PHARMACOLOGY
Pain is a sensation produced by some external agents which may menace the integrity of the normal tissue. By the way, pain saves the organism by informing it in time of disordered condition. Though pain is pinching but it is life saving guardian of protoplasm.

The two principle types of pains are:

(i) Superficial pain and
(ii) Deep pain.

The superficial or cutaneous pain is sharp, intense and sudden, such as due to pin pricks, burns etc. The deep or visceral pain is denoted by a pulling, deep aching quality, such as colic, cardiac etc.

If we can prevent the pain message from reaching the brain or if we temporarily "knock out" the perception mechanism, there will be no feeling of pain. This is what anaesthesia does.

The term anaesthesia is derived from greek word which means, "without perception."

According to the site of application, anaesthetics can be classified into two parts:
General anaesthetics are those which depress the central nervous system to such an extent that all the sensitivity to pain is lost, while definite local regions may be anaesthetised without affecting other parts of nervous system by local anaesthetics. However, analgesics and hypnotics, partly cause insensitivity to pain and loss of consciousness and vice versa, minor dose of certain anaesthetics cause analgesic and hypnotic effects.

Local anaesthetics are capable of blocking nerve conduction when applied locally to nerve tissue in effective concentration. They produce localized insensitivity to pain without causing loss of consciousness. History and discovery of local anaesthetics is no less interesting. Somewhere in the 16th century, Pizzaro found that Andean Indians were accustomed to chew leaves of coca plant which resulted in insensitivity of fatigue. So the first local anaesthetic was cocaine (I). Losses determined its correct molecular formula and showed its structure as benzoyl methyl eegonine. He also described its local anaesthetic properties. Koller, after repeated experiments in 1884, introduced the first practical local anaesthetic-cocaine into therapeutics. Further development then started quickly.
Chemical alteration of cocaine includes principally alteration of carbomethoxy, benzoyloxy and the N-methyl group and in addition, modification of the tropane skeleton.

(i) Alteration of carbomethoxy group does not prove beneficial over cocaine itself.  

(ii) Alteration of benzoyloxy group inactivates the molecule.  

(iii) Alternate of N-methyl group by demethylation increases activity with highly toxic effect. However sometimes active compounds were obtained.  

(iv) Alteration of the tropane skeleton gives simpler compounds like α-eucaine (II) and β-eucaine (III).
So from the above experiments, it has been concluded that neither the configuration nor the structure of this natural product is a specific requirement for the bio-chemical effect. So experiments showed that the phenyl group can be connected to the amino group by either ester, amide, anilide, urethane, ureide, ketone or ether linkage to give different classes of the compounds with local anaesthetic properties.

Group 1: Ester

\[
R \quad \text{CONH(CH}_2\text{)}_nN<
\]

Group 2: Amide
Group 3: Urethane

Group 4: Ureide

Group 5: Anilide

Group 6: Ketone

Group 7: Ether

Group 8: Miscellaneous
Applying the principles of molecular modification the parts of molecule were jointly altered and valuable compounds were found in the process.

Requirements for an ideal local anaesthetic:

(i) Potent and effective in low concentration so that it does not injure body tissue.
(ii) Must be water soluble and should not decompose on boiling.
(iii) Have no toxic effect.
(iv) Must be nonirritant.
(v) Must have good penetration power.
(vi) Duration of action must be long enough and reversible.
(vii) If at all toxic effect is caused by undue absorption, a suitable antidote must be available.
(viii) It should be free of side effects like addiction and central stimulation.

Mode of action of local anaesthetics:

The application of a local anaesthetic to a nerve that is actively conducting impulses will result in elevation of the threshold for electrical excitement, reduction in the rate of rise of the action potential, slowing of the propagation of the impulse and if the drug concentration is sufficiently high complete block of conduction.
Classification of local anaesthetics:

They can be classified according to
1. Clinical use.
2. According to site of action.
3. According to functional groups.

Local anaesthetics are either esters or amides. They consist of an aromatic portion, an intermediate chain and an amine portion. The aromatic portion confers lipophilic properties to the molecule whereas the amine portion is hydrophilic. The ester and amide components of the molecule determines the characteristics of metabolic degradation. The esters are mostly hydrolysed in the plasma by pseudocholinesterase, where the amides are destroyed largely in the liver.

Classification according to functional groups.

Group 1. Esters of benzoic acid:

e.g. Tetracaine (IV), Cocaine, Piperocaine, Hexylcaine, Ethylaminobenzoate, Butacaine

\[
\text{COOCH}_2\text{CH}_2\text{N(CH}_3\text{)}_2\text{HCl}
\]

\[
\begin{array}{c}
\text{NH}_2
\\
\text{C}_4\text{H}_9
\end{array}
\]

Tetracaine (IV)
Group 2. Esters of PABA:
e.g. Procaine (V), Butathamine, Chloroprocaine, Properacaine

\[
\text{\textbf{COOCCH}_2\text{C}_3\text{N(C}_2\text{H}_5\text{)}_2}
\]

\[
\text{\textbf{NH}_2}
\]

\textbf{Procaine (V)}

Group 3. Esters of meta-aminobenzoic acid:
e.g. Cyclomathylacaine, Metabutoxycaaine

Group 4. N-Alkoxy xylidides and Toluidides:
e.g. Lignocaine (VI), Prilocaine, Butanilicaine, Mepivacaine, Bupivacaine

\[
\text{\textbf{NHCOCH}_2\text{N(C}_2\text{H}_5\text{)}_2}
\]

\[
\text{\textbf{HC-C\text{H}_3}}
\]

\textbf{Lignocaine (VI)}

Group 5. Urethane and urea derivatives:
e.g. Carbocaine (VII)

\[
\text{\textbf{COOCCH}_2\text{CH}_2\text{N(C}_2\text{H}_5\text{)}_2}
\]

\textbf{Carbocaine (VII)}
Group 6. Alkyl and aminoalkyl ethers:
e.g. Dimethiosoquin (VIII)

\[
\text{\text{C}_4\text{H}_9} \\
\text{OCH}_2\text{CH}_2\text{N(CH}_3)_2
\]

(VIII)

Group 7. Aminoalkylketones:
e.g. Diclone (IX)

\[
\text{COCH}_2\text{CH}_2\text{N} \\
\text{OC}_4\text{H}_9
\]

(IX)

Group 8. Amidines and Guanidines:
e.g. Holocaine (X)

\[
\text{CH}_3 \\
\text{N=CNH} \\
\text{OC}_2\text{H}_5 \\
\text{OC}_2\text{H}_5
\]

(X)
Group 9. Miscellaneous drugs with local action:
Clove oil, phenol, chlorpromazine, certain antihistaminics like diphenhydramine. Other synthetic non-nitrogenous compounds are benzyl alcohol, propanediol etc.
DIURETICS:

The kidney is not just a simple excretory organ but it plays an important role in regulating the volume and the composition of the body fluids. The functional unit of the kidney is termed as the nephron. Drugs can modify the renal functions either indirectly by modifying its circulation or directly by affecting the nephron function. Most of the therapeutically useful agents acts mainly by modifying various functions of the nephron.

Drugs which increase the rate of urine formation are called diuretics.

Classification of diuretics:

I Weak diuretics

(a) Osmotic diuretics.

(i) Electrolytes e.g. sodium and potassium salts.

(ii) Nonelectrolytes e.g. mannitol, isosorbide, sucrose and urea.

(b) Acidifying salts such as ammonium chloride and arginine hydrochloride.

(c) Xanthine derivative e.g. aminophylline.

(d) Carbonic anhydrase inhibitor e.g. acetazolamide.
II Moderately effective diuretics
e.g. Benzothiadiazine compounds, chlorthalidone, chloroxolone and clopamide.

III Very potent diuretics e.g. parenteral organic mercurial compounds, furosemide, mefruside, bumetamide and ethacrynic acid.

IV Potassium retaining diuretics e.g. triameterene and amiloride.

Water: Water, given in excess, can act as a physiological diuretic. It also helps to increase the clearance of substances like urea and various drug metabolites which irritate the urinary tract.

(a) Osmotic diuretics:
(i) Sodium chloride: It is effective at dose of more than 10gm.
(ii) Sodium bicarbonate: It is sometimes used to produce alkaline urine.
(iii) Sodium sulfate: Only if given intravenously it can act as a diuretic.
(iv) Potassium salts: It diminishes the hydrogen ion exchange with sodium, thus decrease in hydrogen ion concentration of the urine, making it alkaline.
(v) Mannitol: It is a sugar (polyhydroxy aliphatic alcohol) which, when injected intravenously is not metabolised and is rapidly filtered.

(b) Acidifying salts:

(1) Ammonium chloride: It is given orally.

(c) Xanthines:

The diuretic properties of the methylated xanthines, theophylline and caffeine has been known and employed clinically since later half of nineteenth century. But compared to more recent potent diuretics, these are moderate in action. Of the xanthines, theophylline has been applied most extensively since it is most active and produces the least central nervous system stimulation.

Destennvsn tried to improve xanthines activity by structural modification. These investigations have led to discovery of active heterocyclic compounds that have clinical application.

Two heterocyclic system (i) Pyrimindines and (ii) imidazoles constitute the bicyclic xanthines, has been studied for diuretic properties.
1,3-Disubstituted-6-aminouracil (XI) are key intermediates for xanthines. In 1951, Papesch and Schroeder\textsuperscript{7} reported that a series of 1,3-disubstituted-6-aminouracil produced strong diuresis in rats and dogs comparable with that of theophylline. Further research by them led to the clinical utility of aminometradine (XII) and amisometradine(XIII). They showed diuretic activity but they caused gastro-intestinal irritation.

\[
\text{XI} \quad \text{XII} \quad \text{XIII}
\]

Carbonic anhydrase inhibitors:

Acetazolamide (XIV) : It was studied in detail by Marčan\textsuperscript{8} and et al. By increasing the number of carbon atoms in the acyl group increased diuretic activity as well as side effects. Removal of the acyl group leads to loss in activity in-vitro (Ford et al.).
By methylation of acetazolamide two isomeric products were active.

By methylation of acetazolamide two isomeric products were active.

\[
\begin{align*}
\text{H}_3\text{C} & \text{COHN} \quad \text{SO}_2\text{NH}_2 \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{L} \\
\text{C} & \quad \text{C} \\
\text{OH} & \quad \text{N} \\
\end{align*}
\]

\[\text{XIV}\]

Benzothiadiazines:

\[
\begin{align*}
\text{R}_4 & \quad \text{R}_5 \\
\text{N} & \quad \text{N} \\
\text{R}_3 & \quad \text{R}_2 \\
\text{H}_2\text{NOS} & \quad \text{SO}_2 \quad \text{N} \\
\end{align*}
\]

Benzothiadiazine nucleus (XV)

Introduction of thiazide diuretics revolutionized the oral diuretic therapy, since before chlorothiazide, no effective and reliable oral diuretic was available.

Chlorothiazide (XVI) was the first member of this class to be studied extensively. Bayer showed that upon administration of chlorothiazide, there was 35 fold increase in the sodium ion excretion, 25 fold increase in the chloride ion excretion and 3.8 fold increase in the potassium ion excretion. Urinary pH increased from 6 to 8 which was interpreted as increase of bicarbonate ion in urine.
Structure activity relationship in this class has been reviewed by Bayer et al., and Maren and Wiley.

Chlorothiazide is chemically 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide.

There are some other sulfonamide diuretics that differ chemically from thiazides by the nature of the heterocyclic ring, however, their pharmacological actions are similar.

Ethacrynic acid: Unsaturated ketone derivative of phenoxyacetic acid were synthesized by Schultz et al., in 1962 (XVII). Its activity depends on (1) methylene group, adjacent to the carbonyl carbon and (2) substituents in the aromatic ring.
Frusemide (Furosemide): It is a potent, oral non-mercurial diuretic possessing a halogenated sulfamoylbenzene ring common to thiazide diuretics (XVIII).

\[ \text{Frusemide (XVIII)} \]

Bumetanide: Feit \(^{12}\) investigated the diuretic activity of 3-amino-5-sulfamoylbenzoic acid derivatives. They synthesized 3-butylamino-4-phenoxy-5-sulfamoylbenzoic acid which was more active than other derivatives. Other diuretics in this class are Indapamide, Piretanide, Triflocin and Basunide.

Potassium retaining diuretics:

Spironolactone: This is a commonly employed aldosterone antagonist. Spironolactone is a steroid with structural similarity to aldosterone. Cella et al.\(^{13}\) reported the structure activity relationship of a series of spirolactones(XIX)
Spirolactone (XIX)

Triamterene: This drug is chemically different from thiazides. Wiebelhaus\textsuperscript{14} showed that triametrine (XX) caused diuresis without $K^+$ loss. Another drug in this class is Amiloride (XXI).

Triamterene (XX)
Natural products which are used as diuretics are Betula Alba (Leclerc\textsuperscript{15}), Mikania Hirustissima (Gomer\textsuperscript{16}), Cox Lacryma Jobe (Tashima\textsuperscript{17}), Othosiphon Stamines (Fieser\textsuperscript{18}) and Digitalus Purpurea.
ANTIDIABETIC DRUGS:

Diabetes mellitus is usually defined as chronic disorder of carbohydrate metabolism characterised by hyperglycaemia and glycosourea. It is caused to due to insufficient secretion of the hormone insulin by pancreas. Insulin regulates several metabolic and anabolic processes and consequently lowers the blood sugar level due to the following phenomena.

(1) Conversion of carbohydrates to glycogen and its storage in the lever and skeletal muscles is regulated by insulin.
(2) The utilisation of glucose is accelerated.
(3) The syntheses of proteins and fats is promoted.

Insulin:
Insulin is a polypeptide with a molecular weight of about 6000, consisting two amino acid chains, A and B, linked by two disulfide bridges. The chains contain 21 and 30 amino acids respectively, all in a known sequence. The "active Centre" of insulin has not been identified but the disulfide bridges are essential for its biological activity. Insulin has now been completely synthesized in the laboratory. The present supplies of insulin are, however, obtained from animal sources, mainly the pancreas of cattle. Beef and pig insulin are structurally similar to human insulin in all except a few amino acid residues.
The major drawback of insulin is its ineffectiveness when given orally. Hence, the search was continued for an orally effective agent for the treatment of diabetes mellitus. Synthalin A, a biguanide, was the earliest oral hypoglyemic agent to be used in therapy but was found to be too toxic. It is now of historical interest. A chance observation by Janbon et al., led to the discovery of hypoglycemic action of sulfonamides. This was confirmed by Frank and Fuchs, who observed the blood sugar lowering action of carbutamide a sulfonamide, during its trial in infectious diseases. Since then, many sulfonylurea compounds have been introduced as successful oral anti-diabetic agents.

Chiefly following three classes of compounds are important as oral hypoglycemic agents.

1. Sulfonylureas
2. Biguanides
3. Miscellaneous

Sulfonylureas: These compounds are chemically related to sulfonamides and have basic structure as follows,

\[ R_1-\text{SO}_2\text{NHCONH}R_2 \]

General structure of sulfonylureas.
Janbon et al. reported that a potential antithyroid compound, 5-isopropyl-2-sulfanilamide-1,3,4-thiadiazole (XXII) produced marked hypoglycemia in man.

\[
\begin{align*}
\text{XXII} \\
(\text{H}_2\text{C})\text{HC} & \text{N} \text{NH}_2 \\
\text{S} & \text{SO}_2 \\
\end{align*}
\]

The study of structure-activity relationship revealed that when the alkyl group attached to urea, in simple chain of three or four carbon atoms peak activity was found e.g. Chlorpropamide and to Tolbutamide. Substitution in para position i.e. direct attachment to the ring increased the activity e.g. Chlorpropamide is more active than Carbutamide.

In Europe, Glycodiazine (XXIII) is used which is sulphonyl derivative of cyclic guanidine.

\[
\begin{align*}
\text{XXIII} \\
\text{SO}_2\text{NH} & \text{N} \text{OCH}_2\text{CH}_2\text{OCH}_3 \\
\end{align*}
\]
While the corresponding open chain sulphonyl guanidine does not possess hypoglycemic activity (Gutsche\textsuperscript{21}).

The detail study on a large group of sulphonylurea derivatives 1-[4-(2-methoxy-5-chlorobenzamido) ethyl]-benzenesulphonyl-3-cyclohexylurea, glibenclamide (XXIV) (Aumullar\textsuperscript{22}).

Frank and Fuchs introduced 1-butyl-3-sulphanilylurea (XXV) known as carbutamide. It was quite potent but too toxic. A large number of arylsulphonamides, N-arylsulphonylcarbamates and substituted sulphonylureas were clinically tested, out of hundreds of compounds, only two drugs chloropropamide (XXVI) and tolbutamide (XXVII) are clinically used.

\[
\text{XXIV}
\]

\[
\text{XXV}
\]
These two drugs are still in current usage as they do not contain an amino group, attached to the benzene ring, unlike carbutamide, which is responsible for antibacterial and bone marrow depressant.

Similarly many hypoglycemic sulphonylureas (Wiseman), N-sulphamylcarbamates (McFarland) and sulphamylsemicarbazides (Mcmannus) were studied.

Cycloheptamide had not shown significant therapeutic advantage (Balodimos et al.). Potent compounds were obtained from these, were obtained from these, were as active as chloropropamide. 1-Cycloheptyl-3-(4,4-dimethyl-piperidine-sulphamyl) urea (XXVIII) was quite active.
By modifying tolbutamide, a compound possessing twice the activity of tolbutamide was found namely p-acetobenzenesulphonyl-3-cyclohexylurea (XXIX) (Marshall).  

\[ \text{SO}_2\text{NHCONH-COCH}_3 \]

Grinnell found a compound glyhexamide (XXX) which was found to be as potent as tolbutamide.

\[ \text{SO}_2\text{NHCONH-COMe} \]

The principle mechanism of hypoglycemic activity of sulphonylurea is stimulation of insulin release by the beta-cells of the pancreas (Duncan).

2. Biguanides: The general chemical structures of biguanides(XXXI) is as follows:

\[ \text{R}_1 > \text{N-C-NH-C-NH}_2 \]

\[ \text{R}_2 \text{NH} \quad \text{NH} \]

XXXI
Earlier it was reported that on administration of guanidine(XXXII) lowered the blood sugar concentration.

\[
\begin{align*}
\text{NH}_2 & \\
_2N - C - \text{NH}_2 & \\
\text{XXXII}
\end{align*}
\]

But as guanidine was found to be very toxic, particularly to the liver, attempts were made to prepare compounds having less toxicity. Two notable compounds were prepared namely synthalin A and synthalin B (XXXIII)

\[
\begin{align*}
\text{H}_2\text{NCH}_2\text{N(C}_2\text{H}_2)\text{NH}_2 & \\
\text{H}_2\text{N} & \\
\text{NH}_2 & \\
\text{XXXIII}
\end{align*}
\]

synthalin A: n=10  
synthalin B: n=12

These compounds may be put in the group of diguanides instead of biguanides, as there is slight difference in the chemical structure between the two groups.

The diguanides are the combination of two molecules of guanidines while, biguanides are obtained by combination of two molecules of guanidine but with elimination of ammonia.

After the failure of diguanides, as these compounds were highly toxic to the liver and kidney, this group came up with the discovery of phenylethyl biguanides i.e. phenformin, after testing several mono and disubstituted
alkyl or arylalkyl derivatives of formamidinyliminourea, (Shapiro) (XXXIV). From the same study another important compound was reported namely dimethylbiguanide i.e. Metformin (Sterne).

\[
\begin{align*}
\text{XXXIV}
\end{align*}
\]

A series of S-triazenes were synthesized, but found to possess very weak activity e.g. 2-phenylethylamino-4,6-diamino-S-triazene (XXXV).

\[
\begin{align*}
\text{XXXV}
\end{align*}
\]

3. Miscellaneous hypoglycemic agents: Heterocyclic compounds like isoxazole and pyrazole derivatives also possess hypoglycemic activity e.g. 5-carboxyl-3-methylisoxazole (XXXVI).

\[
\begin{align*}
\text{XXXVI}
\end{align*}
\]
The only active metabolite found in the pyrazolones was 5-methyl-3-pyrazolecarboxylic acid (XXXVII), but these compounds i.e. both isoxazole and pyrazole cannot lower the blood sugar.

![XXXVII]

A series of observations has drawn attention to naphthyl acetic acid nucleus as a potential hypoglycemic activity (Goppi\textsuperscript{31}) e.g. 2,2-bis(3-dimethylaminoxopropyl)-1-naphtyl-acetic acid is as active as chlorpropamide (XXXVIII)

![XXXVIII]

Indole-2-carboxylic acids are a new class of hypoglycemic compounds, effective in alloxan-diabetic mouse, the detail study of 5-methoxyindole-2-carboxylic acid was carried out by Bauman.\textsuperscript{32} Among some new orally active hypoglycemic heterocyclic compounds, indenopyrrole derivatives are found
to be as potent as tolbutamide (Lahiri 33 ) e.g. 3a,8,8a-
hexahydro-2-butyl-5,6-dimethoxyindeno-(1,2-c)-pyrrole
(XXXIX).

\[
\begin{array}{c}
\text{H}_3\text{C-} \\
\text{H}_3\text{C-} \\
\text{N-CH}_2\text{CH}_2\text{CH}_2\text{CH}_3
\end{array}
\]

(XXXIX)

Chernykh et al., reported hypoglycemic and diuretic,
activity of benzothiazolyl-2-oxamic acid derivatives (XL)

\[
\begin{array}{c}
\text{R-NHCOCOCH}_2\text{R}
\end{array}
\]

(XL)

Chernykh et al., also reported hypoglycemic activity of
N-substituted-5-alkyl-1,3,4-thiadiazolyl-2- oxamic acid and
amides (XLI).

\[
\begin{array}{c}
\text{R-NHCOCOCH}_2\text{R}
\end{array}
\]

(XLI)
A series of aryl (heteryl) amides of 2-amino-1,3,4-thiadiazole-5-sulphonyloxamic acid derivatives (XLII) was synthesized and its biological activity was studied by Chernykh et al.\textsuperscript{36}, and found to possess hypoglycemic activity.

![Chemical structure of XLII]

N-o-Carboxylphenylamides of N-arenesulphonyl-hydrazides of oxalic acid (XLIII) possessing diuretic activity had been reported by Chernykh\textsuperscript{37}.

![Chemical structure of XLIII]

Petyunin et al., has reported a series of arenesulphonylurea and arenesulphonyloxamides having general formula (XLIV) with sugar reducing activity.

\[ p-RNHCONHC_6H_4SO_2NHCOCO_2Et \]
Local anaesthetic activity (conduction anaesthesia) in mice:

Method:

Adult albino mice of either sex weighing 20-25gm in group of 6 were used for the experiment. A small artery clip with its blades covered by a rubber tube was applied to the root of the tail. These animals received 0.1ml of 2% drug subcutaneously about 1cm from the root of the tail.

After 15 minutes the artery clip was applied to the tail near the site of injection and the insensitivity of the animal to this noxious stimulus was taken as the response. They were tested every 30 minutes till normal pain reflex returned. The results were compared with lignocaine (Bianchi).

The result are reported in the Table 1 to 3.
Diuretic activity:

Method:

Male albino rats, weighing 140 to 200gm, were maintained in an airconditioned room at a temperature of 23±1°C and were kept on a standard pellet diet and water and libitum. Food was withdrawn 16 hours before the experiment and water was withdrawn during the test period. They were given 25ml/kg of 0.9% sodium chloride solution, 18 hours prior to the experiment. The rats were divided in groups of 4 animals each. On the day of experiment one group of 4 animals served as control while, the remaining rats were given orally 25ml/kg of distilled water containing different amount of drugs in a suspension (0.5% gum arabic). Urine sample is collected for 5 hours. From the data obtained diuretic activity is calculated.

\[
\text{Diuretic Activity} = \frac{\text{Urine excreted per 1000 gm body weight in test group}}{\text{Urine excreted per 1000 gm body weight in control.}}
\]

The results are reported in the Tables 4 to 6.
Hypoglycemic activity:

Method:

Male rats weighing 120gm to 150gm are fasted overnight. Drugs under test are suspended in 1% C.M.C. and are administered orally. Samples of blood are taken from the vein at 2 and 4 hours after drug administration and analysed for glucose. One group served as control.

Blood glucose is determined by enzymatic method. A comparison between the effects of the test compound and control suggests the presence or absence of hypoglycemic effects. (Hoffelt and Johnson).

The result are reported in Tables 7 to 9.
Anaesthetic activity of 2-N'(p-bromobenzenesulphonyl)-oxamoylhydrazinocarbonyl-4-ketoquinazoline with substitution in position '3' and '6'.

```
<table>
<thead>
<tr>
<th>Substitution</th>
<th>Dose</th>
<th>%Activity 30minutes</th>
<th>%Activity 1 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 R=-H</td>
<td>0.1ml</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>X=-H</td>
<td></td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>2 R=-COCH₃</td>
<td>0.1ml</td>
<td>8.5</td>
<td>8.5</td>
</tr>
<tr>
<td>X=-H</td>
<td></td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>3 R=-SO₂C₆H₄CH₃-Br</td>
<td>0.1ml</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>X=-H</td>
<td></td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>4 R=-H</td>
<td>0.1ml</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>X=-Br</td>
<td></td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>
```
TABLE-2

Anaesthetic activity of 2-N-(p-chlorobenzenesulphonyl)-oxamoylhydrazinocarbonyl-4-ketoquinazoline with substitution in position '3' and '6'.

\[
\begin{align*}
\text{Substitution} & \quad \text{Dose} \quad \% \text{Activity} \quad \% \text{Activity} \\
1 & \quad R=-H, X=-H \quad 0.1 \text{ml} \quad 16 \quad 16 \\
2 & \quad R=-\text{SO}_2C_6H_4\text{CH}_3-, X=-H \quad 0.1 \text{ml} \quad 10 \quad 10 \\
3 & \quad R=-H, X=-\text{Br} \quad 0.1 \text{ml} \quad 15 \quad 15 \\
\end{align*}
\]
TABLE-3

Anaesthetic activity of 2-N'-(p-tolunesulphonyl)-oxamoyl -
hydrazinocarbonyl-4-ketoquinazoline with substitution in
position '3' and '6'.

\[
\begin{align*}
\text{Substitution} & & \text{Dose} & & \% \text{Activity} & & \% \text{Activity} \\
& & \text{mg/kg.} & & \text{30 minutes} & & \text{1 hour} \\
1 & R=-H & 0.1\text{ml} & 5 & 5 \\
& X=-H & & 2\% \\
2 & R=-\text{COCH}_3 & 0.1\text{ml} & 6.5 & 6.5 \\
& X=-H & & 2\% \\
3 & R=-\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3-p & 0.1\text{ml} & 4 & 4 \\
& X=-H & & 2\% \\
4 & R=-H & 0.1\text{ml} & 4.5 & 4.5 \\
& X=-\text{Br} & & 2\% \\
\end{align*}
\]
TABLE-4

Diuretic activity of 2-N-(p-bromobenzenesulphonyl)-oxamoyl-hydrazinocarbonyl-4-ketoquinazoline with substitution in position '3' and '6'

![Chemical Structure]

<table>
<thead>
<tr>
<th>Substitution</th>
<th>Dose mg/kg P.O.</th>
<th>Diuretic activity Compared to control gr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 R=-H X=-H</td>
<td>50</td>
<td>0.9</td>
</tr>
<tr>
<td>2 R=-COCH X=-H</td>
<td>50</td>
<td>0.81</td>
</tr>
<tr>
<td>3 R=-SO₂C₆H₄CH₃·P X=-H</td>
<td>50</td>
<td>1.0</td>
</tr>
<tr>
<td>4 R=-H X=-Br</td>
<td>50</td>
<td>1.0</td>
</tr>
</tbody>
</table>
**TABLE-5**

Diuretic activity of 2-N-(p-chlorobenzenesulphonyl)-oxamoyl-hydrazinocarbonyl-4-ketoquinazoline with substitution in position '3' and '6'.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Substitution</th>
<th>Dose mg/kg P.O.</th>
<th>Diuretic activity compared to control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 R=-H</td>
<td>50</td>
<td>0.9</td>
</tr>
<tr>
<td>X=-H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 R=-COCH₃</td>
<td>50</td>
<td>1.1</td>
</tr>
<tr>
<td>X=-H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 R=-SO₂C₆H₄CH₃-p</td>
<td>50</td>
<td>0.89</td>
</tr>
<tr>
<td>X=-H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 R=-H</td>
<td>50</td>
<td>1.08</td>
</tr>
<tr>
<td>X=-Br</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE-6

Diuretic activity of 2-N\textsuperscript{-1}(p-toluenesulphonyl)oxamoyl-hydrazinocarbonyl-4-ketoquinazoline with substitution in position '3' and '6'.

\[
\text{\begin{tabular}{lccc}
\text{Substitution} & \text{Dose} & \text{Diuretic activity compared to control group.} \\
1 & R=-H & 50 & 1.0 \\
& X=-H & & \\
2 & R=-\text{COCH}_3 & 50 & 1.24 \\
& X=-H & & \\
3 & R=-\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3-p & 50 & 1.5 \\
& X=-H & & \\
4 & R=-\text{H} & 50 & 1.21 \\
& X=-\text{Br} & & \\
\end{tabular}}
\]
Hypoglycemic activity of 2-N-(p-bromobenzenesulphonyl)-
oxamoylhazinocarbonyl-4-ketoquinazoline with substitution 
in position '3' and '6'.

![Chemical Structure]

<table>
<thead>
<tr>
<th>Substitution</th>
<th>Dose (mg/kg P.O.)</th>
<th>Initial blood glucose (mg %)</th>
<th>Blood glucose after 2 hrs. 4hrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 R=-H X=-H</td>
<td>500</td>
<td>47.0</td>
<td>40.0 40</td>
</tr>
<tr>
<td>2 R=COCH₃ X=-H</td>
<td>500</td>
<td>58.0</td>
<td>55.0 50.5</td>
</tr>
<tr>
<td>3 R=SO₂C₆H₄CH₃-p X=-H</td>
<td>500</td>
<td>63.95</td>
<td>60.0 60.1</td>
</tr>
<tr>
<td>4 R=-H X=-Br</td>
<td>500</td>
<td>50.5</td>
<td>48 46.5</td>
</tr>
</tbody>
</table>
Hypoglycemic activity of 2-N-(p-chlorobenzenesulphonyl)-oxamoylhydrazinocarbonyl-4-ketoquinazoline with substitution in position '3' and '6'.

![Chemical structure](image)

**TABLE-8**

<table>
<thead>
<tr>
<th>Substitution</th>
<th>Dose mg/kg P.O.</th>
<th>Initial Blood glucose (mg%) after 2 hrs. 4hrs. Blood Glucose (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 R=-H X=-H</td>
<td>500</td>
<td>58.95 56.0 52.0</td>
</tr>
<tr>
<td>2 R=COCH X=-H</td>
<td>500</td>
<td>58.95 55.0 53.95</td>
</tr>
<tr>
<td>3 R=SO_2CH_2CH_p X=-H</td>
<td>500</td>
<td>60.75 58.65 56.85</td>
</tr>
<tr>
<td>4 R=H X=-Br</td>
<td>500</td>
<td>58.89 57.0 55.75</td>
</tr>
</tbody>
</table>
Hypoglycemic activity of 2-N-(p-toluenesulphonyl)-oxamoyl-hydrazinocarbonyl-4-ketoquinazoline with substitution in position '3' and '6'.

\[
\begin{align*}
&\text{Substitution} & \text{Dose mg/kg P.O.} & \text{Initial blood glucose (mg %)} & \text{Blood Glucose (mg %) after 2 hrs. 4hrs.} \\
1 & R=-H, X=-H & 500 & 77.65 & 70.0 \quad 70.0 \\
2 & R=-\text{COCH}_3, X=-H & 500 & 64.95 & 83.3 \quad 101.8 \\
3 & R=-\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3-p, X=-H & 500 & 75.85 & 70.5 \quad 70.5 \\
4 & R=-H, X=-\text{Br} & 500 & 65.0 & 62.0 \quad 60.7 \\
\end{align*}
\]
REFERENCES:

22 W. Aumullar et al., ibid, 16, 1640 (1966).
24 J.M. Mcfarland et al., ibid, 8, 781 (1965).
34 Chernykh et al., Khim Farm. Zh., 5, 43-6, (Russ) (1985).