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Catalysis: The pharmaceutical perspective

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ABSTRACT

The striking impact of enzymatic and organometallic catalysis on the design of environmentally friendly processes for the discovery and production of pharmaceutical products is discussed. Four case studies namely ST1535, Idarubicin, Rubitecan and 7ACA are analysed in the context of a modern synthetic design based on the application of the 12 green chemistry principles.

1. Introduction

Organometallic and enzymatic catalysis are key technologies for the pharmaceutical industries for both discovery and development of new chemical entities (NCE). The discovery of NCE in the area of small molecules is centred on the design of flexible synthesis to allow a high level of chemical diversity. In spite of the increasing complexity of the molecular architecture and the increasing number of chemical steps the rapid production of molecules for screening is a must. In this context, organometallic catalysis is useful because it is a flexible technology, suitable for parallel synthesis and microwave acceleration. An aromatic halide can be subjected to several palladium-catalysed transformations (Stille, Heck, Heck/Cassar, Sonogashira, Negishi, Suzuky, Kumada, Hyama, Buchwald–Hartwig, carbonylation, reduction, cyanation, ether synthesis, etc.) generating a high degree of chemical diversity.

However, catalysis is even more important for the design of synthesis for the development of NCE to produce material for clinical trials and the pharmaceutical market.

The popularity of chemistry among the public reached the lowest level possible 30 years ago and this economic sector is still struggling [1]. The effect of poor technical and safety design approaches to industrial processes and plants determined several accidents that completely changed the Environment Health & Safety (EH&S) laws in Europe and in the western world in general. In Europe, Flixborough (1 June 1974) and Seveso (10 July 1976) accidents were the point of no-return [2]. The new legislations increased the level of control both on safety and environmental pollution [3]. But the perception of chemistry among the public did not change: a chemical substance is bad for you and the environment. The introduction of the 12 principles of green chemistry (Fig. 1) [4] and the use of simple words improving the communication to the external world allowed several chemists to have access to public grants. However, most of the publications have a misleading approach focusing the attention on technologies that violate the main GC principles: microwaves (energy), ionic liquid (biodegradability and non-toxic products), water chemistry (water is becoming one of the most important resources world wide and the production of waste water is not "green"), fluorous phase chemistry (biodegradability), etc. [5]. For these reasons these technologies have few or no industrial applications.

The most important revolution of the 21st century are the EH&S laws made by the governments and the globalisation that forced western world industries to compete with countries like India and China with completely different cost structures. The only way to compete in the actual market is technological excellence. Thinking green is the only way to design low cost and competitive industrial processes in the western world. The violation of any of the 12 principles determines cost increases of the overall process.

For process research chemists in the pharmaceutical industry, the challenge of process design is increasing. In fact, the architectural design by medicinal chemists is more complex, the number of synthetic steps and the development of enantiomerically pure drugs is increasing [6]. The process chemist must use the 12 principles for the design of the synthesis from the beginning of the development process. It is worth noting that a green approach to pharmaceutical production must be focused on "taking out of the trash." This was the title of an interesting paper published in 1993 by Braithwaite and Ketterman, based on the simple consideration that only a small number of atoms in a synthetic process are incorporated into the final molecule (70–80% are simply solvents) [7]. But there are other aspects that must be taken into consideration: cooling/heating agitation, filter aid, etc. (Fig. 2).

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1. **Prevention.** It is better to prevent waste than to treat or clean it up after it's been created.
2. **Atom Economy.** Synthetic methods should be designed to maximize the incorporation of all the materials that are used in the process.
3. **Less Hazardous Chemical Synthesis.** Synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment wherever possible.
4. **Designing Safer Chemicals.** Chemical products should be designed to effect their desired function while minimizing their toxicity.
5. **Safer Solvents and Auxiliaries.** The use of solvents, separation agents and other auxiliary substances should be made unnecessary wherever possible and innocuous when used.
6. **Design for Energy Efficiency.** Energy requirements should be minimized, synthetic methods should be conducted at ambient temperature and pressure.
7. **Use of Renewable Feedstocks**. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. **Reduce Derivatives.** Unnecessary derivatization should be minimized or avoided because such steps require additional reagents and can generate waste.
9. **Catalysis. Catalytic reagents are superior to stoichiometric reagents.**
10. **Design for Degradation.** Chemical products should be designed so that at the end of their function they break down into innocuous degradation products that do not persist in the environment.
11. **Real-time Analysis for Pollution Prevention.** Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention.** Substances and their form used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions and fires.

Fig. 1. The 12 green chemistry principles.

All these factors have an impact on the cost. Some case studies will be discussed.

2. Discussion of case studies

2.1. Discovery

ST1535 **8d** (Scheme 1) is a selective adenosine A_{2a} receptor antagonist [8]. Recent data substantiate the evidence that adenosine A_{2a} receptor antagonists are able to reverse motor deficits in a highly predictive model of clinical efficacy in Parkinson's disease. The data suggests that ST1535 will be an effective anti-Parkinson agent in combination with l-DOPA and allow a reduction in l-DOPA usage [9]. This molecule is now in phase I clinical trial for the treatment of Parkinson disease. The discovery of this molecule was a result of the joint efforts of the Sigma-Tau (Minetti/Gallo/Giorgi labs) and Urbino University (Tarzia group) teams. A focused library of potential A_{2a} antagonist was designed [8] using the Stille type reaction [10] to introduce chemical diversity. The Stille protocol was simply applied with no optimization of the reaction conditions. At this stage the amount of material necessary for the screening in vitro is very limited 5–10 mg and the yield has no importance. The substitution at C-4 was critical to get and tune the A_{2a} activity. The synthesis designed for discovery has a high degree of flexibility. The overall yields range from 0.6% to 15%. ST1535 **8d** resulted among the best product in terms of activity and selectivity (Tables 1 and 2). The Stille reaction, that was very useful for the discovery process, has several drawbacks like toxicity of the reagents [11], low turnover number (TON), and problematic final purification at least in this specific case. In addition, the overall yield for the synthesis of ST1535 **8d** is only 11%. The discovery synthesis did not meet the basic requirements for scale-up and the process was modified using as guideline the green chemistry principles.

3. Development

3.1. Idarubicin (Idamycin®)

Anthracycline antibiotics are an important class of molecules used in anticancer therapy (Fig. 3. Daunorubicin **9**, Doxorubicin **10**, Epirubicin **11** and Idarubicin **12** are on the market while

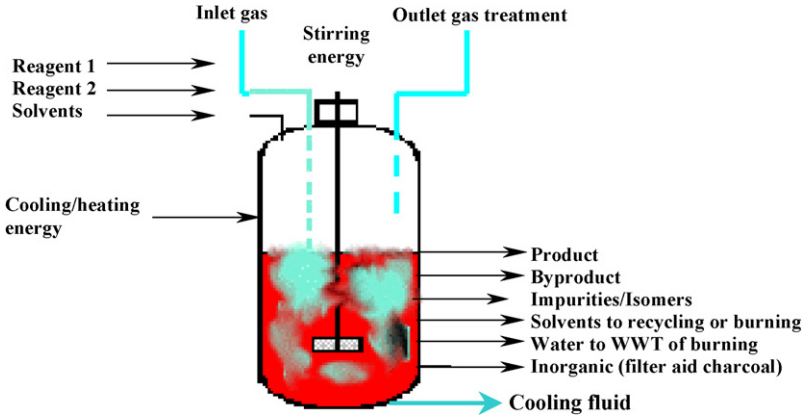
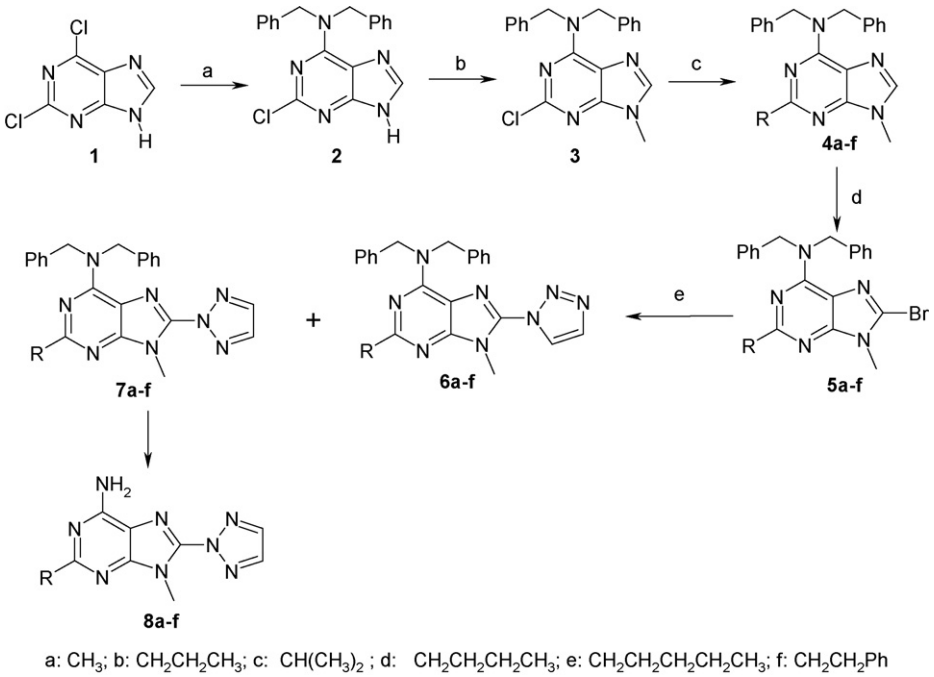


Fig. 2. What is going into a reactor is going out mainly as a waste.



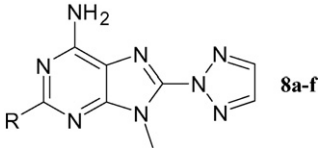
Scheme 1. (**a**) EtOH, Bn_2NH, iPr_2EtN, reflux, 20 h. (**b**) DMF, K_2CO_3, CH_3I, rt, 12 h. (**c**) NMP, Bu_3SnR, reflux (for R = CH_2 = $C(CH_3)$; CH_3CH = CH; PhCH = CH the Stille product was immediately hydrogenated). (**d**) CH_3OH, THF, sodium acetate buffer (pH 4), Br_2, rt. (**e**) DMF, K_2CO_3, 1*H*-1,2,3-triazole, 60 °C. (**f**) CH_2Cl_2, CF_3SO_3H, reflux.

Annamycin **13** and Sabarubicin **14** are under clinical trial) [12]. These molecules are DNA intercalating agents but also capable of inhibiting topoisomerase II. Idarubicin **12** in combination with other approved antileukemic drugs is indicated for the treatment of acute myeloid leukemia (AML) in adults. Several total syntheses of Idarubicin **12** have been described but the only efficient processes are semisynthetic approaches based on the use of daunorubucin **9** as starting material. In fact, daunorubicin **9** can be efficiently produced industrially by fermentation of an over-producing strain of *Streptomyces peucetius* using limited fermentation volumes (10–20,000 L) in consistent quantities (tons) [13].

The main characteristic of the aglicone of Idarubicin **12**, Annamycin **13** and Sabarubicin **14** is the absence of the methoxy group at C-4. The first semisynthesis of idarubicin aglicone **20**, described in Scheme 2, was based on demethylation of the C-4 ether of **15**, C13 ketone protection, selective triflation of the phenol in C-4 followed by palladium(0)-catalysed reduction under homogeneous conditions using formate as stoichiometric hydride source [14]. The final deprotection of **19** afforded the final product in five steps. The goal was achieved defining a palladium-catalysed reduction protocol based on the use of bidentate phosphine ligands [15]. Triflate **18** is unstable and generates at 50–60 °C two typical process impurities **21** and **22**. The use of a bidentate phosphine ligand palladium(0) catalyst allowed to carry out the reduction at 40 °C avoiding the formation of **22** and the decomposition of the homogeneous catalyst to palladium black. Palladium black can decompose formic acid to hydrogen and CO_2 and under typical heterogeneous conditions perform the reduction of the C-7 alcohol generating **21**. This synthesis is incredibly efficient with respect to any total synthesis described in literature [16]. In addition, daunomycinon **15** was a waste of the industrial process to get the activated daunosamine **25**. In fact, compound **25** was obtained from daunorubicin **9** by trifluoroacethylation, followed by acidic treatment and activation of the anomeric position (Scheme 3).

The amount of side products **21** and **22** generated during the reduction process was kept under control by a fine tuning of the reaction conditions. The palladium metal could be easily recovered by charcoal treatment of the final reduction mixture and recycled. A few years later, Antibioticos researchers patented a three step synthesis of **20** eliminating the ketone protection [17]. In fact, the fine tuning of the triflation conditions allowed the selective functionalization of the C-4 phenol avoiding the formation of the enoltriflate at the C-13 ketone (**16** → **26**). The enoltriflate interferes with the palladium(0)-catalysed reduction process [18]. The elimination of two synthetic steps (protection–deprotection) increases the atom economy of the process. The industrial Idarubicin **12** preparation centred on the short semisynthesis of aglicon **20** is described in Scheme 4 and is the best and shortest synthesis developed so far.

Table 1
Affinity K_i (nM) and selectivity for the adenosine receptors



Compounds	*R*	Affinity[a] K_i (nM)				
		A_{2a}	A_{2B}	A_1	A_1/A_{2a}	A_{2B}/A_{2a}
8a	CH_3	70.4	*b*	10.4	0.15	
8b	$(CH_2)_2CH_3$	83.7	18.0	266.0	3.18	0.22
8c	$CH(CH_3)_2$	481.3	*b*	2270.0	4.72	
8d	$(CH_2)_3CH_3$	6.6	352.3	71.8	11.92	58.53
8e	$(CH_2)_4CH_3$	3.3	153.0	26.2	7.84	45.81
8f	$(CH_2)_2Ph$	4.7	2330.0	80.0	17.02	495.74

[a] K_i values represent replicate determinations and S.E.M. are typically within ±20%.

3.2. 9-NO_2-camptothecin (Rubitecan®) and 9-NH_2-camptothecin

Camptotechin (CPT) **27** (Fig. 4) is a plant alkaloid present in wood, bark and fruit of the Asian tree *Camptotheca Acuminata* isolated back in 1967 by Wani and Wall at the Research Triangle Institute [19]. CPT

Table 2
Values of affinity and selectivity, expressed as K_i (nM) for the adenosine A_3 receptors

Receptors	**8d**		**8e**			Reference compounds	
	1 μM	K_i (nM)	1 μM	K_i (nM)		IC_{50} (nM)	K_i (nM)
A_3 (*h*)		>1000		760	*IB-MECA*	1.2	0.84
$ADO_{transporter}$	24		34		NBTI	0.30	
α_1 (non-selective)	–	–	–		Prazosin	0.86	
α_2 (non-selective)	–		–		Yohimbine	95	
β_1	–		–		Atenolol	1.770	
β_2	–		–		ICI 118551	2.3	
BZD (central)	–		–		Diazepam	12	
D1	–		–		SCH 23390	0.66	
D2	–		–		(+)Butaclamol	8.9	
D3	–		–		(+)Butaclamol	5.1	
D4 (*h*)	–		–		Clozapine	156	
D5 (*h*)	–		–		SCH 23390	0.61	
GABAa	–		–		Muscimol	16	
GABAb	–		–		Baclofen	50	
$GABA_{transporter}$	–		–		Nipecotic acid	10.100	
AMPA	–		–		L-Glutamate	613	
Kainate	–		–		Kainic acid	77	
PCP	–		–		MK-801	2.0	
P2X	–		–		α,β-MeATP	14	
P2Y	–		–		dATPα S	22	
NMDA	–		–		CGS 19755	967	
H_1 (central)	–		–		Pyrilamine	1.3	
M_1	–		–		Pirenzepine	22	
M_2	–		–		Methoctramine	34	
M_3	–		–		4-DAMP	3.5	
M_4	–		–		4-DAMP	1.9	
M_5	–		–		4-DAMP	2.0	
$Choline_{transporter}$	–		–		Hemicholinium-3	12	
Opiate	–		–		Naloxone	1.6	
$5\text{-}HT_{1A}$	–		–		8-OH-DPAT	0.66	
$5\text{-}HT_{2A}$	–		–		Ketanserin	2.7	
$5\text{-}HT_{2C}$ (*h*)	–		–		Mesulergine	1.9	
$5\text{-}HT_3$ (*h*)	–		–		MDL 72222	9.3	
$5\text{-}HT_4$	–		–				
$5\text{-}HT_{5A}$ (*h*)	–		–		Serotonin	79	
$5\text{-}HT_6$ (*h*)	–		–		Serotonin	421	
NE transporter	–		–		Protriptyline	1.1	
DA transporter	–		–		GBR 12909	5.0	
5-HT transporter					IMIPRAMINE	4.4	

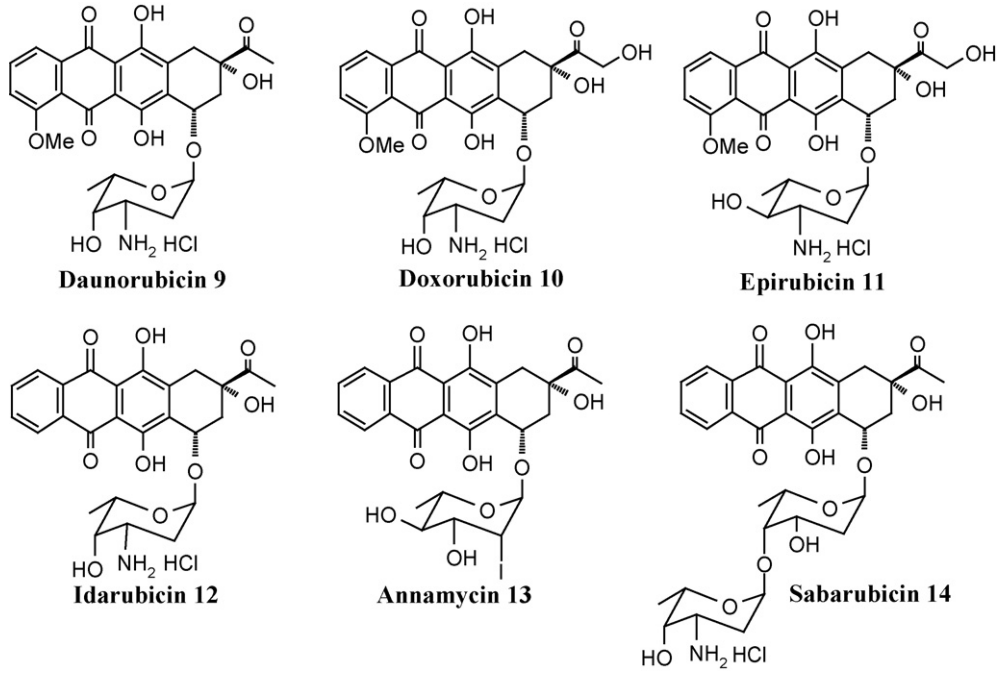
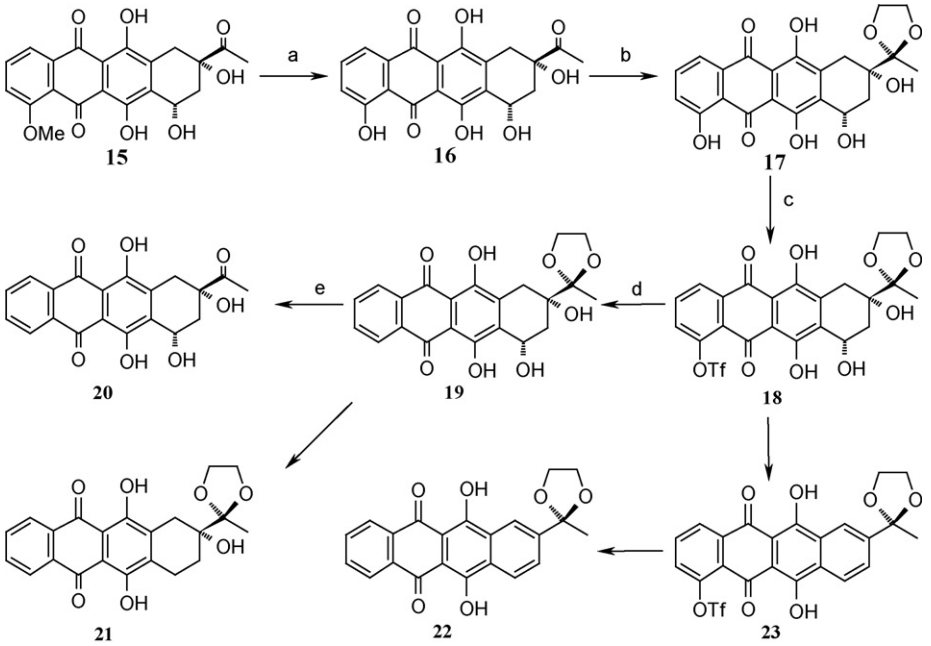
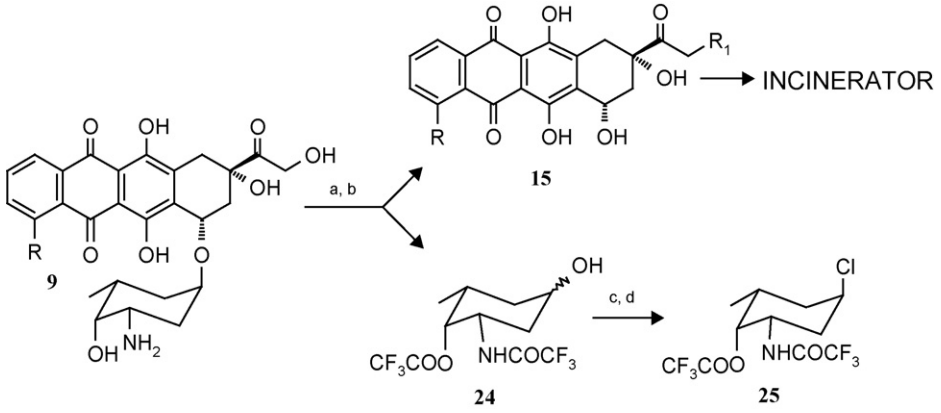


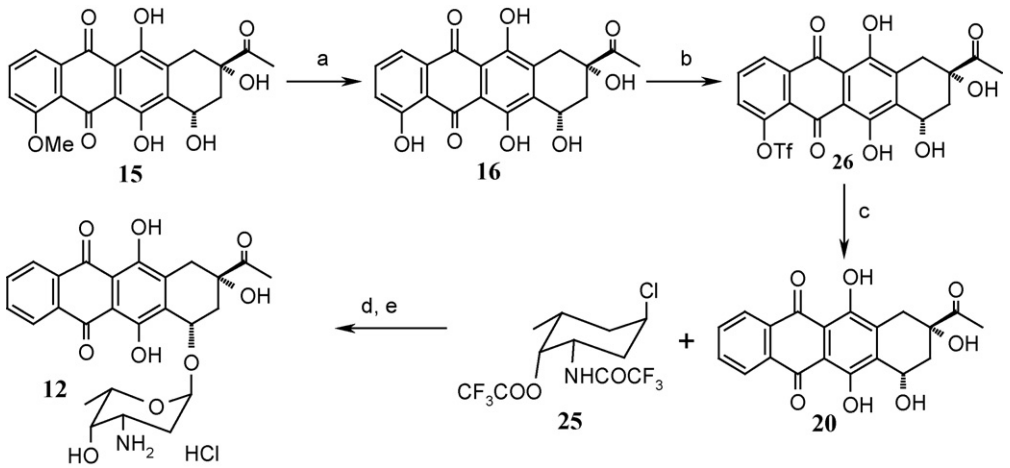
Fig. 3. Anthracyclins.



Scheme 2. (a) $AlCl_3$, CH_2Cl_2, reflux, 2 h (88%). (b) $(CH_2OH)_2$, PTSA, toluene, 2 h (90%). (c) Tf_2O, DIPEA, 4-DMAP, Py, 0 °C (≈70%). (d) $Pd(OAc)_2$/DPPF (1/1.1), DMF, HCOOH, TEA, 40 °C, 7 h (82%). (e) CF_3COOH, 0 °C, 0.3 h (90%).



Scheme 3. (a) $(CF_3CO)_2O$, CH_2Cl_2. (b) HCl dioxane. (c) $(CF_3CO)_2O$, CH_2Cl_2. (d) HCl gas.



Scheme 4. (a) $AlCl_3$, CH_2Cl_2, reflux, 2 h (88%). (b) Tf_20, DIPEA, 4-DMAP, Py, 0 °C (65%). (c) $Pd(OAc)_2$/DPPF (1/1.1), DMF, HCOOH, TEA, 40 °C, 7 h (70%). (d) CF_3COOAg, CH_2Cl_2. (e) OH^-.

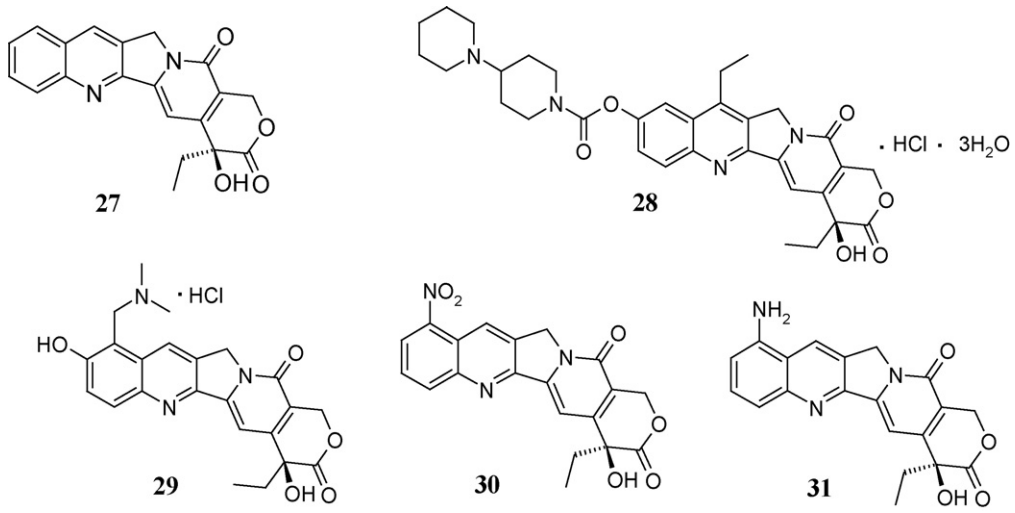
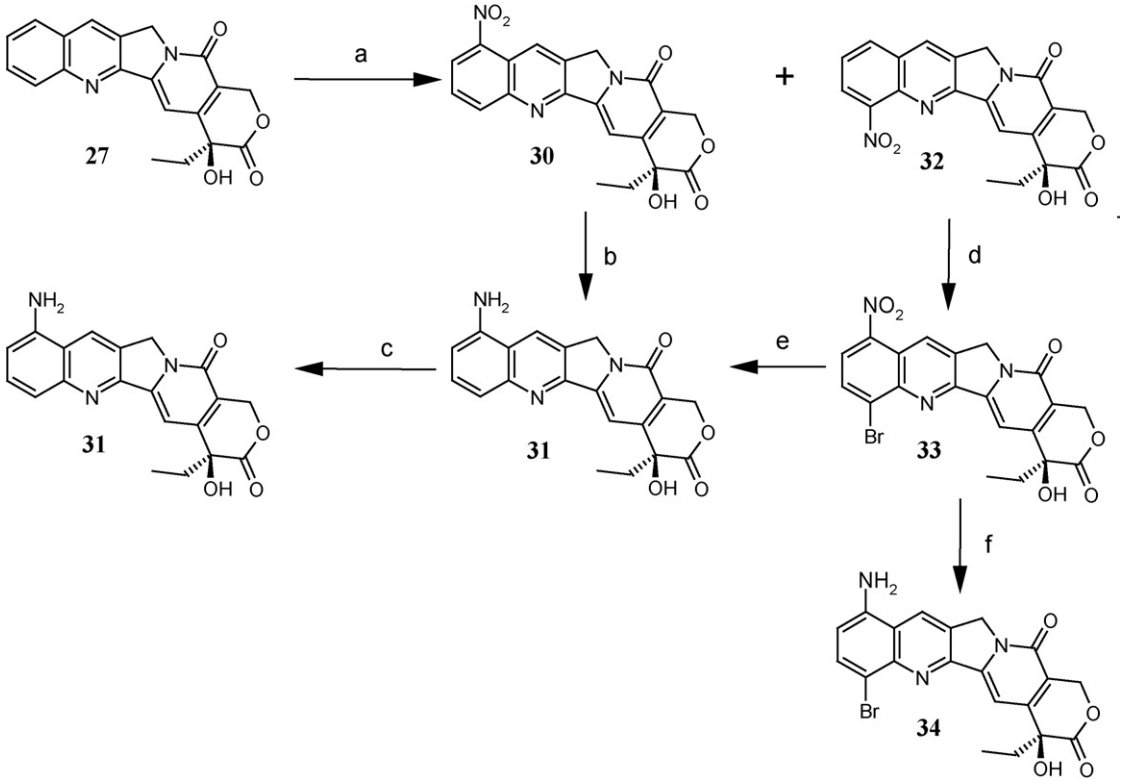


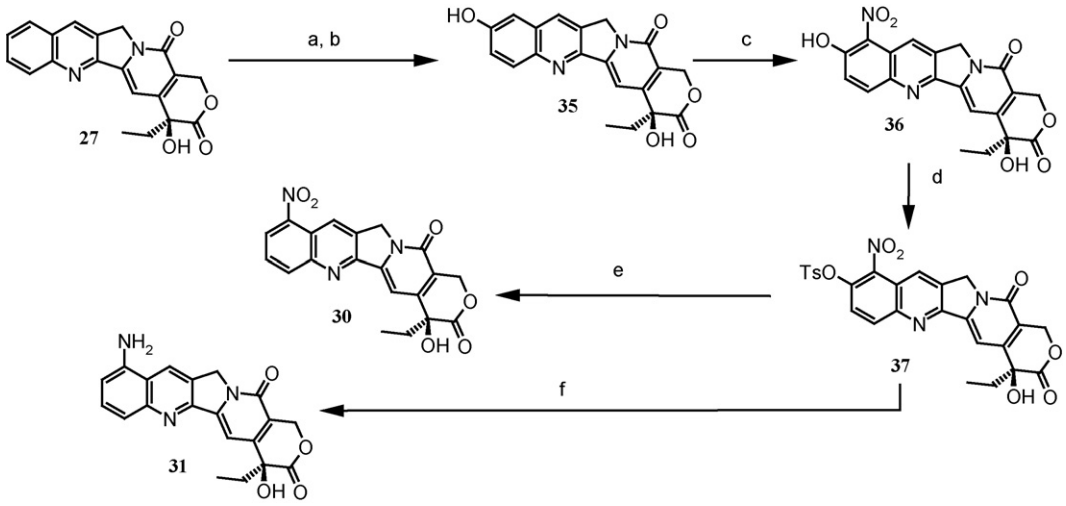
Fig. 4. The camptothecins.

derivatives are strong DNA topoisomerase I inhibitors and the success of irinotecan **28** and topotecan **29** for the treatment of several solid tumors, stimulated the search of new derivatives [20]. 9-NO_2-camptothecin **30** and 9-NH_2-camptothecin **31** have been identified in the nineties as potential new drug candidates [21].

Theoretically the synthesis of the 9-NO_2 derivative **30** could be easily achieved by simple nitration that, followed by catalytic hydrogenation, could generate **31**. Unfortunately, the quinoline fragment affected the selectivity of the nitration step and the 12 isomer **32** resulted the main product (Scheme 5). In addition to the yield loss, the poor regioselectivity affected the process efficiency because of the several purification steps necessary to get pharmaceutical grade material. The recycling of **32** was achieved by a four-step sequence. Compound **32** was reduced and after Sandmayer and nitration the 9-NO_2-12-Br camptothecin **33** was isolated. The palladium-catalysed reduction under homogeneous conditions of the bromo in 12 followed by heterogeneous reduction of the nitro group was achieved using $Pd(OAc)_2$ in the absence of any ligand with triethyl ammonium formate as stoichiometric reducing agent. $Pd(OAc)_2$ can generate very fine particles of palladium(0) in DMF (DMF is a weak electron donor ligand) able to catalyse the homogeneous reduction of the aromatic bromide using the formate as hydride source. The palladium metal is also able to reduce the nitro group in the



Scheme 5. (a) H_2SO_4 conc., HNO_3 conc.; the separation of the two regioisomers was achieved by crystallization. (b) Pd/C, H_2, DMF. (c) Purifications, the overall yield from **27** was 7% (the yield increase up to 14% by adding the recycling of **32**). (d) 1. Pd/C, H_2, DMF. 2. $NaNO_2$/HCl, CuBr. 3. H_2SO_4 conc., HNO_3 conc. (e) $Pd(OAc)_2$, HCOOH·Et_3N·DMF, 80 °C. (f) Pd/C, HCOOH·Et_3N·DMF, 80 °C.



Scheme 6. (a) H_2O_2, AcOH. (b) Dioxane, hν. (c) HNO_3, diluted. (d) TsCl, Et_3N, CH_2Cl_2. 45% overall yield from **26**. (e) $Pd(OAc)_2$/DPPF(1/2), HCOOH/Et_3N (1.5 equiv.), 90 °C, dioxane, 60% yield. (f) $Pd(OAc)_2$/DPPF(1/1.1), HCOOH/Et_3N(3.5 equiv.), 90 °C, dioxane, 80% yield.

presence of the H_2 that was generated by decomposition of the formate. The same reaction carried out in the presence of Pd/C as catalyst afforded the 9-NH_2-12-Br camptothecin **34**. The overall yield comprising the recycling of **32** was 14%.

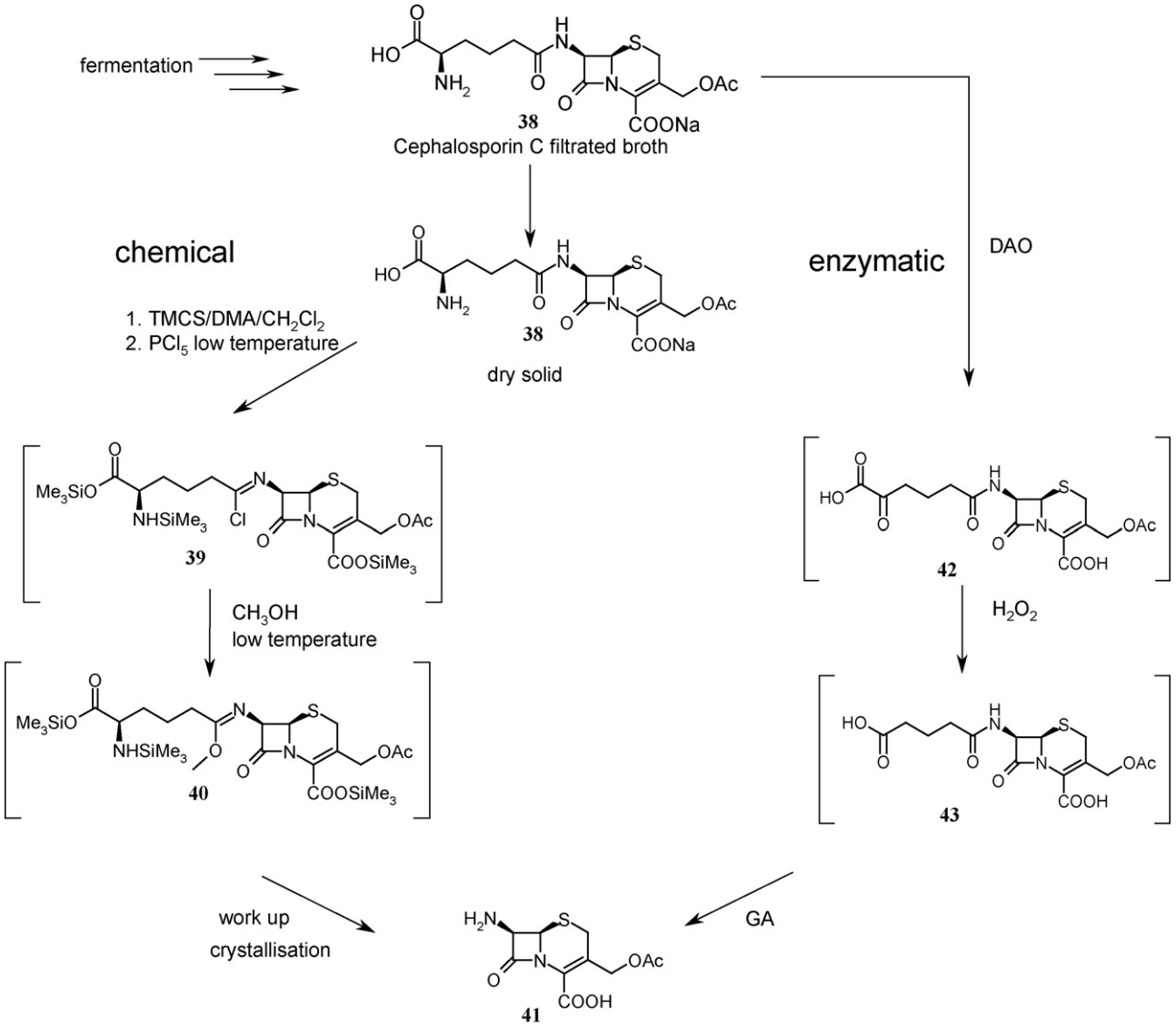
To overcome the drawbacks of this process a new strategy was developed to get selective nitration of the C-9 (Scheme 6). The introduction of a hydroxyl group at C-10 allowed to get selective nitration under mild conditions (diluted HNO_3). The deoxygenation of **36** was achieved by tosylation followed by palladium-catalysed homogeneous reduction using $Pd(OAc)_2$ and DPPF as precatalyst. The amount of triethyl ammonium formate was critical to guide the reaction to the nitro or the amino derivative [22]. The palladium-catalysed reduction of aryl sulfonates is a general methodology ($Pd(OAc)_2$/DPPP (1/1.1) or $Pd(OAc)_2$/DPPF (1/1.1) (5 mol%), Et_3N·HCOOH in DMF at 90 °C) developed to have an alternative to the use of the expensive triflate [15]. The homogeneous palladium(0) complex was unstable at 90 °C and the formation of palladium black start the heterogeneous reaction sequence, namely decomposition of the formate followed by reduction of the nitro group. Compounds **30** and **31** have been, respectively isolated in 27% and 36% overall yield from camptothecin **27**.

3.3. 7-ACA (7-aminocephalosporanic acid)

7ACA **41** is a key starting material for the synthesis of several cephalosporins of III and IV generation like Cafazolin sodium, Cefdinir monohydrate and anhydrous, Cefuroxime sodium and axetil, Ceftobiprole medocaril, Cefprozil monohydrate, Cefepime dihydrochloride, Cefotaxime sodium, Ceftriaxone disodium emiheptahydrate, etc. Cephalosporin C **38** is obtained by fermentation of genetically modified *Cephalosporium Acremonium*. There are two industrial processes to remove the side chain of cephalosporin C **38** [23]. The first one is a chemical cleavage of the side chain that is a modification of the original Morin protocol (Scheme 7). This process is mainly used in China and the average molar yield from Cephalosporin C **38** is around 70%, however, the best industrial process could reach the 85% molar yield by a fine tuning of the reaction conditions. The chemical process starts from isolated and dry sodium cephalosporin C **38**. 7-ACA **41** is obtained by silylation, followed by formation of iminium chloride (**38** → **39**), imino methyl ether (**39** → **40**), and hydrolysis. The second industrial synthesis is a two-step enzymatic process (D-aminoacid oxidase + glutaryl acylase) (Scheme 7). The enzymatic route was first industrialized by Antibioticos to remain competitive against Koreans and Chinese companies. The side chain with the unnatural configuration is transformed into the corresponding α-ketoglutaryc acid **42** by the DAO. The decomposition of intermediate by hydrogen peroxide (that is produced by the DAO as side product) afforded the glutaryl derivative **43**. The overall yield is similar to the best chemical route, but there are several industrial advantages, like the almost complete elimination of chemicals and consequently waste treatments, the use of the cephalosporin C **38** in solution coming from work up of the fermentation broth. The 7-ACA **41** is obtained by a semicontinuous process directly from the treated fermentation broth (ultrafiltration, resin absorption/desorption, reverse osmosis). The advantages of the enzymatic approach versus the chemical one are schematically described in Fig. 5. The mild reaction conditions of the enzymatic transformations are directly related to the better potency and the purity of the enzymatic 7-ACA compared to the chemical one.

The companies that did not industrialise the two-step enzymatic process closed their industrial plants (Glaxo Smith Kline, Bristol Meyers Squibb and Fujisawa). However, the continuous price pressure and the sensibility of the market to the Euro/Dollar/Yuan rate exchange, create consistent competitive problem to companies in the western world. Technically, the only improvement that could be introduced to decrease the cost is the one step enzymatic process. Several approaches to the development of a cephalosporin C acylase have been described: mutagenesis *of Penicillin G acylase*; [24] random mutagenesis followed by saturation mutagenesis of residue N266 of *Pseudomonas SY-77 acylase* [25] and site saturation mutagenesis of residue identified by ligand-bound structures of *Pseudomonas diminuita acylase* [26]. The availability of the crystal structure of the enzyme from *Pseudomonas diminuita* [27] allowed Ho to increase by mutagenesis the activity of this acylase by eightfold [26]. However, all these enzymes are not suitable for industrial application. Several companies tried to develop the single enzyme process: Fujisawa, Sandoz, Antibioticos. Only Antibioticos succeeded.

Pilone/Pollegioni group from Insubria University in connection with the Cabri/Verga group at Antibioticos S.p.A. developed a different and successful approach to a cephalosporin C acylase suitable for industrial application. The synthetic gene VAC designed using the primary structure of a GA from *Pseudomonas N176* was the starting scaffold [28]. The goal of the isolation of an enzyme suitable for industrial enzymatic production of 7ACA was achieved by a combination of random mutagenesis, molecular modelling, and site



Scheme 7. Enzymatic versus chemical route to 7-ACA.

	ENZYMATIC	CHEMICAL
	The process is semicontinuous; there are no isolation steps between fermentation and 7ACA isolation. This determines a very high productivity	Cephalosporin C sodium must be isolated in a dry form to be subjected to the silylation step.
Temperature range	20°C/25°C	-50°C/30°C
pH range	7.0-8.0	0.0-4.0
Isolation steps	1	2
Solvents	One solvent for drying of 7ACA	Methanol, dichloromethane
Reagents	No chemicals	DMA, TMSiCl, PCl5
Potency	>98%	95-97%
Purity	>99.5%	>98%
Open β-lactams	Absent	1%

Fig. 5. Enzymatic versus chemical route to 7-ACA. Process performances.

saturation and site directed mutagenesis approaches [29]. This process is a revolution in the industrial production of 7-ACA.

4. Conclusions

Catalysis is an important tool for drug discovery, however, it is even more important for the development of industrial synthesis. The discussion of specific case history showed that catalysis is one of the most powerful instruments for the design of environmentally friendly, cheap and competitive processes. This is not a dogma, because there are important factors like intellectual property, toxicity and cost that could hamper the industrial application of catalytic technologies.

The use of the 12 principles for process design is a standard approach in the pharmaceutical industry and catalysis is the most efficient and green technology available. Therefore, the scientific efforts for the discovery of new reactions, catalysts, or ligands are critical for the development of efficient and competitive green processes.

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