RESUMÉ AND DISCUSSION

Theophylline remains one of the most widely prescribed antiasthma drug worldwide because of its dual bronchodilatory and antiinflammatory activities. The use of theophylline for the treatment of asthma is associated with unpleasant side effects such as insomnia and diuresis and a low therapeutic index. In recent years, use of theophylline as a bronchodilator for relief of asthma has been supplanted by drugs of other classes, e.g., selective \( \beta_2 \)-adrenergic agonists, corticosteroids and more recent leukotriene antagonists. As all these compounds have some sort of limitations; therefore the development of a theophylline-like drug with reduced side effects is still desirable. The discovery that alkylated xanthines are also potent antagonists at adenosine receptors has further renewed interest in this class of antiasthmatics. Therefore, it was thought worthwhile to design and develop new alkylxanthines with a better therapeutic index for the treatment of asthma.

Synthesis and pharmacological activity of a large variety of xanthine derivatives substituted at 1-, 3-, 7- and 8-positions have been reported in the present study. The synthetic work carried out has been discussed under following heads:

- 1,3-Dimethyl-8-phenylxanthines
- 8-[4-(Aminoalkoxy)-3-methoxyphenyl] derivatives
- 8-[3-(Aminoalkoxy)phenyl] derivatives
- 8-[(Cyclopentyloxy)phenyl] derivatives
- 8-(2-Nitroaryl) derivatives
- 8-[4-(Aminoalkoxy)-5-methoxy-2-nitrophenyl] derivatives

- 1,3-Dimethyl-7-propyl-8-phenylxanthines

Some more imidazolyl substituted 8-phenylxanthines with variable substituents in 1-, 3- and 7-positions

Nitrate esters of some 1,3-dimethyl-8-phenylxanthines

Ditheophylline derivatives

Miscellaneous

- 7-Substituted-1,3-dimethylxanthines
- 8-Substituted-1,3-dimethylxanthines
1,3-DIMETHYL-8-PHENYLXANTHINES

It has been observed that the most dramatic alterations in the potency of dialkylxanthines as antiasthmatics result from substitution in the 8-position of the heterocyclic system. Addition of aryl group at this position yields potent compounds with high selectivity for adenosine $A_{2B}$ receptors. Therefore, various 8-aryl-substituted-1,3-dimethylxanthines have been synthesized. Synthesis of 5,6-diamino-1,3-dimethyluracil (124), a key intermediate to the synthesis of all the 8-substituted derivatives, was performed according to the general method $^{295,296}$ summarized in scheme 1. 1,3-Dimethyl-5-nitrosouracil (123) was prepared by condensing $N,N'$-dimethylurea and cyanoacetic acid in the presence of acetic anhydride to obtain 6-aminouracil and subsequent nitrosation with sodium nitrite. Reduction of nitrosouracil 123 with sodium dithionite in concentrated ammonium hydroxide afforded quite an unstable diaminouracil 124 $^{296}$ which was then reacted with different aldehydes to afford...
corresponding benzylidene derivatives/Schiff bases. Subsequent cyclization with thionyl chloride yielded the desired 8-substituted 1,3-dimethylxanthines in accordance with the earlier literature reports.  

8-[4-(Aminoalkoxy)-3-methoxyphenyl] derivatives

Aldehydes 125-131 were prepared by treating vanillin with hydrochlorides of β-dimethylaminoethyl chloride, β-diethylaminoethyl chloride, 1-(2-chloroethyl)piperidine, 4-(2-chloroethyl)morpholine, 1-(2-chloroethyl)pyrrolidine, 1-bromo-3-chloropropane and 1-bromo-2-chloroethane, respectively, in refluxing ethyl methyl ketone in the presence of anhydrous potassium carbonate. The completion of the reaction was monitored by thin layer chromatography (TLC). The oily residues obtained after processing the reaction mixture were used as such for further reaction. Treatment of these vanillin derivatives 125-131 with 5,6-diamino-1,3-dimethyluracil (124) in MeOH-AcOH (4:1) at
room temperature resulted in the formation of corresponding benzylidene derivatives 132-138. The completion of the reaction was monitored by TLC. A singlet integrating for one proton appeared at ~\( \delta \) 9.75 for N=CH in \(^1\)H NMR spectra of all the benzylidenes. Subsequent ring closure of these intermediates by refluxing in thionyl chloride for 30-40 min afforded the desired target compounds 139-145. The structures of these 8-phenyl derivatives were confirmed using various spectral analyses. NMR signals appeared at \( \delta \) 2.23 [s, -N(CH\(_3\)_2)] for 139, \( \delta \) 1.08 [t,6H, -N(CH\(_2\)CH\(_3\)_2)] for 140, \( \delta \) 1.45 (m, 2H, CH\(_2\), piperidine) for 141, \( \delta \) 3.62 [(t, 4H, O-(CH\(_2\)_2), morpholine] for 142, \( \delta \) 2.57 [(s, 4H, -N(CH\(_2\)_2), pyrrolidine)] for 143, \( \delta \) 3.79 (t, 2H, -CH\(_2\)Cl) for 144 and \( \delta \) 3.86 (t, 2H, -CH\(_2\)Cl) for 145. Singlets for two methyls at 1- and 3- positions of purine nucleus and a triplet for -OCH\(_2\) appeared in NMR spectra of all the compounds.

To observe the effect of imidazolyl group on the pharmacological activity of compounds, imidazolylalkoxy derivatives

\[
\begin{align*}
\text{H}_3\text{C} & \text{N} \\
\text{O} & \text{N} \\
\text{N} & \text{O} \\
\text{CH}_3 & \text{OCH}_3
\end{align*}
\]

146 and 147 were prepared by fusion of chloroalkoxy derivatives 144 and 145 with powdered imidazole at 160°C for 2 h. Imidazolyl protons appeared in the range of \( \delta \) 6.90-8.00 in the NMR spectra of both the compounds.
8-[3-(Aminoalkoxy)phenyl]derivatives

Another series of 8-(substituted)phenylxanthines was prepared in which 8-phenyl ring was substituted only at meta position. For this purpose, different aldehydes 148-153 were prepared by treating 3-hydroxybenzaldehyde with hydrochlorides of various dialkylaminoethyl chlorides such as β-dimethylaminoethyl chloride, β-diethylaminoethyl chloride, 1-(2-chloroethyl)piperidine, 4-(2-chloroethyl)morpholine, 1-(2-chloroethyl)pyrrolidine; and 1-bromo-3-chloropropane, respectively, using a similar method as described already. The oily residues obtained after processing the reaction mixture were used as such for further reaction. Aldehydes 148-153 were then condensed with 5,6-diamino-1,3-dimethyluracil (124) in MeOH-AcOH (4:1) at room temperature to afford the corresponding benzylidene derivatives 154-159, which on subsequent cyclization by refluxing in thionyl chloride for 30-40 min gave the desired target.
8-(m-substituted)phenyl-1,3-dimethylxanthines (160-165). The infrared and nuclear magnetic resonance spectra of these compounds were consistent with the proposed structures. A triplet for -OCH₂ appeared at ~ δ 4.15 in NMR spectra of all the compounds. N-Methyl and N-methylene protons appeared at δ 2.37 (s, 6H) and at δ 2.65 (q, 4H) for 8-substituted derivatives 160 and 161, respectively. N-Methylene of heterocyclic ring appeared at δ 2.57 for piperidinoethoxy 162, at δ 2.60 for morpholinoethoxy 163 and at 3.10 for pyrrolidinoethoxy 164 derivatives, respectively. A triplet at δ 3.79 (CH₂Cl) was present in the NMR spectrum of chloropropoxy derivative 165. Singlets for two methyls attached to nitrogen at 1- and 3- positions of purine nucleus appeared at their appropriate places in all the nuclear magnetic resonance spectra.

Fusion of 165 with imidazole at 160°C for 2 h yielded the imidazole derivative 166. Proton of -CH- attached to two nitrogen atoms of imidazole ring appeared downfield at δ 7.54 in nuclear magnetic resonance spectrum.

8-[(Cyclopentyloxy)phenyl] derivatives

The structural components of a known PDE4 inhibitor, rolipram (31) were combined with xanthine nucleus with the hope to obtain compounds with synergistic antiasthmatic effects. For the preparation of these hybrid structures, alkylation of vanillin, isovanillin and 3-hydroxybenzaldehyde was carried out with cyclopentyl bromide in refluxing ethyl methyl ketone in presence of anhydrous potassium carbonate to obtain cyclopentyloxy derivatives 167-169 as
oily residues, respectively, which could not be crystallized and used as such for further reactions. Treatment of 167-169 with 5,6-diamino-1,3-dimethyluracil (124) in MeOH-AcOH (4:1) at room temperature gave respective benzylidene derivatives 170-172. The completion of the reaction was monitored by TLC. A singlet integrating for one proton appeared at ~ δ 9.6 for N=CH in ¹H NMR spectra of all the Schiff bases. Oxidative cyclization of 170-172 was affected on refluxing with thionyl chloride for 30-40 min to afford the desired 8-[(cyclopentyloxy)phenyl] derivatives 173-175. The structures of these compounds were confirmed using various spectral data. ¹H NMR showed two singlets each integrating for three protons at ~ δ 3.40 and ~ δ 3.60 for N-CH₃ groups and a multiplet integrating for one proton at ~ δ 4.80 for -OCH of cyclopentyl ring. Elemental analysis further supported the structures of the compounds.
8-(2-Nitroaryl) derivatives

To synthesize these compounds, nitration of various aromatic aldehydes was carried out in a mixture of concentrated nitric and sulphuric acid (HNO₃-H₂SO₄) (1.5:1) in ice to yield yellow solid nitroaldehydes 177-180. Nitropiperonal (176) was prepared by using a procedure as reported in the literature. The structures and purity of these compounds were confirmed using various spectral analyses and TLC studies. Infrared asymmetric and symmetric stretching vibrations for nitro group appeared near 1520 and 1340 cm⁻¹, respectively. Condensation of 176-180 with intermediate diaminouracil 124 in MeOH-AcOH (4:1) at room temperature gave
RESUMÉ AND DISCUSSION

Schiff bases 181-185. The completion of the reaction was monitored by TLC. These unstable Schiff bases were used immediately for further cyclization in refluxing thionyl chloride to afford 8-(2-nitroaryl) derivatives 186-190. Vibrational bands for nitro group appeared near 1520 and 1340 cm$^{-1}$ in the infrared spectra. $^1$H NMR signals, integrating for one less aromatic proton for all the compounds, further confirmed the intact nitro group. Peaks for protons of O-CH$_2$-O, -(OCH$_3$)$_2$, -(OCH$_3$)$_3$, -O-cyclopentyl and -OCH$_3$ functionalities appeared in NMR spectra of corresponding 8-(2-nitroaryl) derivatives 186-190.

(4-Aminoalkoxy-5-methoxy-2-nitrophenyl) derivatives

Some more 8-substituted-1,3-dimethylxanthines possessing nitro group were prepared. For this, nitration of vanillin derivatives

124 + OHC\_\text{MeOH}/AcOH $\rightarrow$ 191-197

125-131 was carried out in an ice-cold mixture of concentrated HNO$_3$-H$_2$SO$_4$ (1.5:1) to obtain the nitrovanillin derivatives 191-197.
The completion of the reaction was monitored by TLC. The compounds were used as such for further preparation of nitrated Schiff bases 198-204 by condensing with intermediate 5,6-diamino-1,3-dimethyluracil (124) in MeOH-AcOH (4:1) as described previously. The purity of compounds 198-204 was established by TLC. Subsequent ring closure in refluxing thionyl chloride afforded the desired 8-substituted xanthines 205-211. Imidazole derivatives 212 and 213 were prepared by fusing chloroalkoxy derivatives 210 and 211 with imidazole at 120°C for 3 h. The structures of the compounds were confirmed using various spectral analyses, which were found consistent with the proposed structures as detailed in experimental part.

1,3-DIMETHYL-7-PROPYL-8-PHENYLXANTHINES

It has been reported in the literature that alkylation of nitrogen at 7-position (N-7) of 1,3-dimethylxanthines increases the phosphodiesterase inhibitory potency of theophylline. Therefore propyl group was introduced at N-7 of some of the synthesized 8-substituted xanthine derivatives to observe its effect on pharmacological and physicochemical properties. Propylation was carried out by adding propyl bromide to a heated mixture of various 8-[4-(aminoalkoxy)-3-methoxyphenyl]-1,3-dimethylxanthines (139-144)
in DMF and anhydrous potassium carbonate to afford respective 7-propyl derivatives 214-219. Compounds 215, 217 and 219 showed NMR signals at δ 0.88 (t, 3H, -CH₂CH₃), δ 1.86 (m, 2H, -CH₂CH₃) and δ 4.29 (t, 2H, N-CH₂) for protons of propyl group. Interestingly, in the process, 7-alkylated derivatives 214, 216 and 218 were obtained as water soluble quaternized salts. It seems that traces of propyl bromide left in the residue were responsible for quaternization of product during crystallization. This method can be used to synthesize water soluble 8-phenylxanthine derivatives, which otherwise have very limited water solubility.

Their structures were confirmed by presence of NMR signals for two methylene groups attached to quaternary nitrogen. Peaks of ¹⁰N(CH₃)₂ were observed at δ 3.55 for 214 and of ¹⁰N(CH₂)₂ at δ 3.62 for 216. Methylenes of pyrrolidino functionality attached to quaternary nitrogen appeared separately as multiplets at δ 3.51 and δ 3.76 for 216.
compound 218. Quaternary products 214, 216 and 218 also exhibited signals for N-propyl group in nuclear magnetic resonance spectra. Fusion of 219 with imidazole at 120°C for 2 h yielded the imidazole derivative 220.

Similarly N-7 propyl group was also introduced in 8-(3-chloropropoxy)phenyl derivative 165 to afford 221, which on fusion with imidazole at 120°C for 3 h gave 8-(3-imidazolylpropoxyphenyl)-7-propyl-1,3-dimethylxanthine (222). The structures of these 7-propylxanthine derivatives were confirmed using various spectral analyses. Triplets for N-CH$_2$CH$_2$CH$_3$ and N-CH$_2$CH$_2$CH$_3$ and multiplet for N-CH$_2$CH$_2$CH$_3$ appeared in NMR spectra of all the compounds. In some of the compounds triplet for N-CH$_2$ of propyl group merged with N-CH$_2$ of 8-(substituted)phenyl residue to form a multiplet.
SOME MORE IMIDAZOLYL SUBSTITUTED 8-PHENYL-XANTHINES WITH VARIABLE SUBSTITUENTS IN 1-, 3- AND 7- POSITIONS

The effects of varying the alkyl substituents in the 1-, 3- and 7-positions on the activity of 8-substituted xanthines at adenosine receptors are well known.\textsuperscript{300,301} These observations prompted us to vary the alkyl groups in some of the newly synthesized 8-(substituted)phenylxanthines. On the basis of initial pharmacological
screening results, 8-phenylxanthines containing imidazole group were mainly preferred.

The standard synthesis for the preparation of xanthines with different substituents in the 1-, 3-, 7- and 8-positions starts from monosubstituted urea as shown in scheme 2. Condensation of monomethyl urea with cyanoacetic acid in acetic anhydride, followed by alkaline ring closure gave 6-amino-1-methyluracil (223)$^{295,302}$ with unsubstituted 3-position (corresponding to the 1-position of xanthine), which was used as starting material for the synthesis of 1-unsubstituted and 1-propyl substituted xanthine derivatives.

For the preparation of 1-unsubstituted-3-methylxanthine derivatives, nitrosation of 223 with sodium nitrite and acetic acid to afford nitroso derivative 224 and further reduction of 224 with sodium dithionite was carried out to obtain 5,6-diaminouracil 225.$^{267,283}$ Condensation of 225 with vanillin derivative 130 in MeOH-AcOH (4:1) gave the benzylidene 230, which on subsequent ring closure in refluxing...
thionyl chloride gave 1-unsubstituted-3-methyl-8-(substituted)phenyl derivative 232.

Fusion of chloropropoxy derivative 232 with imidazole afforded 234. Presence of only one singlet for N-methyl of purine nucleus in the NMR spectrum confirmed the formation of 1-unsubstituted derivatives.

![Chemical Structure](image)

Preparation of 1-propyl-3-methylxanthine derivatives was performed by alkylating 3-position (corresponding to 1-position of xanthine) of 223 with propyl bromide in dimethylformamide in presence of anhydrous potassium carbonate. It was observed that during this process 6-amino group was replaced by 6-amidino functionality by interaction of amino group with dimethylformamide and 226 was obtained instead of 227. This was confirmed by presence of proton signals at δ 3.07 and δ 3.12 along with peaks at δ 0.93, δ 1.65 and δ 3.89 for propyl group and at δ 7.67 for N=CH in the NMR spectra. Formamidino derivative 226 was stirred at room temperature in methanol and aqueous ammonia for 1-3 days, by monitoring with TLC, to obtain 6-amino-1-methyl-3-propyluracil (227) (Scheme 2). Sequential nitrosation and reduction of 227 afforded 228 and the desired intermediate 229, which was used as starting material for the preparation of 8-(substituted)phenyl-1-methyl-3-propylxanthines. Treatment of 229 with vanillin derivative 130 afforded Schiff base 231, which on subsequent ring closure gave chloropropoxy derivative 233. Further fusion of 233 with imidazole...
afforded 8-(imidazolylpropoxyphenyl)-1-methyl-3-propylxanthine (235). The structures of compounds were confirmed by using various spectral analysis as explained in experimental section.

Continuing with the synthesis of imidazole containing xanthines, 1,3,7-trimethyl-8-(imidazolylpropoxyphenyl)xanthine (237) was prepared by heating chloropropoxy derivative 130 with methyl iodide at 70-80°C in DMF in the presence of anhydrous potassium carbonate to obtain 236, which on fusion with imidazole gave the desired imidazole containing tetrasubstituted xanthine 237. Three singlets for N-methyls of purine nucleus appeared in the nuclear magnetic resonance spectra of 236 and 237, confirming the formation of 1,3,7-trimethylxanthine derivatives.

1-Methyl group of another promising newly synthesized hybrid molecule 173 was replaced by 1-propyl group to observe its effect on adenosine receptor selectivity. For this purpose vanillin derivative 167 was condensed with 5,6-diamino-1-methyl-3-propyluracil (229) in
MeOH-AcOH (4:1) to obtain benzylidene 238 which on subsequent ring closure in refluxing thionyl chloride gave 8-[(4-cyclopentyloxy)-3-methoxyphenyl]-3-methyl-1-propyl-xanthine (239).

**NITRATE ESTERS OF SOME 7-ALKYL-1,3-DIMETHYL-8-PHENYLXANTHINES**

It is established now that the organic nitrates relax vascular smooth muscle due to their ability to generate nitric oxide, a physiological messenger, which display a variety of biological actions.\textsuperscript{305,306} Therefore, it was thought worthwhile to synthesize some 8-nitrooxyaryl derivatives of theophylline to observe its effect on smooth muscle relaxation.

8-[4-(3-Chloropropoxy]phenyl derivatives 219 and 236 were treated with silver nitrate in acetonitrile at 60°C to obtain nitrate esters 240 and 241, respectively. The structures of the compounds were confirmed using various spectral analyses. Asymmetric and symmetric stretching bands for \(\text{ONO}_2\) were present near 1540 and 700 cm\(^{-1}\).
1280 cm\(^{-1}\), respectively, in the infrared spectra of both the compounds. A downfield shift (\(\delta 4.72\)) of CH\(_2\)-ONO\(_2\) protons was observed as compared to CH\(_2\)-Cl (\(\delta 3.90\)) of starting chloro derivatives 219 and 236 in the NMR spectra.

Similarly treatment of 8-[3-(3-chloropropoxy)phenyl] derivative 221 with silver nitrate afforded the meta substituted nitrooxy derivative 242. Various spectral analyses data of the compound was consistent with the proposed structure. A downfield shift (\(\delta 4.69\)) of CH\(_2\)-ONO\(_2\) was observed as compared to CH\(_2\)-Cl (\(\delta 3.77\)) of starting chloro derivative 221 in the NMR spectra.

**DITHEOPHYLLINE DERIVATIVES**

Ditheophyllines, in which we combined one 8-substituted theophylline moiety with another 7-substituted one in a single molecule, were prepared to observe the effect of such combination on pharmacological activity.
carbonate at 70-80°C for 3 h gave the corresponding 7-substituted theophylline derivatives 244 and 243. Aldehydic protons appeared at ~ δ 9.85 for both the compounds.

Condensation of these aldehydes 243 and 244 with 5,6-diamino-1,3-dimethyluracil (124) in MeOH-AcOH (4:1) at room temperature resulted in Schiff bases 245 and 246, which cyclized in refluxing thionyl chloride to desired ditheophyllines 247 and 248, respectively.

In NMR, four singlets each integrating for three protons for 4 X N-CH₃, confirmed the presence of two theophylline nuclei. A singlet at ~ δ 8.0 for 8-CH was also present for the 7-substituted theophylline nuclei.
MISCELLANEOUS

7-Substituted-1,3-dimethylxanthines

Hybrid structures containing active principles of two or more drugs in a single molecule are of much interest now a days for the development of more potent chemical moieties. It was thought to combine 4-aryl-1,4-dihydropyridine, a nucleus with potent calcium channel blocking activity, with the xanthine skeleton to observe its effect on smooth muscle relaxation. 7-(3-Chloropropyl)-1,3-dimethylxanthine (249) was refluxed with 4-hydroxy-3-methoxyphenyl-1,4-dihydropyridine (250) in ethyl methyl ketone in the presence of anhydrous potassium carbonate for 5 hrs to obtain the hybrid molecule (251).

7-(3-Chloropropyl)-1,3-dimethylxanthine (249) was prepared by treating theophylline (66) with 1-bromo-3-
chloropropane in dimethylformamide in the presence of anhydrous potassium carbonate at 70-80°C for 3 h. The structure of the compound 251 was confirmed using spectral analyses.

8-Substituted-1,3-dimethylxanthines

As a part of the research programme, some more 8-(substituted)phenylxanthine derivatives were prepared by incorporating different substituents to study the structure-activity relationship. For this, vanillin was treated with chloroethanol and chloroacetonitrile in ethyl methyl ketone in the presence of potassium carbonate under anhydrous conditions to obtain corresponding derivatives 252 and 253. These aldehydes 252 and 253 were then condensed with 5,6-diamino-1,3-dimethyluracil (124) in MeOH-AcOH (4:1) at room temperature to obtain Schiff bases 254 and 255, respectively. The completion of the reaction was monitored by thin layer chromatography. Cyclization of these intermediates by refluxing in thionyl chloride afforded the desired 8-substituted derivatives 256 and 257. Infrared band at 3480 cm\(^{-1}\) for -OH group was observed for compound 256. Unfortunately infrared spectroscopy did not help much in detecting C\(\equiv\)N stretching for cyano derivative 257. Peaks for -CH\(_2\)OH and -CH\(_2\)CN appeared at \(\delta\) 4.45 and \(\delta\) 5.05 in the NMR.
spectra of 256 and 257, respectively, which were fully consistent with the proposed structures. 7-Methylation was also carried out by heating 256 and 257 with methyl iodide in DMF under anhydrous conditions in the presence of potassium carbonate at 70-80°C to obtain 1,3,7-trimethylxanthines 258 and 259. Spectral data of the compounds was consistent with the proposed structures as detailed in the experimental section. The structure of 259 was further confirmed using $^{13}$C NMR spectroscopy as it again failed to give any peak for nitrile group in infrared spectrum.

Similarly cyano derivative was also prepared in 3-hydroxybenzaldehyde series by treating the aldehyde with chloroacetonitrile to afford 260 as explained earlier. Condensation with diaminouracil 124 and subsequent ring closure of the
**RESUME AND DISCUSSION**

Table II

<table>
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<th>COMPOUND NO.</th>
<th>CODE</th>
<th>% INHIBITION (n=6)</th>
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<td></td>
<td><strong>cGMP PDE ACTIVITY</strong></td>
<td></td>
</tr>
<tr>
<td>174</td>
<td>RG-DPJ-63</td>
<td>20 ± 35%</td>
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<tr>
<td></td>
<td><strong>cAMP PDE ACTIVITY</strong></td>
<td></td>
</tr>
<tr>
<td>174</td>
<td>RG-DPJ-63</td>
<td>28 ± 9%</td>
</tr>
<tr>
<td>140</td>
<td>RG-24</td>
<td>26 ± 10%</td>
</tr>
<tr>
<td>141</td>
<td>RG-26</td>
<td>22 ± 10%</td>
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<tr>
<td>187</td>
<td>RG-DPJ-51</td>
<td>24 ± 12%</td>
</tr>
<tr>
<td>210</td>
<td>RG-DPJ-57</td>
<td>24 ± 9%</td>
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</tbody>
</table>

**Smooth muscle relaxant activity**

Smooth muscle relaxant activity of compounds 141 (RG-DPJ-26), 187 (RG-DPJ-51) and 210 (RG-DPJ-57) was studied using guinea-pig ileum preparations pre-contracted with histamine (10 μM). The % relaxation at 100 μM is given in Table III.

Table III

<table>
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<tr>
<th>COMPOUND NO.</th>
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<th>% INHIBITION (n=4)</th>
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<td>141</td>
<td>RG-26</td>
<td>82 ± 8%</td>
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<tr>
<td>187</td>
<td>RG-DPJ-51</td>
<td>37 ± 7%</td>
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<tr>
<td>210</td>
<td>RG-DPJ-57</td>
<td>75 ± 7%</td>
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<td></td>
<td>Rolipram</td>
<td>47 ± 13%</td>
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The detailed pharmacological studies of some of the potent compounds are in progress.