Design, synthesis, cyclooxygenase inhibition and anti-inflammatory activity of 3-ethyl-2-pheny-1-substituted-indole derivatives as indomethacin analogs

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ABSTRACT

A new series of 3-ethyl-2-pheny-1-substituted-indole derivatives **10a-l** as indomethacin analogues were synthesized *via* Fisher indole synthesis reaction of butyrphenone with appropriately substituted phenylhydrazine hydrochloride followed by the addition of the appropriate benzyl or benzoyl derivatives. All the synthesized compounds were evaluated for their anti-inflammatory activity (*in vitro*, *in vivo and* ED_{50}) and ulcerogenic liability**.** The newly synthesized compounds showed higher anti-inflammatory activity, were more selective for COX-2 and less ulcerogenic than the parent drug indomethacin. Compounds (**10a-f**), containing methanesulphonyl moiety which is expected to act as COX-2 pharmacophore, showed the highest anti-inflammatory and were less ulcerogenic than compounds (**10g-l**) with no methanesulphonyl moiety.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most prescribed medications for the treatment of pain, fever and inflammation[(Shoman, Abdel-Aziz et al. 2009, Abuo-Rahma Gel, Abdel-Aziz et al. 2014, Abdellatif, Abdelgawad et al. 2015)]. Their activity were attributed to enzymatic inhibition of cyclooxygenase (COX) which catalyze bioconversion of arachidonic acid to pro-inflammatory prostaglandins (PGs), and thromboxanes (TXs)[(Zebardast, Zarghi et al. 2009, Abdelazeem, Abdelatef et al. 2014)]. Cyclooxygenase enzyme exists in two distinct isoforms, the constitutive form COX-1 and the inducible form COX-2[(Jawabrah Al-Hourani, Sharma et al. 2014)], the constitutive COX-1 is widely synthesized in most tissues and is responsible for maintaining physiological functions such as gastric mucosa protection, regulation of renal functions, vascular homeostasis and platelet aggregation[(Yoshimura 2011, Bakr, Azouz et al. 2016)]. While, COX-2 isoform is rapidly induced in response to mitogenic and pro-inflammatory stimuli and it significantly contributes in the progression of inflammation[(Abdellatif, Lamie et al. 2016)], traditional non-steroidal anti-inflammatory drugs such as aspirin (**1**), ibuprofen (**2**) and indomethacin (**3**) have major drawbacks for their chronic use, involving gastric ulceration and renal injury, these could be attributed to inhibition of COX-1 isozyme[(Abdellatif, Chowdhury et al. 2009)].Thus, selective COX-2 inhibitor drugs (coxibs) as celecoxib (**4**), rofecoxib (**5**), and valdecoxib (**6**) were more useful for the treatment of chronic inflammation than the non-selective traditional NSAIDs[(Chowdhury, Abdellatif et al. 2010)]. Unfortunately, highly selective COX-2 inhibitors showed cardiovascular side effects including the increased incidences of high blood pressure and myocardial infarction, consequently, rofecoxib and valdecoxib were withdrawn from the market[(Chowdhury, Abdellatif et al. 2010, Huang, Velazquez et al. 2010, Dogne JM (2005))] (Figure 1).

[Please insert Figure 1 about here]

As mentioned before, indomethacin (**3**) is one of the most potent and effective NSAIDs which is widely prescribed for the treatment of rheumatoid arthritis, osteoarthritis of large joints, and other types of inflammatory diseases[(Kaur, Bhardwaj et al. 2012)] but also, it is one of the most ulcerogenic NSAIDs because of its high COX-1 selectivity and the acidic nature of the drug[(Bandgar, Sarangdhar et al. 2011)]. Our main goal in this study is the development of indomethacin (**3**) drug to obtain a series of newly synthesized compounds with less gastrointestinal toxicity and with the same potency and efficacy. This strategy is based on maintaining the potency of the indomethacin by keeping the main scaffold of the drug with trials to increase COX-2 selectivity *via* some modifications of the side groups (figure 2). Accordingly, the current work described the synthesis, molecular modeling studies, *in vitro* and *in vivo* evaluation of a newly synthesized series of *N*-substituted indole derivatives as indomethacin analogs **10a-l**in which; i) the chlorobenzoyl moiety of indomethacin in position 1, which is important for anti-inflammatory activity[(Chowdhury, Huang et al. 2010)], is maintained in **10b**, **10h**, replaced with un substituted, flouro or methoxybenzoyl in (**10a-10g**),**(10c-10i)** or **(10d-10j)** respectively or replaced with benzyl or chlorobenzyl in **(10e-10k)** or **(10f-10l)**, ii) the methyl group in position 2 was replaced with phenyl group which is expected to maximize the interaction with the hydrophobic residues within COX-2 active site and to enhance COX-2 selectivity, iii)the-CH_2COOH moiety in position 3 was replaced with an ethyl group which is expected to decrease the acidity of the new compounds and iv) the methoxy group in position 5 is replaced with H in compounds(**10a-f)** or with COX-2 pharmacophore methanesulfonyl moiety(SO_2Me) in compounds **(10g-l)** to study the effect of SO_2Me moiety on COX selectivity and anti-inflammatory activity (Figure 2).

[Please insert Figure 2 about here]

Results and discussion

Chemistry

The target compounds 1-substituted-2-phenyl-3-ethyl indole derivatives **10a-l** were synthesized using the reaction sequence illustrated in scheme1. Reaction of butyrophenone(**7**) with either phenylhydrazine hydrochloride (**8a**), or 4-methylsulfonylphenylhydrazine hydrochloride (**8b**) in glacial acetic acid under Fisher indole synthesis reaction conditions afforded the respective 2-phenyl-3-ethylindole derivative**9a** (82%) or **9b** (73%). Then, indole (**9a**, **9b**) were undergo reaction with either benzoyl chloride and its derivatives (*p*-chloro, p-flouro and *p*-methoxy) or benzyl chloride and it`s *p*-chloro derivative in DMF under basic conditions (NaH) afforded the target products (**10a-l**) in moderate yield (42-61%). All the prepared compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analyses.

Biological evaluation

Anti-inflammatory activity

In vitro cyclooxygenase (COX) inhibition assay

In vitro (COX-1/COX-2) isozyme inhibition studies for indomethacin derivatives (**10a-l**) showed that they are relatively weak inhibitors of COX-1 (IC_{50} = 4.48 – 6.8μM) and moderately to highly potent inhibitors of COX-2 (IC_{50} =0.14 – 0.97μM) in comparison with the reference drug indomethacin (COX-1 IC_{50} = 0.039μM) and (COX-2 IC50 =0.49 μM),(see data in Table 1). From that table we showed that 1) all tested compounds were more potent inhibitors for COX-2 than COX-1, 2) compounds having a SO_2Me moiety (COX-2 pharmacophore) were also more potent inhibitors of COX-2 than the corresponding analogs

free of SO_2Me, 3) presence of carbonyl spacer (C=O) in some compounds increased potency for inhibiting COX-2 isozyme than presence of methylene spacer (CH_2) and 4) compounds having a SO_2Me moiety especially that having chloro or flourobenzoyl moiety were more potent inhibitor of COX-2 isozyme with selectivity index (S.I.) = 57.78 or 65.71 than that having methoxybenzoyl or benzoyl ones with selectivity index (S.I.) = 23.05 or 25.48. In general, all compounds were more selective to COX-2 isozyme with selectivity index (S.I.) = 4.02 to 65.71 compared to indomethacin (COX-2/COX-1 S.I. = 0.079).The selectivity could be attributed to the size of compounds (**10a-l**) which is too large to fit into the smaller COX-1 active site. Moreover, the presence of COX-2 pharmacophore in some analogs (**10g-l**) increased the selectivity to COX-2 isozyme. The most potent COX-2 inhibitor (**10i**) with IC_{50} = 0.14 μM and S.I. = 65.71, was 831 times more COX-2 selective than indomethacin (COX-2 IC_{50} = 0.49 μM, S.I. = 0.079).

[Please insert Table 1 about here]

***In vivo* anti-inflammatory activity**

The anti-inflammatory activity of the synthesized Indomethacin derivatives was evaluated compared to indomethacin by using carrageen-induced rat paw edema test. Results indicated that, compounds **(10a-f)** didn`t show any significance activity after 1 h, (23.3 – 40.1 %) after 3 h and (24.1– 47.4 %) after 5 h, while indomethacin derivatives with SO_2Me **(10g-l)** showed higher percentage of anti-inflammatory activity (25.9 – 38.6 %), (67 – 90.5 %) and (65.4 – 85 %) after 1 h, 3 h and 5 h respectively. The obtained in vivo results represented in Table 2 was compatible with the in vitro results consequently, Compounds **(10a-f)** didn`t show any significance activity at one hour interval while, the maximum inhibition in inflammation showed at five hour interval. On the other hand, compounds **(10g-l)** showed significance

activity at all time intervals while, the maximum effect showed at three hour interval. Compounds **(10h) and (10i)** showed higher anti-inflammatory activity (88.6-90.5% respectively) at three hour interval (more than indomethacin, 86.7%). These data indicate that; i) presence of methanesulfonyl (SO_2Me) moiety(in compounds **10g-l)**increases the anti-inflammatory activity for this class of compounds, ii) compounds with carbonyl spacer (**C=O**) (in compounds **10g-j**) showed higher activity than that having benzyl (**CH_2**) (in **10k-10l**), and iii) maintaining chloro or flourobenzoyl moiety as in compound **10h**, **10i**increase the anti-inflammatory activity while its replacement with benzoyl or methoxybenzoyl moiety (compound **10g, 10j**) decreases the anti-inflammatory activity.

Also, ED_{50} values for The most potent compounds **(10g, 10h, 10i and 10j)**were calculated by using three different doses (5, 10, 15 mg) after three hours from drug administration in comparison with reference drug indomethacin. All mentioned compounds showed good anti-inflammatory activities (ED_{50} = 0.79- 1.55µmol/kg) while, indomethacin showed (ED_{50} = 0.4 µmol/kg).

[Please insert Table 2 about here]

Ulcerogenic liability

Ulcerogenic liability was tested for the most potent anti-inflammatory compounds **(10g, 10h, 10iand 10j)** comparable with indomethacin. Results showed in Table 3 indicated that, all tested compounds exhibited lower ulcerogenic liability with (Ulcer Index = 7,3 - 11.7) in relative with indomethacin with Ulcer Index = 20.2 .The previously tested compounds characterized by the presence of a SO_2Me moiety (Cox-2 pharmacophore) and absence of an acidic centre, in contrast to indomethacin which having an acidic center and free of a SO_2Me moiety consequently, these compounds possess more selectivity to COX-2 isozyme and

exhibited an excellent gastric safety profile compared to indomethacin which exhibiting a great damage on gastric membrane, that could be attributed to high potency against COX-1.

[Please insert table 3 about here]

Molecular modeling

In order to be able to understand the binding interactions and selectivity difference of the newly synthesized indole derivatives toward COX-2 isozyme, two compounds, **10h** and **10l**, were selected to be docked into the active sites of COX-2 using LIGANDFIT embedded in Discovery Studio software[(Diego 2007)]. The 3D crystal structure of COX-2 complexed with a cocrystallized inhibitor (PDB code: 1CX2) was selected for this study. It was proven that the substitution of amino acid such as Ile523 in COX-1 with Val523 ,which is less bulky, in COX-2 creates an additional polar side pocket and increases the volume of the COX-2 active site so, makes it more suitable for more bulky structures[(R.G. Kurumbail, D. Gildehaus et al. (1996))]. The presence of such additional side pocket allows an additional interactions with amino acids such as Arg513, replaced by His513 in COX-1. Arg513 in COX-2 is often utilized via methylsulphone or sulphonamide groups which are common in COX-2 inhibitors. In this regard, it was noticed from the docking of compound **10h** that it has high selectivity for COX-2 isozyme as it is fully fitted within COX-2 active site, **Fig.3(A),** where: 1) methylsulphone moiety is in the side pocket**.** 2) chlorophenyl moiety ,attached with indole nucleus, forms a hydrophobic interaction with Phe381, Tyr385 and Leu384. Furthermore, another hydrophobic interaction is formed between phenyl ring and Leu359 and Leu531. Clearly from **Fig. 3(B)**, cocrystallized ligand **S-58**, 1-Phenylsulfonamide-3-trifluoromethyl-5-p-bromophenylpyrazole, is also fitted with COX-2 active site. Finally, 10h and cocrystallized ligand **S-58** have the same orientation and binding mode as shown in **Fig. 3(C)**.

On the other hand, the docking of other compound **10l** explained low selectivity for COX-2 as it exhibit a different orientation and binding interaction with COX-2 where, methylsulphone moiety is not in the side pocket, **Fig. 4(A)**. In contrast to, cocrystallized ligand **S-58** which shows high binding interaction with COX-2 active site, **Fig. 4(B)**. Finally there is a different orientation and binding mode between **10l** and cocrystallized ligand which explain the decrease in activity and selectivity, **Fig. 4(C)**.

[Please insert Figure 3 about here]

[Please insert Figure 4 about here]

Conclusion

A series of newly synthesized indomethacin derivatives **(10a-l)** were prepared and evaluated for their selectivity against COX-2 isozyme, anti-inflammatory activity and ulcerogenic liability. From results displayed in in-vitro studies, all tested compounds, especially compounds with SO2Me moiety as COX-2 pharmacophore, showed higher selectivity against COX-2 than COX-1 (COX-2 S.I. = 4.02 to 65.71) than indomethacin (COX-2 S.I. = 0.079), especially compound **10i** (about 832 times more COX-2 selective than reference drug indomethacin).While, the *in vivo* anti-inflammatory activity studies indicated that i) all compounds having a SO_2Me moiety exhibited good anti-inflammatory activity in all time intervals, especially at three hour interval compounds **10h, 10i** were more potent than reference drug indomethacin. ii) Presence of carbonyl moiety as a spacer increase anti-inflammatory activity more than that compounds having methylene moiety. In addition, all compounds possessed a gastric profile more safe than indomethacin.

Experimental

Chemistry

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on KBr plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance III 400 MHz spectrophotometer, Faculty of Pharmacy, Beni-Suef University, Egypt in DMSO-d_6 with TMS as the internal standard, where *J* (coupling constant) values are estimated in Hertz (Hz) and chemical shifts were recorded in ppm on δ scale. Mass spectra (MS) were recorded on Hewlett Packard 5988 spectrometer. Microanalyses for C, H and N were carried out on Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA) at the regional centre for mycology and Bio-technology, Al-Azhar University, Egypt. Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70-120 mesh). All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification. 4-Methylsulfonylphenylhydrazine hydrochloride (**8b**) and 3-ethyl-2-phenyl-1H-indole (**9a**) were prepared according to literature procedures[(Abdellatif, Chowdhury et al. 2008, Zhao 2013, HS Mun (2005))].

3-Ethyl-5-(methylsulphonyl)-2-phenyl-1*H*-indole (9b). A mixture of butyrophenone (**7**, 0.01 mol) and 4-methylsulphonylphenyl hydrazine hydrochloride (**8b**, 0.01 mol) in glacial acetic acid (30 mL) was heated under reflux for 15 h. After cooling, the reaction mixture was poured onto ice-cold water. The separated solid was filtered, dried, washed with hexane (2×10 ml) and the residue was dried and crystallized from acetone to give pure compound **9b** as brown solid; Yield 73%; mp 171-173°C; IR (KBr) 3304 (NH), 3055 (CH aromatic), 2922, 2865 (CH aliphatic), 1380, 1141 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.31(t, 3H, *J*= 7.2 Hz, C*H*$_3$), 2.98 (q, 2H,*J* = 6.9Hz, CH_2), 3.12 (s, 3H, SO_2CH_3), 7.44 (t, 1H, *J* = 7 Hz, phenyl H-4), 7.54-7.57 (m, 3H, phenyl H-3, H-5 and indole H-7), 7.65-7.72 (m, 3H, phenyl H-2, H-6 and

indole H-6), 8.15 (s, 1H, indole H-4), 11.81 (s, 1H, N*H*, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ 16.00 (*C*H_3), 17.74 (*C*H_2), 44.94 (SO_2*C*H_3), 112.35, 115.60, 119.07, 120.14, 128.12, 128.21, 128.50, 129.45, 131.20, 132.42, 136.73, 138.57; EIMS (m/z) 300 (M+1, 23.15%), 299 ($M^{+\cdot}$, 100%). Anal. Calc for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.37; H, 5.79; N, 4.76.

General procedure for synthesis of 3-ethyl-2-phenyl-1-substituted-indole derivatives 10a-l.

A solution of the respective 2-phenyl indole derivative **9a** or **9b** (2.5 mmol) in dry DMF (5 mL) was stirred with NaH (0.11 g, 4.5 mmol), slowly added, at room temperature for 30 min. Then, the reaction flask was cooled down on a bath of ice followed by a slow addition for a solution of the appropriate alkyl or acyl halide derivatives (2.5 mmol) in DMF (5 mL) and the mixture was stirred at room temperature overnight. The reaction mixture was poured onto ice-cold water and extracted with EtOAc (3 x10 mL). The organic layer was dried and the residue was purified with silica gel column chromatography using EtOAc/hexane (1:1, v/v) as eluent to give pure compounds **10a-l**. Physical and spectral data are listed below.

(3-Ethyl-2-phenyl-indol-1-yl)-phenyl-methanone (10a). Brown solid; Yield 54%; mp 224-226°C; IR (KBr) 3057 (CH aromatic), 2932 (CH aliphatic), 1687(C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.22 (t, 3H, *J*= 7.4 Hz, C*H*$_3$), 2.67 (q, 2H, *J* = 7.4 Hz, CH_2), 7.17 (t, 1H, *J* = 6.4 Hz, phenyl H-4), 7.25-7.35 (m, 7H, 4 indolyl protons, phenyl H-3, H-5 and benzoyl H-4), 7.44-7.55 (m, 4H, phenylH-2, H-6 and benzoyl H-3, H-5), 7.72 (d, 2H, *J* = 8 Hz, benzoyl H-2, H-6); ^{13}C NMR (DMSO-d_6) δ 15.42 (*C*H_3), 17.54 (*C*H_2), 114.02, 119.86, 122.45, 123.27, 124.75, 127.90, 128.52, 128.88, 129.47, 129.94, 130.08, 132.45, 133.20, 135.42, 136.08, 137.10, 169.73 (*C*=O); EIMS (m/z) 326 (M+1, 7.46%), 325 ($M^{+\cdot}$, 33.14%), 105 ($C_7H_5O^+$,

100%). Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 85.04; H, 6.06; N, 4.36.

(4-Chlorophenyl)-(3-ethyl-2-phenyl-indol-1-yl)-methanone (10b). Pale yellow solid; Yield 57%; mp 113-115°C; IR (KBr) 3050 (CH aromatic), 2969 (CH aliphatic), 1683 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.21 (t, 3H, J = 7.4Hz, CH_3), 2.66 (q, 2H, J = 7.4 Hz, CH_2), 7.21 (t, 1H,J =6, phenyl H-4), 7.24-7.37 (m, 6H, phenyl H-3, H-5 and 4 indolyl protons), 7.51 (d, 2H, J = 8.4Hz, benzoyl H-3, H-5), 7.60-7.63 (m, 2H, phenyl H-2,H-6), 7.73 (m, 2H, benzoyl H-2, H-6); ^{13}C NMR (DMSO-d_6) δ 15.35 (CH$_3$), 17.54 (CH$_2$), 114.24, 119.89, 123.54, 125.01, 127.84, 128.01, 128.57, 128.88, 130.12, 130.52, 131.91, 132.24, 134.17, 136.17, 137.76, 139.58, 168.65(C=O); EIMS (m/z) 356 (M+2, 1.70%), 354 ($M^{+\cdot}$, 4.55%), 139 ($C_7H_4ClO^+$, 100%). Anal. Calcd for $C_{23}H_{18}ClNO$: C, 76.77; H, 5.04; N, 3.89. Found: C, 76.89; H, 5.11; N, 4.02.

(3-Ethyl-2-phenyl-indol-1-yl)-(4-fluorophenyl)methanone (10c). Buff solid; Yield 61%; mp 156-158°C; IR (KBr) 3077 (CH aromatic), 2971 (CH aliphatic), 1682 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.22 (t, 3H, J = 7.4 Hz, CH_3), 2.66 (q, 2H, J = 7.4 Hz, CH_2), 7.10-7.15 (m, 2H, benzoyl H-3, H-5), 7.20-7.28 (m, 5H, phenyl H-4, 4 indolyl protons), 7.28-7.32 (m, 2H, phenyl H-3, H-5), 7.56-7.61 (m, 2H, phenyl H-2, H-6), 7.72 (m, 2H, benzoyl H-2, H-6); ^{13}C NMR (DMSO-d_6) δ 15.35 (CH$_3$), 17.52 (CH$_2$), 114.10, 115.81, 116.03, 119.89, 122.64, 123.47, 124.93, 127.98, 128.57, 129.45, 130.03, 131.91, 132.30, 133.09, 135.86, 166.01, 168.67(C=O); EIMS (m/z) 344 (M+1, 7.01%), 343 ($M^{+\cdot}$, 31.33%), 123 ($C_7H_4FO^+$, 100%). Anal. Calcd for $C_{23}H_{18}FNO$: C, 80.45; H, 5.28; N, 4.08. Found: C, 80.64; H, 5.34; N, 4.15.

(3-Ethyl-2-phenyl-indol-1-yl)-(4-methoxyphenyl)methanone (10d). Buff solid; Yield 52%; mp 200-202°C; IR (KBr) 3026 (CH aromatic), 2980 (CH aliphatic), 1685 (C=O) cm^{-1}; ^1H

NMR (DMSO-d_6) δ 1.24 (t, 3H, J = 7.4Hz, CH_3), 2.68 (q, 2H, J = 7.4 Hz, CH_2), 3.79 (s, 3H, CH_3), 6.91 (d, 2H, J =8.4 Hz, benzoyl H-3, H-5), 7.23-7.31 (m, 7H, phenyl H-3, H-4, H-5, 4 indolyl protons), 7.52 (d, 2H, J = 8.4Hz, phenyl H-5, H-6), 7.72 (d, 2H, J = 7.2Hz, benzoyl H-2, H-6); ^{13}C NMR (DMSO-d_6) δ 15.52 (CH$_3$), 17.56 (CH$_2$), 56.04 (OCH$_3$), 113.62, 114.42, 119.84, 121.79, 122.81, 124.44, 127.24, 127.91, 128.62, 129.33, 129.71, 132.54, 132.79, 136.27, 137.14, 163.54, 168.94 (C=O); EIMS (m/z) 356 (M+1, 0.73%), 343 ($M^{+\cdot}$, 2.50%), 91 ($C_6H_3O^+$, 100%). Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.23; H, 6.02; N, 4.01.

1-Benzyl-3-ethyl-2-phenyl-1*H*-indole (10e).Yellow solid; Yield 49%; mp 94-96°C; IR (KBr) 3056, 3024 (CH aromatic), 2962, 2923 (CH aliphatic) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.16 (t, 3H,J = 7.4Hz, CH_3), 2.66 (q, 2H, J = 7.4 Hz, CH_2), 5.27 (s, 2H, CH_2), 6.84 (d, 2H, J = 6.8Hz, benzyl H-2, H-6), 7.05-7.18 (m, 5H, benzyl H-3, H-4, H-5 and indole H-5, H-6), 7.33 (d, 1H, J = 7.4Hz, indole H-7), 7.37-7.48 (m, 5H, phenyl protons), 7.62 (d, 1H, J = 8 Hz, indole H-4); ^{13}C NMR (DMSO-d_6) δ 16.35 (CH_3), 17.97 (CH_2), 46.96 (CH$_2$), 111.00, 115.54, 119.25, 119.64, 122.06, 126.45, 127.41, 127.72, 128.69, 128.88, 129.05, 130.70, 131.91, 136.78, 137.34, 138.85; EIMS (m/z) 312 (M+1, 1.31%), 311 ($M^{+\cdot}$, 4.92%), 91($C_7H_7^+$, 100%). Anal. Calcd for $C_{23}H_{21}N$: C, 88.71; H, 6.80; N, 4.50. Found: C, 88.94; H, 6.89; N, 4.54.

1-(4-Chlorobenzyl)-3-ethyl-2-phenyl-1*H*-indole (10f). Buff solid; Yield 59%; mp 120-122°C; IR (KBr) 3048, 3021 (CH aromatic), 2957, 2924 (CH aliphatic) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.16 (t, 3H, J = 7.4 Hz, CH_3), 2.66 (q, 2H, J = 7.4 Hz, CH_2), 5.28 (s, 2H, CH_2), 6.82 (d, 2H, J = 8 Hz, benzyl H-2, H-6), 7.06-7.14 (m, 2H, benzyl H-3, H-5), 7.25 (d, 2H, J = 8.4 Hz,indole H-5, H-6), 7.32-7.50 (m, 6H, indole H-7, 5 phenyl protons), 7.62 (d, 1H, J = 7.6 Hz, indole H-4); ^{13}C NMR (DMSO-d_6) δ 16.28 (CH_3), 17.95 (CH$_2$), 46.35 (CH$_2$), 110.89,

115.67, 119.32, 119.76, 122.20, 127.75, 128.30, 128.75, 128.85, 129.07, 130.66, 131.78, 131.96, 136.73, 137.24, 137.888; EIMS (m/z) 346 (M+1, 7.95%), 345 ($M^{+\cdot}$, 29.79%), 125($C_7H_6Cl^+$, 100%). Anal. Calcd for $C_{23}H_{20}ClN$: C, 79.87; H, 5.83; N, 4.05.Found: C, 80.06; H, 5.88; N, 4.08.

(3-Ethyl-5-(methanesulphonyl)-2-phenyl-indol-1-yl)-phenyl-methanone (10g). Pale yellow solid; Yield 51%;mp 100-102°C; IR (KBr) 3070 (CH aromatic), 2963, 2921 (CH aliphatic), 1688 (C=O), 1307, 1150 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.24 (t, 3H, *J* = 7.6Hz, C*H*$_3$), 2.75 (q, 2H, *J* = 7.6Hz, CH_2), 3.27 (s, 3H, SO_2CH_3), 7.22-7.37 (m, 6H, phenyl H-3, H-4, H-5 and benzoyl H3, H4, H5), 7.50-7.58 (m, 3H, phenyl H-2, H-6 and indolyl H-7), 7.73-7.76 (m, 2H, benzoyl H-2, H-6), 7.81-7.84 (dd, 1H,*J* = 8.4, 1.6 Hz, indolyl H-6)8.29 (d, 1H, *J* =1.6 Hz, indolyl H-4); ^{13}CNMR (DMSO-d_6) δ 15.48 (CH_3), 17.34 (CH_2), 44.56 (SO_2CH_3), 114.57, 119.48, 122.33, 123.00, 128.49, 128.72, 129.05, 129.19, 129.48, 130.01, 130.33, 131.58, 133.85, 134.51, 135.57, 138.49, 139.14, 169.62 (*C*=O); EIMS (m/z) 404 (M+1, 0.67%), 403 ($M^{+\cdot}$, 1.51%), 91 ($C_6H_3O^{+\cdot}$, 100%). Anal.Calcd for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47.Found: C, 71.59; H, 5.31; N, 3.51.

(4-Chlorophenyl)-(3-ethyl-5-(methanesulphonyl)-2-phenyl-indol-1-yl)-methanone (10h). Pale yellow solid; Yield 58%; mp 208-210°C; IR (KBr) 3052 (CH aromatic), 2972, 2933 (CH aliphatic), 1684 (C=O), 1312, 1088 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.24 (t, 3H, *J* = 7.4Hz, C*H*$_3$), 2.76 (q, 2H, *J* = 7.4Hz, CH_2), 3.27 (s, 3H, SO_2CH_3), 7.24-7.28 (m, 5H, phenyl protons), 7.37 (d, 2H, *J* = 8.4 Hz, benzoyl H-3, H-5), 7.55 (d, 2H, *J* = 8.8 Hz, benzoyl H-2, H-6), 7.81 (d, 1H, *J* = 8.4Hz, indolyl H-7), 7.86 (dd, 1H, *J* = 8.4, 1.6 Hz, indolyl H-6), 8.29 (d, 1H,*J* =1.6Hz, indolyl H-4); ^{13}C NMR (DMSO-d_6) δ 15.62 (CH_3), 17.44 (CH_2), 44.57 (SO_2CH_3), 114.31, 119.25, 122.40, 123.52, 125.77, 128.15, 128.54, 128.89, 129.40, 130.05,

131.61, 132.34, 135.86, 136.75, 138.15, 138.55, 139.24, 168.65 (*C*=O); EIMS (m/z) 425 (M+2, 4.51%), 437 ($M^{+\cdot}$, 11.23%), 139 ($C_7H_4ClO^+$, 100%). Anal. Calcd for $C_{24}H_{20}ClNO_3S$: C, 65.82; H, 4.60; N, 3.20. Found: C, 66.01; H, 4.67; N, 3.18.

(3-Ethyl-5-(methanesulphonyl)-2-phenyl-indol-1-yl)(4-fluorophenyl)methanone (10i). Buff solid; Yield 46%; mp 248-250°C; IR (KBr) 3067 (CH aromatic), 2967, 2930 (CH aliphatic), 1696 (C=O), 1311, 1152 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.24 (t, 3H, *J* = 7.4 Hz, C*H*$_3$), 2.75 (q, 2H, *J* = 7.4Hz, CH_2), 3.25 (s, 3H, SO_2CH_3), 7.14 (t, 2H, *J* =8.2Hz, benzoyl H-3, H-5), 7.28 (m, 5H, phenyl protons), 7.64-7.76 (m, 2H, benzoyl H-2, H-6), 7.84 (d, 1H, *J* = 8.4 Hz, indolyl H-7), 7.92-7.96 (dd, 1H, *J* = 8.4, 1.6 Hz, indolyl H-6), 8.29 (d, 1H, *J* = 1.6Hz, indolyl H-4); ^{13}C NMR (DMSO-d_6) δ 15.44 (CH_3), 17.36 (CH_2), 44.57 (SO_2CH_3), 114.83, 119.47, 122.59, 123.22, 128.34, 128.57, 128.76, 129.04, 129.22, 130.1, 131.49, 131.61, 132.17, 135.85, 138.24, 138.41, 166.95, 168.62 (*C*=O); EIMS (m/z) 422 (M+1, 0.08%), 421 ($M^{+\cdot}$, 1.59%), 123 ($C_7H_4FO^+$, 100%). Anal. Calcd for $C_{24}H_{20}FNO_3S$: C, 68.39; H, 4.78; N, 3.32. Found: C, 68.48; H, 4.87; N, 3.39.

(3-Ethyl-5-(methanesulphonyl)-2-phenyl-indol-1-yl)(4-methoxyphenyl)methanone (10j). Pale yellow solid; Yield 44%; mp 174-176°C; IR (KBr) 3022(CH aromatic), 2978, 2938 (CH aliphatic), 1686 (C=O), 1303, 1164 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.26 (t, 3H, *J* = 8 Hz, C*H*$_3$), 2.78 (q, 2H, *J* = 8 Hz, CH_2), 3.26 (s, 3H, SO_2CH_3), 3.80 (s, 3H, OCH_3), 6.95 (d, 2H, *J* = 9.2Hz, benzoyl H-3, H-5), 7.28-7.36 (m, 5H, phenyl protons), 7.53 (d, 1H, *J* = 8.4 Hz, indolylH-7), 7.63 (d, 2H, *J* = 8.8 Hz, benzoyl H-2, H-6), 7.79 (dd, 1H, *J* = 8.8, 1.6 Hz, indolyl H-6), 8.28 (d, 1H, *J* = 1.6 Hz, indolyl H-4); ^{13}C NMR (DMSO-d_6) δ 15.58 (CH_3), 17.88 (CH_2), 44.61 (SO_2CH_3), 56.13 (OCH_3), 114.65, 119.23, 119.75, 121.60, 122.73, 124.28, 127.18, 128.03, 128.51, 128.82, 129.14, 129.76, 130.28, 131.81, 133.14, 136.86, 164.28,

168.69(*C*=O); EIMS (m/z) 425 (M+1, 3.47%), 437 ($M^{+\cdot}$, 9.25%), 125 ($C_6H_3SO^+$, 100%). Anal. Calcd for $C_{25}H_{23}NO_4S$: C, 69.26; H, 5.35; N, 3.23. Found: C, 69.42; H, 5.42; N, 3.20.

1-Benzyl-3-ethyl-5-(methanesulfonyl)-2-phenyl-1*H*-indole (10k). Buff solid; Yield 42%; mp 189-191°C; IR (KBr) 3063, 3020 (CH aromatic)2964, 2922, 2871 (CH aliphatic), 1308, 1146 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.18 (t, 3H, *J* = 7.4Hz, CH_3), 2.69 (q, 2H, *J* =7.4 Hz, CH_2), 3.20 (s, 3H, SO_2CH_3), 5.36 (s, 2H, CH_2), 6.84 (d, 2H, *J* =7.6 Hz, benzyl H-2, H-6), 7.17-7.21 (m, 3H, benzyl H-3, H-4, H-5), 7.41-7.66 (m, 5H, phenyl protons), 7.76 (d, 1H, *J* = 8.4 Hz, indolyl H-7), 7.96 (d, 1H, *J* = 8.4Hz, indolyl H-6), 8.20 (s, 1H, indolyl H-4); ^{13}C NMR (DMSO-d_6) δ 16.30 (*C*H_3), 17.74 (*C*H_2), 44.89 (SO_2*C*H_3), 47.25 (*C*H_2), 111.73, 114.42, 119.33, 119.84, 122.81, 126.45, 127.00, 127.67, 128.62, 128.91, 129.48, 130.27, 130.70, 132.13, 138.66, 139.09, 140.10; EIMS (m/z) 399(M+1, 0.07%), 389 ($M^{+\cdot}$, 1.8%), 91 ($C_7H_7^+$, 100%). Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N, 3.60.Found: C, 74.13; H, 5.98; N, 3.67.

1-(4-Chlorobenzyl)-3-ethyl-5-(methanesulfonyl)-2-phenyl-1*H*-indole (10l). Buff solid; Yield 47%; mp 214-216°C; IR (KBr) 3065, 3024 (CH aromatic)2958, 2925, 2857 (CH aliphatic), 1370, 1150 (SO_2)cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.18 (t, 3H, *J* = 7.4Hz, CH_3), 2.69 (q, 2H, *J* = 7.4Hz, CH_2), 3.21 (s,3H, SO_2CH_3), 5.36 (s, 2H, CH_2), 6.83 (d, 2H, *J* = 8.4 Hz, benzyl H-2, H-6), 7.31 (d, 2H, *J* = 8.4Hz, benzyl H-3, H-5), 7.37-7.54 (m, 5H, phenyl protons), 7.60-7.68 (m, 2H, indolyl H-6, H-7), 8.21 (s, 1H, indolyl H-4); ^{13}C NMR (DMSO-d_6) δ 16.27 (*C*H_3),17.73 (CH_2), 44.89 (SO_2*C*H_3), 46.66 (*C*H_2), 111.66, 117.26, 119.39, 120.48, 127.03, 128.34, 128.76, 129.00, 129.23, 129.32, 129.78, 130.34, 130.87, 132.22, 137.16, 138.63, 139.88; EIMS (m/z) 399(M+1, 0.47%), 389 ($M^{+\cdot}$, 1.49%), 125 ($C_7H_6Cl^+$, 100%). Anal. Calcd for $C_{24}H_{22}ClNO_2S$: C, 67.99; H, 5.23; N, 3.30. Found: C, 68.21; H, 5.29; N, 3.39.

Biological evaluation

Animals

Adult male wister albino rats (120-150 g) were obtained from the animal house, (Nahda University, Beni-Suef, Egypt) were used throughout the study and were kept at controlled conditions (temperature 27±2 °C, humidity 60±10%) and a 12/12 h light/dark cycle. The animals were housed in stainless steel cages, divided into groups of four animals each and deprived of food not water 24h before the experiment. All procedures relating to animal care and treatments were conducted in accordance with protocols approved by the Research Ethical Committee of Faculty of Pharmacy Beni-Suef University (2016-Beni-Suef, Egypt).

COX-1/COX-2 inhibition colorimetric assay

The ability of compounds listed in **Table 1** was measured using colorimetric COX (ovine) Inhibitor Screening Assay Kit (catalog no.560131, Cayman Chemical, Ann Arbor, MI, USA) according to the previous reported method[(Roschek B Jr and RS (2009))]. This assay directly measures $PGF_{2\alpha}$ that was produced by stannous chloride reduction of COX derived PGH_2 by enzyme immunoassay. All assays were conducted in triplicates and IC_{50} values are the average of three determinations for each compound.

Carrageenan-induced rat paw edema assay

The anti-inflammatory activity of newly synthesized indomethacin derivatives was evaluated by using carrageenan-induced rat paw edema test[(El-Nezhawy, Biuomy et al. 2013)]. Rats were divided into 14 groups (4 animals per each group) then, they were administered with a suspension of vehicle, tested compounds or indomethacin in 10%DMSO at a dose of 10 mg/kg orally (one group per one compound).After 30 min, the rats received 100 µL of carrageenan (1% in saline) subcutaneously on the sub plantar

region of the left hind paw. The left paw thickness was measured after 1, 3 and 5h after carrageenan injection. The right hind paw served as a reference of non-inflamed paw for comparison. Results are expressed as percentage decrease in edema thickness induced by carrageenan. Compounds (**10g-j**) and indomethacin were experimented for calculating ED_{50} values by using the least three doses.

Ulcerogenic liability

Compounds (**10g-j**) and indomethacin were experimented for their ulcerogenic liability according to the reported standard method [(El-Nezhawy, Biuomy et al. 2013, Abdellatif, Abdelall et al. 2015)]. Rats were divided into groups of 5 animals each, and then were fasted for about 18h before drug administration. Treatment was continued once daily for 3 successive days in all groups. One hour after the last dose, animals were scarified under general anesthesia and stomachs were removed, collected, opened along the greater curvature, washed with distilled water and rinsed with saline. The gastric mucosa of each stomach was examined for the presence of lesions by using magnifying lens (10X). Ulcer index was calculated by summing three values percentage incidence of ulcer divided by 10, average number of ulcer per stomach and average severity of ulcers.

Molecular modeling and docking

The binding site was generated from the co-crystallized ligand, **S-58,** within COX-2 protein structure (PDB code: 1CX2). Selected two ligand **10h** and **10l,** are energy minimized using CHARMm Force Field and then docked into the former prepared proteins active sites using LIGANDFIT imbedded into Discovery Studio Software with the following docking protocol: (i) number of Monte Carlo search trials = 30000, search step for torsions with polar hydrogen = 30°. (ii) The Root Mean Square Difference

(RMS) threshold for ligand-to-binding site shape match was set to 2.0 employing a maximum of 1.0 binding site partitions and 1.0 site partition seed. (iii) The interaction energies were assessed employing Consistent Force Field (CFF) force field with anon-bonded cutoff distance of 10.0 Å and distance-dependent dielectric. An energy grid extending 3.0 Å from the binding site was implemented. (iv) Rigid body ligand minimization parameters were: 10 iterations of steepest descend (SD) minimization followed by 20 Broyden–Fletcher–Goldfarb–Shanno (BFGS) iterations applied to every successful orientation of the docked ligand. (v) A maximum of 10 diverse docked conformations/poses of optimal interaction energies were saved. (vi) The saved conformers/ poses were further energy-minimized within the binding site for a maximum of 1000 rigid-body iterations.

Declaration of interest

The authors have declared no conflict of interest.

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Figures, Schemes and Table captions

Figure 1. Chemical structures of some traditional NSAIDs (**1-3**) and some selective cyclooxygenase-2 (COX-2) inhibitor drugs (**4-6**).

Figure 2. Chemical structures of the traditional NSAID indomethacin (**3**) and the designed indomethacin analogues **10a-l**.

Figure 3: (A) Docking and binding mode of compound **10h** within COX-2 active site (PDB code: 1CX2). (B) Docking and binding mode of co-crystallized **S-58**into the same COX-2 binding pocket. (C) The superposition of the docked poses **10h** (green) and the cocrystallized

S-58 (cyan) within active site of COX-2. Hydrogen bonds are represented by dashed green lines. All hydrogens were removed for the purposes of clarity.

Figure4: (A) Docking and binding mode of compound **10l** within COX-2 active site (PDB code: 1CX2). (B) Docking and binding mode of co-crystallized **S-58**into the same COX-2 binding pocket. (C) The superposition of the docked poses **10l** (green) and the cocrystallized **S-58** (cyan) within active site of COX-2. Hydrogen bonds are represented by dashed green lines. All hydrogens were removed for the purposes of clarity.

Scheme 1. Reagents and conditions: : (a) glacial acetic acid, reflux, 15 h; (b) benzoyl chloride, 4-chlorobenzoyl chloride,4-flourobenzoyl chloride,4-methoxy benzoyl chloride, benzyl chloride or 4-chloro benzyl chloride, NaH, DMF, RT, overnight.

Table 1. *In vitro* COX-1 and COX-2 inhibition for compounds **10a-l**, and reference drug (indomethacin).

Table 2. Anti-inflammatory activities for compounds **10a-l**, and reference drug (indomethacin) in carrageen-induced rat paw edema test and ED_{50} values for compounds **10g-j** and reference drug (indomethacin)

Table 3. Ulcerogenic liability for compounds **10g-j** and reference drug (indomethacin).