APPENDIX
The methods described in literature for the preparation of N-arylanthranilic acids, N-benzylanthranilic acids, 2-anilinononicotinic acids, 1-substituted isatoic anhydrides and 1-substituted quinazolin-4-ones are outlined here.

**N-Arylanthranilic acids**

N-Arylanthranilic acids are usually prepared by the Ullmann reaction. A large number of N-phenylanthranilic acid derivatives synthesised by this method have been used as intermediates in the synthesis of 9-chloroacridines\(^1\). The latter have been employed in the preparation of a variety of chemotherapeutic agents.

The following examples cited from literature will show the various conditions under which N-arylanthranilic acids have been obtained employing the Ullmann reaction.

\[
\text{N-(α,α,α-Trifluoro-m-tolyl)anthranilic acid (I, } R^1 = R^3 = R^4 = H, \quad R^2 = CF_3) \text{ was prepared by Wilkinson and Finar}^2 \text{ by the condensation of } \\
\text{o-iodobenzoic acid, dissolved in a solution of potassium carbonate in water, with } m\text{-aminobenzotrifluoride in the presence of copper-bronze as the catalyst.}
\]

![Chemical structure](image)
Scherrer treated the potassium salt of 2-bromobenzoic acid with 2,3-dimethylaniline in the presence of cupric acetate, N-ethylmorpholine and diglyme to obtain N-(2,3-xylyl)anthranilic acid (I, $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$).

Hirano and Masuda employed amylalcohol as solvent in the condensation of o-chlorobenzoic acid with 4-methylsulphonylaniline to obtain N-(4-methylsulphonylphenyl)anthranilic acid (I, $R^1 = R^2 = R^4 = H$, $R^3 = SO_2CH_3$).

N-(2,6-Dichlorophenyl)anthranilic acid was prepared by Levai et al by the reaction of 2,6-dichloro-1-bromobenzene with anthranilic acid using isoamyl alcohol as the solvent and copper oxide as the catalyst (I, $R^1 = R^4 = Cl$, $R^2 = R^3 = H$).

Soda and coworkers synthesised 5-trifluoromethyldiphenylamine-2,2'-dicarboxylic acid (II) by reacting 4-trifluoromethyl-2-aminobenzoic acid with 2-chlorobenzoic acid in the presence of isoamylalcohol and powdered copper.

All these compounds have been claimed as possessing antiinflammatory activity.
N-Benzylanthranilic acid derivatives

N-Benzylanthranilic acid (III, $R^1 = R^2 = H$) has been prepared by Houben and Brassert by reacting benzyl chloride with anthranilic acid in the presence of aqueous potassium carbonate solution.

\[
\text{III}
\]

N-(4-Chlorobenzyl)anthranilic acid (III, $R^1 = H$, $R^2 = \text{Cl}$) has been prepared by the reaction of anthranilic acid, dissolved in aqueous sodium hydroxide solution, with 4-chlorobenzyl chloride.

N-Benzyl-4-chloroanthranilic acid (III, $R^1 = \text{Cl}$, $R^2 = H$) has been obtained by heating for 6 hr a mixture of methyl-4-chloroanthranilate, benzyl chloride and sodium acetate at 150°. The ester so obtained furnished the required acid upon hydrolysis.

Scarborough et al. reacted p-chlorobenzaldehyde with 5-chloroanthranilic acid to obtain 5-chloro-N-(p-chlorobenzylidene)anthranilic acid, which was hydrogenated under pressure using Raney nickel to get 5-chloro-N-(p-chlorobenzyl)anthranilic acid.
2-\textit{Anilinonicotinic acids}

2-\textit{Anilinonicotinic acids} (IV) have been obtained by condensing 2-chloronicotinic acid with an aniline derivative in the presence of copper powder or potassium iodide. This reaction has also been carried out in the presence of excess of aniline or ethanol as the solvent\textsuperscript{11}.

![Chemical Structure](image)

Where $R =$

(a) $2,3-(\text{CH}_3)_2$
(b) $2,6-(\text{CH}_3)_2$
(c) $4-\text{OCH}_3$
(d) $4-\text{OC}_2\text{H}_5$
(e) $2-\text{CH}_3, 4-\text{Cl}$
(f) $3-\text{CF}_3$
(g) $4-\text{CO}_2\text{Me}$

Hoffmann and Faure\textsuperscript{12} condensed 2-chloronicotinic acid with 2,3-\textit{dimethyl}aniline and 3-trifluoromethylaniline to prepare 2-(2,3-\textit{dimethyl}-), and 2-(3-trifluoromethyl)\textit{anilinonicotinic acids} (IV a & f) in the presence of xylene as the solvent and they found that the use of the catalyst was not necessary.

Evans \textit{et al.}\textsuperscript{13} prepared compounds (IVa) and (IVf) by heating 2-chloronicotinic acid with 2,3-\textit{dimethyl}-, and m-trifluoromethylaniline. No catalyst or solvent was employed.
1-Substituted isatoic anhydrides

N-Phenylisatoic anhydride has been prepared by reacting N-phenylanthranilic acid with ethylchloroformate.

Armarego employed acetyl chloride and ethylchloroformate for the preparation of N-benzylisatoic anhydride from N-benzylanthranilic acid.

Scherrer reacted N-(2,3-dimethylphenyl)anthranilic acid with ethylchloroformate in the presence of triethylamine to get N-(2,3-dimethylphenyl)isatoic anhydride.

\[
\text{\includegraphics[width=0.5\textwidth]{anhydride.png}}
\]

1-Substituted quinazolin-4-ones

Scarborough prepared 1-(4-chlorobenzyl)-6-chloro-1,4-dihydro-quinazolin-4-one \( V \) \( (R^1 = R^2 = Cl) \), by heating N-(4-chlorobenzyl)-5-

\[
\text{\includegraphics[width=0.5\textwidth]{quinazolin.png}}
\]

chloroanthranilic acid with formamide.
Again the same author prepared 1-benzyl-1,4-dihydro-quinazolin-4-one \( (V, R^1 = R^2 = H) \) by refluxing a mixture of \( N \)-benzylantranilamide and formic acid.

For the preparation of \( N \)-alkylquinazolin-4-ones a convenient method is to react \( N \)-alkylantranilamide with an appropriate acid anhydride.
References

