Asian Journal of Chemistry; Vol. 26, No. 24 (2014), 8514-8520

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.18253

Synthesis and Anti-Inflammatory Activities of Some New Substituted Benzocarboxamide Pyrimidine Derivatives Using *N*-(4-Acetylphenyl)-5-chloro-2-methoxybenzamide as Starting Material

AZZA A. HUSSAIN[1,*], MOHAMED M. ABDULLA[2], ABD EL-GALIL E. AMR[3,4], MOHAMED A. AL-OMAR[3] and AHMED F.A. SHALABY[1]

[1]Chemistry Department, Faculty of Science, Cairo University, Giza Egypt
[2]Research Unit, Saco Pharm. Co., 6th October City 11632, Egypt
[3]Pharmaceutical Chemistry Department, Drug Exploration and Development Chair, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
[4]Applied Organic Chemistry Department, National Research Center, Dokki, Cairo, Egypt

*Corresponding author: E-mail: hussainazza2014@yahoo.com

Received: 5 June 2014; *Accepted*: 19 August 2014; *Published online*: 1 December 2014; AJC-16393

A series of substituted pyrimidine derivatives (**2-6**) were prepared from corresponding chalcones, which were prepared from *N*-(4-acetylphenyl)-5-chloro-2-methoxybenzamide as starting material. The structure assignments of the newly synthesized compounds are based on chemical and spectroscopic evidence. The pharmacological screening showed that many of these compounds have less toxicity and good anti-inflammatory activities.

Keywords: 5-Chloroanisic acid, Cinnamoyl derivatives, Pyrimidines, Antiinflammatory activities.

INTRODUCTION

In our previous work, we found that certain substituted steroidal derivatives showed α-reductase inhibition[1] androgenic and anabolic activities[2]. Some new heterocyclic compounds containing nitrogen atom have been synthesized and used as antiparkinsonian[3], antitumor[4,5], antimicrobial[6-8] and antiinflammatory activities[9,10]. Recently, some of the pyridine derivatives were synthesized and evaluated as antimycobacterial[11,12], new class of cytotoxic Hsp90 inhibitors[13], antitumor[14], antiproliferative[15] and antiinflammatory[16-19] agents. They are also evaluated as analgesic[20,21] and antioxidant[22] agents. Among these types of heterocyclic molecules have been shown to have various important biological activities such as antimicrobial[23], antileukemic[24], anti-helminthes, anticonvulsant[25], antibacterial activity[26], antifungal[27] and anticancer[28] activity. In view of these observations and in continuation of our previous works in heterocyclic chemistry, we have herein synthesized some new heterocyclic pyridine derivatives and tested their antiinflammatory activities.

EXPERIMENTAL

Melting points are uncorrected and determined with electro thermal capillary apparatus and were uncorrected. Elemental analyses were performed in the Microanalytical Unit, Faculty of Science, Ain Shams University using Perkin Elmer CHN 2400 (one Run), Egypt and were found within ± 0.4 % of the theoretical values. The IR spectra were recorded in (KBr) on a Shimadzu CVT-04 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were determined on Varian Gemini 270 MHz using $CDCl_3$ as solvent using TMS as an internal standard. The mass spectra were performed using a Varian MAT CH-5 spectrometer (70 eV). All reactions were followed by TLC (silica gel, aluminum sheets $60F_{254}$, Merck).

Synthesis of compounds 3a-g and 4a-g: A mixture of (**2a-g**) (1 mmol), urea or thiourea (2 mmol) and sodium methoxide (108 mg, 2 mmol) in absolute ethanol (20 mL) was heated under reflux for 5 h. The reaction mixture was concentrated under reduced pressure, then poured into ice water. The solid formed was filtered off and crystallized from acetone-methanol give oxopyrimidine and thioxopyrididine derivatives (**3a-g**) and (**4a-g**), respectively.

5-Chloro-*N*-[4-(1,2-dihydro-2-oxo-6-phenylpyrimidin-4-yl)phenyl]-2-methoxy benzamide (3a): Yield 56 %, m.p. 268-270 °C; IR (KBr, ν_{max} cm^{-1}): 3538 (NH), 1671 (amide I), 1637 (amide II); ^{1}H NMR ($CDCl_3$, ppm): δ = 3.48 (s, 3H, OCH_3), 6.64 (s, 1H, pyrimidinyl-H), 7.00-7.76 (m, 12H, Ar-H), 10.85, 11.11 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.65 (OCH_3), 163.70 (CONH), 167.84, 154.66, 138.00, 146.42 (4C, pyrimidinyl-C), 134.09, 127.21, 133.77, 125.91, 114.97, 155.18, 137.12, 117.60, 131.90, 145.10, 140.70, 127.83, 128.71, 130.26 (18C, Ar-C);

MS (EI, 70 eV): *m/z* (%): 432 [M^+]. Elemental analysis for $C_{24}H_{18}N_3O_3Cl$ (431.87): Calcd. C, 66.75; H, 4.20; Cl, 8.21; N, 9.73; found: C, 66.66; H, 4.12; Cl, 8.13; N, 9.65.

***N*-[4-{6-(4-Bromophenyl)-1,2-dihydro-2-oxopyrimidin-4-yl}phenyl]-5-chloro-2-methoxy benzamide (3b):** Yield 46 %, m.p. 122-124 °C; IR (KBr, ν_{max} cm^{-1}): 3545 (NH), 1670 (amide I), 1635 (amide II); ^1H NMR ($CDCl_3$, ppm): δ = 3.46 (s, 3H, OCH_3), 6.68 (s, 1H, pyrimidinyl-H), 7.08-7.86 (m, 11H, Ar-H), 10.94, 11.14 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.50 (OCH_3), 163.73 (CONH), 167.92, 154.70, 138.05, 146.46 (4C, pyrimidinyl-C), 134.90, 127.55, 134.23, 124.30, 116.18, 153.15, 140.80, 117.88, 129.12, 141.70, 148.91, 130.70, 131.70, 123.70 (18C, Ar-C); MS (EI, 70 eV): *m/z* (%): 510 [M^+]. Elemental analysis for $C_{24}H_{17}N_3O_3BrCl$ (510.77): Calcd. C, 56.44; H, 3.35; Cl, 6.94; N, 8.23; found: C, 56.33; H, 3.28; Cl, 6.90; N, 8.14.

5-Chloro-*N*-[4-{6-(2-chlorophenyl)-1,2-dihydro-2-oxopyrimidin-4-yl}phenyl]-2-methoxy benzamide (3c): Yield 55 %, m.p. 167-169 °C; IR (KBr, ν_{max} cm^{-1}): 3542 (NH), 1672 (amide I), 1630 (amide II); ^1H NMR ($CDCl_3$, ppm): δ = 3.47 (s, 3H, OCH_3), 6.62 (s, 1H, pyrimidinyl-H), 7.12-7.89 (m, 11H, Ar-H), 10.96, 11.08 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.51 (OCH_3), 163.81 (CONH), 167.90, 154.74, 138.10, 146.51 (4C, pyrimidinyl-C), 134.91, 127.54, 134.23, 124.30, 116.18, 153.15, 140.80, 117.88, 129.12, 141.70, 148.91, 130.70, 131.70, 123.70 (18C, Ar-C); MS (EI, 70 eV): *m/z* (%): 466 [M^+]. Elemental analysis for $C_{24}H_{17}N_3O_3Cl_2$ (466.32): Calcd. C, 61.82; H, 3.67; Cl, 15.21; N, 9.01; found: C, 61.72; H, 3.60; Cl, 15.10; N, 8.86.

5-Chloro-*N*-[4-{6-(4-chlorophenyl)-1,2-dihydro-2-oxopyrimidin-4-yl}phenyl]-2-methoxy benzamide (3d): Yield 62 %, m.p. 142-144 °C; IR (KBr, ν_{max} cm^{-1}): 3541 (NH), 1672 (amide I), 1623 (amide II); ^1H NMR ($CDCl_3$, ppm): δ = 3.45 (s, 3H, OCH_3), 6.63 (s, 1H, pyrimidinyl-H), 7.10-7.74 (m, 11H, Ar-H), 10.77, 11.00 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.55 (OCH_3), 163.84 (CONH), 167.91, 154.76, 138.13, 146.52 (4C, pyrimidinyl-C), 128.71, 132.70, 133.96, 133.72, 114.97, 140.71, 155.18, 117.61, 134.18, 131.90, 145.10, 128.83, 125.93, 130.28 (18C, Ar-C); MS (EI, 70 eV): *m/z* (%): 466 [M^+]. Elemental analysis for $C_{24}H_{17}N_3O_3Cl_2$ (466.32): Calcd. C, 61.82; H, 3.67; Cl, 15.21; N, 9.01; found: C, 61.70; H, 3.61; Cl, 15.08; N, 8.85.

5-Chloro-*N*-[4-{1,2-dihydro-6-(2-nitrophenyl)-2-oxopyrimidin-4-yl}phenyl]-2-methoxy benzamide (3e): Yield 65 %, m.p. 180-182 °C; IR (KBr, ν_{max} cm^{-1}): 3538 (NH), 1670 (amide I), 1625 (amide II); ^1H NMR ($CDCl_3$, ppm): δ = 3.52 (s, 3H, OCH_3), 6.68 (s, 1H, pyrimidinyl-H), 7.35-8.12 (m, 11H, Ar-H), 10.72, 11.04 (2s, 2H, 2 NH exchangeable with D_2O); MS (EI, 70 eV): *m/z* (%): 477 [M^+]. Elemental analysis for $C_{24}H_{17}N_4O_5Cl$ (476.87): Calcd. C, 60.45; H, 3.59; Cl, 7.43; N, 11.75; found: C, 60.38; H, 3.50; Cl, 7.35; N, 11.68.

5-Chloro-*N*-[4-{1,2-dihydro-6-(4-nitrophenyl)-2-oxo-pyrimidin-4-yl}phenyl]-2-methoxy benzamide (3f): Yield 58 %, m.p. 119-121 °C; IR (KBr, ν_{max} cm^{-1}): 3543 (NH), 1672 (amide I), 1622 (amide II); ^1H NMR ($CDCl_3$, ppm): δ = 3.48 (s, 3H, OCH_3), 6.65 (s, 1H, pyrimidinyl-H), 7.26-8.08 (m, 11H, Ar-H), 10.75, 11.10 (2s, 2H, 2 NH exchangeable with D_2O); MS (EI, 70 eV): *m/z* (%): 477 [M^+]. Elemental analysis for $C_{24}H_{17}N_4O_5Cl$ (476.87): Calcd. C, 60.45; H, 3.59; Cl, 7.43; N, 11.75; found: C, 60.39; H, 3.51; Cl, 7.36; N, 11.67.

5-Chloro-*N*-[4-{1,2-dihydro-6-(4-methoxyphenyl)-2-oxopyrimidin-4-yl}phenyl]-2-methoxy benzamide (3g): Yield 58 %, m.p. 119-121 °C; IR (KBr, ν_{max} cm^{-1}): 3543 (NH), 1672 (amide I), 1622 (amide II); ^1H NMR ($CDCl_3$, ppm): δ = 3.48, 3.72 (2s, 6H, $2OCH_3$), 6.66 (s, 1H, pyrimidinyl-H), 7.08-7.95 (m, 11H, Ar-H), 10.70, 11.00 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.56 (OCH_3), 163.82 (CONH), 167.88, 154.72, 138.10, 146.48 (4C, pyrimidinyl-C), 128.11, 158.74, 133.76, 125.91, 114.90, 155.20, 134.16, 117.62, 131.90, 145.09, 140.70, 114.60, 128.74, 130.23 (18C, Ar-C); MS (EI, 70 eV): *m/z* (%): 477 [M^+]. Elemental analysis for $C_{25}H_{20}N_3O_4Cl$ (461.90): Calcd. C, 65.01; H, 4.36; Cl, 7.68; N, 9.10; found: C, 64.86; H, 4.30; Cl, 7.60; N, 9.03.

5-Chloro-N-[4-(1,2-dihydro-6-phenyl-2-thioxopyrimidin-4-yl)phenyl]-2-methoxy benzamide (4a): Yield 80 %, m.p. 213-215 °C; IR (KBr, ν_{max} cm^{-1}): 3498 (NH), 1687 (amide I), 1625 (amide II); ^1H NMR ($CDCl_3$, ppm): δ = 3.47 (s, 3H, OCH_3), 7.16 (s, 1H, pyrimidinyl-H), 7.21-7.98 (m, 12H, Ar-H), 10.75, 11.20 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.26 (OCH_3), 163.75 (CONH), 176.73, 155.10, 136.95, 165.98 (4C, pyrimidinyl-C), 134.12, 127.24, 133.75, 125.90, 114.95, 155.16, 137.15, 117.61, 131.91, 145.08, 140.71, 127.83, 128.71, 130.28 (18C, Ar-C); MS (EI, 70 eV): *m/z* (%): 448 [M^+]. Elemental analysis for $C_{24}H_{18}N_3O_2SCl$ (447.94): Calcd. C, 64.35; H, 4.05; Cl, 7.91; N, 9.38; S, 7.16; found: C, 64.30; H, 4.00; Cl, 7.82; N, 9.30; S, 7.10.

***N*-[4-{6-(4-Bromophenyl)-1,2-dihydro-2-thioxopyrimidin-4-yl}phenyl]-5-chloro-2-methoxy benzamide (4b):** Yield 78 %, m.p. 226-228 °C; IR (KBr, ν_{max} cm^{-1}): 3495 (NH), 1685 (amide I), 1622 (amide II); ^1H NMR ($CDCl_3$, ppm): δ = 3.45 (s, 3H, OCH_3), 7.12 (s, 1H, pyrimidinyl-H), 7.14-7.94 (m, 11H, Ar-H), 10.66, 11.12 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.26 (OCH_3), 163.68 (CONH), 176.70, 155.15, 136.88, 165.94 (4C, pyrimidinyl-C), 134.88, 127.52, 134.25, 124.31, 116.22, 153.18, 140.84, 117.88, 129.16, 141.72, 148.91, 130.75, 131.72, 123.68 (18C, Ar-C); MS (EI, 70 eV): *m/z* (%): 527 [M^+]. Elemental analysis for $C_{24}H_{17}N_3O_2SBrCl$ (526.83): Calcd. C, 54.72; H, 3.25; Cl, 6.73; N, 7.98; S, 6.09; found: C, 54.64; H, 3.20; Cl, 6.65; N, 7.90; S, 6.00.

5-Chloro-*N*-[4-{6-(2-chlorophenyl)-1,2-dihydro-2-thioxopyrimidin-4-yl}phenyl]-2-methoxy benzamide (4c): Yield 70 %, m.p. 259-261 °C; IR (KBr, ν_{max} cm^{-1}): 3508 (NH), 1688 (amide I), 1618 (amide II); ^1H NMR ($CDCl_3$, ppm): δ = 3.52 (s, 3H, OCH_3), 7.08 (s, 1H, pyrimidinyl-H), 7.16-7.98 (m, 11H, Ar-H), 10.65, 11.14 (2s, 2H, 2 NH exchangeable with D_2O); MS (EI, 70 eV): *m/z* (%): 482 [M^+]. Elemental analysis for $C_{24}H_{17}N_3O_2SCl_2$ (482.38): Calcd. C, 59.76; H, 3.55; Cl, 14.70; N, 8.71; S, 6.65; found: C, 59.67; H, 3.50; Cl, 14.62; N, 8.65; S, 6.60.

5-Chloro-*N*-[4-{6-(4-chlorophenyl)-1,2-dihydro-2-thioxopyrimidin-4-yl}phenyl]-2-methoxy benzamide (4d): Yield 92 %, m.p. 263-265 °C; IR (KBr, ν_{max} cm^{-1}): 3512 (NH), 1686 (amide I), 1622 (amide II); ^1H NMR ($CDCl_3$, ppm): δ = 3.46 (s, 3H, OCH_3), 7.04 (s, 1H, pyrimidinyl-H), 7.18-7.96 (m, 11H, Ar-H), 10.82, 11.15 (2s, 2H, 2 NH exchangeable with D_2O);

^{13}C NMR ($CDCl_3$, ppm): δ = 56.54 (OCH_3), 163.69 (CONH), 176.67, 155.18, 136.85, 165.95 (4C, pyrimidinyl-C), 133.95, 132.75, 133.72, 125.90, 114.95, 155.14, 134.15, 117.61, 131.92, 145.11, 140.72, 128.83, 128.70, 130.32 (18C, Ar-C); MS (EI, 70 eV): *m/z* (%): 482 [M^+]. Elemental analysis for $C_{24}H_{17}N_3O_2SCl_2$ (482.38): Calcd. C, 59.76; H, 3.55; Cl, 14.70; N, 8.71; S, 6.65; found: C, 59.67; H, 3.50; Cl, 14.62; N, 8.65; S, 6.60.

5-Chloro-*N*-[4-{1,2-dihydro-6-(2-nitrophenyl)-2-thioxopyrimidin-4-yl}phenyl]-2-methoxy benzamide (4e): Yield 78 %, m.p. 214-216 °C; IR (KBr, ν_{max} cm^{-1}): 3515 (NH), 1687 (amide I), 1624 (amide II); ^{1}H NMR ($CDCl_3$, ppm): δ = 3.52 (s, 3H, OCH_3), 7.00 (s, 1H, pyrimidinyl-H), 7.22-8.22 (m, 11H, Ar-H), 10.80, 11.10 (2s, 2H, 2 NH exchangeable with D_2O); MS (EI, 70 eV): *m/z* (%): 493 [M^+]. Elemental analysis for $C_{24}H_{17}N_4O_4SCl$ (492.93): Calcd. C, 58.48; H, 3.48; Cl, 7.19; N, 11.37; S, 6.50; found: C, 58.40; H, 3.40; Cl, 7.10; N, 11.30; S, 6.41.

5-Chloro-*N*-[4-{1,2-dihydro-6-(4-nitrophenyl)-2-thioxopyrimidin-4-yl}phenyl]-2-methoxy benzamide (4f): Yield 66 %, m.p. 220-222 °C; IR (KBr, ν_{max} cm^{-1}): 3518 (NH), 1689 (amide I), 1625 (amide II); ^{1}H NMR ($CDCl_3$, ppm): δ = 3.46 (s, 3H, OCH_3), 7.10 (s, 1H, pyrimidinyl-H), 7.22-8.34 (m, 11H, Ar-H), 10.83, 11.55 (2s, 2H, 2 NH exchangeable with D_2O); MS (EI, 70 eV): *m/z* (%): 493 [M^+]. Elemental analysis for $C_{24}H_{17}N_4O_4SCl$ (492.93): Calcd. C, 58.48; H, 3.48; Cl, 7.19; N, 11.37; S, 6.50; found: C, 58.41; H, 3.41; Cl, 7.09; N, 11.30; S, 6.40.

5-Chloro-*N*-[4-{1,2-dihydro-6-(4-methoxyphenyl)-2-thioxopyrimidin-4-yl}phenyl]-2-methoxy benzamide (4g): Yield 58 %, m.p. 236-238 °C; IR (KBr, ν_{max} cm^{-1}): 3534 (NH), 1689 (amide I), 1626 (amide II); ^{1}H NMR: δ 3.45, 3.62 (2s, 6H, $2OCH_3$), 7.14 (s, 1H, pyrimidinyl-H), 7.20-7.94 (m, 11H, Ar-H), 10.60, 11.42 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 55.14 (OCH_3), 56.18 (OCH_3), 163.65 (CONH), 176.66, 155.22, 136.88, 165.90 (4C, pyrimidinyl-C), 128.15, 158.75, 133.70, 125.86, 114.90, 155.32, 134.24, 117.64, 131.93, 145.11, 140.70, 114.60, 128.68, 130.20 (18C, Ar-C); MS (EI, 70 eV): *m/z* (%): 478 [M^+]. Elemental analysis for $C_{25}H_{20}N_3O_3SCl$ (477.96): Calcd. C, 62.82; H, 4.22; Cl, 7.42; N, 8.79; S, 6.71; found: C, 62.70; H, 4.12; Cl, 7.33; N, 8.70; S, 6.62.

Synthesis of compounds 5a-g and 6a-g: A mixture of (**2a-g**) (2 mmol), guanidine hydrochloride or cyanoguanidine (2.4 mmol) and ammonium acetate (231 mg, 3 mmol) in absolute ethanol (25 mL) was heated under reflux for 3 h. The reaction mixture was concentrated under reduced pressure. The obtained solid was filtered off, washed with water, dried and crystallized from methyl acetate give aminopyrimidine derivatives (**5a-g**) and (**6a-g**), respectively.

5-Chloro-*N*-[4-(1,2-dihydro-2-imino-6-phenylpyrimidin-4-yl)phenyl]-2-methoxy benzamide (5a): Yield 90 %, m.p. 277-279 °C; IR (KBr, ν_{max} cm^{-1}): 3558 (NH), 1678 (amide I), 1630 (amide II); MS (EI, 70 eV): *m/z*: 431 [M^+]. Elemental analysis for $C_{24}H_{19}N_4O_2Cl$ (430.89): Calcd. C, 66.90; H, 4.44; Cl, 8.23; N, 13.00; found: C, 66.80; H, 4.35; Cl, 8.14; N, 12.88.

***N*-[4-{6-(4-Bromophenyl)-1,2-dihydro-2-iminopyrimidin-4-yl}phenyl]-5-chloro-2-methoxy benzamide (5b):** Yield 92 %, m.p. 234-236 °C; IR (KBr, ν_{max} cm^{-1}): 3556 (NH), 1679 (amide I), 1628 (amide II); ^{1}H NMR: δ 3.41 (s, 3H, OCH_3), 7.07 (s, 1H, pyrimidinyl-H), 7.12-8.07 (m, 11H, Ar-H), 10.98, 11.32 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.19 (OCH_3), 164.71 (CONH), 154.74, 135.93, 147.90, 161.70 (4C, pyrimidinyl-C), 134.90, 127.55, 134.23, 124.30, 116.18, 153.15, 140.80, 117.88, 129.12, 141.70, 148.91, 130.70, 131.70, 123.70 (18C, Ar-C); MS (EI, 70 eV): *m/z*: 510 [M^+]. Elemental analysis for $C_{24}H_{18}N_4O_2BrCl$ (509.78): Calcd. C, 56.55; H, 3.56; Cl, 6.95; N, 10.99; found: C, 56.46; H, 3.50; Cl, 6.87; N, 10.90.

5-Chloro-*N*-[4-{6-(2-chlorophenyl)-1,2-dihydro-2-iminopyrimidin-4-yl}phenyl]-2-methoxy benzamide (5c): Yield 95 %, m.p. 226-228 °C; IR (KBr, ν_{max} cm^{-1}): 3554 (NH), 1668 (amide I), 1630 (amide II); MS (EI, 70 eV): *m/z*: 465 [M^+]. Elemental analysis for $C_{24}H_{18}N_4O_2Cl_2$ (465.33): Calcd. C, 61.95; H, 3.90; Cl, 15.24; N, 12.04; found: C, 61.86; H, 3.81; Cl, 15.16; N, 11.94.

5-Chloro-*N*-[4-{6-(4-chlorophenyl)-1,2-dihydro-2-iminopyrimidin-4-yl}phenyl]-2-methoxy benzamide (5d): Yield 88 %, m.p. 146-148 °C; IR (KBr, ν_{max} cm^{-1}): 3538 (NH), 1659 (amide I), 1630 (amide II); ^{1}H NMR: δ 3.43 (s, 3H, OCH_3), 7.12 (s, 1H, pyrimidinyl-H), 7.12-7.96 (m, 11H, Ar-H), 10.95, 11.44 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.22 (OCH_3), 164.68 (CONH), 154.75, 135.90, 147.88, 161.66 (4C, pyrimidinyl-C), 128.70, 132.68, 133.95, 133.70, 114.95, 140.70, 155.16, 117.60, 134.19, 131.91, 145.11, 128.82, 125.94, 130.30 (18C, Ar-C); MS (EI, 70 eV): *m/z*: 465 [M^+]. Elemental analysis for $C_{24}H_{18}N_4O_2Cl_2$ (465.33): Calcd. C, 61.95; H, 3.90; Cl, 15.24; N, 12.04; found: C, 61.86; H, 3.81; Cl, 15.16; N, 11.94.

5-Chloro-*N*-[4-{1,2-dihydro-2-imino-6-(2-nitrophenyl)-pyrimidin-4-yl}phenyl]-2-methoxy benzamide (5e): Yield 90 %, m.p. 210-212 °C; IR (KBr, ν_{max} cm^{-1}): 3558 (NH), 1666 (amide I), 1625 (amide II); ^{1}H NMR: δ 3.42 (s, 3H, OCH_3), 7.05 (s, 1H, pyrimidinyl-H), 7.18-8.04 (m, 11H, Ar-H), 10.94, 11.46 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.18 (OCH_3), 164.68 (CONH), 154.75, 135.90, 147.92, 161.68 (4C, pyrimidinyl-C), 134.18, 127.16, 136.72, 128.21, 116.70, 154.80, 139.80, 117.71, 129.81, 144.90, 147.80, 125.30, 130.18, 134.60, 125.70, 140.70, (18C, Ar-C); MS (EI, 70 eV): *m/z*: 476 [M^+]. Elemental analysis for $C_{24}H_{18}N_5O_4Cl$ (475.88): Calcd. C, 60.57; H, 3.81; Cl, 7.45; N, 14.72; found: C, 60.46; H, 3.72; Cl, 7.36; N, 14.62.

5-Chloro-*N*-[4-{1,2-dihydro-2-imino-6-(4-nitrophenyl)-pyrimidin-4-yl}phenyl]-2-methoxy benzamide (5f): Yield 88 %, m.p. 227-229 °C; IR (KBr, ν_{max} cm^{-1}): 3560 (NH), 1668 (amide I), 1629 (amide II); ^{1}H NMR: δ 3.43 (s, 3H, OCH_3), 7.12 (s, 1H, pyrimidinyl-H), 7.24-8.08 (m, 11H, Ar-H), 10.95, 11.44 (2s, 2H, 2 NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.24 (OCH_3), 164.65 (CONH), 154.78, 135.88, 147.90, 161.65 (4C, pyrimidinyl-C), 142.15, 146.68, 133.76, 125.90, 114.91, 155.20, 134.17, 117.60, 131.90, 145.14, 140.72, 121.64, 128.75, 130.10 (18C, Ar-C); MS (EI, 70 eV): *m/z*: 476 [M^+]. Elemental analysis for $C_{24}H_{18}N_5O_4Cl$ (475.88): Calcd. C, 60.57; H, 3.81; Cl, 7.45; N, 14.72; found: C, 60.45; H, 3.70; Cl, 7.35; N, 14.64.

5-Chloro-*N*-[4-{1,2-dihydro-2-imino-6-(4-methoxyphenyl)pyrimidin-4-yl}phenyl]-2-methoxy benzamide (5g): Yield 85 %, m.p. 200-202 °C; IR (KBr, ν_{max} cm^{-1}): 3564 (NH), 1670 (amide I), 1626 (amide II); MS (EI, 70 eV): *m/z*: 476

[M^+]. Elemental analysis for $C_{25}H_{21}N_4O_3Cl$ (460.91): Calcd. C, 65.15; H, 4.59; Cl, 7.69; N, 12.16; found: C, 65.05; H, 4.50; Cl, 7.60; N, 12.02.

5-Chloro-*N*-[4-(2-cyanamide-6-phenylpyrimidin-4-yl)phenyl]-2-methoxy benzamide (6a): Yield 54 %, m.p. 170-1702 °C; IR (KBr, ν_{max} cm^{-1}): 3555 (NH), 2231 (CN), 1672 (amide I), 1621 (amide II); ^1H NMR: δ 3.42 (s, 3H, OCH_3), 6.85 (s, 1H, NHCN, exchangeable with D_2O), 7.10 (s, 1H, pyrimidinyl-H), 7.14-7.86 (m, 12H, Ar-H), 11.04 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.54 (OCH_3), 163.65 (CONH), 117.92 (CN), 161.28, 153.64, 134.65, 161.72 (4C, pyrimidinyl-C), 133.24, 126.95, 133.01, 128.42, 114.75, 159.04, 138.75, 117.42, 129.56, 137.66, 136.19, 123.47, 126.86, 132.01 (18C, Ar-C); MS (EI, 70 eV): *m/z*: 456 [M^+]. Elemental analysis for $C_{25}H_{18}N_5O_2Cl$ (455.90): Calcd. C, 65.86; H, 3.98; Cl, 7.78; N, 15.36; found: C, 65.76; H, 3.90; Cl, 7.70; N, 15.30.

***N*-[4-{6-(4-Bromophenyl)-2-cyanamidepyrimidin-4-yl}-phenyl]-5-chloro-2-methoxy benzamide (6b):** Yield 52 %, m.p. 300-302 °C; IR (KBr, ν_{max} cm^{-1}): 3556 (NH), 2230 (CN), 1670 (amide I), 1624 (amide II); MS (EI, 70 eV): *m/z*: 534 [M^+]. Elemental analysis for $C_{25}H_{17}N_5O_2BrCl$ (534.79): Calcd. C, 56.15; H, 3.20; Cl, 6.63; N, 13.10; found: C, 56.02; H, 3.11; Cl, 6.55; N, 13.02.

5-Chloro-*N*-[4-{6-(2-chlorophenyl)-2-cyanamidepyrimidin-4-yl}phenyl]-2-methoxy benzamide (6c): Yield 60 %, m.p. 340-342 °C; IR (KBr, ν_{max} cm^{-1}): 3565 (NH), 2226 (CN), 1675 (amide I), 1630 (amide II); ^1H NMR: δ 3.47 (s, 3H, OCH_3), 6.82 (s, 1H, NHCN, exchangeable with D_2O), 7.02 (s, 1H, pyrimidinyl-H), 7.14-8.12 (m, 11H, Ar-H), 10.95 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 56.31 (OCH_3), 163.62 (CONH), 117.80 (CN), 161.25, 153.60, 134.70, 161.65 (4C, pyrimidinyl-C), 133.42, 127.05, 133.83, 128.12, 114.10, 159.60, 139.48, 117.39, 130.00, 137.70, 136.10, 123.00, 131.1, 126.70, 128.44, 131.09 (18C, Ar-C); MS (EI, 70 eV): *m/z*: 490 [M^+]. Elemental analysis for $C_{25}H_{17}N_5O_2Cl_2$ (490.34): Calcd. C, 61.24; H, 3.49; Cl, 14.46; N, 14.28; found: C, 61.10; H, 3.40; Cl, 14.38; N, 14.20.

5-Chloro-*N*-[4-{6-(4-chlorophenyl)-2-cyanamidepyrimidin-4-yl}phenyl]-2-methoxy benzamide (6d): Yield 52 %, m.p. 133-135 °C; IR (KBr, ν_{max} cm^{-1}): 3528 (NH), 2238 (CN), 1668 (amide I), 1628 (amide II); ^1H NMR: δ 3.40 (s, 3H, OCH_3), 6.88 (s, 1H, NHCN, exchangeable with D_2O), 6.98 (s, 1H, pyrimidinyl-H), 7.12-7.95 (m, 11H, Ar-H), 10.98 (s, 1H, NH exchangeable with D_2O); MS (EI, 70 eV): *m/z*: 534 [M^+]. Elemental analysis for $C_{25}H_{17}N_5O_2Cl_2$ (490.34): Calcd. C, 61.24; H, 3.49; Cl, 14.46; N, 14.28; found: C, 61.07; H, 3.41; Cl, 14.36; N, 14.21.

5-Chloro-*N*-[4-{2-cyanamide-6-(2-nitrophenyl)pyrimidin-4-yl}phenyl]-2-methoxy benzamide (6e): Yield 45 %, m.p. 117-119 °C; IR (KBr, ν_{max} cm^{-1}): 3545 (NH), 2230 (CN), 1669 (amide I), 1626 (amide II); ^1H NMR: δ 3.45 (s, 3H, OCH_3), 6.90 (s, 1H, NHCN, exchangeable with D_2O), 6.99 (s, 1H, pyrimidinyl-H), 7.22-8.16 (m, 11H, Ar-H), 10.88 (s, 1H, NH exchangeable with D_2O); MS (EI, 70 eV): *m/z*: 501 [M^+]. Elemental analysis for $C_{25}H_{17}N_6O_4Cl$ (500.89): Calcd. C, 59.95; H, 3.42; Cl, 7.08; N, 16.78; found: C, 59.83; H, 3.33; Cl, 7.00; N, 16.70.

5-Chloro-*N*-[4-{2-cyanamide-6-(4-nitrophenyl)pyrimidin-4-yl}phenyl]-2-methoxy benzamide (6f): Yield 54 %, m.p. 169-171 °C; IR (KBr, ν_{max} cm^{-1}): 3545 (NH), 2230 (CN), 1669 (amide I), 1626 (amide II); ^1H NMR: δ 3.46 (s, 3H, OCH_3), 6.88 (s, 1H, NHCN, exchangeable with D_2O), 6.96 (s, 1H, pyrimidinyl-H), 7.18-8.05 (m, 11H, Ar-H), 10.74 (s, 1H, NH exchangeable with D_2O); MS (EI, 70 eV): *m/z*: 501 [M^+]. Elemental analysis for $C_{25}H_{17}N_6O_4Cl$ (500.89): Calcd. C, 59.95; H, 3.42; Cl, 7.08; N, 16.78; found: C, 59.82; H, 3.34; Cl, 7.01; N, 16.72.

5-Chloro-*N*-[4-{2-cyanamide-6-(4-methoxyphenyl)-pyrimidin-4-yl}phenyl]-2-methoxy benzamide (6g): Yield 45 %, m.p. 117-119 °C; IR (KBr, ν_{max} cm^{-1}): 3550 (NH), 2225 (CN), 1672 (amide I), 1625 (amide II); ^1H NMR: δ 3.41, 3.76 (2s, 6H, $2OCH_3$), 6.78 (s, 1H, NHCN, exchangeable with D_2O), 6.96 (s, 1H, pyrimidinyl-H), 7.12-8.16 (m, 11H, Ar-H), 10.70 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, ppm): δ = 55.45, 56.71 ($2OCH_3$), 163.72 (CONH), 117.82 (CN), 161.10, 154.60, 134.70, 167.60 (4C, pyrimidinyl-C), 133.30, 127.15, 133.78, 128.22, 114.19, 159.61, 139.48, 117.58, 130.13, 137.73, 136.02, 126.15, 128.52, 133.32 (18C, Ar-C); MS (EI, 70 eV): *m/z*: 486 [M^+]. Elemental analysis for $C_{26}H_{20}N_5O_3Cl$ (485.92): Calcd. C, 64.27; H, 4.15; Cl, 7.30; N, 14.41; found: C, 64.17; H, 4.07; Cl, 7.16; N, 14.33.

Antiinflammatory activity: Carrageenan-induced edema (rats paw test) groups of adult male albino rats (150-180 g), each of eight animals were orally dosed with tested compounds at a dose level of 2.5-5 mg/kg 1 h before the carrageenan challenge. Foot paw edema was induced by subplantar injection of 0.05 cm^3 of a 1 % suspension of carrageenan in saline into the plantar tissue of one hind paw. An equal volume of saline was injected to the other hind paw and served as control. 4 h after drug administration, the animals were decapitated, blood was collected and the paws were rapidly excised. The average weight of edema was examined for the treated as well as for the control group and the percentage inhibition of weight of edema was evaluated. Diclofenac potassium (5 mg/kg) was employed as standard reference to which the tested compounds were compared (Tables 1 and 2).

Estimation of plasma prostaglandin E2 (PGE2): Heparinized blood samples were collected from rats (n = 8), plasma was separated by centrifugation at 12000 g for 2 min at 40 ºC, immediately frozen and stored at 20 ºC until use. The design correlate EIA prostaglandin E2 (PGE2) kit (Aldrich, Steinheim, Germany) is a competitive immuno assay for the quantitative determination of PGE2 in biological fluids. The kit uses a monoclonal antibody to PGE2 to bind, in a competitive manner, the PGE2 in the sample after a simultaneous incubation at room temperature. The excess reagents were washed away and the substrate was added. After a short incubation time, the enzyme reaction was stopped and the yellow colour generated was read on a microplate reader DYNATech, MR 5000 at 405 nm (Dynatech Industries Inc., McLean, VA, USA). The intensity of the bound yellow colour is inversely proportional to the concentration of PGE2 in either standard or samples.

Cyclooxygenase inhibition activity: The colorimetric COX (ovine) Inhibitor Screening Assay utilizes the peroxidase component of cyclooxygenase. The peroxidase activity is assayed colorimetrically by monitoring the appearance of oxidized *N*,*N*,*N*,*N*-tetramethyl-*p*-phenylenediamine (TMPD) at 590 nm. The estimation of COX-1 and COX-2 enzyme inhibitor activity was done using the kit supplied by Cayman

TABLE-1
ANTI-INFLAMMATORY AND INHIBITION OF PLASMA PGE2 FOR SYNTHESIZED COMPOUNDS

Comp. No.	Dose (mg/kg)	Protection against edema (%)	Inhibition of plasma PGE2 (%)
3a	2.5	82.02 ± 0.7	83.81 ± 0.8
	5	84.16 ± 0.7	85.25 ± 0.7
3b	2.5	82.43 ± 0.5	84.23 ± 0.6
	5	84.59 ± 0.6	85.68 ± 0.7
3c	2.5	83.27 ± 0.4	85.08 ± 0.9
	5	85.44 ± 0.4	86.54 ± 0.8
3d	2.5	82.85 ± 0.3	84.66 ± 0.7
	5	85.01 ± 0.4	86.11 ± 0.6
3e	2.5	81.61 ± 0.8	83.39 ± 0.7
	5	83.74 ± 0.8	84.83 ± 0.8
3f	2.5	81.20 ± 0.8	82.98 ± 0.9
	5	83.32 ± 0.8	84.40 ± 0.0
3g	2.5	80.80 ± 0.8	82.56 ± 0.9
	5	82.91 ± 0.8	83.98 ± 0.8
4a	2.5	84.95 ± 0.7	86.81 ± 0.9
	5	87.17 ± 0.8	88.30 ± 0.8
4b	2.5	85.38 ± 0.7	87.24 ± 0.8
	5	87.61 ± 0.8	88.74 ± 0.8
4c	2.5	85.81 ± 0.7	87.68 ± 0.8
	5	88.05 ± 0.8	89.19 ± 0.7
4d	2.5	86.24 ± 0.7	88.12 ± 0.7
	5	88.49 ± 0.8	89.64 ± 0.8
4e	2.5	84.53 ± 0.7	86.37 ± 0.7
	5	86.73 ± 0.8	87.86 ± 0.7
4f	2.5	84.10 ± 0.7	85.94 ± 0.7
	5	86.30 ± 0.6	87.42 ± 0.8
4g	2.5	85.38 ± 0.7	87.24 ± 0.8
	5	87.61 ± 0.8	88.74 ± 0.8
5a	2.5	87.99 ± 0.7	89.91 ± 0.4
	5	90.28 ± 0.7	91.45 ± 0.3
5b	2.5	88.43 ± 0.8	90.36 ± 0.4
	5	90.74 ± 0.7	91.91 ± 0.3
5c	2.5	89.32 ± 0.8	91.27 ± 0.4
	5	91.65 ± 0.7	92.84 ± 0.3
5d	2.5	88.87 ± 0.8	90.81 ± 0.4
	5	91.19 ± 0.7	92.37 ± 0.5
5e	2.5	87.55 ± 0.8	89.46 ± 0.4
	5	89.83 ± 0.8	90.99 ± 0.4
5f	2.5	87.11 ± 0.7	89.01 ± 0.5
	5	89.38 ± 0.8	90.54 ± 0.5
5g	2.5	86.67 ± 0.7	88.56 ± 0.6
	5	88.94 ± 0.8	90.09 ± 0.6
6a	2.5	91.59 ± 0.7	93.58 ± 0.5
	5	93.98 ± 0.8	95.19 ± 0.4
6b	2.5	92.05 ± 0.6	94.05 ± 0.7
	5	94.45 ± 0.6	95.67 ± 0.6
6c	2.5	92.97 ± 0.6	95.00 ± 0.6
	5	95.40 ± 0.7	96.63 ± 0.6
6d	2.5	92.51 ± 0.8	94.53 ± 0.7
	5	94.92 ± 0.7	96.15 ± 0.8
6e	2.5	91.13 ± 0.7	93.12 ± 0.3
	5	93.51 ± 0.8	94.72 ± 0.3
6f	2.5	90.67 ± 0.7	92.65 ± 0.3
	5	93.04 ± 0.6	94.24 ± 0.3
6g	2.5	90.22 ± 0.7	92.19 ± 0.3
	5	92.57 ± 0.6	93.77 ± 0.6
Diclofenac Sodium	2.5	69.59 ± 0.3	55.49 ± 0.3
	5	72.19 ± 0.3	70.59 ± 0.3

TABLE-2
EFFECT OF TESTED DERIVATIVES ON COX-1 AND COX-2 ENZYME INHIBITORY ACTIVITY FOR SYNTHESIZED COMPOUNDS

Comp. No.	Drug in (µg/mL)	Percentage inhibition* COX-1	COX-2
Background wells	-	-	-
100 % initial activity wells	-	-	-
3a	10	4.46	54.07
3b	10	4.41	54.56
3c	10	4.32	55.56
3d	10	4.37	55.06
3e	10	4.50	53.59
3f	10	4.55	53.10
3g	10	4.59	52.62
4a	10	4.16	57.60
4b	10	4.11	58.13
4c	10	4.07	58.66
4d	10	4.03	59.19
4e	10	4.24	56.57
4f	10	4.55	53.10
4g	10	4.07	58.66
5a	10	3.88	61.37
5b	10	3.84	61.93
5c	10	3.76	63.05
5d	10	3.80	62.49
5e	10	3.92	60.82
5f	10	3.95	60.27
5g	10	3.99	59.73
6a	10	3.58	65.97
6b	10	3.54	66.57
6c	10	3.47	67.78
6d	10	3.51	67.17
6e	10	3.62	65.38
6f	10	3.65	64.79
6g	10	3.69	64.21

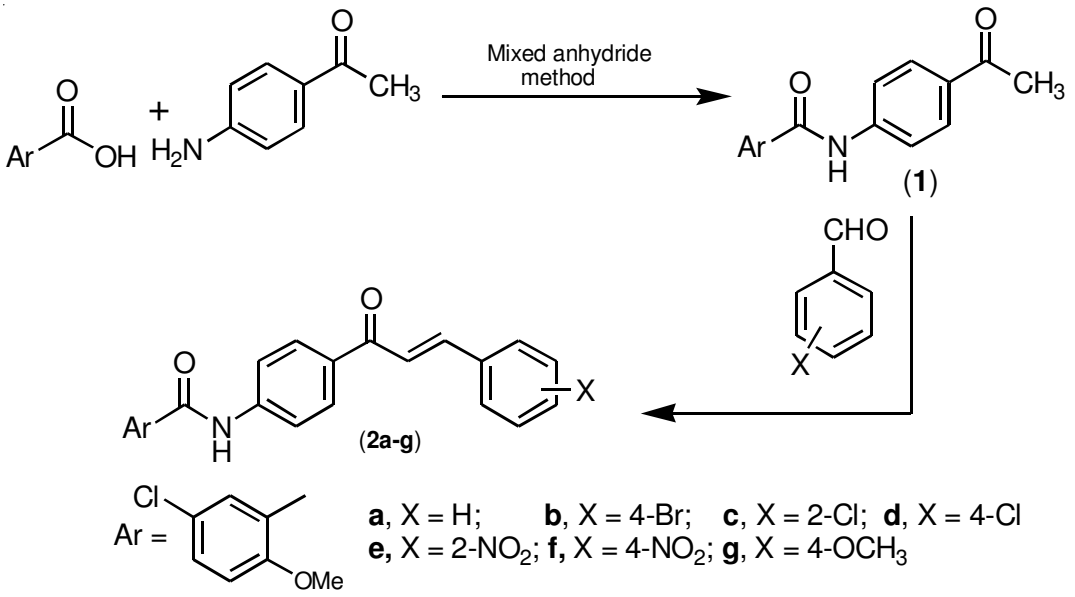
Chemical (USA). The kit contained assay buffer (10X), heme, COX-1 (Ovine), COX-2 (Ovine), arachidonic acid, potassium hydroxide, colorimetric substrate, 96 well plate.

Statistical analysis: The Statistical analysis was performed by using One Way ANOVA followed by Dunnet's Test. and the $P < 0.01$ was taken as significant

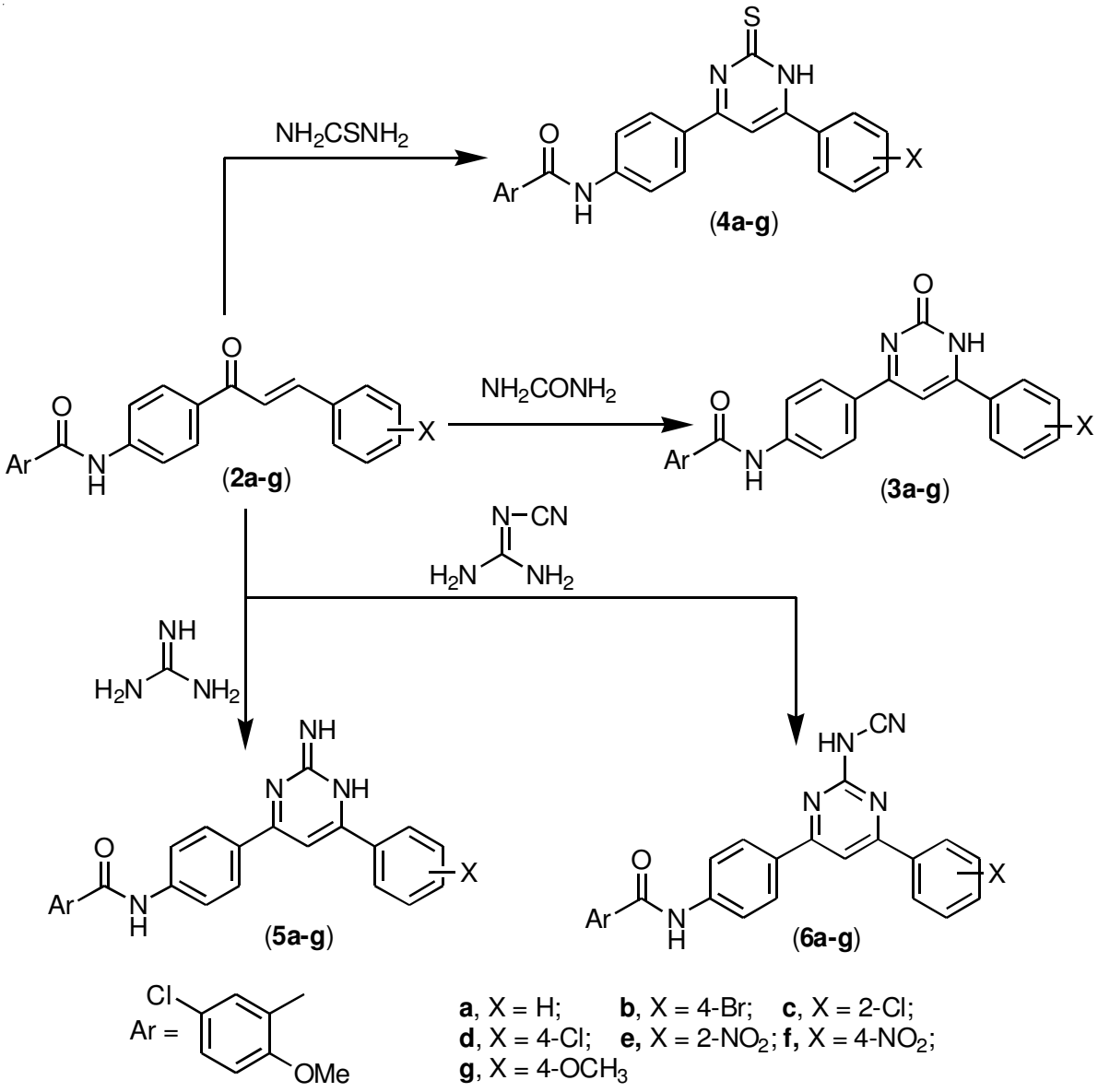
RESULTS AND DISCUSSION

Synthesis: In continuation of our previous work, a series of substituted pyrimidine derivatives (**3-6**) were synthesized by using *N*1-[4-(substituted acryloyl)phenyl]-5-chloro-2-methoxybenzamide derivatives (**2a-g**) as starting materials, which were synthesized according to our reported methods[29-31] (**Scheme-I**).

Treatment of **2a-g** with urea in refluxing in ethanol in the presence of sodium methoxide gave the cyanoaminopyrane pyrimidinone derivatives **3a-g**, but, it was condensed with thiourea in refluxing ethanol in the presence of sodium methoxide to give the cooresponding pyrimidinethione derivatives **4a-g**, respectively. Additionally, condensation of **2a-g** with guanidine derivatives, namely, guanidine hydrochloride or cyanoguanidine in absolute ethanol in the presence sodium acetate afforded the corresponding aminopyrimidine derivatives **5a-g** and **6a-g**, respectively (**Scheme-II**).



Scheme-I: Synthetic routes for starting materials (**2a-g**) [Ref. 1-3]



Scheme-II: Synthetic routes for compounds (**3-6**)

Antiinflammatory activities: All the tested newly synthesized compounds showed potent anti-inflammatory activities where it induces high protection percentages against rat paw edema. Its was worth to mention that these compounds also induces high percentages Inhibition of plasma PGE2. Searching for the mechanism of action of these antiinflammatory activities, it was found that these compounds inhibit both COX-1 and COX-2 but mainly act on COX-2 (Tables 1 and 2).

The activities of the newly synthesized tested compounds are higher than that of declofenac®, careful examination of the structural activity relationship leads to the following assumptions.

(1) Belonging to the groups or atoms on the aromatic part the descending order of activities in the following manner F > 2-Cl > 4-Cl > Br > H > 2-NO_2 > 4-NO_2 > OCH_3.

(2) The effect of the 6 member two hetero atoms ring systems on the activities were in the following descending order N-cyanopyridine > amino pyridine > pyridine thiol > pyrimidone.

Purpose and pational: For the determination of the antiphlogistic potency of the synthesized compounds, two standard tests were realized at 25 and 50 mg/kg body weight of the rats, namely the protection against carrageenan-induced edema according to Winter *et al*.[32] and the inhibition of plasma PGE2. The latter is known as a good confirming indicator for the carragenan-induced rat paw edema[33]. From the resulting data, regarding the protection against carrageenan-induced edema, all the tested compounds showed potent antiinflammatory activities.

ACKNOWLEDGEMENTS

The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding this work through Research Group no RGP-172.

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