SHORT COMMUNICATION

Quinoline based furanones and their nitrogen analogues: Docking, synthesis and biological evaluation

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Received 19 March 2015; accepted 24 May 2015

KEYWORDS
In silico; Butenolide; Pyrrolone; Antimicrobial; Analgesic; Anti-inflammatory

Abstract A small library of twenty-four quinoline based butenolides also known as furanones and their nitrogen analogues was prepared by using two different aroylpropionic acids, viz. 3-(2-naphthoyl)propionic acid (3) and 3-(biphenyl-4-yl)propionic acid (4), as starting materials. The 3-arylopropionic acids were reacted with different 6-substituted-2-chloroquinolin-3-carbaldehydes (2a–d) to obtain the corresponding furan-2(3H)-ones (5a–h). The purified and characterized furanones were then converted into their corresponding 2(3H)-pyrrolones (6a–h) and N-benzylpyrrol-2(3H)-ones (7a–h). The antimicrobial activities of the title compounds were evaluated against two strains of each Gram +ve (Staphylococcus aureus and Bacillus subtilis), Gram –ve bacteria (Escherichia coli and Pseudomonas aeruginosa) and against fungal strains of Aspergillus niger and Aspergillus flavus. In vivo anti-inflammatory potential of the title compounds was investigated by standard method. Majority of the compounds showed significant antibacterial activity against both the Gram +ve strains. Eight most potent anti-inflammatory compounds (5b, 5d, 5h, 6b, 7b, 7d, 7f, 7h) which exhibited >53% inhibition in edema, were also screened for their in vivo analgesic activity. All the tested compounds were found to have significant reduction in ulcerogenic action but only three compounds (5d, 5h and 7h) showed comparable analgesic activity to standard drug, diclofenac. The results were also validated using in silico approach and maximum mol doc score...
was obtained for compounds 7a–h. On comparing the in vivo and in silico anti-inflammatory results of synthesized compounds, N-benzyl pyrrolones (7a–h) emerged as the potent anti-inflammatory agents. It was also observed that compounds that possess electron withdrawing group such as —Cl or NO₂ are more biologically active.

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1. Introduction

Butenolides, also known as butyrolactones, are five membered heterocyclic compounds occurring naturally in many medicinal plants (Mao et al., 2011). Natural products containing butenolide ring system have been known to exhibit a wide range of useful and significant biological actions. Chemically these are oxidized furans, which are considered as an important scaffold to synthesize compounds of biological and pharmaceutical importance. In recent years, a large number of synthetic compounds containing butenolide nucleus were prepared and studied for various interesting biological actions in search of potent therapeutic agents (Lattmann et al., 2004; Rossi et al., 1998; Hashem et al., 2014). Butenolides consist of four carbon unsaturated γ-lactone ring and occur in numerous phytochemicals in three different forms (Fig. 1) depending upon the relative positions of the carbonyl group and the double bond in the hetero ring such as 2,3-dihydrofuran-2-ones or furan-2(3H)-ones, 2,5-dihydrofuran-2-ones or furan-2(5H)-ones and 3,2-dihydrofuran-3-ones or furan-3(2H)-ones (Allison et al., 1992).

Furanones and their open ring (acyclic) products serve as precursors for the syntheses of large number of physiologically active heterocyclic compounds vis-a-vis can also be fused or combined with other heterocyclic moieties (Allison et al., 1992; Flower, 2003). A number of nitrogen containing heterocyclic systems which exhibit promising biological activities and are prepared from butenolides include pyrrolones, pyridazines, pyrazoles, isothiazolones, oxadiazoles, triazoles, etc (Bekhit and Abdel-Azeim, 2004; Bailly et al., 2008; Hashem et al., 2014). Several research studies conducted elsewhere have shown that butenolides (furanones) possess wide spectrum of biological activities such as antibacterial, antifungal, antiviral, antioxidant, antimalarial, anticonvulsant, anti-inflammatory, COX-II inhibition, analgesic, antitumor, and anticancer properties (Albrecht et al., 2008; Mosavvi-Movahedi et al., 2003; Levy et al., 2003; Lattmann et al., 2004; Hashem et al., 2014). Recently, there has been a great interest in preparing aryldiene butenolides, which have a large spectrum of important and potential biological activities (Lattmann et al., 2005; Khan and Husain, 2002; Leite et al., 1999). The γ-lactone ring of butenolides is quite reactive and therefore employed as a building block to construct diverse classes of nitrogen heterocyclic compounds possessing significant pharmacological activities (Black et al., 2003; Zarghi et al., 2007; Hashem et al., 2007; Husain et al., 2005).

Quinoline ring system is present in number of bioactive natural products and quite a few are used therapeutically. Quinolines and their synthetic derivatives are reported to exhibit anti-inflammatory and analgesic activities (Husain et al., 2013) in addition to other useful pharmacological activities (Jashim Uddin et al., 2004; Pohle et al., 2001).

Biphenyl based furanones and pyrrolones show interesting antimicrobial and anti-inflammatory activities (Khan and Husain, 2002). Naproxen and Nabumetone are examples of naphthalene containing NSAIDs which are usually indicated in the management of pain and inflammatory conditions. Also it has been reported that several other naphthalene derivatives inhibit cyclooxygenase enzyme, block the synthesis of inflammatory mediators and therefore, display good anti-inflammatory activities (Harrak et al., 2007).

Prompted by these findings, and as a part of our current research interest on furanone derivatives, we thought to prepare compounds having three biological moieties in one i.e. biphenyl and naphthalene based furanones or pyrrolones having quinoline moiety in search of potent lead/drug molecules for anti-inflammatory or antimicrobial therapy. A total of twenty-four title compounds viz. eight furan-2(3H)-ones, eight pyrrol-2(3H)-ones and eight N-benzyl-pyrrol-2(3H)-ones were prepared and screened for antibacterial, antifungal, in vivo analgesic and anti-inflammatory activities.

2. Experimental

2.1. General

The reagents and solvents used in all experiments were obtained from Merck (Mumbai, India), S.D. Fine (Mumbai, India), CDH (New Delhi) and Qualigens (India). Melting points were recorded in open end capillary tubes using MR-VIS Visual melting point apparatus (LAB India) and are uncorrected. The IR spectra were recorded on Hitachi 150–200 spectrophotometer using Kbr. 1H NMR spectra were recorded on Bruker spectrospect DPX-300 MHz in CDC₁₃ or DMSO using tetramethylsilane (TMS) as an internal reference. Chemical shift (δ) values are reported in parts per million (ppm) while splitting patterns of peaks as singlets, doublet or triplet in proton NMR spectra are indicated by abbreviations s, d, t and m, respectively. Mass spectrometry for title compounds was performed on a JEOL JMS-D 300 instrument. Perkin-Elmer 240 analyzer was used to perform elemental analyses (C, H, N) and was found in the range of ±0.4% for each analyzed element. Progress of reaction was monitored on thin-layer chromatography using silica gel G as stationary phase in the solvent system-Toluene:Ethyl acetate:Formic acid (5:4:1, v/v/v) or Petroleum ether:Toluene:Ethyl acetate (5:4:1,
To equimolar quantities a mixture of furanone substituted-2-chloroquinoline-3-carbaldehydes (2a–d) (1.5 mmol) and benzylamine (2 mmol) in dry benzene was refluxed briefly for 10–15 min and then poured into ice cold water (300 mL). The mixture was contin-
ously agitated for 30 min to yield a solid product. The compound so obtained was filtered, dried and recrystallized from ethyl acetate to get TLC pure compound (2a–d).

A freshly distilled phosphorus oxychloride (0.35 mol) was added dropwise with stirring to a previously cooled solution of dimethylformamide (0.15 mol) and then oxime (1a–d) (0.05 mol) was added in small portions. The resulting mixture was heated at 60 °C for 16 h, followed by decomposition by pouring into ice cold water (300 mL). The mixture was contin-
uously agitated for 30 min to yield a solid product. The compound so obtained was filtered, dried and recrystallized from ethyl acetate to get TLC pure compound (2a–d).

3-(2-Naphthoyl) propionic acid (3,4) and 3-(biphenyl-4-yl) propionic acid (3) and 3-(biphenyl-4-yl) pro-
pionic acid (4) were synthesized according to the literature method (Alam et al., 2009).

2.4. General procedure for the synthesis of 3-(2-chloro-6-
substituted quinoline-3-yl) methylidene}-5-(aryl)-furan-2(3H)-
one (5a–h). (Alam et al., 2009). To equimolar quantities of 3-(2-chloro-6-
substituted quinoline-3-yl) methylidene}-5-(aryl)-furan-2(3H)-
one (5a–h). A solid mass was pre-
r fluxed for 1 h. After the completion of reaction, excess ben-
zenized was removed under vacuum. The solid so obtained was washed with petroleum ether, dried in air and then refluxed for 1 h in 6 N hydrochloric acid (15 mL). A solid mass was precipitated out on cooling the mixture content which on usual workup and crystallization in methanol yielded the desired N-benzyl-pyrrol-2(3H)-ones 7a–h. The physical and spectral data are shown in Table 3.

2.3. Antimicrobial studies

2.3.1. Antibacterial activity

The antibacterial activity of the title compounds was tested against following four strains: Staphylococcus aureus (MTCC 96), Bacillus subtilis (MTCC 121), Escherichia coli (MTCC 1652) and Pseudomonas aeruginosa (MTCC 741), by standard method (Cruickshank et al., 1975). Ciprofloxacin was used as standard antibiotic for comparison of the activity. The compounds showing activity at 100 μg/mL concentration were further tested for their MIC.

2.3.2. Antifungal activity

The antifungal activity of the prepared compounds was evaluated against Aspergillus niger and Aspergillus flavus fungal strains by the standard poison food technique method (Cruickshank et al., 1975). Fluconazole was used as the standard drug for comparison purpose.

2.4. Pharmacological studies

2.4.1. Animals

Anti-inflammatory and analgesic activities of furanones and their nitrogen analogues were carried out on Wistar rats and Swiss albino mice, respectively, after getting necessary permission of animal’s usage from Kurukshetra University animal ethics committee (Regd. No. 563/02/a/CPCSEA). Albino rats 160–200 g and male mice weighing 25–30 g were housed in polypropylene cages in group of six and acclimated to the conditions for 48 h before the commencement of study.

2.4.2. Anti-inflammatory activity

Anti-inflammatory activity of the title compounds was evaluated by the method of Winter et al. (1962) in Wistar rats of either sex, weighing 160–200 g. The percentage inhibition of edema was calculated at 1 h, 2 h, 3 h and 4 h and the results were compared with the standard drug, diclofenac.

2.4.3. Analgesic activity

Eight compounds which displayed good anti-inflammatory activity (>53% inhibition) were selected for evaluation of peripheral and central analgesic activity in mice by two meth-
ods viz. acetic acid induced writhing method and tail immersion method (Seigmund et al., 1957).

2.4.3.1. Acetic acid induced constrictions method.

The peripheral analgesic activity of selected compounds was evaluated by acetic acid induced writhing method. Aqueous acetic acid was used to induce writhing in Swiss Albino mice (20–30 g)
Table 1  Physical data and spectral data of 3-[(2-chloro-6-substituted-quinolin-3-yl)methylene]-5-(aryl)furans-2(3H)-one (5a-h).

| Compd | –R | Physical data and spectral data |
|-------|----|--------------------------------|
| 5a    | H  | 3-[(2-Chloroquinolin-3-yl)methylene]-5-(naphthalene-2-yl) furan-2(3H)-one: Yield 65%; m.p. 221–222 °C, Rf 0.92, IR (KBr) cm⁻¹ 1763 (C=O), 1566 (Ar=–C), 1063 (Ar=–N), 847 (Ar=–H). ¹H NMR (CDCl₃): 6.92 (1H, ArH), 7.25 (1H, olefinic H), 7.63–8.25 (complex m, 12H, aryl protons), MS (m/z): 383 (M⁺), 384 (M + 1), 385 (M + 2); Analyt. Calcd. for C₁₇₆H₁₅ClN₅O₂: C, 75.10; H, 6.38; N, 3.65; Found: C, 75.22; H, 3.44; N, 3.52 |
| 5b    | Cl | 3-[(2,6-Dichloroquinolin-3-yl)methylene]-5-(naphthalene-2-yl) furan-2(3H)-one: Yield 57%; m.p. 245–246 °C, Rf 0.88, IR (KBr) cm⁻¹ 1767 (C=O), 1558 (Ar=–C), 1066 (Ar=–N), 849 (Ar=–H). ¹H NMR (CDCl₃): 6.60 (1H, ArH), 7.29 (1H, olefinic H), 7.42–8.20 (complex m, 11H, aryl protons), MS (m/z): 417 (M⁺), 418 (M + 1), 419 (M + 2); Analyt. Calcd. for C₁₇₆H₁₅Cl₂N₅O₂: C, 75.89; H, 3.13; N, 3.35; Found: C, 75.87; H, 3.05; N, 3.23 |
| 5c    | CH₃| 3-[(2-Chloro-6-methylquinolin-3-yl)methylene]-5-(biphenyl-4-yl) furan-2(3H)-one: Yield 61%; m.p. 214–215 °C, Rf 0.91, IR (KBr) cm⁻¹ 1759 (C=O), 1561 (Ar=–C), 1061 (Ar=–N), 852 (Ar=–H). ¹H NMR (CDCl₃): 6.78 (1H, ArH), 7.22 (1H, olefinic H), 7.28–8.26 (complex m, 11H, aryl protons), MS (m/z): 397 (M⁺), 398 (M + 1), 399 (M + 2); Analyt. Calcd. for C₁₇₆H₁₅ClN₅O₂: C, 75.67; H, 3.83; N, 3.44 |
| 5d    | NO₂| 3-[(2-Chloro-6-nitroquinolin-3-yl)methylene]-5-(naphthalene-2-yl) furan-2(3H)-one: Yield 59%; m.p. 257–258 °C, Rf 0.85, IR (KBr) cm⁻¹ 1774 (C=O), 1570 (Ar=–C), 1063 (Ar=–N), 857 (Ar=–H). ¹H NMR (CDCl₃): 6.81 (1H, ArH), 7.28 (1H, olefinic H), 7.45–8.18 (complex m, 11H, aryl protons), MS (m/z): 428 (M⁺), 429 (M + 1), 430 (M + 2); Analyt. Calcd. for C₁₇₆H₁₅ClN₅O₂: C, 76.22; H, 3.06; N, 6.53; Found: C, 76.07; H, 3.28; N, 6.25 |
| 5e    | H  | 3-[(2-Chloro-6-methylquinolin-3-yl)methylene]-5-(biphenyl-4-yl) furan-2(3H)-one: Yield 66%; m.p. 210–212 °C, Rf 0.86, IR (KBr) cm⁻¹ 1769 (C=O), 1563 (Ar=–C), 1059 (Ar=–N), 865 (Ar=–H). ¹H NMR (CDCl₃): 6.88 (1H, ArH), 7.37 (1H, olefinic proton), 7.53–8.23 (m, 14H, aryl protons), MS (m/z): 409 (M⁺), 410 (M + 1), 411 (M + 2); Analyt. Calcd. for C₁₇₆H₁₅ClN₅O₂: C, 76.19; H, 3.93; N, 3.42; Found: C, 76.35; H, 4.03; N, 3.37 |
| 5f    | Cl | 3-[(2-Dichloroquinolin-3-yl)methylene]-5-(biphenyl-4-yl) furan-2(3H)-one: Yield 46%; m.p. 246 °C, Rf 0.76, IR (KBr) cm⁻¹ 1713 (C=O), 1518 (Ar=–C), 1038 (Ar=–N), 824 (Ar=–H). ¹H NMR (CDCl₃): 6.85 (1H, ArH), 7.40 (1H, olefinic proton), 7.46–8.35 (m, 13H, aryl protons), MS (m/z): 444 (M⁺), 445 (M + 1), 446 (M + 2); Analyt. Calcd. for C₁₇₆H₁₅ClN₅O₂: C, 70.28; H, 3.40; N, 3.15; Found: C, 70.13; H, 3.32; N, 3.09 |
| 5g    | CH₃| 3-[(2-Chloro-6-methylquinolin-3-yl)methylene]-5-(biphenyl-4-yl) furan-2(3H)-one: Yield 58%; m.p. 214 °C, Rf 0.74, IR (KBr) cm⁻¹ 1752 (C=O), 1556 (Ar=–C), 1054 (Ar=–N), 829 (Ar=–H). ¹H NMR (CDCl₃): 2.13 (3H, CH₃), 6.89 (1H, ArH), 7.33 (1H, olefinic proton), 7.38–8.24 (m, 13H, aryl protons), MS (m/z): 423 (M⁺), 424 (M + 1), 425 (M + 2); Analyt. Calcd. for C₁₇₆H₁₅ClN₅O₂: C, 76.50; H, 4.28; N, 3.30; Found: C, 76.26; H, 4.18; N, 3.43 |
| 5h    | NO₂| 3-[(2-Chloro-6-nitroquinolin-3-yl)methylene]-5-(biphenyl-4-yl) furan-2(3H)-one: Yield 65%; m.p. 184–186 °C, Rf 0.71, IR (KBr) cm⁻¹ 1767 (C=O), 1553 (Ar=–C), 1051 (Ar=–N), 838 (Ar=–H). ¹H NMR (CDCl₃): 6.91 (1H, ArH), 7.39 (1H, olefinic proton), 7.46–8.31 (m, 13H, aryl protons), MS (m/z): 454 (M⁺), 455 (M + 1), 456 (M + 2); Analyt. Calcd. for C₁₇₆H₁₅ClN₅O₂: C, 68.65; H, 3.32; N, 6.16; Found: C, 68.43; H, 3.45; N, 6.07 |

of either sex which were divided into groups of six animals in each. The analgesic activity was calculated by using the following formula:

\[
\% \text{Protection} = \left\{ \frac{(W_c - W_t)}{W_c} \right\} \times 100
\]

where \( W_c \) = mean number of writhing of control group, and \( W_t \) = mean number of writhing of test group.

2.4.3.2. Tail immersion method. The mice used in the writhing test were again used for tail immersion method after washing period (Seigmund et al., 1957). Mice of each group were placed in a suitable restrainer such that their tail protrudes outside. The protruding tail (up to 5 cm) is dipped into hot water (55 °C) and the time taken by the mice to withdraw its tail out of water is recorded as the reaction time. Readings were taken at 1 h and 2 h after the dosing.

2.4.4. Acute ulcerogenic activity

Acute ulcerogenic studies were performed in Albino rats as per the method of Ciolfi et al. (1979). The mucosal damage was examined at the end of study and ulcerogenic potential of the compounds was calculated by comparing the average score of treatment group with the mean score of rats in control group.
Table 2 Physical data and spectral data of 3-[(2-chloro-6-substituted-quinolin-3-yl)methylene]-5-(aryl)-1H-pyrrolo-[2,3-](6a–f).

| Compd | –R | Physical and spectral data |
|-------|----|---------------------------|
| 6a    | –H | 3-[(2-Chloroquinolin-3-yl)methylene]-5-(naphthalene-2-yl)-1H-pyrrolo-[2,3-]one: yield 78%, m.p. 280 °C, Rf 0.79, IR (KBr, cm–1): 3410 (NH), 1696 (C=O), 1562 (Ar=C=C), 1033 (Ar=C=N), 802 (Ar=CH). 1H NMR (CDCl3) δ = 6.46 (1H, βH, 7.08 (1H, olefinic H), 7.41–8.13 (complex m, 13H, 12 aryl protons + NH), MS[EI] m/z 382 (M'), 383 (M + 1), 384 (M + 2). Elemental Analysis. Calcd. for C24H16ClN2O: C, 70.44; H, 3.64; N, 6.32; Found: C, 70.31; H, 3.58; N, 6.25 |
| 6b    | –Cl| 3-[(2,6-Dichloroquinolin-3-yl)methylene]-5-(naphthalene-2-yl)-1H-pyrrolo-[2,3-]one: yield 74%; m.p. 205 °C, Rf 0.80, IR (KBr) cm–1: 3443 (NH), 1706 (C=O), 1602 (Ar=C=C), 1057 (Ar=C–N), 801 (Ar=CH). 1H NMR (CDCl3) δ = 6.32 (1H, βH, 7.11 (1H, olefinic H), 7.38–8.15 (complex m, 13H, 12 aryl protons + NH), MS (m/z): 416 (M'), 417 (M + 1), 418 (M + 2); Anal. Calcd. for C25H13Cl2N2O: C, 68.80; H, 3.55; N, 9.26; Found: C, 68.63; H, 3.28; N, 9.55 |
| 6c    | –CH3| 3-[(2-Chloro-6-methylquinolin-3-yl)methylene]-5-(naphthalene-2-yl)-1H-pyrrolo-[2,3-]one: yield 71%; m.p. 240 °C, Rf 0.78, IR (KBr) cm–1: 3388 (NH), 1683 (C=O), 1607 (Ar=C=C), 1019 (Ar=C–N), 801 (Ar=CH). 1H NMR (CDCl3) δ = 2.23 (3H, CH3), 6.54 (1H, βH, 7.12 (1H, olefinic H), 7.31–8.18 (complex m, 12H, 11 aryl protons + NH), MS (m/z): 396 (M'), 397 (M + 1), 398 (M + 2). Anal. Calcd. for C25H17ClN2O: C, 75.66; H, 4.32; N, 7.06; Found: C, 75.46; H, 4.27; N, 7.22 |
| 6d    | –NO2| 3-[(2-Chloro-6-nitroquinolin-3-yl)methylene]-5-(naphthalene-2-yl)-1H-pyrrolo-[2,3-]one: yield 68%; m.p. 281 °C, Rf 0.73, IR (KBr) cm–1: 3435 (NH), 1692 (C=O), 1591 (Ar=C=C), 1036 (Ar=C–N), 814 (Ar=CH). 1H NMR (CDCl3) δ = 6.63 (1H, βH, 7.22 (1H, olefinic H), 7.25–8.29 (complex m, 12H, 11 aryl protons + NH), MS (m/z): 427 (M'), 428 (M + 1), 429 (M + 2); Anal. Calcd. for C25H16ClN3O: C, 76.37; H, 4.19; N, 6.84; Found: C, 76.14; H, 4.14; N, 6.61 |
| 6e    | –H | 3-[(2-Chloro-6-nitroquinolin-3-yl)methylene]-5-(naphthalene-2-yl)-1H-pyrrolo-[2,3-]one: yield 66%; m.p. 148–150 °C, Rf 0.76, IR (KBr) cm–1: 3392 (NH), 1687 (C=O), 1590 (Ar=C=C), 1018 (Ar=C–N), 792 (Ar=CH). 1H NMR (CDCl3) δ = 6.28 (1H, βH, 7.13 (1H, olefinic H), 7.15–8.29 (complex m, 15H, 14 aryl protons + NH), MS (m/z): 408 (M'), 409 (M + 1), 410 (M + 2); Anal. Calcd. for C25H15ClN3O: C, 76.37; H, 4.19; N, 6.85; Found: C, 76.47; H, 4.14; N, 6.61 |
| 6f    | –Cl| 3-[(2-Chloro-6-nitroquinolin-3-yl)methylene]-5-(naphthalene-2-yl)-1H-pyrrolo-[2,3-]one: yield 70%; Rf 0.67, IR (KBr) cm–1: 3451 (NH), 1689 (C=O), 1601 (Ar=C=C), 1026 (Ar=C–N), 813 (Ar=CH). 1H NMR (CDCl3) δ = 6.36 (1H, βH, 7.12 (1H, olefinic H), 7.24–8.31 (complex m, 14H, 13 aryl protons + NH), MS (m/z): 442 (M'), 443 (M + 1), 444 (M + 2); Anal. Calcd. for C25H16ClN3O: C, 70.44; H, 3.64; N, 6.32; Found: C, 70.31; H, 3.58; N, 6.25 |
| 6g    | –CH3| 3-[(2-Chloro-6-nitroquinolin-3-yl)methylene]-5-(naphthalene-2-yl)-1H-pyrrolo-[2,3-]one: yield 72%; Rf 0.71, IR (KBr) cm–1: 3441 (NH), 1696 (C=O), 1594 (Ar=C=C), 1019 (Ar=C–N), 788 (Ar=CH). 1H NMR (CDCl3) δ = 2.25 (3H, CH3), 6.31 (1H, βH, 7.12 (1H, olefinic H), 7.17–8.20 (complex m, 14H, 13 aryl protons + NH), MS (m/z): 422 (M'), 423 (M + 1), 424 (M + 2); Anal. Calcd. for C25H17ClN3O: C, 76.68; H, 4.53; N, 6.62; Found: C, 76.54; H, 4.49; N, 6.54 |
| 6h    | –NO2| 3-[(2-Chloro-6-nitroquinolin-3-yl)methylene]-5-(naphthalene-2-yl)-1H-pyrrolo-[2,3-]one: yield 65%; Rf 0.70, IR (KBr) cm–1: 3435 (NH), 1708 (C=O), 1611 (Ar=C=C), 1037 (Ar=C–N), 805 (Ar=CH). 1H NMR (CDCl3) δ = 6.36 (1H, βH, 7.08 (1H, olefinic H), 7.12–8.34 (complex m, 14H, 13 aryl protons + NH), MS (m/z): 452 (M'), 454 (M + 1), 455 (M + 2); Anal. Calcd. for C25H16ClN3O: C, 68.80; H, 3.55; N, 9.26; Found: C, 68.63; H, 3.28; N, 9.55 |

2.5. Docking studies

The ligand dataset was virtually screened with the protein targets using Molegro software (MVD 4.2) and the binding energy values were analyzed for each docked conformation (William et al., 2008; Reyes and Kollman, 2000). Conformations having low energy and exhibited favorable hydrogen bonding with the amino acids side chain and its amide nitrogen were considered (Table 7). Binding energies of the protein–ligand interactions are of significant importance because they tell us how well the ligand binds to the target macromolecule. Docking simulations of furanones against 3LN1 protein target lead to the identification of few potential compounds which were evaluated based on the binding compatibility [docked energy (kcal/mol)] with the receptor.

3. Results and discussion

3.1. Chemistry

The title compounds were prepared as per the protocol outlined in Scheme 1. The present work involved clubbing of furanone and pyrrolines with quinoline moiety to obtain newer effective compounds. The synthetic methodology involves the synthesis of quinoline-3-carbaldehyde derivatives (2a–d) by reacting N,N-dimethylformamide (DMF) with acetoephene.
Table 3 Physical and spectral data of 1-benzyl-3-[(2-chloro-6-substituted quinolin-3-yl)methylidene]-5-(aryl)-1H-pyrrrol-1(3H)-one (7a–h).

| Compd | –R | Physical and spectral data |
|-------|----|---------------------------|
| 7a    | –H | Physical and spectral data |
| 7b    | –Cl | Physical and spectral data |
| 7c    | –CH3 | Physical and spectral data |
| 7d    | –NO2 | Physical and spectral data |
| 7e    | –H | Physical and spectral data |
| 7f    | –Cl | Physical and spectral data |
| 7g    | –CH3 | Physical and spectral data |
| 7h    | –NO2 | Physical and spectral data |

oxime (1a–d) in the presence of phosphorous oxychloride (POCl3). The reaction proceeds via Beckmann rearrangement followed by Vilsmeier–Haack formylation. The 3-aryl propionic acids (3,4) were prepared by Friedel–Craft acylation of naphthalene and biphenyl with succinic anhydride. Condensation of quinolone-3-carbaldehyde (2a–d) with 3-aryl propionic acid (3,4) in the presence of acetic anhydride resulted in the formation of 3-{(2-chloro-6-substituted quinolin-3-yl) methylidene}-5-(aryl)-furano-2(3H)-one (5a–h). The 3-{(2-chloro-6-substituted quinolin-3-yl) methylidene}-5-(aryl)-pyrrol-2(3H)-ones (6a–h) were prepared by reacting furan-2(3H)-ones (5a–h) with dry ammonia in absolute ethanol. The 1-benzyl-3-[(2-chloro-6-substituted quinolin-3-yl) methylidene]-5-(aryl)-pyrrol-2(3H)-ones (7a–h) were obtained by reacting furan-2(3H)-ones with benzylamine in dry benzene to give γ-ketobenzamides, which were then lactamized in 6 N HCl to furnish the corresponding N-benzyl-2(3H)-pyrrolole (7a–h). The chemical structures of the title compounds were characterized by IR, 1H NMR, Mass spectral data and are well supported by elemental analysis.

The infrared spectral studies (IR; cm⁻¹) of furan-2(3H)-ones 5a–h showed peaks at 1774–1713 (lactone C=O); 1570–1518 (ArC=C), 1066–1033 (ArC=N), and 865–824 (ArC=H). IR band for Pyrrolole-2(3H)-one 6a–h appeared at 3451–3388 (pyrroline N=H), 1708–1683 (C=O); 1611–1582 (ArC=C) and 814–788 (ArC=H). IR spectra of N-

Please cite this article in press as: Khokra, S.L. et al., Quinoline based furanones and their nitrogen analogues: Docking, synthesis and biological evaluation. Saudi Pharmaceutical Journal (2013), http://dx.doi.org/10.1016/j.jspj.2013.05.002.
Benzylpyrrol-2(3H)-ones 7a–h gave bands at 1753–1737 (lactone C=O); 1613–1592 (ArC=O), 1046–1033 (ArC=N), and 821–796 (ArC=H). In 1H NMR spectra, signal at around δ 6.6 indicates the formation of furan ring. The absence of aldehydic proton and presence of alkenic proton further indicate the conversion of aldehydic group to the desired compound. The δ values were calculated using incremental parameters for the hydrogen (semicyclic double bond) which indicated an (E)-configuration. The Mass spectra of the title compounds displayed M+ peak in reasonable intensities. The molecular ion peak and isotopic peaks and fragment peaks were quite clear due to the presence of chlorine atom(s) in all the title compounds. The physical and spectral data of all the synthesized compounds (5a–h, 6a–h and 7a–h) are presented in Tables 1–3.

3.2. Antimicrobial activity

All the three series of synthesized compounds (5a–h, 6a–h and 7a–h) were screened for the antimicrobial activity against few selected bacterial and fungal strains.

3.2.1. Antibacterial and antifungal activity

All the screened compounds showed variable antimicrobial activity against the tested microbes. The results of antibacterial testing indicate that four pyrroline compounds 6b, 6d, 6f and 6h are highly active against S. aureus and three compounds 6b, 6d and 6f against B. subtilis, with MIC 6.25 μg/mL. The most potent antibacterial compounds among furanones and N-benzyl pyrrolones against S. aureus were found to be 5b, 5d, 5f and 7f, respectively with MIC of 12.5 μg/mL. However, compounds 5a, 5c, 5g, 7e and 7g did not show any inhibition against the gram negative bacteria E. coli and P. aeruginosa. The most potent compounds against E. coli and P. aeruginosa were observed to be 5d, 6d, 7b and 6d, respectively with a MIC of 12.5 μg/mL. Compounds 6d and 6f also exhibited significant antifungal activity against A. niger with MIC 6.25 μg/mL. Their activity was at par with the standard drugs, ciprofloxacin or fluconazole which also had MIC of 6.25 μg/mL. In general, majority of the tested compounds were found to be less active against the E. coli, P. aeruginosa and A. flavus. Results of antibacterial and antifungal activity are summarized in Table 4.

A closer look at the results revealed that the title compounds possess better antifungal activity as compared to antibacterial activity. Among all the prepared compounds, 6d and 6f were found to be the most promising antibacterial and antifungal agents. It was interesting to note that substitution of oxygen atom with the nitrogen i.e. converting furans into corresponding pyrrolones, significantly enhances the antimicrobial activity; however, introduction of benzylamine...
moiety in place of oxygen atom (benzylpyrrolones) in the furanone ring leads to decreased antimicrobial activity. This change in activity may be due to proton donor capacity of pyrrolones.

Thus, based on the above results, the following structure activity relationship (SAR) can be proposed for the synthesized compounds (Fig. 2):

1. Presence of a chloro group on the quinoline nucleus with attached biphenyl ring was found to increase activity of pyrrolone toward inhibition of S. aureus and B. subtilis.
2. Presence of N-benzyl pyrrolone with attached biphenyl ring and quinoline ring was found to be highly active. But any substitution in quinoline ring at 6-position causes decrease in activity.

| Compd | Antibacterial activity | Antifungal activity |
|-------|------------------------|---------------------|
|       | S. aureus | E. coli | P. aeruginosa | B. subtilis | A. niger | A. flavus |
| 5a    | 50 | – | – | 50 | 50 | – |
| 5b    | 12.5 | 25 | 50 | 12.5 | 25 | 50 |
| 5c    | 25 | – | – | 50 | 50 | >100 |
| 5d    | 12.5 | 12.5 | 25 | 25 | 25 | 25 |
| 5e    | 25 | – | – | 50 | 25 | 50 |
| 5f    | 12.5 | 50 | >100 | 25 | 25 | 25 |
| 5g    | 25 | – | – | 50 | 50 | 50 |
| 5h    | 25 | 50 | – | >100 | 25 | 25 |
| 6a    | 25 | – | 50 | 25 | 25 | 25 |
| 6b    | 6.25 | 50 | 50 | 6.25 | 12.5 | 12.5 |
| 6c    | 12.5 | – | 50 | 12.5 | 25 | 12.5 |
| 6d    | 6.25 | 12.5 | 12.5 | 6.25 | 12.5 | 12.5 |
| 6e    | 12.5 | – | 50 | 50 | 50 | 25 |
| 6f    | 6.25 | 50 | 25 | 6.25 | 6.25 | 12.5 |
| 6g    | 25 | 50 | 50 | 12.5 | 25 | 12.5 |
| 6h    | 6.25 | 25 | 25 | 12.5 | 25 | 25 |
| 7a    | 50 | 25 | – | >100 | 50 | >100 |
| 7b    | 25 | 12.5 | >100 | 25 | 50 | 25 |
| 7c    | 25 | 50 | – | 50 | 50 | 25 |
| 7d    | 25 | 25 | >100 | 25 | 25 | 50 |
| 7e    | 50 | – | – | – | 50 | >100 |
| 7f    | 12.5 | 25 | 50 | 12.5 | 25 | 50 |
| 7g    | 25 | – | – | 50 | 25 | 50 |
| 7h    | 25 | 50 | 50 | – | 50 | >100 |
| Standard-1 | 6.25 | 6.25 | 6.25 | nt | nt | Nt |
| Standard-2 | Nt | Nt | Nt | 6.25 | 6.25 | 6.25 |

– Indicates microbes are resistant to the compounds >100 µg/mL; nt = not tested.

* Standard-1 = Ciprofloxacin, Standard-2 = Fluconazole; MIC = minimum inhibitory concentration.
3. Presence of a chloro group on the quinoline nucleus with attached naphthalene ring was found to increase activity of pyrrolone toward inhibition of *A. niger* and *A. flavus*.

### 3.3. Anti-inflammatory activity

The results of anti-inflammatory activity presented in Table 5 showed that furanones (5a–h) inhibited carrageenan induced edema from 56% to 63%, pyrrolones (6a–h) 36–53%, N-benzyl pyrrolones (7a–h) 40–71% in comparison with the standard diclofenac, 92%. Compound 3-[{2-Chloro-6-nitroquinolin-3-yl}(methylene)-5-{(biphenyl-4-yl)furan-2(3H)-one (5h) among furanones (63% inhibition), 6b among pyrrolones (53% inhibition) and 1-benzyl-3-[{2-chloro-6-nitroquinolin-3-yl}methylene]-5-{naphthalene-2-yl}-1H-pyrrol-2(3H)-one (7d) among N-benzyl pyrrolones (71% inhibition) were observed to be the most potent compounds. Thus, it could be concluded that furanones are potent anti-inflammatory agents and substitution of oxygen atom of furanone ring with -NH-(pyrrolone) leads to markedly decreased anti-inflammatory activity, while replacement by benzylamine moiety (N-benzyl pyrrolone) enhanced the anti-inflammatory action (Table 5). Thus, it could be concluded that to exhibit the potent anti-inflammatory activity, nitrogen atom of pyrrolone ring should be tertiary. Among 1-benzyl-2(3H)-Pyrrolones (7a–h), the maximum anti-inflammatory activity was shown by 7d and closely followed by 1-benzyl-3-[{2,6-dichloroquinolin-3-yl}methylene]-5-(naphthalene-2-yl)-1H-pyrrol-2(3H)-one 7b with 71% and 70% inhibition respectively. The other two compounds, 1-Benzyl-3-[{2,6-dichloroquinolin-3-yl}methylene]-5-(biphenyl-4-yl)-1H-pyrrol-2(3H)-one 7f and 1-Benzyl-3-[{2-chloro-6-nitroquinolin-3-yl}methylene]-5-(biphenyl-4-yl)-1H-pyrrol-2(3H)-one 7f also showed good inhibition of 69% and 64% respectively.

### 3.4. Analgesic activity

A total of eight test compounds (5h, 5d, 5h, 6b, 7d, 7f, 7h) displaying good inhibition of rat paw edema was selected for further investigation of their analgesic and ulcerogenic actions. Acetic acid induced writhing method and tail-immersion method were used to evaluate peripherally and centrally mediated analgesic effects of the selected compounds. The results of central analgesic activity by tail immersion method indicated a gradual increase in reaction time at 1 h and 2 h, respectively (Table 6). The tested compounds showed reaction time of 1–8.5 min at 1 h while it was much higher at 2 h (3.4–6.5 min). The compounds 5d, 5h and 7f showed very significant analgesic activity (4.4, 4.3 and 5.5 min) comparable to that of standard at 1 h (8.2 min) while the compounds 5d, 5h, 7f and 7h also showed good activity (6.5, 6.2, 6.2 and 6.4 min) at 2 h in tail immersion method. It was interesting to note that 5d, 5h, 7f and 7h also were found to be the most potent peripheral acting analgesic agents (Table 6), suggesting that these compounds act both peripherally and centrally to abolish pain. The percent protection against the acetic acid induced constrictions for 5d, 5h, 7f and 7h was in the range 64% respectively.

### Table 5 Anti-inflammatory activity of the title compounds (5a–h, 6a–h and 7a–h).

| Compound | % Inhibition ± SEMb | After 1 h | After 2 h | After 3 h | After 4 h |
|----------|---------------------|-----------|-----------|-----------|-----------|
| Control  | –                   | –         | –         | –         | –         |
| Standard | 84 ± 0.02**         | 79 ± 0.12*| 66 ± 0.25*| 58 ± 0.21*| 49 ± 0.18*|
| 5a       | 67 ± 0.14**         | 62 ± 0.11*| 60 ± 0.22*| 53 ± 0.17*| 50 ± 0.13*|
| 5b       | 74 ± 0.18**         | 67 ± 0.06*| 58 ± 0.21*| 46 ± 0.33*| 53 ± 0.18*|
| 5c       | 69 ± 0.12*          | 66 ± 0.25*| 53 ± 0.17*| 50 ± 0.13*| 53 ± 0.18*|
| 5d       | 79 ± 0.12*          | 61 ± 0.15*| 53 ± 0.17*| 50 ± 0.13*| 53 ± 0.18*|
| 5e       | 63 ± 0.09*          | 60 ± 0.22*| 53 ± 0.17*| 50 ± 0.13*| 53 ± 0.18*|
| 5f       | 63 ± 0.13*          | 58 ± 0.21*| 53 ± 0.17*| 50 ± 0.13*| 53 ± 0.18*|
| 5g       | 67 ± 0.12*          | 62 ± 0.11*| 53 ± 0.17*| 50 ± 0.13*| 53 ± 0.18*|
| 5h       | 73 ± 0.08*          | 58 ± 0.15*| 50 ± 0.13*| 53 ± 0.18*| 53 ± 0.18*|
| 5a       | 64 ± 0.06           | 66 ± 0.18*| 53 ± 0.17*| 50 ± 0.13*| 53 ± 0.18*|
| 6a       | 62 ± 0.09           | 55 ± 0.22*| 47 ± 0.24*| 44 ± 0.33*| 42 ± 0.20*|
| 6b       | 58 ± 0.25           | 62 ± 0.22*| 59 ± 0.16*| 48 ± 0.15*| 35 ± 0.32*|
| 6c       | 38 ± 0.21           | 48 ± 0.21*| 29 ± 0.16*| 42 ± 0.20*| 36 ± 0.19*|
| 6f       | 48 ± 0.13           | 63 ± 0.27*| 25 ± 0.34*| 42 ± 0.20*| 36 ± 0.19*|
| 6g       | 52 ± 0.08           | 48 ± 0.24*| 25 ± 0.34*| 42 ± 0.20*| 36 ± 0.19*|
| 6h       | 58 ± 0.19           | 50 ± 0.05*| 28 ± 0.34*| 48 ± 0.15*| 35 ± 0.32*|
| 7a       | 52 ± 0.13           | 62 ± 0.27*| 28 ± 0.34*| 48 ± 0.15*| 35 ± 0.32*|
| 7b       | 84 ± 0.06           | 74 ± 0.21*| 70 ± 0.23*| 48 ± 0.15*| 35 ± 0.32*|
| 7c       | 78 ± 0.12           | 71 ± 0.28*| 57 ± 0.25*| 36 ± 0.21**| 36 ± 0.19*|
| 7d       | 83 ± 0.06           | 73 ± 0.15*| 66 ± 0.26*| 44 ± 0.08*| 41 ± 0.08*|
| 7f       | 84 ± 0.12           | 74 ± 0.19*| 63 ± 0.14*| 64 ± 0.21**| 41 ± 0.08*|
| 7g       | 69 ± 0.03           | 54 ± 0.14*| 30 ± 0.20*| 40 ± 0.16*| 36 ± 0.13*|
| 7h       | 36 ± 0.13           | 65 ± 0.24*| 58 ± 0.34*| 69 ± 0.15**| 65 ± 0.24*|

Data are arranged as mean ± SEM ANOVA followed by Dunnet’s t test where *p < 0.05; **p < 0.01.

Please cite this article in press as: Khokra, S.L. et al., Quinoline based furanones and their nitrogen analogues: Docking, synthesis and biological evaluation. *Saudi Pharmaceutical Journal* (2015), http://dx.doi.org/10.1016/j.jsps.2015.05.002
of 69.52–85.71%, which was quite close to the standard drug diclofenac (90%). All these compounds possess electron withdrawing groups i.e. Cl and NO₂ in the quinoline ring. It was also observed that 5d exhibited the most powerful analgesic activity by peripheral and central mechanism and it is a furanone derivative containing a naphthyl ring at position 5 in contrast to other three compounds that possess a biphenyl ring. Although, compound 6b, a pyrrolone derivative, displayed moderate activity by tail immersion method it showed 67.14% protection in acetic acid induced writhing model.

### 3.5. Acute ulcerogenic test

Results of severity index (ulcerogenic activity) of selected eight compounds indicated better tolerability and safer gastrointestinal profile in contrast to the standard drug diclofenac. Compounds 5d and 7h appeared to be the least toxic (0.30 ± 0.31 and 0.30 ± 0.53) as compared to diclofenac (0.86 ± 0.28). The result indicates that compounds were less toxic in terms of ulcerogenicity as compared to standard NSAID (Table 6).

| Compound | Central analgesic activity [tail immersion (reaction time in min)] | Peripheral analgesic activity (writhing test) | Ulcerogenic activity (severity index) |
|----------|---------------------------------------------------------------|-------------------------------------------|-------------------------------------|
|          | 1 h               | 2 h               | No. of writhing | % Protection |             |             |
| Control  | 1.4 ± 0.2         | 2.8 ± 0.2         | 42 ± 11.6     | 0            | 0.00 ± 0.00 |
| Diclofenac | 8.2 ± 0.2**      | 8.8 ± 0.2**      | 4.2 ± 1.0**   | 90           | 0.86 ± 0.28 |
| 5b       | 3.2 ± 0.2         | 4.4 ± 0.5         | 26.2 ± 4.1    | 37.61        | 0.33 ± 0.35* |
| 5d       | 4.4 ± 0.6**       | 6.5 ± 0.2*        | 6.0 ± 2.2**   | 85.71        | 0.30 ± 0.31* |
| 5h       | 4.3 ± 0.4**       | 6.2 ± 1.5*        | 7.6 ± 2.3**   | 81.9         | 0.40 ± 0.36 |
| 6b       | 1.8 ± 0.2         | 4.2 ± 0.6         | 13.8 ± 4.4*   | 67.14        | 0.43 ± 0.33 |
| 7b       | 2.4 ± 0.3         | 3.4 ± 0.2         | 25.4 ± 4.8    | 39.52        | 0.36 ± 0.35* |
| 7d       | 3.2 ± 0.4*        | 5.4 ± 1.9         | 21.0 ± 10.0*  | 50           | 0.40 ± 0.32 |
| 7f       | 3.2 ± 0.2**       | 6.2 ± 1.5*        | 12.8 ± 3.8**  | 69.52        | 0.53 ± 0.12 |
| 7h       | 5.5 ± 0.3**       | 6.4 ± 0.3*        | 10.4 ± 3.7**  | 75.23        | 0.30 ± 0.53* |

Data are arranged as mean ± SEM ANOVA followed by Dunnet’s t test where *p < 0.05; **p < 0.01.

### 3.6. Docking studies

The results of docking against COXII (PDB3LN1) are listed in Table 7. Docking scores of almost all synthesized compound were greater than the internal ligand value. The docking scores of tested compounds range between −104.82 and −160.96. The maximum number of hydrogen bond interactions shown by tested compounds was 6 comparable to internal ligand interaction values i.e., 9. The compounds which showed maximum docking score values are 7h (−160.96) (Fig. 3), 7f (−138.27), and 7g (−137.53) in comparison with internal ligand value (−86.29) while the compounds that showed maximum interaction with receptor residues are 5d (6) (Fig. 4), 5h (5) and 6d (6).

The binding mode of standard, 7h and 5d into the COX 2 is illustrated in Figs. 3–5. From the docking results (Table 7) for anti-inflammatory activity it was observed that N-benzyl pyrrolones showed maximum mol dock score in comparison with pyrrolones, it may be due to increase in hydrophobicity and due to substitution of hydrogen atom of pyrrolone with benzyl group. On comparing the in vivo and in silico activity result of synthesized compounds, it was observed that

![Figure 3](https://example.com/figure3.png)
whole series of N-benzyl pyrrolones (7a–h) was most effective as anti-inflammatory agents as they exhibited maximum inhibition in edema volume and maximum mol dock score, respectively.

4. Conclusion

A total of 24 new quinoline derivatives containing five membered heterocyclic ring viz. furan-2(3H)-ones (5a–h), pyrrol-2(3H)-ones (6a–h) and N-benzyl-pyrrol-2(3H)-ones (7a–h) was designed and synthesized. In vivo biological testing results indicated some of the compounds to possess significant anti-inflammatory and analgesic activities with lesser GI toxicity. N-Benzyl-pyrrol-2(3H)-ones (7a–h) exhibited better anti-inflammatory activity than furan-2(3H)-ones and pyrrol-2(3H)-ones. Tested compounds also showed less GI toxicity and better tolerability than the standard drug diclofenac. Among the newer derivatives, four compounds 5d, 5h, 7f and

Figure 4  Binding mode of Compound 5d into COX-2 (Maximum number of hydrogen bond interaction = 6). It has docking score −130.34 and forms 6 hydrogen bonds as shown by blue dotted lines showing 6 hydrogen bond interactions, two between N of NO2, one with N(Arg 95) of distance 3.42 Å other with N(Arg 95) of distance 3.35 Å, two with O of NO2, both with N(Arg 95) of distance 2.74 Å and 2.72 Å, respectively, and other two between (=O of furanone) with O(Asp 254) of distance 3.10 and 3.10 Å, respectively.

Figure 5  Binding mode of standard into COX-2 with Moldock score −86.29 and 9 hydrogen bond interactions, three between 4-OH of pyranose, one with N(Trp 531) of distance 2.60 Å, second with O(Glu 31) of distance 2.51, third with O(Glu 350) of distance 3.44 Å, fourth between 3-OH of Pyranose and O(Glu 250) of distance 3.42 Å, two between 5-OH(Pyranose) and O(Phe 347) of distance 2.46 Å other with O(Asn 546) of distance 3.20 Å, three between O(CH2OH), one with O(Phe 347) of distance 3.09 Å, other with N(Lys 328) and O(Asn 546) of distance 3.15 Å and 3.09 Å, respectively.
| Compound no. | Mol dock score | No. of interaction | Ligand atom | PDB atom | Distance (Å) |
|--------------|----------------|--------------------|-------------|----------|--------------|
| Standard (PDB3LN2) | −86.29 | 9 | O of 4-OH(pyranose) | N(Trp 531) | 2.60 |
| | | | O of 4-OH(pyranose) | O(Glu 350) | 3.44 |
| | | | O of 4-OH(pyranose) | O(Glu 350) | 3.42 |
| | | | 3- OH | O(Asn 546) | 3.20 |
| | | | 5- OH | O(Tyr 347) | 2.46 |
| | | | O(CH2OH) | N(Lys 328) | 3.15 |
| | | | O(CH2OH) | O(Asn 546) | 3.09 |
| 5a | −110.78 | 2 | O(furanone) | N(Lys 41) | 3.38 |
| 5b | −131.18 | 3 | O(furanone) | N(Lys 239) | 2.76 |
| | | | O(furanone) | N(Lys 239) | 2.76 |
| | | | O(furanone) | O(Asp 254) | 3.10 |
| 5c | −104.82 | 3 | O(furanone) | N(Lys 41) | 3.21 |
| | | | O(furanone) | O(Asp 254) | 3.21 |
| | | | O(furanone) | N(Thr 255) | 3.10 |
| | | | O(furanone) | N(Asp 254) | 3.10 |
| 5d | −120.34 | 6 | N(NO2) | N(Arg 95) | 3.41 |
| | | | O(NO2) | N(Arg 95) | 2.74 |
| | | | O(NO2) | N(Arg 95) | 2.72 |
| | | | O(NO2) | N(Arg 95) | 3.34 |
| | | | N(NO2) | O(Asp 254) | 3.10 |
| | | | O(furanone) | N(Thr 255) | 3.26 |
| 5e | −113.38 | 1 | O(furanone) | N(Lys 239) | 2.61 |
| 5f | −112.40 | 3 | O(furanone) | N(Lys 41) | 3.34 |
| | | | O(furanone) | N(Thr 255) | 3.55 |
| | | | O(furanone) | N(Asp 254) | 3.33 |
| 5g | −113.65 | 3 | O(furanone) | N(Lys 41) | 3.26 |
| | | | O(furanone) | N(Asp 254) | 3.42 |
| | | | O(furanone) | N(Cys 44) | 3.33 |
| 5h | −123.80 | 5 | O(furanone) | N(Asp 254) | 2.86 |
| | | | O(NO2) | N(Asp 254) | 2.95 |
| | | | O(NO2) | N(Arg 95) | 2.68 |
| | | | O(NO2) | N(Arg 95) | 3.82 |
| 6a | −113.41 | 2 | N(Pyrrole) | N(Cys 42) | 3.26 |
| 6b | −118.08 | 3 | O(Pyrrole) | N(Cys 44) | 2.73 |
| | | | N(Quinoline) | O(Glu 332) | 3.14 |
| | | | O(Pyrrole) | O(Ser 549) | 2.67 |
| 6c | −116.86 | 2 | O(Pyrrole) | N(Cys 44) | 2.77 |
| | | | N(Pyrrole) | N(Cys 42) | 3.32 |
| 6d | −109.29 | 6 | N(NO2) | N(Lys 328) | 3.29 |
| | | | O(NO2) | N(Arg 95) | 3.10 |
| | | | O(NO2) | N(Lys 328) | 2.88 |
| | | | O(NO2) | N(Glu 332) | 3.37 |
| | | | O(Quinoline) | O(Asp 254) | 3.51 |
| | | | O(Pyrrole) | O(Asp 254) | 2.72 |
| | | | O(Pyrrole) | O(Ser 549) | 3.05 |
| 6e | −113.15 | 1 | O(Pyrrole) | N(Lys 239) | 2.61 |
| 6f | −116.74 | 1 | O(Pyrrole) | N(Lys 239) | 2.60 |
| 6g | −117.22 | 1 | O(Pyrrole) | N(Lys 239) | 2.61 |
| 6h | −115.98 | 1 | O(Pyrrole) | N(Lys 328) | 3.48 |
| 7a | −129.12 | 2 | N(Quinoline) | O(Lys 253) | 3.56 |
| | | | O(Pyrrole) | N(Lys 239) | 3.25 |
| 7b | −126.69 | 1 | N(Quinoline) | O(His 228) | 3.32 |
| 7c | −128.27 | 1 | N(Quinoline ring) | O(Ser 549) | 2.98 |
| 7d | −134.12 | 1 | O(NO2) | N(Try 531) | 3.07 |
| 7e | −131.26 | 1 | O(Pyrrole) | N(Lys 239) | 2.60 |
| 7f | −138.27 | 1 | O(Pyrrole) | N(Arg 95) | 3.52 |
| 7g | −137.53 | 1 | O(Pyrrole) | N(Arg 95) | 3.53 |
| 7h | −160.96 | 1 | O(Pyrrole) | N(Arg 95) | 3.11 |
7h emerged as lead compounds. Further detailed studies are needed to confirm the potential of the furanone and N-benzyl-pyrrolone derivatives in anti-inflammatory therapy.

Acknowledgment

The authors are thankful to UGC, Govt. of India, New Delhi, for providing financial assistance.

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