Research Paper

N-Substituted Quinazolin- 2,4-diones as Adenosine Receptor Ligands

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ABSTRACT: Six new N-substituted quinazolinones were synthesized and evaluated for their adenosine antagonistic activity using allergic mice model where 1, 3-di benzyl and 1, 3-dibutyl-quinazolindiones were found to be potent than 1, 3-dimethylanalogues. They were not significant in controlling the neutrophil and lymphocyte count but effective in controlling the eosinophil influx. In adenosine receptor binding studies, 1,3-dimethyl and 1,3-dibutyl derivatives were found to have significant adenosine A1 receptor binding efficiency with Ki values 9nM and 10nM, respectively, while 1,3-dibenzylnquinazolinone was found to have significant binding to adenosine A2A receptor showing the influence of alkyl and aralkyl groups present in these compounds. Thus, the present work indicates the possibility to explore quinazolinolindiones as adenosine receptor ligands.

KEY WORDS: Adenosine ligands; N-alkyl quinazolin-diones; Allergic mice model; Radioligand binding studies

Introduction

The stimulation of cell surface adenosine receptors (ARs) is largely responsible for broad variety of effects produced by adenosine through several organ systems. It has been proposed recently that antagonists of distinct AR subtypes (A1, A2A, A2B and A3) may be used in the treatment of asthma or certain neurological disorders such as Parkinson’s disease (Moro et al. 2006; Jacobson et al. 1996; Holgate, 2004; Cacciari et al. 2005). The role of adenosine receptors in the pathogenesis of asthma prompted many laboratories to search for potent adenosine antagonists to treat asthma (Kalla and Jablocki, 2009). The natural lead molecule, theophylline (a methyl xanthine) was found to act through A2B antagonism. However, this alkaloid has side effects like CNS stimulation, cardiac arrhythmias, hypotension and convulsions, which have been attributed to its nonselectivity towards adenosine receptors (Muller, 2003; Daly, 2007).

Various xanthine congeners as well as nonxanthine molecules were evaluated for their adenosine antagonistic activity. CVT-6883 (a xanthine derivative) (Kalla et al. 2004) and pyrimidinyl bipyrimidines (Vidal and Trias, 2005; Vidal et al. 2007) (non xanthine derivatives) are now in clinical trials for selectivity towards A2B receptors. Pyrrolopyrimidines (Stewart et al. 2004) were also reported as selective antagonists, which are now used as pharmacological tools.

As part of ongoing research to develop novel bronchodilatory agents (Carotti et al. 2006; Elzein et al. 2006), several isosteric modifications of xanthine skeleton, adenine derivatives, pyrrolopyrimidines and pyrazolopyrimidines were performed. Various modifications on imidazole ring in the xanthine system were also designed, synthesized and evaluated to investigate the possible role of imidazole nitrogens in binding with adenosine receptors (Baraldi et al. 2008). However, the replacement of imidazole with benzene resulting in quinazolin-2,4-diones was not investigated, as the selective adenosine receptor antagonists, so far. Although synthesis of some of the molecules (El-Khamry et al. 2006) was reported earlier, their pharmacology is yet to be explored. This observation has led to the synthesis of few quinazolinolindiones with a view to evaluate them for adenosine antagonistic activity using allergic mice model and radioligand binding studies. Several quinazoline derivatives have been found to exhibit interesting biological activities. As such there is only one report on adenosine antagonistic activity of quinazoline derivatives, where CMB-6446 was found to be potent and selective towards A2B receptor (Thomas and Webb, 2003). This left much scope to investigate the synthesis and evaluation of
some N-substituted quinazolin-3, 4-diones as adenosine receptor antagonists.

Materials and Methods

Chemistry

Melting points were recorded on Casia-siamia (VMP-AM) melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectro photometer using KBr optics. $^1$H NMR spectra were recorded on Gemini varian 200 MHz, Bruker AV 300 MHz and Unity 400 MHz spectro meter in DMSO-d$_6$ or CDCl$_3$ using TMS as an internal standard. Electron impact (EI) and chemical ionization mass spectra were recorded on a VG 7070 H instrument at 70 ev. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh); Spots were visualized with UV light. Merck silica gel (100-200 mesh) was used for chromatography. CHN analyses were recorded on a Vario EL analyser.

There are various approaches to achieve synthesis of quinazolin-2,4(1H, 3H)-diones in which ‘Niementowski reaction’ makes use of a nthranilic acid and acid amides (Bogert and Golthelf, 1900). The reported yields are generally good with aliphatic amides and decrease with the increase in the molecular weight of the amides. Substituted anthranilic acids require higher temperature and longer reaction times. In the present investigation, anthranilic acid was used along with urea to obtain quinazolin-2,4(1H,3H)dione following literature procedure (Reisch et al. 1990). The quinazolin-dione on reaction with alkyl halides in presence of potassium carbonate in dimethyl sulfoxide yielded mono/dialkyl quinazoli-2,4-diones as presented in scheme-1.

General method for preparation of N-mono/di substituted quinazolin-2,4(1H, 3H) diones (2,3):

Quinazolindione 1 (6.1 mmol), K$_2$CO$_3$ (6.1mmol), an appropriate halide (12.5mmol) were taken in DMSO and heated under reflux for 8-14 hours while monitoring the progress of the reaction by thin layer chromatography. The reaction mixture was added to crushed ice and neutralized with dilute hydrochloric acid to get the product which was filtered, dried and purified using column chromatography.

3-Methylquinazolin-2,4(1H, 3H) dione (2a): Yield: 0.687gms (64%); m.p:156-158°C, IR (KBr): 1671(C=O), 3168, 3056 (NH); $^1$H NMR (CDCl$_3$) δ: 3.64 (3H, s, N-CH$_3$), 7.35(2H, m, Ar-H), 7.71 (1H, m, Ar-H), 8.26(1H, m, Ar-H), MS m/z: 176 (M$^+$), Anal. Calcd for C$_8$H$_6$N$_2$O$_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.17; H, 4.81; N, 15.78.

3- n-Butylquinazolin-2,4(1H,3H) dione (2b): Yield: 0.985gms (74%); m.p:136-139°C, IR (KBr): 1658, 1708 (C=O), 3128 (NH); $^1$H NMR (CDCl$_3$) δ: 1.1 (3H, t, CH$_3$), 1.44(2H, m, CH$_2$), 1.75 (2H, m, CH$_2$), 4.65 (2H, t, N-CH$_2$), 7.13(1H, m, Ar-H), 7.25 (1H, m, Ar-H), 7.62 (1H, m, Ar-H), 8.18(1H, d, Ar-H), 10.20 (1H, s, NH), MS m/z: 219 (M$^+$+1), Anal. Calcd for C$_{12}$H$_{12}$N$_2$O$_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.13; H, 6.68; N, 13.05.

1-Benzylquinazolin-2,4(1H,3H) dione (2c): Yield: 1.352gms (88%); m.p:102-106°C, IR (KBr): 1713 (C=O), 3190 (NH); $^1$H NMR (CDCl$_3$) δ: 5.22 (2H, s, N-CH$_2$), 7.25 (5H, m, Ar-H), 7.58(3H, m, Ar-H), 8.16(1H, m, Ar-H), 10.8 (1H, s, NH), MS m/z: 253 (M$^+$+1), Anal Calcd for C$_{15}$H$_{12}$N$_2$O$_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.70; H, 4.66; N, 11.28.

1,3-Dimethylquinazolin-2,4(1H,3H) dione (2a): Yield: 0.788gms (68%); m.p:162-164°C, IR (KBr): 1658 (C=O); $^1$H NMR (CDCl$_3$) δ: 3.52(3H, s, N-CH$_3$), 3.65(3H, s, N-CH$_3$), 7.25(2H, m, Ar-H), 7.67 (1H, m, Ar-H), 8.26 (1H, m, Ar-H); MS m/z: 190 (M$^+$), Anal Calcd for C$_{10}$H$_{10}$N$_2$O$_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.98; H, 5.57; N, 14.88.

1,3-Dibutylquinazolin-2,4(1H,3H)dione (2a): Yield: 1.104gms (66%); m.p:140-142°C, IR (KBr): 1658, 1708 (C=O); $^1$H NMR (CDCl$_3$) δ: 0.98 (6H, s, 2CH$_3$), 1.45 (4H, m, 2CH$_2$), 2.25 (4H, m, 2CH$_2$), 4.16(2H, t, N-CH$_2$), 5.22(2H, t, N-CH$_2$), 7.12 (1H, m, Ar-H), 7.25 (1H, m, Ar-H), 7.62 (1H, m, Ar-H), 8.18(1H, m, Ar-H); MS m/z: 275 (M$^+$+1), Anal Calcd for C$_{16}$H$_{22}$N$_2$O$_2$: C, 70.04; H, 5.57; N, 10.21. Found: C, 70.25; H, 7.89; N, 10.49.

R = CH$_3$, n-C$_4$H$_9$ or CH$_2$-ph

Scheme-1 Synthesis of various 1-alkyl/aryl or 1,3-dialkyl/diarylquinazolinidiones
1,3-Dibenzylquinazolin-2,4(1H,3H)-dione (3c): Yield: 1.71gms (82%); m.p: 200-202°C, IR (KBr): 1715 (C=O); $^1$H NMR (CDCl$_3$) $\delta$: 5.26(4H, m, NCH$_2$), 7.4(13H, m, Ar-H), 8.20(1H, m, Ar-H); MS $m/z$, 343 ($M^+1$); Anal Calcd for C$_{22}$H$_{18}$N$_2$O$_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.32; H, 5.57, N, 8.26.

Pharmacology

Some quinazoline derivatives are reported to exhibit bronchodilatory and antiasthmatic activities (Rao and Bahekar, 1999; 2000, 2001). Jindal et al. 2002; Alagarsamy et al. 2008). The synthesized molecules were designed based on the isosteric modification of xanthine derivatives like aminophylline and theophylline, which are used as antiasthmatic agents with adenosine antagonism. Adenosine is present in higher concentrations in the bronchoalveolar lavage (BAL) fluid from asthmatic patients in comparison to normal individuals. Allergen provocation leads to an immediate release of adenosine from actively sensitized animal’s lungs and this can influence the activity of inflammatory cells in asthma. These include adenosine’s ability to modulate mediator release from mast cells, influence eosinophil function, enhance neutrophil chemotaxis and stimulate mucus secretion by airway epithelial cells.

In the present investigation, synthesized quinazolindiones were evaluated for their adenosine antagonistic activity since adenosine receptors are known to involve in the pathogenesis of asthma. Series of exposures of allergens like egg albumin resulted in asthmatic condition in mice. The measurement of bronchoalveolar lavage fluid cells after aerosolization with adenosine was performed and compared with control group to evaluate the compounds for their adenosine antagonistic activity.

Male BALB/c mice of age between 5-8 weeks and of weight 25-30gms, free of pathogens were obtained from National Institute of Nutrition, Hyderabad, India. The animals were maintained on allergen-free diet and were under the protocol approved by the Institutional Animal Ethics Committee. Since adenosine induces bronchoconstriction only in asthmatic condition, the animals were made sensitive to adenosine by exposing them to allergens systematically, to induce asthma. Sensitization was performed according to the method reported previously (Fan and Mustafa, 2002; Fan et al. 2003; Gelfand et al. 2004; Sur et al. 1996). The protocol used for sensitization of animals was presented in Table-1. Binding assays for adenosine A$_1$ and A$_{2A}$ receptors were also performed to study the selectivity of these molecules towards adenosine receptor subtypes using reported procedure (Prasad et al. 2008).

<table>
<thead>
<tr>
<th>Day</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day (0.1 ml, i.p)</td>
<td>Control (C)</td>
</tr>
<tr>
<td>4th day (0.1 ml, i.p)</td>
<td>Saline</td>
</tr>
<tr>
<td>10th, 11th, 12th days</td>
<td>Spray saline in Histamine chamber</td>
</tr>
<tr>
<td>13th day</td>
<td>Spray saline in Histamine chamber</td>
</tr>
</tbody>
</table>
Allergic mice model

Male mice of age between 5-8 weeks weighing 25-30 gms each, free of pathogens were obtained from National Institute of Nutrition, Hyderabad and divided into various groups: control (C), control + adenosine (C+A), control + adenosine + theophylline (C+A+T), sensitized (with egg albumin (S), sensitized + adenosine (S+A), sensitized + theophylline + adenosine (S+T+A) and sensitized + adenosine + synthesized molecule (S+A+ Compound code) before performing sensitization. The animals were maintained on allergen -free diet and under the protocol approved by the Institutional Animal Ethics Committee. Sensitization of mice in such specific groups on days one and six was effected with i.p. injection of egg albumin (200µg/200µl), where as the control animals receive only water for injection by the same route. The overall schedule of spraying allergens for inducing asthmatic condition in mice was presented in table3. Twenty four hours after the last challenge with egg albumin spray, mice were sprayed for one minute with (a) 0.9% saline for control group (C), (b) 6mg/ml of adenosine for control + adenosine group (C+A), (c) 6mg/ml of adenosine + 100mg/kg body weight theophylline (by oral route) for control + adenosine + theophylline group (C+A+T), (d) 0.9% saline for sensitized group (S) (e) 6mg/ml solution of adenosine for sensitized + adenosine group (S+A), (f) 6mg/ml adenosine solution and oral administration of theophylline (100mg/kg body weight) for sensitized + adenosine + theophylline group (S+A+T) (g) adenosine (6mg/ml) and oral administration of test compounds at 100mg/kg body weight for sensitized + adenosine + test compound group (S+A+Compound Code).

Mice were killed by i.p. injection of 0.1ml of pentobarbital sodium (200 mg/ml) one hour after the above treatments. The trachea was cannulated to collect the broncho alveolar lavage fluid by introducing 1ml phosphate buffered saline (PBS) into the lungs via the tracheal cannula and carefully withdrawn the lavage fluid. The lavage fluid was collected into a polystyrene tube maintained on ice. This was repeated to collect the remaining cells.

To study the influence of adenosine on airway inflammation, the broncho alveolar lavage (BAL) fluid was centrifuged at 1500rpm at room temperature for six minutes. After removing the supernatant, the BAL cells were resuspended in 1ml of PBS. The total cells were then counted manually in a hemocytometer chamber. The differential count of at least 300 cells was performed according to the standard morphologic criteria after treating with Leishmann stain. The number of cells recovered per mouse was calculated and expressed as mean ± SEM /ml, for each group.

Radioligand Binding Studies

Materials: [¹H] CCPA was obtained from NEN Life Science (48.6 Ci/mmol) and [¹H] MSX-2 was obtained from Amersham (85 Ci/mmol).

Membrane preparations

Frozen rat brains were obtained from Pel Freez, Rogers, AR, USA. Rat brains were dissected to obtain cortical membrane preparations for A₁ and striatal membrane preparations for A₂A assay.

Radioligand binding assays

Binding assays for A₁ and A₂A were performed essentially as described in the literature.²⁸ Stock solutions of the test compounds were prepared in dimethyl sulphoxide (DMSO); the final concentration of DMSO in the assay was 2.5%. The radioligand concentrations were [¹H] CCPA: 0.5 nM (rat A₁) and [³H] MSX-2: 1.0 mM (rat A₂A).

Drug solution (50µl) was added into a 96-well plate followed by 50µl of radioligand solution and 100 µl (30 µg/vial) of protein suspension of rat brain cortex (A₁) or rat brain striatal membranes (A₂A) and incubated at room temperature. CADO (2-chloroadenosine)/NECA [5’-(N-ethylcarbamoyl)adenosine] was used for nonspecific binding for A₁ and A₂A AR binding studies, respectively. After 90/30 min respectively, the incubation was terminated by rapid filtration over Whatman GF/B filters using a Brandell cell harvester (Brandell, Gaithersburg, MD). To the filter plate scintillation liquid was added (40 µl/vial – Microscent - 20) and incubated at room temperature for 10 hours and radioactivity was measured by a scintillation counter. Those compounds whose percentage inhibition was found to be more than 20% at a test concentration of 1 µM were taken and a full concentration – inhibition curve was determined.

Data analysis

Data were analyzed using Graph Pad PRISM version 3.0 (San Diego, CA). For nonlinear regression analysis, the Cheng – Prusshoff equation and a Kᵦ value of 0.5 nM for [¹H] CCPA at rat A₁ AR and 157 ± 6 for [³H]MSX-2 at rat A₂A AR was used to calculate Kᵦ values from EC₅₀ values.

Results and Discussion

Chemistry

In view of the tautomerism, alkylation of quinazolin- 2, 4 (1H, 3H) dione (I) may lead to the formation of O and N-alkylated products. Since only N-alkylation is feasible under basic conditions, formation of N-alkylated products was anticipated from the reaction. The reaction is a simple
nucleophilic substitution in which potassium carbonate abstracts proton from nitrogen and leads to formation of mono- and / or dialkylated derivatives, based on the quantity of halide employed in the reaction. Monosubstituted derivatives were formed with stoichiometric ratio of reactants where as a mixture of mono- and substituted derivatives resulted with the use of excess amounts of halide. Mono substitution was occurring at only third position of quinazoline ring due to high acidity of that NH proton in the molecule.

Presence of carbonyl absorption peak at 1670-1700cm⁻¹ region in mono- and substituted derivatives in their infrared spectrum (KBr pellet method) indicates the N-alkylation of the molecules thereby ruling out their O-alkylation. All the compounds were characterized with the help of their I. R, 1H-NMR and mass spectra and elemental analyses data.

Pharmacology

The total and differential count of the BAL fluid was performed and results obtained were presented in table-2. There is not much variation observed in the cell counts of control, control + adenosine and control + adenosine + theophylline groups indicating that inhalation of adenosine at 6mg/ml concentration in normal (unsensitized) animals could not have any effect on modification of cellular levels in BAL fluid. In contrast, in sensitized animals, the neutrophils, eosinophils and total cellular counts were observed to increase and the number of macrophages tend to decrease, where the lymphocyte count was remained the same. After adenosine inhalation, the variation of cellular counts from control animals was still observed to vary in the same fashion when compared to sensitized animals. The total count in control and sensitized group was lower than the adenosine aerosolized group. This indicated the increase in sensitivity of the animal to adenosine and allergens. The 3-benzylquinazolindione (2c) was able to antagonize the influence of adenosine on bronchial tract. The number of neutrophils, lymphocytes and eosinophils were decreased when compared to S+A group but not less than the sensitized group and number of macrophages was similar to S+A group.

1,3-Dimethylquinazolindione (3a) also exhibited a similar profile of cell counts, where neutrophils, lymphocytes and eosinophils were decreased when compared to cellular counts obtained from BAL of S + A group mice. But the reduction in number of eosinophils was higher in case of 1,3-dibutyl (3b) and 1,3 – dibenzyl (3c) derivatives. Of all these molecules 1,3-dibenzylquinazolindione was found to be potent in reducing the number of eosinophils. However, the number of macrophages was reduced in all the cases including sensitized, adenosine aerosolized and theophylline treated animals along with test molecule treated mice, which requires further investigation. However, it was already reported that theophylline can show its anti-inflammatory action only at lower concentrations.

<table>
<thead>
<tr>
<th></th>
<th>Neutrophils</th>
<th>Lymphocytes</th>
<th>Eosinophils</th>
<th>Macrophages</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>20±5</td>
<td>20±4</td>
<td>10±2</td>
<td>30±2</td>
<td>6±1</td>
</tr>
<tr>
<td>C+A</td>
<td>23±2</td>
<td>19±2</td>
<td>11±1</td>
<td>31±1</td>
<td>8±0.5</td>
</tr>
<tr>
<td>C+A+T</td>
<td>18±4</td>
<td>20±2</td>
<td>09±3</td>
<td>28±2</td>
<td>8±3</td>
</tr>
<tr>
<td>S</td>
<td>51±3</td>
<td>24±1</td>
<td>15±2</td>
<td>9±1</td>
<td>13±0.5|</td>
</tr>
<tr>
<td>S + A</td>
<td>55±0.5</td>
<td>28±0.3</td>
<td>21±3</td>
<td>5±0.9</td>
<td>27±2</td>
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<tr>
<td>S + A + T</td>
<td>56±3</td>
<td>28±0.6</td>
<td>21±1</td>
<td>8±1</td>
<td>26±0.5</td>
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<tr>
<td>S+A+ 1</td>
<td>53±1</td>
<td>25±0.8</td>
<td>17±0.5</td>
<td>5±1</td>
<td>20±2</td>
</tr>
<tr>
<td>S+A+ 2a</td>
<td>53±0.9</td>
<td>20±3</td>
<td>18±1</td>
<td>6±1</td>
<td>24±1</td>
</tr>
<tr>
<td>S+A+ 2b</td>
<td>51±2</td>
<td>22±1</td>
<td>15±2</td>
<td>6±0.5</td>
<td>23±2</td>
</tr>
<tr>
<td>S+A+ 2c</td>
<td>52±0.6</td>
<td>20±1</td>
<td>17±1</td>
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<td>7±0.5</td>
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<tr>
<td>S+A+ 3a</td>
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<td>S+A+ 3b</td>
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<tr>
<td>S+A+ 3c</td>
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<td>25±1</td>
<td>9±0.5</td>
<td>3±0.5</td>
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</tr>
</tbody>
</table>

Table 2 Total and differential cell counts obtained in BAL fluid analysis.
Table 3 Radioligand binding data for N-substituted quinazolindiones.

<table>
<thead>
<tr>
<th>Compound code</th>
<th>$A_1$ Adenosine receptor (rat brain cortical membranes) $[^{3}H]$CCPA</th>
<th>$A_{2A}$ Adenosine receptor (rat brain striatal membranes) $[^{3}H]$MSX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$K_i$ ± SEM [nM] (n=3 if unspecified)</td>
<td>$K_i$ ± SEM [nM] (n=3 if unspecified)</td>
</tr>
<tr>
<td>1</td>
<td>$(-2$ $±$ $1)$</td>
<td>$30400$ $±$ $16300$</td>
</tr>
<tr>
<td>3a</td>
<td>$(9$ $±$ $4)$</td>
<td>$3700$ $±$ $995$</td>
</tr>
<tr>
<td>3b</td>
<td>$(10$ $±$ $4)(n=4)$</td>
<td>$2230$ $±$ $610$</td>
</tr>
<tr>
<td>3c</td>
<td>$(-10$ $±$ $5)(n=4)$</td>
<td>$(40$ $±$ $2)(n=4)$</td>
</tr>
<tr>
<td>DPCPX</td>
<td>$0.5+0.2$</td>
<td>$157+6.0$</td>
</tr>
</tbody>
</table>

It could be observed that all the test compounds exhibited the adenosine antagonistic activity by reducing the number of neutrophils, lymphocytes and especially eosinophils when compared to S + A group.

To confirm their adenosine binding activity, adenosine receptor binding studies were performed for synthesized molecules. The molecules were evaluated for $A_1$ and $A_{2A}$ receptor binding studies using specific ligands to each of the receptor types, where all the compounds were found to show selectivity towards $A_1$ receptor subtype as presented in Table-3. 1, 3-Dimethyl (3a) and 1,3-dibutyl (3b) derivatives were found to have a significant $A_1$ antagonistic activity with Ki values 9nM and 10nM, respectively where as 1,3-dibenzylquinazolindione (3c) was found to have significant $A_{2A}$ antagonistic activity showing the significance of alkyl chain and aromatic rings present in these three derivatives.

Conclusion

Adenosine antagonistic activity of the mono/dialkyl quinazolinones was assotated. The activity of the molecules was not very significant in controlling the number of neutrophils and lymphocytes but found to be effective in controlling the eosinophil influx. Substitution at 1, 3 positions of quinazolindione with alkyl groups found to influence the binding efficiency at $A_1$ receptor where as the substitution with the aralkyl groups found to be effective at $A_2$ receptor. This work emphasizes the need to explore quinazolindiones as adenosine receptor ligands.

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