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Research Article

A NOVEL APPROACH TOWARDS DEVELOPMENT OF QUINAZOLINE DERIVATIVES IN PAIN MANAGEMENT

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ABSTRACT

Objective: To synthesize and evaluate the analgesic and anti-inflammatory activities of pyrazoline bearing 4(3H)-quinazolinone derivatives.
Methods: Synthesis of Chalcone (3a-3j) involves the *Claisen-Schmidt* condensation of equimolar quantities of substituted acetophenone with aromatic aldehyde in the presence of aqueous alkali (10%). Comp. (3a-3j) undergoes cyloaddition reaction with semicarbazide HCl in the presence of suitable solvent to yield comp. (4a-4j). It undergoes addition cyclization reaction with anthranillic acid to yield final comp. (6a-6j). Acute toxicity study of synthesized compound was found according to OECD guidelines 423. The test compound do not showed any toxicity up to 200mg/kg dose. Mortality was not observed during the course of study. The analgesic and anti-inflammatory activity of all synthesized compounds were carried by using hot plate method and Carrageenan induced Rat Paw Edema Method respectively.
Results: All compounds synthesized are obtained in crystalline form with good practical yield. The purity and homogeneity of compounds synthesized were determined by sharp melting points and TLC method. The chemical structures were confirmed by FTIR, ^{1}HNMR, and Mass spectrum.
Conclusion: The synthesized compound **6b, 6d, 6e, 6i** and **6j** showed good analgesic and anti-inflammatory activities whereas others showed significant activities.

Keywords: Quinazoline, pyrazole, analgesic and anti-inflammatory activity.

INTRODUCTION

Quinazoline is a compound made up of two fused six-membered simple aromatic rings, structure compound containing benzene fused to pyrimidine. Medicinally it has been used in various areas as an analgesic and anti-inflammatory [1-4], antihypertensive [5-6], antimicrobial [7-9], antibacterial [10], anticonvulsant [11-13], anticancer [14-15], antimalarial [16] and antidepressant activities [17]. Pyrazole derivatives also exhibit some similar set of activities such as antimicrobial [18] and analgesic, anti-inflammatory [19]. It has been reported that substitution pattern by different aryl or heteroaryl moieties at 2/3 position of quinazoline nucleus markedly influences the anti-inflammatory activity [20]. On the other hand, sulphonamides [21], imidazoles [22], pyrazoles [23] are other important pharmacodynamic heterocyclic nuclei which when incorporated into different heterocyclic templates, have been reported to possess potent anti-inflammatory activity. Based on the above observations and in continuation of our anti-inflammatory and analgesic drug research program, it was of interest to adjoin the above said moiety to obtain expectedly more potent compounds with lesser side effects. The structures were confirmed by IR, ^{1}HNMR, mass spectra and elemental analysis. These compounds were screened for analgesic and anti-inflammatory activity using hot plate method and rat paw edema method respectively.

MATERIALS AND METHODS

The chemicals used in the present work were AR grade and LR grade, purchased from Loba, Merck and Fisher scientific fine chemicals. The synthesized compounds were scaled for yield and purified by recrystallization with suitable solvent system. The melting point of the synthesized compounds were determined in open capillary using LABHOSP melting point apparatus and recorded in ^oC without correction. Thin layer chromatography was performed on silica gel G plates using Hexane: Ethyl acetate (7:3) solvent system. The structures were further confirmed by elemental (CHN) and spectral analysis like Infrared spectroscopy, Nuclear magnetic resonance spectroscopy and mass spectroscopy.

General Procedure

The title compounds were prepared in following steps:

Synthesis of 1, 3-Diphenyl prop-2-en-1-one derivatives (Chalcone) (3a-3j).

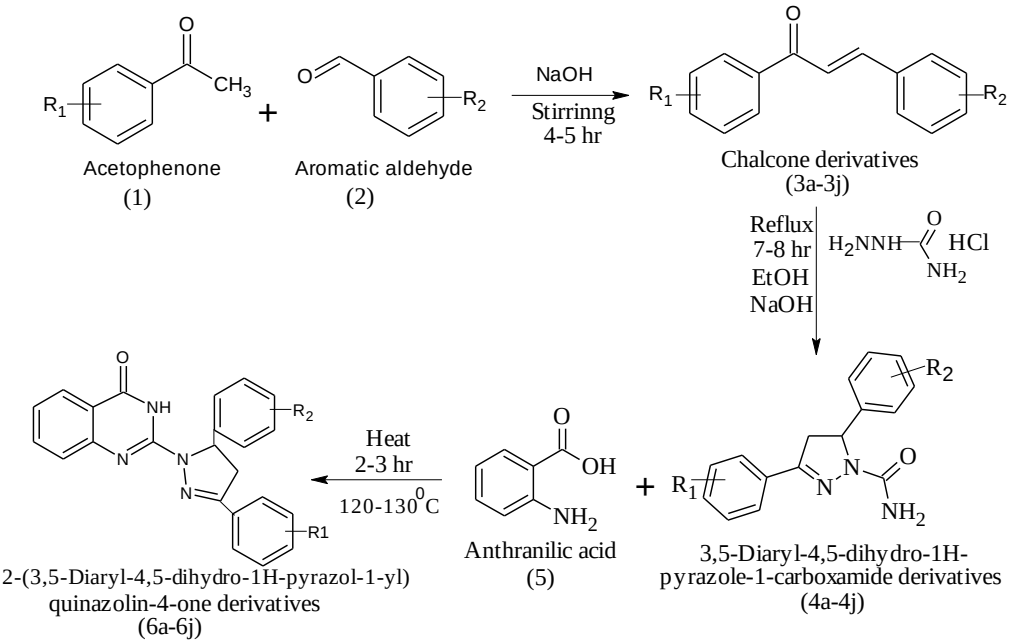
A mixture of benzaldehyde (0.01 mol) and acetophenone (0.01 mol) was dissolved in 10 ml rectified spirit in a 250 ml round-bottomed flask equipped with a magnetic stirrer. Then added 10 ml (10%) NaOH solution drop wise to the reaction mixture on vigorous stirring for 30 minutes when solution became turbid, the reaction temperature was maintained between 20-25° C using a cold water bath on the magnetic stirrer. After vigorous stirring for 4-5 hr the reaction mixture was neutralized by 0.1N HCl whereby the precipitation occurred. The crude chalcone was filterd, dried in air and recrystallized by rectified spirit. By adopting the above procedures comp. (3b-3j) were synthesized using different benzaldehydes and acetophenones in equimolar concentration.

Synthesis of 3,5-Diaryl-4,5-dihydropyrazole-1-carboxamide derivatives (4a-4j).

A mixture of the respective chalcone derivatives (3a) (0.01 mol), semicarbazide HCl (0.01 mol) and NaOH (0.5 g, 0.0125 mol) was heated under reflux in absolute ethanol (25 ml) for 7-8 hrs. The reaction mixture was cooled and poured into ice cold water. The solid separated was filtered, dried and crystallized from the ethanol. By using above procedure comp. (4b-4j) were synthesized.

Synthesis of 2-(3, 5-Diaryl-4,5-dihydro-1H-pyrazol-1-yl) quinazoline-4-one (6a-6j).

A mixture of anthranilic acid (0.01 mol) and Comp. 4a (0.01 mol) was heated on an oil bath at 120 -130^{0}C for 2-3 hr. Subsequently, the melt was allowed to cool for 30 min at room temperature. During this period, the melted mass solidified. It was treated with an aqueous solution of sodium bicarbonate (10%) in order to dissolve any unreacted acid into the cyclised product. An additional quantity of sodium bicarbonate solution was added to ensure the complete dissolution of the acid (until there was no effervescence of carbon dioxide). The solid was filtered off and washed with water in order to remove any inorganic materials. It was dried under vacuum over night and recrystallized from ethanol as white crystalline mass. Using the above procedure, nine different derivatives comp. (6b-6j) were synthesized.



Schematic representation of synthesis of 2-(3, 5-Diaryl-4, 5-dihydro-1H-pyrazol-1-yl) quinazolin-4-one derivatives

Table 1: physicochemical properties of synthesized compounds

Comp code	Compound Name	Mol Formula	Mol Wt.	Mp (°C)	% Yield	R_f Value
6a	2-(3,5-Diphenyl-4,5-dihydro-1H- pyrazol-1-yl)quinazolin-4-one	$C_{22}H_{18}N_4O$	366	183-185	69	0.75
6b	2-[5-(4-Chlorophenyl)-3-phenyl- 4,5-dihydro-1H- pyrazole-1-yl] quinazolin-4-one	$C_{23}H_{17}N_4OCl$	400	211-213	57	0.61
6c	2-[5-(4-Dimethylaminophenyl)-3-phenyl-4,5-dihydro-1H- pyrazol-1-yl] quinazolin-4-one	$C_{25}H_{23}N_5O$	409	202-204	59	0.68
6d	2-[3-(4-Bromophen yl)-5-(4-chlorophen yl)-4,5-dihydro-1H- pyrazol-1-yl]quinazolin-4-one	$C_{23}H_{16}N_4OBrCl$	479	213-215	60	0.87
6e	2-[3-(4-Bromophenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl]quinazolin-4-one	$C_{23}H_{16}N_4OBrCl$	479	217-219	52	0.62
6f	2-[3-(4-Bromophenyl)-5-(4-dimethylamino phenyl)- 4,5-dihydro-1H- pyrazol-1-yl] quinazolin-4-one	$C_{25}H_{22}N_5OBr$	489	189-191	59	0.73
6g	2-[3-(4-Aminophenyl)-5-(4-chlorophenyl)-4,5-dihydro-1H- pyrazol-1-yl]quinazolin-4-one	$C_{23}H_{18}N_5OCl$	415	202-204	64	0.61
6h	2-[3-(4-Aminophenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H- pyrazol-1-yl]quinazolin-4-one	$C_{23}H_{18}N_5OCl$	415	205-207	60	0.71
6i	2-[3-(4-Hydroxy phenyl)-5-(4-chloro phenyl)-4,5-dihydro-1H- pyrazol-1-yl]quinazolin-4-one	$C_{23}H_{16}N_4O_2Cl$	415	225-227	53	0.58

6j	2-[3-(4-Hydroxy phenyl)-5-(2-chloro phenyl)-4,5-dihydro-1H-pyrazol-1-yl]quinazolin-4-one	$C_{23}H_{16}N_4O_2Cl$	416	215-217	57	0.67

RESULTS

All compounds synthesized were obtained in crystalline form with good practical yield. The physicochemical properties of synthesized were given in Table1.

Spectral data

2-(3, 5-Diphenyl-4,5-dihydro-1H- pyrazole -1-yl)quinazolin-4-one (Comp.6a)

IR (KBr, cm^{-1}):1650 (N-H), 1550 (C=C aromatic ring), 1700 (C=O), 1100 (C=N),**^{1}HNMR (CDCl3) δppm;** 7.0-7.8 (m, Ar-H), 3.8 (s, Ar C-NH), 2.3 (d, J=3.3,CH_2), **MS (m/z):** [M+]:367, Anal Calcd for $C_{22}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29;. Found C, 75.42; H, 4.90; N,15.23.

2-[5-(4-Chlorophenyl)-3-phenyl- 4, 5-dihydro-1H- pyrazole -1-yl] quinazolin-4-one (Comp.6b)

IR (KBr, cm^{-1}):1657 (N-H), 1552 (C=C aromatic ring), 1711 (C=O), 1123 (C=N), 757 (C-Cl), **^{1}HNMR (CDCl3) δppm;** 7.0-7.8 (m, Ar-H), 3.4 (s, Ar C-NH), 2.1 (d, J=3.3,CH_2), **MS (m/z):** [M+]:401, Anal Calcd for $C_{23}H_{17}N_4OCl$: C, 68.91; H, 4.27; N, 13.98;. Found C, 68.87; H, 4.31; N, 13.89.

2-[5-(4-Dimethylaminophenyl)- 3-phenyl-4,5-dihydro-1H-pyrazole -1-yl] quinazolin-4-one (Comp.6c)

IR (KBr, cm^{-1}):1653 (N-H), 1549 (C=C aromatic ring), 1713 (C=O), 1127 (C=N), **^{1}HNMR (CDCl3) δppm;** 7.0-7.8 (m, Ar-H), 3.1 (s, Ar C-NH), 3.8 (m, N-CH_3), 2.0 (d, J=3.3, CH_2), **MS (m/z):** [M+]:410, Anal Calcd for $C_{25}H_{23}N_5O$: C, 73.33; H, 5.66; N, 17.10;. Found C, 73.39; H, 5.72; N, 17.18.

2-[3-(4-Bromophenyl)-5-(4-chlorophenyl)- 4,5-dihydro-1H-pyrazole -1-yl]quinazolin-4-one (Comp.6d)

IR (KBr, cm^{-1}):1661 (N-H), 1561 (C=C aromatic ring), 1700 (C=O), 1127 (C=N), 757 (C-Cl), 531 (C-Br), **^{1}HNMR (CDCl3) δppm;** 7.0-7.8 (m, Ar-H), 3.1 (s, Ar C-NH), 2.0 (d, J=3.3, CH_2), **MS (m/z):** [M+]:480, Anal Calcd for $C_{23}H_{16}N_4OBrCl$: C, 57.58; H, 3.36; N, 11.68;. Found C, 58.51; H, 3.41; N, 11.82.

2-[3-(4-Bromophenyl)-5-(2-chlorophenyl)-4, 5-dihydro-1H-pyrazole-1-yl] quinazolin-4-one (Comp.6e)

IR (KBr, cm^{-1}):1652 (N-H), 1588 (C=C aromatic ring), 1700 (C=O), 1121 (C=N), 757 (C-Cl), 531 (C-Br), **^{1}HNMR (CDCl3) δppm;** 7.0-7.8 (m, Ar-H), 3.0 (s, Ar C-NH), 2.7 (d, J=3.3, CH_2), **MS (m/z):** [M+]:480, Anal Calcd for $C_{23}H_{16}N_4OBrCl$: C, 57.58; H, 3.36; N, 11.68;. Found C, 58.51; H, 3.41; N, 11.82.

2-[3-(4-Bromophenyl)-5-(4-dimethylaminophenyl)-4,5-dihydro-1H-pyrazole-1-yl]quinazolin-4-one (Comp.6f)

IR (KBr, cm^{-1}):1658 (N-H), 1568 (C=C aromatic ring), 1714 (C=O), 1104 (C=N), 536 (C-Br). **^{1}HNMR (CDCl3) δppm;** 7.0-7.8 (m, Ar-H), 3.5 (s, Ar C-NH), 3.8 (m, N-CH_3), 2.9 (d, J=3.3, CH_2), **MS (m/z):** [M+]:490, Anal Calcd for $C_{25}H_{22}N_5OBr$: C, 61.48; H, 4.54; N, 14.34;. Found C, 61.52; H, 4.39; N, 14.39.

2-[3-(4-Aminophenyl)-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole -1-yl]quinazolin-4-one (Comp.6g)

IR (KBr, cm^{-1}):1664 (N-H), 1554 (C=C aromatic ring), 1707 (C=O), 1113 (C=N), 761 (C-Cl), 3371 (NH_2) **^{1}HNMR (CDCl3) δppm;** 7.0-7.8 (m, Ar-H), 3.7 (s, Ar C-NH), 2.4 (d, J=3.3, CH_2), **MS (m/z):** [M+]:416, Anal Calcd for $C_{23}H_{18}N_5OCl$: C, 66.43; H, 4.36; N, 16.84;. Found C, 66.48; H, 4.39; N, 16.91.

2-[3-(4-Aminophenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-yl]quinazolin-4-one (Comp.6h)

IR (KBr, cm^{-1}):1663 (N-H), 1575 (C=C aromatic ring), 1703 (C=O), 1113 (C=N), 764 (C-Cl), 3374 (NH_2) **^{1}HNMR (CDCl3) δppm;** 7.0-7.8 (m, Ar-H), 3.8 (s, Ar C-NH), 2.7 (d, J=3.3, CH_2), **MS (m/z):** [M+]:416, Anal Calcd for $C_{23}H_{18}N_5OCl$: C, 66.43; H, 4.36; N, 16.84;. Found C, 66.48; H, 4.39; N, 16.91.

2-[3-(4-Hydroxyphenyl)-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-yl]quinazolin-4-one (Comp.6i)

IR (KBr, cm^{-1}):1665 (N-H), 1583 (C=C aromatic ring), 1700 (C=O), 1105 (C=N), 786 (C-Cl), 3400 (OH), **^{1}HNMR (CDCl3) δppm;** 7.0-7.8 (m, Ar-H), 3.8 (s, Ar C-NH), 2.7 (d, J=3.3, CH_2), **MS (m/z):** [M+]:416, Anal Calcd for $C_{23}H_{16}N_4O_2Cl$: C, 66.27; H, 4.11; N, 13.44;. Found C, 66.39; H, 4.39; N, 13.33.

2-[3-(4-Hydroxyphenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-yl]quinazolin-4-one (Comp.6j)

IR (KBr, cm^{-1}):1667 (N-H), 1588 (C=C aromatic ring), 1700 (C=O), 1107 (C=N), 778 (C-Cl), 3452 (OH) **^{1}HNMR (CDCl3) δppm;** 7.0-7.8 (m, Ar-H), 3.8 (s, Ar C-NH), 2.7 (d, J=3.3, CH_2), **MS (m/z):** [M+]:416, Anal Calcd for $C_{23}H_{16}N_4O_2Cl$: C, 66.27; H, 4.11; N, 13.44;. Found C, 66.39; H, 4.39; N, 13.33.

PHARMACOLOGICAL ACTIVITY

All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of College, constituted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA), Government of India.

Registration number and date of registration

648/02/c/CPCSEA/08 date: 30/10/2012

Toxicity Study [24]

Acute toxicity was determined in rats by employing various logarithmic doses administered by oral route. Each group contained six wistar rats were orally administered with 50 mg/kg, 100 mg/kg and 200 mg/kg of synthesized compounds and kept in polystyrene cages. Behavioural changes were recorded at the interval of 30 min. for 4 hr and also mortality after 24 h was recorded. One group was used as a control receiving only 1% w/v solution of tween 80 and calculated LD_{50}.

All the compounds synthesized were tested for acute toxicity test. No toxicity was observed at the doses of 50, 100, 200 mg/kg of body weight. It was observed no animal was died at the dose of 200 mg/kg of body weight.

Analgesic activity [25]

Swiss albino mice of either sex were divided into twelve different groups each containing six animals, the animals were marked on tail individually. Food was withdrawn 12 hr prior to drug administration till completion of experiment. The animals were weighed and numbered appropriately. To control group (0.3 mL) 2% v/v solution of tween 80, standard (Tramadol, dose: 20 mg/kg), and synthetic derivatives (Comp. 6a-6j, dose: 20 mg/kg) were given by oral route and after 0 min and 90 min behavioural changes count. The jumping and paw licking was noted at 0 min, and 90 min. The percentage inhibition in analgesic activity was evaluated using the following formula.

% inhibition = 1- [latency before treatment/latency after treatment] x 100

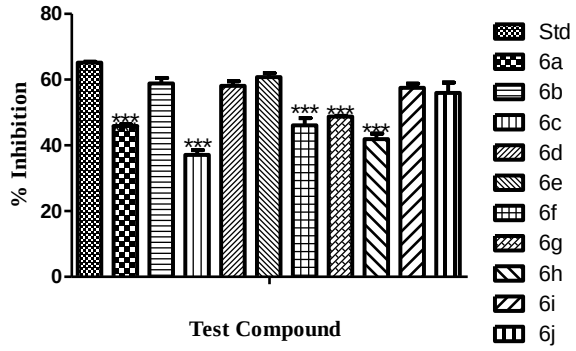


Fig 1: Analgesic activity of synthesized compounds (6a-6j)

Note: Data are expressed as mean latency of before and after drug, one way ANOVA followed by Bonferroni test was applied to determine the significances of the difference between the control group and mice treated with the test compounds. The differences in results were considered significant when, **p<0.01 ***p<0.001.Dose of test group 20mg/kg.

Anti inflammatory activity [25]

Carrageenan induced Rat Paw Edema Method

Wistar rats of either sex were divided into twelve different groups each containing six animals, the animals were marked on tail individually. Food was withdrawn 12 hr prior to drug administration till completion of experiment. The animals were weighed and numbered appropriately. To control group (0.3 mL) 2% v/v solution of tween 80, standard (Diclofenac sodium, dose: 20 mg/kg), and synthetic derivatives (Comp. 6a-6j, dose: 20 mg/kg) were given by oral route. After 1hr, 0.1mL of 1% w/v carrageenan was injected in the sub plantar region of the left paw of control and test drug treated groups. The thickness of paw of all the groups of rats were noted at 0 hr and 5 hr after carrageenan injected. The percentage inhibition of inflammation in the standard or test drug treated animals was recorded and calculated using the formula: -

% inhibition = 1-[a-x/b-y] x 100

where,

a = paw thickness of test group after 5-hr after carrageenan injected
x = paw thickness of test group initially
b = paw thickness of control group after 5-hr after carrageenan injected
y = paw thickness of control group initially

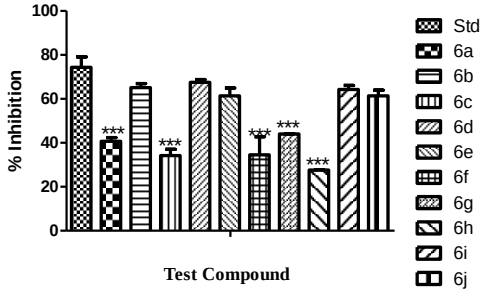


FIG. 2: Anti-inflammatory activity of synthesized compounds (6a-6j)

Note: Anti-inflammatory activities of the test compounds were compared w.r.t control. Data are expressed as % inhibition ± S.E.M. and analyzed by one-way ANOVA followed by Bonferroni test to determine the significance of the difference between the control group and rats treated with the test compounds. The difference in results were considered significant when ** P < 0.01, *** P < 0.001 Vs Std. Dose of test group 20 mg/kg.

DISCUSSION

The IR spectra of all derivatives shows aromatic C=C stretching vibration at 1550-1589cm^{-1}, NH stretching vibration at 1598-1667cm^{-1}, C=O stretching vibration at 1690-1714cm^{-1}, C=N stretching vibration at 1090-1127cm^{-1}, C-N stretching vibration at 1224-1228cm^{-1}. **Comp. 6b, 6d, 6e, 6g, 6h, 6i and 6j** showed absorbance at wavelength 754-764cm^{-1} stretching vibration indicating presence of chloro group. **Comp. 6d, 6e and 6f** showed absorbance at wavelength 531-536 cm^{-1} stretching vibration indicating presence of chloro group. **Comp. 6g and 6h** showed absorbance at wavelength 3371-3374cm^{-1} stretching vibration indicating presence of primary amino group. **Comp. 6i and 6j** showed absorbance at wavelength 3400-3450cm^{-1} stretching vibration indicating presence of hydroxy group. The structures of synthesized derivative were further confirmed by NMR spectra. In ^{1}HNMR spectra of Comp. **6a and 6e** shows a sharp multiplet peak at 7.0-8.0 ppm indicating hydrogen attached to an aromatic ring. The sharp singlet peak at 3.5-4.0 ppm indicates the presence of NH group. A sharp doublet peak at 2.0-3.0 ppm showed the presence of CH_2 group. The structures of synthesized derivative were further confirmed by Mass spectra. Mass spectra of Comp. 6a-6j showed base peak M+ and the relative abundances of all the other peaks in the spectrum are reported as percentage of the abundance of the peak. The results of analgesic and anti-inflammatory activity of test compounds were given in Table 3 and 4 shows that **Comp. 6b, 6d, 6e, 6i and 6j** showed good analgesic and **Comp. 6b, 6d, 6e, 6i and 6j** showed good anti-inflammatory activity and others showed significant activity, when compared to standard drugs Tramadol and Diclofenac sodium respectively.

CONCLUSION

All derivatives were synthesized by convenient route and prepared in good yield. The pharmacological screening showed that the compounds are less toxic and possess good to moderate analgesic and anti- inflammatory activity. **Comp. 6b, 6d, 6e, 6i** and **6j** are the derivatives of interest as they exhibit both activities and may be studied in near future.

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