Synthesis and Pharmacological Evaluation of Some Pyrazoles, Thiazolopyrimidine, Triazolopyrimidine, Pyridone and 2-Iminochromene Containing Naproxenoyl Moiety as NSAIDs

***MA Salem[1], HKH Thabet[1], MH Helal[1], AS Abdelaal[1], YA Ammar[2]**

[1]Al-Azhar University, Faculty of Science, Department of Chemistry, Nasr City, Cairo, Egypt.
[2]King Khalid University, Faculty of Science, Department of Chemistry, Abha, Saudi Arabia.

*Correspondence to: MA Salem, m_eltayyeb@hotmail.com

Accepted: May 12, 2011; Published: August 30, 2011

Abstract

Some novel pyrazoles, thiazolopyrimidine, triazolopyrimidine derivatives containing naproxenoyl moiety were synthesized from the reaction of enaminone derivative **2** with some hydrazines and aminoheterocyclic compounds. Also, some thiazoles were obtained via condensation of acetyl derivative **1** with thiosemicarbazide followed by *in situ*heterocyclization with α-halogenated reagents. Most of the target compounds were then evaluated for their animal toxicity, analgesic and anti-inflammatory activities as NSAIDs.

Keywords: Naproxenoylchloride; enaminone; pyrazoles; thiazolopyrimidine; pyridine;analgesic and anti-inflammatory activities.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed classes of medications worldwide. Aspirin, naproxen and other chemically related compounds, used systemically for many decades for their analgesic, antipyretic, and anti-inflammatory properties, have more recently been prepared in topical ophthalmic formulation. As such, they have proven useful to enhance mydriasis, reduce post-operative inflammation, prevent and treat cystoids macular oedema (CME) associated with cataract surgery. In addition, they can be used to decrease pain and photophobia after refractive surgery and to alleviate itching associated with allergic conjunctivitis [1-5]. Prompted by these observations and as continuation of our research program directed towards the development of a new, simple and efficient procedure for the synthesis of biologically active heterocyclic compounds [6-10], we report herein the synthesis of the versatile, hitherto unknown, compounds containing asymmetric carbon atom using accessible *N*-(4-acetylphenyl)-2-(6-methoxynaphthalen-2-yl) propanamide **(1)** and simple experimental procedures.

2. Methods

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm-^{1}). The ^{1}HNMR spectra were recorded in DMSO-d_6 at 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analyses were carried out by the Microanalytical Research Centre, Faculty of Science, Cairo University.

***N*-(4-acetylphenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (1)**

Equimolar amounts of naproxenoyl chloride (0.01 mole) and p-aminoacetophenone (0.01 mole) with a few drops of triethylamine in xylene (30 mL) were refluxed for 3h, then allowed to cool. The solid product was collected and recrystallized from ethanol to give **1**. m.p. 168-170ºC, IR spectrum νmax /cm^{-1}; 3332 (NH), 2928 (CH-aliph.) and 1672 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.51 (d, 3H, CH_3), 2.37 (s, 3H, $COCH_3$), 3.99 (s, 3H, OCH_3), 4.01(q, 1H, CH), 7.26-7.91 (m, 10H, Ar-H), 10.42 ppm (s, 1H, NH); MS: m/z = 347 (M^+), 185 (100%), 141 (43%) and 63 (25%). Anal. Calc. for $C_{22}H_{21}NO_3$ (347.41): C, 76.06; H, 6.09; N, 4.03. Found: C, 76.30; H, 6.19; N, 4.28.

N-(4-(3-(dimethylamino) acryloyl) phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (2)

Equimolar amounts of compound **1** (0.01 mole) and dimethylformamide-dimethylacetal (DMF-DMA) (0.01 mole) in xylene (30 mL) were refluxed for 3h, and then allowed to cool. The solid product was collected and recrystallized from benzene to give **2**. m.p. 119-120ºC, IR spectrum νmax /cm^{-1}; 3318 (NH), 2936 (CH-aliph.)

and 1660 (C═O). ^{1}HNMR (DMSO-d_6): δ = 1.51 (d, 3H, CH_3), 2.88, 3.09 (2s, 6H, $N(CH_3)_2$), 3.99 (s, 3H, OCH_3), 4.01 (q, 1H, asymmetric-H), 5.77, 7.15 (dd, 2H, olefinic CH=CH; J = 12 Hz), 7.26-7.91 (m, 10H, Ar-H) and 10.42 (s, 1H, NH). MS: m/z = 402 (M^+), 185 (100%). Anal. Calc. for $C_{25}H_{26}N_2O_3$ (402.49): C, 74.60; H, 6.51; N, 6.96. Found: C, 74.46; H, 6.30; N, 6.58.

N-(4-(1-acetyl-1H-pyrazol-3-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (4)
Equimolar amounts of enaminone derivative **2** (0.01 mole) and hydrazine hydrate (0.01 mole) in ethanol/acetic acid (10 ml: 10 ml) were refluxed for 3h, and then allowed to cool. The solid product was collected and recrystallized from ethanol to give **4**. m.p. 256-258ºC, IR spectrum vmax/cm^{-1}; 3298 (NH), 2941 (CH-aliph.) and 1658 (C═O). ^{1}HNMR (DMSO-d_6): δ = 1.52 (d, 3H, CH_3), 2.24 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 4.00 (q, 1H, asymmetric-H), 7.13, 7.53 (dd, 2H, pyrazol-H_4, H_5), 7.26-7.86 (m, 10H, Ar-H) and 10.25 (s, 1H, NH). Anal. Calc. for $C_{25}H_{23}N_3O_3$ (413.47): C, 72.62; H, 5.61; N, 10.16. Found: C, 72.39; H, 5.38; N, 9.92.

2-(6-Methoxynaphthalen-2-yl)-N-(4-(1-phenyl-1H-pyrazol-3-yl)phenyl)-propanamide (5)
Equimolar amounts of enaminone derivative **2** (0.01 mole) and phenylhydrazine (0.01 mole) in ethanol/acetic acid (10 ml: 10 ml) were refluxed for 3h, and then allowed to cool. The solid product was collected and recrystallized from ethanol to give **5**. m.p. 205-207ºC, IR spectrum vmax /cm^{-1}; 3314 (NH), 3000 (CH-arom.), 2950 (CH-aliph.) and 1656 (C═O). MS: m/z 447 (M^+), 361 (55%), 141 (43%), 77 (100%) and 63 (25%). Anal. Calc. for $C_{29}H_{25}N_3O_2$ (447.53): C, 77.83; H, 5.63; N, 9.39.Found: C, 77.68; H, 5.30; N, 9.08.

N-(4-([1,2,4]triazolo[4,3-a]pyrimidin-5-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (7)
Equimolar amounts of enaminone derivative **2** (0.01 mole) and 2-aminotriazole (0.01 mole) in ethanol/acetic acid (10 ml: 10 ml) were refluxed for 3h, and then allowed to cool. The solid product was collected and recrystallized from ethanol to give **7**. m.p. 160-162ºC, IR spectrum vmax /cm^{-1}; 3330 (NH), 3050 (CH-arom.), 2926 (CH-aliph.) and 1670 (C═O). ^{1}HNMR (DMSO-d_6): δ = 1.50 (d, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.00 (q, 1H, asymmetric-H), 7.16-7.91 (m, 10H, Ar-H), 8.25, 8.95 (dd, 2H, pyrmidin-H5, H6), 8.85 (s, 1H, triazol-H) and 10.41 (s, 1H, NH). Anal. Calc. for $C_{25}H_{21}N_5O_2$ (423.47): C, 70.91; H, 5.00; N, 16.54. Found: C, 70.66; H, 4.72; N, 16.22.

N-(4-(8aH-thiazolo[3,2-a]pyrimidin-5-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (8)
Equimolar amounts of enaminone derivative 2 (0.01 mole) and 2-aminothiazole (0.01 mole) in ethanol/acetic acid (10 ml: 10 ml) were refluxed for 3h. The solid product was collected on heating and recrystallized from dioxane to give **8**. m.p. 195-197ºC, IR spectrum vmax /cm^{-1}; 3290 (NH), 3050 (CH-arom.), 2956 (CH-aliph.) and 1652 (C═O). ^{1}HNMR (DMSO-d_6): δ = 1.52 (d, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.00 (q, 1H, asymmetric-H), 6.25, 6.65 (dd, 2H,thiazol-H4, H5), 7.55, 8.15 (dd, 2H, pyrimidine H_4, H_5), 7.12-7.90 (m, 11H, Ar-H + pyrimidine H2) and 10.37 (s, 1H, NH). Anal. Calc. for $C_{26}H_{23}N_3O_2S$ (441.54): C, 70.72; H, 5.25; N, 9.52. Found: C, 70.57; H, 4.86; N, 9.40.

N-(4-(9aH-pyrido[1,2-a]pyrimidin-4-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (9)
Equimolar amounts of enaminone derivative **2** (0.01 mole) and 2-aminopyridine (0.01 mole) in ethanol/acetic acid (10 ml: 10 ml) were refluxed for 3h. The solid product was collected on heating and recrystallized from dioxane to give **9**. m.p. 205-207ºC, IR spectrum vmax /cm-1; 3270 (NH), 3000 (CH-arom.), 2950 (CH-aliph.) and 1656 (C═O). MS: m/z (%) 435 (M^+; 0.2), 402 (65), 185 (50), 141(15) and 119 (100).Anal. Calc. for $C_{28}H_{25}N_3O_2$(435.52): C, 77.22; H, 5.79; N, 9.65. Found: C, 77.05; H, 5.51; N, 9.47.

N-(4-(1-hydrazonoethyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propaneamide (11a)
A mixture of **1** (0.01 mole), hydrazine hydrate **10a** (0.01 mole) in ethanol (30 mL) was refluxed for 3h. The solid product was collected on heating and recrystallized from acetic acid to give **11a**. m.p. 285-287ºC, IR spectrum ν_{max} /cm^{-1}; 3362, 3278 (NH_2/NH), 2930 (CH-aliph.) and 1658 (C═O).^{1}HNMR (DMSO-d_6): δ = 1.50 (d, 3H, CH_3),1.97 (s, 3H, CH_3), 3.85(s, 3H, OCH_3), 4.00 (q, 1H, asymmetric-H), 6.20 (s, 2H, NH_2), 7.27-7.81 (m, 10H, Ar-H) and 10.07 (s, 1H, NH). Anal. Calc. for $C_{22}H_{23}N_3O_2$ (361): C, 73.11; H, 6.41; N, 11.63. Found: C, 72.97; H, 6.06; N, 11.46.

2-(6-Methoxynaphthalen-2-yl)-N-(4-(1-(2-phenylhydrazono)ethyl)phenyl)propanamide (11b)
A mixture of **1** (0.01 mole), phenylhydrazine**10b** (0.01 mole) in ethanol (30 mL) was refluxed for 3h. The solid product was collected on heating and recrystallized from acetic acid to give **11b**. m.p. 220-222ºC, IR spectrum vmax /cm^{-1}; 3312 (NH), 2998 (CH-aliph.) and 1658 (C═O). MS: m/z 437 (M^+), 402 (65%), 345 (5%), 224 (10%) and 185 (100%).Anal. Calc. for $C_{28}H_{27}N_3O_2$(437.53): C, 76.86; H, 6.22; N, 9.60. Found: C, 76.63; H, 5.96; N, 9.42.

N-(4-(1-(2-Carbamothioylhydrazono)ethyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (11c)
A mixture of **1** (0.01 mole), thiosemicarbazide**10c** (0.01 mole) in ethanol (30 mL) was refluxed for 3h. The solid product was collected on heating and recrystallized from acetic acid to give **11c**. m.p. 190-92ºC, IR spectrum

ν_{max} /cm^{-1}; 3312, 3236 (NH_2/NH), 2950 (CH-aliph.)and 1662 (C═O).^{1}HNMR (DMSO-d_6): δ = 1.52 (d, 3H, CH_3),2.25 (s, 3H, CH_3), 3.85(s, 3H, OCH_3), 3.99 (q, 1H, asymmetric-CH), 7.13-7.88 (m, 10H, Ar-H)8.20 (s, 2H, NH_2; cancelled with a D_2O) and 10.11, 10.20 (2s, 2H, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{23}H_{24}N_4O_2S$ (420.53): C, 65.69; H, 5.75; N, 13.32. Found: C, 65.50; H, 5.51; N, 13.12.

N-(4-(1-(2-(2-cyanoacetyl)hydrazono)ethyl)phenyl)-2-(6-methoxynathal-en-2-yl)propanamide (11d)
A mixture of **1** (0.01 mole), cyanoacetic acid hydrazide**10d** (0.01 mole) in dioxane (30 mL) was refluxed for 3h, and then allowed to cool. The solid product was collected and recrystallized from acetic acid to give **11d**. m.p.178-180ºC, IR spectrum ν_{max} /cm^{-1}; 3264 (NH), 2936 (CH-aliph.), 2260 (C≡N)and 1670 (C═O).^{1}HNMR (DMSO-d_6): δ = 1.51 (d, 3H, CH_3),2.20 (s, 3H, CH_3), 3.85(s, 3H, OCH_3), 3.99 (q, 1H, asymmetric-H), 4.20 (s, 2H, CH_2), 7.12-7.82(m, 10H, Ar-H) and 10.22, 10.93 (2s, 2H, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{25}H_{24}N_4O_3$ (428.48): C, 70.08; H, 5.65; N, 13.08. Found: C, 69.82; H, 5.41; N, 12.87.

Reaction of compound 11c with α-halocompounds (general procedure)
A mixture of compound **11c** (0.01 mole), appropriate α-halo compounds namely: ethyl chloroacetate, ethylα-bromo-propionate, ethylα-bromobutyrate and/or chloroacetone (0.01 mole) and sodium acetate (0.01 mole) in ethanol (30 mL) was refluxed for 3h. The solid product which was produced on heating was collected and recrystallized from the proper solvent.

2-(6-Methoxynaphthalen-2-yl)-N-(4-(1-(2-(4-oxo-4,5-dihydro-thiazol-2-yl)hydrazono)ethyl)phenyl)propanamide (13). This compound was obtained in 70% yield as brown crystals (EtOH/Benzene),m.p. 245-247ºC, IR spectrum νmax /cm^{-1}; 3190 (NH), 2950 (CH-aliph.), 1730 (thiazolidinone, C═O) and 1670 (C═O). ^{1}HNMR (DMSO-d_6): δ = 1.50 (d, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.00 (q, 1H, asymmetric-CH), 7.15-7.81 (m, 10H, Ar-H) and 7.27, 10.24 (2s, 2H, 2NH). Anal. Calc. for $C_{25}H_{24}N_4O_3S$ (460.55): C, 65.20; H, 5.25; N, 12.17. Found: C, 65.10; H, 5.00; N, 12.00.

2-(6-Methoxynaphthalen-2-yl)-N-(4-(1-(2-(5-methyl-4-oxo-4,5-dihydro-thiazol-2-yl)hydrazono)ethyl)-phenyl)propanamide (15). This compound was obtained in 70% yield as brown crystals (dioxane),m.p. 260-261ºC, IR spectrum ν_{max} /cm^{-1}; 3436 (NH), 2926 (CH-aliph.) and 1726 (thiazolidinone, C═O).^{1}HNMR (DMSO-d_6): δ =1.47 (2d, 6H, $2CH_3$),2.22 (s, 3H, CH_3), 3.85(s, 3H, OCH_3), 4.05 (br, 2H, thiazol-H_5& asymmetric-CH), 7.15-7.83 (m, 10H, Ar-H) and 7.26, 10.25 (2s, 2H, 2NH). Anal. Calc. for $C_{26}H_{26}N_4O_3S$ (474.57): C, 65.80; H, 5.52; N, 11.81. Found: C, 66.00; H, 5.40; N, 11.70.

N-(4-(1-(2-(5-Ethyl-4-hydroxythiazol-2-yl) hydrazono) ethyl)-phenyl)-2-(6-methoxynaphthalen-2-yl) propanamide (18). This compound was obtained in 70% yield as brown crystals (acetic acid),m.p.220-222ºC, IR spectrum νmax /cm^{-1}; 3462 (OH), 2950 (CH-aliph.) and 1640 (C═O). ^{1}HNMR (DMSO-d_6): δ = 0.9 (t, 3H, CH_3), 1.49 (q, 3H, CH_2), 1.51 (d, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.01 (q, H, asymmetric-CH), 7.12-7.91 (m, 11H, Ar-H + NH) and 10.23, 10.59 (2s, 2H, NH & OH). Anal. Calc. for $C_{27}H_{28}N_4O_3S$ (488.60): C, 66.37; H, 5.78; N, 11.47. Found: C, 66.20; H, 5.50; N, 11.08.

2-(6-Methoxynaphthalen-2-yl)-N-(4-(1-(2-(4-methylthiazol-2-yl)hydrazono)ethyl)phenyl)propanamide(20). This compound was obtained in 70% yield as brown crystals (dioxane),m.p. 290-292ºC, IR spectrum νmax /cm^{-1}; 3298 (NH), 2936 (CH-aliph.) and 1670 (C═O). ^{1}HNMR (DMSO-d_6): δ = 1.51 (d, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.05 (q, 1H, asymmetric-CH), 7.27 (s, 1H, thiazol-H_5), 7.12-7.86 (m, 10H, Ar-H) and 10.28, 10.45 (2s, 2H, 2NH). ^{13}C NMR (DMSO-d_6): δ = 12.40, 14.30, 18.54, 40.32, 55.05, 105.4, 105.71, 118.6, 121.7, 126.1, 126.19, 128.5, 128.99, 129.4, 132.8, 133.0, 133.1, 136.79, 140.8, 156.1, 156.99, 157.25, 172.44. Anal. Calc. for $C_{26}H_{26}N_4O_2S$ (458.58): C, 68.10; H, 5.71; N, 12.22. Found: C, 68.00; H, 5.50; N, 12.00.

N-(4-(1-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2H)-ylimino)ethyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (22). Equimolar amounts of **11d** (0.01 mole) and acetyl acetone (0.01 mole) with a few drops of piperidine in an oil bath were refluxed for 1h at 160°C, then allowed to cool. The solid product was collected and recrystallized from acetic acid to give **22**. m.p. 245-247ºC, IR spectrum νmax/cm^{-1}; 3274 (NH), 2970 (CH-aliph.), 2218 (C≡N) and 1690 (C═O). ^{1}HNMR (DMSO-d_6): δ = 1.50 (d, 3H, CH_3), 2.08, 2.22, 2.36 (3s, 9H, $3CH_3$), 3.85 (s, 3H, OCH_3), 4.01 (q, 1H, asymmetric-CH), 6.43 (s, 1H, pyridine-H), 7.12-7.98 (m, 10H, Ar-H) 10.39 (s, 1H, NH).Anal. Calc. for $C_{30}H_{28}N_4O_3$(492.57): C, 73.15; H, 5.73; N, 11.37. Found: C, 72.93; H, 5.40; N, 11.00.

Formation of 2-iminochromene and 2-iminobenzochromene derivatives (23) and (24): General procedure. A mixture of compound **11d** (0.01 mole), appropriate aldehyde (salicylaldehyde or 2-hydroxynaphthaldehyde;

0.01 mole) and ammonium acetate (0.01 mole) in ethanol (30 mL) was refluxed for 1h. The solid product which produced on heating was collected and recrystallized to furnish **23** and **24**.

N-(4-(1-(2-(2-imino-2H-chromene-3-carbonyl)hydrazono)ethyl)-phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (23). This compound was obtained in 70% yield as brown crystals (dioxane), m.p. 254-256ºC, IR spectrum vmax /cm^{-1}; 3342, 3248 (NH), 2898 (CH-aliph.) and 1678 (C═O). ^{1}HNMR (DMSO-d_6): δ = 1.51 (d, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.05 (q, 1H, asymmetric-CH), 7.12-7.81 (m, 14H, Ar-H), 8.58 (s, 1H, chromene-H_4), and 9.25, 10.25, 13.49 (3s, 3H, 3NH). Anal. Calc. for $C_{32}H_{28}N_4O_4$ (532.59):C, 72.16; H, 5.30; N, 10.52. Found: C, 72.00; H, 5.05; N, 10.31.

N-(4-(1-(2-(3-imino-3H-benzo[f]chromene-2-carbonyl)hydrazono) ethyl-)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (24). This compound was obtained in 70% yield as brown crystals (dioxane),m.p. 240-243ºC, IR spectrum vmax /cm^{-1}; 3266 (NH), 2920 (CH-aliph.) and 1674 (C═O). ^{1}HNMR (DMSO-d_6): δ = 1.50 (d, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.00 (q, 1H, asymmetric-CH), 7.13-8.47 (m, 16H, Ar-H), 8.50 (s, 1H, benzo-chromene-H_4), and 9.19, 10.27, 13.45 (3s, 3H, 3NH). Anal. Calc. for $C_{36}H_{30}N_4O_4$ (582.65):C, 74.21; H, 5.19; N, 9.62. Found: C, 74.29; H, 5.30; N, 9.43.

2.1. Biological Experiments

1. **Animal toxicity study method (Spearmane Karber method)** [28] and several doses i.e. 75, 150, 300, 600, and 1200mg/kg were chosen at equal logarithmic dose interval and each dose is injected orally, 1ml oral suspension in 1% CMC (carboxymethyl cellulose) sodium salt by a stomach tube into each mice in a group of 6 animals and the number of dead animals from each dose was recorded.

2. **Analgesic screening (hot-plate method) [29]:** In this method, female albino mice (Swiss strain) were put on a hot plate with constant temperature 55ºC, the time taken by the mice to lick their feet or to jump within a cylinder placed on a hot plate surface was determined. This reaction time was taken as the end point and the increase in hot plate latency was taken as a measure of the analgesic activity. Animals which showed positive pain response (elevation of paws licking of fore-paws or jumping out of the hot plate) within 15 s were selected. Mice were divided into twelve groups, each of six animals. Five test compounds and the reference drug were injected i.p. at a dose level of 50 mg/kg into mice. Control group of animals was similarly treated with 1% CMC. The reaction time was evaluated directly after 0.5 and 1 h of injection.

3. **Anti-inflammatory screening** was done using *in vivo* carrageenan induced rat paw oedema model [29]which is considered the most conventional one for acute inflammation. Adult albino rats of both sexes weighing (120-200 gm) were randomly distributed in twelve groups of six animals each. The rats were kept fasted for 24 h prior to the experiment but allowed free access to water. The rats were injected intraperitoneally with equimolar doses (equivalent to 0.169 M/kg) of the tested compounds and reference drug (diclofenac sodium). One hour later, 0.05 ml of freshly prepared suspension of carrageenan (1% w/v in saline suspension) was injected subcutaneously into the subplantar region of the right hind paw. The left hind paw of each rat received a subplantar injection of equal volume of normal saline. Three hours after carrageenan injection, rats were killed by cervical dislocation then the right and the left hind paws of each rat were cut at the tibiotarsic articulation and weighed. The difference in weight between right and left paws was recorded for each rat. The percentage increase in weight of the carrageenan-injected paw over the other paw was calculated and percentage reduction of oedema from the control group was used as a measure of the activity.

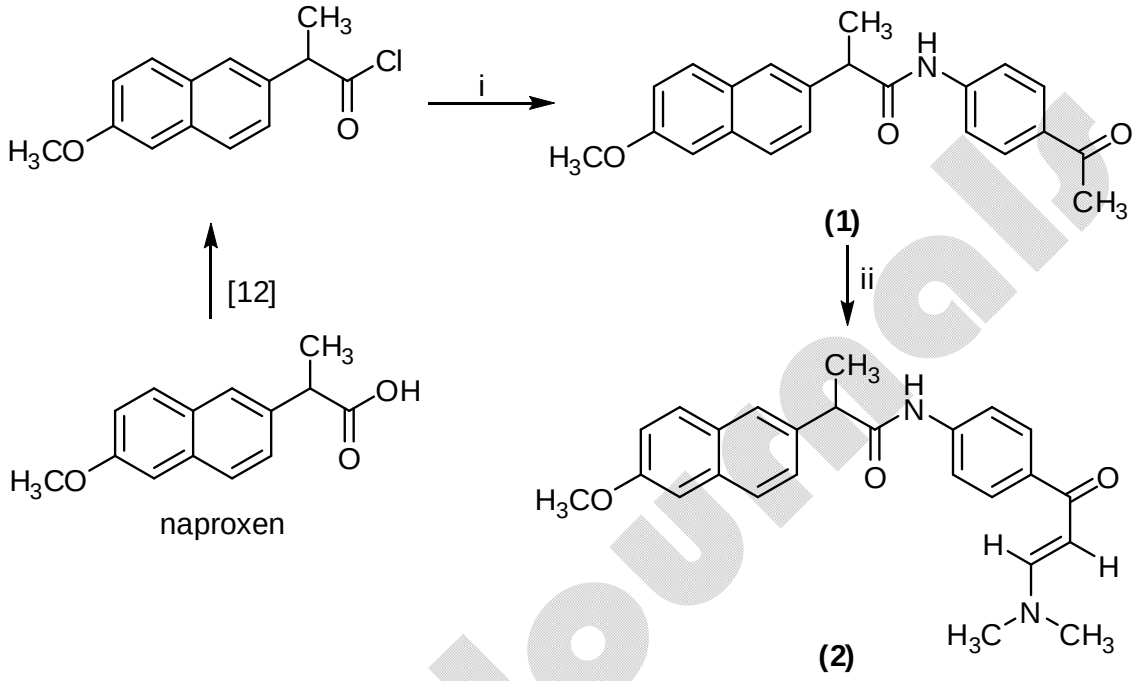
3. Results and Discussion

3.1. Chemistry

It was found that the acetyl derivative **1** was prepared by reaction of naproxenoyl chloride [11] with p-aminoacetophenone in refluxing dry *m*-xylene (scheme 1). Compound **1** was characterized by its elemental analysis and spectral data. Infrared spectrum of compound **1** revealed two characteristic absorption bands at 3332 and 1672 cm^{-1} assignable to imino and carbonyl groups, whereas its ^{1}HNMR spectrum displayed a doublet at δ 1.51 corresponding to CH_3 and quartet at δ 4.01 for asymmetric CH with three singlet at 2.37, 3.99, and 10.42 ppm for $COCH_3$, OCH_3 and NH groups. Also, in the mass spectrum of compound (**1**, $C_{22}H_{21}NO_3$) a molecular ion peak was found at m/z 347 (25%) and the base peak was observed in the spectrum at m/z 185.

Enaminones are readily obtainable reagents and constitute an interesting class of compounds that are versatile precursors for the synthesis of several heterocyclic compounds [12-14]. Thus, treatment of equimolar quantities of acetyl derivative **1** with dimethylformamide-dimethylacetal (DMF-DMA) in refluxing xylene

afforded the corresponding enaminone as *N*-(4-(3(dimethylamino)-acryloyl)-phenyl)-2-(6-methoxynaphthalen-2-yl) propanamide**(2)** (Scheme 2). The structure of the enaminone **2** was confirmed on the basis of elemental analysis and spectral data. IR spectrum of compound **2** revealed absorption bands at 3318 (NH), 2936 (CH-aliphatic) and 1660 cm^{-1} (C=O), while its ^{1}HNMR spectrum (DMSO-d_6) indicated signals at 2.88, 3.09 (2s, 6H, $N(CH_3)_2$), 5.77 and 7.15 (dd, 2H, olefinic CH=CH; J = 12Hz), (Scheme 1). Mass spectrum of this compound showed a molecular ion peak at m/z 402 with base peak at m/z 185.

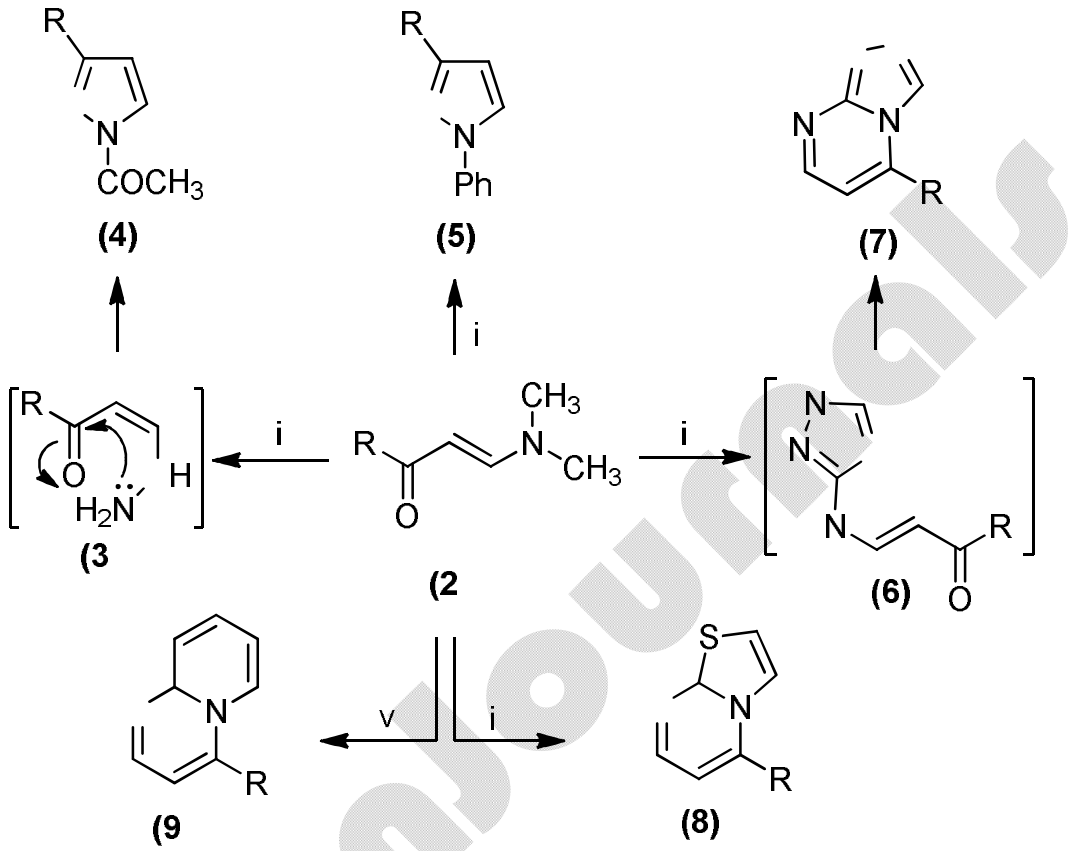


(i) p-aminoacetophenone,xylene, (ii) DMFDMA,xylene

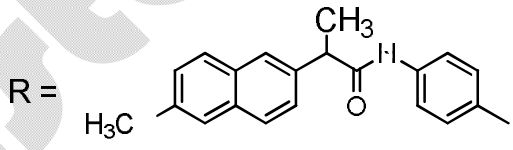
(Scheme 1)

The reactivity of enaminone**2** towards some nitrogen nucleophiles was investigated to afford the pyrazole derivatives. Thus, interaction of enaminone**2** with hydrazine hydrate in ethanol/acetic acid medium at reflux temperature afforded N-methyl pyrazole derivative **4**, (Scheme 2). The structure of the isolated product **4** was confirmed on the basis of elemental analysis and spectral data. The ^{1}HNMR spectrum of **4** revealed two doublet signals at 7.13 and 7.53 ppm assigned for H_4, H_5 of pyrazole with singlet at δ 2.24 ppm assigned for $COCH_3$ group. The formation of compound **4** was assumed to proceed through initial nucleophilic addition of amino group of hydrazine to β-carbon atom of enaminone **2** followed by elimination of dimethylamine to yield acyclic intermediate **3** which undergo cyclization via elimination of water molecule and acylation by boiling acetic acid. Similarly, *N*-phenyl pyrazole derivative **5** was obtained via reaction of enaminone **2** with phenyl hydrazine. Assignment of structure **5** was confirmed on the basis of itsmass spectrum which is compatible with molecular formula $C_{29}H_{25}N_3O_2$ and indicated a molecular ion peak at m/z 447. The reaction of enaminone derivative**2** was extended to synthesize some condensed pyrimidine derivatives via its reaction with some aminoheterocyclic compounds. Thus, the enaminone **2** was condensed with 3-amino-*1H*-1,2,4-triazole in ethanol/glacial acetic acid under reflux to afford [1,2,4]triazolo[4,3-a]pyrimidine derivative **7**. The structure of isolated product **7** was confirmed on the basis of ^{1}HNMR spectrum which revealed two doublets at 8.25 and 8.95 ppm assigned for two pyrimidine-H and singlet signal at 8.85 ppm for triazole-H. The formation of compound **7** may be assumed via the addition of the exo-amino group of amino triazole to α,β-unsaturated moiety in enaminone**2** followed by elimination of dimethylamine molecule to yield the corresponding acyclic non-isolable intermediate **6** which undergoes intramolecular cyclization by elimination of water molecule. Also, thiazolo[3,2-a]pyrimidine derivative **8** was obtained via reaction of enaminone **2** with 2-aminothiazole. The structure of isolated product **8** was confirmed on the basis of elemental analysis and spectral data. ^{1}HNMR spectrum of **8** revealed signals at 6.25, 6.65 (dd, 2H, thiazole-H_4, H_5), 7.55, 8.15 (dd, 2H, pyrimidine -H_5, H_6). In

addition, enaminone **2** was reacted with 2-aminopyridine in acetic acid under reflux to afford pyrido[1,2-a]pyrimidine derivative **9** (Scheme 2). The mass spectrum of compound **9** showed a molecular ionic peak at m/z 435 (0.2%) which is characteristic for the molecular formula $C_{28}H_{25}N_3O_2$.

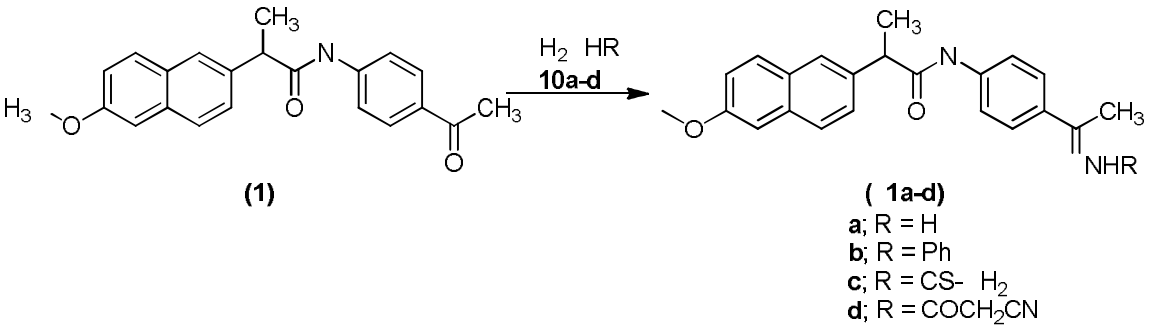


(i) hydrazine hydrate, EtOH/acetic acid; (i) phenyl hydrazine, EtOH/acetic acid;
(ii) 3-aminotriazole, EtOH/acetic acid; (iv) 2-aminothiazole, EtOH/acetic acid;
(v) 2-aminopyridine, EtOH/acetic acid



(Scheme 2)

Here, compound **1** was used as starting material in the synthesis of many compounds containing a naproxenoyl moiety. Thus, condensation of **1** with hydrazines **10a-d** (namely, hydrazine, phenyl hydrazine, thiosemicarbazide and cyanoacetic acid hydrazide) produced the corresponding hydrazine derivatives **11a-d**, (Scheme 3) (see experimental part).



(1) **(1a-d)**

a; R = H
b; R = Ph
c; R = CS- H_2
d; R = $COCH_2CN$

(Scheme 3)

Many thiazole derivatives have been demonstrated to possess antibacterial [15], antifungal [16], anticonvulsant [17], anticancer [18] and antituberculosis [19] activities. Thus, the reaction of thiosemicarbazone derivative **11c** with ethyl chloroacetate **(12)** in ethanol containing a catalytic amount of sodium acetate afforded the corresponding 4-thiazolidinone derivative **13**. The structure of isolated compound was established on the basis of elemental analysis and spectral data. The infrared spectrum of **13** revealed a characteristic absorption band at 1730 cm^{-1} for carbonyl group. The ^{1}HNMR spectrum of **13** showed a signals at δ 1.50 (d, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 3.85 (s, 2H, OCH_3), 4.00 (q, 1H, asymmetric-H) and 7.27, 10.24 (2s, 2H, 2NH). Similarly, reaction of thiosemicarbazone derivative **11c** with ethyl-α-bromopropionate **(14)** resulted in the formation of 5-methyl-4-thiazolinone derivative **15** according to the spectral data of the isolated product (Scheme 4). The IR spectrum of the isolated product **15** revealed absorption bands at 3436, 1726 cm^{-1} corresponding to imino and carbonyl groups, respectively. On the other hand, treatment of **11c** with ethyl α-bromobutyrate **(16)** gave 4-hydroxy-thiazole derivative **18**. The structure of **18** was preferred rather than the isomer **17** according to the elemental analyses and spectral data. Infrared spectrum showed a broad absorption band at 3462 cm^{-1} corresponding to hydroxyl group. ^{1}HNMR spectrum revealed signals at δ 0.9 (t, 3H, CH_3), 1.49 (q, 2H, CH_2), 1.51 (d, 3H, CH_3), 2.23 (s, 3H, CH_3), with singlet at 10.59 for OH. The formation of compound **18** may be assumed to proceed through initial alkylation followed by intramolecular cyclization and elimination of ethanol to afford **18**. In addition, cyclocondensation of thiosemicarbazone derivative **11c** with chloroacetone **(19)** afforded the corresponding 4-methyl-thiazole derivative **20** (Scheme 4). Mass spectrum of compound **20** showed a molecular ion peak at m/z 458 (50%) with base peak at m/z 185. Also, the structure of compound **20** was confirmed on the basis of the ^{13}C NMR (Chart 1).

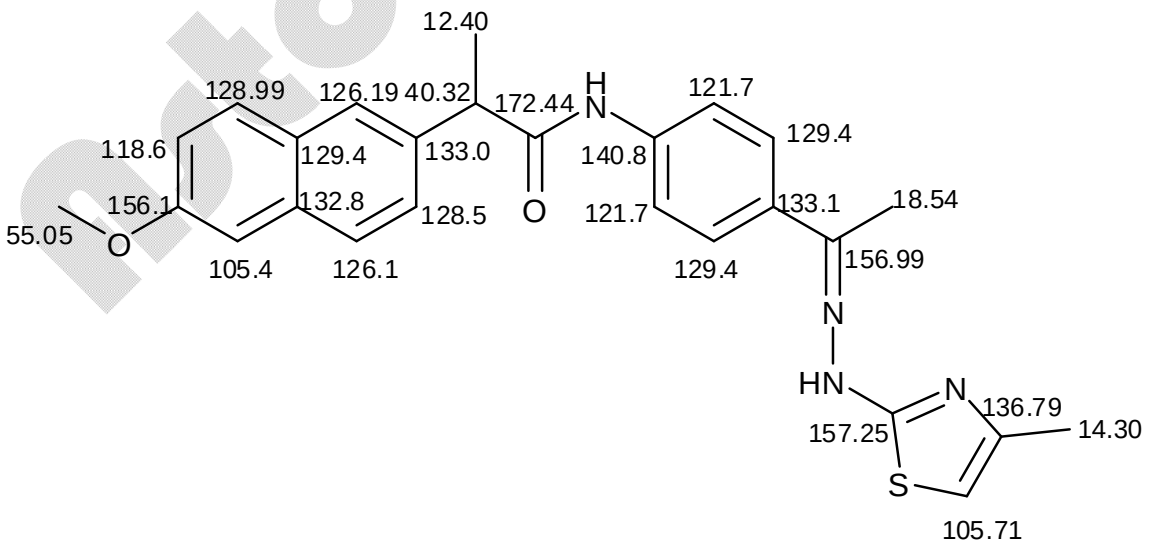


Chart 1: ^{13}C NMR spectrum of compound **(20)**.

The hydrazone derivatives have proven to be valuable synthon for the synthesis of a wide variety of biologically active heterocyclic systems like pyridine [20-22] and 2-iminochromenes [23-25]. Thus, cyclocondensation of hydrazone derivative **11d** with acetylacetone under reflux condition furnished 4,6-dimethyl-2-pyridone derivative **22**. Both of elemental analysis and spectral data were in agreement with structure of **22**. The ^{1}HNMR spectrum of compound **22** revealed signals corresponding to aliphatic and aromatic protons. The formation of **22** may be assumed to proceed via the intermolecular cyclization of non-isolable intermediate **21** followed by loss of water molecule. Finally, 2-iminochromene **23** and 2-iminobenzo[f]chromene **24** were obtained via cyclocondensation of hydrazone derivative **11d** with salicylaldehyde and 2-hydroxy-1-naphthaldehyde in refluxing ethanol containing a catalytic amount of ammonium acetate (Scheme 5). The structure of compounds **23** and **24** were established by elemental analysis and spectral data. The infrared spectra of **23** and **24** showed the absence of carbonitrile absorption bands. Also, ^{1}HNMR spectra of **23** and **24** revealed singlet signals at 8.58, 8.50 ppm for chromene-H and benzochromene-H, respectively.

3.2. Biological activity

a. Animal toxicity studies

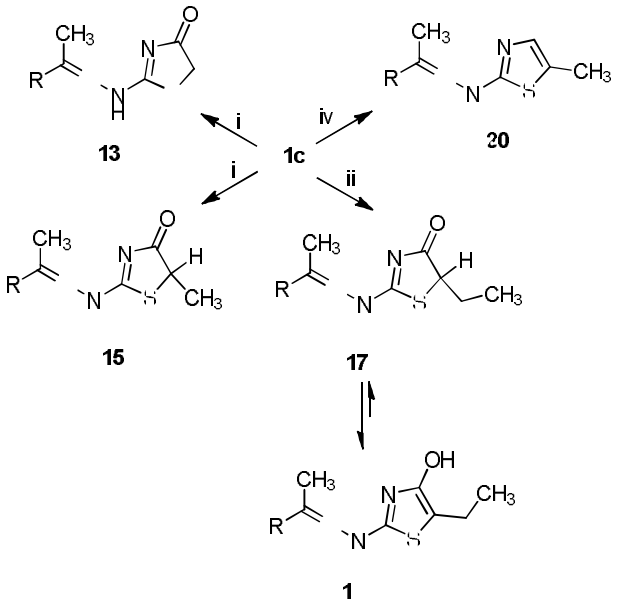
The acute toxicity is usually measured by LD_{50} (the median lethal dose) which is the dose that kills 50% of the experimental animals underspecified conditions. The LD_{50} will vary according to many factors, e.g. animal strain, room temperature, route of administration, season of the year, etc. all of which have to be taken in consideration. Acute toxicity studies have to be carried out on several animal species generally on mice and rats. The basic principle of the determination of the LD_{50} depends on the determination of the highest dose that fails to kill any animal and this refers as the threshold dose or the maximal tolerated dose and determination of the minimal dose that kills all the animals, the former dose is referred to as LD_{50}; while the latter dose is referred to as LD_{100}. In between these two doses, several doses are chosen which produce different percentage of mortality. The methods of determination of the LD_{50} differ in the design of the experiment and the method of calculation of LD_{50}. The acute LD_{50} of the screened compounds were determined by Spearmane Karber method [27]. The compounds **1**, **2, 4, 5, 8, 11c, 15, 18, 22** and **23** were well tolerated up to the doses of 1200mg/kg without any toxic manifestations. The fact that compounds showed no toxic effects in doses up to 1200mg/kg in mice (equivalent to oral LD_{50} of diclofenac sodium in mice) suggest a very low toxicity of compounds.

b. Analgesic screening

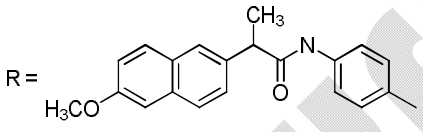
Experimental model used in this study were selected to investigate narcotic analgesic activity of some tested compounds. For this purpose, the hot-plate test [28] to reveal narcotic analgesic activity. In this method, female albino mice (Swiss strain) were put on a hot plate with constant temperature 55ºC, the time taken by the mice to lick its feet or to jump within a cylinder placed on a hot plate surface was determined. Five test compounds were injected i. p. at a dose level of 50 mg/kg into mice. Control group of animals was similarly treated with1% CMC (carboxy methyl cellulose). The reaction time was evaluated directly after 0.5 and 1h of injection. Comparison between the narcotic analgesic activity of the tested compounds and the standard diclofenac sodium (2mg/kg) from weak, moderate and potent analgesic activity was carried out (Table 1). From the tabulated data the following points could be picked out: Compounds **11c** & **15** showed generally remarkable analgesic activity. Moderate to weak analgesic activity was shown for all other tested compounds.

c. *In vivo* anti-inflammatory studies

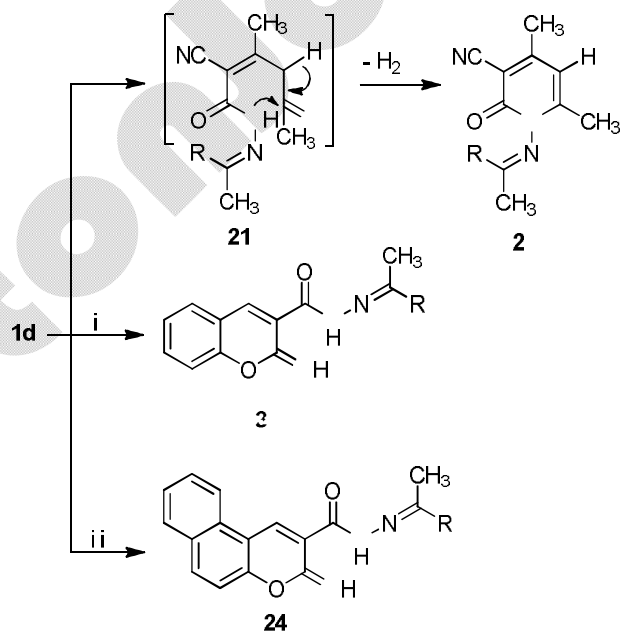
All the newly synthesized compounds and diclofenac sodium, as a reference drug, were subjected to *in vivo* anti-inflammatory studies using carrageenan-induced rat paw oedema model [29]. From the tabulated value (table 2) compounds **(11c)** was the most potent anti-inflammatory activity (67.31%) comparable to the reference drug diclofenac sodium (72.13%). A mild to weak effect was exerted by the other compounds.



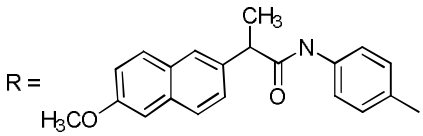
i; **(12)**, Et O/sod.a etate, i; **(14)**, Et O/sodium a etate, ii; **(16)**, Et O/sod.a etate, iv; **(19)**, Et O/sodium a etate



(Scheme 4)



i; $CH_2(COCH_3)$, reflux, i; sa icylalde yde, EtOH/CH_3C O H_4, ii; 2- ydroxy-1-na hthalde yde, EtOH/CH_3C O H_4



(Scheme 5)

Table 1: Narcotic analgesic activity of the tested compounds.

Compound no.	Analgesic activity in seconds (Mean)	
	0.5 h	1.0 h
Control	5.5 ± 0.3	5.5 ± 0.3
1	15 ± 0.3	29 ± 0.3
2	17 ± 0.3	28 ± 0.3
4	17 ± 0.3	28 ± 0.3
5	17 ± 0.3	29 ± 0.3
8	17 ± 0.3	28 ± 0.3
11c	26 ± 0.3	31 ± 0.3
15	26 ± 0.3	31 ± 0.3
18	24 ± 0.3	30 ± 0.3
22	16 ± 0.3	27 ± 0.3
23	16 ± 0.3	26 ± 0.3
Diclofenac sodium	13.20 ± 0.3	8.5 ± 0.39

Table 2: Result of anti-inflammatory activity of the tested compounds against carrageenan-induced rat paw oedema in rats.

Compound no.	Mean % increase in paw weight ± SE	% Inhibition of paw oedema from control group
Control	29.13 ± 1.03	-
Diclofenac	8.12 ± 0.49 $^{\delta}$	72.13
1	16.84 ± 0.43 $^{\delta}$	42.19
2	17.90 ± 0.46 $^{\delta}$	38.55
4	22.80 ± 0.41 $^{\delta}$	21.73
5	22.80 ± 0.40 $^{\delta}$	21.73
9	19.23 ± 0.45 $^{\delta}$	33.98
11c	9.52 ± 0.42 $^{\delta}$	67.31
15	19.20 ± 0.44 $^{\delta}$	32.99
18	19.52 ± 0.33 $^{\delta}$	32.99
22	24.63 ± 0.25 $^{\delta}$	15.44
23	23.40 ± 0.36 $^{\delta}$	19.67

$^{\delta}$Significant difference from diclofenac-treated group using unpaired student's «*t*»test, $p < 0.05$.

Competing Interests
Authors declare that they have no competing interests.

Authors' Contributions
All authors contributed equally to this work.

Acknowledgement
The authors thank Dr. Ahmed Kamal, El-Nasr Pharmaceutical Industry, for doing the pharmacological screening.

References

[1] Kim SJ, Flach AJ, Jampol LM, 2010. Nonsteroidal anti-inflammatory drugs in ophthalmology. Survey of Ophthalmology, 55(2): 109-133.

[2] Flach AJ, 2002. Topical nonsteroidal anti-inflammatory drugs in ophthalmology. In: Tasman (ed), Duanes Foundations of Clinical Ophthalmology, Philadelphia, PA, Lippincott, 42(1): 1-11.

[3] Flach AJ, 1994. Nonsteroidal anti-inflammatory drugs. In: Tasman (ed), Duanes Foundations of Clinical Ophthalmology, Philadelphia, PA, Lippincott, 2: 1-32.

[4]Flach AJ, 1992. Cyclooxygenase inhibitors in ophthalmology. Survey of Ophthalmology, 36(4): 259-84.

[5] Samiy N, Foster CS, 1996. The role of nonsteroidal anti-inflammatory drugs in ocular inflammation. In: Tasman (ed), Duanes Foundations of Clinical Ophthalmology, Philadelphia, PA, Lippincott, 36(1): 195-206.

[6] Sawaoka H, Tsuji S, Tsujii M, 1999. Cyclooxygenase inhibitors suppress angiogenesis and reduce tumor growth in vivo. Laboratory Investigation, 79(12): 1469-77.

[7] Ammar YA, Ali MM, Salem MA, et al., 2009. Cyanoacetanilidesintermediates in heterocyclic synthesis, part 5: preparation of unknown 5-aminopyrazole and pyrazolo[1,5-a]pyrimidine derivatives containing sulfamoyl moiety. Journal of the Chinese Chemical Society, 56: 1064-1071.

[8] Elzahabi HSA, Salem MA, Thabet HKh, 2011. Synthesisand anticancer activity of some novel diphenic acid derivatives. Der PharmaChemica, 3(2): 48-58.

[9] Khalifa MA, Thabet HKh, Helal MH, et al., 2008. Synthesis and evaluation of some new thiazolo[3,2-a]pyrimidines as potential anti-inflammatory. Al-Azhar Journal of Pharmaceutical Sciences, 37: 167-174.

[10] Ammar YA, Ali MM, Mohamed YA, et al., 2008. Cyanoacetanilides intermediates in heterocyclic synthesis, Part 4: Preparation of some hitherto unknown thiazolidine and bisthiazolidine derivatives. Phosphorus, Sulfur and Silicon and the Related Elements, 183(7): 1710-1721.

[11] Ammar YA, El-Sharief AMSh, Mohamed YA, et al., 2004. Cyanoacetanilides intermediates in heterocyclic synthesis. Part 1: a facile synthesis of polysubstituted and condensed pyridones. Journal of Chinese Chemical Society, 51: 975-981.

[12] Al-Sehemi AG, El-Sharief AMSh, Ammar YA, 2006. Propionic acids in organic synthesis: Novel synthesis of benzimidazole, 3,1-benzo-oxazine, 3-aminoquinazoline and 3-aminothieno[2,3-d]pyrimidine derivatives containing 2-naphthyl propionyl moiety. Indian Journal of Chemistry, 45B: 450-455.

[13] Greenhill JV, 1997. Enaminones in heterocyclic synthesis. Advances in Heterocyclic Chemistry, 67: 207-343.

[14] Al-Enezi A, Al-Saleh B, Elnagdi MH, 1997. Studies with heteroaromatic amines: the reaction of some heteroaromatic amines with 1-substituted 3-dimethylaminopropanones, enaminones and cinnamonitriles. Journal of Chemical Research (S), 4-5, Ibid (M): 116-138.

[15] Al-Saleh B, Al-Awadi N, Al-Kandari H, et al., 2000. Studies with 2H pyranones: Synthesis of new 3-substituted-4-hydroxy-2H-pyran-2-ones. Journal of Chemical Research (S), 16-17, Ibid (M): 201-214.

[16] Kucukguzel SG, Oruc E, Rollas S, et al., 2002. Synthesis, characterization and biological activity of novel 4-thiazolidinones, 1, 3, 4-oxadiazoles and some related compounds. European Journal of Chemistry, 37: 197.

[17] Capan G, Ulusoy N, Fragenc N, et al., 1999. New 6-phenyl-imidazo[2,1-b]thiazole derivatives: Synthesis and antifungal activity. Monatshefte Fur Chemie, 130: 1399-1407.

[18] Ergenc N, Capan G, 1994. Synthesis and anticonvulsant activity of new 4-thiazolidone and 4-thiazoline derivatives. IL Farmaco, 49: 133-135.

[19] Turan-Zitounia G, Kaplancıklı ZA, Özdemira A, 2010. Synthesis and antituberculosis activity of some N-pyridyl-N′-thiazolylhydrazinederivatives. European Journal of Medicinal Chemistry, 45(5): 2085-2088.

[20] Bukowski L, Janwiec M, Zwolska Z, et al., 1998. Some reactions of 2-cyanomethylimidazo[4,5-b]pyridine with isothiocyanates. Antituberculotic activity of the obtained compounds. Pharmazie, 53: 373.

[21] Al-Salahi RA, Al-Omar MA, Amr AE, 2010. Synthesis of chiral macrocyclic or linear pyridine carboxamides from pyridine-2,6-dicarbonyl dichloride as antimicrobial agents. Molecules, 15: 6588-6597.

[22] Mohareb R, Ezz El-Arab ME, El-Sharkawy KA, 2009. The reaction of cyanoacetic acid hydrazide with 2-acetylfuran: synthesis of coumarin, pyridine, thiophene and thiazole derivatives with potential antimicrobial activities. Scientia Pharmaceutica, 77: 355–366.

[23] Hagan DO, 2000. Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. Natural Product Reports, 17: 435-446.

[24] Klayman DL, Scovill JP, Bartosevich JF, et al., 1979. 2-acetylpyridine thiosemicarbazones. 2. n4, n4-disubstituted derivatives as potential antimicrobial agents. Journal of Medicinal Chemistry, 22: 1367-1373.

[25] Yang EB, Zhao NY, Zhang K, et al., 1999. Daphnetin, one of coumarin derivatives, is a protein kinase inhibitor. Biochemical and Biophysical Research Communications, 260: 682-685.

[26] Ukama K, Ishiguro T, Wada Y, et al., 1986. Synthesis of 5-oxo-5H-[1]benzopyrano[4,3-b]pyridine derivatives. Heterocycles, 24: 1931-1941.

[27] Hamilton MA, Russo RC, Thurston RV, 1977. Trimmed Spearman-Karber method for estimating median lethal concentrations in toxicity bioassays. Environmental Science & Technology, 11: 714-719.

[28] Tzschentke TM, Christoph T, Kögel B, et al., 2007. (–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel μ-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. Journal of Pharmacology and Experimental Therapeutics, 323(1): 265-276.

[29] Winter CA, Risley EA, Nuss GW, 1962. Carrageenan-induced oedema in hind paw of the rat as an assay for anti-inflammatory drugs. Proceedings of the Society for Experimental Biology and Medicine, 111: 544-547.