ± 0.049		0.544 ± 0.081		0.63 ± 0.037	

Swel = mean difference in rat paw volume between right and left paw ± S.E. % inhibition = (1 − rt/rc) × 100; [rt = swel. of tested group; rc = swel. of control group] [a]: Significantly different from control at the same time interval at $p < 0.05$ Swel = swelling, SE = standard error, %inh. = % inhibition, benzyl = CH_2Ph, Ar = 3,4-$Cl_2C_6H_3$, Anti = antipyrine

(M^++2, 2.51%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.83 (s, 3H, CH_3), 5.68 (s, 2H, CH_2), 7.3–7.8 (m, 15H, Ar–H), 9.3 (s, 1H, NH, pyrazole). Anal. calcd. for $C_{27}H_{21}N_5O$ (431.489): C, 75.16; H, 4.91; N, 16.23; O, 3.71. Found: C, 75.38; H, 4.98; N, 16.42; O, 3.65.

*8-(3,4-Dichlorophenyl)-3-methyl-6-phenyl-1H-pyrrolo[2,3-d]-[1,2,4] triazolo[4,3-a]pyrimidin-5(8H)-one (**11b**)*

Yield 42%, m.p. 170–173°C. IR (KBr) ν (cm^{-1}): 1675 (C=O). MS (EI) *m/z* (%): 410 (M^+, ^{35}Cl, 20%), 412 (M^++2, ^{37}Cl, 8.2%), 414 (M^++4, 2 (^{37}Cl), 2.1%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.56 (s, 3H, CH_3), 6.8 (s, 1H, C_6-H), 7.1–7.9 (m, 8H, Ar-H), 9.15 (s, 1H, NH, pyrazole), 10.8 (s, 1H, NH, pyrimidine). Anal. calcd. for $C_{20}H_{13}Cl_2N_5O$ (410.256): C, 58.55; H, 3.19; Cl, 17.28; N, 17.07; O, 3.90. Found: C, 58.82; H, 3.51; Cl, 17.06; N, 17.39; O, 3.75.

Biological assay

Anti-inflammatory activity

Animals

70 adult male Sprague-Dawley rats (5 rats per group), weighing 150–170 g, were housed in cages in a temperature-controlled (25 ± 1°C) environment and provided free access to pelleted food and purified drinking water *ad libitum*. The animal experiments described below comply with the ethical principles and guidelines for the care and use of laboratory animals adopted by the National Egyptian Community.

Assessment of anti-inflammatory activity

Rat paw edema assay was carried out according to Winter *et al.* [32]. Prepared compounds (equimolar to the reference drug) were dissolved in DMSO and administrated subcutaneously. One hour later, paw edema was induced by subplantar injection of 0.1 ml of 1% carrageenan (Sigma-Aldrich, St. Louis, USA) into the right hind paw. Paw volume was measured using a water plethysmometer (Basile, Comerio, Italy). The difference between the right and left paw volume was measured at 1, 2, 3 and 4 h after induction of inflammation. Control group (five rats per group) received DMSO subcutaneously and carrageenan in subplantar region. Results were expressed as percentage inhibition of inflammation. Ibuprofen (70 mg/kg) was used as the reference drug [33].

Statistical analysis

Results are expressed as the mean ± SEM, and different groups were compared using one way analysis of variance (ANOVA) followed by Tukey-Kramer test for multiple comparisons, using GraphPad Instant (version 3.05) as the statistical software to calculate the statistics (Table 1).

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