J. Chem. Sci., Vol. 118, No. 4, July 2006, pp. 291–309.

Creative research in the chemical industry – Four decades in retrospect*

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MS received 30 January 2006; revised 5 July 2006

Abstract. My professional research career spanning more than four decades has been largely devoted to synthetic medicinal chemistry (Ciba, Bombay – now Mumbai – 21 years) followed by an equal number of years in process development of drugs, crop protection chemicals (Searle, Bombay) and drugs and speciality chemicals (Recon and Hikal, Bangalore). These efforts have involved several collaborators including many from other institutions and offered multitudinous challenges calling for continuous creativity in industrial setups. I was fortunate to have had a conducive environment to be able to respond to these challenges. I attempt to offer the readers in the ensuing pages a flavour of the excitement that has marked these years.

Keywords. Creative research; new drugs; alkaloids; heterocycles; structure–activity studies.

1. Introduction

I started my professional career in January 1963 at the Ciba Research Centre in Goregaon of suburban Bombay when I returned to India after a year's postdoctoral work (1961–62) with Prof H Schmid at Zurich University on strychnine[1] and the Kopsia alkaloids,[2,3] followed by practical training for 4 months at the Ciba laboratories in Basel. Earlier I had done my PhD with Prof T R Govindachari at Presidency College, Madras (1950–54) and continued with him in the same field as a research fellow in a CSIR scheme (1954–57). This work included structural elucidation of the alkaloids tylophorine[4] and gentianine,[5] and the oxygen heterocycle, wedelolactone,[6] besides synthesis of aporphines[7,8] and benzylisoquinolines[9] and benzophenanthridines.[10] Subsequently, I postdoctored with Prof C L Stevens at Wayne State University, Detroit in the area of aminosugar nucleosides[11,12] and with Prof J D Roberts at the California Institute of Technology, Pasadena in cyclobutadiene chemistry[13] and the then-emerging area of nuclear magnetic resonance spectroscopy (NMR).[14,15]

*Presented at the 7th Chem. Res. Soc. of India (CRSI) Conference in Kolkata, February 4–6, 2005

2. Ciba Research Centre, Bombay (now Mumbai)

The Centre started functioning from January 1963 under the direction of Prof T R Govindachari and was formally inaugurated by Pandit Jawaharlal Nehru later in March. It was devoted to the discovery of new drugs. It had in place the required interdisciplinary team of chemists, biologists, biochemists, toxicologists and clinical investigators and was uniquely well equipped with contemporary instrumentation required by the various disciplines for carrying out research to international standards. The research centre had a beautiful sprawling campus with aesthetically built laboratories and residential quarters which provided an exhilarating atmosphere supportive of creative and productive research. By June 1984 when the author moved to Searle, India to take up the leadership of their R&D Centre, about 18,000 preparations, most of them new synthetic compounds and the rest, plant-derived extracts or single entities had been screened using a variety of biological parameters for effects on the cardiovascular, central nervous and endocrine systems and in infectious diseases due to bacteria, amoeba and helminths. Promising compounds which had passed through advanced biology and toxicology were taken to the clinic, of which *five survived Phase I, II and III clinical trials in humans and were afforded registration by the Drug Controller of India*.

3. Drug discovery research, then and now

The process of new drug development in those days was largely driven by chemistry and involved synthesis of new compounds based upon analogy to existing drugs of synthetic or natural origin or simple biochemical concepts. It was aided by *random* screening of novel chemical types and serendipity (as it is even now and will always be). Compounds were synthesized one at a time; a productive chemist with a couple of associates on the average submitted 10–20 compounds per month. Plants were extracted and examined systematically. There were not many 'rational' approaches available to optimize leads but as the years passed by, methods such as quantitative structure–activity relationships evolved and were exploited. Compounds were mostly screened directly in animal models rather than against biological targets. There were relatively few *in vitro* tests to help scientists anticipate activity. This was also the case with amoebic and helminthic infections but microbiology was aided more by *in vitro* tests prior to *in vivo* studies. After activity was obtained and optimized, mechanistic studies were carried out to the extent that science had progressed. Compounds chosen for further development underwent full biological characterization, ADME (absorption, drug metabolism, excretion) and toxicology studies of various durations and kinds. With the results of these studies and appropriate formulations, the candidate drugs would undergo clinical trials and the successful ones would eventually get marketing permission.

Dramatic changes have taken place since the 1980s in the discovery search for new drugs. Revolution in molecular biology, the unraveling of several genomes and the arrival of micro array technology have made possible the isolation and expression of several proteins – enzymes and receptors that are relevant to various disease conditions. Binding/inhibition by test compounds offers a rational approach as a first step towards finding drugs for these diseases. The development of high throughput screening (HTS) has made this process very rapid. To engage the unbottled genie fully, increasingly larger numbers of compounds are required. Chemists have risen to the occasion by providing vast libraries of compounds using combinatorial/parallel chemistry. Unlike the earlier days, since HTS is done *in vitro*, only milligram quantities of the test compounds are needed. With the right chemistry and instrumentation in place, a chemist with a couple of associates can easily churn out hundreds of compounds in a month. It is not unusual now for discovery-based MNC Pharma companies to have libraries of 100,000 compounds or more. Hits thrown up by such screening of *random* libraries are studied for binding strengths or inhibitory concentrations and optimized using well-established parameters. A notable departure from the practice prior to 1980 is that the DMPK (drug metabolism; pharmacokinetics) characteristics of important lead compounds are studied at this stage to ensure proper bioavailability/protein binding properties for representative compounds of the chemical class when exposed to *in vivo* situations. The compounds progress only then to time-consuming and expensive *in vivo* animal studies. The project enters lead optimization stage at this point wherein the medicinal chemist utilizes principles that are well established and accepted for synthesizing 'druglike' or 'druggable' molecules. One favourite concept relates to Lipinski's 'rule of five' consisting of four important and desirable properties – molecular mass <500, calculated log *P* (partition coefficient of the test compound between octanol and water) <5, hydrogen bond donors <5 and hydrogen bond acceptors <10. More advanced approaches to optimization involve X-ray crystal structures of proteins without and with ligands which provide sophisticated methods of docking putative drugs for maximal desired interactions. High-field NMR has been marshalled to investigate the more meaningful interactions in biological milieus.

The lead-optimized compound would then be characterized extensively biologically and some understanding of its mechanism of action arrived at. Further development through drug metabolism, toxicology and clinical studies follows essentially the earlier route except there is a serious move now to use biomarkers to follow clinical trials rather than disease end points. During recent years, emphasis has been generally on finding molecules that would have a single target in a disease but this is being increasingly questioned vociferously. 'The idea of magic bullets is great but in practice it is probably not going to be the right approach for complex diseases.' There has been also widespread concern over the declining trend in new drug introductions despite the enormous resources of knowledge, technology, instrumentation and money invested by Pharma companies leading inevitably to skeptics making snide remarks over the so-called 'rational' approaches.

Medicinal chemists have always played a pivotal role in the discovery and development of new drugs. In the light of current challenges, several skills are required for the medicinal chemist. These have been outlined in an excellent article by Lombardino and Lowe III in a recent article in *Nature Reviews*.[16] I can do no better than quote:

"*These (the skills) include a thorough knowledge of modern organic chemistry and medicinal chemistry, an understanding of the biology that relates to the target disease, an understanding of the pharmacological tests used in the project and sufficient knowledge of the factors that influence ADME characteristics of chemicals in vivo. Furthermore, they should also have an understanding of clinical medicine that pertains to the target disease; knowledge of the regulatory requirements for related drugs, a current knowledge of competitive therapies, both in the market and under development by competitors; a thorough knowledge of the literature that is relevant to the target disease; familiarity with the many newer technologies available to facilitate drug discovery; and an entrepreneurial attitude in behaving as an innovator and inventor. Finally – and of crucial importance to the timely success of the project – the chemist must show superior interpersonal skills throughout the life of the project to interact effectively with colleagues from other disciplines to achieve project goals*."

The author will now proceed to give a brief account of important results from his foray into medicinal chemistry as it was practised *then* (1963–1984).

4. Contributions to medicinal chemistry

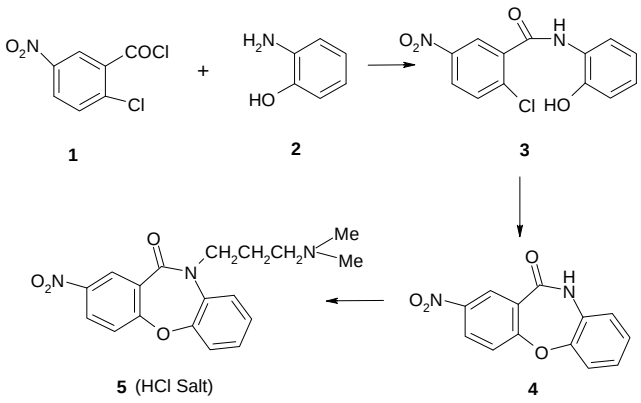
4.1 *Antidepressant activity – Sintamil*

The synthesis of the antidepressant, sintamil **5** (scheme 1) exploited the double activation of the chlorine atom in the readily available 2-chloro-5-nitrobenzoic acid. The acid chloride **1** acylates selectively the amine in 2-aminophenol **2** to yield the amide **3**. This undergoes facile *intramolecula*r cyclization by merely heating its solution in aqueous alkali to afford the dibenzoxazepinone **4** in very high yield, offering easy access to the tricyclic system which requires otherwise several steps and unfriendly reagents. Antidepressant activity is expected to be elicited from **4** by introducing an aminoalkyl side chain on the lactam nitrogen and is achieved, again, under surprisingly mild conditions by treating **4** with aminoalkyl chloride hydrochlorides in aqueous alkali–acetone solution.[17] Aminoalkylation of lactams generally require dry, aprotic solvents, sodium hydride or amide and the none-too-stable aminoalkyl halide bases. The products have the expected antidepressant activity, the dimethyaminopropyl drivative, sintamil **5** (code No. Go 2330) being the most potent[17]. Sintamil is found to be superior to imipramine, the standard antidepressant at that time in selected parameters.[18] ^{14}C-labelled drug was synthesized for absorption–excretion studies.[19] Sintamil was granted marketing permission by the Drug Controller of India and Ciba launched it after an introductory symposium in 1972.[20] The actual marketing however took place some years later due to the peculiar restrictive licensing policies of the Central Government at that time.

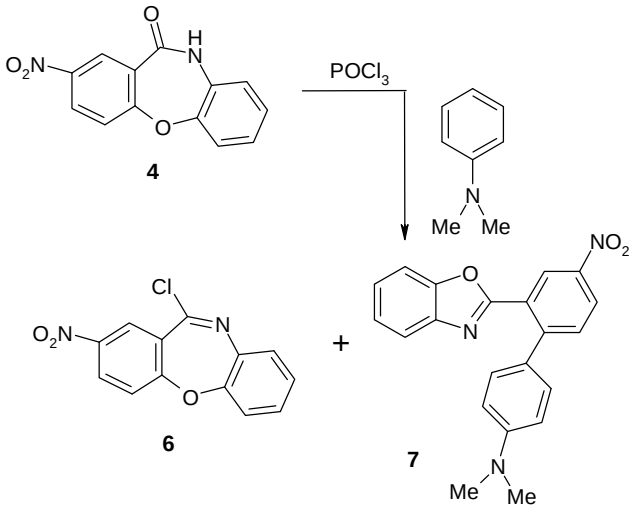
An interesting and beneficial fallout of having the nitro group was the patentability of **5**. Earlier patents on the dibenzoxazepine system had not covered the nitro substituent since the synthetic routes precluded the use of this group! Many tri- and tetracyclic molecules produced in this project have varied activity on the central nervous system.[17,21] Interestingly, years later some are found to have even anti HIV activity, particularly the tetracyclic analogues of **4**[22]!

Among various studies carried out on **5** can be mentioned the determination of structure and conformation in the solid state[23] and in solution[24] in collaboration with Profs K Venkatesan and G Govil respectively.

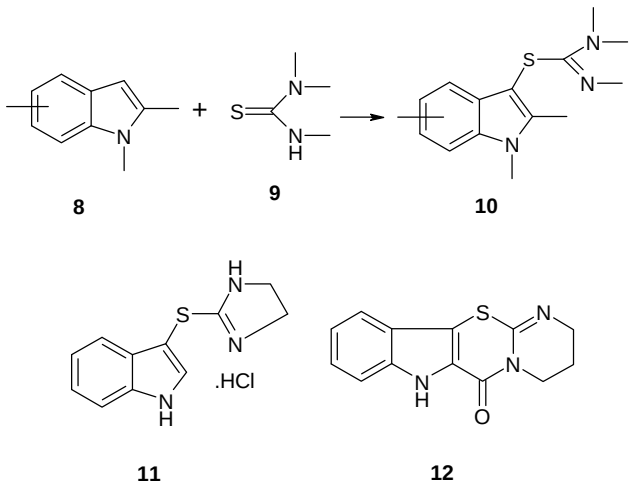
Several fascinating transformations were encountered in this chemistry. The formation of the benzoxazole **7** along with the expected iminochloride **6** from **4** by the action of $POCl_3$ in the presence of dimethylaniline is one illustrative example (scheme 2).[25]



Scheme 1.



Scheme 2.



Scheme 3.

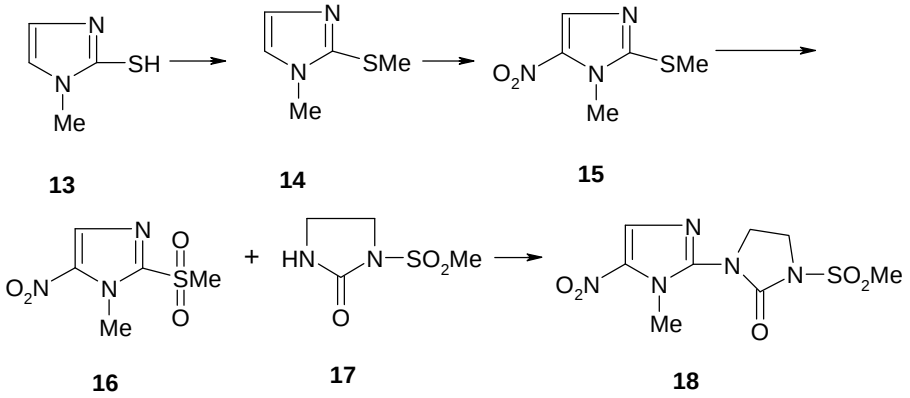
In a different exercise involving the replacement of an active chlorine in *a*-alpha-chlorodiphenylacetamides, a novel observation was made of the unusual entrance of the nucleophile at the position *para* to the side chain.[26]

4.2 *Nasal decongestant – Tinazoline*

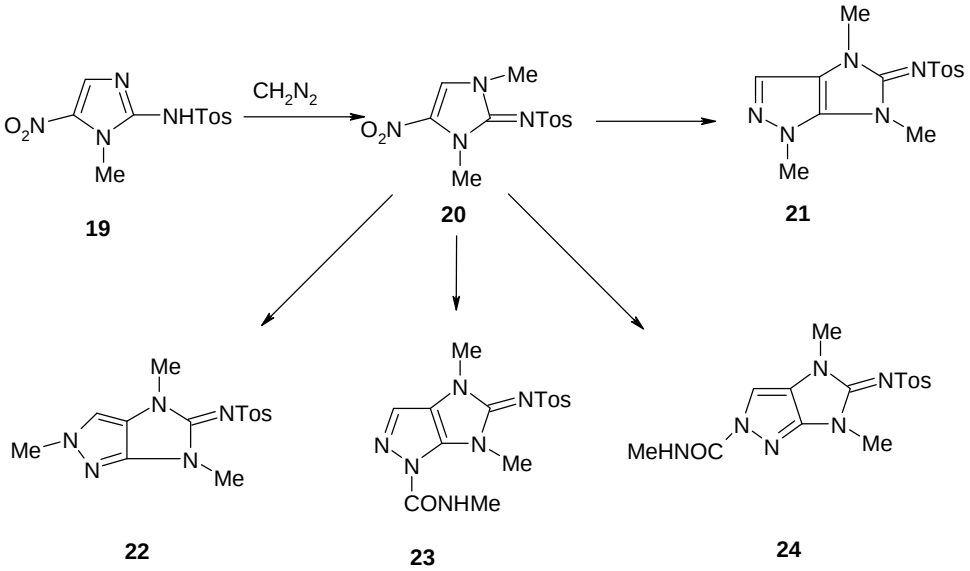
Tinazoline **11** (code No. Go 7996 B), a vasoconstrictor useful as a nasal decongestant, was synthesized, based upon the pharmacological activity of imidazolines and the facile introduction of an isothiourea moiety in the beta position of indoles by thiourea in the presence of potassium triiodide. Thus indoles **8** and cyclic and acyclic thioureas **9** undergo oxidative coupling to afford 3-indolyl mercapto derivatives **10**[27] among which tinazoline **11** derived from indole and imidazolinethione (scheme 3), is the most potent vasoconstrictor,[28] and was given marketing permission in India. Although **11** had some advantages over the classical Ciba drug, xylometazoline (otrivin), the company chose not to market it lest it should cannabilize the sales of the latter. The chemistry afforded the interesting tetracyclic system **12**[27] which was inactive in this indication. **12** was not tested for tumor-inhibiting properties.

4.3 *Antiamoebic activity – Satranidazole*

Following the world-wide merger of Ciba and Geigy in the early seventies, the development of an antimicrobial agent active against both luminal and hepatic amoebiasis became a high priority for the Goregaon Research Centre. A promising nitroimidazole lead discovered in the Basel laboraotories was also transferred to Goregaon. The project taken up on a war footing culminated in the development of a new analogue, satranidazole **18** (Code No. Go 10213). The synthetic sequence started with 1-methyl-2-mercaptoimidazole **13** which was S-methylated to **14**. This was then nitrated to **15** and oxidized to the sulphone **16**. Reaction of **16** with the sodium salt of 1-methanesulphonylimidazolidinone **17** gave satranidazole **18** in high yield (scheme 4).[29–31] The compounds significantly superior to the standard drug, metronidazole in caecal and hepatic amoebiasis,[32] giardiasis and trichomoniasis.[33] The superiority extends to activity against anaerobic bacteria also. Methanesulphonyl residue was introduced in **17** as a blocking group with a view to knocking it off in **18** and replacing it with an acetyl group, which was the initial lead. In the event, it turns out that **18** is unwilling to part with the methanesulphonyl group but is more potent and is obtained in higher yields with less hassles than the initial acetyl anlogue! Blocking groups have apparently better roles to play! **18** underwent the entire gamut of new drug development, which among other activities required the synthesis of ^{14}C-labelled drugs[34,35] and was projected in an international seminar.[36] Ciba (by then Ciba-Geigy) obtained marketing permission for **18** from the Drug Controller of India but abstained from introducing it for some reasons. It was left to Alkem Laboratories to make it available to the public in 2000,[37] long after the original patents had expired. The author's extensive work on satranidazole-related chemistry unveiled several interesting reactions, one of which is outlined below.



Scheme 4.



Scheme 5.

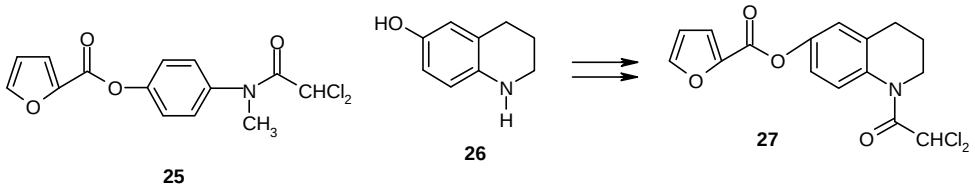
An attempt to methylate the sulphonamide nitrogen atom in **19** with excess diazomethane gave a plethora of products, which were isolated by painstaking chromatography and identified as **20–24**. Methylation of the nuclear nitrogen in **19** followed by cycloaddition of diazomethane to the nitrovinyl moiety and elimination of nitrite affords an imidazopyrazole which undergoes further methylation at the pyrazole nitrogen sites to form **21** and **22** or is attacked by adventitious methyl isocyanate present in diazomethane to afford the carbamoyl derivatives **23** and **24** (scheme 5).[38,39]

4.4 *Antiamoebic activity – Quinfamide*

Diloxanide furoate **25** has been all along a useful luminal amoebicide. During our exercises to develop amoebicides, a cyclic analogue **27** was synthesized starting from 6-hydroxy-1,2,3,4-tetrahydroquinoline **26** in two obvious steps (scheme 6). **27** like **25** does not exhibit antiamoebic activity in the caecal model. The hamster model, more relevant for luminal amoebiasis, was unavailable to us at that time. **27** was considered by Ciba to be of no interest. Subsequently, Sterling–Winthrop established its potency and superiority to **25** in the latter model and patented it as quinfamide. Searle India got interested in the drug and manufactured it for export. My colleague, Sharada Shenoy, and I developed the process for the drug in the Searle laboratories and obtained an Indian patent.

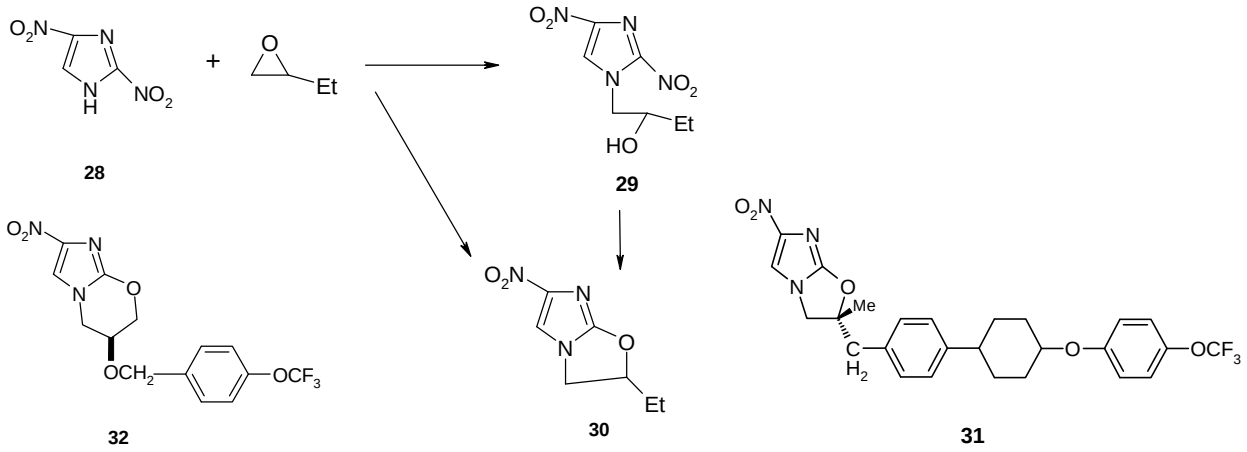
4.5 *Antitubercular activity – CGI 17341*

An unexpected offshoot of my protracted engagement in nitroimidazole chemistry was the synthesis



25 **26** **27**

Scheme 6.



28 **29** **32** **30** **31**

Scheme 7.

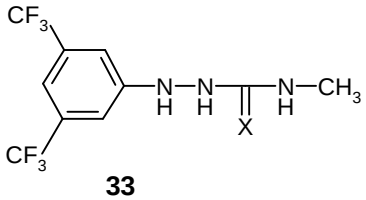
of CGI 17341 (**30**) with potent antitubercular activity.[40] This has come to be regarded as an important lead in a therapeutic area where there was a crying need for new drugs (more so for HIV-associated TB) but which was bereft of breakthroughs since the days of rifampicin, isoniazid, ethambutol and pyrazinamide. **30** is synthesized from 2,4-dinitroimidazole **28**, which upon treatment with butylene oxide gives a mixture of the alcohol **29** and the imidazooxazole **30** along with isomeric nitro compounds. Exposure of **29** to piperidine gives a further amount of **30** (scheme 7). **30** has good anti TB activity in *vitro* against sensitive and resistant TB strains and is also active *in vivo*. The *in vitro* and *in vivo* efficacies compare well with those of rifampicin and isoniazid. In the absence of a planned effort to exploit the lead, I was allowed to publish the results; further elaborate characterization of the activity and presentation in an international conference and a leading journal[41] brought the molecule widespread attention. Sure enough, the lead was picked up by two different laboratories resulting in the development of two potent analogues, the nitroimidazooxazole **31** and the nitroimidazooxazine **32**, which have entered phase I clinical trials. It is a matter of eternal regret to me that Ciba did not deem it worthwhile to continue with the CGI 17341 project. However, the opening of a research centre by Novartis in Singapore devoted to discovery of new anti TB drugs recently is an encouraging development! If either **31** or **32** or both succeed in the clinic, scientists of the Goregaon Research Centre can feel fulfilled.

4.6 *Antifertility activity*

For several years since its inception, the Goregaon Research Centre had a strong and sustained programme to develop synthetic antifertility agents which could hopefully address the population problem of India. Several interesting and potent leads were obtained but none reached the clinic.

Go 2696: Investigation of a series of 1-arylthiosemicarbazides revealed strong antifertility activity for **33** (X = S) which acts by virtue of its antiuterotropic activity but was abandoned because of its toxicity and teratogenic properties.[42,43] Undaunted, the involved scientists were valiantly talking for some time of its potential use as a rodenticide-cum-rodent population control agent! Interestingly, the corresponding semicarbazide (GO3165, **33**, X = O) is a powerful anticonvulsant.[44] This class of com-

pounds offered an opportunity for testing the utility of the concept of quantitative structure activity relationships (QSAR) which was becoming quite popular at that time. My colleague, Dr Rajappa, had developed great fascination for the subject and undertook the analysis with great avidity.



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Go 5380: 1,2-Diaryldihydronaphthalenes were being studied seriously in the late fifties and early sixties as antiimplantation agents. This inspired the synthesis of 1,2-diaryltetrahydroisoquinolines **37** by a classical route from **34** via **35** and **36** (scheme 8). Among these, fluorine-substituted derivatives have significant activity. The *p*-fluorophenyl derivative **38** (Go 5380) is the most potent and has been studied in detail, and its activity attributed to its weak estrogenic–antiestrogenic properties.[45] Later this was not considered a promising mechanism for antifertility activity and **38** was not pursued although centchroman **39** of Central Drug Research Institute, a contemporary molecule with similar structure and properties was developed and introduced in the market. However, more than three decades later, **38** and analogues have been found to be attractive candidates for Prof T N Guru Row's investigations on intermolecular F–F interactions in organic compounds in the solid state (*vide infra*)!

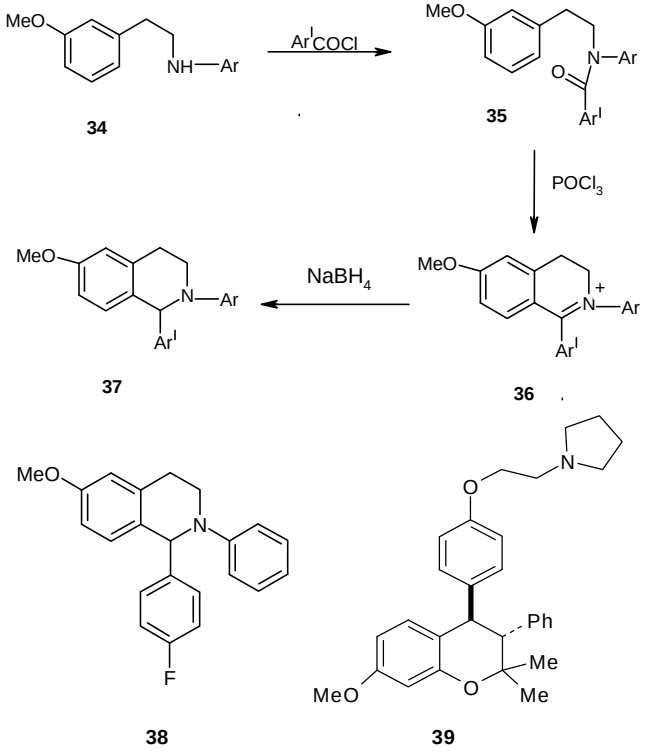
Several other 1,2-diaryl heterocycles were synthesized by me during those years which are discussed in the next section on enamine chemistry.

5. Enamine chemistry

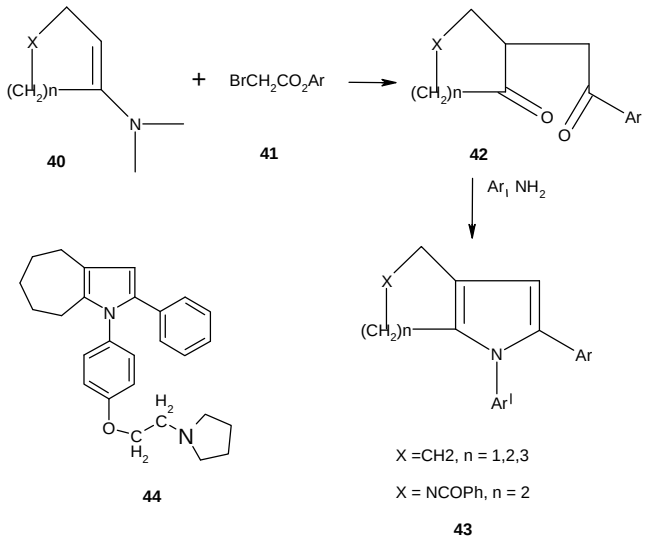
The versatile applications of enamines as synthons are well documented. I have had an enduring interest in the theoretical studies of enamine characteristics by NMR studies (*vide infra*) and their use in constructing diverse biologically active condensed pyrroles and perhydrocinnolines. These exercises also divulged some unexpected reactions. These as well as some novel properties of imidazoisoquinolines and 1-methyl-3,4-dihydroisoquinolines are discussed in this section.

5.1 *Condensed pyrroles and cinnolines*

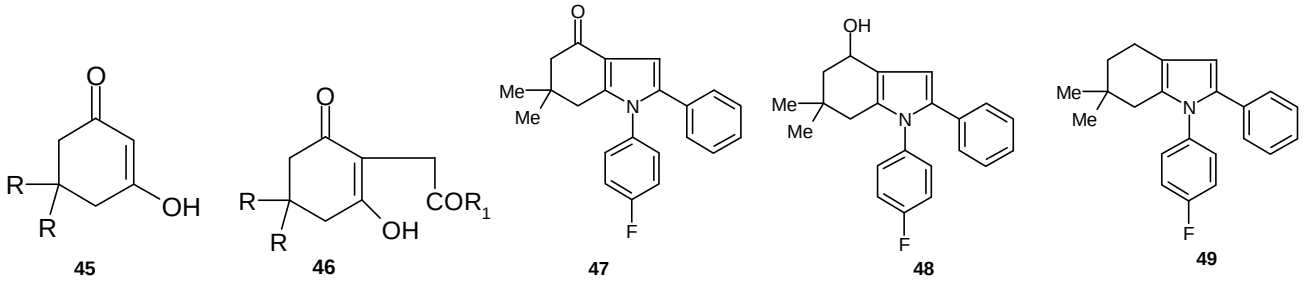
Reaction of enamines **40** of cycloalkanones with *a*-bromoacetophenones **41** give the 1,4-diketones **42**, which undergo facile ring closure to pyrroles **43** (scheme 9) when heated with anilines. Among these **44** has potent antiimplantation properties.[46]



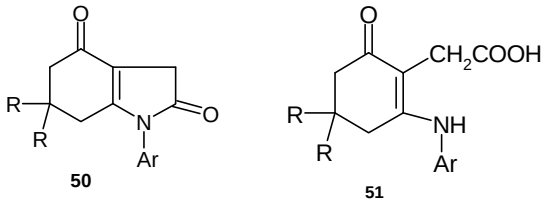
Scheme 8.



Scheme 9.



Scheme 10.

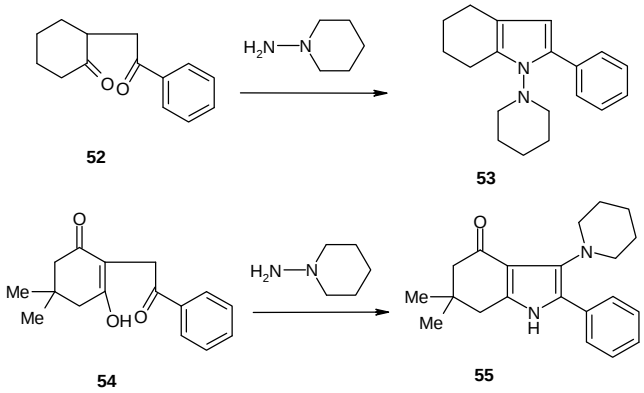


Scheme 11.

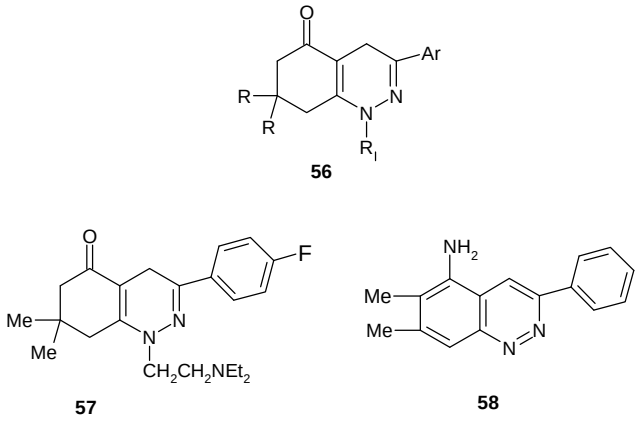
Cyclohexane-1,3-diones **45** undergo C-alkylation by *a*-haloketones to give triones **46** (R_1 = alkyl, aryl) which again can be converted by aromatic amines to ketotetrahydroindoles of the type **47**. **47** has very good antiimplantation activity which is surpassed by the derived alcohol **48** and even more so by the hydrogenolysis product **49**[46] (scheme 10). They were not developed further for the reason mentioned earlier but nevertheless they have become good candidates for Prof Guru Row's studies.

Alkylation of **45** with ethylchloroacetate affords **46** (R = OEt) which upon heating with anilines gives the ketotetrahydrooxindoles **50**, which are hydrolyzed to the acids **51** (scheme 11). The latter been close resemblance to the classical anti-inflammatory agent, diclofenac and in fact the molecule **51** (R = H, Ar = 2,6-dichlorophenyl) should yield diclofenac on dehydrogenation. While this was not realized, **50** and **51** are by themselves antiinfammatory, the former being more potent. However, the most active oxindole of this series, **50** (R = H, Ar = 4-fluorophenyl) is much less potent than diclofenac.[47]

An unexpected novel reaction is encountered when triketones **46** (R_1 = aryl) are exposed to N,N-disubstituted hydrazines. Reaction of the 1,4-diketone **52** with N-aminopiperidine affords the expected pyrrole **53** whereas a similar one with the triketone **54** gives the totally unexpected 3-piperidino derivative **55** (scheme 12) in high yield. The reaction was demonstrated to be a general one and its mechanism elucidated.[48,49]



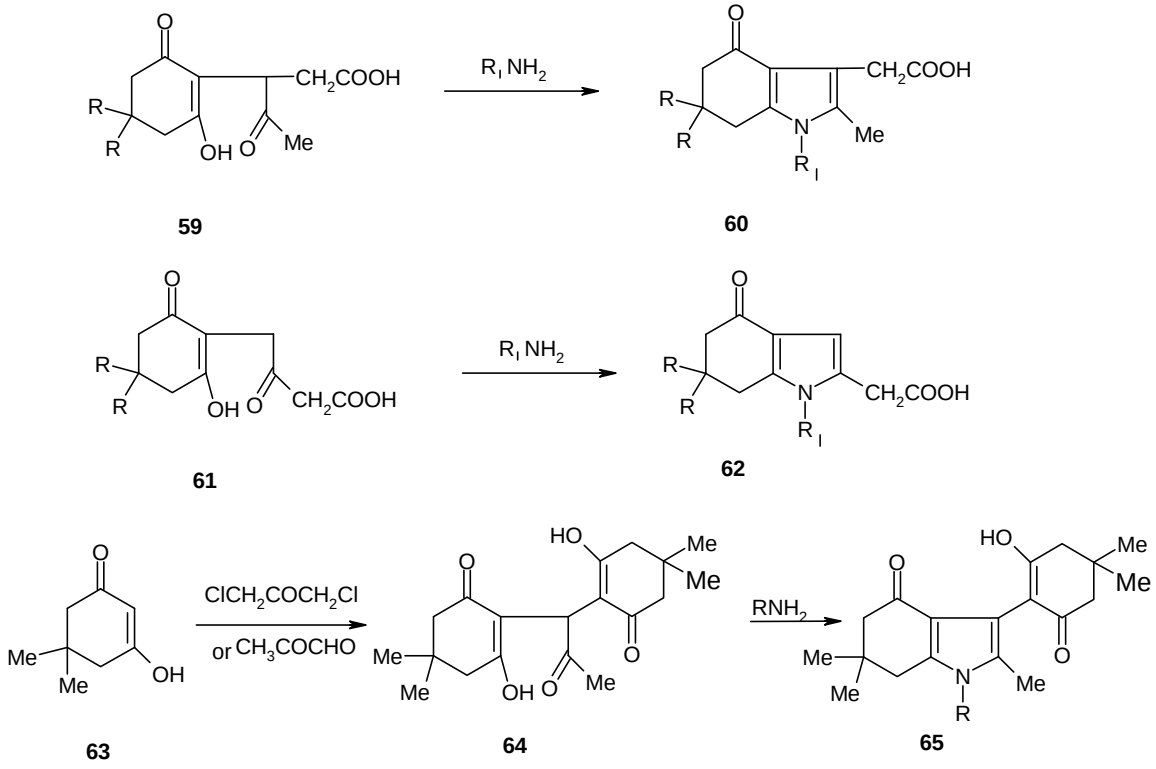
Scheme 12.



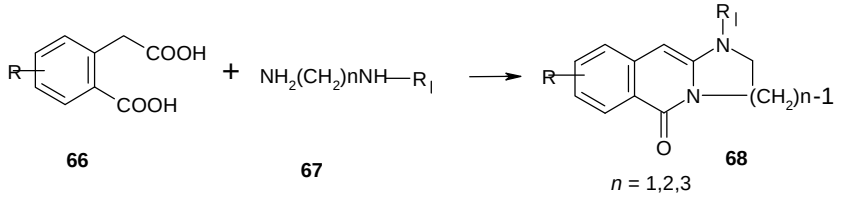
Scheme 13.

Reaction of triketones of the type **46** (R_1 = aryl) with hydrazine and monosubstituted hydrazines gives perhydrocinnolines **56**, among which **57** has some CNS depressant properties[50] (scheme 13).

An attempt to carry out a Beckman transformation on the oxime obtained from **56** (R = Me, R_1 = H, Ar = Ph) with $POCl_3$ took a novel turn to provide the fully aromatic aminocinnoline **58** (scheme 13) with a methyl shift via a Semmler–Wolff rearrange-



Scheme 14.



Scheme 15.

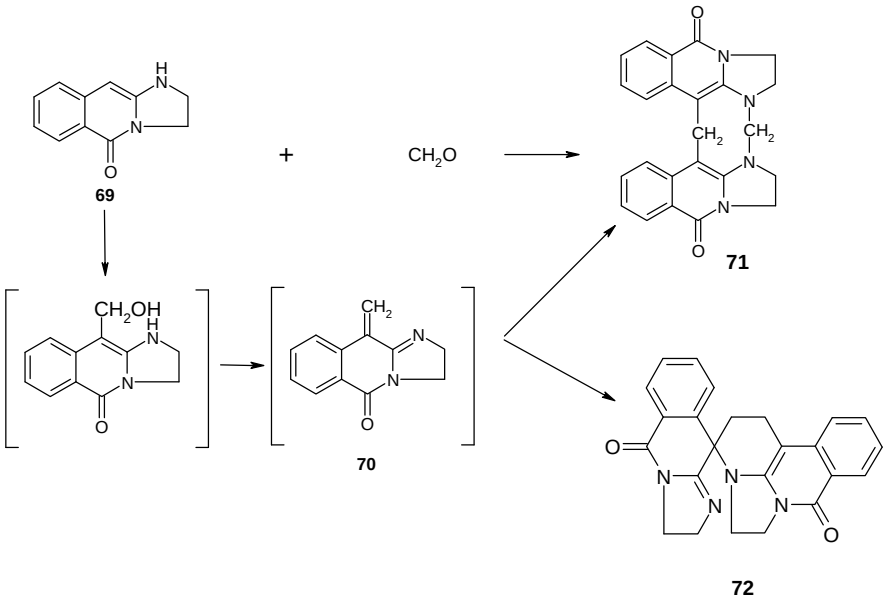
ment. The reaction is general. Similar products are obtained directly from the ketones under Schmidt reaction conditions.[51,52] Other types of compounds which evolved out of this chemistry are summarized below.

Several 4-oxoperhydroindole-3-acetic acids **60** derived from **59** (scheme 14) show modest hypoglycemic activity among which Go 8778 (R = Me, R_1 = *n*-Bu) and Go 9001 (R = Me, R_1 = *iso*-Bu) were equipotent with tolbutamide.[53,54] Strangely, moving the acetic acid side chain to position 2 as in **62** destroys the activity. However, the series typified by **65** obtained from dimedone **63** via **64** having a dimedonyl moiety at position 3 (scheme 14), is highly active. The most potent of them, CGI 14600 (**65** R = Ph), exhibits hypoglycemic effects in normal fasted rats even at 1·5 mg/kg p.o. nearly matching the potency of glibenclamide.[55,56] 1H NMR and mass spectra of CGI 14600 present many interesting features. Particularly intriguing is the observation of a major fragment in the latter indicating the loss of CH_2CO_2H. Insight using the deuterium-labelled molecule was obtained by Dr W J Richter.[57]

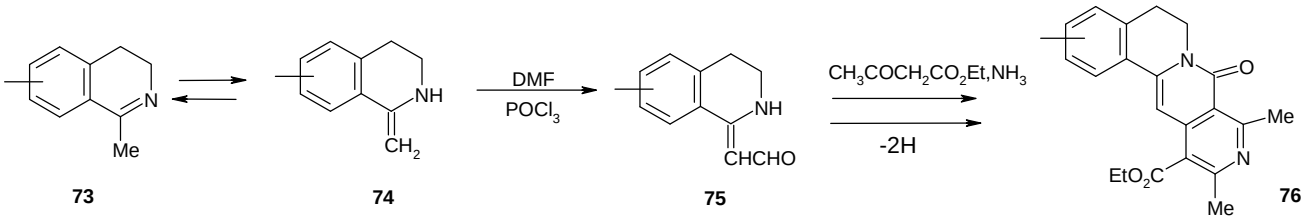
5.2 *Imidazoisoquinolines*

Condensation of homophthalic acids **66** with 1,2 and 1,3-diamines **67** gave a group of imidazo and pyrimidoisoquinolones **68** (scheme 15) with an active enamine system,[58] which gave me much pleasure and excitement.

One reaction in particular is worth highlighting since it afforded a '*synthetic*' *alkaloid* and is recorded below. An attempted Mannich reaction of imi-



Scheme 16.



Scheme 17.

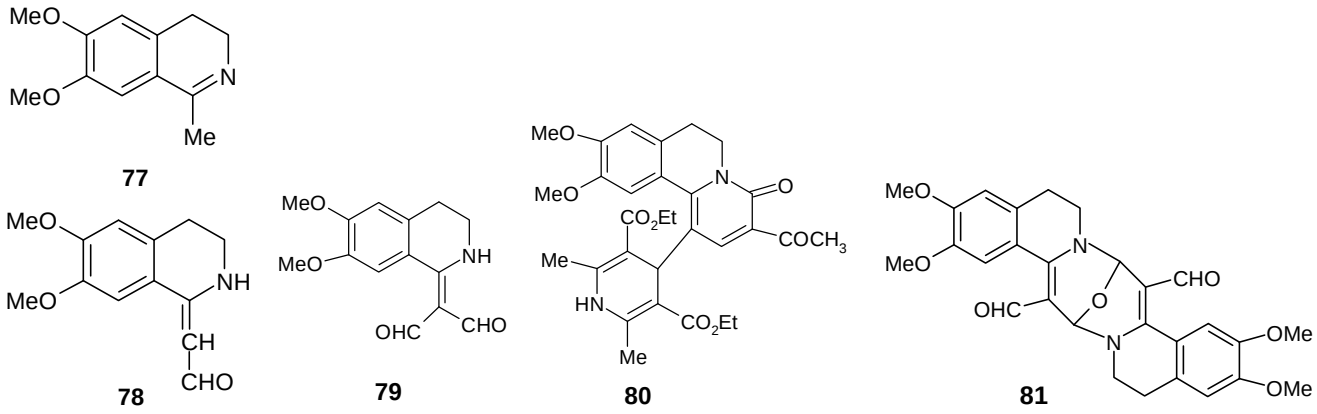
dazoisoquinolone **69** with formaldehyde and morpholine gave two products in high yields, neither having a morpholine residue. The same products were obtained with formaldehyde alone. Molecular weights by mass spectrometry and NMR studies (^1H and ^{13}C) revealed that the less soluble product had the expected symmetrical structure **71** while the more soluble one had the more complex architecture depicted in **72**. The formation of **72** was explained by postulating the formation of an intermediate azadiene **70** two units of which undergo a hetero Diels–Alder Reaction (scheme 16).

5.3 *Villsmeyer–Haack (VH) reaction products from 1-methyl-3,4-dihydroisoquinolines*

1-Methyl-3,4-dihydroisoquinolines **73** are known to exist in equilibrium with the enamines **74** which can be attacked by electrophiles at the carbon terminus. An ambitious plan was initiated by P J Rodriguez (a PhD scholar in the Searle Laboratories – Searle was recognised by Bombay University as Ciba also was but I was leaving Ciba by the time the recognition was granted) to carry out a VH reaction on **73**, and to subject the carboxaldehyde **75** so produced to conditions of the Hantsch dihydropyridine synthesis to enter into the azaberberine system **76** present in the Alangium alkaloids as shown in scheme 17. The objective was only partly realized but some unusual transformations occurred which are worth recording.

VH reaction of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **77** with 5 molar equivalents each of $POCl_3$ and DMF at 28°C gives the expected formyl drivative **78** as the major product. With 2 equivalents of $POCl_3$ and 5 of DMF at 80–90°, **77** gives preponderantly the diformyl product **79**. The formation of products like **78** and **79** are general reactions of **73** (scheme 18).

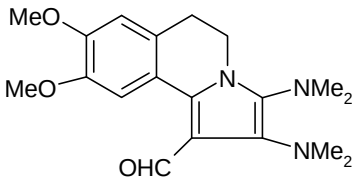
Various attempts to perform a Hantsch reaction with **78** failed. When subjected to same reaction, **79**



Scheme 18.

does not yield the desired azaberberine system but a product identified as **80** is obtained. Under the optimistic belief that blocking the nitrogen atom by an acyl group, thus strengthening the carbonyl character of the formyl group may direct the reaction suitably, **79** was allowed to react with acetic anhydride. The product however was the unexpected oxadiazozine **81** (scheme 19). Analytical and spectral data as well as single-crystal X-ray studies by Dr R Parthasarathy were provided in favour of **81**.[59] This again is a general reaction of the analogues of **79**.

While this was gratifying *per se*, more exciting was the outcome of the VH reaction on **77** with 5 moles each of DMF and $POCl_3$ at 80–90°, which results in the formation in good yield of a product carrying *two dimethylamino* groups. The structure was deduced to be **82** by analytical and spectroscopic measurements and was confirmed by single-crystal X-ray studies by Dr Nethaji. The unusual reaction is again a general one for dihydroisoquinolines **73** and was rationalized.[60,61]



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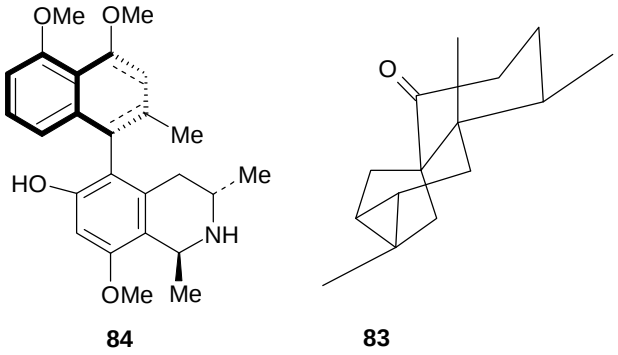
6. Natural products chemistry

I had seven years of experience in this field from my association with Prof T R Govindachari and for one year with Prof H Schmid. Nevertheless at the start of

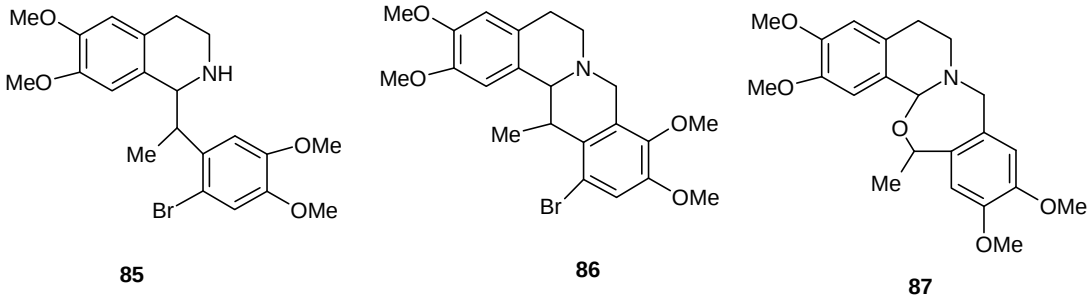


Scheme 19.

independent professional career I switched over to synthetic medicinal chemistry by destiny rather than desire. However, the interest persisted and there were ample opportunities to work with Prof Govindachari at Ciba and Prof B R Pai at Presidency College, Madras on structural elucidation of natural products as well as synthesis.

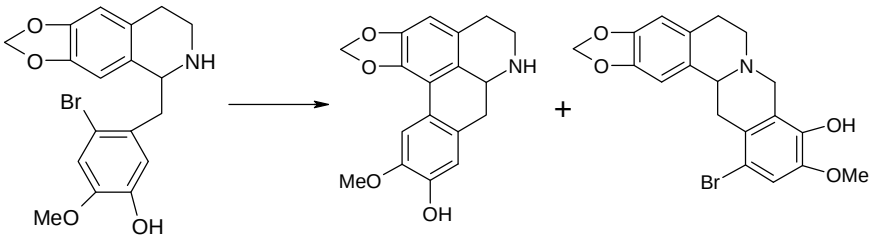
6.1 *Ishwarone **83** and ancistrocladine **84***

The structure of ishwarone, a carryover from Madras was established as **83** by degradation as well as using high field NMR data with decoupling studies[62,63] (scheme 19). Ancistrocladine, isolated from *Ancystrocladus heyneanus* at Ciba, was shown to have the novel polyketide derived isoquinoline structure **84**[64] (scheme 19). Both **83** and **84** are prototypes of their scaffolds. Dr P C Parthasarathy was the lead chemist in these investigations. I also played a small role in the elucidation of the absolute configuration of cantharic acid and palasonine by Prof H Schmid.[65]



85 **86** **87**

Scheme 20.



88 **89**

Scheme 21.

6.2 *Protoberberine chemistry*

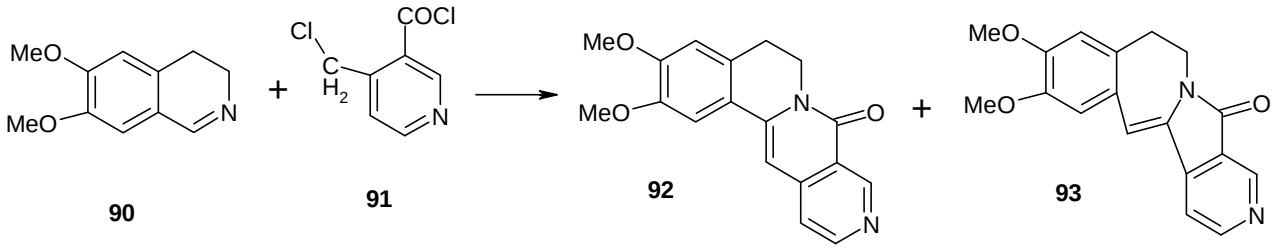
Association with Prof Pai in work on protoberberine alkaloids was very productive[66] and resulted in several publications – structure of neooxyberberineacetone,[67] synthesis of 13-methylprotoberberines and their conformation[68] etc. The unexpected formation of the fragment CH_2CO_2H in the mass spectrum of neooxyberberineacetone called for some explanation which was provided with the help of Dr W J Richter.[67] Two exercises resulted in much excitement and would bear discussion.

An attempt was made to construct a 13-methyltetrahydroberberine **86** from the 1-(*a*-methylbenzyl)-1,2,3,4-tetrahydroisoquinoline **85** with formaldehyde under acid catalysis. The product is not the prosaic target **86** but one of profound rearrangement, the isoquinobenzoxazepine **87**[68] (scheme 20). The structure was deduced from analytical/spectroscopic data and degradation studies and confirmed by X-ray.[69]

A second interesting observation was made during photolytic debenzylation or exposure to acidic conditions of 1-benzyltetrahydroisoquinolines such as **88** carrying methoxy groups in the aromatic rings. Apart from the expected products, tetrahydroprotoberberines **89** (scheme 21) are also isolated as significant byproducts. Careful experimentation revealed that formaldehyde implicated in the side reaction arises from the CH_2NH moiety under photolytic and the aromatic methoxyl under acidic conditions.[70] There was also a three-way collaboration with Prof T Kametani of Japan in synthetic work on protoberberines and aporphines.[71]

6.3 *Azaberberines and ring B, C isomers*

Mention was made earlier of the unsuccessful attempts to build the azaberberine framework **76** of Alangium alkaloids but even if they had been successful, the product would have undesired encumbrances which are inevitable from the synthetic route chosen. In a different classical approach, the naturally occurring alkaloid **92** could be obtained from 3,4-dihydroisoquinoline **90** and 4-chloromethylnicotinoyl chloride **91**. Interestingly apart from the targeted azaberberinone **92**, the novel pyridopyrrolobenzazepinone **93** is also obtained and characterized by analytical and spectroscopic data (scheme 22). Additionally single crystal X-ray studies carried out by Prof Nethaji confirmed the structure. Compounds corresponding to **92** and **93** with methylenedioxy and trimethoxy groups were obtained from the corresponding dihydroisoquinolines. Although **93** and analogues have not been isolated so far from plants, there is reason to believe that they may be produced biogenetically in *Alangium lamarcki* by rearrangement of **92** and its congeners through a transformation with precedence in protoberberine chemistry.[72]



Scheme 22.

7. Studies on NMR spectroscopy

My exposure to this field during postdoctoral association with Prof J D Roberts at Caltech has left an indelible lifelong imprint on my activities. Highly successful applications of NMR spectroscopy were made in association with Prof H Schmid and Dr W von Philipsborn at Zurich University in the structural elucidation of the Kopsia alkaloids and their rearrangement products.

For quite a few years after work started at the Ciba Research Centre, a Varian A-60 proton NMR spectrometer was the 'owner's pride and neighbour's envy'! Much later a low resolution mass spectrometer and a 90 MHz Bruker $^{1}H/^{13}C$ NMR spectrometer were added to strengthen the Centre's capabilities. Compared to the facilities available in most academic and industrial laboratories today, this instrumentation would look primitive but quite a good mileage could be obtained from them. In collaboration with Dr S Rajappa, extensive studies were made in the proton[73] and ^{13}C NMR[74] spectra of enamines and nitroenamines correlating chemical shifts with reactivity.

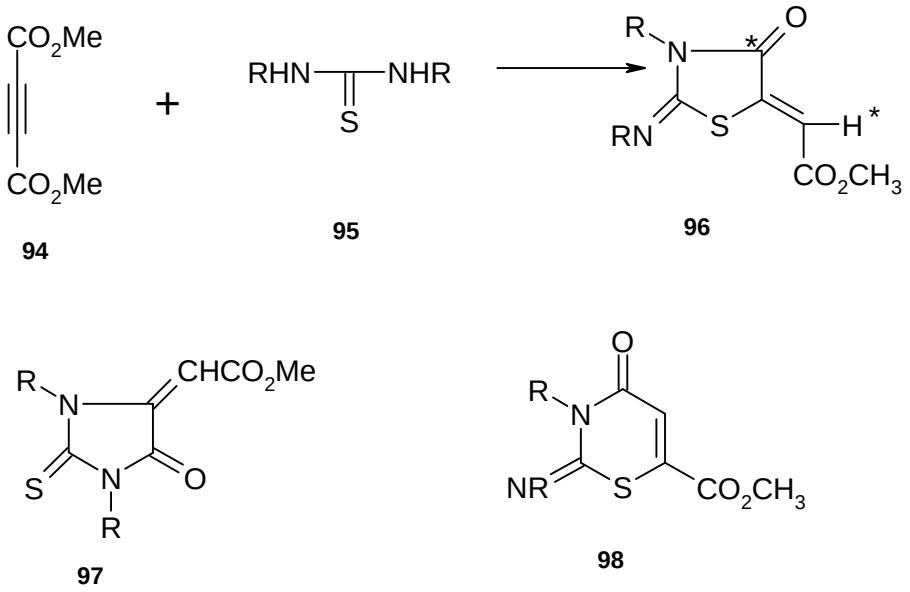
Restricted rotation of the amide bond in N-acylindolines and tetrahydroisoquinolines was investigated in association with Dr M D Nair[75–77] and Prof G Kartha.[78] This resulted in the discovery of allylic A(1,3) interactions in some of the molecules and the synthesis of strained tetracyclic pyridophenanthridines.[79]

The rest of this section will highlight selected NMR studies related to *bioactive* heterocycles.

7.1 *Applications of ^{13}C NMR spectroscopy to structure elucidation of bioactive heterocycles*

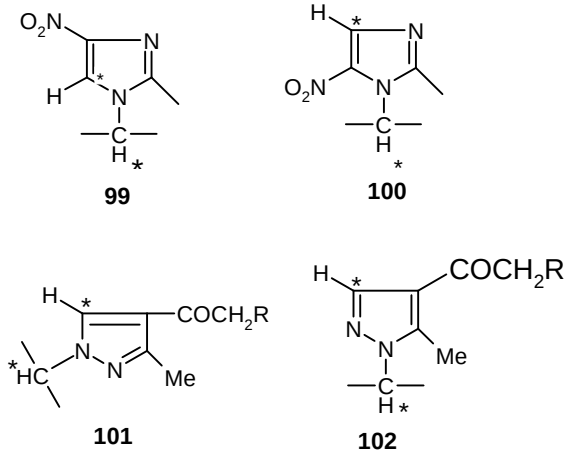
Thiazole derivatives: Thiazoles show a variety of biological activities, e.g. thiamine, a vitamin with the thiazolium moiety. Among other examples can be mentioned nizatidine (antiulcer), niridazole (antiprotozoal) and thiabendazole (anthelminthic). Among reduced thiazole derivatives can be cited the diuretic, etozoline, which is a thiazolidinylidene acetic acid. A particularly facile and versatile route to thiazolidinones, which was the rage in the 1960s and 70s, is the addition of acetylene dicarboxylic ester **94** to thiocarbamoyl derivatives **95**. Considerable controversy surrounded the assignment of structures to these products. The possibilities were enormous and different structures were proposed by various groups. My collaboration with Prof W von Philipsborn allowed an unequivocal and unique solution to the vexatious issue. Study of chemical shifts and coupling constants in the ^{13}C NMR spectra of a large number of these adducts established unambiguously the *E*-thiazolidinone structure **96**, ruling out many other alternatives such as imidazoline and thiazine representations **97** and **98** respectively (scheme 23). *Crucial to the solution was the identification of the carbon atoms of the ester and lactam C=O groups* and the 3 *J* C–H coupling of the latter with the vinylic proton (both starred). The method also helped structural assignments in the case of most unsymmetrical thioureas.[80] Single crystal X-ray studies on the product from N-(4-bromophenyl)-N′-methylthiourea by G Kartha[81] confirmed such structures. The study was extended to several other addition products of **94**.[82]

Imidazoles and pyrazoles: The three-bond C–H coupling helped correct assignment of structures to isomeric 4- and 5-nitroimidazoles **99** and **100**[83] and to isomeric pyrazoles **101** and **102**[84] (scheme 24). The starred carbon atoms in **99–102** are easily identified by the large one-bond C, H coupling. Of these four structures, those in **99** and **101** have an additional three-bond C, H coupling which is strikingly absent in **100** and **102**. Additionally, there are diagnostic differences in the chemical shifts between the starred carbons in **99** and **101** and between **101** and **102**. It should be mentioned that 5-nitroimidazoles **100** are potent antiprotozoals (e.g. satranidazole **18**), while the 4-nitroisomers **99** are devoid of this acti-



94 **95** **96** **97** **98**

Scheme 23.



99 **100** **101** **102**

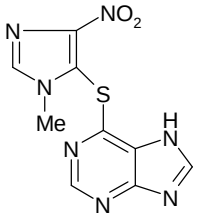
Scheme 24.

vity, although in bicyclic molecules incorporating **99**, such as the imidazooxazole CGI 17341, **30**, potent antitubercular activity has been discovered, which is absent in the 5-nitroisomer.[41]

Compounds **101** and **102**, with R = arylpiperazines, are potent antihypertensives.[84] Significant results were also obtained in collaboration with Prof Von Philipsborn in the 15N spectra of azoles containing two hetero atoms.[85]

8. Contributions to process development

The change from basic research of the type carried out at Ciba to applied research at Searle in Bombay and later at Recon and now at Hikal in Bangalore provided different types of challenges with fruitful results. Process development of quinfamide **27** by Sharada Shenoy and manufacture at Searle India was mentioned earlier. An equally satisfactory experience was the elaboration of a commercially viable route to the life-saving purine immunosuppressant, azathioprine **103** by Dr Shenoy and commercialization by Searle which brought her the coveted Vasvik Award for lady scientists in 1990. Process development of drugs again has been the major thrust at Recon and Hikal and has resulted in the production of a large number of drugs of varying complexity.



103

Searle India, uniquely among G D Searle's outfits, was also involved in process development of pesticides in those days due to the peculiar economic compulsions of the MNC industry in India. This gave me good exposure to this chemistry, which has significant similarities to medicinal chemistry. Among many known pesticide molecules for which processes were developed at Searle, mention may be made of butachlor, a herbicide, diflubenzuron **105**, a

chitin synthesis inhibitor, fluocythrinate and MTI 500 (**107**) (scheme 25), the last two insecticides belonging to the synthetic pyrethroid group. A simple viable route was developed by Dr K R Ramachandran for **105** which was patented in India, involving synthesis of the corresponding acylthiourea **104** and replacement of sulphur by oxygen. A synthesis of MTI 500 (**107**) was also achieved wherein the thioester **106** was desulphurised! The lead chemist for this patented route was Dr T V Radhakrishnan.

9. Current interests

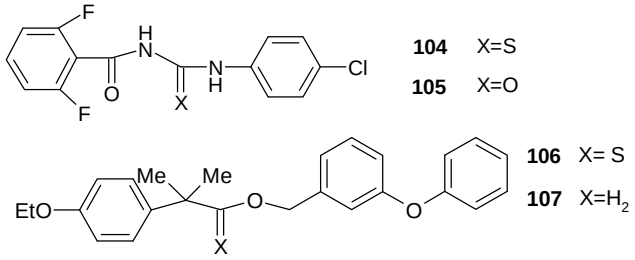
9.1 *Binding sites of active drugs*

In recent years, I have been collaborating more intensely with X-ray crystallographers and biophysicists in studies involving binding sites of bioactive molecules and supramolecular interactions in the solid state. For this purpose I can draw upon a library of about 2000 compounds I had prepared at Ciba Research Centre and carry out a limited amount of new chemistry with minimal human and material resources available for new research in laboratories largely devoted to process development.

9.2 *Studies on bioactive molecules*

During nearly a decade of association with Prof Vasantha Pattabhi, crystal structures of the hypoglycemic perhydroindoles **60** (Go8778, R = Me, R_1 = *n*-Bu)[86] and (Go 9001, R = Me, R_1 = *iso*-Bu)[87] and **65** (CGI 14600, R = Ph) and its active and inactive analogues were studied and attempts made to map putative binding sites by overlaying them on the structures of tolbutamide and glibenclamide.[88]

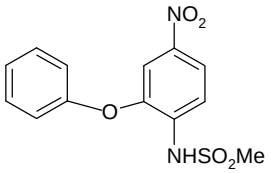
Polymorphism (or its absence) of the antiamoebic drug, satranidazole **18**, was the focus of another investigation.[89] An interesting sequel to this publication was an invitation to submit several nitroimidazoles synthesized by me for screening against leishmaniasis and trypanasomiasis by the not-for-profit organization, Drugs for Neglected Diseases.



Scheme 25.

Interesting papers were published on anti-inflammatory agents, which act by inhibition of cyclooxygenase. This enzyme is known to exist in two isoforms, COX 1 and COX 2. The former is a constitutive enzyme and has the housekeeping task of cytoprotection. The latter is generated at the site of injury and induces the synthesis of proinflammatory prostaglandins. Selective or specific inhibitors of COX-2 may be expected to provide relief without production of ulcers. Nimesulide **108** and meloxicam **109** (scheme 26) belong to the class of selective COX 2 inhibitors. Their crystal structures were elucidated and the drugs docked in the known active sites of COX 1 and COX 2 proteins. Binding, destabilizing and intermolecular energies were then derived. The values clearly showed that **108** and **109** bound COX 2 better than COX 1, thus presenting a theoretical explanation for the observed selectivity. Modifications to the structure of meloxicam **109** were proposed to enhance the selectivity.[90–92]

In a collaborative project with Prof P Balaram, the conformations of the aminomethyl and carboxymethyl side chains in gabapentin **110**, a blockbuster anticonvulsant and several relatives were delineated using X-ray crystal studies and high field 1H NMR investigations at various temperatures.[93] To understand the conformation in which the aminomethyl group in **110** binds to a receptor, analogues **111** and **112** (scheme 27), with the classical *t*-butyl anchoring group have been made.



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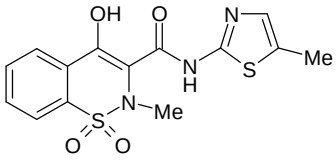

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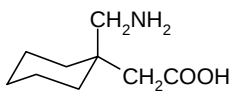
Scheme 26.



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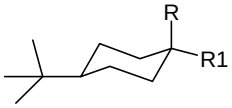


111 R= CH_2NH_2, R_1=CH_2COOH

112 R=CH_2COOH, R_1=CH_2NH_2

Scheme 27.

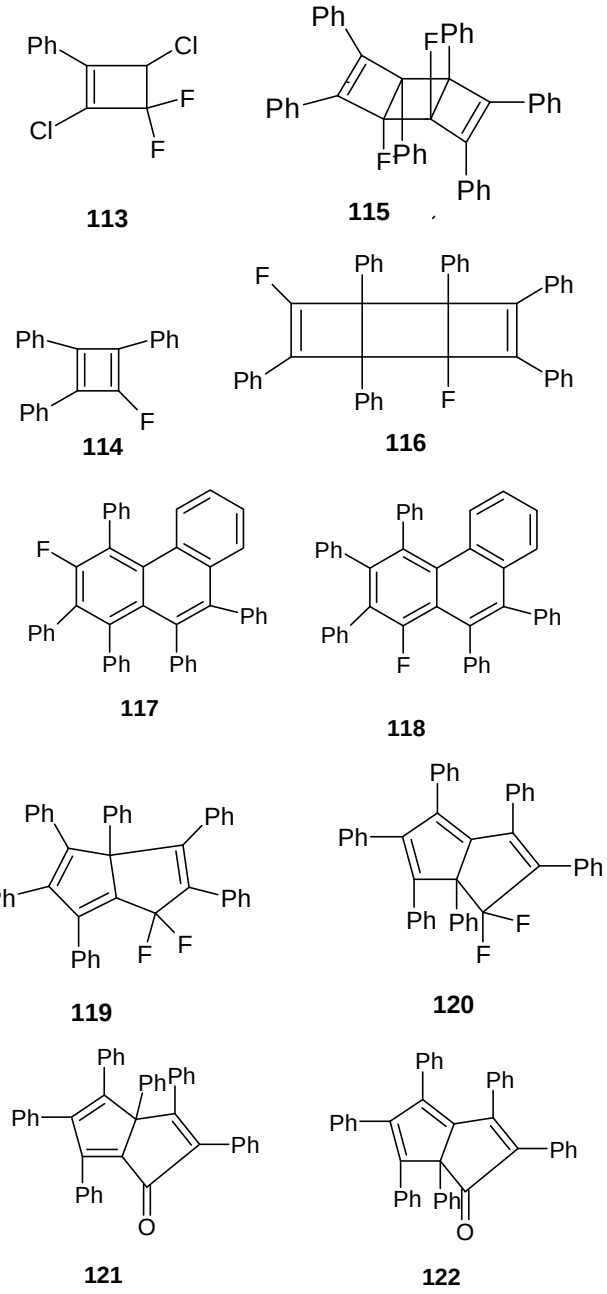
9.3 *Supramolecular interactions*

Sustained collaboration with Prof T N Guru Row started with a chance remark by the latter that he was looking for biologically interesting fluorine-containing organic molecules to study possible F,F interactions in the solid state. I could provide him a number of samples with the templates in **33**, **38**, **47** and **50**. Out of several structures solved, uniquely **38** showed appreciable intermolecular F–F interaction.[94–96] The availability of old analogues and synthesis of newer ones made it possible to have structure-substituent analysis.[97,98] After initial skepticism, F–F interactions are slowly but steadily receiving international acceptance. The occurrence of F–F interactions and their nature have been put on a firm foundation by Guru Rao and Chopra, based on charge density calculations on an analogue of **47** with an additional methyl group at position 3 on the indole which displays two polymorphic modifications, one of them showing the intriguing F–F interaction.

9.4 *Cyclbutadiene chemistry revisited – A parting shot*

It is only appropriate to end this review with interesting results which unfolded when I revisited the cyclobutadiene chemistry I had carried out in 1959–1960 with Prof J D Roberts at Caltech. This was inspired by the availability of samples with him even after the lapse of 45 years and Prof Guru Row's interest in the crystal structures of fluoroorganics and the X-ray crystallographic facilities available to him at IISc, which enabled rapid solutions of crystal structures (provided suitable crystals can be made). Available samples from the cyclobutadiene chemistry were obtained from Caltech and subjected to investigation. Mass and high field NMR data inaccessible in 1959–1960 were gathered and a number of reactions run or rerun. The fascinating conclusions are presented below.

In 1959, the reaction of cyclobutene **113** with excess phenyl lithium had been studied with the hope that this would lead to the heavily loaded triphenylfluorocyclobutadiene **114**. However, the major product obtained in moderate yield was a white dimer $C_{44}H_{30}F_2$ whose structure was deduced to be **115** on the basis of analytical and spectroscopic, particularly Raman data and also interestingly by dipole moment measurement.[13] The structure was confirmed by X-ray studies details of which were not fully published.[99] A minor sparingly soluble product **A** having the molecular composition $C_{44}H_{29}F$ has now been shown to be the fluoropentaphenylphenanthrene **117**, probably arising from a dimer **116** similar to **115** but with different dispositions of phenyl groups and the fluorine atom, by the loss of elements of hydrogen fluoride. The dimer **115** also loses the elements of HF upon short boiling in decalin to afford a sparingly soluble, high melting product **B** which is considered to be the phenanthrene **118**. The



Scheme 28.

major product of this reaction is a yellow compound **C** which is solely obtained upon *short* heating of **115** at its melting point. The product having the same molecular formula as **115** was originally assigned the dihydropentalene structure **119** but has been now found to be **120**. The structure of the orange ketone **D** obtained from **C** by sulphuric acid hydrolysis, originally considered to be **121**, has been now corrected as **122**. Finally, the photolysis product of **115**, a yellow ketone isomeric with **D** has been found in fact to have the structure **121** (scheme 28). Plausible explanations for the deep-seated rearrangements and transformations encountered in this study have been proposed.[100] Of course Prof. Guru Row was not too happy with the crystal structures since they all show only CH-π interactions and no H–F contacts, not to speak of F–F associations!

10. Conclusion

I have tried to show that interesting research can be carried out within the constraints of industrial requirements, which can offer great challenges and provide ample excitement.

Acknowledgements

I have been singularly fortunate to have worked under managements which supported and encouraged creativity. Of course, such work is invariably possible only with extensive collaboration. I have had plenty of this both in-house as well as with external academia. Important collaborators have been named in the above account, while all joint authors have been named in the references cited.

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