ISSN 1110-5089

Zagazig J. Pharm. Sci., December, 2011
Vol. 20, No. 2, pp. 6-18

SYNTHESIS OF SOME NOVEL PYRROLE AND PYRROLO[2,3-d]PYRIMIDINE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS.

Makarem M. Korra, Maha M.Khalifa*, Hend M.EL-Sahrawi*, Marwa T.Sarg**, Shaimaa M.Abd El-Gilil**

Department of Organic Chemistry, Faculty of Pharmacy, Cairo University.
* Department of Pharmaceutical Chemistry, Faculty of Pharmacy (girls branch), Al-Azhar University.
** Department of Organic Chemistry, Faculty of Pharmacy (girls branch), Al-Azhar University.

ABSTRACT

Some novel pyrrole and pyrrolo[2,3-d]pyrimidine derivatives were synthesized and evaluated for their anti-inflammatory activities. 2-(4-Substitutedphenylamino)-1-(4-substitutedphenyl) ethanones (3a-i) were reacted either with malononitrile or ethyl cyanoacetate to afford 2-amino-1,4-disubstitutedphenyl-1H-pyrrole-3-carbonitriles (4a-i) and ethyl 2-amino-1,4-disubstitutedphenyl-1H-pyrrole-3-carboxylates (5a-g) respectively. Compounds (4a, 4i and 5g) were reacted with acetic anhydride, benzoyl chloride, 4-substitutedphenacyl bromides and benzyl chloride to afford compounds (6a-c), (7a-c), (8a-c) and (9a-c) respectively. Compounds (4a and 4i) were also reacted either with formic acid or triethyl orthoformate to give 5-(4-substitutedphenyl)-7-(4-substitutedphenyl)-3H-pyrrolo[2,3-d] pyrimidin-4(7H)-ones (10a,b) and ethyl N-1,4-disubstitutedphenyl-3-cyano-1H-pyrrol-2-yl-formimidates (11a,b) respectively. Hydrazinolysis of (11a,b) afforded (12a,b).

Sixteen of the newly synthesized compounds were evaluated for their anti-inflammatory and analgesic activities. Most of the screened compounds showed interesting high anti-inflammatory activity compared to ketoprofen (Biprofened®) as a standard drug. The most active compounds were further screened for their ulcerogenic activity. The analgesic activity of the selected compounds was also assessed.

INTRODUCTION

Inflammation is a normal response to any stimulus that threatens the host and may vary from a localized response to a generalized one [1]. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of rheumatism diseases, as rheumatoid arthritis, and pain [2,3]. The pharmacological effects of NSAIDs are due to blocking the metabolism of arachidonic acid through the inhibition of cyclooxygenase enzymes (COX-1 and COX-2) and thereby production of prostaglandin biosynthesis. Classical NSAIDs non selectively inhibit both isoenzymes and cause gastric disorders like bleeding and ulcer [4,5]. The isoform COX-1 is found in healthy populations and has mainly a physiological role in the kidneys and the stomach. In contrast, the isoform COX-2 is involved in the production of prostaglandins mediating pain and supporting the inflammatory process [6,7]. This has led to intense efforts in search for potent and selective COX-2 inhibitors which could provide anti-inflammatory drugs with fewer gastric side effects.

On the other hand, pyrrole derivatives have been widely known for their versatile biological activities such as anti-inflammatory [2,8-11], analgesic [12,13], antimicrobial [14-17], anti-tumor [18-20] and antiviral activities [21-24]. The most significant of which is the anti-inflammatory activity exhibited by the non selective NSAI tolmetin (Rumatol®) and ketorolac (Ketolac®) [25,26].

EXPERIMENTAL

Chemistry

All melting points were measured on Electro thermal LA 9000 SERIS, Digital Melting point Apparatus and are uncorrected. IR spectra (KBr) were recorded on FT-IR 5300 spectrophotometer and Perkin Elmer spectrum RXIFT-IR system (ν, cm^{-1}). ^{1}H-NMR 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 recorded on GC Ms-QP 1000 EX mass spectrometer at 70 eV. Microanalytical data were performed in Micro analytical Research Center, Cairo University. Thin layer chromatography was performed on pre-coated (0.25mm) silica gel GF_{254} plates (E. Merck, Germany). Compounds were detected with 254 nm UV lamp.

General procedure for the synthesis of compounds 3a-i

Equimolar amounts of 4-substitutedphenacyl bromides, namely 1-(biphenyl-4-yl)-2-bromoethanone, 2-bromo-1-(4-nitrophenyl)ethanone, 4-(2-bromoacetyl)-benzonitrile, and 4-(2 bromoacetyl)-N,N-dimethylbenzenesulfonamide(0.01 mol) and the appropriate aromatic amines, namely 4-methoxyaniline, 4-chloroaniline and 4-bromoaniline (0.01 mol) in ethanol 50 ml were heated under reflux for 6h, then left to cool. The solid product was collected by filteration after cooling and recrystallized from the proper solvent to give compounds (3a-i).

1-Biphenyl-2-(4-methoxyphenylamino)ethanone (3a) Yield, 89%; mp 155-157 °C (Ethanol); IR (KBr,

cm^{-1}) ύ: 3400(NH); 1672 (C=O); 1236, 1036(C-O-C); ^1H NMR (DMSO-d_6) δ: 3.64 (s, 3H, OCH_3); 4.65 (s, 2H, CH_2CO); 6.65-6.72 (m, 5H, $C_{2',3',4',5',6'}$-biphenyl-H); 7.49-7.52 (m, 3H, $C_{3,5}$-biphenyl-H, NH); 7.76 (d, 2H, J=8.4 Hz, $C_{2,6}$- biphenyl-H); 7.85 (d, 2H, J=8.1 Hz, $C_{2,6}$-p-C_6H_4-OCH_3); 8.15 (d, 2H, J=8.1 Hz, $C_{3,5}$-p-C_6H_4-OCH_3). **M.S (m/z %)**:317 ($M^{+\bullet}$)(28); 152 (65); 136 (100); 80(33); $C_{21}H_{19}NO_2$,Cal. C, 79.47 ; H, 6.03; N, 4.41, Found C, 80.01; H, 5.60; N, 4.27.

1-Biphenyl-2-(4-chlorophenylamino)ethanone (3b) Yield, 88%; mp 188-190 °C (Ethanol); IR (KBr, cm^{-1}) ύ: 3318(NH); 1676 (C=O); 1092 (p-Cl phenyl); ^1H NMR (DMSO-d_6) δ: 4.71 (s, 2H, CH_2CO); 6.72 (d, 2H, J=8.7 Hz, $C_{3',5'}$- biphenyl-H); 7.10 (d, 2H, J=8.7 Hz, $C_{2',6'}$-biphenyl-H); 7.42-7.55 (m, 6H, $C_{4'}$,$C_{2,3,5,6}$-biphenyl-H, NH); 7.76 (d, 2H, J=8.1 Hz,$C_{2,6}$-p-C_6H_4-Cl); 7.82 (d, 2H, J=8.1 Hz, $C_{3,5}$-p-C_6H_4-Cl). **M.S (m/z%)**: 323 ($M^{+\bullet}$+2)(5); 321 ($M^{+\bullet}$)(13); 152 (67); 140 (100); 74 (27); $C_{20}H_{16}ClNO$,Cal. C, 74.65; H, 5.01; N, 4.35, Found C, 73.99; H, 5.06; N, 4.20.

1-Biphenyl 2-(4-bromophenylamino)ethanone (3c) Yield, 80%; mp 185-186 °C (Ethanol); IR (KBr, cm^{-1}) ύ: 3392(NH); 1670 (C=O); 1075 (p-Br phenyl); ^1H NMR (DMSO-d_6) δ: 4.70 (s, 2H, CH_2CO); 6.60 (d, 2H, J=8.7 Hz, $C_{3',5'}$- biphenyl-H)); 7.22 (d, 2H, J=8.7 Hz, $C_{2',6'}$-biphenyl-H); 7.41-7.52(m, 4H, $C_{4'}$,$C_{2,6}$-biphenyl-H, NH); 7.77 (d, 2H, J=8.4 Hz, $C_{3,5}$-biphenyl-H); 7.87 (d, 2H, J=8.3 Hz, $C_{2,6}$-p-C_6H_4-Br); 8.15 (d, 2H, J=8.3 Hz, $C_{3,5}$-p-C_6H_4-Br). **M.S (m/z%)**: 368 ($M^{+\bullet}$+2)(2); 367 ($M^{+\bullet}$ +1)(17);366 ($M^{+\bullet}$) (17); 186 (93); 184 (100). $C_{20}H_{16}BrNO$ Cal. C, 65.59; H, 4.40; N, 3.82, Found C, 65.30; H, 4.09; N, 3.37.

2-(4-Methoxyphenylamino)-1-(4-nitrophenyl) ethanone (3d) Yield, 83%; mp 130-131 °C (Benzene); IR (KBr, cm^{-1}) ύ: 3316(NH); 1670 (C=O); 1512,1340 (NO_2); 1246,1024 (C-O-C); ^1H NMR (DMSO-d_6) δ: 3.75 (s, 3H, OCH_3); 5.04 (s, 2H, CH_2CO); 6.58 (s, 1H, NH D_2O exchangeable); 7.06 (d, 2H, J=9 Hz, $C_{2,6}$-p-C_6H_4-OCH_3); 7.45(d, 2H, J=9 Hz, $C_{3,5}$-p-C_6H_4-OCH_3); 7.54 (d, 2H, J=9 Hz, $C_{2',6'}$-p-C_6H_4-NO_2); 7.77 (d, 2H, J=9 Hz, $C_{3',5'}$-p-C_6H_4-NO_2). **M.S (m/z%)**: 286 ($M^{+\bullet}$)(6); 284 (17); 280 (24);86 (100). $C_{15}H_{14}N_2O_4$ Cal. C, 62.93; H, 4.93; N, 9.79, Found C, 62.32; H, 4.70; N, 9.30.

2-(4-Chlorophenylamino)-1-(4-nitrophenyl) ethanone (3e) Yield, 57%; mp 180-182 °C (Ethanol); IR (KBr, cm^{-1}) ύ: 3388(NH); 1694 (C=O); 1522,1346 (NO_2); 1098 (p-Cl phenyl); ^1H NMR (DMSO-d_6) δ: 4.69 (s, 2H, CH_2CO); 5.37 (s, 1H, NH D_2O exchangeable); 6.64 (d, 2H, J=9 Hz, $C_{2,6}$-p-C_6H_4-Cl); 8.19-8.44 (m, 4H, p-C_6H_4-NO_2). **M.S (m/z%)**: 292 ($M^{+\bullet}$+2)(12); 290 ($M^{+\bullet}$)(26); 151 (56); 142 (89); 140 (100). $C_{14}H_{11}ClN_2O_3$ Cal. C, C, 57.84; H, 3.81; N, 9.64, found C, 57.80; H, 3.75; N, 9.61.

2-(4-Bromophenylamino)-1-(4-nitrophenyl) ethanone (3f) Yield, 80%; mp 145-147 °C (Ethanol); IR (KBr, cm^{-1}) ύ: 3310(NH); 1692 (C=O); 1516,1338 (NO_2); 1075 (p-Br phenyl); ^1H NMR (DMSO-d_6) δ: 4.76 (s, 2H, CH_2CO); 5.31 (s, 1H, NH D_2O exchangeable); 6.66 (d, 2H, J=8.7 Hz, $C_{2,6}$-p-C_6H_4-Br); 6.95 (d, 2H, J=8.7 Hz, $C_{3,5}$-p-C_6H_4-Br); 7.21 (d, 2H, J=8.7 Hz, $C_{2',6'}$-p-C_6H_4-NO_2); 7.46 (d, 2H, J=8.7 Hz, $C_{3',5'}$-p-C_6H_4-NO_2). **M.S (m/z%)**:336 ($M^{+\bullet}$+1)(29); 334 (30); 186 (98); 184 (100). $C_{14}H_{11}BrN_2O_3$ Cal. C, 50.17; H, 3.31; N, 8.36, Found C, 49.03; H, 3.11; N, 8.15.

2-(4-Chlorophenylamino)-1-(4-cyanophenyl) ethanone (3g) Yield, 69%; mp 160-162 °C (Benzene); IR (KBr, cm^{-1}) ύ: 3276(NH); 2228 (CN); 1690 (C=O); 1095 (*p*-Cl phenyl); ^1H NMR (DMSO-d_6) δ: 4.71 (s, 2H, CH_2CO); 5.32 (s, 1H, NH D_2O exchangeable); 6.69 (d, 2H, *J*=8.7 *Hz*, $C_{2,6}$-*p*-C_6H_4-Cl); 7.07 (d, 2H, *J*=8.7 *Hz*, $C_{3,5}$-*p*-C_6H_4-Cl); 8.04(d, 2H, *J*=8.1 *Hz*, $C_{2',6'}$-*p*-C_6H_4-CN); 8.19 (d, 2H, *J*=8.1 *Hz*, $C_{3',5'}$-*p*-C_6H_4-CN). **M.S (m/z%)**: 272($M^{+\bullet}$+2)(0.4); 271 ($M^{+\bullet}$+1)(1); 149 (20); 57 (100). $C_{15}H_{11}ClN_2O$ Cal. C, 66.55; H, 4.10; N, 10.35, Found C, 66.11; H, 3.95; N, 10.32.

2-(4-Bromophenylamino)-1-(4-cyanophenyl) ethanone (3h) Yield, 54%; mp 150-151 °C (Ethanol); IR (KBr, cm^{-1}) ύ: 3392(NH); 2226 (CN); 1686 (C=O); 1072 (p-Br phenyl); ^1H NMR (DMSO-d_6) δ: 4.70 (s, 2H, CH_2CO); 5.05 (s, 1H, NH D_2O exchangeable); 6.64 (d, 2H, *J*=9 *Hz*, $C_{2,6}$-*p*-C_6H_4-Br); 7.20 (d, 2H, *J*=9 *Hz*, $C_{3,5}$-*p*-C_6H_4-Br); 8.01-8.20 (m, 4H, *p*-C_6H_4-CN). **M.S (m/z%)**:316 ($M^{+\bullet}$+1)(14); 314 (12); 186 (93); 184 (100). $C_{15}H_{11}BrN_2O$ Cal. C, 57.16; H, 3.52; N, 8.89, Found C, 56.98; H, 4.02; N, 8.85.

2-(4-Methoxyphenylamino)-1-[4-(N,N-dimethyl sulfamoyl)phenyl]ethanone (3i) Yield, 55%; mp 140-142 °C (Ethanol); IR (KBr, cm^{-1}) ύ: 3406(NH); ; 1690 (C=O); 1342,1158 (SO_2); 1262,1036 (C-O-C); ^1H NMR (DMSO-d_6) δ: 2.92 (s, 6H, $(CH_3)_2N$); 3.99 (s, 3H, OCH_3); 4.82 (s, 2H, CH_2CO); 6.93-7.02 (m, 5H, $C_{2',3',5',6'}$-*p*-C_6H_4-$SO_2N(CH_3)_2$, NH); 8.08 (d, 2H, *J*=8.4 *Hz*, $C_{2,4}$-*p*-C_6H_4-OCH_3); 8.32 (d, 2H, *J*=8.4 *Hz*, $C_{3,5}$-*p*-C_6H_4-OCH_3). **M.S (m/z%)**: 348 ($M^{+\bullet}$)(3); 212 (24);134 (92); 76 (100). $C_{17}H_{20}N_2O_4S$ Cal. C, 58.60; H, 5.79; N, 8.04, Found C, 57.09; H, 5.34; N, 7.90.

ISSN 1110-5089

General procedure for the synthesis of compounds 4a-i

A mixture of 2-(4-substitutedphenylamino)-1-(4-substitutedphenyl) ethanone (**3a-i**), and malononitrile (0.01 mole) was allowed to fuse together in an oil bath for 10 minutes with controlled temperature at 95°C, then the residue was collected and crystallized to give the target compounds (**4a-i**).

2-Amino-4-biphenyl-1-(4-methoxyphenyl)-1H-pyrrole-3-carbonitrile (**4a**) Yield, 70%; mp 165-166 °C (Ethanol); IR (KBr, cm^{-1}) ύ: 3380,3300 (NH_2); 2198 (CN); 1598 (C=N); 1236,1030 (C-O-C); ^1H NMR (DMSO-d_6) δ: 3.64(s, 3H, OCH_3); 5.47 (s, 2H, NH_2 D_2O exchangeable); 6.65 (s, 1H, CH-pyrrole); 7.37-7.52 (m, 5H, $C_{2',3',4',5',6'}$-biphenyl-H); 7.50-7.62 (m, 4H, *p*-C_6H_4-OCH_3); 7.76 (d, 2H, *J*=8.3 *Hz*, $C_{3,5}$-biphenyl-H); 7.85 (d, 2H, *J*=8.3 *Hz*, $C_{2,6}$- biphenyl-H). **M.S (m/z%):** 365 ($M^{+\bullet}$)(1); 165 (7); 312 (24); 152 (100). $C_{24}H_{19}N_3O$ Cal. C, 78.88; H, 5.24; N, 11.50, Found C, 79.06; H, 5.90; N, 10.19.

2-Amino-4-biphenyl-1-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile (**4b**) Yield, 88%; mp 230-232 °C (Ethanol); IR (KBr, cm^{-1}) ύ: 3266,3240 (NH_2); 2224 (CN); 1598 (C=N);1090 (*p*-Cl phenyl); ^1H NMR (DMSO-d_6) δ: 5.30 (s, 2H, NH_2 D_2O exchangeable); 6.63 (s, 1H, CH-pyrrole); 7.38-7.49 (m, 5H, $C_{2',3',4',5',6'}$- biphenyl-H); 7.54-7.72 (m, 4H, $C_{2',3',5',6'}$-biphenyl-H); 7.85 (d, 2H, *J*=8.3 *Hz*, $C_{2,6}$-*p*-C_6H_4-Cl), 8.15 (d, 2H, *J*=8.3 *Hz*, $C_{3,5}$-*p*-C_6H_4-Cl). **M.S (m/z%):** 370 ($M^{+\bullet}$+1)(20); 323 (19); 321 (40); 181 (57); 152(100). $C_{23}H_{16}ClN_3$ Cal. C, 74.69; H, 4.36; N, 11.36, Found C, 74.40; H, 4.29; N, 11.30.

2-Amino-1-(4-bromophenyl)-4-biphenyl-1H-pyrrole-3-carbonitrile (**4c**) Yield, 64%; mp 208-210 °C (Ethanol); IR (KBr, cm^{-1}) ύ: 3350,3274 (NH_2), 2216 (CN); 1596 (C=N);1070 (*p*-Br phenyl); ^1H NMR (DMSO-d_6) δ: 6.17 (s, 2H, NH_2 D_2O exchangeable); 6.67 (s, 1H, CH-pyrrole); 7.21 (d, 2H, *J*=7.8 *Hz*, $C_{2,6}$- biphenyl-H); 7.34-7.55 (m, 5H, $C_{2',3',4',5',6'}$-biphenyl-H); 7.62 (d, 2H, *J*=8.8 *Hz*, $C_{2,6}$-*p*-C_6H_4-Br); 7.74 (d, 2H, *J*=8.8 *Hz*, $C_{3,5}$-*p*-C_6H_4-Br); 7.86 (d, 2H, *J*=7.8 *Hz*, $C_{3,5}$-biphenyl-H). **M.S (m/z%):** 416 ($M^{+\bullet}$+2)(1); 280 (40); 181 (100). $C_{23}H_{16}BrN_3$ Cal. C, 66.68; H, 3.89; N, 10.14, Found C, 66.20, H, 3.81; N, 10.30.

2-Amino-1-(4-methoxyphenyl)-4-(4-nitrophenyl)-1H-pyrrole-3-carbonitrile (**4d**) Yield, 82%; mp 150-152 °C (Ethanol); IR (KBr, cm^{-1}) ύ: 3258,3200 (NH_2); 2200 (CN); 1594 (C=N); 1512,1340 (NO_2); 1246,1028 (C-O-C); ^1H NMR (DMSO-d_6) δ: 3.83 (s, 3H, OCH_3); 6.84 (br, 2H, NH_2 D_2O exchangeable); 6.87 (s, 1H, CH-pyrrole); 7.14-7.38 (m, 4H, *p*-C_6H_4-OCH_3); 8.04-8.29 (m, 4H, *p*-C_6H_4-NO_2). **M.S (m/z%):** 334 ($M^{+\bullet}$)(2); 167 (20); 166 (11); 149 (100). $C_{18}H_{14}N_4O_3$ Cal. C, 64.66; H, 4.22; N, 16.76, Found C, 64.20; H, 4.02; N, 16.70.

2-Amino-1-(4-chlorophenyl)-4-(4-nitrophenyl)-1H-pyrrole-3-carbonitrile (**4e**) Yield, 78%; mp 230-232°C (Benzene); IR (KBr, cm^{-1}) ύ: 3444, 3304 (NH_2); 2216 (CN); 1596 (C=N); 1526,1344 (NO_2); 1095 (*p*-Cl phenyl); ^1H NMR (DMSO-d_6) δ: 5.36 (s, 2H, NH_2 D_2O exchangeable); 6.80 (s, 1H, CH-pyrrole); 8.21 (dd, 4H, *J*=5.1,9 *Hz*, *p*-C_6H_4-Cl); 8.42-8.45 (m, 4H, *P*-C_6H_4-NO_2). **M.S (m/z%):** 338 ($M^{+\bullet}$) (8); 182 (39); 181 (22); 153 (24); 152 (100). $C_{17}H_{11}ClN_4O_2$ Cal C, 60.28; H, 3.27; N, 16.54, Found C, 60.99; H, 3.15; N, 16.34.

2-Amino-1-(4-bromophenyl)-4-(4-nitrophenyl)-1H-pyrrole-3-carbonitrile (**4f**) Yield, 83%; mp 165-167°C (Pet.ether); IR (KBr, cm^{-1}) ύ: 3590,3516 (NH_2); 2216 (CN); 1592 (C=N); 1516,1340 (*p*-NO_2 phenyl); 1075 (*p*-Br phenyl); ^1H NMR (DMSO-d_6) δ: 5.17 (s, 2H, NH_2 D_2O exchangeable); 6.67 (s, 1H, CH-pyrrole); 7.20-7.58 (m, 4H, *p*-C_6H_4-Br); 8.05-8.38 (m, 4H, *p*-C_6H_4-NO_2). **M.S (m/z%):** 385($M^{+\bullet}$+2) (0.6); 383 ($M^{+\bullet}$) (1); 184 (20); 157 (13);75 (100). $C_{17}H_{11}BrN_4O_2$ Cal C, 53.28; H, 2.89; N, 14.62, Found C, 53.14; H, 2.73; N, 14.19.

2-Amino-1-(4-chlorophenyl)-4-(4-cyanophenyl)-1H-pyrrole-3-carbonitrile (**4g**) Yield, 82%; mp 173-175°C (Hexane); IR (KBr, cm^{-1}) ύ: 3205,3150 (NH_2); 2224 (two CN); 1598 (C=N); 1092 (*p*-Cl phenyl); ^1H NMR (DMSO-d_6) δ: 6.80 (s, 1H, CH-pyrrole); 6.82-6.87 (m, 2H, $C_{2,6}$-*p*-C_6H_4-Br); 7.04-7.07 (m, 2H, $C_{3,5}$-*p*-C_6H_4-Br); 7.34-7.36 (m, 2H, $C_{2',6'}$-*p*-C_6H_4-CN); 7.49-7.60 (m, 2H, $C_{3',5'}$-*p*-C_6H_4-CN); 8.50 (s, 2H, NH_2 D_2O exchangeable). **M.S (m/z%):** 318 ($M^{+\bullet}$) (1); 229 (43); 102 (100). $C_{18}H_{11}ClN_4$ Cal C, 67.82; H, 3.48; N, 17.58, Found C, 67.25; H, 3.70; N, 17.26.

2-Amino-1-(4-bromophenyl)-4-(4-cyanophenyl)-1H-pyrrole-3-carbonitrile (**4h**) Yield, 65%; mp 170-172°C (Benzene); IR (KBr, cm^{-1}) ύ: 3500,3384 (NH_2); 2224 (two CN); 1592 (C=N); 1070 (*p*-Br phenyl); ^1H NMR (DMSO-d_6) δ: 2.10 (br, s, 2H, NH_2); 2.81 (s, 6H, $(CH_3)_2N$); 3.94 (s, 3H, OCH_3); 6.95-8.00 (m, 9H, Ar-H, CH-pyrrole). **M.S (m/z%):** 363 ($M^{+\bullet}$) (3); 229 (36);102 (100). $C_{18}H_{11}BrN_4$ Cal C, 59.52; H, 3.05; N, 15.43, Found C, 59.85; H, 3.54; N, 15.60.

2-Amino-1-(4-methoxyphenyl)-4-[4-(N,N-dimethylsulfamoyl)phenyl]-1H-pyrrole-3-carbonitrile (**4i**) Yield, 50%; mp 160-162°C (Ethanol/Benzene); IR (KBr, cm^{-1}) ύ: 3235,3226 (NH_2); 2200 (CN); 1596

(C=N); 1340,1160 (SO_2); 1248,1030 (C-O-C); ^{1}H NMR (DMSO-d_6) δ: 3.64(s, 3H, OCH_3); 5.47 (s, 2H, NH_2 D_2O exchangeable); 6.65 (s, 1H, CH-pyrrole); 7.37-7.52 (m, 5H, $C_{2',3',4',5',6'}$-biphenyl-H); 7.50-7.62 (m, 4H, *p*-C_6H_4-OCH_3); 7.76 (d, 2H, *J*=8.3 *Hz*, $C_{3,5}$-biphenyl-H); 7.85 (d, 2H, *J*=8.3 *Hz*, $C_{2,6}$- biphenyl-H). **M.S (m/z%):** 369 ($M^{+\bullet}$) (1); 212 (12);108 (66); 51 (100). $C_{20}H_{20}N_4O_3S$ Cal C, 60.59; H, 5.08; N, 14.13, Found C, 60.23; H, 5.01; N, 14.06.

General procedure for the synthesis of compounds 5a-g

2-(4-Substitutedphenylamino)-1-(*4*-substituted phenyl)ethanone (**3a-c,e-h**) and ethyl cyanoacetate (0.01 mol) were allowed to fuse together in an oil bath for 20 minutes at 95°C, then the residue was collected and crystallized from the proper solvent.

Ethyl 2-amino-4-biphenyl-1-(4-methoxyphenyl)-1H-pyrrole-3-carboxylate; (**5a**) Yield, 69%; mp 130-132°C (Pet.ether); IR (KBr, cm^{-1}) ύ: 3300,3238 (NH_2); 1674 (C=O); 1598 (C=N); 1292,1032 (C-O-C); ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, CH_2CH_3); 3.80 (s, 3H, OCH_3); 4.31 (q, 2H, CH_2CH_3); 5.20 (s, 2H, NH_2 D_2O exchangeable); 6.77 (s, 1H, CH-pyrrole); 7.48-7.60 (m, 5H, $C_{2',3',4',5',6'}$-biphenyl-H); 7.88-8.30 (m, 8H, Ar-H). **M.S (m/z%):** 412 ($M^{+\bullet}$) (4); 328 (21); 312 (85);151 (100). $C_{26}H_{24}N_2O_3$ Cal. C, 75.71; H, 5.86; N, 6.79, Found C, 76.03; H, 5.81; N, 6.20.

Ethyl 2-amino-4-biphenyl-1-(4-chlorophenyl)-1H-pyrrole-3-carboxylate; (**5b**) Yield, 90%; mp 218-220°C (Ethanol/Benzene), IR (KBr, cm^{-1}) ύ: 3396,3252 (NH_2); 1676 (C=O); 1596 (C=N); 1088 (*p*-Cl phenyl). **M.S (m/z%):**416 ($M^{+\bullet}$) (1); 316 (8); 281 (10); 153 (20); 152 (100). $C_{25}H_{21}ClN_2O_2$ Cal. C, 72.02; H, 5.08; N, 6.72, Found C, 72.70; H, 5.65; N, 6.25.

Ethyl 2-amino-4-biphenyl-1-(4-bromophenyl)-1H-pyrrole-3-carboxylate; (**5c**) Yield, 80%; mp 180-182°C (Ethanol); IR (KBr, cm^{-1}) ύ: 3426,3360 (NH_2); 1672 (C=O); 1594 (C=N); 1068 (*P*-Br phenyl). **M.S (m/z%):** 461 ($M^{+\bullet}$) (1); 184 (8); 181 (30); 179 (20);152 (100). $C_{25}H_{21}BrN_2O_2$ Cal. C, 65.08; H, 4.59; N, 6.07, Found C, 66.01; H, 4.12; N, 6.35.

Ethyl 2-amino-1-(4-chlorophenyl)-4-(4-Nitrophenyl)-1H-pyrrole-3-carboxylate; (**5d**) Yield, 70%; mp 200-202°C (Benzene); IR (KBr, cm^{-1}) ύ: 3200 (NH_2); 1702 (C=O); 1594 (C=N); 1518, 1340 (NO_2); 1098 (*p*-Cl phenyl); ^{1}H NMR (DMSO-d_6) δ: 1.25 (t, 3H, $CH_2\underline{CH_3}$); 4.23 (q, 2H, $\underline{CH_2}CH_3$); 4.62 (s, 2H, NH_2 D_2O exchangeable); 6.82 (s, 1H, CH-pyrrole); 7.10-7.12 (m, 4H, *p*-C_6H_4-Cl); 7.51-7.55 (m, 4H, *p*-C_6H_4-NO_2). **M.S (m/z%):**385 ($M^{+\bullet}$) (4); 181 (70); 178 (16); 154 (20); 153 (38); 152 (100). $C_{19}H_{16}ClN_3O_4$ Cal. C, 59.15; H, 4.18; N, 10.89, Found C, 59.54; H, 4.01; N, 10.96.

Ethyl 2-amino-1-(4-bromophenyl)-4-(4-Nitrophenyl)-1H-pyrrole-3-carboxylate; (**5e**) Yield, 68 %; mp 118-120°C (Pet.ether); IR (KBr,cm^{-1}) ύ: 3250 (NH_2); 1702 (C=O); 1592 (C=N); 1516, 1340 (NO_2); 1075 (*p*-Br phenyl); ^{1}H NMR (DMSO-d_6) δ: 1.64 (t, 3H, $CH_2\underline{CH_3}$); 3.01 (q, 2H, $\underline{CH_2}CH_3$); 4.72 (s, 2H, NH_2 D_2O exchangeable); 6.62 (s, 1H, CH-pyrrole); 7.75-7.80 (m, 4H, *p*-C_6H_4-Br); 7.99-8.03 (m, 4H, *p*-C_6H_4-NO_2). **M.S (m/z%):** 431 ($M^{+\bullet}$+1) (1); 198 (6);150 (42); 75 (100). $C_{19}H_{16}BrN_3O_4$Cal. C, 53.04; H, 3.75; N, 9.77, Found C, 53.70; H, 3.21; N, 9.82.

Ethyl 2-amino-1-(4-chlorophenyl)-4-(4-cyanophenyl)-1H-pyrrole-3-carboxylate, (**5f**) Yield, 80 %; mp 200-201°C (Hexane); IR (KBr,cm^{-1}) ύ: 3384 (NH_2); 2224 (CN); 1698 (C=O); 1598 (C=N); 1095 (*p*-Cl phenyl); ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, $CH_2\underline{CH_3}$); 4.32 (q, 2H, $\underline{CH_2}CH_3$); 4.90 (s, 2H, NH_2 D_2O exchangeable); 6.98 (s, 1H, CH-pyrrole); 7.21-7.44 (m, 4H, *p*-C_6H_4-Cl); 7.77-7.91 (m, 4H, *p*-C_6H_4-CN).**M.S (m/z%):** 365 ($M^{+\bullet}$) (1); 230 (5); 229 (10); 181 (13); 152 (45);102 (100). $C_{20}H_{16}ClN_3O_2$ Cal. C, 65.67; H, 4.41; N, 11.49, Found C, 65.40; H, 4.25; N, 11.67.

Ethyl 2-amino-1-(4-bromophenyl)-4-(4-cyanophenyl)-1H-pyrrole-3-carboxylate; (**5g**) Yield, 90 %; mp 228-230°C (Benzene); IR (KBr,cm^{-1}) ύ: 3236,3354(NH_2); 2226 (CN); 1702 (C=O); 1592 (C=N); 1072 (*p*-Br phenyl), ^{1}H NMR (DMSO-d_6) δ: 1.28 (t, 3H,$CH_2\underline{CH_3}$); 3.96 (q, 2H, $\underline{CH_2}CH_3$); 5.13 (s, 2H, NH_2 D_2O exchangeable); 6.91 (s, 1H, CH-pyrrole), 6.84 (d, 2H, *J*=9Hz, $C_{2,6}$-*p*-C_6H_4-Br); 7.13 (d, 2H, *J*=9Hz, $C_{3,5}$-*p*-C_6H_4-Br); 7.41-7.51 (m, 4H, *p*-C_6H_4CN). **M.S (m/z%):** 412($M^{+\bullet}$+2)(6); 410 ($M^{+\bullet}$) (15); 329 (52); 327 (50);102 (100). $C_{20}H_{16}BrN_3O_2$ Cal C, 58.55; H, 3.93; N, 10.24, Found C, 58.31; H, 4.02; N, 10.63.

General procedure for the synthesis of compounds 6a-c

A mixture of 2-amino-1,4-disubstituted phenyl-3-substituted-1H-pyrrole **4a,i** and **5g** (0.01 mol) and acetic anhydride (30 ml) was refluxed for 7h. The solvent was removed under reduced pressure and the residue was collected and crystallized from the proper solvent.

N-[4-Biphenyl-1-(4-chlorophenyl)-3-cyano-1H-pyrrol-2-yl]acetamide (**6a**) Yield, 85 %; mp 150-

ISSN 1110-5089

152°C (Ethanol); IR (KBr,cm^{-1}) ύ: 3296 (NH); 2224 (CN); 1652 (C=O); 1596 (C=N); 1088 (*p*-Cl phenyl); ^{1}H NMR (DMSO-d_6) δ: 2.15 (s, 3H, CH_3); 2.64 (s, 6H, $(CH_3)_2N$); 3.96 (s, 3H, OCH_3); 7.45-8.06 (m, 9H, Ar-H, CH-pyrrole); 8.60 (s, 1H, NH D_2O exchangeable). **M.S (m/z%):** 413 ($M^{+\bullet}$+2) (1);181 (72);152 (100). $C_{25}H_{18}ClN_3O$ Cal C, 72.90; H, 4.40; N, 10.20, Found C, 72.35; H, 4.89; N, 10.05.

N-[3-Cyano-4-[4-(N,N dimethylsulfamoyl)phenyl]-1-(4-methoxyphenyl)-1H-pyrrol-2-yl]acetamide (**6b**) Yield, 75 %; mp 160-162°C (Ethanol); IR (KBr,cm^{-1}) ύ: 3210 (NH); 2200 (CN); 1672 (C=O); 1594 (C=N); 1340,1162 (SO_2); 1250,1026 (C-O-C); ^{1}H NMR (DMSO-d_6) δ: 1.34 (t, 3H, CH_2CH_3); 2.60 (s, 3H, CH_3); 4.05 (q, 2H, CH_2CH_3); 6.90 (s, 1H, CH-pyrrole); 7.48-7.50 (m, 4H, p-C_6H_4Br); 7.80-8.03 (m, 4H, p-C_6H_4-CN); 10.51 (s, 1H, NH D_2O exchangeable). **M.S (m/z%):** 438 ($M^{+\bullet}$) (1); 212 (13); 108 (24); 75 (100). $C_{22}H_{22}N_4O_4S$ Cal C, 60.26; H, 5.06; N, 12.78, Found C, 60.17; H, 5.01; N, 12.71.

Ethyl 2-acetamido-1-(4-bromophenyl)-4-(4-cyanophenyl)-1H-pyrrole-3-carboxylate (**6c**) Yield, 87 %; mp 200-202°C (Pet.ether); IR (KBr,cm^{-1}) ύ: 3340 (NH); 2226 (CN); 1702, 1604 (C=O); 1594 (C=N); 1075(*p*-Br phenyl); ^{1}H NMR (DMSO-d_6) δ: 2.15 (s, 3H, CH_3); 2.64 (s, 6H, $(CH_3)_2N$); 3.96 (s, 3H, OCH_3); 7.45-8.06 (m, 9H, Ar-H, CH-pyrrole); 8.60 (s, 1H, NH D_2O exchangeable). **M.S (m/z%):** 452 ($M^{+\bullet}$) (2); 313 (15); 229 (8); 181 (45); 152 (100). $C_{22}H_{18}BrN_3O_3$ Cal C, 58.42; H, 4.01; N, 9.29, Found C, 58.38; H, 4.63; N, 9.54.

General procedure for the synthesis of compounds 7a-c

A mixture of 2-amino-1,4-disubstitutedphenyl-3-substituted-1H-pyrrole **4a,i** and **5g** (0.01 mol) and benzoyl chloride (30 ml) was refluxed for 8h. The solvent was removed under reduced pressure, the residue was collected and crystallized from the proper solvent.

N-[4-(Biphenyl-4-yl)-1-(4-chlorophenyl)-3-cyano-1H-pyrrol-2-yl]benzamide(**7a**) Yield,70%; mp 180-182°C (Ethanol); IR (KBr,cm^{-1}) ύ: 3276 (NH); 2300 (CN); 1644 (C=O); 1598 (C=N); 1090 (*p*-Cl-phenyl); **M.S (m/z%):** 475($M^{+\bullet}$+2)(0.4); 473 ($M^{+\bullet}$) (1); 182 (10); 181 (76); 153 (23); 152 (100). $C_{30}H_{20}ClN_3O$ Cal C, 76.02; H, 4.25; N, 8.87, Found C, 75.87; H, 4.02; N, 8.68.

N-(3-Cyano-4-(4-(N,N-dimethylsulfamoyl) phenyl)-1-(4-methoxyphenyl)-1H-pyrrol-2-yl) benzamide (**7b**) Yield,40%; mp 150-152°C (Ethanol/Benzene); IR (KBr,cm^{-1}) ύ: 3400 (NH); 2216 (CN); 1692 (C=O); 1598 (C=N); 1286,1174 (SO_2); 1286,1014 (C-O-C); ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, 3H, OCH_3); 2.93 (s, 6H, $(CH_3)_2N$); 4.63 (s, 1H, NH D_2O exchangeable); 6.72 (s, 1H, CH-pyrrole); 6.94-7.13 (m, 5H, *p*-C_6H_4-CO); 7.70-7.94 (m, 4H, *p*-C_6H_4-OCH_3); 8.04-8.29 (m, 4H, *p*-C_6H_4-CN). **M.S (m/z%):** 502 ($M^{+\bullet}$+2) (18); 317 (35); 316 (44); 55 (100). $C_{27}H_{24}N_4O_4S$ Cal C, 64.78; H, 4.83; N, 11.19, Found C, 64.65; H, 4.69; N, 11.01.

Ethyl 2-benzamido-1-(4-bromophenyl)-4-(4-cyanophenyl)-1H-pyrrole-3-carboxylate (**7c**) Yield,86%; mp 170-172°C (Ethanol/Benzene); IR (KBr,cm^{-1}) ύ: 3276 (NH); 2200 (CN); 1782, 1688 (C=O); 1596 (C=N); 1075 (*p*-Br phenyl); ^{1}H NMR (DMSO-d_6) δ: 1.23 (t, 3H, CH_2CH_3); 4.52 (q, 2H, CH_2CH_3); 6.80 (s, 1H, CH-pyrrole); 7.70 (d, 2H, *J*=8.6 Hz, $C_{2,6}$-*p*-C_6H_4-Br); 7.80 (d, 2H, *J*=8.6 Hz, $C_{3,5}$-*p*-C_6H_4-Br); 7.90-8.10 (m, 4H, *p*-C_6H_4-CN); 11.20 (s, 1H, NH D_2O exchangeable). **M.S (m/z%):** 514 ($M^{+\bullet}$+1) (1); 185 (9);122 (40); 105 (99); 76 (100). $C_{27}H_{20}BrN_3O_3$ Cal C, 63.05; H, 3.92; N, 8.17, Found C, 62.87; H, 3.84; N, 8.02.

General procedure for the synthesis of compounds 8a-c

A mixture of 2-amino-1,4-disubstitutedphenyl-3-substituted-1H-pyrrole **4a,i & 5g** (0.01 mol) and the appropriate 4-substitutedphenacyl bromide (0.01 mol) in ethanol (50 ml) was refluxed for 2h, then left to cool. The obtained product was collected by filtration and crystallized from the proper solvent.

4-(Biphenyl-4-yl)-1-(4-chlorophenyl)-2-(2-(4-cyanophenyl)-2-oxoethylamino)-1H-pyrrole-3-carbonitrile (**8a**) Yield,88%; mp 150-152°C (Ethanol); IR (KBr,cm^{-1}) ύ: 3266 (NH); 2224 (CN); 1678 (C=O); 1594 (C=N); 1090 (*p*-Cl phenyl). **M.S (m/z%):** 514 ($M^{+\bullet}$+2) (9); 498 (6); 334 (21); 332(41);152(100). $C_{32}H_{21}ClN_4O$ Cal. C, 74.92; H, 4.13; N, 10.92, Found C, 74.85; H, 4.08; N, 10.84.

4-[4-Cyano-5-(2-(4-cyanophenyl)-2-oxoethyl amino)-1-(4-methoxyphenyl)-1H-pyrrol-3-yl]-N,N-dimethylbenzenesulfonamide (**8b**) Yield,54%; mp 145-147°C (Ethanol/Benzene); IR (KBr, cm^{-1}) ύ: 3302 (NH); 2216 (two CN); 1690 (C=O); 1422,1180 (SO_2); 1592 (C=N); 1284,1068 (C-O-C); ^{1}H NMR (DMSO-d_6) δ: 3.12 (s, 3H, OCH_3); 2.74 (s, 6H, $(CH_3)_2N$); 4.78 (s, 1H, NH, D_2O exchangeable); 5.41 (s, 2H, CH_2CO); 6.77 (s, 1H, CH-pyrrole); 7.25-7.27 (m, 4H, *p*-C_6H_4-$SO_2N(CH_3)_2$); 7.67-7.71 (m, 4H, *p*-C_6H_4-OCH_3); 8.09-8.16 (m, 4H, *p*-C_6H_4-CN). **M.S (m/z%):** 539 ($M^{+\bullet}$) (5); 248 (11);148 (19);105 (100).

$C_{29}H_{25}N_5O_4S$ Cal. C, 64.55; H, 4.67; N, 12.98, Found C, 64.47; H, 4.52; N, 12.84.

Ethyl 1-(4-bromophenyl)-4-(4-cyanophenyl)-2-(2-oxo-2-p-tolylethylamino)-1H-pyrrole-3-carboxylate (8c) Yield,83%; mp 165-166°C (Pet.ether); IR (KBr,cm^{-1}) ύ: 3056 (NH); 2222 (CN); 1674, 1650(C=O); 1596 (C=N); 1070 (*p*-Br phenyl); ^{1}H NMR (DMSO-d_6) δ: 1.25 (t, 3H, CH_2CH_3); 2.30 (s, 3H, CH_3); 4.23 (q, 2H, CH_2CH_3); 4.62 (s, 2H, CH_2CO); 6.81 (s, 1H, CH-pyrrole); 7.21-7.40 (m, 4H, *p*-C_6H_4-CH_3); 7.60-7.82 (m, 4H, *p*-C_6H_4-Br); 7.87-8.10 (m, 4H, *p*-C_6H_4-CN); 10.36 (s, 1H, NH, D_2O exchangeable) M.S (m/z%): 543 ($M^{+\bullet}$+1) (1); 440 (7); 249 (14);129 (67);74 (100). $C_{29}H_{24}BrN_3O_3$ Cal. C, 64.21; H, 4.46; N, 7.75, Found C, 64.05; H, 4.23; N, 7.64.

General procedure for the synthesis of compounds 9a-c

2-Amino-1,4-disubstituted phenyl-3-substituted-1H-pyrrole 4a,i and 5g (0.01 mol) was refluxed for 8h. in excess benzyl chloride (30 ml). The reaction mixture was concentrated under reduced pressure and the product obtained was collected by filtration and crystallized to give the target compounds.

2-(Benzylamino)-4-(biphenyl-4-yl)-1-(4-chloro phenyl)-1H-pyrrole-3-carbonitrile (9a) Yield,75%; mp 140-142°C (Acetic acid); IR (KBr,cm^{-1}) ύ: 3300 (NH); 2226 (CN); 1598 (C=N); 1092 (*p*-Cl phenyl); M.S (m/z%):459 ($M^{+\bullet}$) (1); 181 (41); 154 (22); 152 (100). $C_{30}H_{22}ClN_3$ Cal. C, 78.34; H, 4.82; N, 9.14, Found C, 78.15; H, 4.59; N, 9.01.

4-[5-(Benzylamino)-4-cyano-1-(4-methoxyphenyl) -1H-pyrrol-3-yl]-N,N-dimethylbenzene- sulfonamide (9b) Yield,47%; mp 153-154°C (Ethanol/Benzene); IR (KBr,cm^{-1}) ύ: 3230 (NH); 2216 (CN); 1340,1162 (SO_2); 1598 (C=N); 1250,1026 (C-O-C), ^{1}H NMR (DMSO-d_6) δ: 2.90 (s, 6H, $(CH_3)_2N$); 3.81 (s, 3H, OCH_3); 4.40 (s, 2H, CH_2); 6.80 (s, 1H, CH-pyrrole); 7.20-7.50 (m, 5H, p-C_6H_5-CH_2); 7.62-7.80 (m, 4H, p-C_6H_4-OCH_3); 7.91-8.20 (m, 4H, p-C_6H_4-$SO_2N(CH_3)_2$); 10.50 (s, 1H, NH, D_2O exchangeable). M.S (m/z%): 486 ($M^{+\bullet}$) (1); 151 (5); 148 (14); 64 (100). $C_{27}H_{26}N_4O_3S$ Cal. C, 66.65; H, 5.39; N, 11.51, Found C, 66.74; H, 5.25; N, 11.38.

Ethyl 2-(benzylamino)-1-(4-bromophenyl)-4-(4-cyanophenyl)-1H-pyrrole-3-carboxylate (9c) Yield,88%; mp 180-181°C (Acetic acid); IR (KBr,cm^{-1}) ύ: 3264 (NH); 2226 (CN); 1670 (C=O ester); 1070 (*p*-Br phenyl); ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, CH_2CH_3); 4.01 (q, 2H, CH_2CH_3); 5.13 (s, 2H, CH_2); 6.60 (s, 1H, CH-pyrrole); 7.01-7.38 (m, 5H, p-C_6H_5-CH_2); 7.51-7.78 (m, 8H,Ar-H); 9.21 (s, 1H, NH, D_2O exchangeable).M.S (m/z%): 501 ($M^{+\bullet}$+1) (1); 500 ($M^{+\bullet}$) (1);105 (25); 91 (100). $C_{27}H_{22}BrN_3O_2$ Cal. C, 64.81; H, 4.43; N, 8.40, Found C, 64.70; H, 4.36; N, 8.32.

General procedure for the synthesis of compounds 10a,b

The selected 2-amino-1,4-disubstitutedphenyl-1H-pyrrole-3-carbonitrile 4a&4i (0.01 mol) was refluxed in excess formic acid 80% (30 ml) for 5h. The solvent was concentrated to the minimum, then left to cool. The solid product obtained was filtered, washed with ethanol then crystallized from the appropriate solvent.

5-(Biphenyl-4-yl)-7-(4-chlorophenyl)-3H-pyrrolo [2,3-d]pyrimidin-4(7H)-one (10a) Yield,90%; mp 160-161°C (Acetic acid); IR (KBr,cm^{-1}) ύ: 3510, 3462 (br., OH, tautomer); 3258 (NH); 1674 (C=O); 1596 (C=N); 1092 (*p*- Cl phenyl); M.S (m/z%): 398 ($M^{+\bullet}$+1) (2); 181 (22); 180 (14); 179 (13); 178 (17);152 (100). $C_{24}H_{16}ClN_3O$ Cal. C, 72.45; H, 4.05; N, 10.56, Found C, 72.25; H, 3.89; N, 10.39.

4-[7-(4-Methoxyphenyl)-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl]-N,N-dimethylbenzene sulfonamide (10b) Yield,89%; mp 170-172°C (Dioxane); IR (KBr,cm^{-1}) ύ: 3520, 3470 (br., OH, tautomer); 3254 (NH); 1680 (C=O); 1338,1160 (SO_2); 1248,1028 (C-O-C); ^{1}H NMR (DMSO-d_6) δ: 2.65 (s, 6H, $(CH_3)_2N$); 3.73 (s, 3H, OCH_3), 3.95 (s, 1/2 H, NH, D_2O exchangeable), 6.76 (s, 1H, CH-pyrrole); 7.44-7.76 (m, 9H, Ar-H, CH-pyrimidine); 8.13 (s, 1/2 H, OH, tautomer, D_2O exchangeable).M.S (m/z%): 425 ($M^{+\bullet}$+1) (1); 418 (14); 212 (30); 181 (20); 76 (100). $C_{21}H_{20}N_4O_4S$ Cal. C, 59.42; H, 4.75; N, 13.20, Found C, 59.22; H, 4.56; N, 13.18.

General procedure for the synthesis of compounds 11a, b

A mixture of 2-amino-1,4-disubstituted phenyl-1H-pyrrole-3-carbonitrile 4a&4i (0.01 mol) and triethyl orthoformate (0.01 mol) was heated under reflux in acetic anhydride (25 ml) for 6h. The reaction mixture was concentrated to the minimum and left to cool. The obtained product was collected and crystallized from the appropriate solvent.

Ethyl N-4-(biphenyl-4-yl)-1-(4-chlorophenyl)-3-cyano-1H-pyrrol-2-ylformimidate (11a) Yield, 85%; mp 150-151°C (DMF); IR (KBr,cm^{-1}) ύ: 2300 (CN); 1596 (C=N); 1340,1026 (C-O-C); 1095 (*p*-Cl phenyl); M.S (m/z%): 426 ($M^{+\bullet}$+1) (1); 225 (7);

ISSN 1110-5089

181 (100). $C_{26}H_{20}ClN_3O$ Cal. C, 73.32; H, 4.73; N, 9.87, Found C, 73.01; H, 4.56; N, 9.77.

Ethyl N-3-cyano-4-[4-(N,N-dimethylsulfamoyl) phenyl]-1-(4-methoxyphenyl)-1H-pyrrol-2-ylformimidate **(11b)** Yield, 80%; mp 160-161°C (Dioxane); IR (KBr,cm^{-1}) ύ: 2216 (CN); 1594 (C=N); 1340,1162 (SO_2); 1250,1090 (C-O-C); ^{1}H NMR (DMSO-d_6) δ: 1.04 (t, 3H, CH_2CH_3); 2.62 (s, 6H, $(CH_3)_2N$); 3.40 (q, 2H, CH_2CH_3); 3.80 (s, 3H, OCH_3); 4.99 (s, 1H, N=CH); 6.79 (s, 1H, CH-pyrrole); 7.00-7.90 (m, 8H, Ar-H). **M.S (m/z%)**: 452 ($M^{+\bullet}$) (3); 330 (11); 222 (14); 212 (17);76 (100). $C_{23}H_{24}N_4O_4S$ Cal. C, 61.05; H, 5.35; N, 12.38, Found C, 60.96; H, 5.14; N, 12.27.

General procedure for the synthesis of compounds 12a, b

To a stirred solution of ethyl N-1,4-disubstitutedphenyl-3-cyano-1H-pyrrol-2-yl-formi midate **(11a,b)** (0.01 mol) in ethanol (50 ml), 98% hydrazine hydrate (0.02 mol) was added and stirring was continued for 7h at room temperature. The solid product was isolated by filtration and crystallized from the appropriate solvent.

5-(Biphenyl-4-yl)-7-(4-chlorophenyl)-4-imino-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-3-amine **(12a)** Yield, 93%; mp 180-182°C (Acetic acid); IR (KBr,cm^{-1}) ύ: 3450,3400 (NH_2); 3316 (NH); 1590 (C=N); 1095 (*p*-Cl phenyl); **M.S (m/z%)**: 413($M^{+\bullet}$+2)(0.8); 411 ($M^{+\bullet}$) (1); 305 (9); 277 (7); 202 (8); 190 (13); 180 (43); 177 (44); 153 (100). $C_{24}H_{18}ClN_5$ Cal. C, 69.98; H, 4.40; N, 17.00, Found C, 69.75; H, 4.25; N, 16.97.

4-[3-Amino-4-imino-7-(4-methoxyphenyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl]-N,N-dimethylbenzenesulfonamide **(12b)** Yield, 70%; mp 210-211°C (DMF); IR (KBr,cm^{-1}) ύ: 3450,3390 (NH_2); 3310 (NH); 1590 (C=N); 1340,1158 (SO_2 ,C-O-C); ^{1}H NMR (DMSO-d_6) δ: 2.90 (s, 6H, $(CH_3)_2N$); 4.40 (s, 2H, NH_2, D_2O exchangeable); 3.74 (s, 3H, OCH_3); 5.06 (s, 1H, CH-pyrimidine); 6.68 (s, 1H, CH-pyrrole); 7.19-8.20 (m, 8H, Ar-H); 11.90 (s, 1H, NH, D_2O exchangeable).**M.S (m/z%)**: 438 ($M^{+\bullet}$) (1); 330 (15); 230 (13); 222 (18); 76 (100). $C_{21}H_{22}N_6O_3S$ Cal. C, 57.52; H, 5.06; N, 19.17, Found C, 57.21; H, 4.97; N, 19.09.

Biology

Anti-inflammatory activity

The percent inhibition of inflammation exerted by the test compounds listed in **(tables 1-3)** was carried out by using the rat paw oedema method [28] that involved the use of one hundred and eight adult albino rats of both sexes weighing 120-150 gm which were obtained from animal house laboratory, Nile company, Cairo, Egypt. The test compounds and the reference standard ketoprofen (Biprofened®) were prepared as suspensions in Tween-80 (2%). The first group was kept as control, while the second group was orally given the standrard reference in a dose of 25mg/Kg, The 3rd-18th groups were administered the test compounds in a dose of 10mg/Kg orally, using intra-gastric tube [29]. The paw thickness of each rat was measured using dial micrometer model (120-1206 Baty, Sussex, England) before carrageenan injection and every one hour for six hours post administration of the test compounds.

% inhibition of oedema thickness = [(Tc-Tt)/Tc)] x 100

Tc: mean increase in thickness of the carrageenan injected paw of the control group

Tt : mean increase in thickness of the carrageenan injected paw of the drug treated groug.

Ulcerogenic activity

Test compounds that exhibited the most potent anti-inflammatory activity were evaluated for their ulcerogenic activity in rats. All animals subjected to this experimental test were sacrificed immediately after the last measurement (6 h), by diethyl ether and stomachs were separated. An opening at the greater curvature was made and the stomachs were washed with distilled water and cleaned gently by dipping in normal saline. The mucosal damage was inspected with a 3x magnifying lens for any evidence of hyperemia, hemorrhage or ulcer. For each stomach the mucosal damage was assessed [30,31].
The percentage ulceration for each group was calculated as follows:

$$\% \text{ Ulceration} = \frac{\text{Number of animals bearing ulcer in a group}}{\text{Total number of animals in the same group}} \times 100$$

Analgesic activity

The analgesic activity was evaluated according to writhing test [32]. The screening for analgesic activity for the test compounds was carried out by using one hundred and eight mices of both sexes weighing 25-30 gm which were divided into eighteen groups, each group consists of 6 mices per cage, group one served as control, orally received distilled water in appropriate volumes, group two received ketoprofen (Biprofened®) (5 mg/kg) orally by using intra-gastric tube followed by injection of 0.6 % acetic acid solution (10 ml/kg) I.P. after 1 h, while groups 3-18 received the tested compounds in a dose of (50 mg/kg) orally by using intra-gastric tube followed by injection of 0.6% acetic acid solution (10mL/kg) after

l h [33]. Stretching movements (arching of the back, developments of the tension in the abdominal muscles, elongation of the body and extension of the forelimbs) were counted as a writhing response. The number of writhes was counted for 15 min immediately after the acetic acid injection. The percentage of inhibition of writhes number was calculated as follows:

% inhibition = [(Nc-Nt)/Nc)] x 100

Nc: is the number of writhes in the control group and drug group respectively.

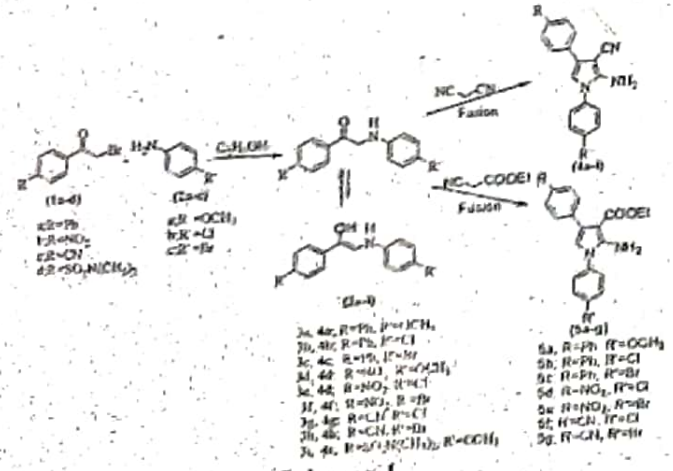
Nt: is the number of writhes in the drug group.

RESULTS AND DISCUSSION

Chemistry

Synthesis of compounds 3-5 (Scheme 1):

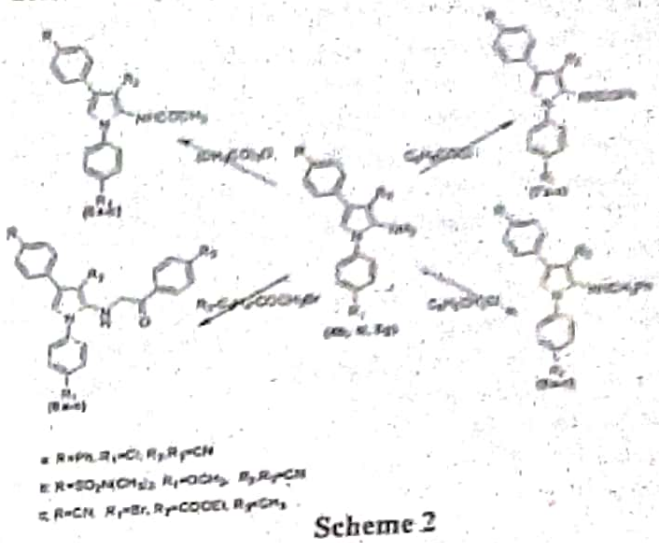
The preparation of the target compounds as shown in scheme 1 is achieved through the interaction of 4- substitutedphenacyl bromides (1) with different aromatic amines (2) in ethanol to afford 2-(4-substitutedphenylamino)-1-(4-substitutedphenyl)ethanones (3a-i) [27] which were further subjected to fusion either with malononitrile to yield 2-amino-1,4-disubstituted phenyl-1H-pyrrole-3-carbonitriles (4a-i) or with ethyl cyanoacetate to produce the respective compounds ethyl 2-amino-1,4-disubstitutedphenyl-1H-pyrrole-3-carboxylate derivatives (5a-g).



Scheme 1

Synthesis of compounds 6-9 (Scheme 2):

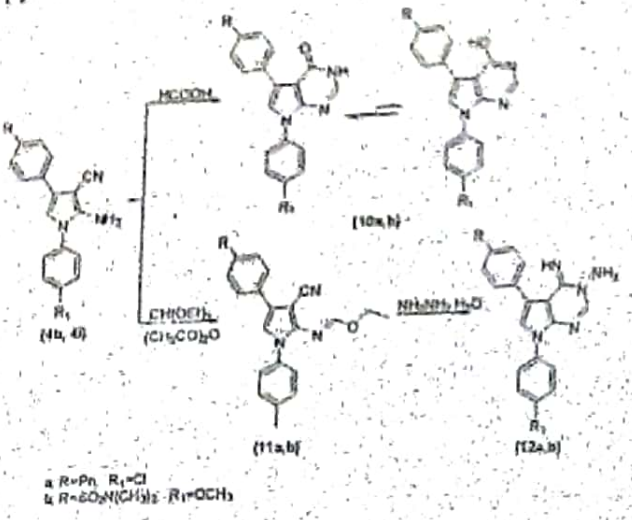
Acetylation of 2-aminopyrrole-3-carbonitrile derivatives (4b,i) and (5g) was achieved *via* reflux with acetic anhydride to yield the target compounds N-[3-substituted-1,4-disubstitutedphenyl-1H-pyrrol-2-yl] acetamides (6a-c). While N-[3-substituted-1,4-disubstitutedphenyl-1H-pyrrol-2-yl]benzamides (7a-c) were synthesized by refluxing the 2-aminopyrrole derivatives (4b,i) and (5g) with benzoyl chloride in presence of pyridine as a catalyst. The target compounds N-[3-substituted-1,4-disubstitutedphenyl-1H-pyrrol-2-yl]-2-(4-substituted phenyl)-2-oxoethylamines (8a-c) were prepared through the reaction of 2-aminopyrrole derivatives (4b,i) and (5g) with the appropriate 4-substitutedphenacyl bromide in ethanol. 2-(Benzylamino)-1,4-disubstitutedphenyl-3-substituted-1H-pyrrole derivatives (9a-c) were synthesized *via* refluxing the 2-aminopyrrole derivatives (4b,i) and (5g) with benzyl chloride.



Scheme 2

Synthesis of compounds 10-12 (scheme 3)

5,7-Disubstitutedphenyl-3H-pyrrolo[2,3-d] pyrimidin-4(7H)-ones (10a,b) were prepared by the reaction of 2-aminopyrrole-3-carbonitrile derivatives (4b,i) with formic acid. Upon the reaction of 2-aminopyrrole-3-carbonitrile derivatives (4b,i) with triethyl orthoformate in acetic anhydride as a solvent; it yielded ethyl N-1,4-disubstitutedphenyl-3-cyano-1H-pyrrol-2-ylformimidates (11a,b); which were further subjected to hydrazinolysis by using hydrazine hydrate 98% to yield the target compounds 5,7-disubstitutedphenyl-4-imino-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-3-amines (12a,b).



Scheme 3

ISSN 1110-5089

Biological activity

Anti-inflammatory screening:

Results of *in-vivo* anti-inflammatory screening of the selected sixteen compounds presented in (tables 1-3) revealed that among the pyrrole derivatives bearing 1-(4-chlorophenyl) moiety; compound **6a** with an acetylated amino group elicited the highest anti-inflammatory activity (P% =1.08), while lengthening the side chain using phenacyl moiety instead of the acetyl group in compound **8a** retained the anti-inflammatory activity showing (P% =1.08), on the other hand compound **9a** bearing a benzyl group showed moderate potency (P% =0.97) comparable to ketoprofen (Biprofened®) as a reference drug.

Moreover, pyrrole derivatives bearing 1-(4-methoxyphenyl) group as compounds **6b** and **7b** with 2-substituted amino by acetyl and benzoyl moieties; respectively, showed moderate potency (P% =0.78) comparable to biprofened. However, replacement strategy of acetyl group by phenacyl moiety and benzyl group in compounds **8b** and **9b** respectively, led to increase in their anti-inflammatory activity (P% =0.82, 0.80). In addition to that; compounds with 1-(4-bromophenyl) group such as compound **6c** bearing an acetyled amino group showed moderate potency (P% =0.78). Replacement of acetyl group by benzoyl function in compound **7c** retained the anti-inflammatory activity (P% =0.79), while lengthening the side chain using phenacyl moiety instead of acetyl group in compound **8c** increased the anti-inflammatory activity (P% =1.08). Besides, compound **9c** bearing benzyl group showed moderate potency (P% =0.76) comparable to the reference drug. Furthermore, the pyrrole derivative **11a** with substituted amino by ethoxymethyleneamino group elicited high anti-inflammatory activity (P%= 1.01) comparable to the reference drug.

Concerning anti-inflammatory activity of pyrrolo[2,3-d]pyrimidine derivatives, compound **10b** bearing 4-oxo function showed moderate potency (P% =0.97); while replacement of 4-oxo function by 4-imino function in compounds **12a** and **12b** led to increase in their anti-inflammatory activities. In which compound **12a** bearing 4-biphenyl moiety is more active (P%= 1.00) than compound **12b** with 4-(N,N-dimethylsulphamoyl)phenyl moiety (P%= 0.84).

Ulcerogenic activity:

The ulcerogenic effects of the most active anti-inflammatory compounds **6a, 8a, 8c, 11b** and **12a** is presented in **(table 4)** which revealed that compounds **(6a, 8a, 8c)** exerted zero percent ulceration compared to 100% of that of ketoprofen (Biprofened®) as a reference drug.

Table (1): Percent of oedema inhibition of compounds (5g-12b) after 1 and 2 h.

Comp. No.	Paw Oedema Thickness (mm)			
	1 hr	% Oedema Inhibition	2 hr	% Oedema Inhibition
	Mean ± S.D		Mean ± S.D	
Control	3.865 ± 0.104	---	4.055 ± 0.045	---
Biprofened	3.417 ± 0.019*	11.591	3.173 ± 0.083*	21.751
5g	3.687 ± 0.052*	4.605	3.532 ± 0.026*	12.898
6a	3.320 ± 0.044*	14.101	3.070 ± 0.041*	24.291
6b	3.665 ± 0.081*	5.175	3.580 ± 0.053*	11.714
6c	3.887 ± 0.068	---	3.710 ± 0.026*	8.508
7b	3.505 ± 0.024	9.314	3.408 ± 0.015	15.956
7c	3.368 ± 0.017*	12.859	3.247 ± 0.021*	19.926
8a	3.310 ± 0.009*	14.360	3.158 ± 0.044*	22.121
8b	3.662 ± 0.017*	5.252	3.558 ± 0.029*	12.256
8c	4.027 ± 0.057	---	3.948 ± 0.015*	2.639
9a	3.545 ± 0.033*	8.279	3.333 ± 0.030*	17.805
9b	3.850 ± 0.040	0.388	3.670 ± 0.021	9.494
9c	3.457 ± 0.051*	10.556	3.248 ± 0.033*	19.901
10b	3.452 ± 0.037*	10.686	3.345 ± 0.035*	17.509
11b	3.325 ± 0.010	13.972	3.160 ± 0.046	22.072
12a	3.295 ± 0.029*	14.748	3.160 ± 0.036*	22.072
12b	3.647 ± 0.032*	5.640	3.542 ± 0.032*	12.651

Table (2): Percent of oedema inhibition of compounds (5g-12b) after 3 and 4 h.

Comp. No.	Paw Oedema Thickness (mm)			
	3 hr	% Oedema Inhibition	4 hr	% Oedema Inhibition
	Mean ± S.D.		Mean ± S.D.	
Control	4.225 ± 0.098	---	4.573 ± 0.068	---
Biprofened	2.903 ± 0.073*	31.290	2.750 ± 0.033*	39.864
5g	3.353 ± 0.099*	20.639	3.210 ± 0.124*	29.805
6a	2.588 ± 0.034*	38.746	2.388 ± 0.049*	47.780
6b	3.445 ± 0.032*	18.462	3.378 ± 0.026*	26.132
6c	3.575 ± 0.023*	15.385	3.525 ± 0.014*	22.917
7b	3.352 ± 0.044	20.663	3.352 ± 0.015	26.700
7c	3.112 ± 0.063*	26.343	2.922 ± 0.012*	36.103
8a	2.948 ± 0.029*	30.225	2.758 ± 0.034*	39.689
8b	3.352 ± 0.031*	20.663	3.270 ± 0.042*	28.493
8c	3.770 ± 0.018	10.769	3.547 ± .0.018	22.436
9a	3.122 ± 0.069*	26.107	2.953 ± 0.037*	35.425
9b	3.535 ± 0.026	16.331	3.368 ± 0.023	26.350
9c	3.140 ± 0.080*	25.680	2.932 ± 0.073*	35.885
10b	3.127 ± 0.069*	25.988	2.842 ± 0.035*	37.853
11b	2.890 ± 0.055	31.598	2.722 ± 0.054	40.477
12a	2.935 ± 0.033*	30.533	2.732 ± 0.044*	40.258
12b	3.437 ± 0.033*	18.651	3.283 ± 0.029*	28.209

Table (3): Percent of oedema inhibition of compounds (5g-12b) after 5 and 6 h and their potencies.

Comp. No.	Paw Oedema Thickness (mm)				
	5 hr	% Oedema Inhibition	6 hr	% Oedema Inhibition	Potency
	Mean ± S.D.		Mean ± S.D.		
Control	5.252 ± 0.301	---	6.000 ± 0.086	---	---
Biprofened	2.423 ± 0.095*	53.865	2.393 ± 0.145*	60.166	1
5g	3.063 ± 0.077*	41.679	2.810 ± 0.103*	53.167	0.88
6a	2.355 ± 0.036*	55.160	2.092 ± 0.020*	65.216	1.08
6b	3.297 ± 0.062*	37.224	3.167 ± 0.152*	47.217	0.78
6c	3.357 ± 0.034*	36.081	3.175 ± 0.039*	47.083	0.78
7b	3.312 ± 0.017*	36.938	3.142 ± 0.079*	47.633	0.79
7c	2.753 ± 0.037*	47.582	2.087 ± 0.019*	47.550	0.79
8a	2.537 ± 0.032*	51.695	2.102 ± 0.088*	65.067	1.08
8b	3.180 ± 0.024*	39.452	3.037 ± 0.150*	49.383	0.82
8c	3.372 ± 0.019*	35.796	3.147 ± 0.083*	65.133	1.08
9a	2.645 ± 0.051*	49.638	2.480 ± 0.040*	58.667	0.97
9b	3.300 ± 0.018*	37.167	3.087 ± 0.070*	48.550	0.80
9c	2.773 ± 0.028*	47.201	2.520 ± 0.015*	58.000	0.96
10b	2.627 ± 0.026*	49.981	2.497 ± 0.021*	58.383	0.97
11b	2.543 ± 0.022*	51.580	2.350 ± 0.028*	60.833	1.01
12a	2.537 ± 0.032*	51.695	2.357 ± 0.049*	60.717	1.00
12b	3.175 ± 0.039*	39.547	2.958 ± 0.025*	50.700	0.84

* Significantly different from control value at $P < 0.05$
* S.D.= Standard deviation.

Table (4): Ulcerogenic effects of the test compounds.

Compounds	Control	Biprofened	6a	8a	8c	11b	12a
% Ulceration	0.0	100	0.0	0.0	0.0	50	33.33

Zagazig J. Pharm. Sci., December, 2011
Vol. 20, No. 2, pp. 6-18

ISSN 1110-5089

Analgesic activity

Results of *in-vivo* analgesic screening is presented in (table 5) revealed that among compounds with 1-(4-chlorophenyl) moiety; compound **6a** with acetylated amino group showed moderate analgesic activity (P% =0.78). However, lengthening the side chain using a phenacyl moiety instead of acetyl group in compound **8a** increased the analgesic activity (P% =0.81), on the other hand, compound **9a** bearing a benzyl group also showed moderate potency (P% =0.71) comparable to the reference drug. Pyrrole derivatives having 1-(4-methoxyphenyl) group as compounds **6b** and **9b** showed moderate potency (P% =0.84 and 0.81) respectively, while substitution of the 2-amino moiety with benzoyl and phenacyl groups as in compounds **7b** and **8b**, respectively led to decrease the analgesic activity (P% =0.62, 0.57). However, among compounds bearing 1-(4-bromophenyl) group; compound **7c** with 2-substituted amino group by benzoyl moiety elicited the highest analgesic activity (P% =1.03), while other derivatives showed poor to moderate activity. Compound **11a** with substituted amino by ethoxymethyleneamino moiety elicited moderate analgesic activity (P%= 0.84) comparable to the Ketoprofen (biprofened®) as a reference drug. Concerning the analgesic activity of pyrrolo[2,3-d]pyrimidine derivatives, compound **10b** bearing 4-oxo function showed moderate potency (P% =0.65), while compounds having 4-imino function as compounds **12a** and **12b** showed higher analgesic activity (P%= 0.78, 0.84) respectively.

Table (5): Number of writhing movements and analgesic activity of compounds (5g-12b).

Comp. No.	Number of writhing movements	% inhibition (analgesic activity)	Potency
Control	37	---	---
Biprofened	5	86.50	1
5g	8	78.40	0.90
6a	12	67.60	0.78
6b	10	72.90	0.84
6c	18	51.40	0.59
7b	17	54.10	0.62
7c	4	89.18	1.03
8a	11	70.30	0.81
8b	20	50.00	0.57
8c	13	67.50	0.78
9a	14	62.20	0.71
9b	11	70.30	0.81
9c	22	41.00	0.47
10b	16	56.80	0.65
11b	10	72.90	0.84
12a	13	67.50	0.78
12b	10	72.90	0.84

CONCLUSION

Results of the carrageenan induced rat paw oedema (CPE) showed that compounds **(6a, 8a, 8c, 11b&12a)** possess the highest anti-inflammatory potency compared to ketoprofen (Biprofened®) as a reference drug, while compounds **(5g, 8b, 9a, 9b, 9c, 10b&12b)** showed moderate potency and compounds **(6b, 6c, 7b&7c)** have the lowest anti-inflammatory potency. Concerning the ulcerogenic activity; compounds **(6a, 8a&8c)** showed zero ulceration compared to ketoprofen (biprofened®) as a reference drug. Furthermore, compound **(7c)** was found to be the most promising analgesic compound as it exhibited the highest activity compared to ketoprofen (Biprofened®); while compounds **(5g, 6a, 6b, 8a, 8c, 9a, 9b, 11b, 12a&12b)** exhibited moderate analgesic activity and compounds **(6c, 7b, 8b, 9c&10b)** showed low analgesic activity.

Acknowledgement

The authors are grateful to Dr. Ragya Taha Proffessor of Pharmacology, Department of Pharmacology, Faculty of Pharmacy (Girls branch), Al-Azhar University for her efforts in carrying out the biological screening of the newly synthesized compounds.

REFERENCES

1. Williams D. A., Lemke T. L., **Foye's Principles of Medicinal Chemistry, Non-**

steroidal Anti-inflammatory Drugs., 5th ed., Lippincott Williams & Wilkins, 751 (2002).
2. Dannhardt G., Kiefer W., Kramer G., Maehrlein S., Nowe U., Fiebich B., **Eur. J. Med. Chem.**, 35, (2000).
3. Dubost J. J., Soubrier M., Sauvezie B., **Rev. Med. Interne.**, 20, (1999).
4. Bayly C. I., Black C., Leger S., Ouimet N., Ouellet M., Percival M. D., **Bioorg. Med. Chem. Lett.**, 9, (1999).
5. Black W. C., Bayly C., Belley M., Chan C. C., Charleson S., Denis D., Gauthier J. Y., Gordon R., Guay D., Kargman S., Lau C.K., Leblanc Y., Mancini J., Ouellet M., Percival D., Roy P., Skorey K., Tagari P., Vickers P., Wong E., Xu L., Prasit P., **Bioorg. Med. Chem. Lett.**, 6, (1996).
6. Crofford L. J., **J. Rheumatol.**, 24 (1997).
7. Seibert K., Zhang Y., Leahy K., Hauser S., Masferrer J., Perkins W., Lee L., Isakson P., **Proc. Natl. Acad. Sci. U.S.A.**, 91, (1994).
8. Grillo M. P., Hua F., **Am. Soc. Pharmacol. Exp. Ther.**, 31, (2003).
9. Lessigiarska I., Nankov A., Bocheva A., Pajeva I., Bijev A., **IL. Farmaco.**, 60, (2005).
10. Harrak Y., Rosell G., Daidone G., Plescia S., Schillaci D., Pujol M. D., **Bioorg. Med. Chem.**, 15, (2007).
11. Ushiyama S., Yamada T., Murakami Y., Kunakura S., Inoue S., Suzuki K., Nakao A., Kawara A., Kimura T., **Eur. J. Pharmacol.**, 578, (2008).
12. Tanko Y., Magaji G. M., Yerima M., Magaji R. A., Mohammed A., **Afr. J. Trad. CAM.**, 5, (2008).
13. Kumar R., Subramanian A., Masand N., Patil V. M., **DJNB.**, 5, (2010).
14. Jana G. H., Jain S., Arora S. K., Sinha N., **Bioorg. Med. Chem. Lett.**, 15, (2005).
15. Jana G. H., Jain S., Arora S. K., Sinha N., **Bioorg. Med. Chem. Lett.**, 16, (2006).
16. Raimondi M. V., Cascioferro S., Schillaci D., Petruso S., **Eur. J. Med. Chem.**, 41, (2006).
17. Biava M., Porretta G. C., Poce G., Logu A. D., Meleddu R., Rossi E. D., Manettic F., Botta M., **Eur. J. Med. Chem.**, 44, (2009).
18. Mai A., Massa S., Ragno R., Cerbara I., Jesacher F., Loidi P., Brosch G., **J. Med. Chem.**, 46, (2003).
19. Hazarika M., White R. M., Johnson J. R., Pazdur R., **The Oncologist**, 9, (2004).
20. Kim M. K., Cho Y. H., Kim J. M., Chun M. W., Lee S. K., Lim Y., Lee C. H., **Cancer Lett.**, 223, (2005).
21. Hilmy K. M. H., **Arch. Pharm. Chem. Life Sci.**, 339, (2006).
22. Varaprasad C.V., Ramasamy K. S., Girardet J. L., Gunic E., Lai V., Zhong W., An H., Hong Z., **Bioorg. Chem.**, 35, (2007).
23. Hong J. H., Oh C. H., **Arch. Pharm. Chem. Life Sci.**, 342, (2009).
24. Dodonova J., Uogintaite I., Masevicius V., Tumkevicius S., **Chem. Heterocycl. Comp.**, 46, (2010).
25. Etcheverry S. B., Barrio D. A., Cortizo A. M., Williams P. A., **J. Inorg. Bio. Chem.**, 88, (2002).
26. Fernandes E., Costa D., Toste S. A., Lima J. L. F. C., Reis S., **Free Radical Biol. Med.**, 37, (2004).
27. Hassan S. M., El-Maghraby A., Abd El- Aal M. M., Bashandy M. S., **Phosphorus, Sulphur Silicon**, 184, (2009).
28. Winter C. A., Risley E. A., Nuss G. W., **Proc. Soc. Exp. Biol. Med.**, 111, (1962).
29. Khalifa M. M., Abdelbaky N. A., **AZ. J. Pharm. Sci.**, 35, (2007).
30. Abouzeit-Har M., Verimer T., Long J., **Die Pharmazie**, 37, (1982).
31. Metwally K. A., Yaseen S. H., Lashine E. M., El-Fayomi H. M., El-Sadek M. E., **Eur. J. Med. Chem.**, 42, (2007).
32. Koster R., Anderson M., Beer D., **Eur. J. Fed. Proc.**, 18, (1959).
33. Narayana B., Raj K. K. V., Ashalatha B. V., Kumari N. S., **Arch. Pharm. Chem. Life Sci.**, 338, (2005).

Received:3/7/2011
Accepted:8/9/2011

Zagazig J. Pharm. Sci., December, 2011
Vol. 20, No. 2, pp. 6-18

ISSN 1110-5089

تشييد بعض مشتقات البيرول والمحتمل أن يكون لها فاعلية ضد الالتهابات

مكارم محمد قراعة[1] ، مها محمد خليفة[2] ، هند محمد السحراوى[2] ، مروة طه سرج[3]، شيماء محمد عبد الجليل[3]

[1]قسم الكيمياء العضوية - كلية الصيدلة - جامعة القاهرة

[2] قسم الكيمياء الصيدلية - كلية الصيدلة (بنات) - جامعة الأزهر

[3]قسم الكيمياء العضوية - كلية الصيدلة (بنات) - جامعة الأزهر

عند النظر إلى النشاط البيولوجى العالي لمركبات البيرول والتي تدخل في صناعة العديد من الأدوية المضادة للالتهابات كان اتجاه البحث إلى تحضير بعض مشتقات البيرول وذلك باستخدام أمينو-١،٤-داى(٤-مشتق الفينيل)-١-هيروجين بيرول-٣-كربونيتريل (٤ أ- ط) والذي تم تحضيره عن طريق تسخين ٢-(مشتق فينيل أمينو)-١-(٤-مشتق الفينيل)ايثانون (٣ أ- ط) مع المالونونيتريل.

كما تم في هذا البحث تحضيربعض مشتقات البيرول الجديدة التى لها نشاط بيولوجى عن طريق تفاعل المركبات (٣ أ- ط) مع الايثيل سيانو اسيتات لينتج المركبات (٥ أ-ز). كما تم تفاعلهم مع انهيدريد حمض الخليك و البنزويل كلوريد و بعض مشتقات الفنيثيل بروميد و البنزيل كلوريد لينتج المركبات (٦ أ-ج)، (٧ أ-ج)، (٨ أ-ج) و (٩ أ-ج) على التوالى.

كذلك وقد تضمن البحث تحضير مشتقات البيرولوبيريميدين وذلك من خلال تفاعل المركبات (٤ ب، ٤ ط) مع حمض الفورميك لينتج (10 أ، ب) ومع خليط من ثلاثى ايثيل اورثوفورمات وانهيدريد حمض الخليك لينتج المركبات (١١ أ،ب) الذين تم تفاعلهم مع هيدرات الهيدرازين لينتج المركبات (١٢ أ،ب).

كما تم تقييم كل المركبات المستحدثه كمضادات للالتهابات ومعظم المركبات أعطت نتائج مرضية بالمقارنة بمركب الكيتوبروفين (باى بروفينيد®) كمرجع للقياس. كذلك قد تم تقييم المركبات التي أعطت أعلى نتائج كمضادات للالتهابات من حيث فاعليتها كمسكن للآلام وتوضيح تأثيرها على المعدة وقد أوضحت النتائج أن اغلب المركبات لا تؤدى إلى قرح بالمعدة.