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Synthesis of quinoline-attached furan-2(3*H*)-ones having anti-inflammatory and antibacterial properties with reduced gastro-intestinal toxicity and lipid peroxidation

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Abstract: A series of 5-aryl-3-[(2-chloroquinolin-3-yl)methylene] furan-2(3*H*)-ones (**3a**–**p**) were synthesized. The required 3-(substituted benzoyl)propionic acids **2a**–**d** were prepared under Friedel–Crafts acylation reaction conditions. The substituted 2-chloroquinoline-3-carboxaldehydes **1a**–**d** were synthesized by reaction of substituted phenylethanone oxime with phosphorus oxychloride in presence of dimethylformamide using the Vilsmeier–Haack reaction method. These compounds were screened for their anti-inflammatory and antibacterial activities along with their ulcerogenic and lipid peroxidation potentials. The compounds that showed significant anti-inflammatory activity were further screened for their analgesic activity. The compounds were less toxic in terms of ulcerogenicity as compared to a standard, which was also supported by lipid peroxidation studies. The antibacterial activities were performed against *Staphylococcus aureus* and *Escherichia coli*. Compounds **3f**, **3n** and **3o** showed significant activity against both *S. aureus* and *E. coli* having an minimum inhibitory concentration (*MIC*) value of 6.25 μg mL^{-1}.

Keywords: furanone; quinoline; anti-inflammatory; analgesic; antibacterial activity.

INTRODUCTION

Inflammation occurs due to the biosynthesis of pro-inflammatory prostaglandins from arachidonic acid by the action of the enzyme cyclooxygenase (COX). In the human system, COX occurs in two isoforms, *viz.* COX-1 and COX-2.[1] Constitutive, COX-1 is responsible for housekeeping functions while inducible

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COX-2 is released during tissue injury, which causes the overproduction of prostaglandins.[2] Overexpressive COX-2 is also responsible for colon cancer.

Drugs used for treating the signs and symptoms of inflammation are referred to as NSAIDs. However the traditional non-steroidal anti-inflamatory drugs (NSAIDs), in addition to suppressing the effects of pathological COX also interfere with the housekeeping functions of the cyclo-oxygenase enzyme, which results in gastrointestinal tract (GIT) irritation, bleeding and ulceration.[3] This explains why the search for novel anti-inflammatory agent is necessary and hence, the need to develop and screen agents which would specifically inhibit the action of COX-2. However, this selective COX-2 inhibition has adverse cardiovascular effects.[4] Thus, there is a continuous need for the development of compounds with a safe analgesic and anti-inflammatory profile.

Quinoline and its derivatives are an important class of pharmaceutical agents known to occur in several natural compounds and found to possess anti-inflammatory[5] and analgesic[6] activity in addition to other pharmacological activities.[7–10] Similarly, furanone and its derivatives have been reported to have anti-inflammatory,[11,12] cardiotonic,[13] analgesic[12,14] and COX-2 inhibition[15,16] activities in addition to antioxidant,[17] cytotoxic,[18] antifungal,[11,12,14,19] antibacterial[11,12,14,20] and antiviral[21] activities.

Previously, the anti-inflammatory activities of a number of 3-arylidene-5--(substituted phenyl)-2(3*H*)-furanones were studied and the results were encouraging.[11,12,14,22,23] In view of these observations and as a part of an ongoing research program on development of newer anti-inflammatory and analgesic agents, the synthesis and pharmacological activities of a series of 2(3*H*)-furanones fused with the quinoline moiety are reported herein.

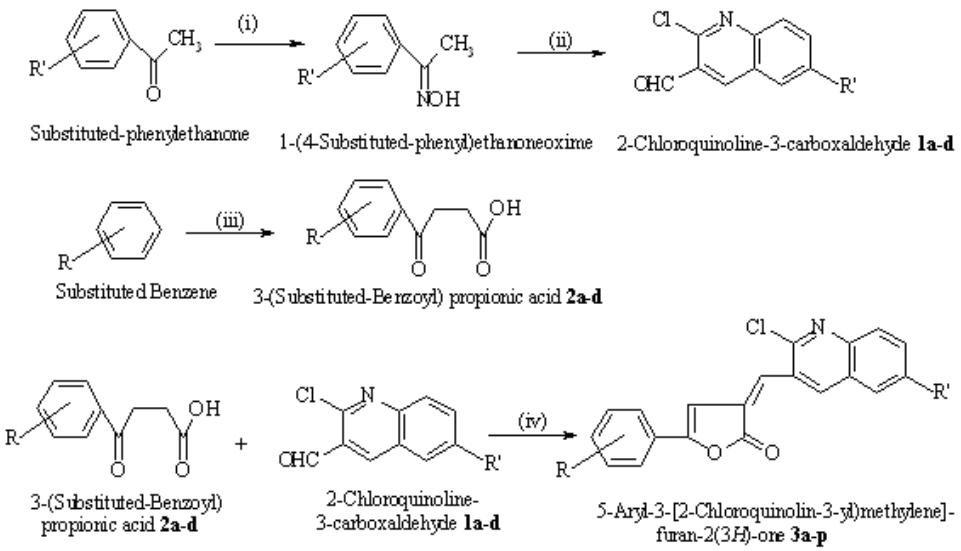
RESULTS AND DISCUSSION

Chemistry

Sixteen new compounds **3a**–**p** were synthesized as outlined in Scheme 1. The required 3-(substituted benzoyl)propionic acids **2a**–**d** were prepared by reacting different substituted benzenes with succinic anhydride in presence of anhydrous aluminium chloride followed by acylation under Friedel–Crafts reaction conditions.[14,22,24] The substituted 2-chloroquinoline-3-carboxaldehydes **1a**–**d** were synthesized by reacting substituted phenylethanone oxime with phosphorus oxychloride in presence of dimethyl formamide using the Vilsmeier–Haack reaction method.[25,26]

5-Aryl-3-[(2-chloroquinolin-3-yl)methylene] furan-2(3*H*)-ones **3a**–**p** were synthesized by condensing different aromatic aldehydes (**1a**–**d**) with a 3-(substituted benzoyl)propionic acids (**2a**–**d**) in presence of triethylamine and acetic anhydride under anhydrous conditions following a modified Perkin reaction.[14,22] Calculations of δ-values using incremental parameters for the hydrogen (semi-

cyclic double bond) suggested the (*E*)-configuration. All the synthesized compounds were characterized by spectroscopic data, *i.e.*, IR, ^{1}H-NMR, ^{13}C-NMR and mass, and elemental analysis. The results are given in the supplementary material to this paper.



3a: R=H, R'=H; **3b**: R=H, R'=Cl; **3c**: R=H, R'=OCH_3; **3d**: R=H, R'=CH_3
3e: R=4-CH_3, R'=H; **3f**: R=4-CH_3, R'=Cl; **3g**: R=4-CH_3, R'=OCH_3; **3h**: R=4-CH_3, R'=CH_3
3i: R=$(CH_3)_{2,4}$, R'=H; **3j**: R=$(CH_3)_{2,4}$, R'=Cl; **3k**: R=$(CH_3)_{2,4}$, R'=OCH_3; **3l**: R=$(CH_3)_{2,4}$, R'=CH_3
3m: R=4-Br, R'=H; **3n**: R=4-Br, R'=Cl; **3o**: R=4-Br, R'=OCH_3; **3p**: R=4-Br, R'=CH_3

Scheme 1. The reaction scheme for the synthesis of compounds **3a**–**p** (i – hydroxylamine hydrochloride and sodium acetate; ii – dimethylformamide and $POCl_3$; iii – anhydrous $AlCl_3$ and succinic anhydride; iv – acetic anhydride and triethylamine).

In general, the infrared spectral data of the furanones **3a**–**p** revealed bands at 1790–1740 cm^{-1} (lactone C=O), 1610–1560 cm^{-1} (ArC=C), 1070–1060 cm^{-1} (ArC–N) and 827–806 cm^{-1} (ArC–H). In the ^{1}H-NMR spectra, all the compounds showed two singlets of one proton each at around δ 6.6 and 8.2 ppm, which could be assigned to the ring β-H and the olefinic hydrogen of the arylidene substituent. Other peaks were observed at the appropriate positions. Some points could be made regarding the fragmentation pattern observed in the electron impact mass spectrum. The 5-aryl-3-[(2-chloroquinolin-3-yl)methylene] furan-2(3*H*)-ones **3a**–**p** gave an M^+ and M+2 (isotopic peak, due to presence of chlorine) peak of reasonable intensities.

Biological evaluation

Anti-inflammatory activity. The *in vivo* anti-inflammatory activity of the synthesized compounds **3a**–**p** was evaluated by the carrageenan-induced rat paw edema method.[27] Ibuprofen was used as the standard drug for comparison (Table I).The anti-inflammatory activity test showed that 5-(4-bromophenyl)-3-[(2--chloro-6-methoxyquinolin-3-yl)methylene] furan-2(3*H*)-one (**3o**) exhibited the maximum anti-inflammatory activity (68.9 % inhibition) in addition to 5-(4-bromophenyl)-3-[(2,6-dichloroquinolin-3-yl)methylene] furan-2(3*H*)-one (**3n**), 5-(4-methylphenyl)-3-[(2-chloro-6-methoxyquinolin-3-yl)methylene] furan-2(3*H*)-one (**3g**) and 5-(4-bromophenyl)-3-[(2-chloro-6-methylquinolin-3-yl)methylene] furan-2(3*H*)-one (**3p**), showing 59.03, 56.62 and 53.01 % inhibition, respectively. The results are presented in Table I.

TABLE I. Anti-inflammatory and analgesic activity along with the ulcerogenic and lipid peroxidation effect of the synthesized compounds **3a**–**p**

Compound	% Inhibition ± *SEM*[a]		Severity index[b]	Lipid peroxidation[c] nmol MDA mg^{-1} protein	Analgesic activity (writhing test)[b]	
	After 2 h	After 3 h			No. of writhes per 30 min	Protection %
Control	–	–	0.00±0.00	0.24±0.002[b]	83±1.31	–
Ibuprofen	67.7±2.05	80.8±2.60	0.83±0.36	0.73±0.001[a]	29±1.15	65.06
3a	9.5±1.79	16.0±1.81	0.4±0.10	0.39±0.005[ab]	–	–
3b	18.6±3.16	23.4±2.87	0.3±0.12	0.40±0.005[ab]		
3c	16.4±1.72	22.8±0.42	0.33±0.12	0.35±0.001[ab]	–	–
3d	18.8±2.83	29.7±3.39	0.5±0.27	0.39±0.007[ab]	–	–
3e	26.6±4.34	36.0±3.22	0.52±0.36	0.54±0.001[ab]	–	–
3f	28±2.74	50.4±1.73	0.41±0.1	0.40±0.002[ab]	–	–
3g	34.1±4.16	53.8±1.38	0.16±0.12	0.36±0.014[ab]	36±1.89	56.62
3h	44.9±5.22	50.0±2.28	0.41±0.1	0.41±0.002[ab]	–	–
3i	10.4±3.86	19.9±3.06	0.46±0.4	0.55±0.001[ab]	–	–
3j	33.7±2.61	39.7±2.80	0.5±0.27	0.42±0.001[ab]	–	–
3k	21.5±4.01	36.6±3.51	0.48±0.36	0.53±0.017[ab]	–	–
3l	20±1.97	37.0±3.27	0.5±0.27	0.49±0.001[ab]	–	–
3m	26.6±3.98	34.5±3.54	0.43±0.36	0.58±0.001[ab]	–	–
3n	38.2±1.97	56.3±3.49	0.16±0.12	0.29±0.001[ab]	34±1.24	59.03
3o	48.6±3.69	68.9±3.07	0.25±0.12	0.38±0.002[ab]	33±1.31	60.24
3p	42.4±1.79	52.0±2.42	0.2±0.12	0.33±0.006[ab]	39±1.94	53.01

[a]Relative to the standard (ibuprofen) and data were analyzed by one-way ANOVA followed by the Tukey test for $n = 6$; [b]relative to their respective control and the data were analyzed by one-way ANOVA followed by the Tukey test for $n = 6$; [c]lipid peroxidation activity is expressed as nmoles of MDA mg^{-1} protein. "±" indicates the minimum and maximum variation in the average values. "–" indicates not tested

Based on the above observations, the following structure–activity relationship can be concluded:

i) presence of an electronegative group on phenyl moiety of the furanone ring increases the anti-inflammatory activity as compared to that of an electropositive group;

ii) an increase in number of electropositive groups on the phenyl moiety of the furanone ring further decreases the activity;

iii) the presence of a methoxy group on the quinoline nucleus showed maximum activity;

iv) replacement of the methoxy group by a methyl group decreases the activity.

All the synthesized compounds were further tested for their ulcerogenic and lipid peroxidation effects. The test compounds (**3o**, **3n, 3g** and **3p**) that exhibited an above 65 % ibuprofen edema inhibition were further evaluated for their analgesic activity.

Analgesic activity. The analgesic activity was evaluated by the acetic acid-induced writhing test.[28] The results indicated that compounds **3o** and **3n** showed 60.24 and 59.03 % activity, respectively, which were comparable to that of the standard ibuprofen (65.06 %). Compounds **3g** and **3p** also showed good analgesic activity (Table I).

Acute ulcerogenesis. The synthesized compounds were screened for their ulcerogenic activity by the Cioli *et al.* method.[29] Compounds **3o** and **3n** showed a severity index of 0.25±0.12 and 0.16±0.12, respectively, which were much lower as compared to that of ibuprofen (0.83±0.36). The results indicated that the compounds were less toxic in terms of ulcerogenicity as compared to standard, which was also supported by lipid peroxidation studies (Table I).

Lipid peroxidation. All the compounds screened for ulcerogenic activity were also analyzed for lipid peroxidation by the Ohkawa *et al*. method.[30] The lipid peroxidation was measured as nmoles of malondialdehyde (MDA) mg^{-1} of protein. Ibuprofen exhibited high lipid peroxidation 0.73±0.001 whereas control group showed 0.24±0.002. It was found that all the furanone derivatives fused with quinoline ring showed less ulcerogenic activity along with reduced lipid peroxidation (Table I).

Antibacterial activity. All the compounds tested for antimicrobial activity showed inhibition of growth. Compounds **3f**, **3n** and **3o** showed significant activity against both *Staphylococcus aureus* and *Escherichia coli* with a minimum inhibitory concentration (*MIC*) value of 6.25 μg mL^{-1} (Table II). Of the sixteen new compounds, two compounds, **3i** and **3j** were found to be more active against *S. aureus* with an *MIC* value of 6.25 μg mL^{-1}. Analyses of the results indicated that:

i) the presence of a chloro group on the quinoline nucleus induced selectivity of the furanone towards inhibition of *S. aureus*;

ii) the presence of an electropositive group on the phenyl moiety of the furanone ring induced inhibition of *S. aureus*. However, an electronegative group favoured inhibition of *E. coli*.

TABLE II. Antibacterial activity, *MIC* / μg mL^{-1}, results of the 2(3*H*)-furanones (the studies were performed in triplicate)

Compound	*S. aureus*	*E. coli*
Nitrofurazone	12.5±0.0	6.25±0.0
3a	133.37±16.67	167.67±33.34
3b	50±0.0	50±0.0
3c	133±33.34	50±0.0
3d	133±33.34	166±33.34
3e	25±0.0	50±0.0
3f	6.25±0.0	6.25±0.0
3g	12.5±0.0	25±0.0
3h	25±0.0	50±0.0
3i	6.25±0.0	12.5±0.0
3j	6.25±0.0	12.5±0.0
3k	25±0.0	50±0.0
3l	12.5±0.0	25±0.0
3m	12.5±0.0	12.5±0.0
3n	6.25±0.0	6.25±0.0
3o	6.25±0.0	6.25±0.0
3p	12.5±0.0	25±0.0

EXPERIMENTAL

Chemistry

Chemicals were purchased from Merck and Sigma-Aldrich as synthesis grade and were used without further purification. Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel G plates (Merck No. 5544) using toluene:ethyl acetate:formic acid (5:4:1) as the solvent system and the spots were located either under ultraviolet light or through exposure to iodine vapour. The IR spectra were measured as potassium bromide pellets using a Perkin-Elmer 1725X spectrophotometer. The ^{1}H-NMR spectra were recorded on Bruker spectrospin DPX-300 MHz in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard; chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS. Mass spectra were recorded at 70 eV on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system. Spectral data are consistent with the assigned structures. Elemental analyses were performed on a Perkin-Elmer model 240 analyzer (C, H, N) and were found within the range of ± 0.4 % of the theoretical values.

General procedure for the synthesis of 1-(4-substituted phenyl)ethanone oximes

The 1-(4-substituted phenyl)ethanone oximes were synthesized from different substituted acetophenones (0.1 mol), hydroxylamine hydrochloride (0.12 mol) and sodium acetate (0.12 mol) using the method reported by Cohn *et al.*[25]

*General procedure for the synthesis of the 2-chloroquinolin-3-carboxaldehydes **1a–d***

To dimethylformaldehyde (0.15 mol) cooled to 0 °C, freshly distilled phosphorous oxychloride (0.35 mol) was added dropwise under stirring, then the respective oxime (0.05 mol) was added portion-wise. The reaction mixture was heated at 60 °C for 16 h. It was then poured into ice water (300 mL) and stirred for 30 min. The 2-chloroquinoline-3-carboxaldehyde was filtered and recrystallized from ethyl acetate.[25,26]

*General procedure for the synthesis of 3-(substituted benzoyl)propionic acids **2a–d***

The 3-(substituted benzoyl)propionic acids were synthesized according to a previously reported method[14,22,24] using dry substituted-benzene (50 mL) under anhydrous conditions in presence of anhydrous aluminium chloride (0.15 mol) and succinic anhydride (0.1 mol). The obtained product was crystallized from aqueous ethanol to give a colourless compound that gave effervescence with sodium bicarbonate.

*General procedure for the synthesis of 3-[(2-chloroquinolin-3-yl)methylene]-5-(substituted phenyl) furan-2(3*H*)-ones **3a–p***

Each compound **2a–d** (3 mmol) and each compound **1a–d** (equimolar, 3 mmol) were fused together in presence of acetic anhydride (5–8 drops) in a round-bottom flask for half an hour. To this fused mixture, triethylamine (2 drops) was added and the heating on a heating mantle was continued for a further 15 min. After the completion of reaction, the obtained solid mass was crystallized from methanol and gave the desired products.

Biological evaluation

Animals. The Wistar rats and albino mice used in the present study were housed and kept in accordance with the Hamdard University Animal Care Unit, which applies the guidelines and rules laid down by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. Wistar rats and albino mice of either sex (Hamdard University, Animal House, New Delhi, India), weighing 180–200 g (12 weeks) and 22–25 g (8 weeks), respectively, were used. The animals were housed in groups of six and acclimatized to ambient conditions for at least 2 days before the experiments. Food and water were freely available up to the time of the experiments. The food was withdrawn on the day before the experiment, but free access to water was allowed.

Anti-inflammatory activity. The synthesized compounds were evaluated for their anti-inflammatory activity using the carrageenan-induced paw edema method of Winter *et al*.[27] The animals were randomly divided into groups of six. Group I was kept as control, and received only 0.5 % carboxymethyl cellulose (CMC) solution. Group II was kept as the standard and received ibuprofen. Carrageenan solution (0.1 % in sterile 0.9 % NaCl solution) in a volume of 0.1 mL was injected subcutaneously into the sub-plantar region of the right hind paw of each rat, 30 min after the administration of the test compounds (20 mg kg^{-1} *p.o.*) and the standard drugs. The paw volume was measured by saline displacement shown on the screen of digital plethysmometer (Ugo Basile) at 2 and 3 h after carrageenan injection. The edema volume in the control group (V_c) and edema volume in the groups treated with test compounds (V_t) was measured and the percentage inhibition of edema was calculated using the formula:

$$\text{Anti-inflammatory activity (\% inhibition)} = 100((V_c - V_t) / V_c)$$

where V_c is the paw volume of the control group and V_t is the paw volume of the test group.

Analgesic activity. The compounds which showed anti-inflammatory activity above 75 % of the ibuprofen inhibition were screened for analgesic activity. The determination of the

analgesic activity was realized by the acetic acid-induced writhing method.[28] Mice were divided into groups with six in each. Group I was taken as the control and received CMC suspension only, group II received the reference drug ibuprofen and the other groups were treated with the test drugs (20 mg kg^{-1}) suspended in 1.0 % CMC orally. A 1 % aqueous acetic acid solution (0.1 mL) was used as writhing-inducing agent. The acetic acid solution was injected intraperitoneally 3 h after the treatment with the reference and test drugs to the various groups, respectively, and writhings were noted for 10–15 min after acetic acid administration.

Acute ulcerogenesis. Acute ulcerogenesis test was performed according to the method of Cioli *et al*.[29] Wistar rats were divided into different groups consisting of six animals in each group. Ulcerogenic activity was evaluated after *p.o.* administration of test compounds or ibuprofen at a dose of 60 mg kg^{-1}. The control rats received *p.o.* administration of the vehicle (suspension of 1 % carboxymethyl cellulose). Food but not water was removed 24 h before administration of the test compounds. After drug treatment, the rats were fed with a normal diet for 17 h and then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in normal saline. The mucosal damage was examined by means of a magnifying glass and compared with that after ibuprofen administration. For each stomach, the mucosal damage was assessed according to the following scoring system: 0.5: redness, 1.0: spot ulcers, 1.5: hemorrhagic streaks, 2.0: ulcers > 3 but < 5, 3.0: ulcers > 5.

The mean score of each treated group minus the mean score of the control group was regarded as the severity index of gastric mucosal damage.

Lipid peroxidation. Lipid peroxidation in the gastric mucosa was determined according to the method of Ohkawa *et al*.[30] After screening for ulcerogenic activity, the gastric mucosa was scraped with two glass slides and 10 % of that tissue was homogenized at 10,000 rpm in 1.8 mL of 1.15 % ice-cold KCl solution. 1 mL of suspension medium was taken from the supernatant, 0.5 mL of 30 % trichloroacetic acid (TCA) followed by 0.5 mL of 0.8 % thiobarbituric acid (TBA) reagent were added to it. The tubes were covered with aluminium foil and kept in a shaking water bath for 30 min at 80 °C. After 30 min, the tubes were taken out and kept in ice-cold water for 10 min. These were then centrifuged at 3000 rpm for 15 min. The absorbance of the supernatant was read at 540 nm at room temperature against the blank on a UV spectrophotometer.

The standard curve used for estimating the concentration of MDA was prepared by using 1,1,3,3-tetraethoxypropane. The results are presented as nmol MDA mg^{-1} of protein.

Antibacterial activity. The antibacterial studies were performed on the synthesized compounds against the microorganisms *S. aureus* and *E. coli* in meat peptone agar medium at a concentration of 100 μg ml^{-1}. Compounds inhibiting growth of one or more of the microorganisms were further tested for their *MIC* value. The test was performed according to the turbidity method[31] using nitrofurazone as the standard.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА ХИНОЛИН-ВЕЗАНИХ ФУРАН-2(3*H*)-ОНА КОЈИ ИМАЈУ АНТИИНФЛАМАТОРНА И АНТИБАКТЕРИЈСКА СВОЈСТВА УЗ СМАЊЕНУ ГАСТРОИНТЕСТИНАЛНУ ТОКСИЧНОСТ И ЛИПИДНУ ПЕРОКСИДАЦИЈУ

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Синтетисана је серија 5-арил-3-[(2-хлорохинолин-3-ил)метилен] фуран-2(3*H*)-она (**3a**–**p**). Потребне 3-(супституент-бензоил)-пропионске киселине **2a**–**d** су добијене Friedel–Crafts--овом реакцијом ациловања. Супституисани 2-хлорохинолин-3-карбалдехиди **1a**–**d** су синтетисани у реакцији супституисаних фенилетанон-оксима са фосфор-оксихлоридом, у присуству диметил-формамида, применом Vilsmeier–Haack-овог реакционог метода. За ова једињења је утврђивана антиинфламаторна, антибактеријска и улцерогена активност, као и способност да изазову липидну пероксидацију. Једињења која су показала значајну антиинфламаторну активност даље су испитивана као аналгетици. Једињења су испољила мању токсичност у поређењу са стандардним препаратима, у погледу улцерогености и липидне пероксидације. Антибактеријска активност је тестирана спрам *S. aureus* и *E. coli*. Једињења **3f**, **3n** и **3o** су показала значајну активност спрам обе бактерије, уз минималну инхибиторну концентрацију од 6,25 μg mL^{-1}.

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REFERENCES

1. J. R. Vane, J. A. Mitchell, I. Appleton, A. Tomilison, D. Bishop-Bailey, J. Crontall, D. A. Willoughby, *Proc. Natl. Acad. Sci.* **91** (1994) 2046
2. A. Hosada, Y. Ozaki, A. Kashimada, M. Mutoh, K. Wakabayashi, K. Mizuno, E. Nomura, H. Taniguchi, *Bioorg. Med. Chem.* **10** (2002) 1189
3. M. Allison, A. Homatson, C. Torrance, F. Lee, R. Russell, *N. Eng. J. Med.* **327** (1992) 749
4. J. M. Dogne, C. T. Supuhan, D. Pratico, *J. Med. Chem.* **48** (2005) 2251
5. Y. Chen, J. Chen, C. Lu, C. Tzeng, H. Tsao, J. Wang, *Bioorg. Med. Chem.* **11** (2003) 3921
6. M. Kidwai, N. Negi, *Monatsh. Chem.* **128** (1997) 85
7. B. P. Nandeshmanappa, D. B. A. Kumar, H. S. B. Naik, K. M. Mahadevan, *J. Sulfur Chem.* **26** (2006) 373
8. H. G. Jin, X. Y. Sun, K. Y. Chai, H. R. Pino, Z. S. Quan, *Bioorg. Med. Chem.* **14** (2006) 6868
9. J. Ghosh, V. Swarup, A. Saxena, S. Das, A. Hazra, P. Paira, S. Banerjee, N. B. Mondal, A. Basu, *Int. J. Antimicrob. Agents* **32** (2008) 349
10. Z. Cai, W. Zhon, L. Sun, *Bioorg. Med. Chem.* **15** (2007) 7809
11. M. S. Y. Khan, A. Husain, *Pharmazie* **57** (2002) 448
12. A. Husain, M. S. Y. Khan, S. M. Hasan, M. M. Alam, *Eur. J. Med. Chem.* **40** (2005) 1394
13. L. Leite, D. Jansone, M. Veveris, H. Cirule, Y. Popelis, G. Melikyan, A. Avetisyan, E. Lukevics, *Eur. J. Med. Chem.* **34** (1999) 859

14. a) A. Husain, M. M. Alam, N. Siddiqui, *J. Serb. Chem. Soc.* **74** (2008) 103; b) M. M. Alam, A. Husain, S. M. Hasan, Suruchi, T. Anwer, *Eur. J. Med. Chem.* **44** (2009) 2636
15. W. C. Black, C. Brideau, C. Chan, S. Charleson, W. Cromlish, R. Gordon, E. L. Grimm, G. Hughes, S. Leger, C. Lii, D. Riendeau, M. Therien, Z. Wang, L. Xu, P. Prasit, *Bioorg. Med. Chem. Lett.* **13** (2003) 1195
16. A. Zarghi, P. N. Praveen Rao, E. E. Knaus, *Bioorg. Med. Chem.* **15** (2007) 1056
17. F. Bailly, C. Queffelec, G. Mdemba, J. Mouscadet, N. Pommery, J. Pommery, J. Henichart, P. Cotelle, *Eur. J. Med. Chem.* **43** (2008) 1222
18. A. Albrecht, J. F. Koszuk, J. Modranka, M. Rozalski, U. Krajewska, A. Janecka, K. Studzian, T. Janecki, *Bioorg. Med. Chem.* **16** (2008) 4872
19. L. A. Vale-Silva, V. Buchta, D. Vokurkova, M. Pour, *Bioorg. Med. Chem. Lett.* **16** (2006) 2492
20. E. Lattmann, S. Dunn, S. Niamsanit, N. Sattayasai, *Bioorg. Med. Chem. Lett.* **15** (2005) 919
21. A. I. Hashem, A. S. Youssef, K. A. Kandeel, W. S. Abou-Elmagd, *Eur. J. Med. Chem.* **42** (2007) 934
22. A. Husain, M. M. Alam, M. S. Zaman, M. V. Ismail, *Int. J. Chem. Sci.* **6** (2008) 1535
23. A. Husain, S. M. Hasan, S. Lal, M. M. Alam, *Indian J. Pharm. Sci.* (2006) 536
24. a) A. Husain, M. Ajmal, *Acta Pharma.* **59** (2009) 223; b) M. S. Y. Khan, A. Husain, S. Sharma, *Indian J. Chem., B* **41** (2002) 2160
25. O. M. Cohn, B. Narine, B. Tarnowski, *J. Chem. Soc. Perkin Trans. 1* (1981) 1520
26. A. Srivastava, R. M. Singh, *Indian J. Chem., B* **44** (2005) 1868
27. C. A. Winter, E. A. Risley, G. W. Nuss, *Proc. Soc. Exp. Biol.* **111** (1962) 544.
28. E. Seigmund, R. Cadmus, G. Lu, *Proc. Soc. Exp. Biol.* **95** (1957) 729
29. V. Cioli, S. Putzolu, V. Rossi, P. Sorza Barcellona, C. Corradino, *Toxicol. Appl. Pharmacol.* **50** (1979) 283
30. H. Ohkawa, N. Ohishi, K. Yagi, *Anal. Biochem.* **95** (1979) 351
31. *Medical Microbiology, Vol. 2*, R. Cruickshank, J. P. Dugid, D. P. Marmion, R. H. A. Swain, Eds., Churchill, London, 1975.