Send Orders for Reprints to reprints@benthamscience.ae

Anti-Cancer Agents in Medicinal Chemistry, 2016, *16*, 898-906

Leuckart Synthesis and Pharmacological Assessment of Novel Acetamide Derivatives

Priyanka Rani[a,*], Dilipkumar Pal[b], Rahul Rama Hegde[c,d] and Syed Riaz Hashim[e]

[a]*Department of Chemistry, School of Sciences, IFTM University Moradabad, Uttar Pradesh., 244001, India;* [b]*Department of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya (A Central University),Koni, Bilaspur, C.G., 495 009, India;* [c]*Department of Pharmaceutics, School of Pharmaceutical Sciences, IFTM University, Moradabad, Uttar Pradesh., 244001, India;* [d]*Quality Assurance, Lupin Ltd, Verna Industrial Area, Verna, Salcete, Goa., 403772, India;* [e]*Retired Professor, Department of Chemistry, School of Pharmaceutical Sciences, IFTM University Moradabad, Uttar Pradesh, India*

P. Rani

Abstract: A new concatenation of *N*-(1-(4-bromophenyl)ethyl)-2-phenoxyacetamide and N-(1-(4-methoxyphenyl) ethyl)-2-phenoxyacetamide derivatives having 2-phenoxy-N-(1-phenylethyl)acetamide nucleus as common in both the types was synthesized for the sake of achieve titled compounds as potential cytotoxic, anti-inflammatory, analgesic and antipyretic agents. All the novel derivatives have been synthesized through multi-step reaction sequence starting from Leuckart reaction. The structural assignments of the new compounds have been determined by virtue of their IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and mass spectrum analysis. All the synthesized compounds were assessed for cytotoxicity and anti-inflammatory, analgesic and antipyretic effects. Among the series, compounds **3a**, **3c**, **3g and 3h** possess cytotoxic, anti-inflammatory, analgesic and antipyretic activities comparable with standard drugs. The synthesized compounds were found to be active because of the presence of bromo, tert- butyl and nitro groups at position 4 of phenoxy nucleus.

Keywords: Anti-inflammatory, anti cancer, analgesic, anti pyretic, phenoxyacetamide.

Received: June 09, 2015 **Revised: October 28, 2015** **Accepted: November 02, 2015**

1. INTRODUCTION

An association between inflammation and cancer was noticed many years ago. Virchow pointed out that chronic inflammation contributed to increased risk of cancer [1]. Later on it was studied that cancer occurs at the site of acute inflammation [2]. However various reviews indicate that chronic inflammatory diseases are linked to cancers [3-5]. Now it has been proven that the process of development of cancer is carried out by an inflammatory microenvironment including cytokines, chemokines and enzymes [6]. Various cytokines such as IL (interleukins) and TNF-α (tumor necrosis factor-α) facilitate the spectrum of tumor progression involving the initiation of cell growth, differentiation and obstruction of apoptosis of cells in the inflammatory region [7, 8]. TNF-α was recognized in the involvement of induction of DNA destruction and inhibition of DNA repair [9]. Chemokines promote invasion and metastasis of tumor by directing migration of leucocytes [10-12]. NF-kB (Nuclear factor-kappa B), a member of transcription factors, leads to the induction of inflammation and plays a role to send survival signals to initiated cells and hence may be marked as critical link between inflammation and cancer [13]. This indicates that there is a strange connection of inflammation to cancer. An inflammatory bowel disease (IBD) is a problem in which colon is inflamed over a long period of time. This disease contains ulcerative colitis (UC) and Crohn's disease (CD). When large intestine occupies a chronic inflammatory condition, it is called ulcerative colitis. Traditional proinflammatory cytokines found to be involved in pathogenesis of UC were Tumor Necrosis Factor-α, Interleukin-1 and Interleukin-6. T helper cells are of two types: Th1 and Th2 cells which produce various cytokines. Now, a complex network including three major Th2 cytokines (IL-6, IL-10 and IL-13) came into light to play different roles in the initiation of UC. People having IBD for many years usually lead to develop dysplasia. Dysplasia is a condition in which appearance of cells takes place in the lining of the colon or rectum that look abnormal under microscope. These cells can change into cancer with the passage of time. Whenever cancer starts in the colon or rectum, it is called colorectal cancer. Various inflammatory cytokines (Tumor Necrosis Factor-α, Interleukin-1, Interleukin-6 and Interleukin-1β) and chemokines for instance CCL2 and CCL5 also facilitate the progression of breast cancer cells. Synthesis of prostaglandin in monocytes and macrophages can be inhibited by COX-2, the principal enzyme accountable for inflammation [14].

The role of COX-2 in inflammation- associated cancers may be illustrated by the expression of COX-2 in the stromal cells during initiation of tumors [15]. COX-2 is upregulated in various types of cancers such as carcinomas of the colon, breast, pancreas, esophagus, lung, head and neck. According to various reviews on COX-2 transgenic mice and COX-2 knockout mice, it is clear that COX-2 directs the colonic cancer development *via* two ways: through angiogenesis and through the stimulation of several oncogenes, like H-Ras, v-src, Wnt and HER-2/neu. The amplification of HER-2/neu is found in some aggressive types of breast cancer. Because of dual role of COX-2 in the development of colonic cancer and its involvement in the activation of HER-2/neu and finally breast cancer, it is necessary to examine the titled compounds as cytotoxic agents especially for colon and breast cancer. The vital cardinal signs of inflammation are redness (rubor, erythema), swelling (tumor), heat (calor) and pain (dolor). Because of these symptoms, it is also an unavoidable requirement to examine analgesic and antipyretic evaluation of the synthesized compounds. Hence, there is a background of using NSAIDs to treat inflammation and cancer because NSAIDs are used in the cure of a broad spectrum of diseases and illness such as inflammation [16], diabetes [17] and cancer [18]. These NSAIDs are also used for diseases of peripheral and central nervous system (CNS) like Alzheimer's, Multiple Sclerosis and Parkinson's [19]. But the use of NSAIDs is limited due to their various side effects such as gastrointestinal toxicity and acute renal failure. NSAIDs are effective due to their ability to inhibit COX enzyme. 2-phenoxyacetamide entity has been recognized as the largest and most diverse class of compounds exerting pharmacological effects such as anti cancer [20], anti tubercular [21] and antiviral [22]. When camphor and 2-bromocyclohexanone were separately used as starting materials, and finally acetamide derivatives were synthesized, it was found that compounds manifested strong anti-inflammatory,

*Address correspondence to this author at the Department of Chemistry, School of Sciences, IFTM University Moradabad, Uttar Pradesh, India; Tel: +91 9837661722; Fax: +91 591 2360818; E-mail: skiftm@gmail.com

1875-5992/16 $58.00+.00

analgesic and anti pyretic effects as reported in our previous work [23]. Later on, aromatic ketones like 1-(4-Chlorophenyl)ethanone and 1-(p-Tolyl)ethanone, were used as initial reactants to find out better biological activities and accordingly resulted in a novel class of anti cancer agents [24]. Various acetamides recently have been reported in the literature in order to evaluate the cytotoxicity against numerous human cancer cell lines and/or for appraisal of anti-inflammatory activity and were found to be active [25, 26].

Our present motive is to focus on the synthesis of a novel series of N-(1-(4-bromophenyl)ethyl)-2-(substituted phenoxy)acetamide and N-(1-(4-methoxyphenyl)ethyl)-2-(substituted phenoxy)acetamide derivatives by using 1-(4-bromophenyl)ethanone and 1-(4-methoxyphenyl)ethanone respectively and pharmacological evaluation of the finally synthesized compounds for inflammation associated cancers. A three pot synthetic pathway was used initiated with Leuckart reaction for the synthesis of titled compounds. Leuckart reaction was used as initial step of the pathway for the conversion of aromatic ketones to aromatic amines. This reductive amination of aromatic ketones takes place by ammonium carbonate and formic acid [27]. These aromatic amines were further used for chloroacetylation with chloroacetylchloride and finally various substituted phenols were added to the chloro compounds. Addition of phenols here seems to be more beneficial because some phenolic compounds like genistein and EGCG (epigallocatechin gallate) have the capability to arrest the initial stage of cell cycle and are widely used as antioxidants. Especially in people with oral leukoplakia (a condition of premalignant lesion), green tea (which contains EGCG), is associated with potent decrease in cancer size [28]. Today, the most important target is to synthesize new molecules and study their biological potency without various side effects. In the light of above facts, the focus of this research was to synthesize novel N-(1-(4-bromophenyl)ethyl)-2-(substituted phenoxy)acetamide and N-(1-(4-methoxyphenyl)ethyl)-2-(substituted phenoxy)acetamide derivatives that should be beneficial for the development of chemoprevention and treatment of inflammation-associated cancers, pain and fever.

2. RESULTS AND DISCUSSION

A series of titled derivatives N-(1-(4-bromophenyl)ethyl)-2-(substituted phenoxy)acetamide 3(a-e) and N-(1-(4-methoxyphenyl) ethyl)-2-(substituted phenoxy)acetamide 3(f-j) derivatives as digrammated in Fig. **1**, were synthesized according to scheme diagrammated in Fig. **2**. 1-(4-bromophenyl)ethanone and 1-(4-methoxyphenyl)ethanone were separately treated with ammonium carbonate and formic acid resulting in the formation of amines 1a and 1b respectively. Separate chloroacetylation of amines 1a and 1b with chloroacetyl chloride in an environment of 0 ^{o}C temperature and 10% sodium hydroxide solution resulted in the formation of chloro compounds 2a and 2b. Compounds 2a and 2b when separately treated with various substituted phenols in presence of potassium carbonate and catalytic amount of potassium iodide and dry acetone as a solvent, final compounds 3(a-j) were obtained. All the synthesized compounds were characterized by their spectroscopic

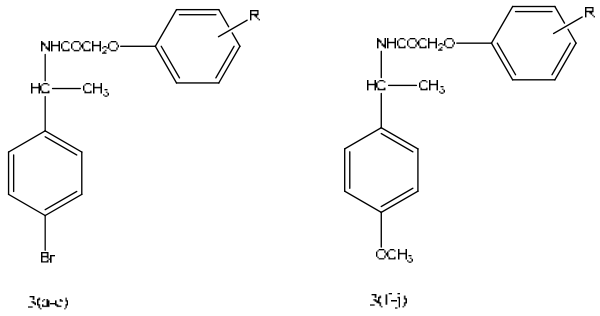


Fig. (1). General structure of the synthesized compounds.

analysis (IR, ^{1}H NMR,^{13}C NMR, mass) and analytical (elemental analysis) data. Physical data of compounds 3(a-j) is given in Table **1**.

Further IR spectrum of compounds 3(a-j) showed characteristic absorption bands at range of 3218-3251 cm-1 was attributed to NH, 1654-1688 cm-1 accounting for C=O of amide group and 1516-1597 for C=C in the aromatic ring. Two peaks at range of 1228-1317 and 1020-1125 indicate the presence of C-O-C linkage. Mass spectrum analysis further supported and finally confirmed the structure of synthesized compounds. Compounds were obtained in good yield ranging from 57.0 to 75.5 %. All the synthesized compounds 3(a-j) were subjected to preliminary toxicity test as per Organization for Economic Co-operation and Development (OECD) guidelines in rats. According to acute toxicity test, 100 mg/kg was used as therapeutic dose. *In-vitro* cytotoxicity assay was performed using SRB based cellular protein content determination against two human cancer cell lines that contained MCF-7 (breast) and HCT-15 (colon) respectively. The result of cytotoxic activity is tabulated below in Table **2**. Images of control for MCF-7, compound 3c for MCF-7, and compound 3h for MCF-7 are represented by Fig. **3**. Images of control for HCT-15, compound 3a for HCT-15 and compound 3h for HCT-15 are represented by Fig. **4** Acute anti-inflammatory effect was performed by carrageenan induced rat paw edema method. Compounds **3a**, **3b**, **3g**, **3i** possess influential anti-inflammatory activity as compared to reference Diclofenac sodium (Table **3**). The Analgesic activity of compounds **3a**, **3b**, **3g** was found to be nearly of standard (Table **4**). Reference drug was Diclofenac sodium for anti-inflammatory and analgesic evaluation of titled compounds. The antipyretic activity of compounds **3a**, **3b**, **3g**, and **3i** was found comparable with the standard drug indomethacin.

2.1. Structure Activity Relationship (SAR) for Cytotoxicity

By comparing the cytotoxic potency of newly synthesized compounds 3a-j, a few inferences could be drawn such as (i) the presence of methyl, methoxy, chloro, nitro substituent at 4 positions does not contribute towards cytotoxicity as can be seen in compounds 3b, 3d, 3e, 3f, 3j which showed poor growth inhibition against both the cancer cell lines used. (ii) Attachment of Br group in the 4 position contributes significantly towards the enhancement of inhibitory activity and (iii) Existence of tert-butyl group at position 4 of phenoxy-N-(1-(4-bromophenyl)ethyl) acetamide nucleus makes the compound potent antiproliferative agent with dual inhibition of both MCF-7 and HCT-15 cell lines. Compounds **3a**, **3c**, **3g, 3h** were found to possess anti cancer, anti-inflammatory, analgesic and antipyretic activities nearly to the standard because of the presence of bromo, tert-butyl and nitro groups at 4 position of phenoxy-N-s(1-(4-bromophenyl)ethyl) acetamide nucleus.

From the results, it is also found that though **3h** presented well ranked cytotoxic activity, but moderately ranked anti inflammation, analgesic and antipyretic activities. On the other hand, **3b**, presented well ranked anti inflammatory, analgesic, and antipyretic activities, but poorly ranked cytotoxic activities. Further correlation as well as structure activity relationship studies for 3h and 3b on the above pharmacological aspects are under investigation and will be communicated in future.

From the comprehensive analysis of the results in current studies, we came to a cessation that among the series, few compounds were found to exhibit anti cancer, anti-inflammatory, analgesic and antipyretic activities. In the light of these observations, we may conclude that this series 3(a-j) may be developed and explored as a novel member of NSAIDs family and may be used for chemoprevention of cancers that are allied with inflammation because prevention is much better and more cheap way to fight against cancers as compared to treating an already existing disease. Nonetheless, more comprehensive pharmacological study is required

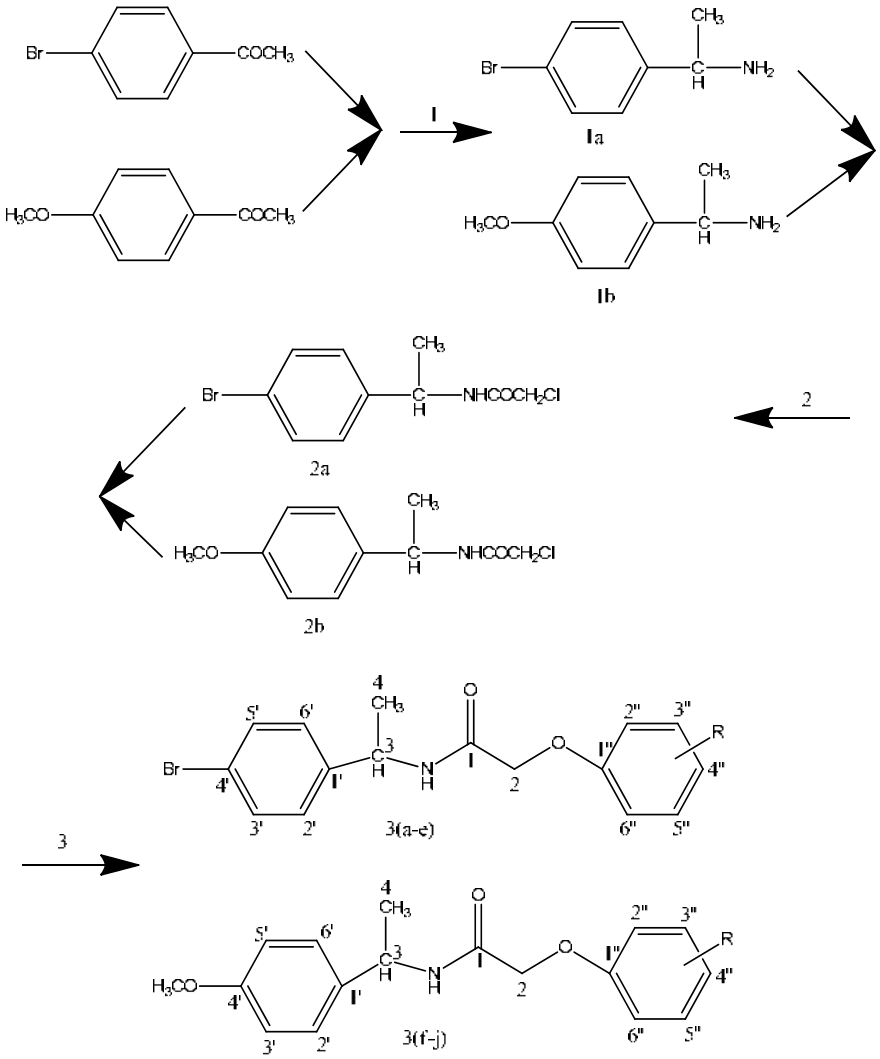


Fig. (2). Synthesis of N-(1-(4-bromophenyl)ethyl)-2-(substituted phenoxy)acetamide (3a-e) and N-(1-(4-methoxyphenyl)ethyl)-2-(substituted phenoxy) acetamide (3f-j) derivatives from 1-(4-bromophenyl)ethanone and 1-(4-methoxyphenyl)ethanone respectively.

Table 1. Characterization data of N-(1-(4-bromophenyl)ethyl)-2-(substituted phenoxy)acetamide (3a-e) and N-(1-(4-methoxyphenyl)ethyl)-2-(substituted phenoxy)acetamide (3f-j).

Compound	R	Yield (%)	Melting Point* (°C)	Rf Value#	Molecular Formula
3a	4-Br	62.5	165-167	0.41	$C_{16}H_{15}Br_2NO_2$
3b	4-NO_2	57.1	161-163	0.37	$C_{16}H_{15}BrN_2O_4$
3c	4-C-$(CH_3)_3$	60.1	145-147	0.46	$C_{20}H_{24}BrNO_2$
3d	4-OCH_3	59.7	115-117	0.43	$C_{17}H_{18}BrNO_3$
3e	2-NO_2	70.2	121-123	0.39	$C_{16}H_{15}BrN_2O_4$
3f	4-CH_3	65.3	134-136	0.34	$C_{18}H_{21}NO_3$
3g	4-NO_2	57.0	192-194	0.52	$C_{17}H_{18}N_2O_5$
3h	4-C-$(CH_3)_3$	75.5	150-152	0.47	$C_{21}H_{27}NO_3$
3i	3-CH_3, 4-Cl	63.6	137-139	0.37	$C_{18}H_{20}ClNO_3$
3j	2-NO_2	71.1	188-190	0.49	$C_{17}H_{18}N_2O_5$

*Recrystallization with ethanol.
#Stationary phase: Silica gel, Mobile phase: n-Hexane: ethyl acetate (1:1), Iodine vapors as visualizing agent.

Table 2. Result of anti cancer activity.

Compound	% Control Growth		Activity
	MCF-7 (Breast)	HCT-15 (Colon)	
**3a	78.8±0.285	13.8±0.266	Active
3b	85.5±0.193	69.8±0.460	Inactive
*3c	29.4±0.225	45.4±0.615	Active
3d	52.5±0.285	46.4±0.667	Inactive
3e	79.3±0.249	100.0±0.984	Inactive
3f	67.7±0.179	62.9±0.819	Inactive
**3g	82.0±0.189	18.9±0.494	Active
***3h	26.8±0.389	27.7±0.354	Active
3i	84.3±0.640	82.9±0.402	Inactive
3j	67.6±0.924	84.4±0.855	Inactive

*Active against MCF-7 (breast) cell line.
**Active against HCT-15 (colon) cell line.
***Active against both MCF-7 (breast) and HCT-15 (colon) cell line.
Less than 32, Growth percentage are considered as active

Table 3. Result of anti-inflammatory activity.

Compound	Mean Changes in paw Edema (ml) Mean±SEM			% Inhibition		
	30 min	2 hr	4 hr	30 min	2 hr	4 hr
Control	0.614±0.017	0.748±0.042	0.633±0.021	--	--	--
Diclofenac sodium	0.244±0.025	0.274±0.017	0.269±0.024	60.26±0.019	63.36±0.017	57.18±0.032
3a**	0.268±0.030	0.316±0.009	0.357±0.019	56.35±0.031	57.75±0.040	43.60±0.014
3b**	0.262±0.008	0.305±0.022	0.321±0.014	57.32±0.049	59.22±0.007	49.28±0.022
3c**	0.508±0.018	0.604±0.026	0.488±0.023	17.26±0.004	19.25±0.035	22.90±0.041
3d*	0.481±0.010	0.567±0.039	0.467±0.031	21.66±0.011	24.19±0.019	26.22±0.022
3e*	0.429±0.028	0.477±0.023	0.490±0.007	30.13±0.001	34.49±0.007	35.22±0.016
3f**	0.545±0.041	0.625±0.028	0.533±0.024	11.23±0.019	16.44±0.018	15.79±0.003
3g**	0.251±0.031	0.298±0.020	0.289±0.003	59.12±0.005	60.16±0.018	54.34±0.023
3h*	0.385±0.022	0.481±0.028	0.416±0.032	37.29±0.031	35.69±0.022	34.28±0.030
3i**	0.269±0.011	0.313±0.031	0.328±0.026	56.18±0.009	58.15±0.022	48.18±0.004
3j**	0.461±0.019	0.552±0.025	0.456±0.016	24.91±0.012	26.20±0.024	27.96±0.027

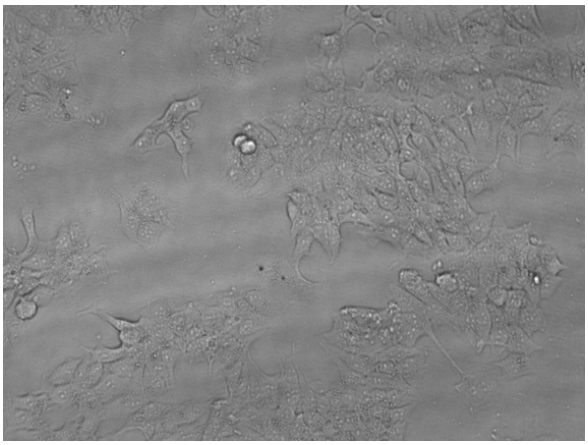
*p<0.05 significant from control.
**p<0.01 significant from control.

Table 4. Result of analgesic activity.

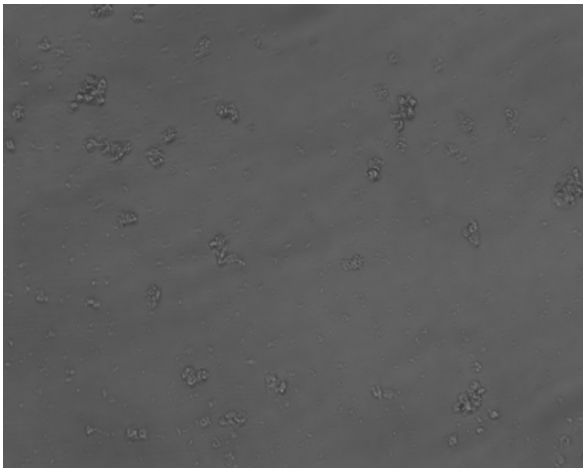
Compound	Reaction time (s) after Drug Administration (mean ± SEM)			% Increase in Reaction Time		
	30 min	60 min	90 min	30 min	60 min	90 min
Control	2.61±0.018	2.63±0.021	2.69±0.041	--	--	--
Diclofenac sodium	5.32±0.011	5.76±0.017	5.85±0.030	103.83±0.011	119.01±0.023	117.47±0.008
3a**	4.91±0.003	4.80±0.019	4.73±0.007	88.12±0.036	82.51±0.021	75.83±0.023
3b**	5.36±0.012	5.67±0.023	5.71±0.016	105.36±0.004	115.58±0.008	112.26±0.011
3c**	3.64±0.039	3.45±0.010	3.13±0.003	39.46±0.007	31.17±0.010	16.35±0.034
3d**	4.23±0.010	4.11±0.032	3.56±0.031	62.06±0.015	56.27±0.017	32.34±0.005
3e**	3.15±0.019	3.22±0.030	3.86±0.006	20.68±0.038	22.43±0.004	43.49±0.016
3f**	3.31±0.007	3.27±0.022	3.17±0.018	26.81±0.006	22.05±0.035	17.84±0.025
3g*	5.39±0.030	5.79±0.010	5.88±0.026	106.51±0.017	120.15±0.039	118.58±0.041
3h**	3.21±0.006	3.47±0.023	4.16±0.026	22.98±0.011	31.94±0.010	54.64±0.028
3i*	4.82±0.005	4.78±0.024	4.64±0.007	84.67±0.014	81.75±0.030	72.49±0.012
3j**	3.11±0.016	3.79±0.025	3.83±0.003	19.15±0.009	44.10±0.014	42.37±0.002

*p<0.05 significant from control.
**p<0.01 significant from control.

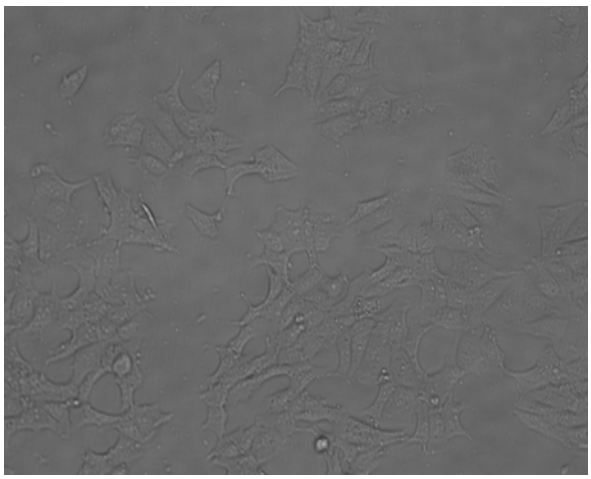
in future to recognize the potent molecule for the refinement of biological potency without various side effects.



3(a) control MCF-7



3(b) compound 3c for MCF-7

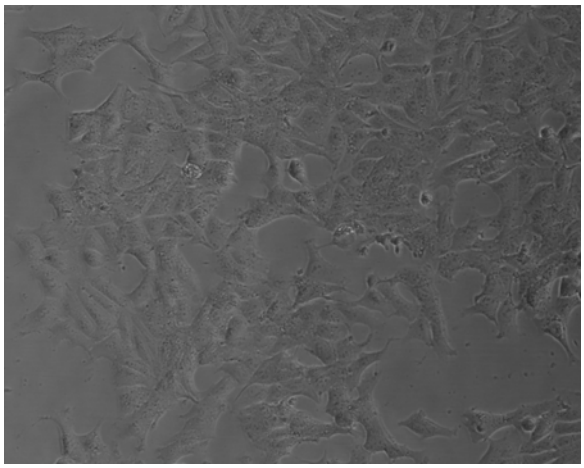


3(c) compound 3h for MCF-7

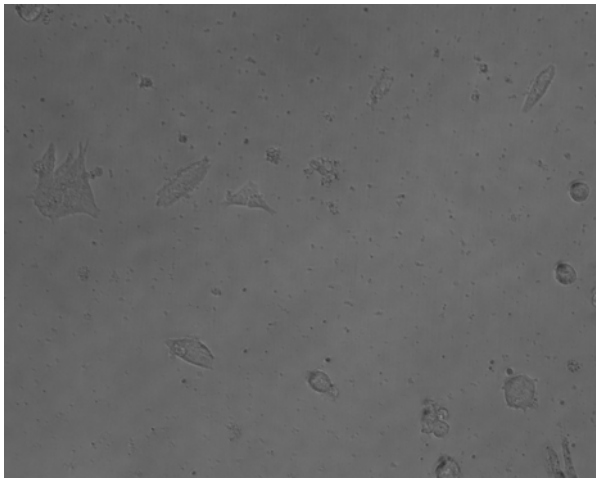
Fig. (3). Magnified 100X microscopic images of 3(a) control MCF-7, 3(b) compound 3c for MCF-7, 3(c) compound 3h for MCF-7.

2.2. Limitations of Study

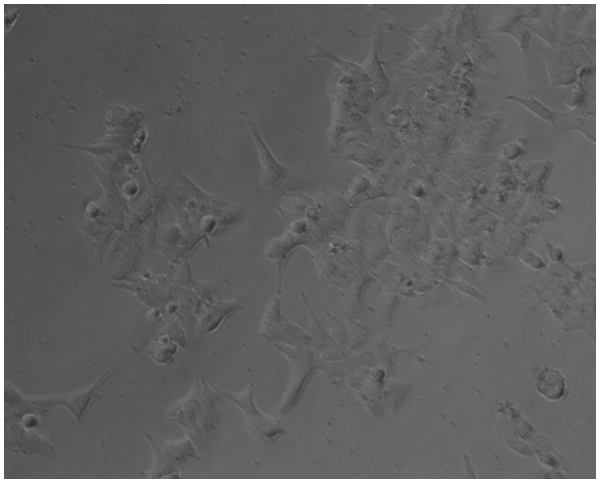
The anti cancer studies in the present research reports the *in vitro* measure of the cytotoxic activity. Therefore, a further study is required so as to correlate the *in vitro* experimental data with *in vivo* results. Results of the studies warrant further exploration of these compounds as anti cancer drugs and need to be evaluated on *in vivo* models so that the synthesized compounds may be developed as potential promising anti cancer agents.



4(a) control HCT-15



4(b) compound 3a for HCT-15



4(c) compound 3h for HCT-15

Fig. (4). Magnified 100x microscopic images of 4(a) control HCT-15, 4(b) compound 3a for HCT-15, 4(b) compound 3h for HCT-15.

3. EXPERIMENTAL

3.1. General Considerations

All research chemicals and anhydrous solvents were purchased from CDH (Central Drug House P. Ltd., New Delhi, India) and used without any purification. Synthesized compounds were purified by the recrystallization with0 appropriate solvent in case of solids but by distillation in case of liquids. Thin layer chromatography (TLC) was used to monitor the homogeneity of compounds and progress of reaction using stationary phase, silica gel G on slide glass plates. Mobile phases used were n-hexane: ethyl acetate (1:1). Spots were detected in an iodine chamber. Melting points of synthesized compounds were determined using open capillary method on Thomas Hoover apparatus and are uncorrected. The infrared (IR) spectra of synthesized compounds were recorded in potassium bromide discs on Shimadzu IR-435 spectrophotometer. ^{1}H and ^{13}C NMR (Nuclear magnetic Resonance) spectrum were recorded on a Bruker 400 MHz spectrometer (Bruker Corporation, Massachusetts, USA) instrument in DMSO-d6 containing tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in parts per million (ppm). ^{1}H and ^{13}C NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, identification. Mass spectra were recorded on Micromass Q-Tof Micro (Waters Corporation Massachusetts, USA). Elemental analyses were recorded using Elementar Vario EL III, elementar Analysensysteme GmbH, Hanau, Germany and agreed with the proposed structures within ± 0.4% of the theoretical values. The cytotoxic activity was carried out at Tata Memorial Hospital, Mumbai. The anti-inflammatory, analgesic and antipyretic screening was carried out at pharmacology laboratory of College of Pharmacy, IFTM University, Moradabad. The anti-inflammatory screening was executed with the help of digital plethysmometer (Orchid Scientific, Maharashtra, India). The analgesic screening was executed by Eddy's hot plate method with the help of analgesiometer (Sanghmeshwar International, Ambala, India). Animal experiments were approved by Institutional Animal Ethical Committee (IAEC).

3.2. Synthesis

3.2.1. General Method for the Synthesis of 1-(4-bromophenyl) ethanamine (1a) and 1-(4-methoxyphenyl)ethanamine (1b) from 1-(4-bromophenyl)ethanone and 1-(4-methoxyphenyl)ethanone Respectively

This procedure of Leuckart reaction was used for the preparation of amines from ketones. Ammonium carbonate (215 gm, 4 mols) was placed in a 1-litre three necked round bottom flask, which was fitted with a thermometer, a dropping funnel and a bent tube attached for distillation to a short condenser. Formic acid (98 %, 109 ml) was taken in the dropping funnel and added drop wise. When the reaction subsided, the mixture was heated slowly until the temperature of the reaction increased to about 165^{o} C. The ketone (1 mol,) was added in one lot and the temperature was slowly raised to 180-185^{o} C. Ammonia, water, carbon dioxide and some of the unreacted ketone distilled over. The distilled ketone was separated and returned to the reaction mixture. The mixture which gradually became homogenous was maintained at 180-185^{o}C for 4-5 hours. After completion of reaction, the mixture was cooled and stirred absolutely with approximately twice its volume of water. The aqueous layer was discarded and the formyl derivative of the amine (non aqueous layer) so obtained was refluxed with 100-150 ml concentrate HCl for 2-3 hr. After the hydrolysis, the reaction mixture was cooled at room temperature and extracted with diethyl ether to detach unreacted ketone. Now add 30% sodium hydroxide solution to make the aqueous solution strongly alkaline and the separated amine was extracted with Diethyl ether. The ethereal extract was dried overnight with anhydrous sodium sulphate and after removal of the solvent, the product distilled under reduced pressure.

3.2.2. General Method for the Synthesis of N-(1-(4-bromophenyl) ethyl)-2-chloroacetamide (2a) and 2-chloro-N-(1-(4-methoxyphenyl) ethyl)acetamide (2b) from (1a) and (1b) Respectively

Aqueous solution of sodium hydroxide (50 ml, 10 %) was ice-cooled in an ice bath and taken in two different well- corked conical flask, 0.1mol of synthesized compound 1a and 1b was added in both the flasks very slowly followed by the addition of chloroacetyl chloride (11.93 ml, 0.15 mol) drop wise with continue stirring and shaking. The reaction was strongly shaken until odor of chloroacetylchloride moved out. The pH of reaction mixture was maintained around 9-10 by adding more sodium hydroxide solution. Filter off the product and solid amides 2a and 2b that formed were washed completely with water. Now these amides were dried and recrystallized by ethanol.

3.2.3. General Method for the Synthesis of N-(1-(4-bromophenyl) ethyl)-2-(substituted phenoxy)acetamide (3a-e) and N-(1-(4-methoxyphenyl)ethyl)-2-(substituted phenoxy)acetamide (3f-j) derivatives from (2a) and (2b) Respectively

Phenoxy acetamide derivatives were prepared by separate reaction of 2a and 2b (0.01mol) with various substituted phenols (0.01 mol) by refluxing in round bottom flask (r. b. f.). Anhydrous potassium carbonate (0.01 mol), catalytic amount of potassium iodide and dry acetone as a solvent were used for reflux. In some cases unreacted phenol was removed from the final product by treating the substance with 10 % w/v sodium carbonate solution in water. The compound was then filtered and washed completely with water and recrystallised from appropriate solvent. TLC was used to monitor completion of the reaction.

3.2.3.1. 2-(4-bromophenoxy)-N-(1-(4-bromophenyl)ethyl)acetamide (3a)

IR (KBr, cm^{-1}): 3242, 3044, 2930, 1660, 1584, 1231 and 1022. ^{1}HNMR (400 MHz, DMSO-d6, δ ppm)**:** 8.85 (s, 1H, NH), 7.85 (d, 2H, H-3', 5'), 7.40 (d, 2H, H-3'', 5''), 7.22 (d, 2H, H-2', 6'), 7.43 (d, 2H, H-2'', 6''), 5.44 (m, 1H, CH-3), 5.18 (s, 2H, CH_2-2), 1.84 (d, 3H, CH_3-4) ^{13}C NMR (DMSO-d_6, δ ppm): 172.2 (C-1), 165.8 (C-1''), 151.7 (C-1'), 145.1 (C-3'', 5''), 133.6 (C-3', 5'), 131.2 (C-2', 6'), 129.6 (C-4'), 122.5 (C-2'', 6''), 119.1 (C-4''), 70.5 (CH_2-2), 62.2 (CH-3), 34.1 (CH_3-4). Mass: m/z 412 (M^+), 410 (M-2, 51.1 %), 414 (M+2, 49.6 %). Anal. Calc. For $C_{16}H_{15}Br_2NO_2$: C 46.52, H 3.66, N 3.39. Found: C 46.22, H 3.61, N 3.25.

3.2.3.2. N-(1-(4-bromophenyl)ethyl-2-(4-nitrophenoxy)acetamide (3b)

IR (KBr, cm^{-1}): 3246, 3040, 2936, 1680, 1582, 1236 and 1028. ^{1}HNMR (400 MHz, DMSO-d6, δ ppm)**:** 8.76 (d, 2H, H-3'', 5''), 8.31 (s, 1H, NH), 8.04 (d, 2H, H-3', 5'), 7.88 (d, 2H, H-2'', 6''), 7.36 (d, 2H, H-2', 6'), 5.43 (m, 1H, CH-3), 5.12 (s, 2H, CH_2-2), 2.11 (d, 3H, CH_3-4) ^{13}C NMR (DMSO-d_6, δ ppm): 174.6 (C-1), 169.7 (C-1''), 151.7 (C-1'), 150.6 (C-4''), 133.9 (C-3', 5'), 131.5 (C-2', 6'), 128.1 (C-3'', 5''), 126.7 (C-4'), 121.7 (C-2'', 6''), 72.2 (CH_2-2), 61.7 (CH-3), 27.9 (CH_3-4) Mass: m/z 378 (M^+), 379 (M+1, 18.6 %), 380 (M+2, 99.1 %). Anal. Calc. For $C_{16}H_{15}BrN_2O_4$: C 50.68, H 3.99, N 7.39. Found: C 50.72, H 3.93, N 7.43.

3.2.3.3. N-(1-(4-bromophenyl)ethyl)-2-(4-(tert-butyl)phenoxy) acetamide (3c)

IR (KBr, cm^{-1}): 3218, 3050, 2982, 2975, 1654, 1594, 1228 and 1020. ^{1}HNMR (400 MHz, DMSO-d6, δ ppm)**:** 8.56 (s, 1H, NH), 8.11 (d, 2H, H-3', 5'), 7.86 (d, 2H, H-3'', 5''), 7.54 (d, 2H, H-2', 6'), 7.13 (d, 2H, H-2'', 6''), 5.78 (m, 1H, CH-3), 5.11 (s, 2H, CH_2-2), 3.17 (d, 3H, CH_3-4), 2.67 (s, 9H, $(CH_3)_3$) ^{13}C NMR (DMSO-d_6, δ ppm): 173.8 (C-1), 167.6 (C-1''), 144.8 (C-4''), 141.6 (C-1'),

138.5 (C-3', 5'), 131.4 (C-2', 6'), 128.1 (C-3'', 5''), 123.6 (C-4'), 118.5 (C-2'', 6''), 71.1 (CH_2-2), 61.7 (CH-3), 42.9 (C, C-$(CH_3)_3$), 34.6 ($(CH_3)_3$), 29.4 (CH_3-4). Mass: m/z 391 (M^+), 390 (M-1, 22.1 %), 389 (M-2, 99.2 %). Anal. Calc. For $C_{20}H_{24}BrNO_2$: C 61.54, H 6.20, N 3.59. Found: C 61.57, H 6.24, N 3.52.

3.2.3.4. N-(1-(4-bromophenyl)ethyl)-2-(4-methoxyphenoxy)acetamide (3d)

IR (KBr, cm^{-1}): 3220, 3036, 2923, 1662, 1597, 1256 and 1068. ^{1}HNMR (400 MHz, DMSO-d6, δ ppm)**:** 8.55 (s, 1H, NH), 8.23 (d, 2H, H-3', 5'), 7.67 (d, 2H, H-2', 6'), 7.13 (s, 4H, H-2'', 3'', 5'', 6''), 5.64 (m, 1H, CH-3), 5.13 (s, 2H, CH_2-2), 4.11 (s, 3H, OCH_3), 1.87 (d, 3H, CH_3-4) ^{13}C NMR (DMSO-d_6, δ ppm): 175.4 (C-1), 161.5 (C-4''), 156.2 (C-1''), 148.6 (C-1'), 141.9 (C-3', 5'), 138.5 (C-2', 6'), 128.4 (C-4'), 122.8 (C-2'', 3'', 5'', 6''), 77.5 (CH_2-2), 71.5 (OCH_3), 54.4 (CH-3), 32.2 (CH_3-4) . Mass: m/z 363 (M^+), 364 (M+1, 18.3 %), 365 (M+2, 97.6 %). Anal. Calc. For $C_{17}H_{18}BrNO_3$: C 56.06, H 4.98, N 3.85. Found: C 56.11, H 4.94, N 3.86.

3.2.3.5. N-(1-(4-bromophenyl)ethyl)-2-(2-nitrophenoxy)acetamide (3e)

IR (KBr, cm^{-1}): 3246, 3052, 2937, 1676, 1583, 1242 and 1035. ^{1}HNMR (400 MHz, DMSO-d6, δ ppm)**:** 8.66 (d, 1H, H-3''), 8.54 (s, 1H, NH), 8.14 (d, 2H, H-3', 5'), 7.98 (t, 1H, H-5''), 7.87 (t, 1H, H-4''), 7.55 (d, 2H, H-2', 6'), 7.17 (d, 1H, H-6''), 5.44 (m, 1H, CH-3), 5.12 (s, 2H, CH_2-2), 3.12 (d, 3H, CH_3-4) ^{13}C NMR (DMSO-d_6, δ ppm): 171.5 (C-1), 163.5 (C-1''), 153.4 (C-1'), 152.5 (C-2''), 145.7 (C-5''), 144.8 (C-3', 5'), 137.3 (C-3''), 136.4 (C-2', 6'), 132.2 (C-4''), 130.6 (C-4'), 123.3 (C-6''), 71.1 (CH_2-2), 59.8 (CH-3), 46.6 (CH_3-4). Mass: m/z 378 (M^+), 379 (M+1, 18.1 %), 380 (M+2, 99.3 %). Anal. Calc. For $C_{16}H_{15}BrN_2O_4$: C 50.68, H 3.99, N 7.39. Found: C 50.64, H 3.96, N 7.37

3.2.3.6. N-(1-(4-methoxyphenyl)ethyl)-2-(p-tolyloxy)acetamide (3f)

IR (KBr, cm^{-1}): 3230, 3056, 3012, 2932, 1672, 1516, 1259, and 1040. ^{1}HNMR (400 MHz, DMSO-d6, δ ppm)**:** 8.56 (s, 1H, NH), 8.13 (d, 2H, H-2', 6'), 7.96 (d, 2H, H-3'', 5''), 7.13 (d, 2H, H-3', 5'), 6.96 (d, 2H, H-2'', 6''), 6.13 (m, 1H, CH-3), 5.64 (s, 2H, CH_2-2), 4.77 (s, 3H, OCH_3), 3.56 (s, 3H, CH_3-4''), 2.11 (d, 3H, CH_3-4) ^{13}C NMR (DMSO-d_6, δ ppm): 173.2 (C-1), 169.9 (C-4'), 162.2 (C-1''), 145.5 (C-1'), 141.7 (C-4''), 138.8 (C-3'', 5''), 134.5 (C-2', 6'), 127.5 (C-2'', 6''), 126.7 (C-3', 5'), 77.6 (CH_2-2), 73.8 (OCH_3), 64.4 (CH-3), 36.4 (CH_3-4), 35.8 (CH_3-4''). Mass: m/z 299 (M^+), 300 (M+1, 19.5 %), 301 (M+2, 19.9 %). Anal. Calc. For $C_{18}H_{21}NO_3$: C 72.22, H 7.07, N 4.68. Found: C 72.25, H 7.03, N 4.70

3.2.3.7. N-(1-(4-methoxyphenyl)ethyl)-2-(4-nitrophenoxy)acetamide (3g)

IR (KBr, cm^{-1}): 3233, 3060, 2940, 1674, 1587, 1246 and 1042. ^{1}HNMR (400 MHz, DMSO-d6, δ ppm)**:** 8.56 (d, 2H, H-3'', 5''), 8.23 (s, 1H, NH), 7.67 (d, 2H, H-2'', 6''), 7.56 (d, 2H, H-2', 6'), 7.11 (d, 2H, H-3', 5'), 5.66 (m, 1H, CH-3), 5.43 (s, 2H, CH_2-2), 4.76 (s, 3H, OCH_3), 3.24 (d, 3H, CH_3-4) ^{13}C NMR (DMSO-d_6, δ ppm): 171.5 (C-1), 169.8 (C-1''), 162.3 (C-4'), 145.5 (C-4''), 141.2 (C-1'), 132.2 (C-2', 6'), 131.4 (C-3'', 5''), 124.3 (C-2'', 6''), 121.9 (C-3', 5'), 72.1 (CH_2-2), 64.3 (OCH_3), 61.1 (CH-3), 35.7 (CH_3-4). Mass: m/z 330 (M^+), 331 (M+1, 19.8 %), 332 (M+2, 2.4 %). Anal. Calc. For $C_{17}H_{18}N_2O_5$: C 61.81, H 5.49, N 8.48. Found: C 61.83, H 5.47, N 8.49

3.2.3.8. 2-(4-(tert-butyl)phenoxy)-N-(1-(4-methoxyphenyl)ethyl) acetamide (3h)

IR (KBr, cm^{-1}): 3241, 3052, 2984, 2935, 1655, 1580, 1311 and 1113. ^{1}HNMR (400 MHz, DMSO-d6, δ ppm)**:** 9.15 (s, 1H, NH), 8.76 (d, 2H, H-3'', 5''), 8.11 (d, 2H, H-2', 6'), 7.56-7.33 (m, 4H, H-2'', 6'', 3', 5'), 6.45 (m, 1H, CH-3), 5.88 (s, 2H, CH_2-2), 4.54 (s, 3H, OCH_3), 3.47 (d, 9H, $(CH_3)_3$), 2.76 (s, 3H, CH_3-4) ^{13}C NMR (DMSO-d_6, δ ppm): 169.7 (C-1), 161.4 (C-4'), 159.6 (C-1''), 153.2 (C-4''), 146.8 (C-1'), 138.5 (C-2', 6'), 136.4 (C-3'', 5''), 132.4 (C-3', 5'), 129.9 (C-2'', 6''), 76.3 (CH_2-2), 71.1 (OCH_3), 68.1 (CH-3), 52.2 (C, C-$(CH_3)_3$), 47.6 ($(CH_3)_3$), 37.5 (CH_3-4). Mass: m/z 341 (M^+), 342 (M+1, 23.9 %), 343 (M+2, 3.5 %). Anal. Calc. For $C_{21}H_{27}NO_3$: C 73.87, H 7.97, N 4.10. Found: C 73.83, H 7.92, N 4.14

3.2.3.9. 2-(4-chloro-3-methylphenoxy)-N-(1-(4-methoxyphenyl) ethyl)acetamide (3i)

IR (KBr, cm^{-1}): 3227, 3053, 2980, 2913, 1688, 1583, 1245 and 1125. ^{1}HNMR (400 MHz, DMSO-d6, δ ppm)**:** 8.85 (s, 1H, NH), 8.12 (d, 1H, H-5''), 7.88 (d, 2H, H-2', 6'), 7.43 (m, 3H, H-2'', 3', 5'), 7.18 (m, 1H, H-6''), 5.86 (m, 1H, CH-3), 5.24 (s, 2H, CH_2-2), 4.91 (s, 3H, OCH_3), 3.56 (s, 3H, CH_3-3''), 3.77 (d, 3H, CH_3-4) ^{13}C NMR (DMSO-d_6, δ ppm): 171.2 (C-1), 167.3 (C-1'', 4'), 153.2 (C-1'), 151.7 (C-5''), 147.6 (C-4''), 143.3 (C-3''), 136.4 (C-2', 6'), 134.7 (C-6''), 129.8 (C-3', 5'), 91.3 (C-2), 82.4 (OCH_3), 68.4 (CH-3), 32.6 (CH_3-4), 29.5 (CH_3-3''). Mass: m/z 333 (M^+), 334 (M+1, 20.5 %), 335 (M+2, 34.1 %). Anal. Calc. For $C_{18}H_{20}ClNO_3$: C 64.77, H 6.04, N 4.20. Found: C 64.80, H 6.01, N 4.22.

3.2.3.10. N-(1-(4-methoxyphenyl)ethyl)-2-(2-nitrophenoxy)acetamide (3j)

IR (KBr, cm^{-1}): 3251, 3069, 2967, 1681, 1586, 1317 and 1120. ^{1}HNMR (400 MHz, DMSO-d6, δ ppm)**:** 8.54 (m, 1H, H-3''), 8.21 (s, 1H, NH), 7.89 (m, 1H, H-5''), 7.51 (m, 1H, H-4''), 7.33 (d, 2H, H-2', 6'), 7.12 (d, 3H, H-6'', 3', 5'), 5.37 (m, 1H, CH-3), 5.22 (s, 2H, CH_2-2), 4.65 (s, 3H, OCH_3), 2.76 (d, 3H, CH_3-4) ^{13}C NMR (DMSO-d_6, δ ppm): 170.7 (C-1), 162.2 (C-4'), 159.6 (C-1''), 150.5 (C-2''), 146.3 (C-1'), 143.3 (C-5''), 139.9 (C-3''), 134.7 (C-2', 6'), 132.4 (C-4''), 128.4 (C-6''), 125.5 (C-3', 5'), 78.6 (C-2), 74.4 (OCH_3), 68.1 (CH-3), 28.4 (CH_3-4). Mass: m/z 330 (M^+), 331 (M+1, 19.1 %), 332 (M+2, 2.6 %). Anal. Calc. For $C_{17}H_{18}N_2O_5$: C 61.81, H 5.49, N 8.48. Found: C 61.83, H 5.47, N 8.44.

3.3. Pharmacological Screening

3.3.1. Animals

Wistar albino rats of either gender weighing in the range of 140-180 g were separated into various groups of five animals each. The animals were housed in cages under standard laboratory conditions (12:12 hour light/dark cycle at 25 ± 2°C and relative humidity of 50 ± 4%). They had free access to standard commercial diet including palletized animal food and water. Animals were starved for 12 hours before the experiments. During the animal experiments and protocols used for this study, ethical guidelines were followed. Institutional Animal Ethical Committee (IAEC) approved all the tests for study.

3.3.2. Preparation of Test Compounds

Reference drugs and test samples were prepared as a suspension in 1% tween 80. Group first (control group) was treated orally with 0.1 ml of tween 80 suspension. A suspension of Diclofenac sodium was given to group second (reference group) at a dose of 50 mg/kg b. w. Final synthesized compounds were administered orally at a dose of 100 mg/kg to all the test groups.

3.3.3. Acute Toxicity

The receipt of ethical clearance was followed by acute toxicity assay on the grounds of OECD guidelines and the goal was to decide the successful dose of the test compounds. Both male and female Wistar albino rats weighing in the range of 140 - 180 g were randomly distributed into numerous groups containing 5 animals per group and were on standard normal diet provided with water *ad libitum*. Rats were fasted for 12 hours before dosing and for 3-4 hours after dosing. The treated groups received orally varying doses

Table 5. Result of antipyretic activity.

Compounds	Body Temperature ^{o}C ± SEM			
	0h	1h	2h	4h
Control	38.19±0.014	38.16±0.022	38.15±0.004	38.17 ±0.018
Indomethacin	38.20±0.003	37.40±0.017	36.33±0.004	36.19±0.024
3a*	38.22±0.018	37.37±0.008	36.44±0.023	36.41±0.032
3b**	38.19±0.044	37.41±0.021	36.31±0.027	36.22±0.002
3c**	38.23±0.036	38.10±0.024	37.78±0.007	37.83±0.017
3d**	38.20±0.034	37.81±0.030	37.86±0.004	38.13±0.012
3e**	38.24±0.008	38.12±0.043	38.14±0.015	38.17±0.010
3f*	38.21±0.023	38.15±0.030	37.74±0.009	37.67±0.018
3g**	38.23±0.040	37.40±0.026	36.34±0.020	36.23±0.036
3h**	38.26±0.010	37.72±0.022	37.69±0.042	37.71±0.030
3i**	38.25±0.019	37.42±0.044	36.47±0.008	36.41±0.006
3j**	38.23±0.041	37.67±0.007	37.70±0.009	37.76±0.017

*p<0.05 significant from control.
**p<0.01 significant from control.

in elevating order (10, 20, 100, 200 and 1000 mg/kg b. w.). They were continuously observed, first of all continuously for 3 hour, then every 30 min for next 4 hour and finally for next 24 hour or till death to detect any changes in autonomic or behavioral responses like vizalterness, spontaneous activity, restlessness, corneal reflex, urination and salivation.

According to above toxicity test, it was found that a highest dose of 1000 mg/kg body weight is safe for the animals. But a very few changes were observed in alertness, touch response and restlessness. Hence, $1/10^{th}$ of the highest safe dose, expressly 100 mg/kg b. w. was selected as successful dose for the studies.

3.3.4. Cytotoxic Activity

Sulforhodamine B assay (SRB) was used for the examination of *in vitro* cytotoxicity of compounds 3(a-j) against two human cancer cell lines, MCF-7 (breast) and HCT-15 (colon) and the assay was based on cellular protein content determination. Drug adriamycin was used as positive control and the results were reported as percent control growth. In this current protocol, each cell line was preincubated on microtitre plate. Results for each test compound were reported as the percent growth of treated cells and were compared with the untreated control cells. The compounds exhibiting reduction in growth of any one of the cell lines to 32% or less are considered as active.

3.3.5. Anti-inflammatory Activity

All the synthesized compounds illustrated by Table **1** were assessed for anti-inflammatory activity employing carrageenan induced rat paw edema model using Plethysmometer instrument which is based on mercury displacement technique [29]. Twelve groups of five animals each were used for the screening. Oral administration of the drug was followed by acute inflammation after one hour. Inflammation was produced by preparing aqueous suspension of carrageenan (1%w/v, 0.1ml) which was injected in the right hind paw in the sub planter region of each rat. A mark was applied on the right hind paw at the malleolus to facilitate measurement of paw volume. The paw volume was measured at the end of 30 min, 2 hr and 4 hr after the injection of carrageenan. The % inhibition was calculated by applying Newbould formula:

$$\%\text{Inhibition} = (1\text{-}Vt/Vc) \times 100$$

Where V_t and Vc are the mean changes in paw volume of treated and control rats respectively.

3.3.6. Analgesic Activity

All the synthesized compounds were evaluated for analgesic activity using Eddy's hot plate method [30]. Eddy's hot plate retained at a fix temperature (55 ± 0.5 ^{o}C) and rats were individually placed on the plate. Latency to exhibit nociceptive responses like paw licking, withdrawal of paws or jump response (whichever appears first) were determined 30, 60 and 90 minutes after administration of the test drugs. The response time was recorded by a stop-watch. A maximum analgesic response time of 15 seconds was considered as cut-off time to prevent tissue damage. A suspension of standard (Diclofenac sodium) was administered to the reference group at a dose of 50 mg/kg b.w.

3.3.7. Antipyretic Activity

The antipyretic activity of synthesized compounds on the feverish body temperature was evaluated according to a procedure already been reported [31-34]. Pyrexia was induced by subcutaneous injection of 100 mg/kg b. w. of 20% suspension of Brewer's yeast in physiological saline in groups of five fasted rats. The rise in temperature was recorded after 17 hours. Every test compound was administered orally and body temperature was measured after 1, 2 and 4 hours. The reference drug was Indomethacin. The result of antipyretic activity is shown in Table **5**.

3.3.8. Statistical Analysis

The results of anti cancer, anti- inflammatory activity and analgesic activity are represented by Tables **2**, **3** and **4** respectively. The values were represented as mean ± SEM (standard error of mean) and were examined using one-way analysis of variance (ANOVA) to study differences among the means followed by Dunnett's t-test for multiple comparisons. The probability of 0.05 or less was considered statistically significant in the experiment. Statistical analysis was computed with the Graph Pad Prism 5.01, Graph Pad Software Inc. USA.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Authors are grateful to Prof. R M Dubey, Vice Chancellor of IFTM University for providing necessary facilities for this research work. The authors acknowledge SAIF, Panjab University, Chandigarh, for providing the instrumental facilities of Mass and NMR spectrophotometer. Authors are also thankful to Tata Memorial Center of Advanced Cancer Treatment Research, Mumbai, for providing facilities for cytotoxic screening of compounds.

REFERENCES

[1] Balkwill, F.; Mantovani, A. Inflammation and cancer: Back to Virchow? *The Lancet*, **2001**, *357*(9255), 539-545.

[2] Philip, M.; Rowley, D.A.; Schreiber, H. Inflammation as a tumor promoter in cancer induction. *Semin. Cancer Biol.,* **2004**, *14*(6), 433-439.

[3] Grivennikov, S.I.; Greten, F.R.; Karin, M. Immunity, Inflammation, and Cancer. *Cell,* **2010**, *140*(6), 883-899.

[4] Eiró, N.; Vizoso, F.J. Inflammation and cancer. *World J. Gastroint. Surg.*, **2012**, *4*(3), 62-72.

[5] Beyaert, R.; Beaugerie, L.; Assche, G.V.; Brochez, L.; Renauld, J.C.; Viguier, M.; Cocquyt, V.; Jerusalem, G.; Machiels, J.P.; Prenen, H.; Masson, Pierre.; Louis, Edouard.; Keyser, F.D. Cancer risk in immune-mediated inflammatory diseases (IMID). *Mol. Cancer*, **2013**, *12*(1), 98.

[6] Coussens, L.M.; Werb, Z. Inflammation and cancer. *Nature*, **2002**, *420*(6917), 860-867.

[7] Pollard, J.W. Tumour-educated macrophages promote tumour progression and metastasis. *Nat. Rev. Cancer,* **2004**, *4*(1), 71-78.

[8] Hudson, J.D.; Shoaibi, M.A.; Maestro, R.; Carnero, A.; Hannon, G.J.; Beach, D.H. A proinflammatory cytokine inhibits p53 tumor suppressor activity. *J. Exp. Med.,* **1999**, *190*(10), 1375-1382.

[9] Jaiswal, M.; LaRusso, N.F.; Burgart, L.J.; Gores, G.J. Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. *Cancer Res.,* **2000**, *60*(1), 184-190.

[10] Hanahan, D.; Weinberg, R.A. The hallmarks of cancer. *Cell*, **2000**, *100*(1), 57-70.

[11] Scotton, C.J.; Wilson, J.L.; Milliken, D.; Stamp, G.; Balkwill, F.R. Epithelial cancer cell migration: A role for chemokine receptors. *Cancer Res*., **2001**, *61*(13), 4961-4965.

[12] Sparmann, A.; Bar-Sagi, D. Ras-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis. *Cancer Cell*, **2004**, *6*(5), 447-458.

[13] Morrison, W.B. Inflammation and Cancer: A Comparative View. *J. Vet. Intern. Med.,* **2012**, *26*(1), 18-31.

[14] Rouzer, C.A.; Marnett, L.J. Cyclooxygenases: Structural and functional insights. *J. Lipid Res.,* **2009**, *50*(Suppl), S29-S33.

[15] Hull, M.A.; Booth, J.K.; Tisbury, A.; Scott, N.; Bonifer, C.; Markham, A.F.; Coletta, P.L. Cyclooxygenase 2 is up-regulated and localized to macrophages in the intestine no of Min mice. *Br. J. Cancer,* **1999**, *79*(9-10), 1399-405.

[16] Meek, I.L.; Van de Laar, Mart, A.F.J.; Vonkeman, H.E. Non-Steroidal Anti-Inflammatory Drugs: An Overview of Cardiovascular Risks. *Pharmaceuticals (Basel),* **2010**, *3*(7), 2146-2162.

[17] Fujita, H.; Kakei, M.; Fujishima, H.; Morii, T.; Yamada, Y.; Qi, Z.; Breyer, M.D. Effect of selective cyclooxygenase-2 (COX-2) inhibitor treatment on glucose-stimulated insulin secretion in C57BL/6 mice. *Biochem. Biophys. Res. Commun.*, **2007**, *363*(1), 37-43.

[18] Ettarh, R.; Cullen, A.; Calamai, A. NSAIDs and Cell Proliferation in Colorectal Cancer. *Pharmaceuticals*., **2010**, *3*(7), 2007-2021.

[19] Gasparini, L.; Ongini, E.; Wenk, G. Non-steroidal anti-inflammatory drugs (NSAIDs) in Alzheimer's disease: Old and new mechanisms of action. *J. Neurochem.*, **2004**, *91*(3), 521-536.

[20] Sun, A.; Prussia, A.; Zhan, W.Q.; Murray, E.E.; Doyle, J.; Cheng, L.T.; Yoon, J.J.; Radchenko, E.V.; Palyulin, V.A.; Compans, R.W.; Liotta, D.C.; Plemper, R.K.; Snyder, J.P. Nonpeptide inhibitors of measles virus entry. *J. Med. Chem.,* **2006**, *49*(17), 5080-5092.

[21] Ang, W.; Lin, Y.N.; Yang, T.; Yang, J.Z.; Pi, W.Y.; Yang, Y.H.; Luo, Y.F.; Deng, Y.; Wei, Y.Q. Synthesis and biological evaluation of 2-(3-Fluoro-4-nitro phenoxy)-N-phenylacetamide derivatives as novel potential affordable antitubercular agents. *Molecules*, **2012,** *17*(2), 2248-4458.

[22] Hedstrom, L.K.; Striepen, B. IMP dehydrogenase inhibitors for treating mammalian gastrointestinal parasitic infections, US patent 20100022547 A1, Jan 28, 2010.

[23] Rani, P.; Pal, D.; Hegde, R.R.; Hashim, S.R. Synthesis, characterization and pharmacological evaluation of substituted phenoxy acetamide derivatives. *Hem. Ind.,* **201**,. *69*(4), 405-415.

[24] Rani, P.; Pal, D.; Hegde, R.R.; Hashim, S.R. Anticancer, Anti-inflammatory, Analgesic activities of Synthesized 2-(Substituted phenoxy) acetamide derivatives*. Biomed. Res. Int.,* **2014**, 2014, Article ID 386473, 1-9.

[25] Rani, P.; Pal, D.; Hegde, R.R.; Hashim, S.R. Acetamides: Chemotherapeutic agents for inflammation associated cancers. *J. Chemother.,* **2015**.

[26] Chiou, C.T.; Lee, W.C.; Liao, J.H.; Cheng, J.J.; Lin, L.C.; Chen, C.Y. Synthesis and evaluation of 3-ylideneoxindole acetamides as potent anticancer agents. *Eur. J. Med. Chem*., **2015**, *98*, 1-12.

[27] Hill, D.T.; Loev, B. 4-(2-Thienvl)-5-methylpyrimidine. Anomalous Leuckart product. *J. Org. Chem.,* **1973**, *38*(11), 2102-2103.

[28] World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical activity, and the Prevention of cancer: a Global Perspective. Washington DC: AICR, **2007**. 'Reference: Available at: http://preventcancer.aicr.org/site/ PageServer?pagename=research_science_expert_report'

[29] Winter, C.A.; Risley, E.A.; Nuss, G.W. Carrageenin-induced edema in hind paw of the rat as an assay for antiiflammatory drugs. *Proc. Soc. Exp. Biol. Med.,* **1962,** *111*(3), 544-547.

[30] Eddy, N.B.; Leimbach, D. Synthetic analgesics II. Dithienylbutenyl and dithienylbutylamines. *J. Pharmacol. Exp. Ther.*, **1953**, 107(3), 385-393.

[31] Ochi, R.; Suemaru, K.; Kawasaki, H.; Araki, H. Effect of Brewer's yeast -induced pyrexia on aminophylline-elicited convulsions in mice. *Acta Med .Okayama.,* **2009**, *63*(5), 273-280.

[32] Pal, D.; Mitra, S. A preliminary study on the *in vitro* antioxidant activity of the stems of Opuntia vulgaris. *J. Adv. Pharm. Tech. Res*., **2010**, *1*(2), 268-272.

[33] Nayak, A.K.; Pal, D.; Pany, D.P.; Mohanty, B. Evaluation of Spinacia oleracea L. leaves mucilage as an innovative suspending agent. *J. Adv. Pharm. Tech. Res*., **2010**, *1*(3), 338-314.

[34] Pal, D.; Banerjee, S.; Ghosh, A. Dietary-induced cancer prevention: An expanding research arena of emerging diet related to healthcare system. *J. Adv. Pharm. Tech. Res*., **2012**, *3(*1), 16-24.