Scientific paper

Synthesis and Structure Activity Relationship of Some Indole Derivatives as Potential Anti-inflammatory Agents

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Abstract

A series of fused pyrroles were synthesized and tested for their *in vivo* anti-inflammatory activity. Among 14 examined derivatives, 5 derivatives (**1b**–**e**, **g** and **5b**), showed a promising anti-inflammatory activity equivalent to reference anti-inflammatory drugs (indomethacin and ibuprofen). A molecular docking study was conducted to interpret the biological activities of the tested compounds. The docking results were complementary with the phase of the biological survey and confirmed the biological effects.

Keywords: Fused pyrroles, tetrahydroindoles, Molecular Docking, anti-inflammatory assay

1. Introduction

Non-steroid anti-inflammatory drugs (NSAIDs) have been amongst the most widely developed drugs.[1–5] They have provided an alternative to steroid therapy, which has revealed many problems related to parallel endocrine and metabolic activity, induced osteoporosis and hypercalcemia, as shown by Lessigiarska *et al.*[6] The postponement in treatment causes severe side effects including rhinnorrhoea, rheumatoid arthritis, and atherosclerosis.[7] With their anti-pyretic and analgesic activities, they represent a choice treatment in various inflammatory diseases such as arthritis and rheumatisms.[8–10]5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl The NSAIDs have exerted their anti-inflammatory activities through cyclooxygenase (COX) inhibition.[11–13]

Structural variation of the heterocyclic rings through the manipulation of the heterocyclic core influences the activity of the resulting fused systemes, among these of pyrroles and their fused deivatives.[14–16] Due to their pharmaceutical importance,[17–22] attention was paid to develop a new synthetic route for pyrroles and their fused forms.[23–28] Pyrrolylacetic acid derivatives such as tolmetin (Rumatol®) and zomepirac (Zomax®) were proved to be NSAIDs[6] with strong anti-inflammatory activity.[29,30] Other pyrrole and fused pyrrole compounds have been recently reported as potent COX-1 and COX-2 inhibitors:[31,32]4-benzodioxine or pyrrole nucleus are described. All the newly synthesized compounds were examined for their in vitro and in vivo anti-inflammatory activity. Several derivatives, including (S indomethacin (Indacin®), acemetacin (Emflex®) and etodolac (Etodine®) as indole derivatives, and ketorolac (Ketolac®) as a pyrrole derivative.[33–36] These compounds blocked prostaglandin synthesis by non-selective inhibition of COX-1 and COX-2 (indomethacin, acemetacin, tolmetin and ketorolac) or by selective inhibition of COX-2 (etodolac) (Fig. 1).

Due to the importance of this ring system,[39] we prepared some fused *o*-aminocyano tetrahydrobenzo[*b*]pyrrole derivatives as an essential propagation step in our search for new pyrrole and pyrrolopyrimidine derivatives,[40–43] and evaluated them for the anti-inflammatory activities. In addition, a molecular docking study has been done to explain the activity of the biologically active compounds.

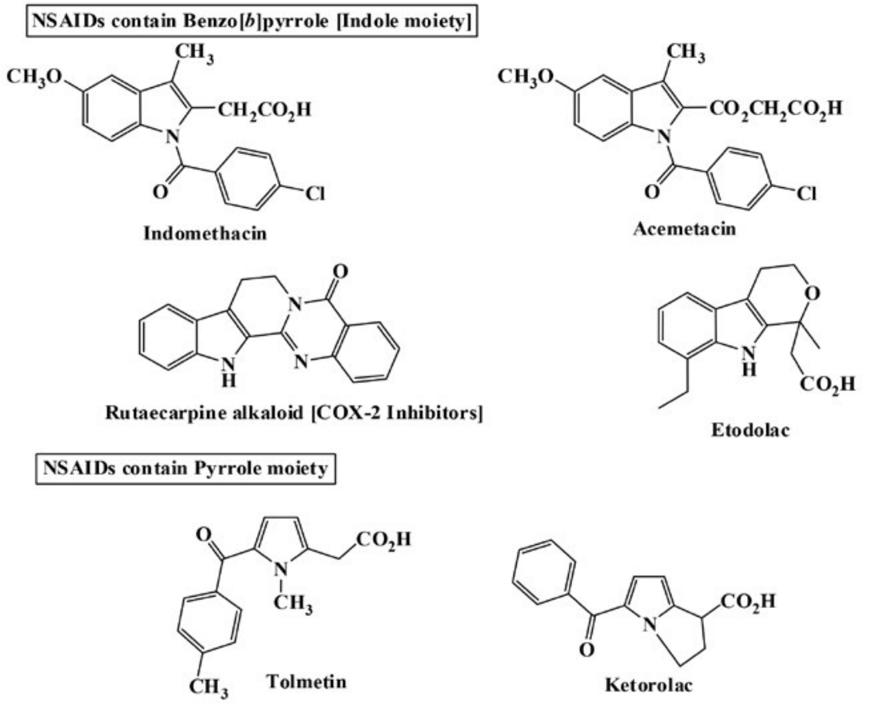


Figure 1: Pyrroles and Indoles derivatives as NSAIDs[37,38]their mechanism of action at the molecular level such as cyclooxygenase (COX

2. Experimental

2. 1. Chemistry

General Information for Chemicals

All melting points were uncorrected and measured using Electro-thermal IA 9100 apparatus (Shimadzu, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin–Elmer 1650 spectrophotometer (USA), Faculty of Science, Cairo University, Cairo, Egypt. ^{1}H-NMR and ^{13}C-NMR spectra were performed on Jeol NMR FXQ-300 MHz and Jeol NMR FXQ-500 MHz spectrometers; chemical shifts are expressed as ppm against TMS as the internal reference (Faculty of Science, Cairo University, Cairo, Egypt). Mass spectra were recorded at 70 eV EI Ms-QP 1000 EX (Shimadzu, Japan), Faculty of Science, Cairo University, Cairo, Egypt. Microanalyses were operated using Vario, Elemental apparatus (Shimadzu, Japan), Organic Microanalysis Unit, Faculty of Science, Cairo University, Cairo, Egypt. Column Chromatography was performed on (Merck) Silica gel 60 (particle size 0.06–0.20 mm). Compounds **1a**,**b**, **3a**,**b** and **5a** were prepared as reported in the literature.[44] All new compounds yielded spectral data consistent with the proposed structures and microanalysis within ±0.4% of the theoretical values.

*General methods for the preparation of 2-oxo-substituded malononitriles **I** and **II***

A mixture of 2-chloroketone (0.01 mol) and malononitrile (1 g, 0.016 mol) in $CHCl_3$ (50 mL), was cooled with stirring to 0–5 °C for 30 min. A cold solution of NaOH (2.5 g in 10 mL of water) was added to the mixture dropwise for 30 min. The stirring was continued for 50 min under ice and the reaction mixture then left for 72 h at room temperature. The precipitate formed was filtered off, recrystallized from appropriate solvent.

*2-(2-Oxocyclohexyl)malononitrile (**I**)*

It was obtained as a brownish red solid [EtOH/H_2O]. Yield 64%, m.p. 142–145 °C, FT-IR (KBr) ν_{max} 2345, 1690 cm^{-1}, EIMS *m/z* (%) 162 [M$^+$] (7.5), 106 (100). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.98; H, 6.54; N, 17.03.

*2-(1-Oxo-2,3-dihydro-1H-inden-2-yl)malononitrile (**II**)*

It was obtained as a reddish brown solid [EtOH/H_2O]. Yield 65%, m.p. 142–147 °C, FT-IR (KBr) ν_{max} 2360, 1705 cm^{-1}, EIMS *m/z* (%) 196 [M$^+$] (4), 144 (100). Anal. Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.78; H, 4.43; N, 14.60.

*2-Amino-1-(aryl)-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile **1a–g***

Method A: A solution of **I** (1 g, 0.016 mol) in ethanol (30 mL), the appropriate aromatic amine (0.01 mol) and conc HCl (4 mL) were added. The reaction mixture was refluxed for 72 h (TLC monitored), cooled to room temperature, poured onto crushed ice (25 g.), and neutralized with NaOH. The precipitate formed was filtered off, dried and recrystallized from appropriate solvent to give compound **1.**

Method B: A solution of **I** (1 g, 0.016 mol) in isopropanol (30 mL), the appropriate aromatic amine (0.01 mol) was added. The reaction mixture was refluxed for 72 h (TLC monitored), then cooled to room temperature, and the solvent was removed under reduce pressure. The residue was dissolved in methanol (10 mL), poured into crushed ice (25 g). The precipitate formed was filtered off, dried and recrystallized from appropriate solvent to give compound **1**

*2-Amino-1-(4-chlorophenyl)-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile (**1c**)*

It was obtained as a brown solid [EtOH]. Yield for method A) 73% and for B) 52%, m.p. 184–188 °C. FT-IR (KBr) ν_{max} 3380–3250, 2315 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.63–1.88 (m, 4H, 2 × CH$_2$), 2.5–2.78 (m, 4H, 2 × CH$_2$), 5.78 (br.s, 2H, NH$_2$, D$_2$O exchangeable), 7.2–7.8 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 34.1(CH$_2$, C-4), 34.9 (CH$_2$, C-7), 35.1 (CH$_2$, C-5), 36.2 (CH$_2$, C-6), 116.1 (N-*C=C, C-4a), 116.9 (N-C=C*, C-7a), 119.8 (C′N), 124.1 (C-2), 125.6 (C-3), 130.9 (CH aromatic, C-2′), 132.2 (CH aromatic, C-3′), 132.8 (CH aromatic, C-5′), 133.4 (CH aromatic, C-6′), 134.1(C-Cl, C-4′), 145.2 (C-N, C-1′) ppm; EIMS *m/z* (%) 271 [M$^+$] (25), 273 [M$^+$+2, ^{37}Cl] (8.5), 149 (100). Anal. Calcd for $C_{15}H_{14}ClN_3$; C, 66.30; H, 5.19; N, 15.46. Found: C, 66.68; H, 5.56; N, 15.30.

*2-Amino-1-o-tolyl-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile (**1d**)*

It was obtained as a brownish red solid [EtOH/H$_2$O]. Yield for method A) 80%, B) 52%, m.p. 195–197 °C. FT-IR (KBr) ν_{max} 3380–3280, 2285 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.53–1.78 (m, 4H, 2 × CH$_2$), 2.12 (s, 3H, CH$_3$), 2.5–2.78 (m, 4H, 2 × CH$_2$), 6.18 (br.s, 2H, NH$_2$, D$_2$O exchangeable), 7.2–7.6 (m, 4H, Ar-H) ppm. EIMS *m/z* (%) 251 [M$^+$] (31) , 149 (100). Anal. Calcd for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.86; H, 6.41; N, 16.77.

*2-Amino-1-p-tolyl-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile (**1e**)*

It was obtained as a brown solid [EtOH/H$_2$O]. Yield for method A) 80%, B) 54%, m.p. 168–172 °C. FT-IR (KBr) ν_{max} 3390–3270, 2260 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ= 1.53-1.78 (m, 4H, 2 × CH$_2$), 1.98 (s, 3H, CH$_3$), 2.4–2.78 (m, 4H, 2 × CH$_2$), 5.58 (br.s, 2H, NH$_2$, D$_2$O exchangeable), 7.2–7.8 (m, 4H, Ar-H) ppm. EIMS *m/z* (%) 251 [M$^+$] (61), 92 (100). Anal. Calcd for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.43; H, 6.91; N, 16.97.

*2-Amino-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile (**1f**)*

It was obtained as a yellowish brown solid [EtOH/H$_2$O]. Yield for method A) 76%, B) 55%, m.p. 234–238 °C. FT-IR (KBr) ν_{max} 3350–3270, 2270, 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.43–1.68 (m, 4H, 2 × CH$_2$), 2.2–2.45 (m, 4H, 2 × CH$_2$), 2.33 (s, 3H, CH$_3$), 3.12 (s, 3H, N-CH$_3$), 5.28 (br.s, 2H, NH$_2$, D$_2$O exchangeable), 7.2–7.6 (m, 5H, Ar-H) ppm. EIMS *m/z* (%) 347 [M$^+$] (38), 173 (100). Anal. Calcd for $C_{20}H_{21}N_5O$: C, 69.14; H, 6.09; N, 20.16; O, 4.61. Found: C, 69.28; H, 6.16; N, 20.30; O, 4.30.

*2-Amino-1-(pyridin-2-yl)-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile (**1g**)*

It was obtained as a brownish black solid [EtOH]. Yield for method A) 65%, B) 48%, m.p. 194–196 °C. FT-IR (KBr) ν_{max} 3370–3290, 2345 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.7–1.75 (m,4H, 2 × CH$_2$), 2.6–2.8 (m,4H, 2 × CH$_2$), 5.28 (br.s, 2H, NH$_2$, D$_2$O exchangeable), 7.6–8.4 (m, 4H, Ar-H) ppm. EIMS *m/z* (%) 238 [M$^+$] (100). Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51. Found: C,70.71; H, 5.83; N, 23.46.

*2-Amino-1-(aryl)-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile **2a**,**b***

A solution of **II** (1 g, 0.016 mol) in ethanol (30 mL), the appropriate aromatic amine (0.01 mol) and conc HCl (4 mL) were added. The reaction mixture was refluxed for 72 h (TLC monitored), then cooled to room temperature, poured into crushed ice (25 g), and neutralized with NaOH. The precipitate formed was filtered off, dried and recrystallized from appropriate solvent to give compound **2a**,**b**

*2-Amino-1-phenyl-1,4-dihydroindeno[1,2-b]pyrrole-3-carbonitrile (**2a**)*

It was obtained as a brownish black solid [EtOH/H$_2$O]. Yield 60%, m.p. 218–220 °C. FT-IR (KBr) ν_{max} 3410–3240, 2335 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 3.4 (s, 2H, CH$_2$), 6.18 (br.s, 2H, NH$_2$, D$_2$O exchangeable), 6.8–7.4 (m, 9H, Ar-H) ppm. EIMS *m/z* (%) 271 [M$^+$] (100). Anal. Calcd for $C_{18}H_{13}N_3$; C, 79.68; H, 4.83; N, 15.49. Found: C, 79.89; H, 4.97; N, 15.80.

*2-Amino-1-(4-methoxyphenyl)-1,4-dihydroindeno[1,2-b]pyrrole-3-carbonitrile (**2b**)*

It was obtained as a brown solid [EtOH/H$_2$O]. Yield 80%, m.p. 200–205 °C. FT-IR (KBr) ν_{max} 3425–3220, 2340 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 3.3 (s, 2H, CH$_2$), 3.7 (s, 3H, OCH$_3$), 6.23 (br.s, 2H, NH$_2$, D$_2$O exchangeable), 6.8–7.51 (m, 8H, Ar-H) ppm. EIMS *m/z* (%) 301 [M$^+$] (7.6), 211 (100). Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94; O, 5.31. Found: C, 75.61; H, 5.39; N, 14.31; O, 5.41.

N-(3-Cyano-1-(aryl)-pyrrol-2-yl) acetamide 3 and 4

A suspension of the appropriate compound **1** or **2** (0.01 mol) in acetic anhydride (40 mL) was refluxed for 2 h, cooled, poured onto ice-water, neutralized with ammonia to give a precipitate which was filtered off, dried, and recrystallized from appropriate solvent, to give compounds **3** and **4**.

*N-(1-(4-Chlorophenyl)-3-cyano-4,5,6,7-tetrahydro-1H-indol-2-yl) acetamide (**3c**)*

It was obtained as a brownish red solid [MeOH/H_2O]. Yield 70%, m.p. 184–188 °C. FT-IR (KBr) ν_{max} 3300, 2300, 1730 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.63–1.88 (m, 4H, 2 × CH_2), 2.5–2.78 (7H, (4H) 2 × CH_2, 3H, CH_3)), 7.2–7.8 (m, 4H, Ar-H), 10.15 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 313 [M$^+$] (19.7), 315 [M$^+$+2, ^{37}Cl] (6), 149 (100). Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; Cl, 11.30; N, 13.39. Found: C, 65.07; H, 5.14; Cl, 11.30; N, 13.39.

*N-(3-Cyano-1-o-tolyl-4,5,6,7-tetrahydro-1H-indol-2-yl) acetamide (**3d**)*

It was obtained as a yellowish brown solid [MtOH/H_2O]. Yield 80%, m.p. 200–205 °C. FT-IR (KBr) ν_{max} 3280, 2223, 1703 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.53-1.78 (m, 4H, 2 × CH_2), 2.12 (s, 3H, CH_3), 2.2–2.58 (m, 7H, (4H) 2 × CH_2, 3H, CH_3), 7.2-7.6 (m, 4H, Ar-H), 9.85 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 293 [M$^+$] (19.7) 92 (100). Anal. Calcd for $C_{18}H_{19}N_3O$; C, 73.69; H, 6.53; N, 14.32. Found: C, 73.99; H, 6.73; N, 14.67.

*N-(3-Cyano-1-p-tolyl-4,5,6,7-tetrahydro-1H-indol-2-yl) acetamide (**3e**)*

It was obtained as a reddish black solid [EtOH/H_2O]. Yield 70%, m.p. 186–190 °C. FT-IR (KBr) ν_{max} 3330, 2210, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.53–1.78 (m, 4H, 2 × CH_2), 1.98 (s, 3H, CH_3), 2.2–2.68 (m, 7H, (4H) 2 × CH_2, 3H, CH_3), 7.2–7.8 (m, 4H, Ar-H), 9.5 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 293 [M$^+$] (17.7) , 91 (100). Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.79; H, 6.41; N, 14.39.

*N-(3-Cyano-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-4,5,6,7-tetrahydro-1H-indol-2-yl)acetamide (**3f**)*

It was obtained as a brownish red solid [MeOH/H_2O]. m.p. 215–218 °C. FT-IR (KBr) ν_{max} 3330, 2230, 1720, 1703 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.43–1.68 (m, 4H, 2 × CH_2), 2.2–2.45 (m, 7H, (4H) 2 × CH_2), 2.33–2.4 (m, 6H, 2 × CH_3), 3.12 (s, 3H, N-CH_3), 7.2–7.6 (m, 5H, Ar-H). 10.3 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 389 [M$^+$] (24.1), 159 (100). Anal. Calcd for $C_{22}H_{23}N_5O_2$; C, 67.85; H, 5.95; N, 17.98. Found: C, 67.78; H, 6.16; N, 17.91.

*N-(3-Cyano-1-(pyridin-2-yl)-4,5,6,7-tetrahydro-1H-indol-2-yl) acetamide (**3g**)*

It was obtained as a brown solid [EtOH/H_2O]. Yield 62%, m.p. 168–170 °C. FT-IR (KBr) ν_{max} 3300, 2300, 1730 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.7–1.75 (m, 4H, 2 × CH_2), 2.4–2.6 (m, 7H, (4H) 2 × CH_2, 3H, CH_3), 7.6–8.4 (m, 4H, Ar-H), 9.9 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 280 [M$^+$] (100). Anal. Calcd for $C_{16}H_{16}N_4O$; C, 68.55; H, 5.75; N, 19.99. Found: C, 68.54; H, 5.42; N, 19.88.

*N-(3-Cyano-1-phenyl-1,4-dihydroindeno[1,2-b]pyrrol-2-yl)acetamide (**4a**)*

It was obtained as a brown solid [MeOH/H_2O]. Yield 64%, m.p. 215–219 °C. FT-IR (KBr) ν_{max} 3450 (NH), 2365 (CN), 1710 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 2.3 (s, 3H, CH_3), 3.58 (s, 2H, CH_2), 7.1–7.67 (m, 9H, Ar-H), 10.47 (br.s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 313 [M$^+$] (8), 146 (100). Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.69; H, 4.98; N, 13.57.

General methods for the preparation of aryl-pyrrolo [2,3-d]pyrimidin-4-ones 5 and 6

A suspension of the appropriate compound **1** or **2** (0.01 mol) in formic acid (20 mL, 85%) was refluxed for 3 h, cooled, poured onto ice-water to give a precipitate which was filtered off, dried, and recrystallized from appropriate solvent to afford ***5*** and ***6***.

*9-(4-Methoxyphenyl)-5,6,7,8-tetrahydro-3H-pyrimido [4,5-b]indol-4(9H)-one (**5b**)*

It was obtained as a brown solid [EtOH]. Yield 65%, m.p. 272–276 °C. FT-IR (KBr) ν_{max} 3230, 1690, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.33–1.58 (m, 4H, 2 × CH_2), 2.2–2.48 (m, 4H, 2 × CH_2), 3.52 (s, 3H, O-CH_3), 6.9–7.5 (m, 4H, Ar-H), 9.3 (s, 1H, C_2-H), 12.40 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 295 [M$^+$] (18.7), 279 (100). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C,69.14; H, 5.80; N, 14.23. Found: C, 69.19; H, 5.98; N, 14.53.

*9-o-Tolyl-5,6,7,8-tetrahydro-3H-pyrimido[4,5-b]indol-4 (9H)-one (**5d**)*

It was obtained as a yellowish brown solid [MeOH]. Yield 79%, m.p. 228–231 °C. FT-IR (KBr) ν_{max} 3230, 1690, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.53–1.78 (m, 4H, 2 × CH_2), 2.12 (s, 3H, CH_3), 2.2–2.58 (m, 4H, 2 × CH_2), 7.2–7.6 (m, 4H, Ar-H), 9.3 (s, 1H, C_2-H), 12.18 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 279 [M$^+$] (17), 118 (100). Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04; O, 5.73. Found: C, 73.39; H, 6.23; N, 15.34; O, 5.94.

*9-p-Tolyl-5,6,7,8-tetrahydro-3H-pyrimido[4,5-b]indol-4 (9H)-one (**5e**)*

It was obtained as a brown solid [EtOH]. Yield 71%, m.p. 206–210 °C. FT-IR (KBr) ν_{max} 3430, 3330, 1720, 1690, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.53–1.78 (m, 4H, 2 × CH_2), 1.98 (s, 3H, CH_3), 2.2–2.68 (m, 4H, 2 × CH_2), 7.2–7.8 (m, 4H, Ar-H), 9.4 (s, 1H, C_2-H), 12.15 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 279 [M$^+$] (19.3), 188 (100). Anal. Calcd for $C_{17}H_{17}N_3O$: C,73.69; H, 6.53; N, 14.32. Found: C, 73.79; H, 6.61; N, 14.19.

*9-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-5,6,7,8-tetrahydro-3H-pyrimido[4,5-b]indol-4(9H)-one (**5f**)*

It was obtained as a yellowish brown solid [EtOH]. Yield 83%, m.p. 260–265 °C. FT-IR (KBr) ν_{max} 3430, 3330, 1720, 1690, 1560 cm^{-1}.^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.43–1.68 (m, 4H, 2 × CH_2), 2.2–2.45 (m, 4H, 2 × CH_2), 2.33 (s, 3H, CH_3), 3.12 (s, 3H, N-CH_3), 7.2–7.6 (m, 5H, Ar-H), 9.1 (s, 1H, C_2-H), 12.3 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 375 [M$^+$] (24.6), 187 (100). Anal. Calcd for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65. Found: C, 67.28; H, 5.36; N, 18.36.

*9-(Pyridin-2-yl)-5,6,7,8-tetrahydro-3H-pyrimido[4,5-b]indol-4(9H)-one (**5g**)*

It was obtained as a brownish red solid [EtOH]. Yield 68%, m.p. 168–170 °C. FT-IR (KBr) ν_{max} 3310, 1682, 1587 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 1.7–1.75 (m, 4H, 2 × CH_2), 2.4–2.6 (m, 4H, 2 × CH_2), 7.6–8.4 (m, 4H, Ar-H), 9.3 (s, 1H, C_2-H), 12.21 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 266 [M$^+$] (16.4), 132 (100). Anal. Calcd for $C_{15}H_{14}N_4$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.54; H, 5.62; N, 21.88.

*10-Phenyl-5,10-dihydro-3H-indeno[2',1':4,5]pyrrolo[2,3-d]pyrimidin-4-one (**6a**)*

It was obtained as an orange solid [MeOH]. Yield 58%, m.p. 215–218 °C. FT-IR (KBr) ν_{max} 3330, 1705, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ = 3.51 (s, 2H, CH_2), 7.3–7.8 (m, 10H, Ar-H + pym H), 12.21 (s, 1H, NH, D_2O exchangeable) ppm. EIMS *m/z* (%) 299 [M$^+$] (18), 221(100). $C_{19}H_{13}N_3O$ (299.33). Anal. Calcd for $C_{19}H_{13}N_3O$: C, 76.24; H, 4.38; N, 14.04. Found: C, 76.57; H, 4.61; N, 14.53.

3. Biological Assay

3. 1. Anti-inflammatory Activity

Animals

Ninety adult male Sprague-Dawley rats (5 rats per group for 14 tested compounds, control (injected with 1 mL DMSO only, 2 standard drugs), weighing 120–150 g, were housed in cages in a temperature-controlled (25 ± 1 °C) environment and provided free access to pelleted food and purified drinking water *ad libitum*. The protocol of the study was approved by the animal ethics committee of the Faculty of Pharmacy, Helwan University on 10-01-2012. The study was conducted in accordance with the EC. DFT -IRective 86/609/EEC for animal experiments.

Assessment of Anti-inflammatory Activity

Rat paw oedema assay was carried out according to Winter *et al.*[45] Prepared compounds (equimolar to active dose of the reference drug), control and 2 standard drugs were dissolved in 1mL DMSO and administrated subcutaneously. One hour later, paw oedema was induced by sub-plantar injection of 0.1 mL of 1% carrageenan (Sigma-Aldrich, St. Louis, USA) into the right paw. Paw volume was measured using a water plethysmometer (Basile, Comerio, Italy). The difference between the right and left paw volume was measured at 1, 2, 3 and 4 h after induction of inflammation. Control group received 1 mL DMSO (as to evaluate the interference of DMSO itself in biological test) subcutaneously and carrageenan in sub-plantar region. Results were expressed as percentage inhibition of inflammation. Ibuprofen (70 mg/kg) and indomethacin (20 mg/kg) were used as the reference drugs.

Statistical Analysis

Results were expressed as the mean ± SEM, and different groups were compared using one way analysis of variance (ANOVA) followed by Tukey–Kramer test for multiple comparisons, using Graph Pad Instant (version 3.05) as the statistical software.

Calculation: equimolar doses of tested compounds were calculated in relation to these of reference drug: swel = mean difference in rat paw volume between right and left paw ± SE. % inhibition = (1 – rt/rc) × 100 [rt = swel of tested group; rc = swel of control group].

3. 2. Molecular Docking Study

MOE 2013.08 Docking

The molecular docking studies were done using MOE 2013.08 and Leadit 2.1.2. All compounds were built and saved as MOE. Rigid receptor was used as a docking protocol. Both receptor-solvent were kept as a »receptor«. Triangle matcher was used as a placement method. Two rescoring were computed, rescoring 1 was selected as London dG. Rescoring 2 was selected as affinity. The force field was used as a refinement.

Leadit 2.1.2 Docking

All compounds were built and saved as Mol2. The crystal structure of COX-2 enzyme complexes with indomethacin was downloaded from protein data bank (PDB: 4COX). The protein was loaded into Leadit 2.1.2 and the receptor components were chosen by selection of chain A as the main chain when complexes with indomethacin. Binding site was defined by choosing indomethacin as the reference ligand to which all coordinates were computed. Amino acids within radius 6.5 Å were selected in the binding site. All chemical ambiguities of residues were left as default. Ligand binding was driven by enthalpy (classic Triangle matching). For scoring, all default settings were restored. Intra-ligand clashes were computed by using clash factor = 0.6. Maximum number of solutions per iteration = 200. Maximum of solution per fragmentation = 200. The base placement method was used as the docking strategy.

4. Result and Discussion

4. 1. Chemistry

The availability of α-amino ketones is key to the preparation of *o*-amino- cyanopyrroles.[46–48] Research indicated that α-amino ketones used for the preparation of *o*-amino-cyanopyrroles were usually obtained *in situ*[49–51] *via* the reaction of α-hydroxy ketones with amines in acid medium,[52–55] or *via* the reaction of α-halo ketones with either amines and/or α-amino acids.[56] As previously mentioned, α-hydroxy ketones and α-halo ketones, malononitriles or suitable substituted alkylidenemalonitrile and primary amines constituted essential components for the synthesis of *o*-amino-cyanopyrrole derivatives.[44,57,58]

Regarding fused pyrrole and fused pyrrolopyrimidine derivatives there are few studies reporting the synthesis of *o*-aminocyano-tetrahydrobenzo[*b*]pyrrole and *o*-aminocyano-octahydroindeno[2,1-*b*]pyrrole derivatives. Literature also revealed that the reaction of α-hydroxycyclohexanone (in place of the α-chloro analogue) with certain amines and malononitrile successfully afforded some *o*-aminocyanotetrahydrobenzo[*b*]pyrroles but in poor yields (20–30%).[44,58,59] These results also indicated that some side reactions happened (Fig. 2a).

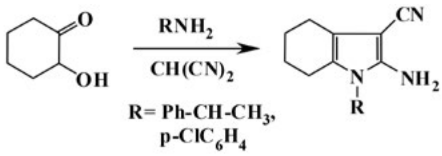


Figure 2a. Typical synthesis of tetrahydrobenzo[*b*]pyrroles

Attempts made to develop such compounds using the regular reactants (α-chlorocyclohexanone and/or 2-chloroindenone, with certain aromatic amines and malononitrile) were unfruitful.[60] We also found that α-chlorocyclohexanone under the reaction conditions EtOH/NaOH (polar basic medium) might undergo what is called **Favorskii rearrangement**,[61] rearrangement of an α-halo ketone upon treatment with a base; the reaction continues through cyclopropanone intermediate formed by nucleophilic attack [EtO$^-$]. In addition to the possibility of condensation with amine to give the anil (Fig. 2b).[62,63]

Taking the previous results into consideration, we tried to diminish the potential of such side reactions. Our plan was to prepare the novel intermediate 2-(2-oxocyclohexyl) malononitrile (**I**) from the reaction of 2-chlorocyclohexanone with malononitrile in a nonpolar solvent, followed by condensation with the appropriate aromatic amines.

By applying this method, we successfully set up the required tetrahydrobenzo[*b*]pyrroles **1** with a fair yield. Using the same conditions with 2-chloroindenone it produced **2** (Scheme 1).

On the other hand, aminocyano pyrrole derivatives **1** and **2** were converted to the corresponding acetylated derivatives **3** and **4** *via* condensation with acetic anhydyride.[64–66]3-d]pyrimidines were reported to act as potent anticancer agents, in this work, a series of novel 2-substituted-

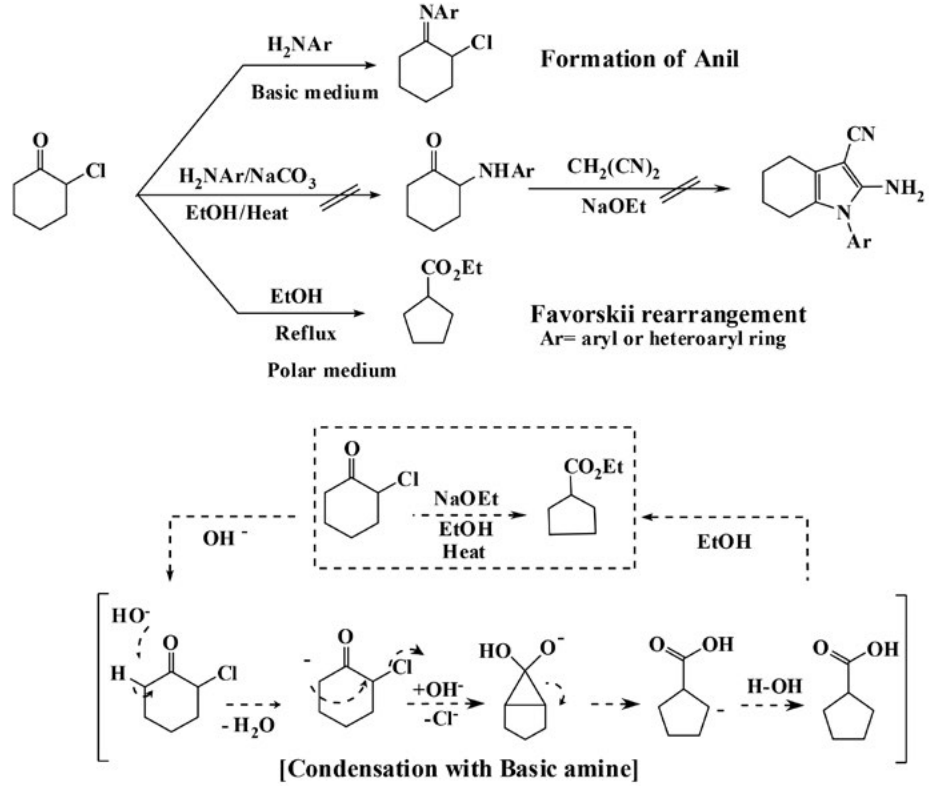
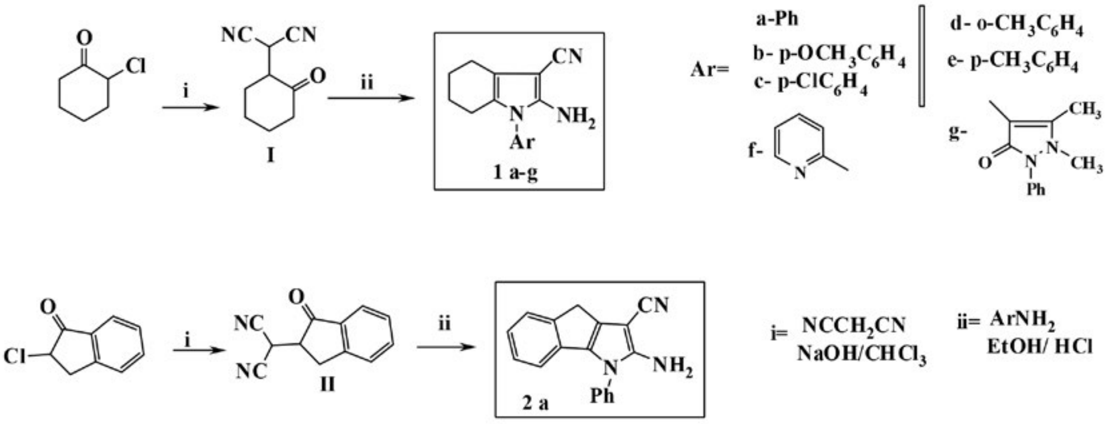
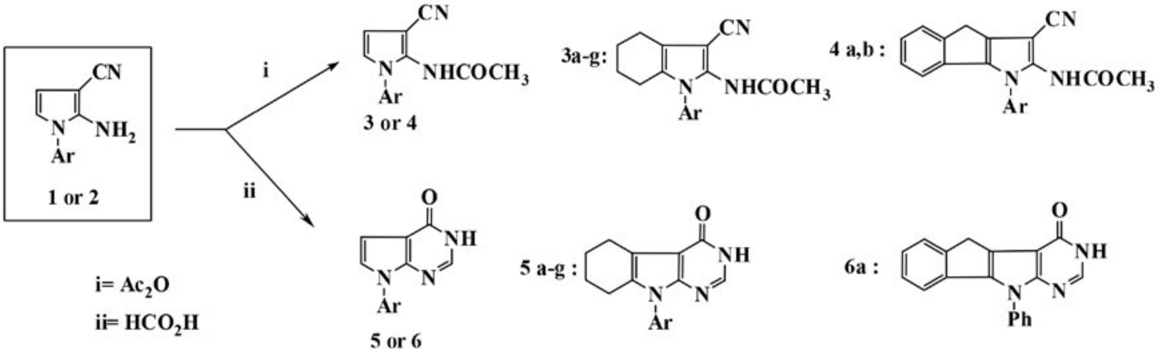


Figure 2b. Favoriskii rearrangement (polar basic medium rearrangement),[57] and anil formation[58,59]



Scheme 1: Synthesis of tetrahydroindoles **1a–g** and **2a**



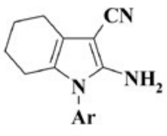
Scheme 2: Synthesis of acetylated pyrroles **3a–g**, **4a**,**b** and pyrrolopyrimidines **5a–g**, **6a**

3-cyano-4-phenyl-pyrrole 5, 6, 11–18, and 5-phenyl-pyrrolo[2,3-d]pyrimidine derivatives 7–10, 19–24 bearing either sulfathiazole or sulfapyridine were synthesized. The structures of these compounds were confirmed by elemental analysis, IR, (1 Compounds **1** and **2** were converted to pyrrolo[2,3-*d*]pyrimidine-4-ones **5** and **6** *via* condensation with formic acid (Scheme 2).[64]

4. 2. Biological Results and Discussion

Fourteen of the synthesized compounds were evaluated for their anti-inflammatory activity, using a method established by Harrk *et al.*[31]4-benzodioxine or pyrrole nucleus are described. All the newly synthesized compounds were examined for their in vitro and in vivo anti-inflammatory activity. Several derivatives, including (S Five of the tested compounds induced significant anti-inflammatory activity, compared with that of ibuprofen and indomethacin. Compound **1b** exerted significant activities compared to standard drugs at all time intervals post-carrageenan (≅ 78%, ≅ 80%, ≅ 84% and ≅ 85% inhibition at 1st, 2nd, 3rd and 4th hour interval post-carrageenan). The activity profile was the same as for standard drugs (response increasing with time). Compound **1c** exerted noticeable activities compared to standard drugs at the 1st and 2 nd hour post-carrageenan (≅ 81% and ≅ 82% inhibition at 1st and 2nd hour interval post-carrageenan). The activity profile was the same as standard drugs (response increasing with time), yet the activity showed weak, yet significant activities, decreasing at 3rd and 4th hour post-carrageenan (≅ 79% and ≅ 75% inhibition at 3rd and 4th hour interval post-carrageenan). Compounds **1d** and **5b** showed a marked anti -inflammatory effect than standard drugs, from the 1st hour to 4th hour post-carrageenan. Compound **5b** showed a moderate inhibitory action at the 4th hour interval: 76% inhibition. Yet, compound **1d** showed the unusual profile compared to standard drugs: it showed ≅ 79% inhibition at 2nd hour post-carrageenan and ≅ 70% inhibition at 3rd hour post-carrageenan and then decreased to 66% inhibition at 4th hour post-carrageenan. Compound **1g** exerted a moderate activity compared to standard drugs at the 3rd and 4th hour post-carrageenan (% inhibition ≅48 at 3rd hour and 61% at 4th hour post-carrageenan), it showed no activity at 1st and 2nd hour intervals post-carrageenan injection. Compounds **1f**, **3c**, **3d**, **3e**, **3f** and **5d**,**e** were all inactive over all tested periods, showing % inhibition < 12, 21, 25 and 38 at 1st to 4th hours, respectively, and were indicated as inactive in Table 1.

Table 1. *In vivo* anti-inflammatory activity results for active compounds.



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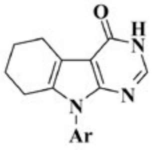

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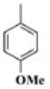
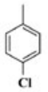
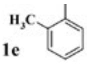
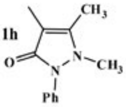
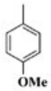
Compounds // (Ar=)	**1 Hr**		**2 Hr**		**3 Hr**		**4 Hr**	
	Swel ± SE	**Swel ± SE**	**% inh**	**Swel ± SE**	**% inh**	**Swel ± SE**	**% inh**	**% inh**
1b 	0.048 ± 0.024^{a}	78.7	0.052 ± 0.02^{a}	80	0.086 ± 0.048^{a}	84.3	0.098 ± 0.04^{a}	84.69
1c 	0.042 ± 0.008^{a}	81.37	0.046 ± 0.009^{a}	82.3	0.116 ± 0.048^{a}	79.6	0.159 ± 0.029^{a}	75.06
1d 	0.19 ± 0.036	15.9	0.076 ± 0.038^{a}	70.76	0.022 ± 0.005^{a}	95.98	0.048 ± 0.007^{a}	92
1e 	0.2137 ± 0.03	6.35	0.054 ± 0.01^{a}	78.16	0.086 ± 0.018^{a}	69.43	0.083 ± 0.068^{a}	66.73
1h 	0.2242 ± 0.031	0.79	0.25 ± 0.007	3.65	0.284 ± 0.04	48.17	0.251 ± 0.031^{a}	60.74
5b 	0.152 ± 0.016	32.74	0.15 ± 0.024	42.3	0.234 ± 0.04^{a}	57.29	0.152 ± 0.057^{a}	76.25
Indomethacin	0.224 ± 0.004	0.88	0.764 ± 0.009	20.7	0.286 ± 0.004	44.65	0.084 ± 0.01	^{a}78.58
Ibuprofen	0.216 ± 0.033	4.42	0.158 ± 0.04	39.23	0.286 ± 0.008	48.175	0.193 ± 0.007^{a}	69.84
Control	0.228 ± 0.027		0.26 ± 0.037		0.548 ± 0.08		0.64 ± 0.038	

swel = mean difference in rat paw volume between right and left paw. ± SE a: significantly different from control at the same time interval at $p<0.05$ % inhibition = (1-rt/rc) × 100 [rt = swel of tested group; rc = swel of control group] swel = swelling SE = standard error %inh = % inhibition

4. 3. Molecular Docking Results

Molecular modeling has become very important in the discovery and design of new agents.[67–70] 3D-QSAR and docking studies were carried out on 23 pyrrole derivatives, to model their HIV-1 gp41 inhibitory activities. The 2D, 3D-QSAR studies were performed using CODESSA software package and comparative molecular field analysis

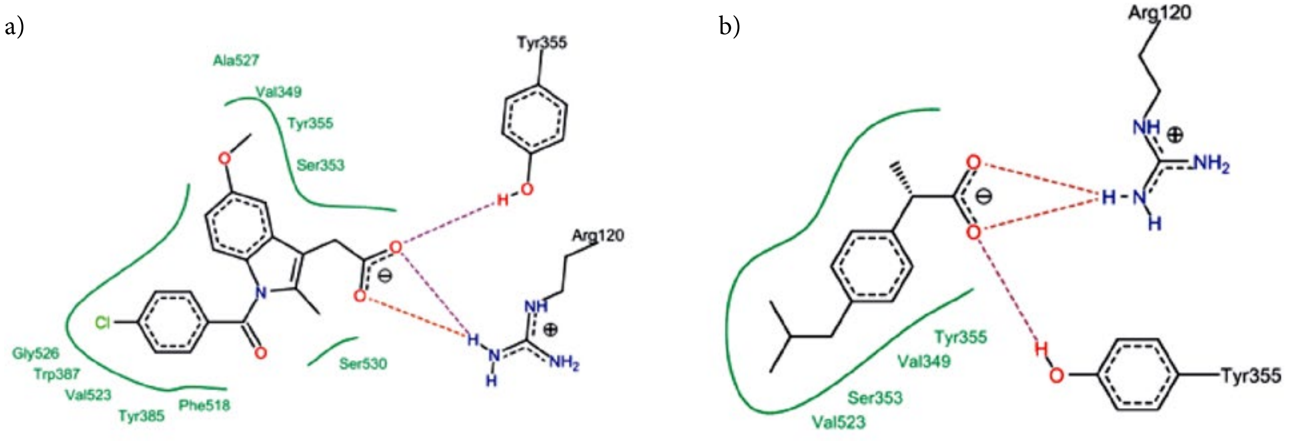


Figure 3a. Binding modes of both A) indomethacin and B) ibuprofen. This was computed with Leadit 2.1.2

(CoMFA It also helps in the interpretation and explanation of the biological results. Molecular docking is one of these approaches and is used to predict the binding mode of organic compounds.[68] A molecular docking study had been done using both MOE 2013.08[71] and Leadit 2.1.2 software.[72,73] Possible binding modes of the active compounds inside the active site of COX-2 were estimated. Indomethacin and ibuprofen were also docked. The presence of a carboxylic group in both indomethacin and ibuprofen was important for the carboxylate anion to form an electrostatic interaction with the cationic guanidine moiety of Arg 120 residue found in the active site of the COX-2 enzyme. The oxygen atom of carbonyl group found in this carboxylic moiety participated with the formation of a hydrogen bond with the hydrogen atom of –OH group of Tyr 355 residue. The binding affinity of indomethacin and ibuprofen was found to be −30.24 kcal/mol and −19.09 kcal/mol, respectively (Fig. 3a).

The clash score was computed with Leadit 2.1.2 software indicating that both drugs have a low clash score (Table 2).

The presence of the *p*-chloro group in the derivative **1c** with higher lipophilic contribution value (−10.90) improving the binding modes and interactions, compared with other tested compounds. All compounds with 2-amino-(substituted)-*1H*-indole-3-carbonitrile shared a hydrogen bond formed between their nitrile groups and the –OH group of Tyr 355. Compound **1g** showed a mode of binding in which three hydrogen bonds with Tyr 355, Arg 120 and Ser 530 were formed. Finally, compound **5b** showed three hydrogen bonds as well with His 90, Tyr 355 and Ser 530 (Fig. 3b).

Compounds **1d** and **1g** had the highest clash penalty score (11.54) which affected their fitting in the binding site and resulted in the lowest affinity values in both MOE 2013.08 and Leadit 2.1.2 docking results. That could expla-

Table 2. The clash score for active compounds and standard drugs using Leadit 2.1.2 software.

Compound/ Standard drugs	% of inhibition	MOE docking score	Leadit docking		
			Docking score (kcal/mol)	Lipo score	Clash
1b	84.69	−11.68	−17.03	−13.84	7.11
Indomethacin	78.58	−15.25	−21.24	−12.93	6.06
5b	76.25	−10.38	−15.47	−12.97	6.94
1c	75.06	−10.52	−17.23	−10.90	7.02
Ibuprofen	69.84	−13.35	−19.09	−10.41	5.87
1d	66.73	−10.24	−16.02	−11.42	10.32
1g	60.73	−10.04	−12.54	−14.63	11.54

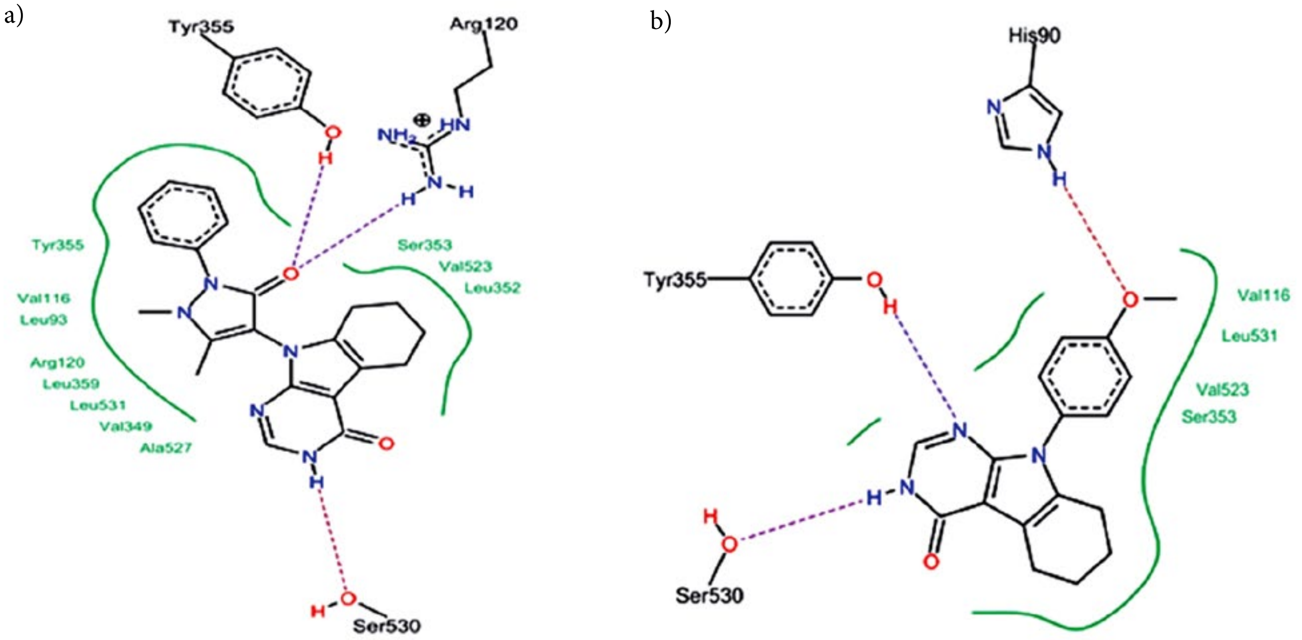


Figure 3b. A) Compound **1g** possible binding mode inside COX-2. B) Compound **5b** predicted interactions.

in their lower inhibition activity compared to the other compounds.

4. 4. Structure–activity Relationships (SAR)

To investigate SAR of any NSAIDs, pathophysiology of inflammation and its treatment have to be well understood. Inflammation represents the response to injury.[74] Many processes are involved in the promotion of the inflammatory process, one of them is the secretion of arachidonic acid (AA) from damaged cells membranes. AA is metabolized by enzyme COX into prostanoids (as prostaglandins) and lipoxygenase (leukotrienes).[75] The major mechanism of action of NSAIDs was found to be the inhibition of PG synthesis, through inhibition of COXs, that is to say preventing the AA from forming PG.[76–78]it has a very short half-live in blood, its oxidization to 15-keto-prostaglandins is catalyzed by 15-hydroxyprostaglandin dehydrogenase (15-PGDH

In order to design any structure with pyrrole moiety or its fused form indole, vital considerations must be taken to ensure its anti-inflammatory activity.[32,74,79,80]

First, the structure should consist of an acidic moiety (carboxylic acid, enols, ester etc.) attached to a planar, aromatic functional group (appears to correlate with the double bond of AA),[31]4-benzodioxine or pyrrole nucleus are described. All the newly synthesized compounds were examined for their in vitro and in vivo anti-inflammatory activity. Several derivatives, including (S and a polar linking group (which attaches the aromatic ring to a lipophilic group in AA).[30] Addition of a second hydrophobic ring, not coplanar with the original aromatic ring, was found to enhance activity,[35] this second heteroaromatic ring or heterocyclic ring was believed to provide the necessary geometry to attach to AA.[81] Taking indomethacin (benzo[*b*] pyrrole) as an example, it was found that *N*-benzoyl moiety seems to play an important role for the COX-1 activity of indomethacin.[32] If the latter moiety is replaced with any other bulkier *N*-substituents, efficient binding to COX-1 pocket is prevented.[12,82–84]

Taking all this into consideration, and to analyze our SAR, two structural components were considered: the nature of the heterocycle nucleus and the character of the side chain (*N*-substitution). First, the influence of the nature of the aromatic heterocyclic system: fused pyrrole **1a**, **1c**, and **1d** showed the highest activity over fused pyrrolopyrimidine **5b**. Regarding the side chain type, addition of bulky heterocyclic ring (anti-pyrine) in compound **1g** causes the activity to decrease over the substituted phenyl in compounds **1a**, **1c**, and **1d**. Also methoxy group at *para*-position in compound **1a** has conferred significantly higher activity during all time intervals than the methyl goup at *ortho*-position in compound **1d**. Replacing the antipyrine moiety in compound **1g** with the halogen group at *para*-position in compound **1c** has conferred significantly higher activity during 1st and 2nd hour time intervals, with decreased activity in 3rd and 4th hour post-carrageenan.

5. Conclusion

A new strategy was developed to prepare a series of 2-amino-1-(aryl)-4,5,6,7-tetrahydro-*1H*-indole-3-carbonitriles **1a–g** and 2-amino-1-(aryl)-4,5,6,7-tetrahydro-*1H* -indole-3-carbonitriles **2a**,**b** as potential anti-inflammatory agents. Based on their structure, we can conclude that the best aromatic nucleus was the pyrrole with a *para* substituted phenyl and cyclization to prepare pyrrolopyrimidine derivatives, added some anti-inflammatory activity in the heterocyclic system. The molecular docking study provided the interpretation of the biological activities of the active compounds compared to the two reference drugs indomethacin and ibuprofen.

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Povzetek

Sintetizirali smo serijo pripojenih pirolov in jih *in vivo* testirali za njihovo aktivnost proti vnetjem. Med 14 preiskovanimi derivati smo ugotovili, da 5 derivatov (**1b**–**e**,**g** and **5b**) kaže obetavno aktivnost proti vnetjem. Njihova aktivnost je primerljiva z aktivnostjo referenčnih proti-vnetnih zdravil (indometacin in ibuprofen). Da bi interpretirali rezultate bioloških študij preiskovanih spojin, smo izvedli tudi študije molekulskega sidranja. Rezultati so bili komplementarni tistim, dobljenim z biološkimi testiranji; poleg tega so potrdili biološke učinke preiskovanih spojin.