Chapter 1
Satranidazole and My Pharmaceutical Research Odyssey: A Success Story

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Abstract The start of my nearly 40 yearlong pharmaceutical research odyssey almost coincides with the beginning of my association with Hindustan Ciba-Geigy Limited, Research Centre, Goregaon, Bombay (now Mumbai), and satranidazole. Satranidazole, an excellent and relatively superior molecule, is the first and the only antiamoebic drug that has been discovered, developed and marketed from India. In future, it may find therapeutic applications for many more indications. It is a product of long-drawn, very expensive and intense scientific and technological efforts, often marred with uncertainties and serendipity, of the dedicated scientists and technicians. Satranidazole had to survive spates of several squabbles but, in the end, has emerged as a champion and seen the light of day. Satranidazole will definitely go a long way to improve and invigorate the quality of human life. Nonetheless, for the new and budding drug researchers, the success story of satranidazole, full of different hues and shades of human complexities, will be a source of distinctive inspiration and has several important lessons to offer.

Keywords Amoebiasis · Antiamoebic drugs · Ciba-Geigy · *Entamoeba cricetti* · *Entamoeba histolytica* · *Entamoeba muris* · Experimental models · Luminal · Satranidazole

My association with Hindustan Ciba-Geigy Limited, Research Centre, Goregaon, Bombay (now Mumbai), and satranidazole (compound no. GO 10213) started on January 1, 1983. Ciba, much ahead of times, believed in research-based global pharmaceutical business. To commemorate the 25th anniversary of Ciba, Summit, NJ, USA (operations started on June 21, 1937), on May 25, 1962, the company organized a dedication ceremony for the nation's $2,700,000 most modern research centre (CIBA 1962). Dr. Robert Kaeppeli, Chairman, Board of Ciba Ltd., Basel, Switzerland, was one of the lead speakers in the ceremony. And just after nearly 1 year, Ciba established another research centre in Goregaon, Bombay, India. The very idea for this research centre was conceived, set in motion and nurtured by Dr.

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Kaeppeli. The basic objective behind the project was to enhance the profitability from the Ciba units in India by boosting their productivity driven by scientific and technological advancements. And soon the centre started evolving from an inchoate notion into one of the world-class pharmaceutical research organizations. The centre, christened as Ciba Research Centre, Goregaon, was officially inaugurated by our first Prime Minister Pt. Jawaharlal Nehru on March 21, 1963 (Figs. 1.1 and 1.2), who, on that occasion, made the following statement:

> *Altogether, if I was very much younger and inclined to do scientific research work, I would rather like to do the work in such surroundings and under the conditions which will no doubt prevail here.*

Fig. 1.1 (**a**, **b**) Prime Minister Pt. Jawaharlal Nehru at the inauguration of the Ciba Research Centre, Goregaon, Bombay (now Mumbai)

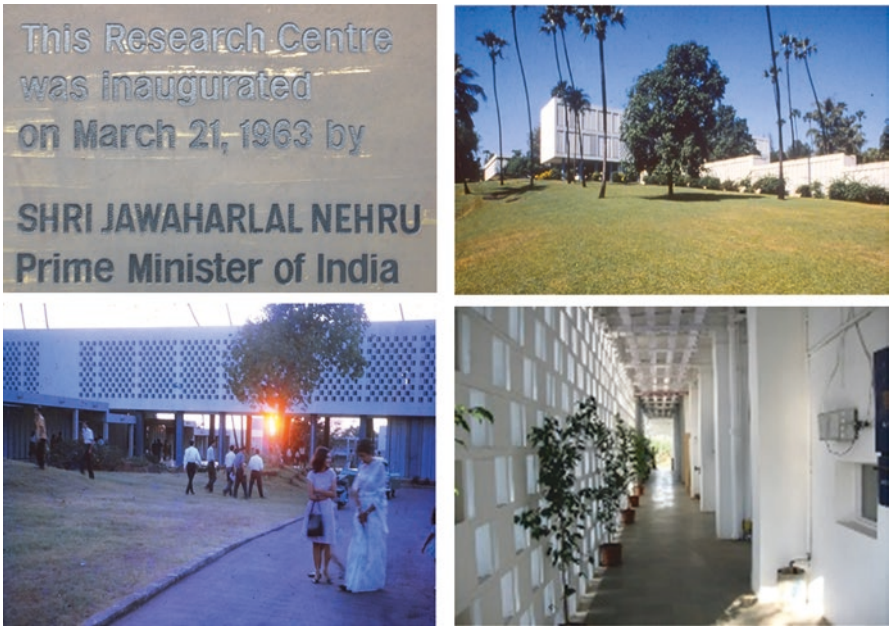

Fig. 1.2 (Clockwise) The inaugural plaque, library, research buildings and a corridor of Hindustan Ciba-Geigy Limited, Research Centre, Goregaon, Bombay (now Mumbai)

In the cool morning of January 3, 1983, I entered my new work place for the first time. More than the laboratories and the facilities, I was greatly moved by the scenic and picturesque surroundings. I and my predecessor had an overlapping period of 1 month to smoothen the transition. I was amazed by the lab management and meticulous record keeping. All the scientists in the lab were highly trained and quite experienced, and a reasonable degree of lab citizenship among them was clearly visible. By the time I joined the centre, it had already been dedicated to tropical disease research. I was to head the protozoan diseases research programme, to be more pointed, to modernize, strengthen, infuse dexterity, accelerate and give a much-needed new dimension(s) to the ongoing new antiamoebic drug discovery programme; and to add new related protozoan diseases to the programme.

Before I go any further, a few words about satranidazole. Briefly, nearly 45 years ago, it all began in Basel, Switzerland, with the merger of Ciba and J. R. Geigy Ltd., in 1971, which resulted in the emergence of a composite identity Ciba-Geigy. This merger, due to several reasons, affected the functioning of Ciba Research Centre, Goregaon, only in the dedication of its research priorities to tropical diseases. This prioritization of the drug discovery programmes was done after careful deliberations and later proved to be a boon to the centre. In October 1967, in a lavish international symposium in New York, Ciba launched its new antischistosomal drug niridazole that was initially marketed with lots of fanfare but eventually had to be withdrawn. Taking the strength from niridazole's good antiamoebic activity, and inspired by metronidazole, a Basel scientist synthesized another compound CGP 291, a potent antiamoebic drug. As the centre in Goregaon now was to concentrate

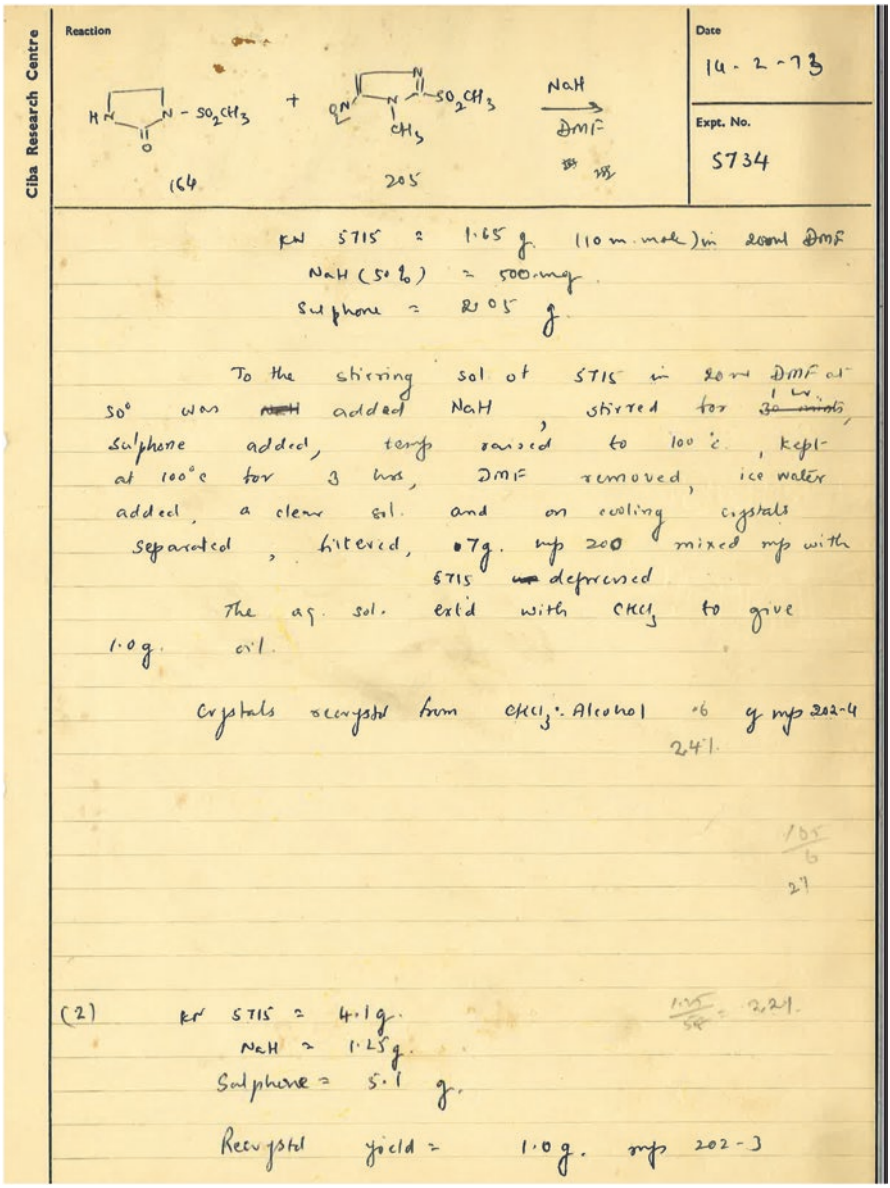

Fig. 1.3 IAB record of first synthesis of GO 10213

on tropical diseases, CGP 291 was shifted to Goregaon for its bulk production for clinical development. Unfortunately, its synthesis yielded a complex mixture of compounds, which warranted an entirely different synthetic approach (Fig. 1.3) leading to GO 10213 (satranidazole) that was synthesized in the laboratory of group leader Dr. K. Nagarajan, along with several other new analogues. GO 10213 stood

superior as compared to CGP 291 and even metronidazole in standard animal models for antiamoebic screening (Nagarajan et al. 1982). Some other analogues of GO 10213 also showed superiority sufficient enough to warrant their consideration. However, after lots of arguments related to patent authorships and several other considerations including short-term toxicity studies, finally, GO 10213 was chosen for further development. A bulk quantity of GO 10213 was synthesized, and after safety pharmacology, metabolic/pharmacokinetic and stability studies, tablets were formulated. Later, an IND was filed, and after phase I, II and III clinical trials, finally, an NDA was filed to the Drug Controller of India.

Soon after joining, to my utter surprise, I found that though the NDA for GO 10213 has been filed, it has only been tested for its antiamoebic activity against *Entamoeba histolytica*, the causative agent of human amoebiasis, either in mixed bacterial cultures, in vitro, or against hepatic and caecal amoebiasis in hamsters and mice, respectively. In these models, *E. histolytica* grows and multiplies along with various other living associates, in the absence of which it will perish. One inherent limitation of such models is that it is not possible to discern whether or not the antiamoebic activity observed is due to the direct antiamoebic activity of the test compound or it is indirect due to the killing of the living associates. Certainly, it was a very important and crucial question. No doubt, to a large extent, the future of GO 10213 was dependent on its direct amoebicidal activity. By now the centre had already gone quite far with GO 10213, and at this stage, even the thought of its failure as a direct antiamoebic drug was a dreadful one and nightmarish. Soon, after holding a series of discussions with the Director, Dr. Nagarajan and other colleagues, I mobilized my team and embarked on the initiation of a new screening activity, i.e. the evaluation of test compounds for their direct antiamoebic activity against axenically grown *E. histolytica* (NIH 200 strain). Well, it wasn't that easy. Besides making arrangements for necessary facilities, the most important thing was to train the scientists for this new screening methodology that required both immense sophistication and dexterity. After lots of efforts, at last, we were successful in establishing the methodology in the lab, and the new antiamoebic screening activity started with a big bang. My team of scientists, though highly efficient and motivated, was not immune to commit mistakes. We were testing several known antiamoebic drugs along with several batches and various analogues of GO 10213. Unfortunately, a mix-up occurred, and the concerned scientist conveyed me the results we were not expecting, and our headlights just went dim. Personally, I am not the one used to hide my own defalcations, I kept my cool and later went through all the procedural details, calculations and records, several times over, and then zeroed on to the lapse. We started again, firm and resolute, with meticulous precision and then came the eureka moment: one fine morning the concerned scientist informed me that GO 10213 (MIC 1.0 μg/ml) was almost twice as potent as metronidazole (MIC 1.95 μg/ml). This revelation came as a new feather in the cap of GO 10213 and was a big delight to all of us. Later, while in the USA, I published this data, something not a high priority to the centre (Singh et al. 1985) (Figs. 1.4 and 1.5).

Fig. 1.4 A photograph of Dr. K. Nagarajan taken in 1974

Fig. 1.5 L to R: Dr. K. Heusler, Prof. Dr. E. F. Jenny, I (Dr. Prati Pal Singh) and Dr. J. A. McFadzean during the Symposium on "Recent Advances in Protozoan Diseases", November 28–29, 1983

Next, we developed a new animal model for screening new potential luminal amoebicides (Singh et al. 1987). Experience has shown that in new drug discovery research, experimental models of diseases play a major role and, at times, even change the entire course of investigations and their outcome. I should like to repeat that after the materialization of Ciba-Geigy as the composite entity, the Goregaon Research Centre having been assigned to concentrate on new antiamoebic drug discovery research also started to synthesize new compounds around the lead molecule diloxanide furoate, a known luminal amoebicide. On June 28, 1972, compound GO 9863 was synthesized but was found to be inactive in both hepatic and caecal models of experimental amoebiasis, and the same was true for the other known luminal amoebicides as well. Those days, at the Goregaon Research Centre, only these commonly used animal models of experimental amoebiasis were established and operational. No specific experimental model of luminal amoebiasis was available. However, in a US patent in 1976 and later in a research paper, Sterling Winthrop reported that the compound GO 9863 was highly active in a hamster/*E. cricetti* model for the screening of potential luminal amoebicides. Later, in 1984, at Mexico, they registered it as quinfamide, a new luminal amoebicidal drug. Thus, just because of the lack of an appropriate experimental model, Ciba-Geigy lost a drug or may be fortunes. I took this as a challenge and started thinking to come out with something to ensure that this doesn't happen again. Instead of establishing and using the known hamster/*E. cricetti* model, I decided to revisit the entire space and come up with something innovative, different and, of course, more meaningful. In literature, I found that akin to hamsters having natural *E. cricetti* infection, Wistar rats also have natural *E. muris* infection, albeit more intense. Wistar rats were easily available in the animal house of the centre. My scientists then got involved in a very labour-intensive and long-drawn project, and after several months of zeal, their efforts were met with success and ended up in the development and standardization of a new model for the identification and evaluation of potential antiamoebic agents for their luminicidal activity. Interestingly, compound GO 10213 turned out to be active, albeit weakly, in this in vivo model also. On my return from the USA, with financial support of the research centre, I published this work (Singh et al. 1987).

Lest I pass over, I should like to mention here some of the difficulties I and my team encountered while developing this new and novel model. In my opinion, difficulties in the execution of a research project are at times equally or even more important than its successful outcome. In the development of rat/*E. muris* model, besides scientific and technical difficulties, we had to face several human problems which were more challenging than the scientific work. When, for the first time, I proposed the very idea of this model, most of my biology colleagues almost ridiculed it. Nevertheless, unfazed, I continued with our work, and after surviving one onslaught after the other, we, over a few months, generated lots of data, which documented the nuances of this model. I remember very well that in one of our review meetings, where some senior scientists from Ciba-Geigy, Basel, were also present, I presented the entire data related to the development of this new model. And then all of a sudden, to my astonishment, one of the senior scientists (obviously, whom I can't name) started, repeatedly and abortively, to interrupt the flow of my presenta-

tion and distract the focused attention of other participants of the meeting. I could read the faces of several participants that they could decipher this attempted gimmick. Well, unabated, I continued my presentation and drove the main punch of my work home, quite convincingly. My presentation was well taken by all the participants. In fact one participant, who had been a regular partaker in such meetings, during the following tea break, told me that this time he was even more convinced of the novelty, authenticity, reproducibility and usefulness of this new experimental model of luminal amoebiasis. In the next few months, we routinely used this model, and several compounds including satranidazole were tested; satranidazole was active albeit at relatively higher doses and thus started a new activity for the testing of potential luminal amoebicides in an experimental model developed in-house.

On the other hand, this time around, Hindustan Ciba-Geigy was in a highly euphoric mood. Despite the fact that our centre had practically given all the relevant data and information to the Basel group, several of their scientific leaders used to visit the Goregaon Research Centre for "hard talks" on satranidazole. Additionally, I remember the visit of late Prof. M. G. K. Menon to the centre on those days, and I had the occasion to discuss with him regarding satranidazole. At that time, I had never imagined that nearly 32 years later, he will be the one to write the foreword of one of my books *Water and Health* (Singh and Sharma 2014). We the scientists at the centre and those from Basel used to have long and intense overhead projection presentation and discussions. And, at the end of the day, we all used to have several get-togethers in the form of sundowners and dinners in the exquisite hilltop guest house in the scenic beauty of the centre. One pleasant afternoon, I learned that the Director has planned for a meeting with all the scientists. Soon after he called the meeting to order, he informed us that it has been decided to organize a symposium on protozoan diseases to commemorate the 20th anniversary of the centre. The occasion was also planned to launch satranidazole. I was chosen as the secretary for the Scientific and Publications Committee. After some deliberations, the symposium was titled Symposium on "Recent Advances in Protozoan Diseases" and was scheduled for November 28–29, 1983. The President of the symposium was chosen to be the Vice-President of Glaxo company Dr. Paul Anand, and we the members of the core organizing committee used to meet in the President's office near the Mumbai TV tower at Worli. R&D heads of some other pharmaceutical companies were also taken as the members of the organizing committee, and we after our meetings used to join in the Band Box restaurant nearby. For some financial help, we also approached the Chairman, Unichem Ltd., who very courteously entertained us at the Racecourse at Mahalaxmi and also generously funded the symposium. I was involved mainly in the development of the scientific programme, preparation and receiving of the scientific material and selection, approach and formally extending the invites to the prospective speakers. I was also entrusted with the responsibility to invite four international scientists, and the entire cost of their participation was to be supported by Ciba-Geigy, Basel. I corresponded with several eminent scientists including Prof. Julius P. Kreier, OH, USA; Dr. A. Martinez Palomo, Mexico; Dr. J. T. Ponnampalam, Malaysia; Dr. R. D. Powell, IL, USA; Dr. J. A. McFadzean, UK; and several national scientists. A big team of relevant scientists from Ciba-

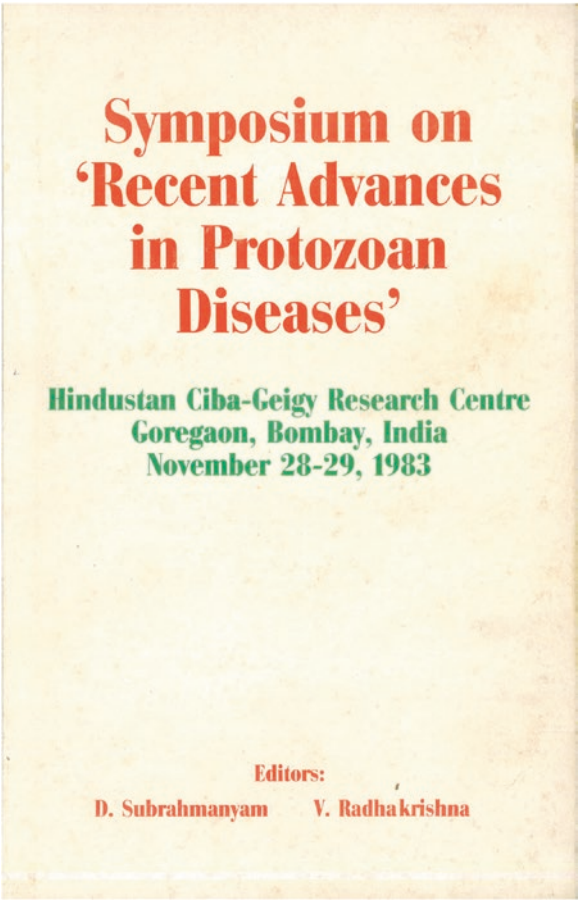

Fig. 1.6 The proceedings of the symposium held to commemorate the 20th anniversary of the centre and to launch satranidazole

Geigy Ltd., Switzerland, was also invited to the symposium. Almost all of them accepted the invite and contributed immensely to objectives of the symposium. Dr. K. Nagarajan and several other scientists involved with the discovery, development and clinical trials of satranidazole also participated and presented volumes of their data in the symposium. The symposium was a grand success. Satranidazole had now become a buzz word. Dr. K. Nagarajan, the brightest star in the constellation, nonetheless, kept his characteristic humility throughout. I was told that, perhaps, no other symposium was ever organized by the centre, at least of this magnitude. The proceedings of the symposium was published a couple of years later (Fig. 1.6; Subrahmanyam and Radhakrishna 1985).

Today, the Goregaon Research Centre with its immense research facilities, beautiful laboratory and housing buildings and lush green gardens and lawns has been subsumed somewhere. During my last visit to Mumbai a few years back, I saw that a huge commercial tower is all that can be seen at that place. All those scientists and research assistants have gone here and there, and some have even passed away. But

the days when I, Dr. A. B. Vaidya and some other colleagues, as members of the package insert team for satranidazole, used to go to our Head Office at Churchgate for the meetings with the medical team over there are still very much alive in my memory. Nevertheless, the good thing is that satranidazole has seen the light of the day and is very much around us. Today, the research centre is not around, but I am sure satranidazole will be around us for a long time. Presently, according to Medindia's database, nine single generics and three combined generic brands of satranidazole are listed, which are being manufactured by five pharmaceutical companies, and new generics are being constantly introduced. For me, personally, the contribution of this article has some special meaning. I got associated with satranidazole almost at the beginning of my research career as a new drug discovery research scientist, and, today, while I write this article, I am left with only a few years to superannuate. And as I look back, the journey had been long and arduous yet, at times, highly rewarding. I never had the slightest comprehension to get reconnected with satranidazole. However, no doubt, now I deem it a pleasant accident. The story of satranidazole further strengthens my belief in the African adage that if you want to go fast, go alone and if you want to go far, go along with others.

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