The Search for New Fragrance Ingredients for Functional Perfumery

by **Anubhav P. S. Narula**

International Flavors and Fragrances, Inc., 1515 Highway 36, Union Beach, New Jersey 07735, USA
(phone: +1 732 335-2523; fax +1 732 335-3524; e-mail: anubhav.narula@iff.com)

Functional perfumery is an integral part of the fragrance business. It demands that the ingredients chosen for compounding withstand the aggressive nature of some of the bases used for soaps, detergents, softeners, bleach, and personal-care products. The synthetic efforts in this area reported in this short personal account, presented in a talk at the *RSC/SCI* conference *Flavours & Fragrances 2004* (Manchester), have resulted in the discovery of the two new proprietary molecules *Fleuranil*® (**5/6**) and *Khusinil*® (**7**), which fulfill the criteria of functional perfumery. The structure – odor relationships of several analogs of *Fleuranil*® and *Khusinil*® prepared in the course of these investigations are also presented.

Introduction. – This article provides a brief overview of our ongoing endeavors at *International Flavors & Fragrances* (*IFF*) in the relentless pursuit of new molecules with unique sensory properties. Carbon – carbon bond-formation is at the heart of organic synthesis [1]. Diverse approaches are being pursued to synthesize novel structures for exploratory purposes. In previous publications [2][3], we have reported the utility of, *e.g.*, *Diels – Alder*, *Mannich*, and ene reactions to prepare new lead compounds, which has led to the discovery of three new proprietary fragrance molecules: *Cassiffix*® (**1/2**), a long-lasting cassis note, *Prismantol*® (**3**), a woody-spicy ingredient, and *Prismylate*® (**4**), a woody-ambery, vetiver-like odorant (*Fig. 1*). In the light of regulatory and labeling issues [4] facing the fragrance and flavor industry, there is an urgent need to discover new molecules that enhance the performance in functional-perfumery applications. As a consequence, we have discovered and commercialized two new fragrance ingredients that address these requirements: *Fleuranil*® (**5/6**), *a powerful, green-anisic and ozone-like, sweet floral note* [5], and *Khusinil*® (**7**), *a strong, fresh, long-lasting nootkatone-type (bergamot, grapefruit), vetiver-woody odorant* [6], which both will hopefully advance the art of perfumery [7].

Background. – Functional perfumery is an integral part of the fragrance-compounding business, and demands that the fragrance ingredients used have good application properties in physical, chemical, and sensory terms [8]. In addition, the ingredients chosen for the perfume must perform well, and must be stable in the bases and alcohols of perfumes, cosmetics, toiletries, deodorants, soaps, detergents, softeners, bleach, LADD-perborate, and personal care products. Aldehydes are widely used as perfumery ingredients, but they suffer from several disadvantages (*Fig. 2*). Because of the lack of stability of aldehydes, the corresponding nitriles have often been used [9], and this replacement of functional groups has been in vogue for functional perfumery

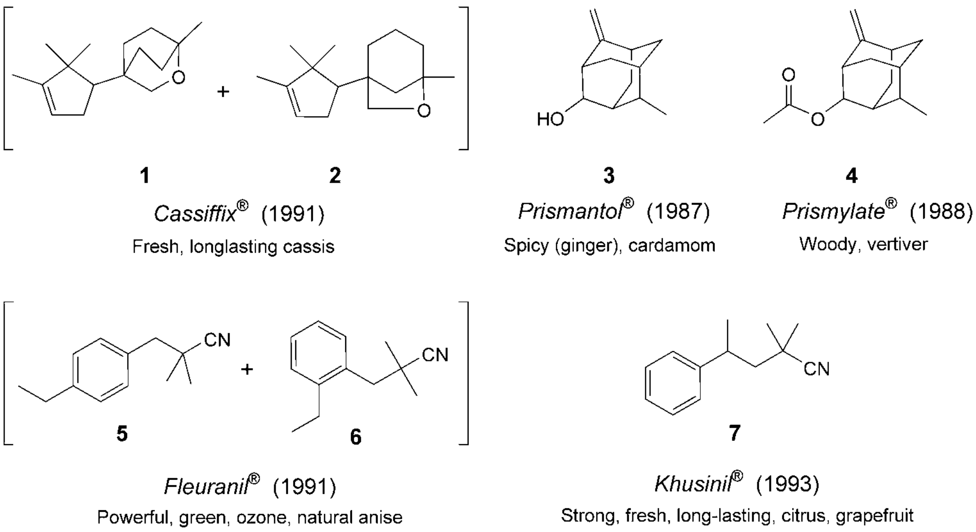
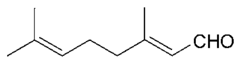
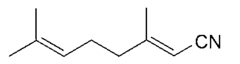


Fig. 1. *New proprietary fragrance ingredients of* IFF



Citral (**8**)
Fresh, lemon, citrus
(oral LD_{50} = 3.1 g/kg)



Citralva® (**9**)
Lemon, citrus, more oily, metallic

- Aldehydes are, in contrast to nitriles, unstable at high and low pH
- Aldehydes (CHO) and nitiles (CN) are formally 'isoelectronic'
- Aldehydes are, in contrast to nitriles, susceptible to degradation by oxidation, condensation, and heat
- Aldehydes are sensitizers even at low concentrations, while nitriles are non-sensitizing
- In alcoholic perfumery, aldehydes form semi-acetals or acetals

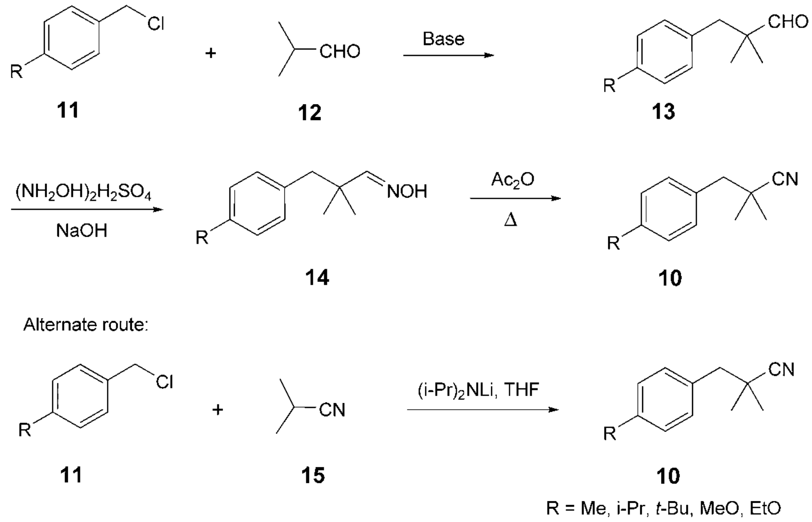
Fig. 2. *Strucutres and properties of citral* (**8**) *and* Citralva® (**9**), *and general comparison of odor and performance of volatile aldehydes* vs. *nitriles*

for well over 50 years now. In *Fig. 2*, a comparison of the aldehyde citral (**8**) with the corresponding nitrile, *Citralva*® (**9**), is made under diverse aspects.

Synthesis of Novel Aromatic Nitriles. – As stated above, several years ago, we began an exploratory program aimed at the re-evaluation of the odor of aromatic nitriles prepared from well-known aldehydes such as *Floralozone*®, *Cyclemax*®, *Lilial*®, or *Cyclamal*®. This research investigation turned into a detailed structure–odor-relationship study. Several new molecules with varying alkyl substituents on the aromatic ring were prepared for olfactory evaluation, and diverse synthetic routes were employed to prepare these analogs (*Schemes 1–6*). A brief description of how these novel structures were prepared is given in the following for some of these exploratory chemicals.

Various *p*-alkyl-substituted *Fleuranil*® (**5**/**6**) analogs of type **10** were synthesized by reacting an appropriately substituted benzyl chloride **11** with the carbanion of isobutyraldehyde **12**, generated under basic conditions, to provide the aldehydes **13** (*Scheme 1*). The desired nitriles **10** were prepared by converting the aldehydes **13** into the corresponding oximes **14** with hydroxylammonium sulfate, and heating the resulting oximes with acetic anhydride at reflux temperature. Alternatively, selected *Fleuranil*® analogs **10** were prepared in one step by reacting an appropriately substituted benzyl chloride **11** with the carbanion of isobutyronitrile (**15**) generated from lithium diisopropylamide (LDA) in tetrahydrofuran (THF).

Scheme 1

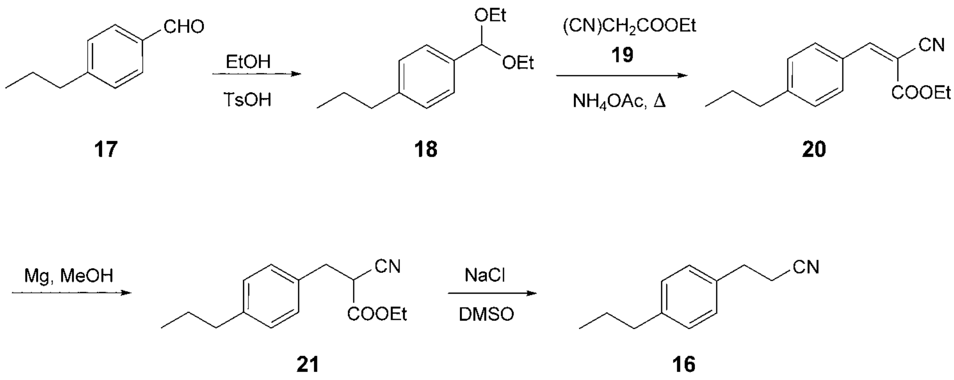


A multistep synthesis of 3-(4-propylphenyl)propanenitrile (**16**) was developed from *p*-propylbenzaldehyde (**17**), which was converted to its diethyl acetal **18**. The latter was condensed with ethyl cyanoacetate (**19**), using NH_4OAc as a base. The intermediate unsaturated ester **20** was hydrogenated to **21** with Mg in MeOH, and subsequent decarboxylation with NaCl in DMSO afforded the *Fleuranil* analog **16** (*Scheme 2*).

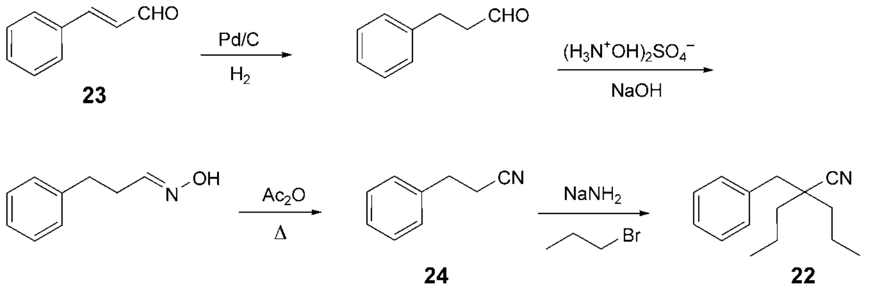
2-Benzyl-2-propylpentanenitrile (**22**) was synthesized from cinnamic aldehyde (**23**; *Scheme 3*), which was first hydrogenated over Pd on activated carbon, and then converted to 3-phenylpropanenitrile (**24**) *via* its oxime, using the standard methodology described before. The nitrile **24** was then doubly alkylated with NaH and propyl bromide to furnish **22**.

3-(4-Ethylphenyl)-3-methylbutanenitrile (**25**) was prepared by conjugate addition of 4-ethylphenyl magnesium bromide (**26**) to the unsaturated ester **27** in the presence of a catalytic amount of elemental Cu (*Scheme 4*). Saponification of the resulting product **28** with 10% aqueous NaOH solution at 40°, and subsequent *in situ* decarboxylation of the intermediary free acid at 200° furnished the target molecule **25** in good yield.

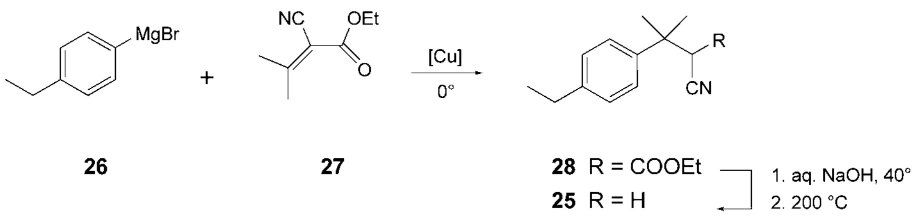
Scheme 2



Scheme 3



Scheme 4



The olfactory comparison of the *Fleuranil*® analogs **31**–**44**, and of the muguet aldehydes **45**–**47**, prepared according to the synthetic routes detailed above, is given in *Fig. 3*. Among the new molecules **31**–**44**, none was found to possess the interesting odor characteristics typical for *Fleuranil*® (**5**/**6**). Unfortunately, most nitriles synthesized had only weak odor profiles.

Since many alkoxy substituted aromatic aldehydes are widely used in perfumery, *e.g.*, *Canthoxal*® and *Helional*® (**48**), we envisaged that it would be interesting from an

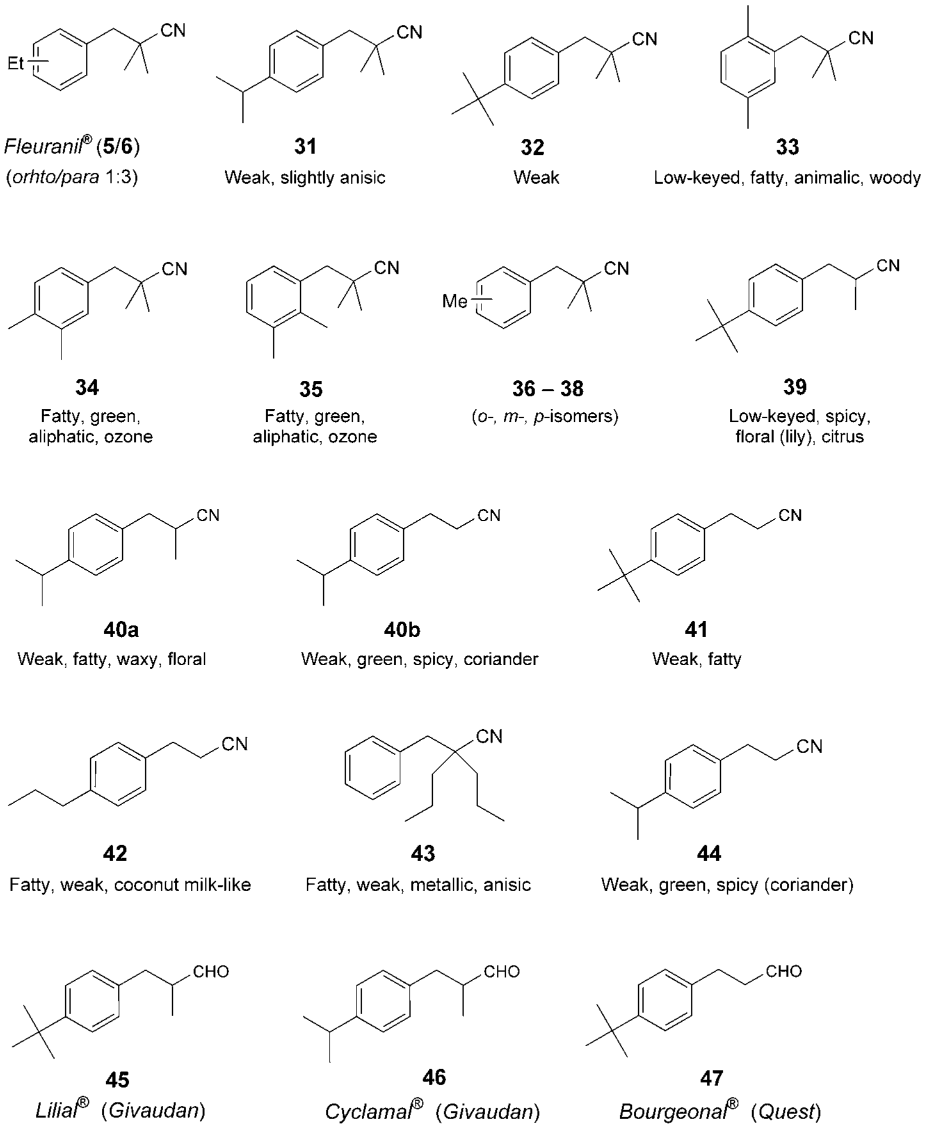


Fig. 3. *Odor comparison of* Fleuranil® *anologs of* IFF. For comparison, the muguet aldehydes **45**–**47** of other companies are also depicted.

olfactory perspective to prepare also alkoxy nitriles [10][11] and to compare their odors with those of the corresponding alkyl nitriles. Again, these derivatives were synthesized by means of the standard methodology elaborated for *Fleuranil®* analogs (see *Schemes 1* and *2*). The structures and odor characteristics of the synthesized alkoxy nitriles **49**–**54** are presented in *Fig. 4*.

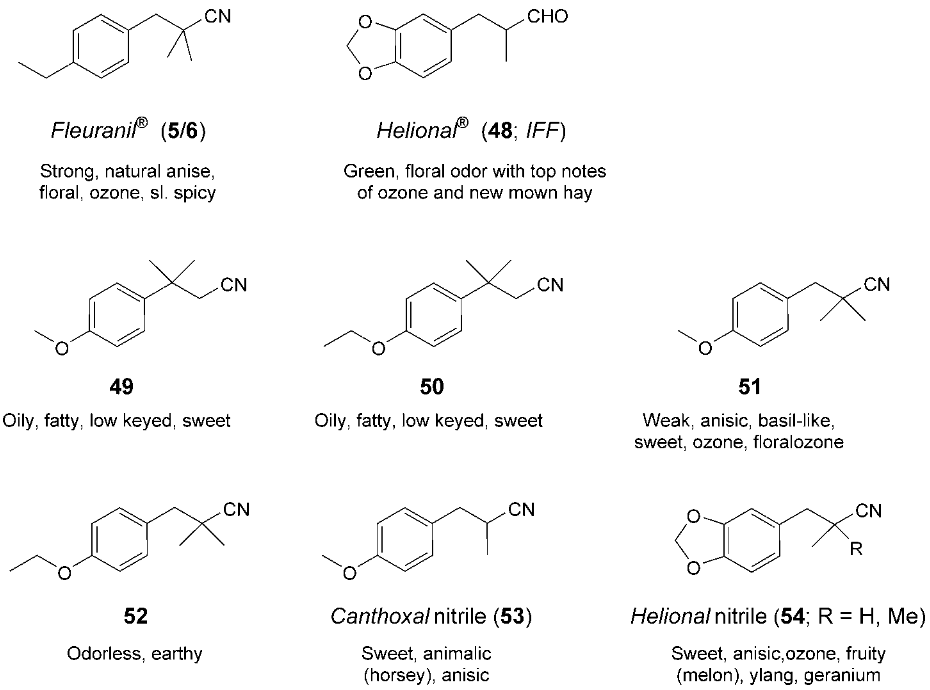


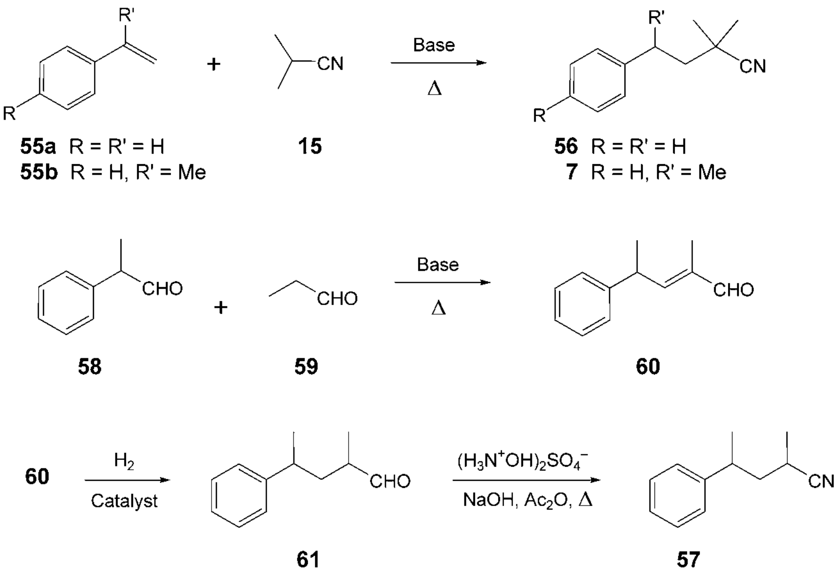
Fig. 4. *Odors of* Fleuranil®*-related alkoxy analogs*

Discovery of *Khusinil*®. – The discovery of *Khusinil*® (**7**; *Fig. 1*) came about as an outgrowth of this structure–odor relationship study [5] carried out during the exploratory work on analogs of *Fleuranil*® (**5/6**). Again, several dimethyl-substituted aryl nitriles were prepared for olfactory comparison, starting from readily available styrenes of type **55** (*Scheme 5*). The nucleophilic addition of a carbanion generated from isobutyronitrile (**15**) to, *e.g.*, styrene proper (**55a**) or the derivative **55b** at 120° gave **56** and *Khusinil*® (**7**), respectively, in good yields. Demethyl Khusinil (**57**) was prepared in two steps from 2-phenylpropanal (**58**) by reaction with propanal (**59**) in the presence of a base. On catalytic hydrogenation of the resulting 2-methyl-4-phenylpent-2-enal (**60**), the saturated aldehyde **61** was obtained in high yield. The latter was converted to the target nitrile **57** *via* its oxime, as described above.

An odor comparison of the *Khusinil*® analogs **63**–**66** with both *Khusinil*® (**7**) and *Pamplefleur*® (**67**) is made in *Fig. 5*. Compounds **63** and **64** have essentially the same odor profiles (*vetiver, grapefruit*) as *Khusinil*® (**7**), but have a *more-metallic odor tonality*, and are weaker as well.

Since there are several valuable fragrance ingredients that contain a pyridine ring, *e.g.*, **68**–**71** (*Fig. 6*), we felt that it would be interesting to prepare also some pyridyl analogs of *Khusinil*® [12] for structure–odor correlation. The two analogs **72** and **73** were prepared from readily available 2- and 4-vinylpyridine (*Scheme 6*), following the same route as developed for *Khusinil*® (*cf. Scheme 5*).

Scheme 5



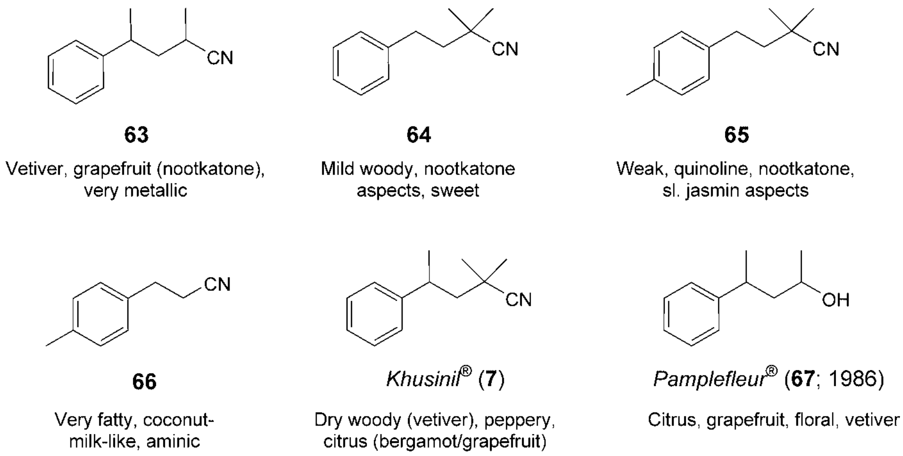


Fig. 5. *Odor relationships of* Khusinil® *analogs*

Finally, we would like to illustrate the importance of nitriles in functional perfumery with a list of nitrile ingredients, including compounds **5**–**7** and **74**–**78** (*Fig. 7*)[1]),

[1]) *Citralva*® and *Citronalva*® were first made at *IFF* in 1949. All trademarks noted in this article are assigned to *International Flavor & Fragrances, Inc.*, unless noted to the contrary. *Lilial*® (**45**) and *Cyclamal*® (**46**) are registered trademarks of *Givaudan SA*, while *Bourgeonal*® is a registered trademark of *Quest International*.

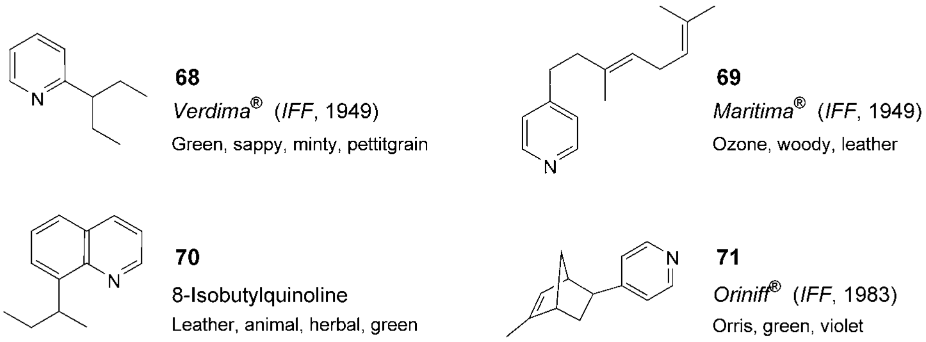
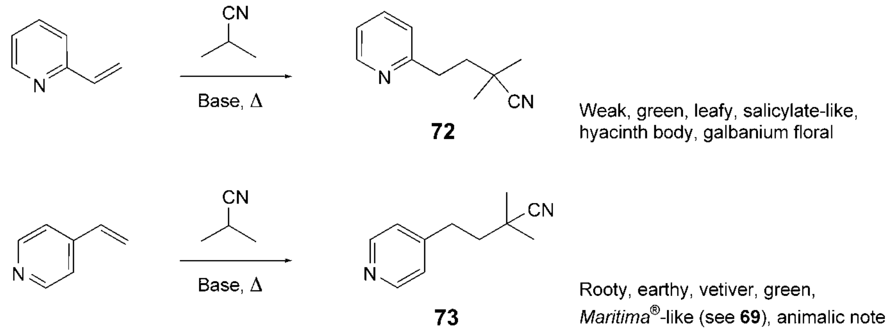


Fig. 6. *Structures and odor characteristics of the known pyridines* **68**–**71** *used in perfumery*

Scheme 6



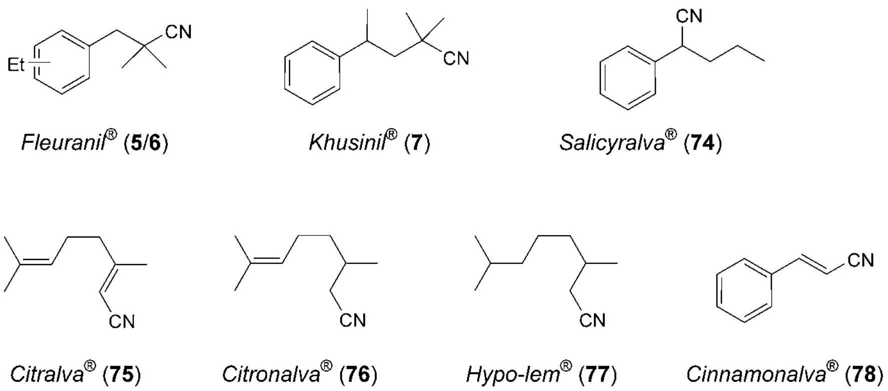


Fig. 7. *Important nitrile-based ingredients developed at* IFF *for functional perfumery*

developed over the years at *IFF.* These ingredients have enhanced the creativity of perfumers engaged in functional perfumery around the world.

Conclusions. – This account has provided just a glimpse of our research efforts on the example of the discovery of *Fleuranil*® (**5**/**6**) and *Khusinil*® (**7**). It is, indeed, refreshing to note that a perfumer's need for new molecules never wanes in spite of *ca.* 3000 fragrance ingredients to choose from. Hence, we would like to assure perfumers world-wide that they can bank on the ingenuity of synthetic organic chemists to provide them with new and unique fragrance ingredients. This would not only enhance their creativity, but also address toxicological as well as environmental concerns. An organic chemist's quest in the pursuit of new fragrance molecules will continue unabated towards that aim.

The author wishes to acknowledge his colleagues at *IFF*, whose names are cited in the following references, for their dedicated synthetic work, and several renowned perfumers for their expert fragrance evaluations of the new chemicals disclosed in this article.

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