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EVALUATION OF THE ANTI-INFLAMMATORY ACTIVITY OF NOVEL SYNTHESIZED PYRROLE, PYRROLOPYRIMIDINE AND SPIROPYRROLOPYRIMIDINE DERIVATIVES

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ABSTRACT

Some new pyrrole, pyrrolo[2,3-d]pyrimidine and spiro pyrrolo[2,3-d]pyrimidine derivatives were synthesized and identified by IR, ^{1}H NMR, MS and elemental analysis. Most of the newly synthesized compounds were tested for their *in vivo* anti-inflammatory activity. Among them, compounds 4a-d, 5b-d and 8d are active compared to the activity of ibuprofen.

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

INTRODUCTION

It was reported that pyrroles and pyrrolo[2,3-d]pyrimidines possess anti-microbial [1-9], analgesic [10], anti-inflammatory [11-13], antiviral [14,15], anti-cancer [16-22], anti-hyperglycemic [23,24] and anticonvulsant activities.[25,26]

It is well known that the anti-inflammatory activity is due to the ability to inhibit the cyclooxygenase (COX) activity of prostaglandin H synthase, an enzyme which mediates the production of prostanoids (including prostaglandins, prostacyclins and thromboxanes) from arachidonic acid, prostaglandins act as mediator in the process of inflammation. This mechanism of action was elicited [27-29]. Tolmetin and Ketorolac [13,30] are well known pyrrole derivatives acting as anti-inflammatory drugs (Figure1), PNU-142731A [31], (Figure1), 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. In continuance to our previous work [32,33] we decided to prepare certain novel pyrrole and pyrrolopyrimidine derivatives and evaluate them for anti-inflammatory activity.

MATERIALS AND METHODS

Chemistry

The synthetic route to compounds 1a-1d is reported.33 Pyrroles 1a-1d reacted with formic acid to yield pyrrolo[2,3-d]pyrimidin-4(3H)-ones 2a-2d, and these reacted with phosphorus oxychloride to afford 4-chloro-pyrrolo[2,3-d]pyrimidines 3a-3d which were converted to pyrrolo[2,3-d]pyrimidin-4(3H)-thiones 4a-

4d by reaction with thiourea in refluxing ethanol as revealed in scheme 1 and this was reported as our previous work.[33]

Preparation of pyrrolo[2,3-d]pyrimidin-4-ylidene-malononitrile 5a-d was accomplished by the reaction of 4a-d with malononitrile in absolute ethanol, treatment of 5a-d with hydrazine hydrate, guanidine hydrochloride or acetylacetone in ethanol in the presence of pyridine[34] afforded the corresponding spiropyrrolo[2,3-d]pyrimidine derivatives of pyrazole, pyrimidine or pyran 6a,b-9b-d as revealed in scheme 2.

Reagents, Instrumentation and Measurements

All commercial chemicals used as starting materials and reagents in this study were purchased from Merck (Darmstadt, Germany) and were of reagent grade. All melting points were uncorrected and measured using Electro-thermal 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. 1H- 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-d- 4a-d were prepared before 33, the other synthesized compounds are new and confirmed with spectral data

Synthesis

General procedure for the synthesis of compounds 5a-5d

Compound 4a-d (0.01 mol) and malononitrile (0.66 g, 0.01 mol) was heated under reflux in dry ethanol (30 mL) for 8 h, cooled, poured onto ice-water to give precipitate which was filtered off, dried, and recrystallized from methanol to give 5a-5d.

2-(7-(4-Methoxyphenyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylidene)-malononitrile (5a)

Yield: 70%; m.p.: 202-204 °C; IR (KBr) υ (cm^{-1}): 3362 (N-H), 2226 (C≡N), 1567 (C=N), 1271 (C-O); MS (EI) m/z:365 (M^+, 35%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 3.42 (s, 3H, OCH_3), 6.8-8.0 (m, 10H, Ar-H), 8.3 (s, 1H, C2-H), 8.9 (s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{22}H_{15}N_5O$ (365.4): C, 72.42; H, 5.02; N, 18.36; O, 4.38%. Found: C, 72.68; H, 5.09; N, 18.71; O, 4.71%.

2-(7-(4-Methylphenyl)-5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylidene)-malononitrile (5b)

Yield: 61%; m.p.: 194-196 °C; IR (KBr) υ (cm^{-1}): 3298 (N-H), 2209 (C≡N), 1608 (C=N); MS (EI) m/z:349 (M^+, 7.9%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 2.75 (s, 3H, CH_3), 6.5-7.8 (m, 10H, Ar-H), 8.1 (s, 1H, C2-H), 9.0 (s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{22}H_{15}N_5$ (349.4): C, 75.60; H, 5.24; N, 19.16%. Found: C, 75.31; H, 5.35; N, 18.92%.

2-(7-(4-Methoxyphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylidene)-malononitrile (5c)

Yield: 67%; m.p.: 212-214 °C; IR (KBr) υ (cm^{-1}): 3325 (N-H), 2210 (C≡N), 1546 (C=N), 1249 (C-O); MS (EI) m/z:441 (M^+, 21%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 3.66 (s, 3H, OCH_3), 6.6-7.9 (m, 14H, Ar-H), 8.65 (s, 1H, C2-H), 8.74 (s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C2_8H_{19}N_5O$ (441.50): C, 76.18; H, 4.34; N, 15.86; O, 3.62%. Found: C, 76.35; H, 4.26; N, 15.98; O, 3.77%.

2-(7-(4-Methylphenyl)-5,6-diphenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylidene)-malononitrile (5d)

Yield: 56%; m.p.: 201-203 °C; IR (KBr) υ (cm^{-1}): 3336 (N-H), 2214 (C≡N), 1588 (C=N); MS (EI) m/z:425 (M^+, 15.3%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 2.34 (s, 3H, CH_3), 6.7-7.8 (m, 14H, Ar-H), 8.0 (s, 1H, C2-H), 9.3 (s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{28}H_{19}N_5$ (425.5): C, 79.04; H, 4.50; N, 16.64%. Found: C, 78.85; H, 4.63; N, 16.75%.

General procedure for the synthesis of compounds 6b-6d

A mixture of compound 5b-d (0.02 mol), hydrazine hydrate (0.64g, 0.02 mol) and pyridine (6-8 drops) was heated under reflux in dry ethanol (50 mL) for 8 h, concentrated, cooled, and the separated compound was filtered off and recrystallized from methanol to give 6b-6d.

3-Amino-7'-(4-Methylphenyl)-5'-phenyl-3',7'-dihydro-4H-spiro[pyrazole-5,4'-pyrrolo[2',3'-d]pyrimidine]-4-carbonitrile (6b)

Yield: 69%; m.p.: 222-224 °C; IR (KBr) υ (cm^{-1}): 3217-3398 (N-H), 2216 (C≡N), 1646 (C=N); MS (EI) m/z:381 (M^+, 23.1%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 2.36 (s, 3H, CH_3), 4.1(s, 1H, C-4H), 5.8(s, 2H, NH_2,D_2O exchangeable),6.9-7.9 (m, 11H, Ar-H + NH), 8.2 (s, 1H, C-2' H), 8.78(s,1H, NH, D_2O exchangeable); Anal. Calcd for $C_{22}H1_9N_7$ (381.44): C, 69.29; H, 4.98; N, 25.72%. Found: C, 69.59; H, 4.68; N, 26.01%.

3-Amino-7'-(4-Methoxyphenyl)-5',6'-diphenyl-3',7'-dihydro-4H-spiro[pyrazole-5,4'-pyrrolo[2',3'-d]pyrimidine]-4-carbonitrile (6c)

Yield: 62%; m.p.: 233-235 °C; IR (KBr) υ (cm^{-1}): 3130-3349 (N-H), 2227 (C≡N), 1612 (C=N), 1256 (C-O); MS (EI) m/z:473 (M^+, 4%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 3.5(s, 3H, OCH_3), 4.3(s, 1H, C-4H), 5.44(s, 2H, NH_2,D_2O exchangeable),7.0-8.1 (m, 15H, Ar-H + NH), 8.4 (s, 1H, C-2' H), 9.02(s,1H, NH, D_2O exchangeable); Anal. Calcd for $C_{28}H_{23}N_7O$ (473.32): C, 71.03; H, 4.86; N, 20.72; O, 3.38%. Found: C, 70.85; H, 4.59; N, 20.98; O, 3.61%.

3-Amino-7'-(4-Methylphenyl)-5',6'-diphenyl-3',7'-dihydro-4H-spiro[pyrazole-5,4'-pyrrolo[2',3'-d]pyrimidine]-4-carbonitrile (6d)

Yield: 53%; m.p.: 241-243 °C; IR (KBr) υ (cm^{-1}): 3234-3445 (N-H), 2205 (C≡N), 1633 (C=N); MS (EI) m/z:457 (M^+, 12.98%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 2.21 (s, 3H, CH_3), 3.4(s, 1H, C-4H), 4.24(s, 2H, NH_2,D_2O exchangeable), 6.8-7.8 (m, 15H, Ar-H + NH), 8.3 (s, 1H, C-2' H), 8.8(s,1H, NH, D_2O exchangeable); Anal. Calcd for $C_{28}H_{23}N_7$ (457.54): C, 73.52; H, 5.03; N, 21.44%. Found: C, 73.52; H, 4.87; N, 21.17%.

General procedure for the synthesis of compounds 7c, 7d

A mixture of compound 5c, d (0.02 mol), acetylacetone (2g, 0.02 mol) and pyridine (6-8 drops) was heated under reflux in dry ethanol (50 mL) for 8 h, concentrated, cooled, and the separated compound was filtered off and recrystallized from methanol to give 7c, 7d.

3-Acetyl-4-amino-2-methyl-7'-(4-Methoxyphenyl)-5',6'-diphenyl-3',7'-dihydro-4H-spiro[pyran-pyrrolo[2',3'-d]pyrimidine]-5-carbonitrile (7c)

Yield: 74%; m.p.: 223-225 °C; IR (KBr) υ (cm^{-1}): 3205-3332 (N-H), 2194 (C≡N), 1616 (C=O), 1558 (C=N), 1261 (C-O); MS (EI) m/z:541 (M^+, 4%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 2.24(s, 3H, C2-CH_3),2.27(s, 3H, $COCH_3$), 3.8(s, 3H, OCH_3), 4.79(brs,2H, NH_2, D_2O exchangeable), 6.9-7.7 (m, 14H, Ar-H, D_2O exchangeable), 8.3(s, 1H, C2'- H). 8.85(s,1H, NH, D_2O exchangeable); Anal. Calcd for $C3_3H_{27}N_5O_3$ (541.32): C, 73.19; H, 4.99; N, 12.93; O, 8.87%. Found: C, 72.89; H, 5.22; N, 12.69; O, 8.55%.

3-Acetyl-4-amino-2-methyl-7'-(4-Methylphenyl)-5',6'-diphenyl-3',7'-dihydro-4H-spiro[pyran-pyrrolo[2',3'-d]pyrimidine]-5-carbonitrile (7d)

Yield: 61%; m.p.: 225-227 °C; IR (KBr) υ (cm^{-1}): 3251-3384 (N-H), 2207 (C≡N), 1648 (C=O), 1632 (C=N); MS (EI) m/z:525 (M^+, 20.62%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 2.2(s, 3H, C2-CH_3),2.31(s, 3H, $COCH_3$), 2.38(s, 3H, CH_3), 5.2(brs,2H, NH_2, D_2O exchangeable), 6.8-79 (m, 14H, Ar-H, D_2O exchangeable), 8.1(s, 1H, C2'- H). 9.0(s,1H, NH, D_2O exchangeable); Anal. Calcd for $C_{33}H_{27}N_5O_2$ (525.62): C, 75.43; H, 5.14; N, 13.33; O, 6.09%. Found: C, 75.59; H, 4.98; N, 13.61; O, 5.75%.

General procedure for the synthesis of compounds 8b-8d

A mixture of compound 5b-d (0.02 mol), guanidine (1.18g, 0.02 mol) and pyridine (6-8 drops) was heated under reflux in dry ethanol (50 mL) for 8 h, concentrated, cooled, and the separated compound was filtered off and recrystallized from methanol to give 8b-8d.

2,6-Diamino-7'-(4-Methylphenyl)-5'-phenyl -3',7'-dihydro-3H-spiro [pyrimidine-4,4'-pyrrolo[2',3'-d]pyrimidine]-5-carbonitrile (8b)

Yield: 39%; m.p.: 209-211 °C; IR (KBr) υ (cm^{-1}): 3262-3409 (N-H), 2221 (C≡N), 1623 (C=N); MS (EI) m/z:408 (M^+, 56.8%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 2.26 (s, 3H, CH_3), 4.3-4.7 (brs, 4H,2NH_2, D_2O exchangeable), 6.8-7.9 (m, 11H, Ar-H + NH), 8.2 (s, 1H, C2'-H), 8.9 (s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{23}H_{20}N_8$ (500.47): C, 67.91; H, 5.70; N, 26.40%. Found: C, 67.76; H, 5.98; N, 26.62%.

2,6-Diamino-7'-(4-Methoxyphenyl)-5',6'-diphenyl -3',7'-dihydro-3H-spiro [pyrimidine-4,4'-pyrrolo[2',3'-d]pyrimidine]-5-carbonitrile (8c)

Yield: 43%; m.p.: 226-228 °C; IR (KBr) υ (cm^{-1}): 3163-3340 (N-H), 2214 (C≡N), 1651 (C=N), 1253 (C-O); MS (EI) m/z:500 (M^+, 30%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 3.76 (s, 3H, OCH_3), 4.2-4.6 (brs, 4H,2NH_2, D_2O exchangeable), 7.0-7.5 (m, 15H, Ar-H + NH), 8.06 (s, 1H, C2'-H), 8.9 (s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{29}H_{24}N_8O$ (500.04): C, 69.60; H, 4.80; N, 22.40; O, 3.20%. Found: C, 69.35; H, 5.06; N, 22.65; O, 3.56%.

2,6-Diamino-7'-(4-Methylphenyl)-5',6'-diphenyl -3',7'-dihydro-3H-spiro [pyrimidine-4,4'-pyrrolo[2',3'-d]pyrimidine]-5-carbonitrile (8d)

Yield: 31%; m.p.: 231-233 °C; IR (KBr) υ (cm^{-1}): 3214-3335 (N-H), 2208 (C≡N), 1634 (C=N), MS (EI) m/z:484 (M^+, 5.25%), ^{1}H NMR (DMSO-d6, 300 MHz) δ (ppm): 2.3 (s, 3H, CH_3), 4.05-4.4 (brs, 4H,2NH_2, D_2O exchangeable), 6.9-7.8 (m, 15H, Ar-H + NH), 8.12 (s, 1H, C2'-H), 8.95 (s, 1H, NH, D_2O exchangeable); Anal. Calcd for $C_{29}H_{24}N_8$ (484.57): C, 71.88; H, 4.99; N, 23.12%. Found: C, 72.03; H, 4.61; N, 23.47%.

ANTI-INFLAMMATORY ACTIVITY

Animals

Young adult male Sprague-Dawley rats (5 rats per group), weighing 140-170g, were housed at 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. [35] 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 [36].

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.

RESULTS AND DISCUSSION

Most of the synthesized compounds were tested for their anti-inflammatory activity. As indicated in Table 1: compounds 4b, 5b and 5c induced a good anti-inflammatory activity at both 3h and 4h interval post carrageenan, comparable with that of ibuprofen and their activity profiles were the same as ibuprofen (response increasing by time). Compounds 5b and 5c exerted a stronger anti-inflammatory effect than ibuprofen (73.54% and 79.42% inhibition respectively at 4 h interval post carrageenan). Likewise, compound 4c showed a significantly higher inhibitory action than ibuprofen at the 4 h interval (69.84% inhibition). Compound 5d also showed significant anti-inflammatory activity at 4h interval but less than ibuprofen (52.38%) and compound 8d showed significant activity at 3h interval post carrageenan also less than ibuprofen (50.36%). Compound 4d showed no activity at 1h and 2h intervals post-carrageenan injection. Yet, it exerted stronger action than Ibuprofen at the 4h post-carrageenan (80.16% inhibition). Also Compound 4a showed no activity at 1h and 2h intervals post-carrageenan injection. But it exerted significant anti-inflammatory activity less than Ibuprofen at the 4h post-carrageenan (53.96% inhibition).

CONCLUSION

In the present study, we described a straightforward and efficient synthesis of novel pyrrole, pyrrolo[2,3-d]pyrimidine and spiro pyrrolo[2,3-d]pyrimidine derivatives as anti-inflammatory agents. To analyze structure-activity relationships, the four pyrrole derivatives 1a-d showed no activity as anti-inflammatory agents, by converting them to pyrrolopyrimidin-4-one derivatives (2a-d) also no anti-inflammatory activity appeared. Introduction of thione group at position 4 of the pyrrolopyrimidine derivatives causes higher activity for compounds 4a-d. Formation of pyrrolopyrimidine-4-ylidine-malononitriles (5a-d) causes an increase in the activity of 5b and 5c but decreases that of 5a and 5d. Converting of pyrrolopyrimidine-4-ylidine-malononitriles to spiro pyrrolo- pyrimidine derivatives (6-8) causes loss of their activity except for spiro[pyrimidine-pyrrolo[2,3-d]pyrimidine] 8d.Some of the synthesized pyrrolopyrimidine compounds are promising anti-inflammatory agents.

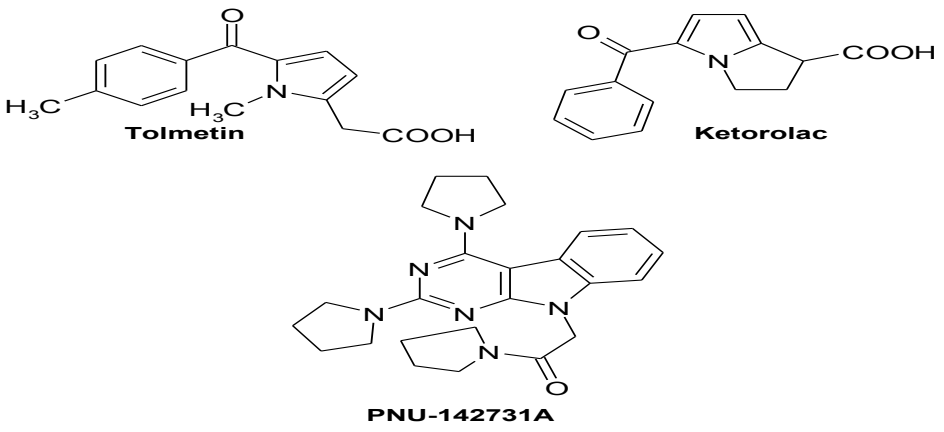


Figure 1: Structures of some anti-inflammatory drugs

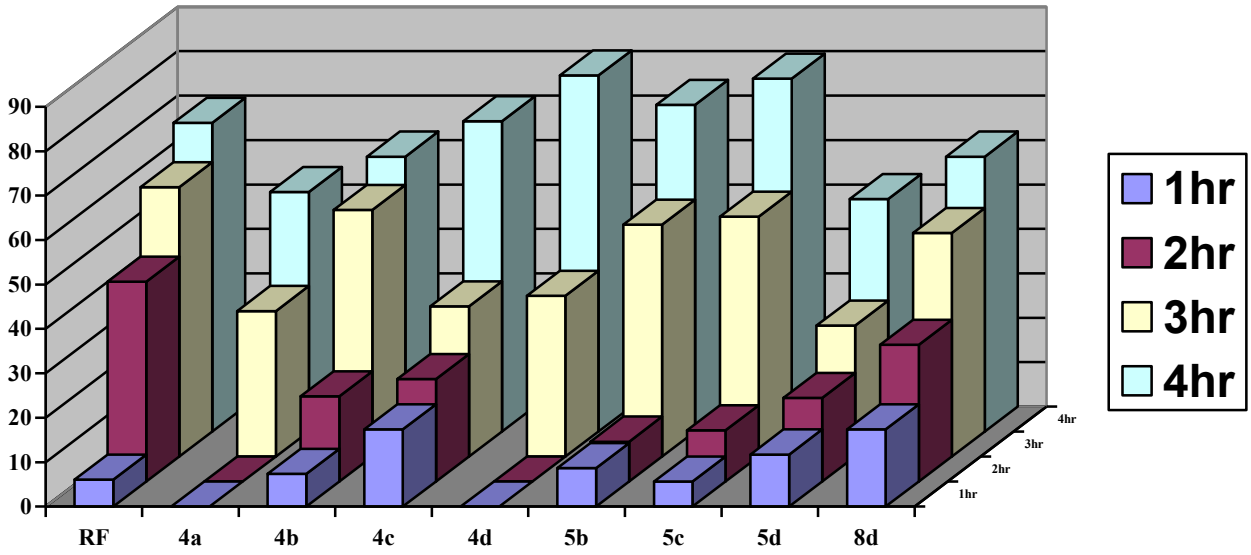
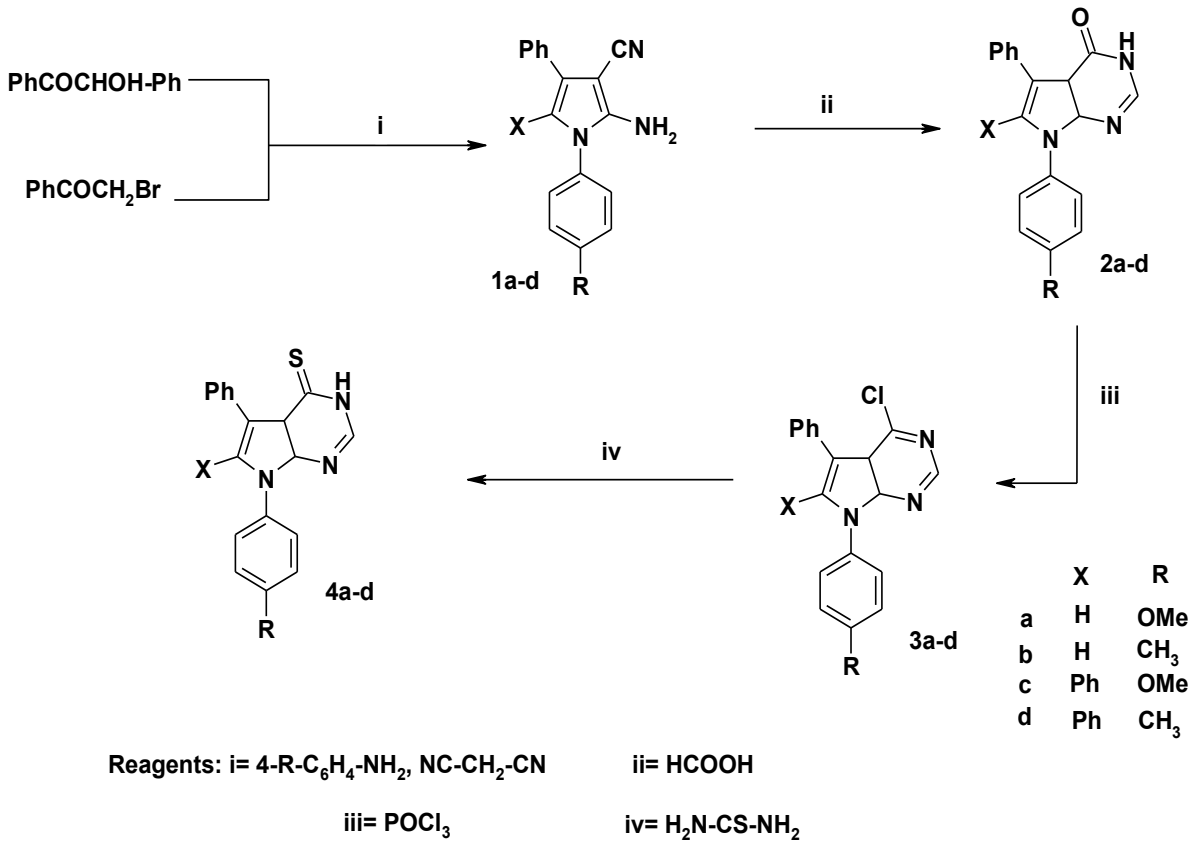
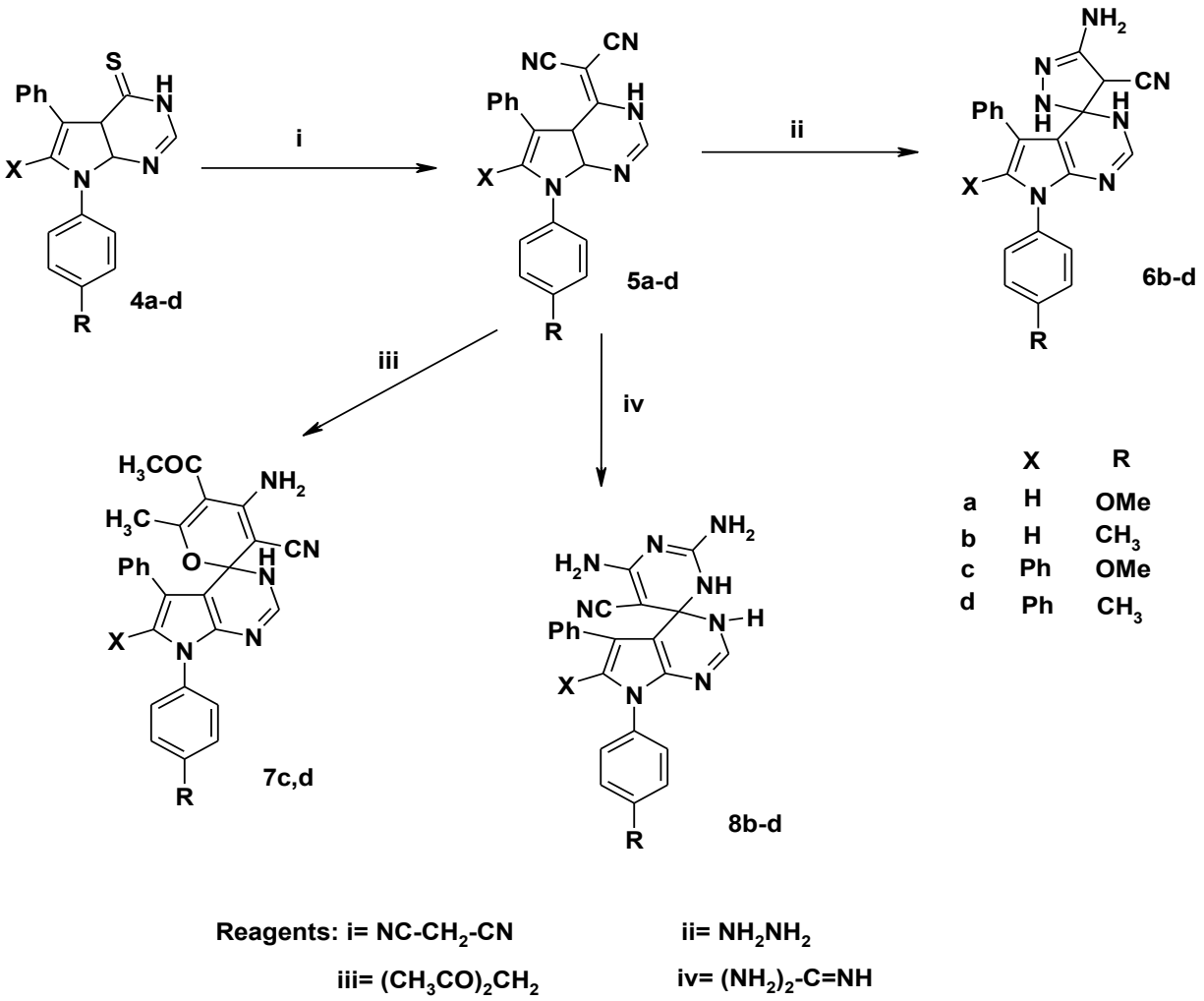


Figure 2: Anti-inflammatory effect of active compound (% inhibition) compared to ibuprofen as reference drug



Scheme 1: Synthesis of compounds 1a-d- 4a-d



Scheme 2: Synthesis of compounds 5a-d- 8b-d

Table 1: *In vivo* anti-inflammatory activity

Compounds	Oedema induced by carrageenan (% Oedema inhibition relative to control)							
	1h		2h		3h		4h	
	Swel ± SE	% inh	Swel ± SE	% inh	Swel ± SE	% inh	Swel ± SE	% inh
1a	0.199 ±0.022	13.4	0.249 ±0.041	4.23	0.365 ±0.033	32.84	0.497 ±0.002	21.06
1b	0.419 ±0.082	0	0.497 ±0.077	0	0.353 ±0.099	35.11	0.322 ±0.035	48.89
1c	0.227 ±0.018	1.45	0.255 ±0.062	1.92	0.374 ±0.027	32.84	0.537 ±0.042	14.76

1d	0.223 ±0.017	3.04	0.231 ±0.073	11.15	0.373 ±0.029	31.43	0.452 ±0.075	28.59
2a	0.2 ±0.0165	13.04	0.21 ±0.043	19.23	0.338 ±0.039	37.87	0.27 ±0.027^{a***}	57.46
2b	0.45 ±0.076	0	0.477 ±0.076	0	0.56 ±0.067	0	0.409 ±0.013	35.08
2c	0.18 ±0.026	21.74	0.243 ±0.062	6.54	0.376 ±0.036	30.88	0.361 ±0.048	42.7
2d	0.22 ±0.063	4.78	0.239 ±0.083	8.08	0.392 ±0.014	27.94	0.45 ±0.053	28.57
4a	0.54 ±0.036	0	0.46 ±0.0229	0	0.366 ±0.045	32.78	0.29 ±0.02 ^{a,b**}	53.96
4b	0.213 ±0.055	7.39	0.21 ±0.018	19.23	0.24 ±0.019 ^{a,b*}	55.5	0.24 ±0.04 ^{a,b**}	61.9
4c	0.19 ±0.016	17.39	0.2 ±0.037	23.08	0.36 ±0.048	33.8	0.19 ±0.08 ي5^{a,b**}	69.84
4d	0.34 ±0.019	0	0.352 ±0.034	0	0.347 ±0.039	36.2	0.13 ±0.026 ^{a,b***}	80.16
5a	0.456 ±0.052	0	0.415 ±0.067	0	0.362 ±0.073	33.46	0.35 ±0.025	44.44
5b	0.21 ±0.048	8.7	0.237 ±0.006	9	0.26 ±0.046 ^{a,b*}	52.2	0.17 ±0.03 ^{a,b***}	73.54
5c	0.217 ±0.022	5.65	0.23 ±0.087	11.54	0.25 ±0.010 ^{a,b*}	54	0.13 ±0.04 ^{a,b***}	79.42
5d	0.203 ±0.028	11.74	0.211 ±0.037	18.85	0.383 ±0.02	29.5	0.3 ±0.017 ^{a,b***}	52.38
6c	0.193 ±0.042	15.94	0.217 ±0.066	16.54	0.397 ±0.068	27.8	0.403 ±0.037	35.98
6d	0.41 ±0.028	0	0.44 ±0.077	0	0.46 ±0.089	15.44	0.423 ±0.087	32.8
7c	0.273	0	0.447	0	0.547	0	0.4	36.5

	±0.033		±0.029		±0.012		±0.039	
7d	0.227 ±0.021	1.45	0.233 ±0.008	10.38	0.44 ±0.013	18.5	0.4 ±0.041	36.5
8c	0.273 ±0.017	0	0.3 ±0.016	0	0.437 ±0.062	19.7	0.36 ±0.013	42.85
8d	0.19 ±0.055	17.39	0.18 ±0.037	30.77	0.27 ±0.035 a,b*	50.36	0.24 ±0.026 a***	61.9
Ibuprofen	0.216 ±0.034	6.08	0.1425 ±0.031	45	0.214 ±0.024	60.66	0192 ±0.012	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, b: Significantly different from ibuprofen as indicated: *P < 0.01; **P < 0.001
- Swel = swelling, SE = Standard Error, %inh = % inhibition

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