



DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITE DE COOPERATION EN MATIÈRE DE BREVETS (PCT)

(51) Classification internationale des brevets ⁶ : C07D 403/12, 403/14, A61K 31/41, C07D 249/14	A1	(11) Numéro de publication internationale: WO 98/51686 (43) Date de publication internationale: 19 novembre 1998 (19.11.98)
(21) Numéro de la demande internationale: PCT/FR98/00905 (22) Date de dépôt international: 6 mai 1998 (06.05.98) (30) Données relatives à la priorité: 97/05850 13 mai 1997 (13.05.97) FR (71) Déposant (pour tous les Etats désignés sauf US): SANOFI [FR/FR]; 32-34, rue Marbeuf, F-75008 Paris (FR). (72) Inventeurs; et (75) Inventeurs/Déposants (US seulement): BIGNON, Eric [FR/FR]; 4, allée de la Garonne, F-31120 Pinsaguel (FR). BRAS, Jean-Pierre [FR/FR]; 16, avenue de Castres, F-31500 Toulouse (FR). DE COINTET, Paul [FR/FR]; 1, rue Furgole, F-31000 Toulouse (FR). DESPEYROUX, Pierre [FR/FR]; 472, chemin de Lagardelle, F-31860 Labarthe sur Leze (FR). FREHEL, Daniel [FR/FR]; Le Burget-Lasserre, F-31160 Estadens (FR). GULLY, Danielle [FR/FR]; 82, route de Roquettes, Saubens, F-31160 Muret (FR). (74) Représentant commun: SANOFI; 32-34, rue Marbeuf, F-75008 Paris (FR).		(81) Etats désignés: AU, BR, BY, CA, CN, CZ, EE, HU, ID, IL, IS, JP, KR, LK, LT, LV, MX, NO, NZ, PL, RU, SG, SI, SK, TR, UA, US, VN, YU, brevet européen (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Publiée <i>Avec rapport de recherche internationale.</i>
(54) Title: N-TRIAZOLYL-2-INDOLECARBOXAMIDES AND THEIR USE AS CCK-A AGONISTS (54) Titre: N-TRIAZOLYL-2-INDOLECARBOXAMIDES ET LEUR UTILISATION COMME AGONISTES DE CCK-A (57) Abstract <p>The invention concerns compounds of formula (I) in which R₁, R₄, X₁, X₂, X₃, X₄, Y₁, Y₂ and Y₃ are as defined in claim 1. These compounds have partial or total agonist activity of CCK-A receptors and are useful for treating eating problems, obesity, tardive dyskinesia and disorders of the gastrointestinal sphere.</p> (57) Abrégé <p>L'invention a pour objet des composés de formule (I) dans laquelle R₁, R₄, X₁, X₂, X₃, X₄, Y₁, Y₂ et Y₃ sont tels que définis à la revendication 1. Ces composés possèdent une activité agoniste partielle ou totale des récepteurs CCK-A, et sont utiles dans le traitement des désordres alimentaires, de l'obésité, de la dyskinésie tardive et des troubles de la sphère gastrointestinale.</p>		

UNIQUEMENT A TITRE D'INFORMATION

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publiant des demandes internationales en vertu du PCT.

AL	Albanie	ES	Espagne	LS	Lesotho	SI	Slovénie
AM	Arménie	FI	Finlande	LT	Lituanie	SK	Slovaquie
AT	Autriche	FR	France	LU	Luxembourg	SN	Sénégal
AU	Australie	GA	Gabon	LV	Lettonie	SZ	Swaziland
AZ	Azerbaïdjan	GB	Royaume-Uni	MC	Monaco	TD	Tchad
BA	Bosnie-Herzégovine	GE	Géorgie	MD	République de Moldova	TG	Togo
BB	Barbade	GH	Ghana	MG	Madagascar	TJ	Tadjikistan
BE	Belgique	GN	Guinée	MK	Ex-République yougoslave de Macédoine	TM	Turkménistan
BF	Burkina Faso	GR	Grèce	ML	Mali	TR	Turquie
BG	Bulgarie	HU	Hongrie	MN	Mongolie	TT	Trinité-et-Tobago
BJ	Bénin	IE	Irlande	MR	Mauritanie	UA	Ukraine
BR	Brésil	IL	Israël	MW	Malawi	UG	Ouganda
BY	Bélarus	IS	Islande	MX	Mexique	US	Etats-Unis d'Amérique
CA	Canada	IT	Italie	NE	Niger	UZ	Ouzbékistan
CF	République centrafricaine	JP	Japon	NL	Pays-Bas	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norvège	YU	Yougoslavie
CH	Suisse	KG	Kirghizistan	NZ	Nouvelle-Zélande	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	République populaire démocratique de Corée	PL	Pologne		
CM	Cameroun	KR	République de Corée	PT	Portugal		
CN	Chine	KZ	Kazakstan	RO	Roumanie		
CU	Cuba	LC	Sainte-Lucie	RU	Fédération de Russie		
CZ	République tchèque	LI	Liechtenstein	SD	Soudan		
DE	Allemagne	LK	Sri Lanka	SE	Suède		
DK	Danemark	LR	Libéria	SG	Singapour		
EE	Estonie						

N-TRIAZOLYL-2-INDOLECARBOXAMIDES ET LEUR UTILISATION COMME AGONISTES DE CCK-A

La présente invention concerne de nouveaux dérivés du triazole, un procédé pour leur préparation et les médicaments les contenant.

5 Plus particulièrement, la présente invention a pour objet de nouveaux composés non peptidiques affins pour les récepteurs de la cholécystokinine (CCK).

La CCK est un peptide qui, en réponse à une ingestion d'aliment, est sécrétée au niveau périphérique et participe à la régulation de nombreux processus digestifs (Crawley J.N. *et al.*, Peptides, 1994, 15 (4), 731-735).

10 La CCK a été identifiée par la suite dans le cerveau, et pourrait être le neuropeptide le plus abondant agissant comme neuromodulateur des fonctions cérébrales par stimulation des récepteurs de type CCK-B (Crawley J.N. *et al.*, Peptides, 1994, 15 (4), 731-735). Dans le système nerveux central, la CCK interagit avec la transmission neuronale médiée par la dopamine (Crawley J.N. *et al.*, ISIS Atlas of Sci., Pharmac, 15 1988, 84-90). Elle intervient également dans des mécanismes impliquant l'acétylcholine, le gaba (acide 4-aminobutyrique), la sérotonine, les opioïdes, la somatostatine, la substance P et dans les canaux ioniques.

Son administration provoque des modifications physiologiques : ptose palpébrale, hypothermie, hyperglycémie, catalepsie; et des modifications comportementales : 20 hypolocomotricité, diminution de l'exploration, analgésie, modification de la faculté d'apprentissage, modification du comportement sexuel et satiété.

Le CCK exerce son activité biologique par l'intermédiaire d'au moins deux types de récepteurs : les récepteurs CCK-A localisés principalement en périphérie, et les récepteurs CCK-B présents essentiellement dans le cortex cérébral. Les récepteurs 25 CCK-A de type périphérique sont aussi présents dans certaines zones du système nerveux central incluant l'area postrema, le noyau de tractus solitaire et le noyau interpédonculaire (Moran T.H. *et al.*, Brain Research, 1986, 362, 175-179 ; Hill D.R. *et al.*, J. Neurosci, 1990, 10, 1070-1081 ; avec cependant des différences d'espèce (Hill D.R. *et al.*, J. Neurosci, 1990, 10, 1070-1081) ; Mailleux P. *et al.*, Neurosci Lett., 1990, 117, 243-247 ; Barrett R.W. *et al.*, Mol. Pharmacol., 1989, 36, 285-290 ; Mercer J.G. *et al.*, Neurosci Lett., 1992, 137, 229-231 ; Moran T.H. *et al.*, Trends in Pharmacol. Sci., 1991, 12, 232-236).

A la périphérie, par l'intermédiaire des récepteurs CCK-A (Moran T.H. *et al.*, Brain Research, 1986, 362, 175-179), la CCK retarde la vidange gastrique, module la 35 motilité intestinale, stimule la contraction vésiculaire, augmente la sécrétion biliaire,

contrôle la sécrétion pancréatique (McHugh P.R. *et al.*, Fed. Proc., 1986, 45, 1384-1390 ; Pendleton R.G. *et al.*, J. Pharmacol. Exp. Ther., 1987, 241, 110-116).

La CCK pourrait agir dans certains cas sur la pression artérielle et influencer les systèmes immunitaires.

5 Le rôle de la CCK dans le signal de satiété est supporté par le fait que les concentrations plasmatiques de CCK, dépendantes de la composition des repas (fortes concentrations de protéines ou de lipides) sont, après les repas, supérieures à celles observées avant les repas (Izzo R.S. *et al.*, Regul. Pept., 1984, 9, 21-34 ; Pfeiffer A. *et al.*, Eur. J. Clin. Invest., 1993, 23, 57-62 ; Lieveise R.J. Gut, 1994, 35, 10 501). Chez les boulimiques, il y a une diminution de la sécrétion de la CCK induite par un repas, (Geraciotti T.D. Jr. *et al.*, N. Engl. J. Med., 1988, 319, 683-688 ; Devlin M.J. *et al.*, Am. J. Clin. Nutr., 1997, 65, 114-120) et une baisse des concentrations de CCK dans le liquide cébrospinal (Lydiard R.B. *et al.*, Am. J. Psychiatry, 1993, 150, 1099-1101). Dans les lymphocytes T, un compartiment cellulaire pouvant refléter les 15 sécrétions neuronales centrales, les concentrations basales de CCK sont significativement inférieures chez les patients atteints de Bulimia nervosa (Brambilla F. *et al.*, Psychiatry Research, 1995, 37, 51-56).

Les traitements (par exemple par la L-phénylalanine, ou les inhibiteurs de trypsine) qui augmentent la sécrétion de la CCK endogène provoquent une réduction de la prise 20 alimentaire dans plusieurs espèces dont l'homme (Hill A.J. *et al.*, Physiol. Behav. 1990, 48, 241-246 ; Ballinger A.B. *et al.*, Metabolism 1994, 43, 735-738). De même, l'administration de CCK exogène réduit la prise de nourriture dans de nombreuses espèces dont l'homme (Crawley J.N. *et al.* Peptides 1994, 15, 731-755).

L'inhibition de la prise de nourriture par la CCK est médiée par le récepteur CCK-A. En 25 effet, le devazepide, un antagoniste sélectif des récepteurs CCK-A, inhibe l'effet anorexigène de la CCK alors que les agonistes sélectifs de ces récepteurs inhibent la prise de nourriture (Asin K.E. *et al.*, Pharmacol. Biochem. Behav. 1992, 42, 699-704 ; Elliott R.L. *et al.*, J. Med. Chem. 1994, 37, 309-313 ; Elliott R.L. *et al.*, J. Med. Chem. 1994, 37, 1562-1568). De plus, les rats OLEFT, n'exprimant pas le récepteur CCK-A 30 sont insensibles à l'effet anorexigène de la CCK (Miyasaka K. *et al.*, 1994, 180, 143-146).

Basé sur ces évidences du rôle clé de la CCK dans le signal de satiété périphérique, l'utilité d'agonistes et d'antagonistes de la CCK comme médicament dans le traitement de certains troubles du comportement alimentaire, de l'obésité et du diabète est 35 indiscutable. Un agoniste des récepteurs de la CCK peut aussi être utilisé en thérapeutique dans le traitement des troubles du comportement émotionnel, sexuel et

amnésique (Itoh S. *et al.*, Drug. Develop. Res., 1990, 21, 257-276), de la schizophrénie, des psychoses (Crawley J.N. *et al.*, Isis Atlas of Sci., Pharmac., 1988, 84-90 et Crawley J.N., Trends in Pharmacol. Sci., 1991, 12, 232-265), de la maladie de Parkinson (Bednar I. *et al.*, Biogenic amine, 1996, 12 (4), 275-284), des dyskinésies tardives (Nishikawa T. *et al.*, Prog. Neuropsychopharmacol. Biol. Psych., 1988, 12, 803-812 ; Kampen J.V. *et al.*, Eur. J. Pharmacol., 1996, 298, 7-15) et de divers troubles de la sphère gastrointestinale (Drugs of the Future, 1992, 17 (3), 197-206).

Des agonistes du récepteur CCK-A de la CCK sont décrits dans la littérature. Par exemple, certains produits ayant de telles propriétés sont décrits dans EP383690 et WO90/06937, WO95/28419, WO96/11701 ou encore WO96/11940

La plupart des agonistes CCK-A décrits à ce jour sont de nature peptidique. Ainsi, le FPL 14294 dérivé de la CCK-7 est un puissant agoniste CCK-A non sélectif *vis-à-vis* des récepteurs CCK-B. Il possède une puissante activité inhibitrice de la prise de nourriture chez le rat et chez le chien après administration intranasale (Simmons R.D. *et al.*, Pharmacol. Biochem. Behav., 1994, 47 (3), 701-708 ; Kaiser E.F. *et al.*, Faseb, 1991, 5, A864). De même, il a été montré que le A-71623, un tétrapeptide agoniste sélectif des récepteurs CCK-A, est efficace dans des modèles d'anorexie sur une période de 11 jours et entraîne une réduction significative de la prise de poids par rapport au contrôle chez les rongeurs et les singes cynomologues (Asin K.E. *et al.*, Pharmacol. Biochem. Behav., 1992, 42, 699-704). De la même façon, des analogues structuraux du A 71623, possédant une bonne efficacité et sélectivité pour les récepteurs CCK-A sont dotés d'une puissante activité anorexigène chez le rat (Elliott R.L. *et al.*, J. Med. Chem., 1994, 37, 309-313 ; Elliott R.L. *et al.*, J. Med. Chem., 1994, 37, 1562-1568). Le GW 7854 (Hirst G.C. *et al.*, J. Med. Chem., 1996, 39, 5236-5245), une benzodiazépine-1,5, est un agoniste des récepteurs CCK-A *in vitro*. Cette molécule est également active par voie orale sur la contraction de la vésicule biliaire chez la souris et sur la prise de nourriture chez le rat.

On a maintenant trouvé, de façon surprenante, qu'une série de dérivés de triazole possède une activité agoniste partielle ou totale des récepteurs CCK-A.

Les composés selon l'invention ont fait l'objet d'études systématiques pour caractériser :

- leur potentialité pour déplacer [¹²⁵I]-CCK de ses sites de liaison présents sur des membranes pancréatiques de rat (récepteur CCK-A) ou de cellules 3T3 exprimant le récepteur recombinant CCK-A humain ;

- leur affinité *vis-à-vis* du récepteur CCK-B présent sur des membranes de cortex de cobaye, certains des composés étant des ligands sélectifs ou non des récepteurs CCK-A ;

- leur propriété agoniste des récepteurs CCK-A à travers leur capacité à induire *in vitro* une mobilisation du calcium intracellulaire dans les cellules 3T3 exprimant le récepteur CCK-A humain.

Les dérivés du triazole, selon la présente invention, sont des agonistes CCK-A puisqu'ils sont capables de stimuler partiellement, ou totalement comme la CCK, la mobilisation du calcium intracellulaire dans une lignée cellulaire exprimant le récepteur recombinant CCK-A humain. Ils sont, de manière surprenante, beaucoup plus puissants que les dérivés : du thiazole décrits dans les demandes de brevets EP518731, EP611766, du thiadiazole décrits dans la demande de brevet EP620221, des benzodiazépines décrits dans le brevet EP667344.

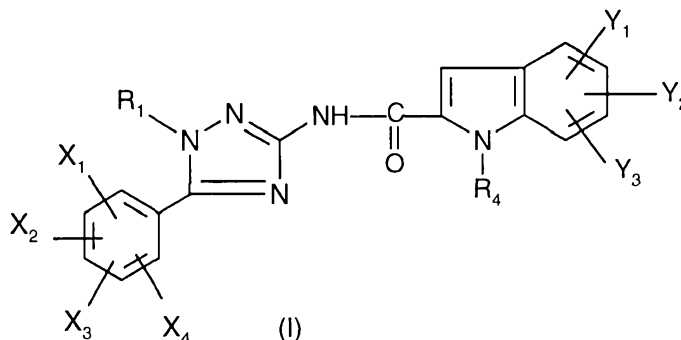
En effet, ces dérivés thiazole, thiadiazole et benzodiazépine sont incapables d'induire cette mobilisation du calcium intracellulaire médiée par le récepteur CCK-A.

Les dérivés du triazole selon l'invention sont également beaucoup plus puissants que ces dérivés thiazole, thiadiazole ou benzodiazépine par leur capacité à bloquer *in vivo*, par la voie intrapéritonéale, la vidange gastrique chez la souris.

Ainsi, les propriétés agonistes CCK-A ont été étudiées *in vivo*, en évaluant leur capacité à bloquer la vidange gastrique chez la souris ou à provoquer, toujours *in vivo*, la vidange de la vésicule biliaire chez la souris.

Certains dérivés possèdent également une activité antagoniste des récepteurs CCK-B.

Ainsi, la présente invention concerne des composés de formule :



dans laquelle :

- R_1 représente un (C_2-C_6) alkyle ; un groupe $-(CH_2)_n-G$ avec n variant de 0 à 5 et G représentant un groupe hydrocarboné mono- ou polycyclique non aromatique en

C₃-C₁₃ éventuellement substitué par un ou plusieurs (C₁-C₃)alkyle ; un phényl(C₁-C₃)alkyle dans lequel le groupe phényle est éventuellement substitué une ou plusieurs fois par un halogène, par un (C₁-C₃)alkyle ou par un (C₁-C₃)alcoxy ; un groupe -(CH₂)_nNR₂R₃ dans lequel n représente un nombre entier de 1 à 6 et R₂ et R₃ identiques ou différents représentent un (C₁-C₃)alkyle ou constituent avec l'atome d'azote auquel ils sont liés un groupe morpholino, pipéridino, pyrrolidinyle ou pipérazinyle ;

- X₁, X₂, X₃ ou X₄ représentent chacun indépendamment un atome d'hydrogène, d'halogène, un (C₁-C₆)alkyle, un (C₁-C₃)alcoxy ou un trifluorométhyle; étant entendu qu'un seul parmi X₁, X₂, X₃ et X₄ représente éventuellement un atome d'hydrogène ;

- R₄ représente l'hydrogène, un groupe -(CH₂)_nCOOR₅ dans lequel n est tel que défini précédemment et R₅ représente un atome d'hydrogène, un (C₁-C₆)alkyle ou un (C₆-C₁₀)aryl-(C₁-C₆)alkyle ; un (C₁-C₆)alkyle ; un groupe -(CH₂)_nOR₅ ou un groupe -(CH₂)_nNR₂R₃ dans lesquels n, R₂, R₃ et R₅ sont tels que définis précédemment ; un groupe -(CH₂)_n- tétrazolyle dans lequel n est tel que défini précédemment, ou R₄ représente l'un de ces groupes sous la forme de sel d'un métal alcalin ou alcalino-terreux;

- Y₁, Y₂ et Y₃ représentent indépendamment un hydrogène, un halogène, un (C₁-C₃)alkyle, un (C₁-C₃)alcoxy, un nitro, cyano, (C₁-C₆)acylamino, carbamoyle, trifluorométhyle, un groupe COOR₆ dans lequel R₆ représente l'hydrogène, ou (C₁-C₃)alkyle;

ou un de leurs sels ou solvates.

Selon la présente invention, par "(C₁-C₆)alkyle" ou "(C₂-C₆)alkyle", on entend un alkyle droit ou ramifié ayant 1 à 6 atomes de carbone ou respectivement 2 à 6 atomes de carbone.

Le radical alkoxy désigne un radical alkyloxy dans lequel alkyle est tel que défini ci-dessus.

Le radical acyle désigne un radical alkylcarbonyle dans lequel alkyle est tel que défini ci-dessus. (C₁-C₆)acylamino est un radical alkylcarbonylamino en C₁-C₆.

Les groupes hydrocarbonés non aromatiques en C₃-C₁₃ comprennent les radicaux mono- ou poly-cycliques, condensés ou pontés, saturés ou insaturés, éventuellement terpéniques. Ces radicaux sont éventuellement mono- ou poly- substitués par un (C₁-C₃)alkyle. Les radicaux monocycliques incluent les cycloalkyles par exemple les cyclopropyle, cyclobutyle, cyclopentyle, cyclohexyle, cycloheptyle, cyclooctyle, cyclododécyle. Les radicaux polycycliques incluent par exemple le norbornane,

l'adamantane, l'hexahydroindane, le norbornène, le dihydrophénalène, le bicyclo [2.2.1]heptane, le bicyclo [3.3.1]nonane ; le tricyclo [5.2.1.0^{2,6}]décane.

Selon la présente invention, par halogène on entend un atome choisi parmi le fluor, le chlore, le brome ou l'iode, de préférence le fluor ou le chlore.

5 Des exemples de groupes aryle sont phényle et naphtyle.

Les cations de métaux alcalins ou alcalino-terreux sont de préférence choisis parmi sodium, potassium ou calcium.

Lorsqu'un composé selon l'invention présente un ou des carbones asymétriques, les isomères optiques de ce composé font partie intégrante de l'invention.

10 Lorsqu'un composé selon l'invention présente une stéréoisomérisation par exemple de type axial-équatorial, l'invention comprend tous les stéréoisomères de ce composé.

Les sels des composés de formule (I) selon la présente invention comprennent ceux avec des acides minéraux ou organiques qui permettent une séparation ou une cristallisation convenable des composés de formule (I), tels que l'acide picrique, l'acide

15 oxalique ou un acide optiquement actif, par exemple un acide tartrique, un acide dibenzoyltartrique, un acide mandélique ou un acide camphosulfonique, et ceux qui forment des sels physiologiquement acceptables, tels que le chlorhydrate, le bromhydrate, le sulfate, l'hydrogénosulfate, le dihydrogénophosphate, le maléate, le fumarate, le 2-naphtalènesulfonate, le paratoluènesulfonate.

20 Les sels des composés de formule (I) comprennent également des sels avec des bases organiques ou minérales, par exemple les sels des métaux alcalins ou alcalino-terreux, comme les sels de sodium, de potassium, de calcium, les sels de sodium et de potassium étant préférés, ou avec une amine, telle que le trométamol, ou bien les sels d'arginine, de lysine, ou de toute amine physiologiquement acceptable.

25 Les groupes fonctionnels éventuellement présents dans la molécule des composés de formule (I) et dans les intermédiaires réactionnels peuvent être protégés, soit sous forme permanente soit sous forme temporaire, par des groupes protecteurs qui assurent une synthèse univoque des composés attendus.

Par groupe protecteur temporaire des amines, alcools ou des acides carboxyliques on entend les groupes protecteurs tels que ceux décrits dans Protective Groups in Organic Synthesis, Greene T.W. et Wuts P.G.M., ed. John Wiley et Sons, 1991 et dans Protecting Groups, Kocienski P.J., 1994, Georg Thieme Verlag.

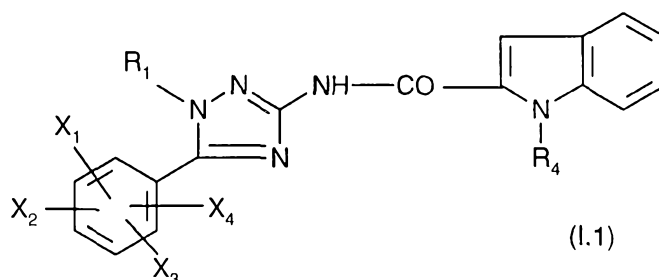
Les composés (I) peuvent comporter des groupes précurseurs d'autres fonctions qui sont générées ultérieurement en une ou plusieurs autres étapes.

35 Les composés de formule (I) dans lesquels R₁ représente un cyclohexyl(C₁.C₃)-alkyle sont des composés préférés.

Egalement préférés sont les composés de formule (I), dans lesquels le phényle en position 5 du triazole est trisubstitué de préférence par un méthoxy en position 2 et 6, et par un méthyle en position 4.

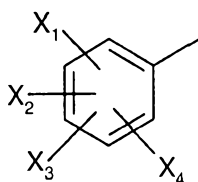
Et encore plus préférés sont les composés de formule (I) dans lesquels le phényle en position 5 du triazole est trisubstitué de préférence par un méthoxy en position 2 et 6 et par un méthyle ou un chlore en position 4.

De façon particulière, on préfère les composés de formule :



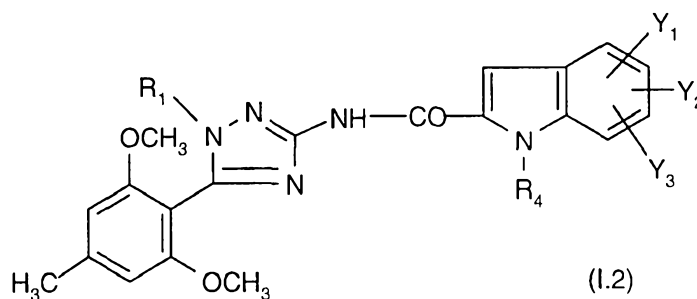
dans laquelle R_1 , R_4 , X_1 , X_2 , X_3 et X_4 sont tels que définis pour (I); un de leurs sels ou solvates.

Parmi ces composés, on préfère ceux dans lesquels



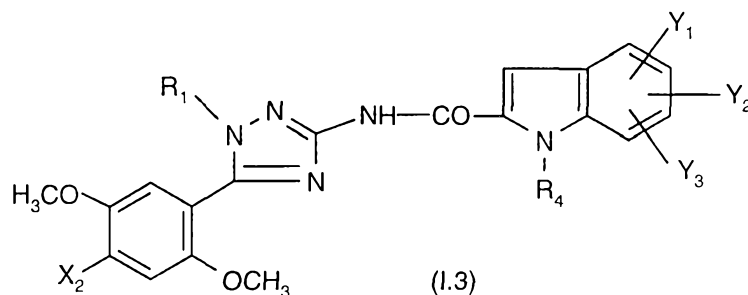
représente 2,6-diméthoxy-4-méthylphényle.

Plus particulièrement préférés sont les composés de formule :



dans laquelle R_1 et R_4 sont tels que définis pour (I); un de leurs sels ou solvates.

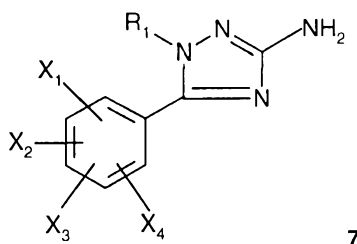
On préfère tout particulièrement les composés de formule :



dans laquelle R_1 , R_4 , Y_1 , Y_2 et Y_3 sont tels que définis pour (I), et X_2 représente un méthyle ou un atome de chlore ; un de leurs sels ou solvates.

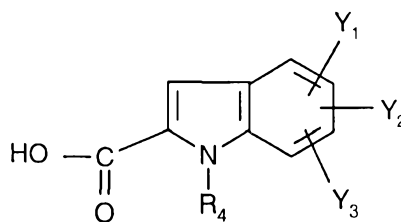
5

La présente invention a également pour objet un procédé pour la préparation des composés de formule (I), comprenant la réaction d'un aminotriazole de formule :



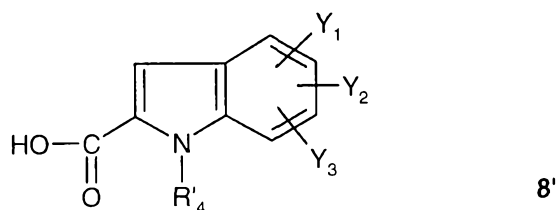
10 dans lequel R_1 , X_1 , X_2 , X_3 et X_4 sont tels que définis pour (I)

- soit avec un dérivé acide indole carboxylique de formule



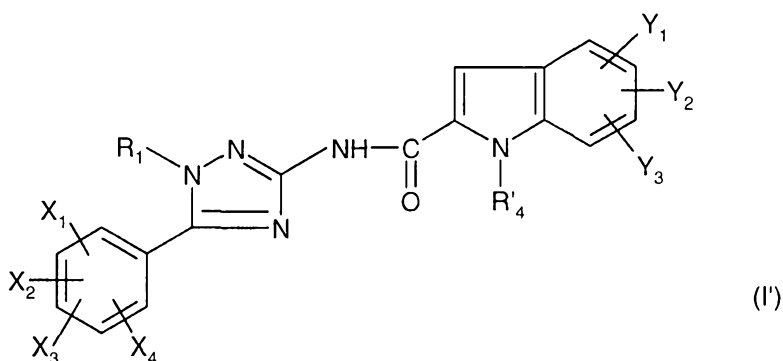
dans laquelle R_4 , Y_1 , Y_2 et Y_3 sont tels que définis ci-dessus pour (I) ;

- soit avec un dérivé acide indole carboxylique de formule :



15

dans laquelle Y_1 , Y_2 , Y_3 sont tels que définis ci-dessus pour (I) et R'_4 est un groupe précurseur de R_4 , auquel cas on forme le composé de formule :



dans laquelle R_1 , X_1 , X_2 , X_3 , X_4 , Y_1 , Y_2 et Y_3 sont tels que définis pour (I) et R'_4 est un groupe précurseur de R_4 , R_4 étant tel que défini pour (I) ;

pour obtenir les composés de formule (I), un de leurs sels ou solvates.

- 5 Les composés intermédiaires (I') conduisent aux composés de formule (I) par transformation du groupe R'_4 en R_4 , laquelle est mise en œuvre de façon connue en soi selon des procédés conventionnels de la chimie organique.

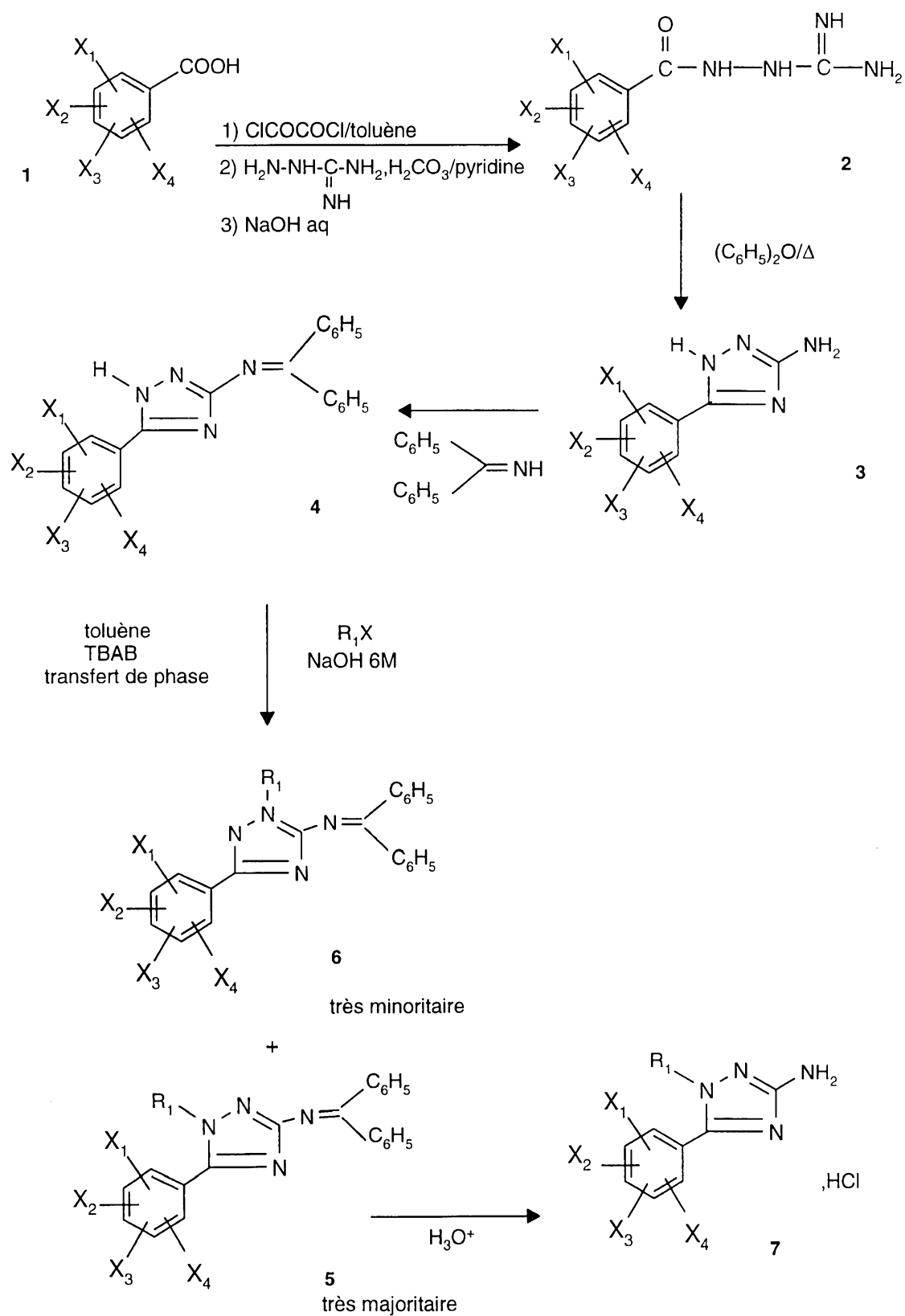
Les aminotriazoles de formule 7 constituent des intermédiaires clés, nouveaux, utiles pour la préparation des composés (I) et forment un objet de l'invention.

- 10 Les produits de départ sont disponibles commercialement ou préparés selon les méthodes ci-après.

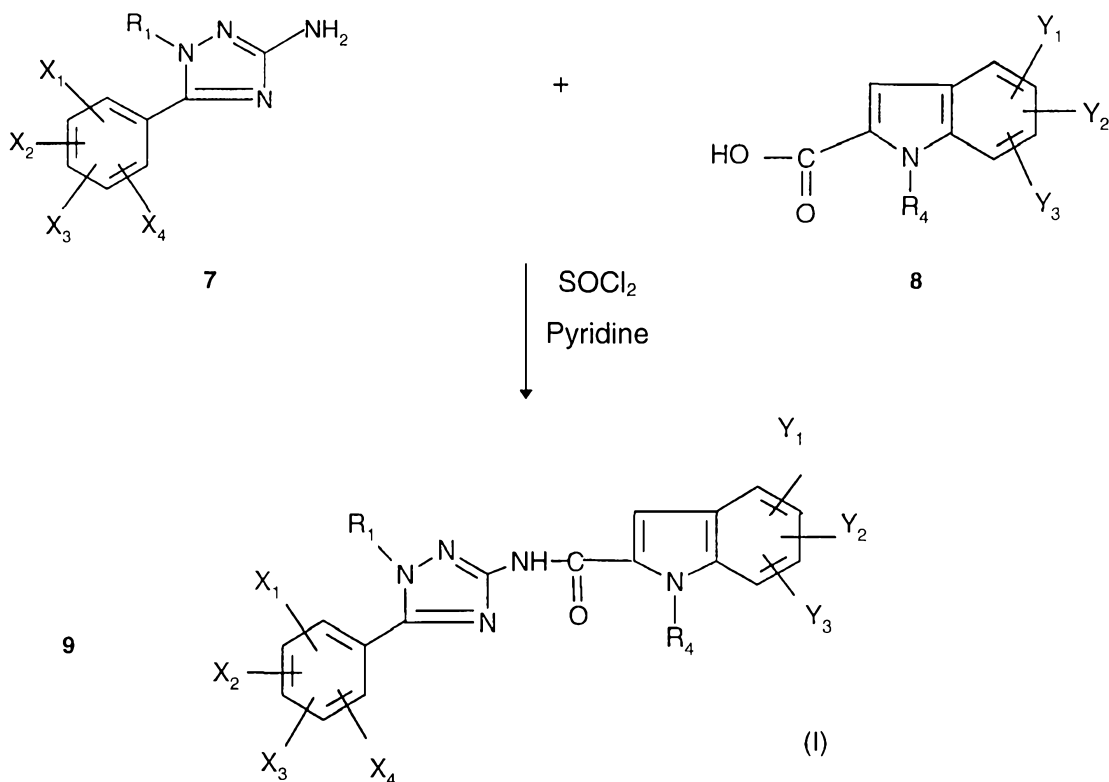
Le schéma 1 suivant illustre une voie de synthèse des composés de formule 7.

Le schéma 2 suivant illustre la préparation des composés de formule (I) à partir des aminotriazoles de formule 7.

SCHEMA 1 : PREPARATION DES 3-AMINOTRIAZOLES SUBSTITUES DE FORMULE 7

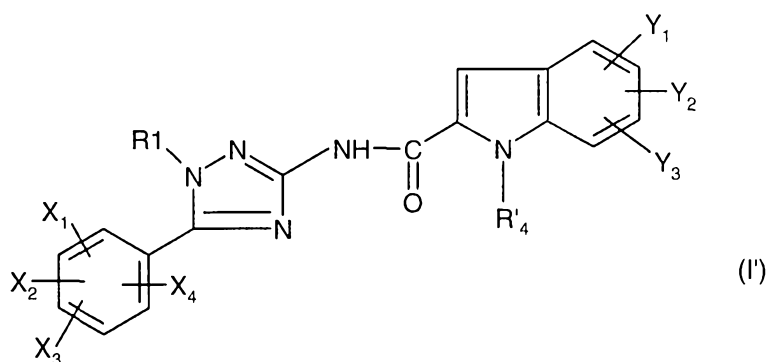


SCHEMA 2 : PREPARATION DES 3-AMIDOTRIAZOLES (I)



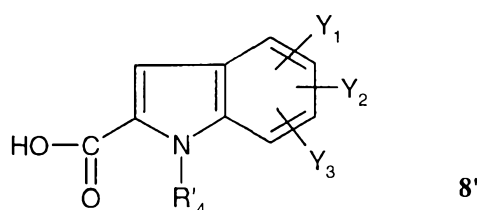
Lorsque $R_4 = -(\text{CH}_2)_n\text{COOH}$, les composés (I) sont obtenus à partir des esters correspondants, eux-mêmes obtenus à partir du SCHEMA 2.

Lorsque $R_4 = -(\text{CH}_2)_n\text{-tétrazolyloyle}$, les composés (I) sont obtenus à partir des nitriles correspondants de formule :



dans laquelle $R'_4 = -(\text{CH}_2)_n\text{-C}\equiv\text{N}$, par action de l'azidotriméthylsilane en présence d'oxyde de dibutylétain selon le procédé décrit dans J.Org. Chem. 1993, 58, 4139-4141.

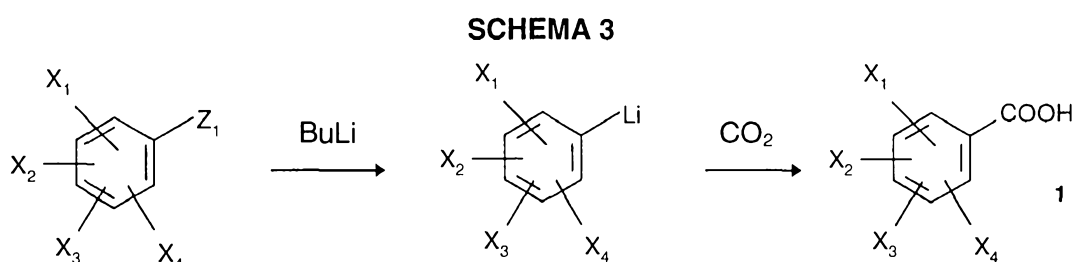
Les composés de formule (I') sont obtenus selon le SCHEMA 2, à partir des composés 7 et 8' de formule :



dans laquelle $R'_4 = -(\text{CH}_2)_n-\text{C}\equiv\text{N}$

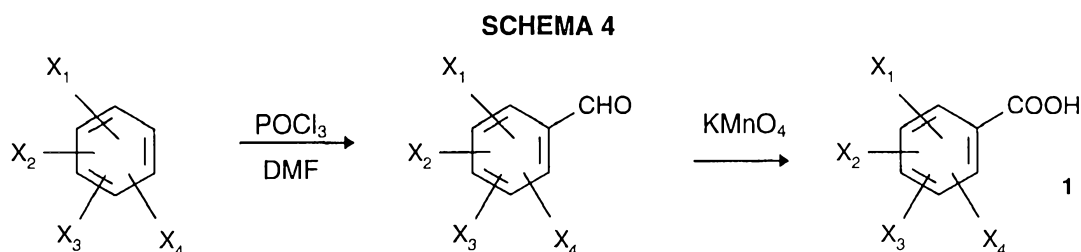
Les acides benzoïques substitués 1 sont disponibles commercialement ou préparés selon une adaptation des procédés décrits dans la littérature, par exemple :

- 1) par lithiation régiosélective de benzènes substitués, suivie de carboxylation du dérivé lithié avec CO_2 selon le SCHEMA 3 :



avec $Z_1 = \text{Br}$ ou H suivant la nature et/ou la position des substituants X_1, X_2, X_3, X_4 selon : N.S. Narasimhan *et al.*, Indian J. Chem., 1973, 11, 1192 ; R.C. Cambie *et al.*, Austr. J. Chem., 1991, 44, 1465 ; T. de Paulis *et al.*, J. Med. Chem., 1986, 29, 61; ou bien

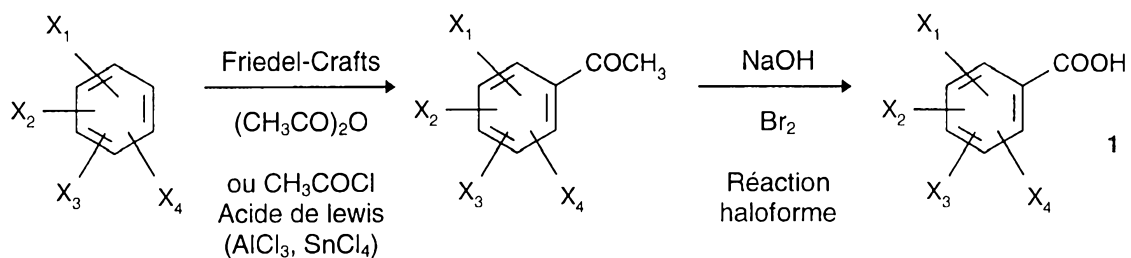
- 2) par formylation régiosélective de benzènes substitués, suivie de l'oxydation du benzaldéhyde substitué par KMnO_4 , selon le SCHEMA 4 :



selon la méthode décrite par S.B. Matin *et al.*, J. Med. Chem., 1974, 17, 877; ou bien

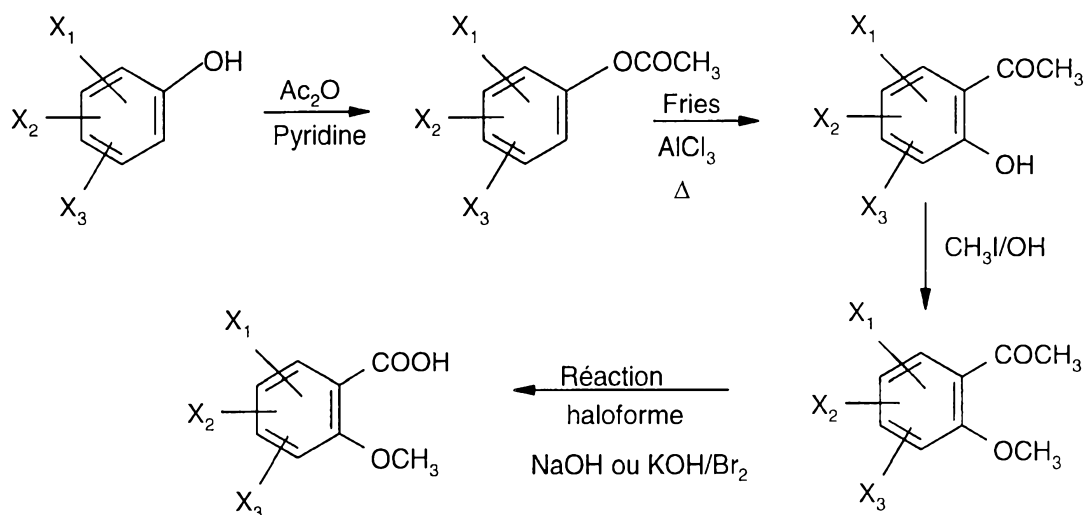
- 3) par oxydation haloforme selon R. Levine *et al.*, J. Am. Chem. Soc., 1959, 72, 1642 de méthylcétones aromatiques, obtenues par acylation de Friedel-Crafts, de benzènes substitués (C.A. Bartram *et al.*, J. Chem. Soc., 1963, 4691) ou par réarrangement de Fries d'acyloxybenzènes substitués selon S.E. Cremer *et al.*, J. Org. Chem., 1961, 26, 3653, selon les SCHEMAS 5 et 6 ci-après :

SCHEMA 5



Les acides substitués en position 2 par un méthoxy peuvent être préparés à partir d'un dérivé phénol substitué par réaction de l'anhydride acétique dans la pyridine, suivie d'une réaction de Fries en présence de chlorure d'aluminium pour conduire à l'hydroxy acétophénone, sur laquelle on fait réagir l'iodure de méthyle en milieu alcalin pour obtenir finalement, par une réaction haloforme, l'acide 1' attendu selon le SCHEMA 6 ci-après :

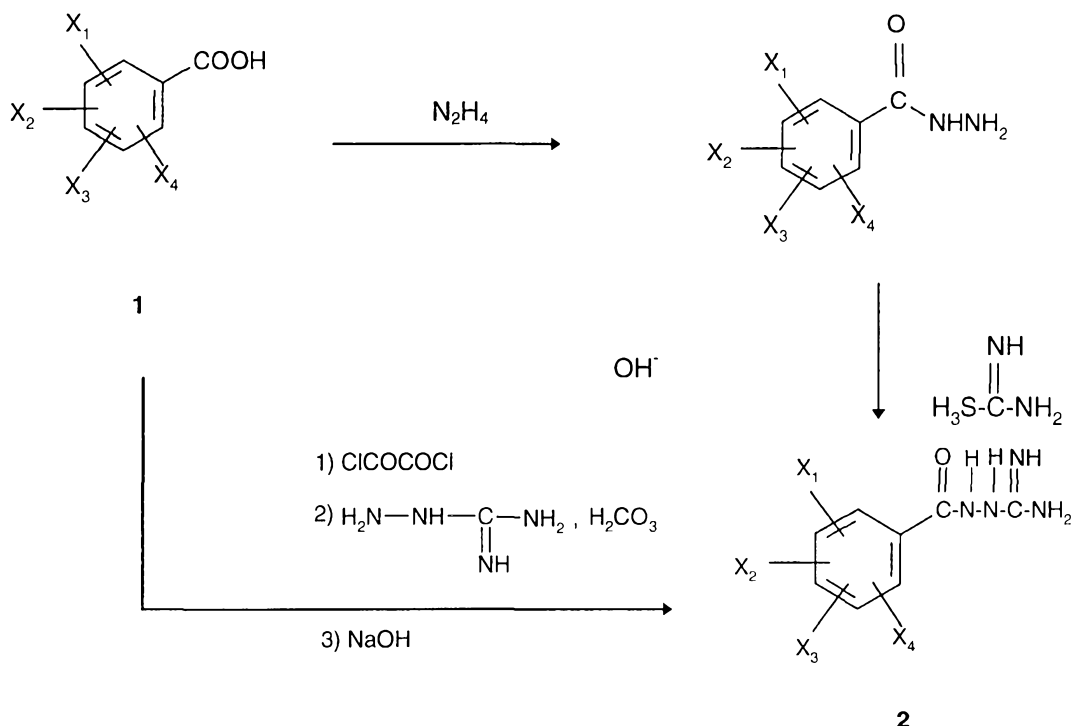
SCHEMA 6



1'

La benzamidoguanidine 2 est obtenue par acylation d'hydrogénocarbonate d'aminoguanidine par le chlorure de l'acide benzoïque obtenu à partir de l'acide benzoïque 1 par des procédés classiques (SOCl_2 , chlorure d'oxalyle dans un solvant inerte), selon une adaptation du procédé décrit par E. Hoggarth, J. Chem. Soc., 1950, 612. Elle peut également être obtenue selon la variante décrite dans cette même publication selon le SCHEMA 7 suivant :

SCHEMA 7



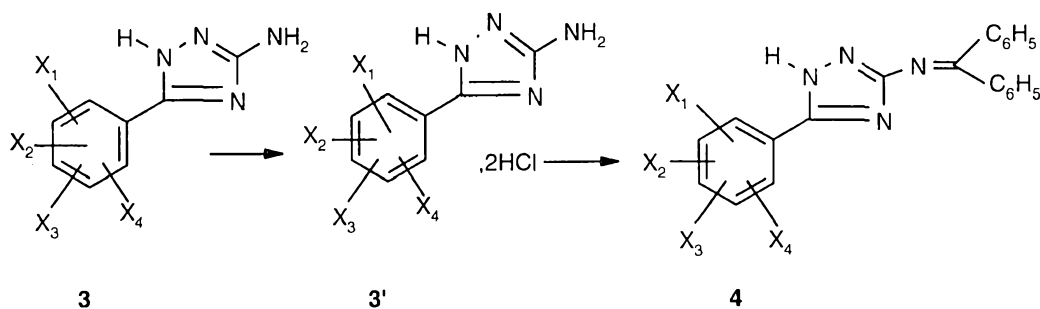
La cyclisation thermique de la benzamidoguanidine **2** dans un solvant à haut point d'ébullition, tel que le diphenyléther, conduit à l'aryl-5-amino-3-triazole **3** selon une adaptation du procédé décrit par E. Hoggarth, J. Chem. Soc., 1950, 612.

5 La protection de la fonction amino primaire du triazole **3** sous forme de diphénylimine conduit au triazole N-protégé **4**, selon une adaptation d'un procédé décrit par M.J. O'Donnell *et al.*, J. Org. Chem., 1982, 47, 2663.

On peut également obtenir le composé **4** selon une variante qui consiste à traiter le triazole **3**, préalablement transformé en chlorhydrate **3'** par la diphénylimine, selon le

10 SCHEMA 8 ci-après :

SCHEMA 8



La N-alkylation du diphényliminotriazole **4**, par un halogénure d'alkyle R_1X , sous des conditions de transfert de phase (base forte en solution aqueuse concentrée, en présence d'un cosolvant organique non miscible et d'un catalyseur ammonium quaternaire) conduit très majoritairement au triazole **5**, accompagné du triazole très

15

minoritaire 6. Les bases fortes utilisées peuvent être des solutions aqueuses de NaOH ou KOH à des concentrations de 6 M à 12 M. Le cosolvant peut être le toluène, le benzène et l'ammonium quaternaire choisi parmi tous les sels d'ammonium quaternaires et, plus particulièrement, le TBAB (bromure de tétrabutylammonium).

a) La N-alkylation du diphenyliminotriazole 4 peut s'opérer dans un milieu non aqueux (diméthylformamide, tétrahydrofurane par exemple) en présence d'une base forte telle que K_2CO_3 ou NaH.

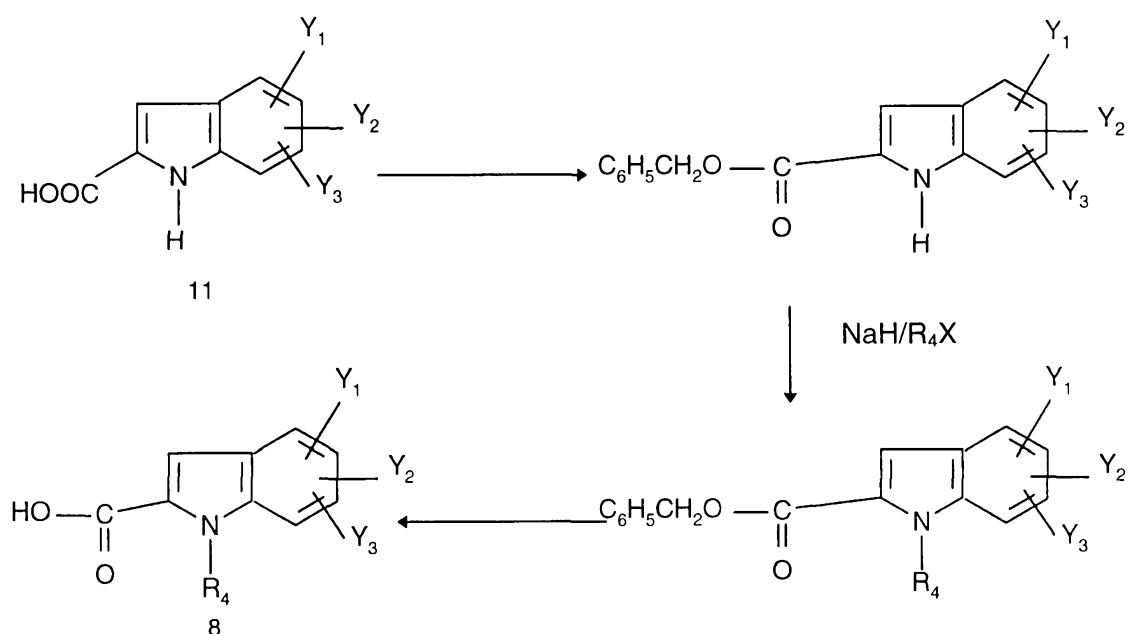
b) On peut également utiliser une variante telle que celle décrite par E. Akerblom, *Acta Chem. Scand.*, 1965, 19, 1142, laquelle met en oeuvre un agent alkylant dans un alcool tel que l'éthanol en présence d'une base forte solide telle que KOH ou NaOH.

Le triazole 5 est très facilement séparé de son isomère 6 par chromatographie sur colonne de silice ou flash-chromatographie, selon la nature du groupement R_1 .

Le clivage du produit 5, obtenu après séparation de son isomère minoritaire, s'opère en milieu aqueux acide tel que HCl 1N, suivant une adaptation du procédé décrit par J. Yaozhong *et al.*, *Tetrahedron*, 1988, 44, 5343 ou M.J. O'Donnell *et al.*, *J. Org. Chem.*, 1982, 47, 2663. Il permet d'obtenir les amino-3-triazole N-alkylés en position 1 de formule 7.

Les indoles carboxyliques de formule 8 ont été préparés selon des procédés décrits dans le brevet n°EP 611766 selon le SCHEMA 9 ci-après :

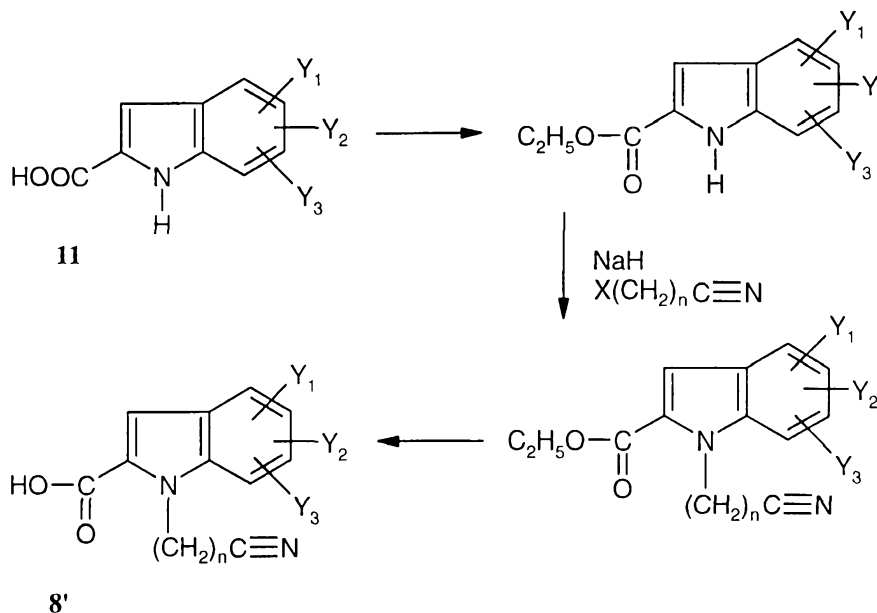
SCHEMA 9



Les indoles carboxyliques 8' dans lesquelles $R'_4 = -(CH_2)_n-C\equiv N$

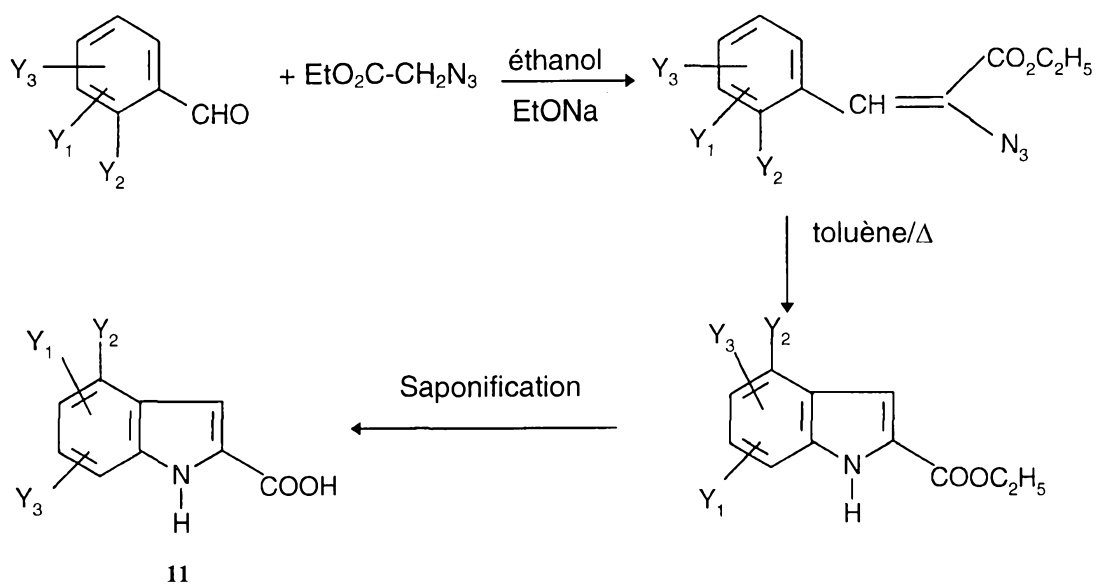
ont été préparés selon un procédé analogue présenté dans le SCHÉMA 9 bis ci-après :

SCHÉMA 9 bis



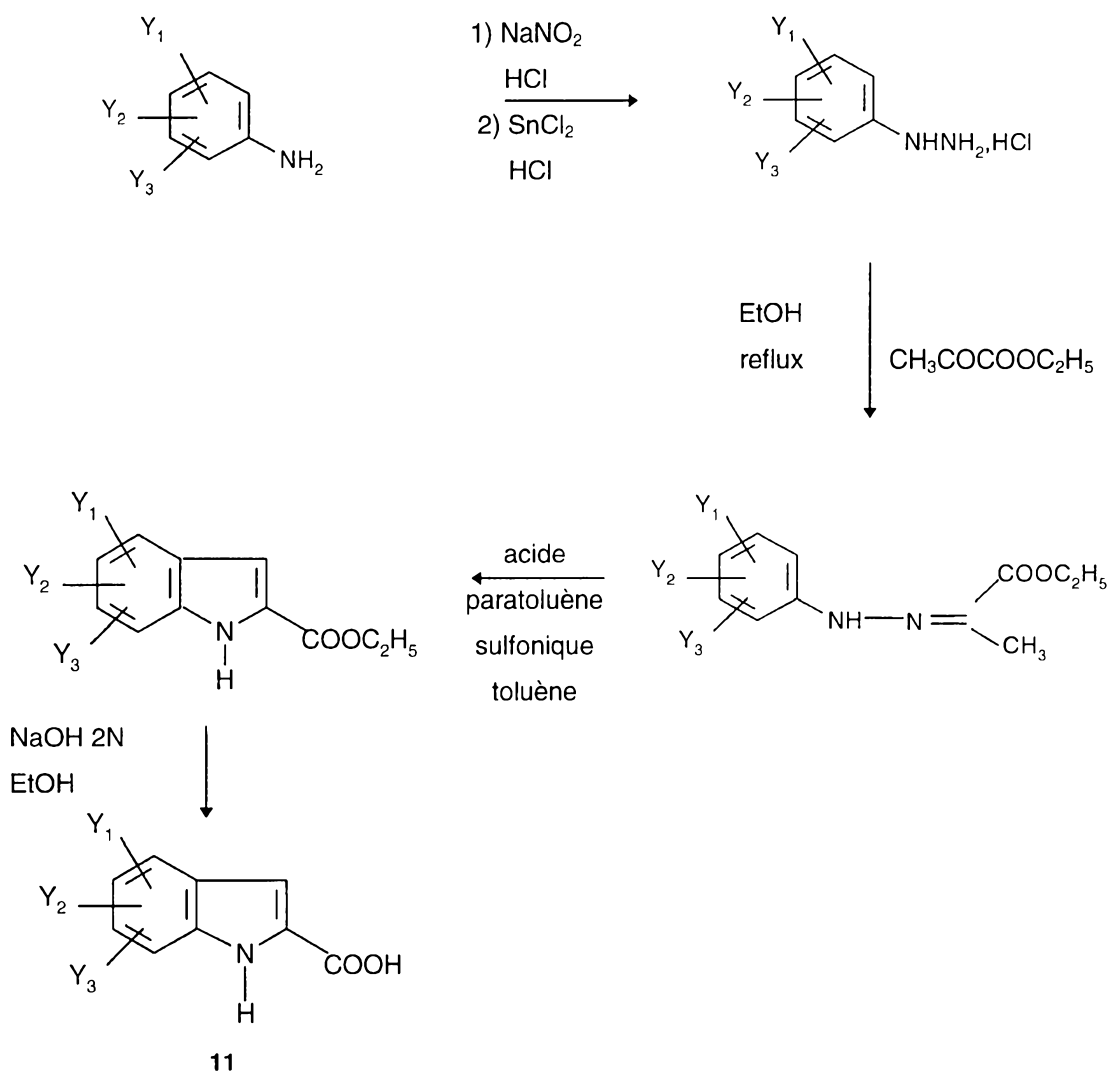
- 5 Les indoles 11 sont commerciaux ou préparés selon une adaptation des procédés décrits dans la littérature, par exemple selon L. Henn *et al.*, J. Chem. Soc. Perkin Trans. I, 1984, 2189 selon le SCHEMA 10 ci-après :

SCHEMA 10



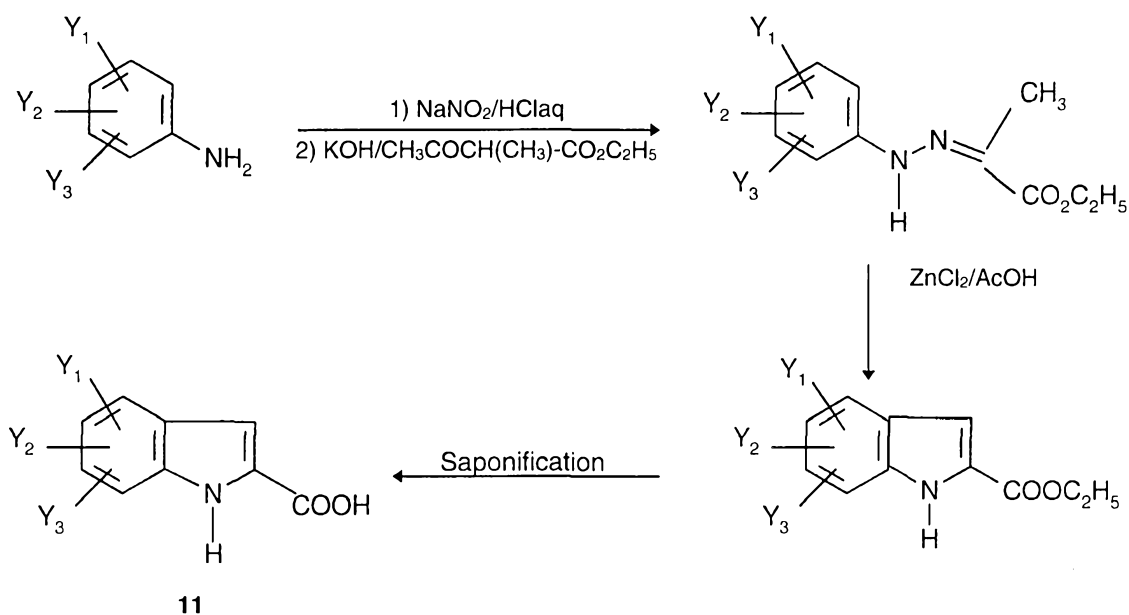
- 10 ou encore, par exemple, selon la synthèse de Fischer (V. Prelog *et al.*, Helv. Chim. Acta., 1948, 31, 1178) selon le SCHEMA 11 ci-après :

SCHEMA 11



- 5 ou encore selon la synthèse de Japp-Klingemann (H. Ishii *et al.*, J. Chem. Soc. Perkin. Trans. 1, 1989, 2407) selon le SCHEMA 12 ci-après :

SCHEMA 12



Les composés de formule (I) ci-dessus comprennent également ceux dans lesquels un ou plusieurs atomes d'hydrogène, de carbone ou d'halogène, notamment de chlore ou de fluor ont été remplacés par leur isotope radioactif par exemple le tritium ou le carbone-14. De tels composés marqués sont utiles dans des travaux de recherche, de métabolisme ou de pharmacocinétique, dans des essais biochimiques en tant que ligand de récepteurs.

Les composés de formule (I) ont fait l'objet d'études de liaison *in vitro* aux récepteurs CCK-A et CCK-B, en utilisant la méthode décrite dans Europ. J. Pharmacol., 1993, 232, 13-19.

L'activité agoniste des composés vis-à-vis des récepteurs CCK-A a été évaluée *in vitro* dans les cellules 3T3 exprimant le récepteur CCK-A humain, par la mesure de la mobilisation du calcium intracellulaire ($[Ca^{++}]_i$), selon une technique dérivée de celle de Lignon MF *et al.*, Eur. J. Pharmacol., 1993, 245, 241-245. La concentration en calcium $[Ca^{++}]_i$ est évaluée avec le Fura-2 par la méthode de la double longueur d'onde d'excitation. Le rapport de la fluorescence émise à deux longueurs d'onde donne la concentration en $[Ca^{++}]_i$ après un étalonnage (Grynkiewicz G. *et al.*, J. Biol. Chem., 1985, 260, 3440-3450).

Les composés selon l'invention stimulent le $[Ca^{++}]_i$ partiellement, ou totalement comme la CCK, et se comportent donc comme des agonistes du récepteur CCK-A.

Une étude de l'effet agoniste des composés sur la vidange gastrique a été réalisée comme suit. Les souris femelles Swiss albino CD1 (20-25g) sont mises à jeun solide

pendant 18 heures. Le jour de l'expérience, les produits (en suspension dans une solution de carboxyméthylcellulose à 1 % ou de méthylcellulose à 0,6 %) ou le véhicule correspondant sont administrés par voie intrapéritonéale, 30 minutes avant l'administration d'un repas de charbon (0,3 ml par souris d'une suspension dans l'eau de 10 % de poudre de charbon, 5 % de gomme arabique et 1 % de carboxyméthylcellulose) ou par voie orale une heure avant. Les souris sont sacrifiées 5 minutes plus tard par dislocation cervicale, et la vidange gastrique est définie comme la présence de charbon dans l'intestin au-delà du sphincter pylorique (Europ. J. Pharmacol., 1993, 232, 13-19). Les composés de formule (I) bloquent la vidange gastrique partiellement ou complètement comme la CCK elle-même, et se comportent donc comme des agonistes des récepteurs CCK. Certains d'entre eux ont des DE₅₀ (dose efficace induisant 50 % de l'effet de la CCK) inférieures à 0,1 mg/kg par la voie intrapéritonéale.

Une étude de l'effet agoniste des composés sur la contraction de la vésicule biliaire a été réalisée comme suit. Les souris femelles Swiss albino CD1 (20-25 g) sont mises à jeun solide pendant 24 heures. Le jour de l'expérience, les produits (en suspension dans une solution de carboxyméthylcellulose à 1 % ou de méthylcellulose à 0,6 %) ou le véhicule correspondant sont administrés par voie orale. Les souris sont sacrifiées par dislocation cervicale une heure après l'administration des produits, et les vésicules biliaires sont prélevées et pesées. Les résultats sont exprimés en mg/kg de poids corporel (Europ. J. Pharmacol., 1993, 232, 13-19). Les composés de formule (I) contractent la vésicule biliaire partiellement ou totalement comme la CCK elle-même, et se comportent donc comme des agonistes des récepteurs CCK. Certains d'entre eux ont des DE₅₀ (dose efficace induisant 50 % de la diminution du poids des vésicules observées avec la CCK) inférieures à 0,1 mg/kg par la voie orale.

Par conséquent, les composés de formule (I) sont utilisés, en tant qu'agonistes des récepteurs de la CCK de type A, pour la préparation de médicaments destinés à combattre les maladies dont le traitement nécessite une stimulation par agonisme total ou partiel des récepteurs CCK A de la cholécystokinine. Plus particulièrement, les composés de formule (I) sont utilisés pour la fabrication de médicaments destinés au traitement de certains troubles de la sphère gastrointestinale (prévention des calculs biliaires, syndrome du colon irritable) du comportement alimentaire, de l'obésité, et des pathologies associées telles que le diabète et l'hypertension. Les composés (I) induisent un état de satiété, et sont ainsi utilisés pour traiter les désordres alimentaires, pour réguler l'appétit et réduire la prise alimentaire, traiter la boulimie, l'obésité et provoquer une perte de poids. Les composés (I) sont également utiles

dans des troubles du comportement émotionnel, sexuel et mnésique, des psychoses et, notamment, la schizophrénie, de la maladie de Parkinson, de la dyskinésie tardive. Ils peuvent aussi servir le traitement des troubles de l'appétence, c'est-à-dire pour réguler les désirs de consommation, en particulier la consommation de sucres, de
5 carbohydrates, d'alcool ou de drogues et plus généralement d'ingrédients appétissants.

Les composés de formule (I) sont peu toxiques ; leur toxicité est compatible avec leur utilisation comme médicament pour le traitement des troubles et des maladies ci-dessus. Aucun signe de toxicité n'est observé avec ces composés aux doses
10 pharmacologiquement actives, et leur toxicité est donc compatible avec leur utilisation médicale comme médicaments.

La présente invention a donc également pour objet des compositions pharmaceutiques contenant une dose efficace d'un composé selon l'invention ou d'un sel pharmaceutiquement acceptable de celui-ci, et des excipients convenables.

15 Lesdits excipients sont choisis selon la forme pharmaceutique et le mode d'administration souhaité.

Dans les compositions pharmaceutiques de la présente invention pour l'administration orale, sublinguale, sous-cutanée, intramusculaire, intra-veineuse, topique, intratrachéale, intranasale, transdermique, rectale ou intraoculaire, les principes actifs
20 de formule (I) ci-dessus, ou leurs sels éventuels, peuvent être administrés sous formes unitaires d'administration, en mélange avec des supports pharmaceutiques classiques, aux animaux et aux êtres humains pour la prophylaxie ou le traitement des troubles ou des maladies ci-dessus. Les formes unitaires d'administration appropriées comprennent les formes par voie orale telles que les comprimés, les gélules, les
25 poudres, les granules et les solutions ou suspensions orales, les formes d'administration sublinguale, buccale, intratrachéale, intranasale, les formes d'administration sous-cutanée, intramusculaire ou intraveineuse et les formes d'administration rectale. Pour l'application topique, on peut utiliser les composés selon l'invention dans des crèmes, pommades, lotions ou collyres.

30 Afin d'obtenir l'effet prophylactique ou thérapeutique désiré, la dose de principe actif peut varier entre 0,01 et 50 mg par kg de poids du corps et par jour.

Chaque dose unitaire peut contenir de 0,5 à 1000 mg, de préférence de 1 à 500 mg, d'ingrédients actifs en combinaison avec un support pharmaceutique. Cette dose unitaire peut être administrée 1 à 5 fois par jour de façon à administrer un dosage
35 journalier de 0,5 à 5000 mg, de préférence de 1 à 2500 mg.

Lorsqu'on prépare une composition solide sous forme de comprimés, on mélange l'ingrédient actif principal avec un véhicule pharmaceutique, tel que la gélatine, l'amidon, le lactose, le stéarate de magnésium, le talc, la gomme arabique ou analogues. On peut enrober les comprimés de saccharose, d'un dérivé cellulosique, ou d'autres matières appropriées ou encore on peut les traiter de telle sorte qu'ils aient une activité prolongée ou retardée et qu'ils libèrent d'une façon continue une quantité prédéterminée de principe actif.

On obtient une préparation en gélules en mélangeant l'ingrédient actif avec un diluant et en versant le mélange obtenu dans des gélules molles ou dures.

Une préparation sous forme de sirop ou d'élixir ou pour l'administration sous forme de gouttes peut contenir l'ingrédient actif conjointement avec un édulcorant, acalorique de préférence, du méthylparaben et du propylparaben comme antiseptique, ainsi qu'un agent donnant du goût et un colorant approprié. Les poudres ou les granules dispersibles dans l'eau peuvent contenir l'ingrédient actif en mélange avec des agents de dispersion ou des agents mouillants, ou des agents de mise en suspension, comme la polyvinylpyrrolidone, de même qu'avec des édulcorants ou des correcteurs du goût.

Pour une administration rectale, on recourt à des suppositoires qui sont préparés avec des liants fondant à la température rectale, par exemple du beurre de cacao ou des polyéthylèneglycols. Pour une administration parentérale, on utilise des suspensions aqueuses, des solutions salines isotoniques ou des solutions stériles et injectables qui contiennent des agents de dispersion et/ou des mouillants pharmacologiquement compatibles, par exemple le propylèneglycol ou le butylèneglycol.

Le principe actif peut être formulé également sous forme de microcapsules, éventuellement avec un ou plusieurs supports ou additifs, ou bien avec des matrices telles qu'un polymère ou une cyclodextrine (patch, formes à libération prolongée).

Les compositions selon l'invention peuvent être utilisés dans le traitement ou la prévention de différentes affections où la CCK est d'un intérêt thérapeutique.

Les compositions de la présente invention peuvent contenir, à côté des produits de formule (I) ci-dessus ou de leurs sels pharmaceutiquement acceptables, d'autres principes actifs qui peuvent être utiles dans le traitement des troubles ou maladies indiquées ci-dessus.

De façon avantageuse les compositions de la présente invention contiennent un produit de formule (I.1), (I.2) ou (I.3) ci-dessus ou un de ses sels, solvates ou hydrates pharmaceutiquement acceptables.

PREPARATION DES INTERMEDIAIRES DE SYNTHESE

A. PREPARATION DES ACIDES 1 (VARIANTES)**Acide 2,5-diméthoxy-4-méthylbenzoïque (Composé A.1)**

5 a) 2,5-Diméthoxy-4-méthylbenzaldéhyde

Après 40 minutes d'agitation à température ambiante d'un mélange de 8,5 ml de N-méthylformanilide (0,068 mole), et de 6,3 ml de trichlorure d'oxyde de phosphore (0,068 mole), on introduit 17,8 g de 2,5-diméthoxytoluène (0,117 mole). On chauffe le mélange réactionnel pendant 6 heures à 50°C puis, après avoir ramené la
10 température à 20°C, on hydrolyse par 100 ml de solution aqueuse à 10 % d'acétate de sodium, on extrait deux fois à l'éther diéthylique et on concentre. Le résidu est repris par une solution aqueuse d'hydrogénosulfite de sodium, et extrait deux fois à l'éther diéthylique. La phase aqueuse est alcalinisée (pH = 12) pour fournir des cristaux blancs ; F = 83°C ; Rendement = 67 %.

15 b) Acide 2,5-diméthoxy-4-méthylbenzoïque

On chauffe à 75°C 23,86 g (0,132 mole) de 2,5-diméthoxy-4-méthylbenzaldéhyde en solution dans 500 ml d'eau, et on introduit 29,3 g (0,185 mole) de permanganate de potassium en solution dans 500 ml d'eau. On abandonne le mélange réactionnel pendant 2 heures à 75°C, puis on filtre à chaud l'insoluble après avoir ajusté le pH à
20 10 avec une solution à 10 % d'hydroxyde de sodium, et on le rince trois fois avec 80 ml d'eau chaude. Le filtrat est refroidi, le précipité formé est filtré, séché sous vide à 40°C pour fournir des cristaux blancs ; F = 120°C ; Rendement = 71 %.

Acide 2,5-diméthoxy-4-chlorobenzoïque (Composé A.2)

a) (2,5-Diméthoxy-4-chlorophényl)méthylcétone

A 2 litres de tétrachlorure de carbone, on additionne à température ambiante, 162,5 g de trichlorure d'aluminium (1,2 mole) puis à 0°C, goutte à goutte, 82 ml de chlorure d'acétyle (1,2 mole), puis 200 g de 1,4-diméthoxy-2-chlorobenzène (1,2 mole). On abandonne le mélange réactionnel pendant 3 heures et demie à 0°C, puis on l'hydrolyse par 700 ml d'eau. La phase organique est lavée avec une
30 solution d'hydroxyde de sodium 2 M, séchée sur sulfate de sodium anhydre et concentrée. Le résidu semi-cristallin est repris à l'éther de pétrole, filtré, séché, pour fournir des cristaux blancs ; F = 96°C ; Rendement = 70 %.

b) Acide 2,5-diméthoxy-4-chlorobenzoïque

A 800 ml d'eau, on additionne 278 g d'hydroxyde de potassium (4,96 moles), puis, à
35 5°C, 84 ml de brome (1,6 mole) goutte à goutte. On laisse le mélange réactionnel pendant une heure à température ambiante. La solution aqueuse d'hypobromite de

sodium obtenue est additionnée à 107 g de (2,5-diméthoxy-4-chlorophényl)méthylcétone (0,494 mole) en solution dans 1,5 litre de 1,4-dioxane. Après une heure à 20°C, on chauffe le mélange réactionnel pendant une heure à reflux. Lorsque la réaction est terminée, on introduit 100 ml d'une solution aqueuse d'hydrogénosulfite de sodium, puis on évapore le solvant. Le résidu est acidifié par une solution d'acide chlorhydrique 6 N, puis on extrait deux fois à l'acétate d'éthyle. La phase organique est séchée sur sulfate de sodium anhydre, et concentrée. Le résidu est concrété dans l'éther diisopropylique, pour fournir des cristaux blancs ; F = 160°C ; Rendement = 91 %.

10 **Acide 2,6-diméthoxy-4-méthylphénylbenzoïque (Composé A.3)**

On dissout 231,6 g (1,5 moles) de 3,5-diméthoxytoluène dans 1 litre d'éther diéthylique, puis on ajoute goutte à goutte sous azote à température ambiante, 1 litre d'une solution 1,6 N de butyllithium (1,6 mole) dans l'hexane. On abandonne le mélange réactionnel pendant 18 heures à température ambiante puis, après refroidissement à -30°C, on ajoute 1 litre d'éther diéthylique et on fait barboter du gaz carbonique pendant une heure, tout en maintenant la température à -30°C. On reprend le mélange réactionnel par 6 litres d'une solution d'hydroxyde de sodium 2 M, on décante la phase aqueuse, et on l'acidifie avec une solution d'acide chlorhydrique 6 N. On filtre le précipité formé, le rince à l'eau et sèche sous vide à 40°C pour obtenir des cristaux blancs ; F = 187°C ; Rendement = 88 %.

B. PREPARATION DES INDOLES SUBSTITUES ET LEURS VARIANTES

Préparation du 5-méthyl-1-H-2 indole carboxylate d'éthyle (Composé B.1)

1ère méthode : (méthode de Japp-Klingemann):

A -5°C on additionne 7,2 g (0,104 mole) de nitrite de sodium en solution dans 40 ml d'eau, sur un mélange de 10,7 g (0,1 mole) de 4-méthylaniline, 74 ml d'acide chlorhydrique 12 N et de 140 ml d'eau. On agite le mélange réactionnel pendant 15 minutes à -5°C, et on neutralise par addition de 8,1 g d'acétate de sodium. Dans un tricol, on introduit 12,33 g (0,085 mole) d' α -méthylacétoacétate d'éthyle, 80 ml d'éthanol, puis à 0°C 4,8 g (0,085 mole) d'hydroxyde de potassium en solution dans 20 ml d'eau et 100 g de glace. A ce mélange réactionnel, on ajoute goutte à goutte à 0°C la solution de diazonium préparée précédemment, et on abandonne pendant 18 heures à 0°C. La phase aqueuse est extraite 4 fois par 50 ml d'acétate d'éthyle, les phases organiques sont rassemblées et séchées sur sulfate de sodium anhydre. Le résidu est repris par 100 ml de toluène et 16,3 g (0,085 mole) d'acide paratoluènesulfonique monohydraté. On chauffe alors lentement à 110°C et

maintient cette température pendant 5 heures. Après refroidissement, puis addition d'une solution saturée de carbonate de sodium, l'insoluble est écarté par filtration, la phase organique est décantée, séchée sur sulfate de sodium anhydre et concentrée. Le résidu est chromatographié sur colonne de gel de silice, éluant :
5 dichlorométhane/cyclohexane 30/70 (v/v) pour fournir des cristaux beiges ; F = 94°C ; Rendement = 25%.

Préparation du 4-méthyl-1H-2-indolecarboxylate d'éthyle (Composé B2)

2ème méthode :

- Etape 1 : préparation de l'azide
10 9,3 g (0,405 mole) de sodium sont additionnés, par portions, à 200 ml d'éthanol. A cette solution d'éthylate dans l'éthanol, on introduit goutte à goutte à -20°C, 16,2 g (0,135 mole) d'ortho-tolualdéhyde en solution, dans 52,2 g (0,405 mole) d'azidoacétate d'éthyle. Après 2 heures à -10°C, on verse le mélange réactionnel sur 400 ml d'eau, et filtre le précipité formé. On sèche 18 heures à 40°C sous vide
15 pour obtenir des cristaux blancs ; F = 55°C ; Rendement = 78 %.

- Etape 2 : cyclisation de l'azide
19,5 g (0,0844 mole) de l'azide préparé selon l'étape 1 sont additionnés, par portions, à 100 ml de xylène chauffés à 140°C. L'addition terminée, on abandonne le mélange réactionnel pendant 1 heure à 140°C. On concentre le xylène et le
20 résidu est repris par de l'éther isopropylique, filtré, séché 18 heures sous vide à 40°C, pour fournir des cristaux blancs ; F = 141°C ; Rendement = 62 %.

Préparation de l'acide 5-éthyl-1H-2-indolcarboxylique (selon la méthode de Fischer) - (Composé B.3)

3ème méthode :

- Etape 1 : Chlorhydrate de 4-éthylphénylhydrazine
25 A 24,2 g (0,2 mole) de 4-éthylaniline, on additionne 150 ml d'eau et 160 ml d'acide chlorhydrique 12 N. On refroidit le mélange à 0°C, puis on introduit goutte à goutte 14 g (0,2 mole) de nitrite de sodium en solution dans 140 ml d'eau. Après 1 heure à 0°C, on ajoute au mélange réactionnel à -10°C, 112 g (0,496 mole) de dihydrate de
30 chlorure stanneux en solution dans 90 ml d'acide chlorhydrique 12 N. Après 1 heure 30 à -10°C, on filtre le mélange réactionnel pour obtenir un solide brun ; F = 198°C ; Rendement = 95 %.

- Etape 2 : 2-[2-(4-Ethylphényl)hydrazono]propanoate d'éthyle
A 34,5 g (0,2 mole) de chlorhydrate de 4-éthylphénylhydrazine préparé
35 précédemment en suspension dans 500 ml d'éthanol, on additionne 23 ml (0,2 mole) de pyruvate d'éthyle, et on chauffe le mélange réactionnel durant 3 heures 30

à reflux. On ramène ensuite la température à 20°C, et évapore l'éthanol. Le résidu solide est lavé au pentane, séché à 40°C sous vide pour obtenir un liquide incolore ; Rendement = 94 %.

- Etape 3 : 5-Ethyl-1H-2-indolecarboxylate d'éthyle

5 A 44 g (0,188 mole) d'hydrazone préparée précédemment en suspension dans 300 ml de toluène, on additionne durant 7 heures, par portions, à reflux, 19 g (0,1 mole) d'acide paratoluènesulfonique monohydraté. On ramène la température à 20°C, on sépare un insoluble par filtration et le rince au toluène. Le filtrat est lavé avec une solution aqueuse saturée en carbonate de potassium; on décante, sèche sur sulfate de sodium anhydre et concentre. Le résidu est purifié par chromatographie sur colonne de gel de silice, éluant : dichlorométhane/cyclohexane 5/5 (v/v) pour obtenir des cristaux beiges ; F = 94°C ; Rendement = 51 %.

- Etape 4 : Acide 5-éthyl-1H-2-indolecarboxylique

15 A 150 ml de 1,4-dioxanne, on additionne 15,8 g (0,073 mole) de 5-éthyl-2-indolecarboxylate d'éthyle préparé selon l'étape 3, puis 45 ml d'une solution 2 M d'hydroxyde de sodium (0,09 mole). On abandonne le mélange réactionnel pendant 48 heures à température ambiante. Après évaporation du 1,4-dioxanne, le résidu est repris par une solution d'acide chlorhydrique 6 N, le précipité formé est filtré, séché sous vide à 60°C pour fournir l'acide 5-éthyl-1H-2-indolecarboxylique sous forme de cristaux blancs ; F = 184 °C ; Rendement = 92 %.

PREPARATION DES ACIDES 1H-2-INDOLECARBOXYLIQUES N-ALKYLES

Acide 5-éthyl-1-(méthoxycarbonylméthyl)-1H-2-indolecarboxylique -

25 **(Composé B.4)**

Etape 1 : 5-Ethyl-1H-2-indolecarboxylate de benzyle

A 70 ml de diméthylformamide, on additionne successivement 12,7 g (0,067 mole) d'acide 5-éthyl-1H-2-indolecarboxylique, 10 ml de 1,8-diazabicyclo[5.4.0]undéc-7-ène (0,067 mole). On laisse le mélange réactionnel pendant 40 minutes à 0°C, puis on introduit goutte à goutte 10,6 ml de bromure de benzyle (0,089 mole). Après 18 heures de réaction à température ambiante, le mélange réactionnel est versé sur 300 ml d'eau, le précipité formé est filtré, rincé à l'eau, puis séché pendant 18 heures à 50°C sous vide pour fournir des cristaux jaunes ; F = 99°C ; Rendement = 90 %.

Etape 2 : 5-Ethyl-1-(méthoxycarbonylméthyl)-1H-2-indolecarboxylate de benzyle

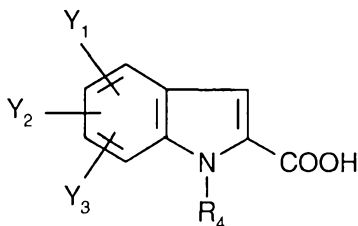
A 1,5 g (0,031 mole) d'hydruure de sodium à 50 % en suspension dans l'huile, on additionne 75 ml de diméthylformamide puis, par portions, 7,9 g (0,0283 mole) de 5-éthyl-1H-2-indolecarboxylate de benzyle préparé selon l'étape 1. Après 40 minutes à 0°C, on introduit goutte à goutte 3,5 ml (0,0315 mole) de bromoacétate de méthyle, et abandonne le mélange réactionnel pendant 2 heures à 20°C. On additionne 300 ml d'acétate d'éthyle, et lave avec 2x300 ml d'eau puis on décante, sèche la phase organique sur sulfate de sodium anhydre et concentre. On obtient 9,5 g d'huile incolore ; Rendement = 95 %.

Etape 3 : Acide 5-éthyl-1-(méthoxycarbonylméthyl)-1H-2-indolecarboxylique

A 9,5 g (0,0269 mole) de 5-éthyl-1-(méthoxycarbonylméthyl)-1H-2-indolecarboxylate de benzyle préparé selon l'étape 2 en solution dans 150 ml d'éthanol, on additionne 2,5 g de Pd/C à 10 %, puis 40 ml de cyclohexène (0,395 mole). On chauffe le mélange réactionnel pendant 2 heures à 70°C, puis ramène la température à 20°C. Le mélange réactionnel est filtré sur talc et le filtrat est évaporé à sec. Le résidu est séché pendant 18 heures à 40°C sous vide, pour fournir des cristaux beiges ; F = 181°C ; Rendement = 90 %.

En procédant selon les PREPARATIONS ci-dessus à partir des intermédiaires de synthèse appropriés, on synthétise les Composés B5 à B70 décrits dans le TABLEAU I ci-après.

TABLEAU I



COMPOSE N°	Y ₁	Y ₂	Y ₃	R ₄	F ; °C
B5	5-C ₂ H ₅	H	H	-(CH ₂) ₂ CO ₂ CH ₃	128
B6	5-C ₂ H ₅	H	H	-(CH ₂) ₃ CO ₂ C ₂ H ₅	94
B7	5-C ₂ H ₅	H	H	-(CH ₂) ₄ CO ₂ C ₂ H ₅	huile
B8	4-CH ₃	5-CH ₃	H	-CH ₂ CO ₂ CH ₃	208
B9	4-CH ₃	5-CH ₃	H	-(CH ₂) ₂ CO ₂ CH ₃	170
B10	4-CH ₃	5-CH ₃	H	-(CH ₂) ₃ CO ₂ C ₂ H ₅	163
B11	5-C ₂ H ₅	H	H	-(CH ₂) ₅ CO ₂ C ₂ H ₅	huile
B12	5-Cl	H	H	-CH ₂ CO ₂ CH ₃	207
B13	5-Cl	H	H	-(CH ₂) ₂ CO ₂ CH ₃	175
B14	5-Cl	H	H	-(CH ₂) ₃ CO ₂ C ₂ H ₅	152
B15	5-Cl	H	H	-(CH ₂) ₄ CO ₂ C ₂ H ₅	99
B16	5-Cl	H	H	-(CH ₂) ₅ CO ₂ C ₂ H ₅	93
B17	5-CH ₃	H	H	-CH ₂ CO ₂ CH ₃	211
B18	5-CH ₃	H	H	-(CH ₂) ₂ CO ₂ CH ₃	174
B19	5-CH ₃	H	H	-(CH ₂) ₃ CO ₂ C ₂ H ₅	146
B20	5-CH ₃	H	H	-(CH ₂) ₄ CO ₂ C ₂ H ₅	186
B21	5-CH ₃	H	H	-(CH ₂) ₅ CO ₂ C ₂ H ₅	91

TABLEAU I (suite 1)

COMPOSE N°	Y ₁	Y ₂	Y ₃	R ₄	F ; °C
B22	4-OCH ₃	5-CH ₃	6-OCH ₃	-CH ₂ CO ₂ CH ₃	220
B23	4-OCH ₃	5-CH ₃	6-OCH ₃	-CH ₂ CH ₂ CO ₂ CH ₃	200
B24	4-OCH ₃	5-CH ₃	6-OCH ₃	-(CH ₂) ₃ CO ₂ C ₂ H ₅	134
B25	5-OCH ₃	H	H	-CH ₂ CO ₂ CH ₃	195
B26	5-OCH ₃	H	H	-(CH ₂) ₂ CO ₂ CH ₃	157
B27	5-OCH ₃	H	H	-(CH ₂) ₃ CO ₂ C ₂ H ₅	119
B28	5-OCH ₃	H	H	-(CH ₂) ₄ CO ₂ C ₂ H ₅	87
B29	5-OCH ₃	H	H	-(CH ₂) ₅ CO ₂ C ₂ H ₅	70
B30	5-CH ₃	H	H	-CH ₃	230
B31	5-CH ₃	H	H	-CH ₂ CH ₃	206
B32	5-CH ₃	H	H	-CH ₂ CH ₂ OCH ₃	158
B33	5-OCH ₃	H	H	-CH ₂ CH ₂ OCH ₃	170
B34	4-CH ₃	H	H	-CH ₂ CO ₂ CH ₃	206
B35	4-CH ₃	H	H	-(CH ₂) ₂ CO ₂ CH ₃	118
B36	5-OC ₂ H ₅	H	H	-CH ₂ CO ₂ CH ₃	186
B37	5-OC ₂ H ₅	H	H	-(CH ₂) ₂ CO ₂ CH ₃	158
B38	5-OC ₂ H ₅	H	H	-(CH ₂) ₃ CO ₂ C ₂ H ₅	131
B39	4-OCH ₃	6-OCH ₃	H	-CH ₂ COOCH ₃	195
B40	4-OCH ₃	6-OCH ₃	H	-(CH ₂) ₂ COOCH ₃	191
B41	4-OCH ₃	6-OCH ₃	H	-(CH ₂) ₃ COOC ₂ H ₅	154
B42	4-OCH ₃	5-CH ₃	6-OCH ₃	-(CH ₂) ₃ CO ₂ C ₂ H ₅	132
B43	5-Cl	H	H	-CH ₃	248

TABLEAU I (suite 2)

COMPOSE N°	Y ₁	Y ₂	Y ₃	R ₄	F ; °C
B44	5-CH ₃	H	7-CH ₃	-CH ₂ CO ₂ CH ₃	209
B45	5-CH ₃	H	7-CH ₃	-(CH ₂) ₂ CO ₂ CH ₃	--
B46	5-CH ₃	H	7-CH ₃	-(CH ₂) ₃ CO ₂ C ₂ H ₅	183
B47	5-Cl	H	H	-(CH ₂) ₂ OCH ₃	162
B48	4-CH ₃	5-CH ₃	6-OCH ₃	-CH ₂ CO ₂ CH ₃	185
B49	4-CH ₃	5-CH ₃	6-OCH ₃	-CH ₂ CH ₂ CO ₂ CH ₃	197
B50	4-CH ₃	5-CH ₃	6-OCH ₃	-(CH ₂) ₃ COOC ₂ H ₅	143
B51	4-CH ₃	H	7-CH ₃	-CH ₂ COOCH ₃	118
B52	4-CH ₃	H	7-CH ₃	-(CH ₂) ₃ COOC ₂ H ₅	108
B53	5-OCH ₃	H	7-CH ₃	-CH ₂ COOCH ₃	215
B54	4-CH ₃	6-CH ₃	H	-CH ₂ COOCH ₃	112
B55	4-CH ₃	6-CH ₃	H	-(CH ₂) ₃ COOC ₂ H ₅	152
B56	6-C ₂ H ₅	H	H	-CH ₂ COOCH ₃	158
B57	6-C ₂ H ₅	H	H	-(CH ₂) ₃ COOC ₂ H ₅	142
B58	5-OCH ₃	H	7-CH ₃	-(CH ₂) ₃ COOC ₂ H ₅	Huile
B59	6-C ₂ H ₅	H	H	-(CH ₂) ₂ COOCH ₃	166
B60	5-Cl	H	7-CH ₃	-CH ₂ COOCH ₃	209
B61	5-OCH ₃	H	7-OCH ₃	-CH ₂ COOCH ₃	186
B62	5-OCH ₃	H	7-OCH ₃	-(CH ₂) ₃ COOC ₂ H ₅	138
B63	5-OCH ₃	6-OCH ₃	H	-CH ₂ COOCH ₃	202
B64	5-F	H	7-CH ₃	-CH ₂ COOCH ₃	242
B65	5-F	H	7-CH ₃	-(CH ₂) ₃ COOC ₂ H ₅	142

TABLEAU I (suite 3)

COMPOSE N°	Y ₁	Y ₂	Y ₃	R ₄	F ; °C
B66	5-Cl	H	7-CH ₃	-(CH ₂) ₃ COOC ₂ H ₅	181
B67	5-OCH ₃	6-OCH ₃	H	-(CH ₂) ₂ COOCH ₃	166
B68	5-OCH ₃	6-OCH ₃	H	-(CH ₂) ₃ COOC ₂ H ₅	Huile
B69	5-CH ₃	7-Cl	H	-CH ₂ COOCH ₃	210
B70	4-CH ₃	6-OCH ₃	7-CH ₃	-CH ₂ COOCH ₃	211

Acide 4,5-diméthyl-1-(3-cyanopropyl)-1H-2-indolecarboxylique (Composé B71)

Etape 1 : 4,5-Diméthyl-1-(3-cyanopropyl)-1H-2-indolecarboxylate d'éthyle

5 A 1,92 g (0,040 mole) d'hydru de sodium à 50 % en suspension dans l'huile, on additionne 75 ml de diméthylformamide puis, par portions, 7,9 g (0,0363 mole) de 4,5-diméthyl-1H-2-indolecarboxylate d'éthyle. Après 40 minutes d'agitation à 0°C, on introduit goutte à goutte 4,0 ml (0,040 mole) de 4-bromobutyronitrile, et maintient le mélange réactionnel pendant 2 heures à 20°C. On additionne 300 ml d'acétate d'éthyle, et lave avec 2 fois 300 ml d'eau puis on décante, sèche la phase organique sur sulfate de sodium anhydre et concentre. On obtient 9,8 g d'huile incolore ;

Rendement = 95 %.

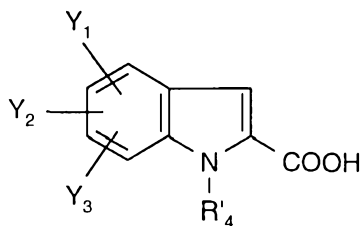
Etape 2 : Acide 4,5-Diméthyl-1-(3-cyanopropyl)-1H-2-indolecarboxylique

15 A 150 ml de 1,4-dioxane, on additionne 9,8 g (0,0345 mole) de 4,5 -diméthyl-1-(3-cyanopropyl)-1H-2-indolecarboxylate d'éthyle, puis 25 ml d'une solution 2M d'hydroxyde de sodium (0,05 mole). On maintient le mélange réactionnel pendant 48 heures à température ambiante. Après évaporation du 1,4-dioxane, le résidu est repris par une solution d'acide chlorhydrique 6M, le précipité formé est filtré, séché sous pression réduite à 60°C pour fournir l'acide 4,5-diméthyl-1-(3-cyanopropyl)-1H-2-indolecarboxylique sous forme de cristaux blancs ; F = 175°C,

Rendement = 92 %.

De la même manière, on prépare les composés B72 à B75 présentés dans le TABLEAU I bis ci-après.

TABLEAU I bis



COMPOSE N°	Y ₁	Y ₂	Y ₃	R' ₄	F ; °C
B72	5-C ₂ H ₅	H	H	-(CH ₂) ₃ -C≡N	137
B73	5-C ₂ H ₅	H	H	-CH ₂ -C≡N	229
B74	5-OCH ₃	H	H	-CH ₂ -C≡N	190
B75	5-CH ₃	6-CH ₃	7-OCH ₃	-(CH ₂) ₃ -C≡N	181

C. PREPARATION DES DERIVES BENZAMIDOGUANIDINE

5 *Préparation de la 2,6-diméthoxy-4-méthylbenzamidoguanidine (Composé C.1)*

A 353 g (1,8 mole) d'acide 2,6-diméthoxy-4-méthylbenzoïque en suspension dans 1,5 litre de toluène, on additionne 1 ml de diméthylformamide puis, goutte à goutte, 190 ml de chlorure d'oxalyle (2,16 moles). Le mélange réactionnel est abandonné pendant deux heures à température ambiante, puis évaporé à sec. Le résidu cristallin est ajouté par portions à une suspension de 293,8 g d'hydrogénocarbonate d'aminoguanidine (2,16 moles) dans 2,5 litres de pyridine à $\pm 5^{\circ}\text{C}$, et abandonné pendant 18 heures à 20°C . Le mélange réactionnel est évaporé à sec, puis le résidu est repris par 1 litre d'une solution d'hydroxyde de sodium 2 M. On filtre le précipité et on le rince avec un minimum d'eau, puis on sèche sous vide à 60°C pour obtenir un résidu cristallin ; F = 222°C ; Rendement = 81 %.

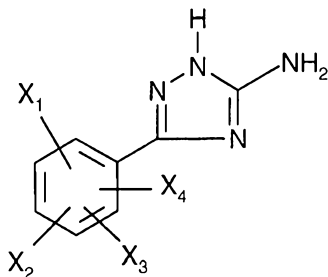
D. PREPARATION DES DERIVES 3-AMINOTRIAZOLES

20 *3-Amino-5-(2,6-diméthoxy-4-méthylphényl)-1,2,4-triazole (Composé D.1)*

A 230 g (0,91 mole) de 2,6-diméthoxy-4-méthylbenzamidoguanidine, on additionne 2 litres de diphenyléther, puis on chauffe le mélange réactionnel pendant 5 minutes à 220°C . On ramène la température à 80°C , puis on filtre le précipité, le rince à l'éther diisopropylique, et sèche sous vide à 60°C pour obtenir des cristaux ; F = 286°C ; Rendement = 93 %.

En procédant selon cette PREPARATION, et en utilisant les produits de départ appropriés, on synthétise de la même façon les *Composés D2 à D11* décrits dans le TABLEAU II ci-après.

TABLEAU II



COMPOSE N°	X ₁	X ₂	X ₃	X ₄	F ; °C
D2	2-OCH ₃	4-OCH ₃	6-OCH ₃	H	297
D3	2-OCH ₃	4-OCH ₃	5-OCH ₃	H	240
D4	2-OCH ₃	4-CH ₃	5-OCH ₃	H	248
D5	2-OCH ₃	4-Cl	5-OCH ₃	H	262
D6	2-OCH ₃	4-CH ₃	6-CH ₃	H	266
D7	2-OCH ₃	4-OCH ₃	5-CH ₃	H	248
D8	2-OCH ₃	4-CH ₃	5-CH ₃	H	286
D9	2-OCH ₃	3-Cl	6-OCH ₃	H	215
D10	2-OCH ₃	3-CH ₃	6-OCH ₃	H	236
D11	2-OCH ₃	4-CH ₃	5-CH ₃	6-OCH ₃	237

5

E. PREPARATION DES DERIVES DIPHENYLIMINO

Préparation de la N-[3-(2,6-diméthoxy-4-méthylphényl)-1H-1,2,4-triazol-5-yl]-N-diphénylméthylèneamine (Composé E.1)

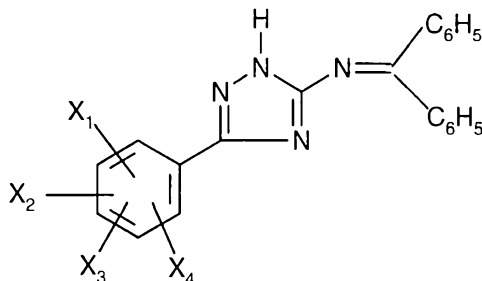
On chauffe à 140°C, 105 g (0,45 mole) de 3-amino-5-(2,6-diméthoxy-4-méthylphényl)-1,2,4-triazole en suspension dans 200 ml de xylène et 150 g (0,9 mole) de benzophénoneimine, pendant 48 heures, sous courant d'argon. On

10

ramène la température à 80°C, puis on verse le mélange réactionnel dans 4 litres d'éther isopropylique, on filtre le précipité formé, le rince à l'éther diisopropylique, et le sèche pendant 18 heures à 50°C ; F = 126°C ; Rendement = 90 %.

5

TABLEAU III



COMPOSE N°	X ₁	X ₂	X ₃	X ₄	F ; °C
E2	2-OCH ₃	4-OCH ₃	6-OCH ₃	H	143
E3	2-OCH ₃	4-OCH ₃	5-OCH ₃	H	235
E4	2-OCH ₃	4-CH ₃	5-OCH ₃	H	228
E5	2-OCH ₃	4-Cl	5-OCH ₃	H	236
E6	2-OCH ₃	4-CH ₃	6-CH ₃	H	171
E7	2-OCH ₃	4-CH ₃	5-CH ₃	H	240
E8	2-OCH ₃	3-Cl	6-OCH ₃	H	152
E9	2-OCH ₃	3-CH ₃	6-OCH ₃	H	169
E10	2-OCH ₃	4-CH ₃	5-CH ₃	6-OCH ₃	110

10

F. PREPARATION DES 3-AMINO TRIAZOLE-1- SUBSTITUES

Préparation de 1-(2-cyclohexyléthyl)-5-(2,6-diméthoxy-4-méthylphényl)-1H-1,2,4-triazol-3-amine (Composé F.1)

a) N-alkylation du triazole

A 400 ml de toluène, on additionne successivement 300 ml d'une solution aqueuse 6 N d'hydroxyde de sodium, 24 g (0,06 mole) de N-[3-(2,6-diméthoxy-4-

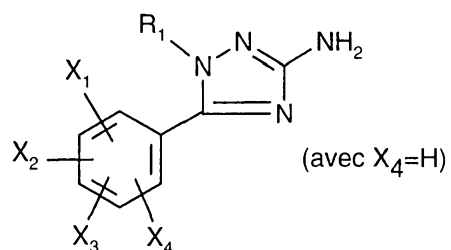
15

méthylphényl)-1*H*-1,2,4-triazol-5-yl]-N-diphénylméthylèneamine et 2,7 g de bromure de tétrabutylammonium. Au mélange réactionnel chauffé à 70°C, on ajoute goutte à goutte 17 g (0,09 mole) de 2-bromoéthylcyclohexane. On maintient la réaction pendant deux heures à 80°C. On décante la phase organique, sèche sur sulfate de sodium anhydre, et évapore à sec. Le résidu est chromatographié sur colonne de gel de silice, éluant : toluène/acétate d'éthyl 90/10 (v/v). On obtient 21,4 g d'huile incolore ; Rendement = 70 %.

b) Hydrolyse de la fonction diphénylimine

A 10,3 g (0,02 mole) de N-[1-(2-cyclohexyléthyl)-5-(2,6-diméthoxy-4-méthylphényl)-1*H*-1,2,4-triazol-3-yl]-N-diphénylméthylèneamine en solution dans 200 ml de méthanol, on additionne 100 ml d'une solution 1 N d'acide chlorhydrique. On abandonne le mélange réactionnel pendant 18 heures à température ambiante, puis on évapore à sec. Le résidu huileux est concrétisé dans l'éther diéthylique, le précipité obtenu est filtré et séché sous vide à 40°C ; F = 136°C (chlorhydrate) ; Rendement = 90 %.

TABLEAU IV



COMPOSE N°	X ₁	X ₂	X ₃	R ₁	F ; °C (chlorhydrate)
F2	2-OCH ₃	4-CH ₃	6-OCH ₃		135
F3	2-OCH ₃	4-CH ₃	6-OCH ₃	-CH ₂ -C ₆ H ₅	215
F4	2-OCH ₃	4-CH ₃	6-OCH ₃	-(CH ₂) ₄ -CH ₃	143
F5	2-OCH ₃	4-CH ₃	6-OCH ₃		236
F6	2-OCH ₃	4-CH ₃	6-OCH ₃	-CH ₂ CH ₂ -C ₆ H ₅	200
F7	2-OCH ₃	4-CH ₃	6-OCH ₃	-(CH ₂) ₂ -CH-(CH ₃) ₂	172
F8	2-OCH ₃	4-CH ₃	6-OCH ₃		187
F9	2-OCH ₃	4-CH ₃	6-OCH ₃		160
F10	2-OCH ₃	4-CH ₃	6-OCH ₃	-(CH ₂) ₂ -N(CH ₃) ₂	148
F11	2-OCH ₃	4-CH ₃	6-OCH ₃		190

TABLEAU IV (suite 1)


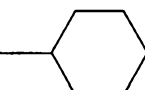
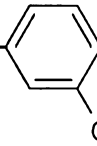


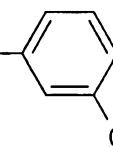
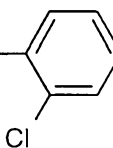
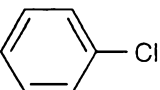

COMPOSE N°	X ₁	X ₂	X ₃	R ₁	F ; °C (chlorhydrate)
F12	2-OCH ₃	4-CH ₃	6-OCH ₃	-(CH ₂) ₃ -CH ₃	212
F13	2-OCH ₃	4-CH ₃	6-OCH ₃	—(CH ₂) ₃ —N 	198
F14	2-OCH ₃	4-CH ₃	6-OCH ₃		219
F15	2-OCH ₃	4-CH ₃	6-OCH ₃	-CH ₂ -CH-(C ₂ H ₅) ₂	132
F16	2-OCH ₃	4-CH ₃	6-OCH ₃	—CH ₂ — 	197
F17	2-OCH ₃	4-CH ₃	6-OCH ₃	—(CH ₂) ₂ — 	217
F18	2-OCH ₃	4-CH ₃	6-OCH ₃	—CH ₂ — 	208
F19	2-OCH ₃	4-CH ₃	6-OCH ₃	—CH ₂ — 	136
F20	2-OCH ₃	4-CH ₃	6-OCH ₃	—CH ₂ — 	204
F21	2-OCH ₃	4-CH ₃	6-OCH ₃	—CH ₂ — 	202
F22	2-OCH ₃	4-Cl	5-OCH ₃	—CH ₂ CH ₂ — 	196

TABLEAU IV (suite 2)

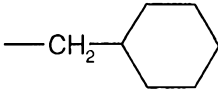
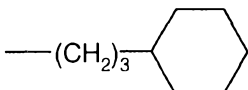
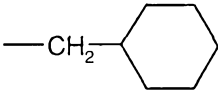
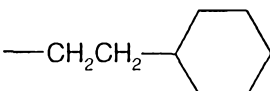
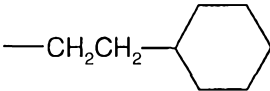
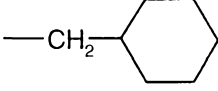
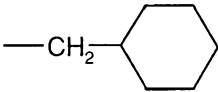
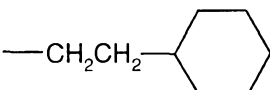
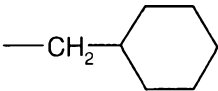
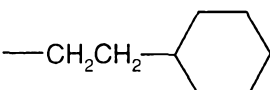
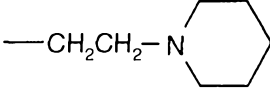

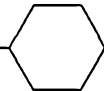
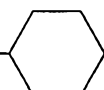
COMPOSE N°	X ₁	X ₂	X ₃	R ₁	F ; °C (chlorhydrate)
F23	2-OCH ₃	4-Cl	5-OCH ₃		148
F24	2-OCH ₃	4-CH ₃	5-OCH ₃		192
F25	2-OCH ₃	4-CH ₃	5-OCH ₃		188
F26	2-OCH ₃	4-CH ₃	5-OCH ₃		166
F27	2-OCH ₃	4-OCH ₃	6-OCH ₃		189
F28	2-OCH ₃	4-OCH ₃	6-OCH ₃		180
F29	2-OCH ₃	4-CH ₃	6-CH ₃		168
F30	2-OCH ₃	4-CH ₃	6-CH ₃		188
F31	2-OCH ₃	4-CH ₃	5-CH ₃		200
F32	2-OCH ₃	4-CH ₃	5-CH ₃		206
F33	2-OCH ₃	4-OCH ₃	6-OCH ₃	-CH ₂ CH ₂ CN	244
F34	2-OCH ₃	4-CH ₃	5-OCH ₃		218

TABLEAU IV (suite 3)

COMPOSE N°	X ₁	X ₂	X ₃	R ₁	F ; °C (chlorhydrate)
F35	2-OCH ₃	4-Cl	5-OCH ₃		127
F36	2-OCH ₃	3-Cl	6-OCH ₃		159
F37	2-OCH ₃	3-CH ₃	6-OCH ₃		168

De la même manière, on prépare à partir du composé E10, le **1-(2-cyclohexyléthyl)-5-(2,6-diméthoxy-4,5-diméthylphényl)-1H-1,2,4-triazol-3-amine (Composé F38)** ;
 5 F = 180°C.

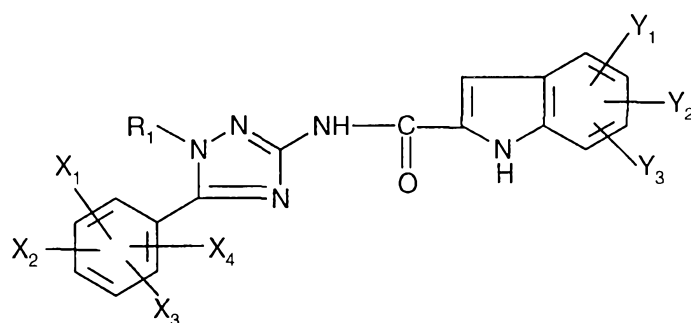
G. PREPARATION DES DERIVES AMIDOTRIAZOLES AVEC INDOLES NON N-SUBSTITUES

Synthèse du N-[1-(2-chlorobenzyl)-5-(2,6-diméthoxy-4-méthylphényl)-1H-1,2,4-triazol-3-yl]-5-chloro-1H-2-indolecarboxamide (Composé G.1)

10 A une solution de 1 ml de pyridine (0,013 mole) dans 30 ml de chlorure de méthylène, on additionne à 0°C 0,2 ml de chlorure de thionyle (0,0028 mole). Après 15 minutes à 0°C, on introduit 500 mg (0,0025 mole) d'acide 5-chloroindole carboxylique, et on abandonne le mélange réactionnel pendant 30 minutes à 0°C. Au chlorure d'acyle formé, on additionne 0,91 g
 15 (0,0028 mole) de chlorhydrate de 1-[(2-chlorophényl)méthyl]-5-(2,6-diméthoxy-4-méthylphényl)-1H-1,2,4-triazol-3-amine, et laisse pendant 18 heures à 20°C.

Le mélange réactionnel est lavé avec une solution 1M d'hydroxyde de sodium. La phase organique est séchée sur sulfate de sodium anhydre et évaporée à sec. Le résidu est chromatographié sur gel de silice, éluant : dichlorométhane/méthanol 95/5
 20 (v/v) pour fournir 0,980 g de cristaux ; F = 262°C ; Rendement = 73 %.

TABLEAU V



COMPOSE N°		R ₁		F ; °C
G2				271
G3				301
G4				251
G5				248
G6				283

TABLEAU V (suite 1)

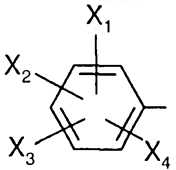
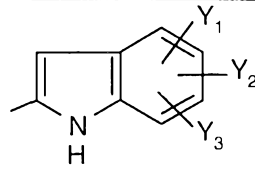
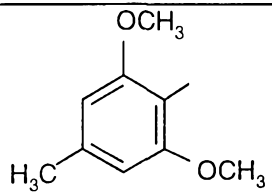
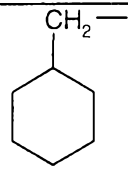
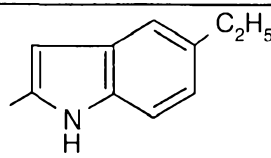
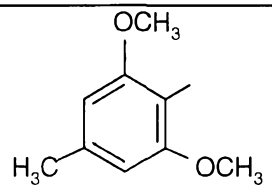
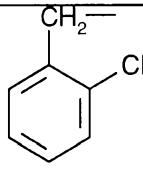
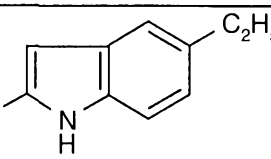
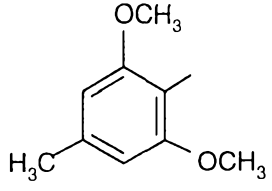
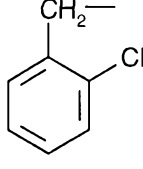
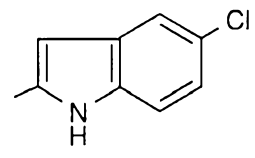
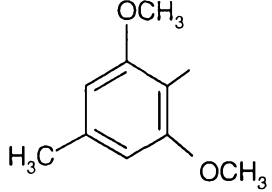
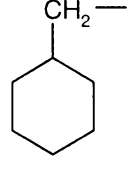
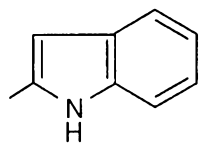
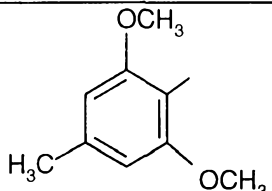
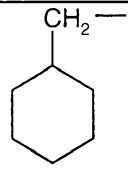
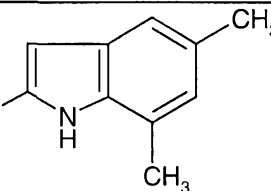
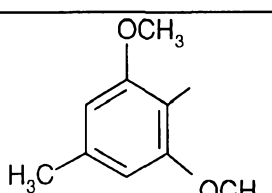
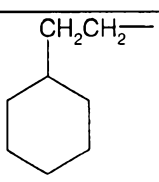
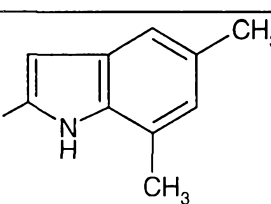
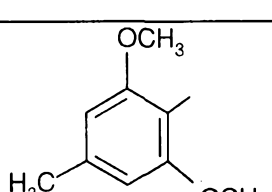
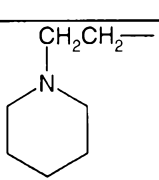
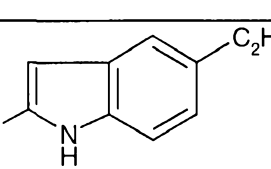
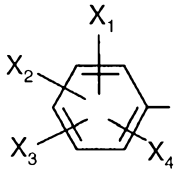
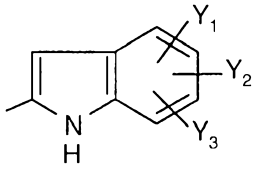
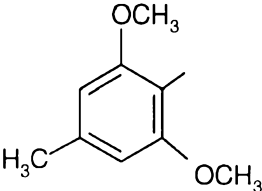
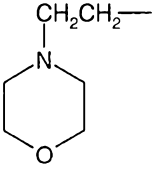
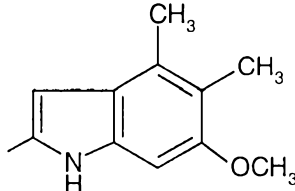
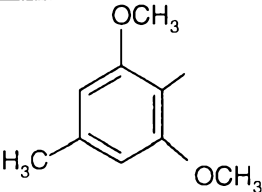
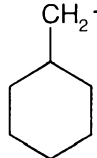
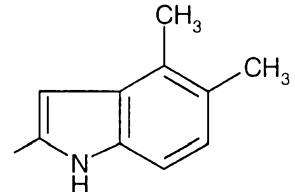
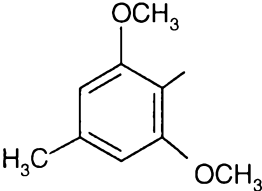
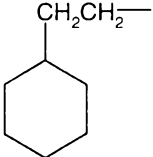
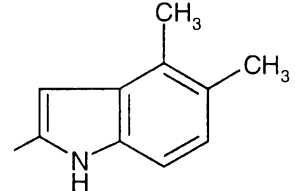
COMPOSE N°		R ₁		F ; °C
G7				253
G8				229
G9				262
G10				270
G11				245
G12				139
G13				210 (HCl)

TABLEAU V (suite 2)

COMPOSE N°		R ₁		F ; °C
G14				210 (HCl)
G15				252
G16				181

H. PREPARATION DES DERIVES AMINOTRIAZOLES AVEC INDOLES N-SUBSTITUES

5

EXEMPLE 1

2-[2-([1-(2-cyclohexyléthyl)-5-(2,6-diméthoxy-4-méthylphényl)-1H-1,2,4-triazol-3-yl]amino)carbonyl]-5-éthyl-1H-indol-1-yl]acétate de méthyle

- 10 A 15 ml de dichlorométhane, on additionne successivement 1 ml de pyridine (0,013 mole) et 0,21 ml de chlorure de thionyle (0,00029 mole). Après 15 minutes à 0°C, on introduit 0,627 g de l'acide 5-éthyl-1-méthoxycarbonylméthyl-1H-2-indolecarboxylique (0,0024 mole), puis 0,9 g de chlorhydrate de 1-(2-cyclohexyléthyl)-5-(2,6-diméthoxy-4-méthylphényl)-1H-1,2,4-triazol-3-amine. On abandonne le mélange réactionnel
- 15 pendant 18 heures à température ambiante, puis on fait un lavage acide, puis un lavage basique. La phase organique est séchée sur sulfate de sodium anhydre et concentrée. Le résidu huileux est chromatographié sur gel de silice, éluant :

dichlorométhane/méthanol 98,5/1,5 (v/v) pour fournir une poudre blanche ; F = 191°C ; Rendement = 87 %.

EXEMPLE 2

5

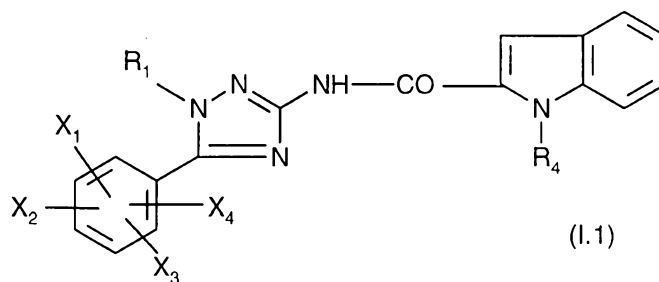
Acide 2-[2-({[1-(2-cyclohexyléthyl)-5-(2,6-diméthoxy-4-méthylphényl)-1H-1,2,4-triazol-3-yl]amino}carbonyl)-5-éthyl-1H-indol-1-yl]acétique

10 A 530 mg (0,0009 mole) de 2-[2-({[1-(2-cyclohexyléthyl)-5-(2,6-diméthoxy-4-méthylphényl)-1H-1,2,4-triazol-3-yl]amino}carbonyl)-5-éthyl-1H-indol-1-yl]acétate de méthyle préparé selon l'EXEMPLE 1 en solution dans 50 ml de méthanol, on additionne 1,8 ml (0,0018 mole) d'une solution 1N d'hydroxyde de sodium. Après 18 heures à température ambiante, on évapore le mélange réactionnel à sec. Le résidu est repris par de l'acétate d'éthyle, et une solution d'acide chlorhydrique 0,5 N. On

15 résidu est purifié par chromatographie sur colonne de gel de silice, éluant : dichlorométhane/méthanol 92/8 (v/v) pour fournir des cristaux blancs ; F = 198°C ; Rendement = 91 %.

20 En procédant selon les EXEMPLES 1 et 2 ci-dessus, on prépare de la même façon, à partir des intermédiaires appropriés, les EXEMPLES 3 à 511 décrits dans les TABLEAUX VI et VII ci-après.

TABLEAU VI



EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
3			-CH ₂ CO ₂ CH ₃	185
4			-CH ₂ CO ₂ H	226
5			-CH ₂ CO ₂ CH ₃	118
6			-CH ₂ CO ₂ H	230
7			-CH ₂ CH ₂ CO ₂ CH ₃	101
8		-(CH ₂) ₄ CH ₃	-CH ₂ CO ₂ CH ₃	192

TABLEAU VI (suite 1)

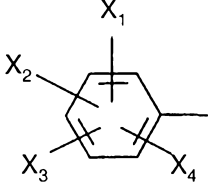
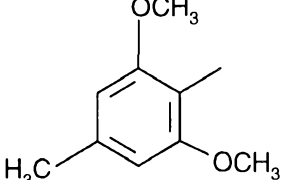
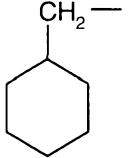
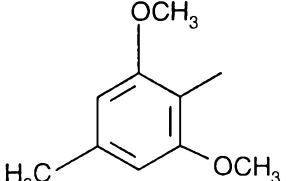
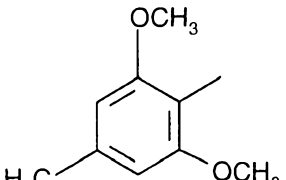
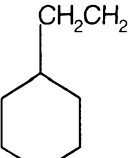
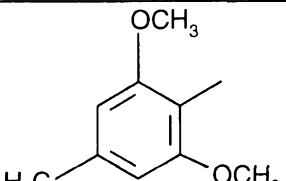
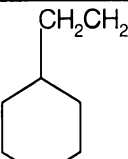
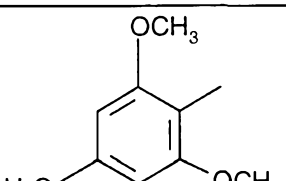
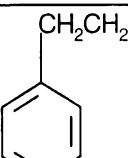
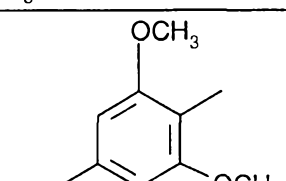
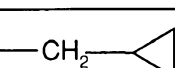
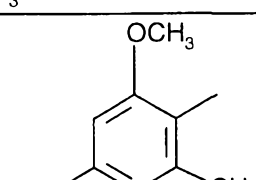
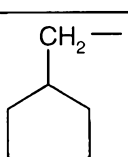
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
9			-CH ₂ CH ₂ CO ₂ H	210
10		-(CH ₂) ₄ CH ₃	-CH ₂ CO ₂ H	205
11			-CH ₂ CO ₂ CH ₃	189
12			-CH ₂ CO ₂ H	218
13			-CH ₂ CO ₂ CH ₃	138
14			-CH ₂ CO ₂ CH ₃	115
15			-CH ₂ CO ₂ CH ₃	167

TABLEAU VI (suite 2)

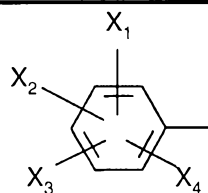
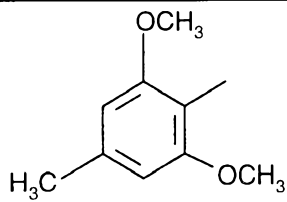
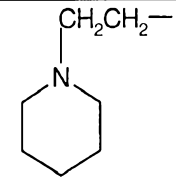
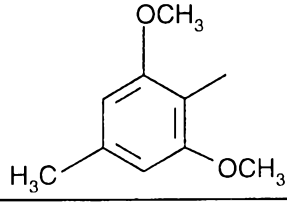
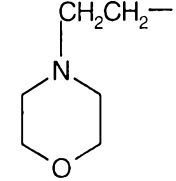
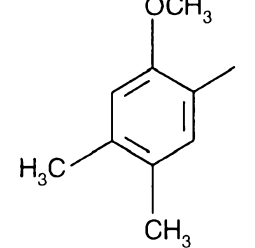
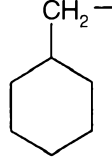
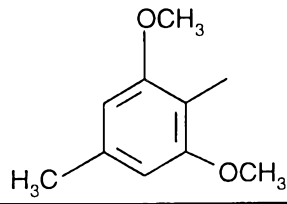
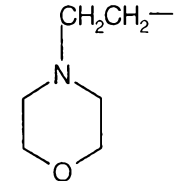
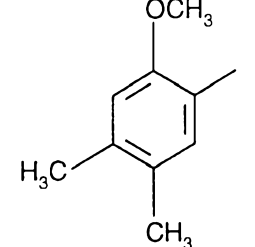
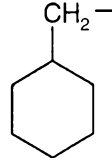
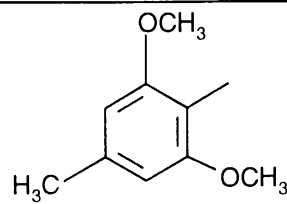
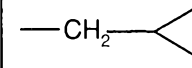
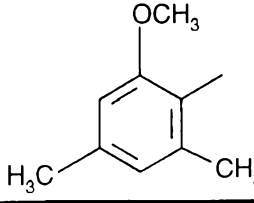
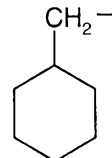
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
16			-CH ₂ CO ₂ CH ₃	180
17			-CH ₂ CO ₂ CH ₃	203
18			-CH ₂ CO ₂ CH ₃	158
19			-CH ₂ CO ₂ H	217 (HCl)
20			-CH ₂ CO ₂ H	169
21			-CH ₂ CO ₂ H	271
22			-CH ₂ CO ₂ H	181

TABLEAU VI (suite 3)

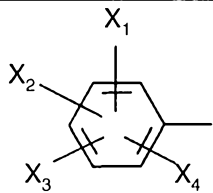
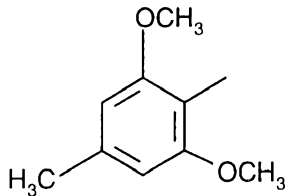
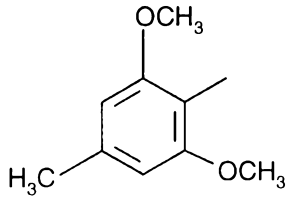
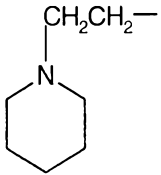
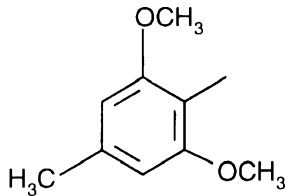
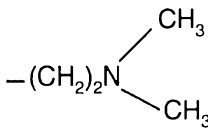
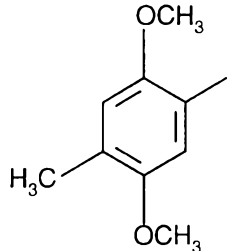
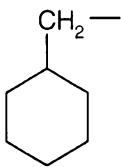
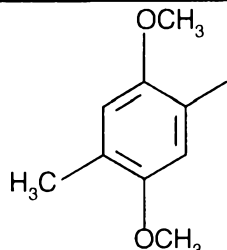
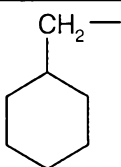
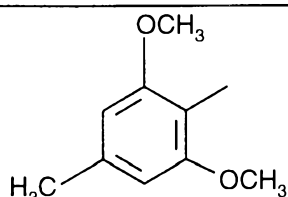
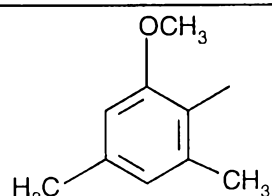
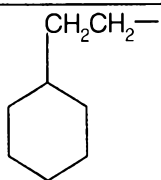
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
23		$-(CH_2)_3CH_3$	$-CH_2CO_2CH_3$	220
24			$-CH_2CO_2H$	220 (HCl)
25			$-CH_2CO_2CH_3$	166
26			$-CH_2CO_2H$	198
27			$-CH_2CO_2CH_3$	132
28		$-(CH_2)_3CH_3$	$-CH_2CO_2H$	220
29			$-CH_2CO_2CH_3$	144

TABLEAU VI (suite 4)

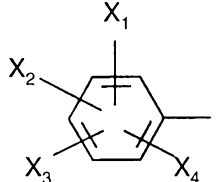
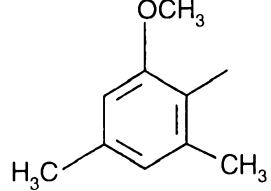
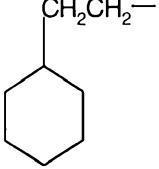
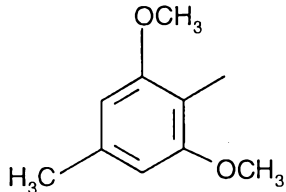
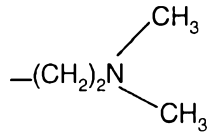
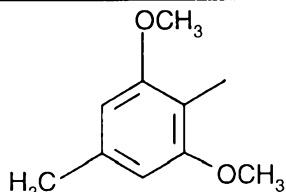
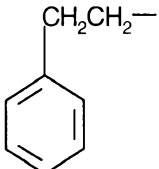
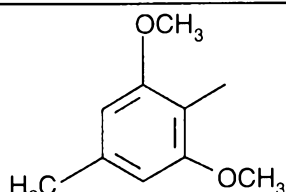
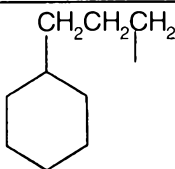
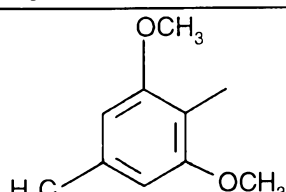
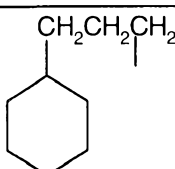
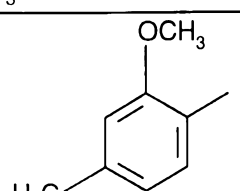
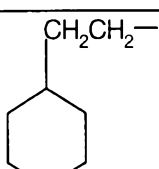
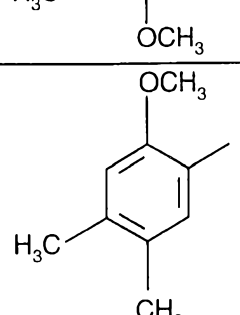
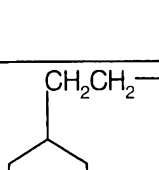
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
30			-CH ₂ CO ₂ H	169
31			-CH ₂ CO ₂ H	203 (HCl)
32			-CH ₂ CO ₂ H	180
33			-CH ₂ CO ₂ CH ₃	172
34			-CH ₂ CO ₂ H	216
35			-CH ₂ CO ₂ CH ₃	126
36			-CH ₂ CO ₂ CH ₃	158

TABLEAU VI (suite 5)

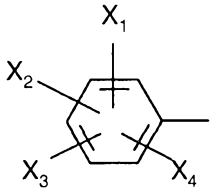
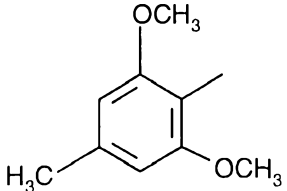
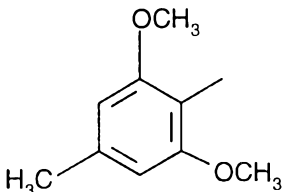
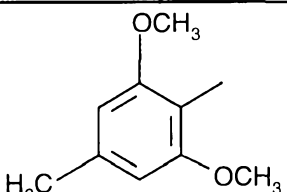
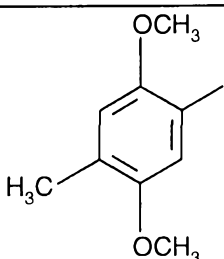
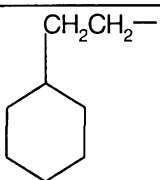
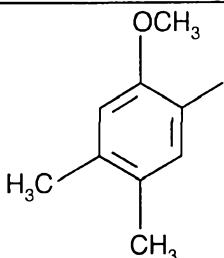
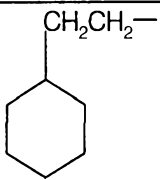
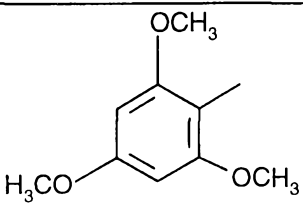
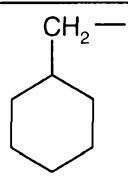
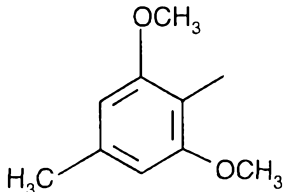
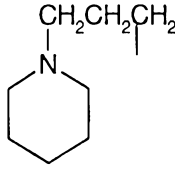
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
37		$-(CH_2)_2CH(CH_3)_2$	$-CH_2CO_2H$	272
38		$-CH_2CH(CH_3)_2$	$-CH_2CO_2CH_3$	206
39		$-CH_2CH(CH_3)_2$	$-CH_2CO_2H$	189
40			$-CH_2CO_2H$	175
41			$-CH_2CO_2H$	156
42			$-CH_2CO_2CH_3$	160
43			$-CH_2CO_2CH_3$	161

TABLEAU VI (suite 6)

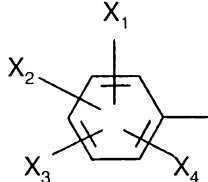
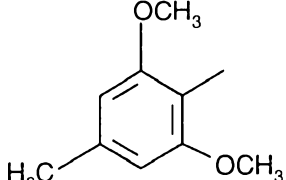
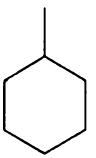
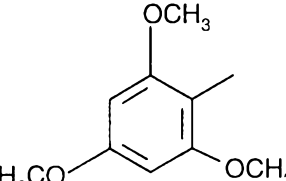
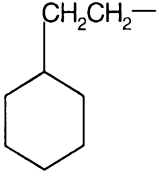
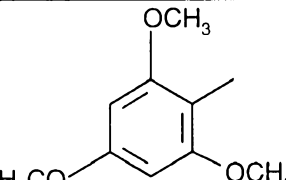
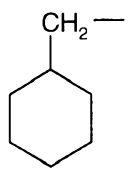
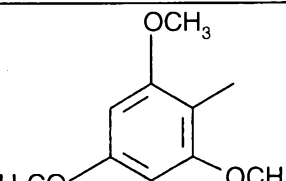
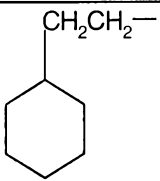
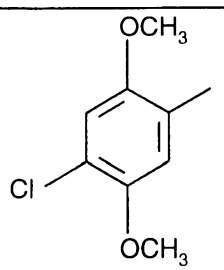
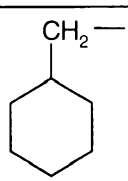
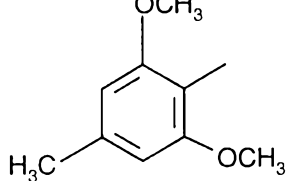
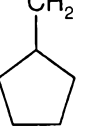
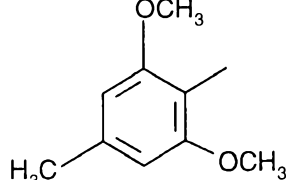
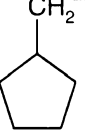
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
44			-CH ₂ CO ₂ CH ₃	210
45			-CH ₂ CO ₂ CH ₃	191
46			-CH ₂ CO ₂ H	182
47			-CH ₂ CO ₂ H	195
48			-CH ₂ CO ₂ CH ₃	201
49			-CH ₂ CO ₂ CH ₃	194
50			-CH ₂ CO ₂ H	204

TABLEAU VI (suite 7)

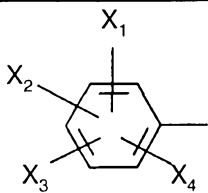
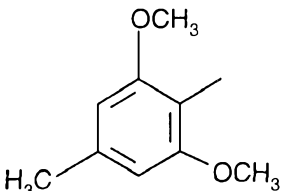
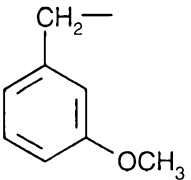
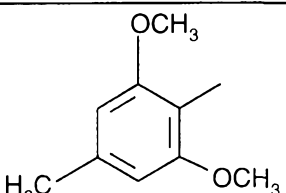
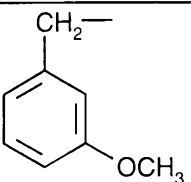
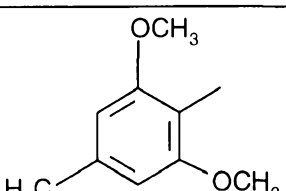
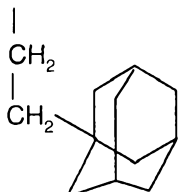
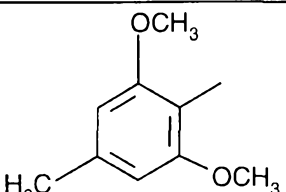
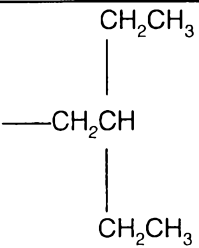
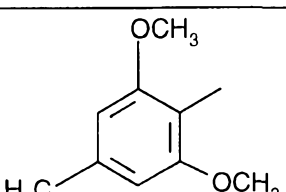
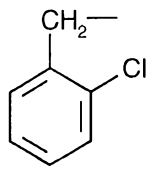
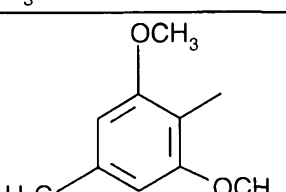
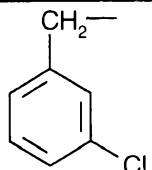
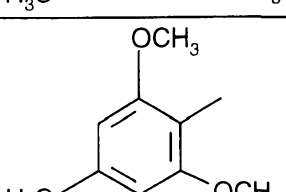
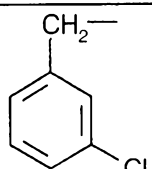
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
51			-CH ₂ CO ₂ CH ₃	129
52			-CH ₂ CO ₂ H	213
53			-CH ₂ CO ₂ H	182
54			-CH ₂ CO ₂ H	151
55			-CH ₂ COOCH ₃	192
56			-CH ₂ CO ₂ CH ₃	173
57			-CH ₂ CO ₂ H	229

TABLEAU VI (suite 8)

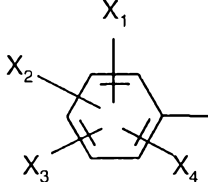
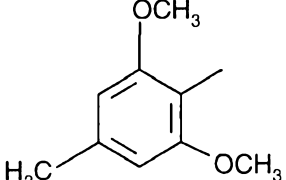
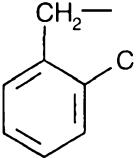
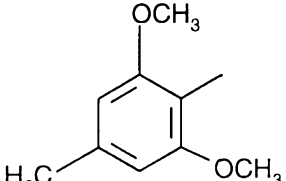
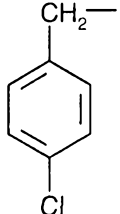
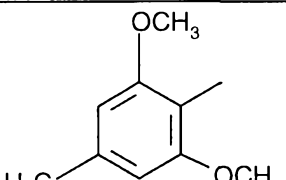
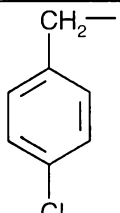
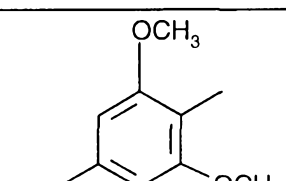
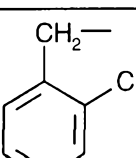
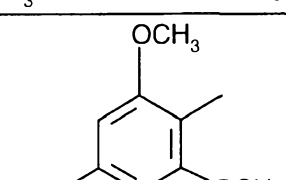
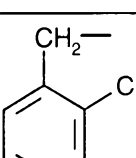
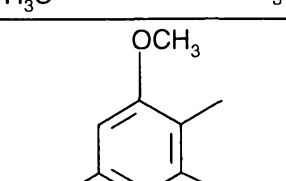
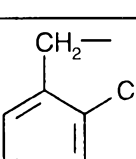
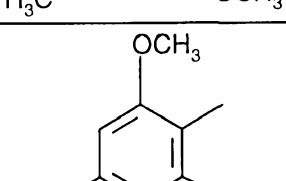
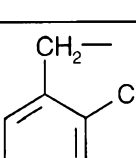
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
58			-CH ₂ CO ₂ H	195
59			-CH ₂ CO ₂ CH ₃	133
60			-CH ₂ CO ₂ H	175
61			-CH ₂ CH ₂ CO ₂ CH ₃	178
62			-CH ₂ CH ₂ CO ₂ H	235
63			-(CH ₂) ₃ CO ₂ C ₂ H ₅	144
64			-(CH ₂) ₃ CO ₂ H	141

TABLEAU VI (suite 9)

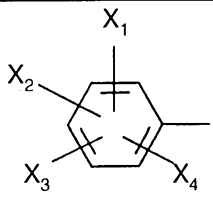
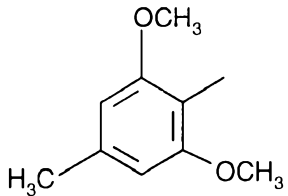
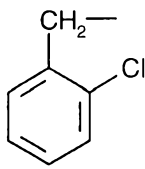
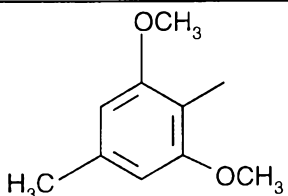
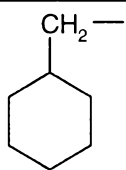
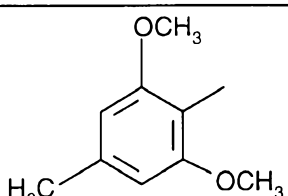
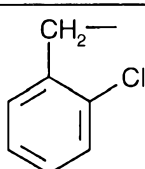
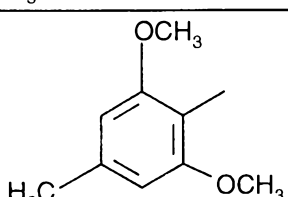
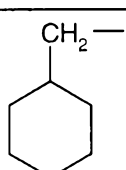
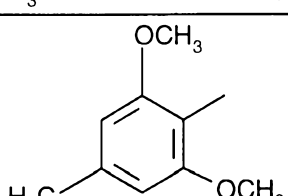
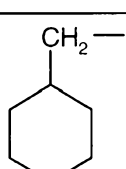
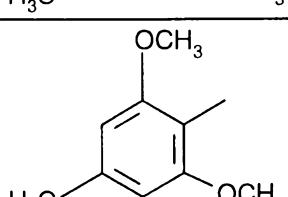
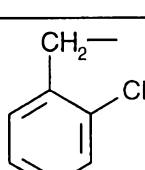
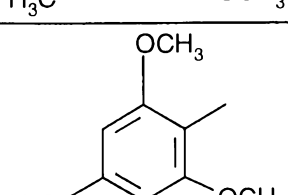
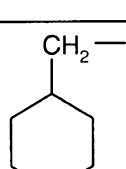
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
65			$-(CH_2)_4CO_2C_2H_5$	95
66			$-(CH_2)_4CO_2C_2H_5$	101
67			$-(CH_2)_4CO_2H$	266
68			$-(CH_2)_4CO_2H$	157
69			$-(CH_2)_3CO_2C_2H_5$	114
70			$-(CH_2)_5CO_2C_2H_5$	76
71			$-(CH_2)_5CO_2C_2H_5$	85

TABLEAU VI (suite 10)

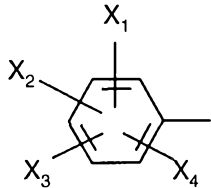
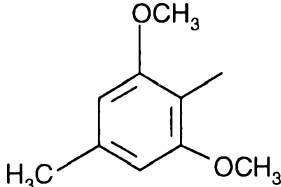
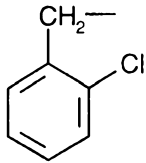
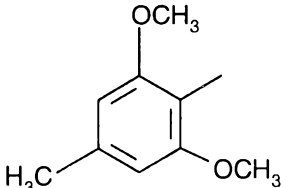
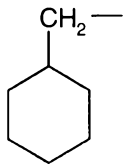
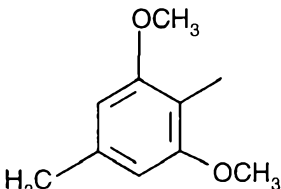
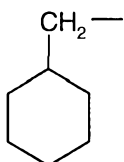
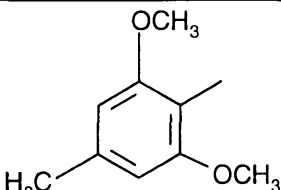
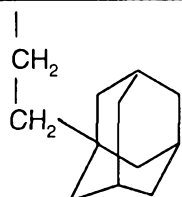
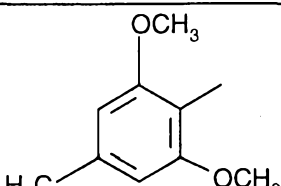
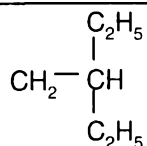
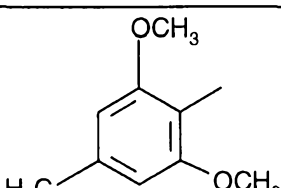
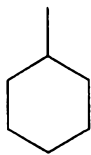
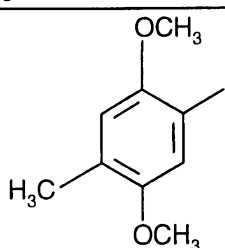
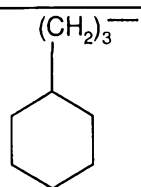
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
72			-(CH ₂) ₅ CO ₂ H	243
73			-(CH ₂) ₅ CO ₂ H	138
74			-(CH ₂) ₃ CO ₂ H	150
75			-CH ₂ CO ₂ CH ₃	201
76			-CH ₂ CO ₂ CH ₃	162
77			-CH ₂ COOH	200
78			-CH ₂ COOH	168 (HCl)

TABLEAU VI (suite 11)

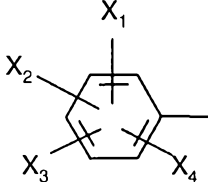
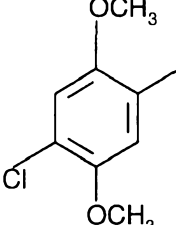
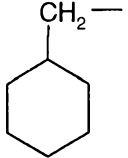
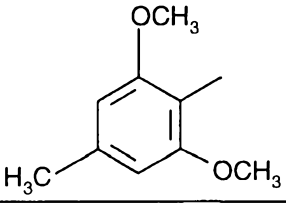
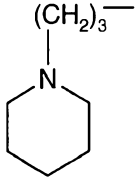
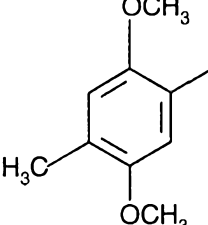
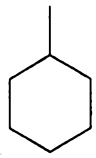
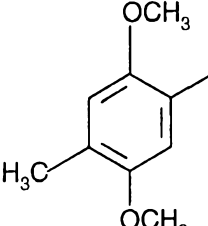
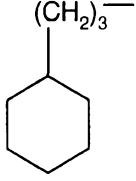
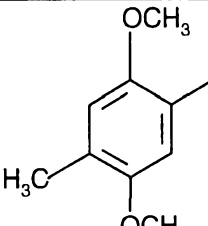
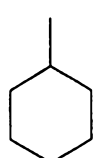
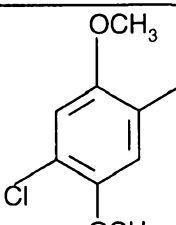
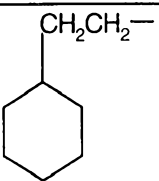
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
79			-CH ₂ COOH	211
80			-CH ₂ COOH	243 (HCl)
81			-CH ₂ COOH	188 (2HCl)
82			-CH ₂ COOCH ₃	200
83			-CH ₂ COOCH ₃	170
84			-CH ₂ COOCH ₃	137

TABLEAU VI (suite 12)

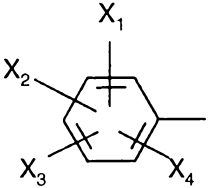
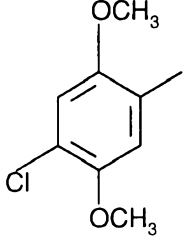
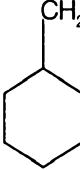
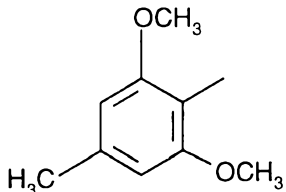
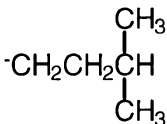
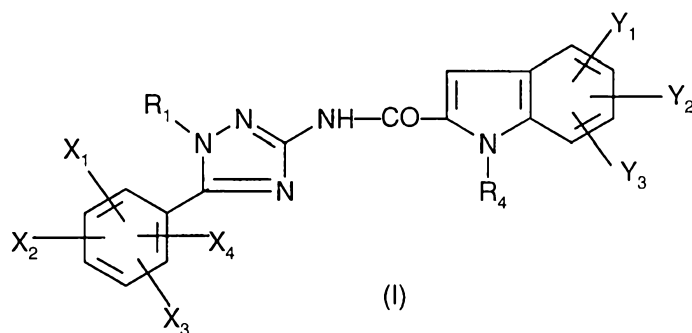
EXEMPLE N°		R ₁	R ₄	F ; °C (sel)
85			-CH ₂ COOH	166
86			-CH ₂ COOCH ₃	156

TABLEAU VII



EXEMPLE N°		R ₁		F ; °C (sel)
87				145
88				147
89				156
90				221
91				243

TABLEAU VII (suite 1)

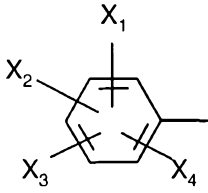
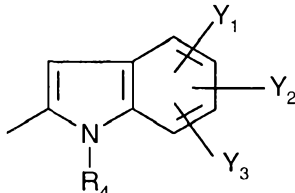
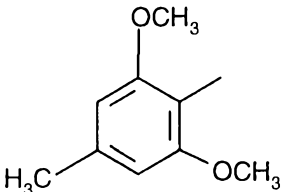
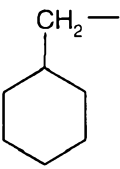
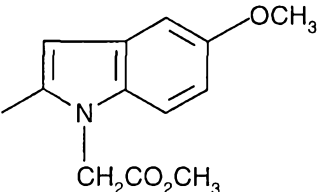
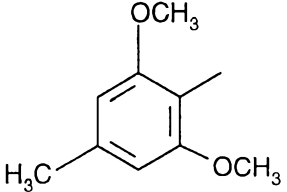
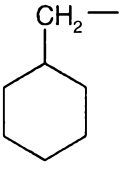
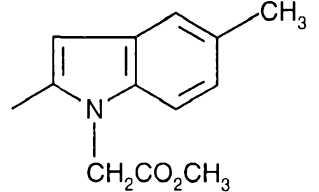
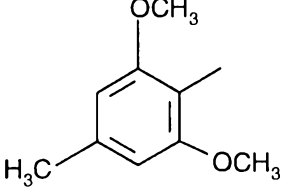
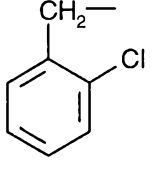
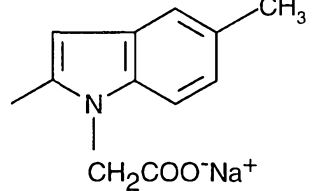
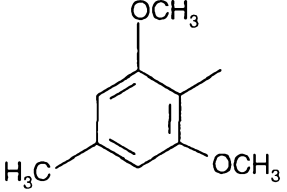
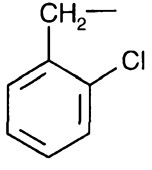
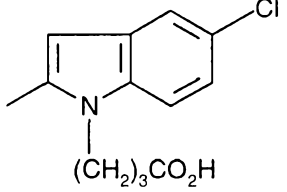
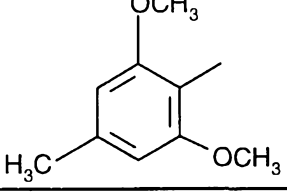
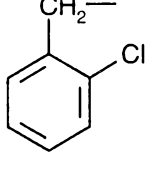
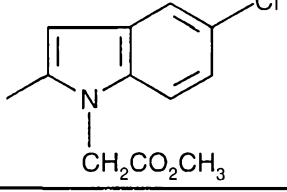
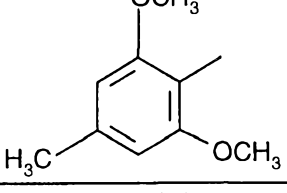
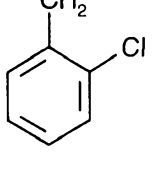
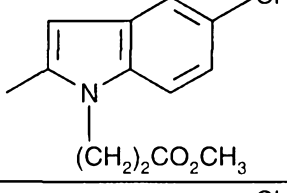
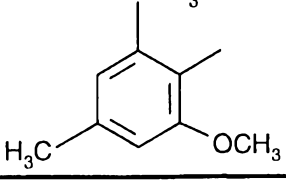
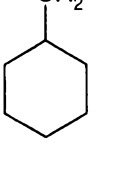
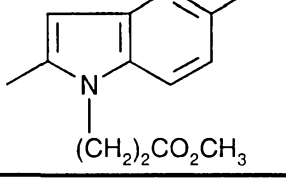
EXEMPLE N°		R ₁		F ; °C (sel)
92				207
93				196
94				310 (sel de Na)
95				221
96				214
97				202
98				194

TABLEAU VII (suite 2)

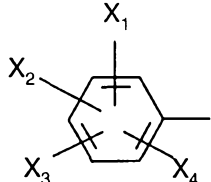
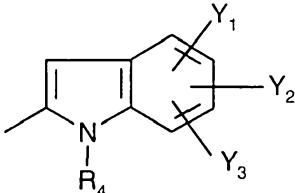
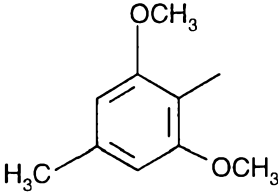
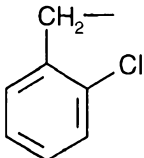
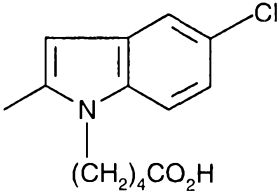
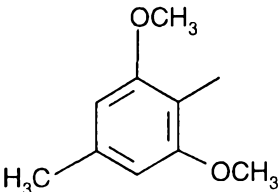
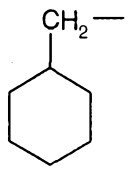
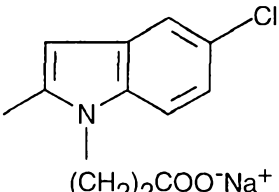
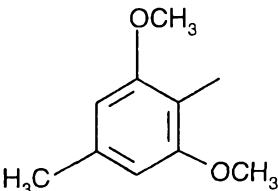
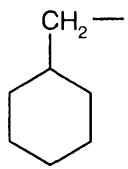
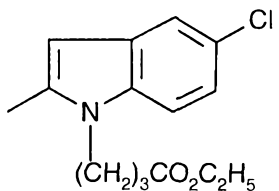
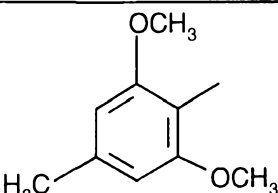
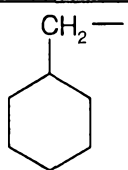
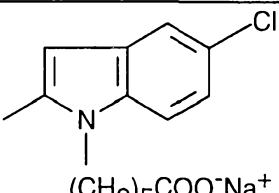
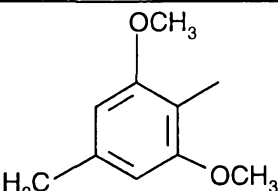
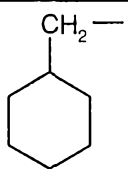
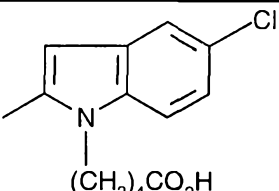
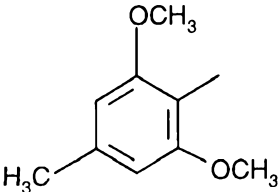
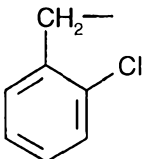
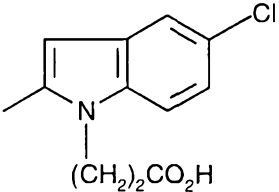
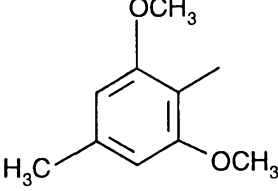
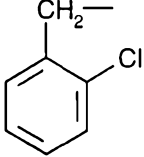
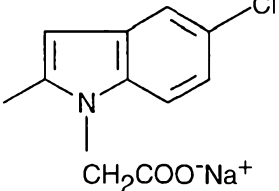
EXEMPLE N°		R ₁		F ; °C (sel)
99				286
100				194 (sel de Na)
101				132
102				277 (sel de Na)
103				195
104				264
105				266 (sel de Na)

TABLEAU VII (suite 3)

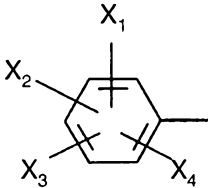
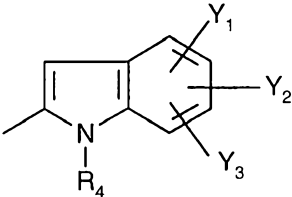
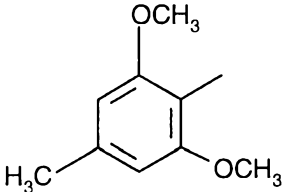
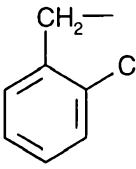
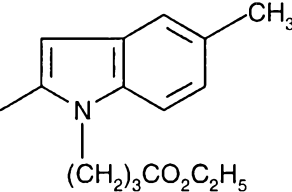
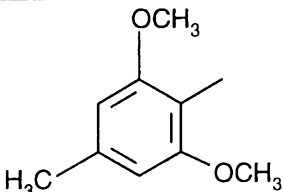
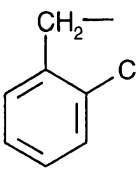
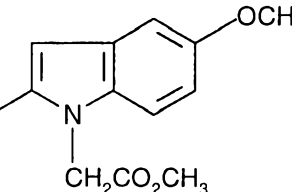
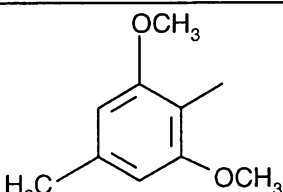
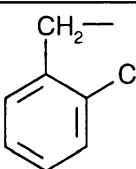
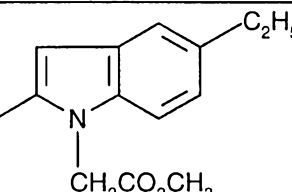
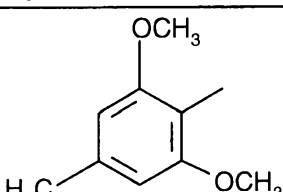
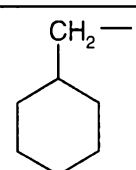
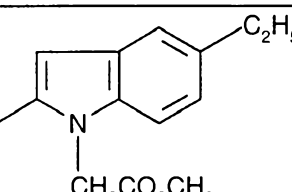
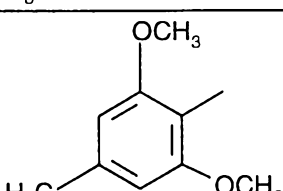
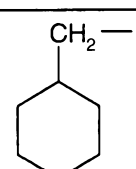
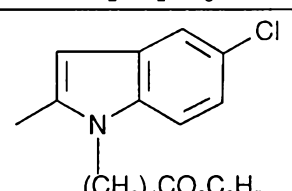
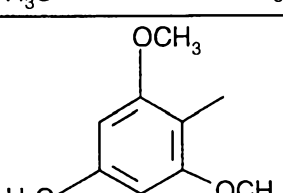
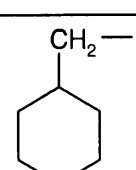
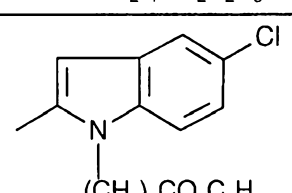
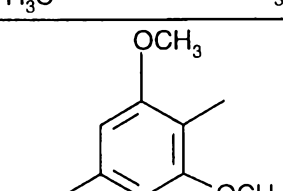
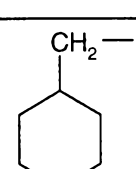
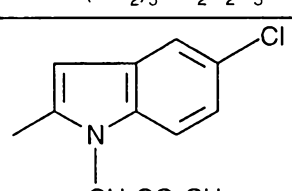
EXEMPLE N°		R ₁		F ; °C (sel)
106				161
107				196
108				174
109				190
110				83
111				242
112				223

TABLEAU VII (suite 4)

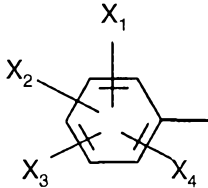
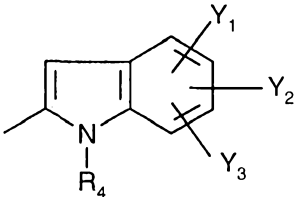
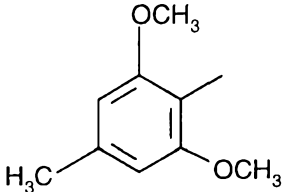
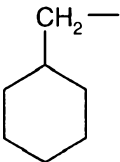
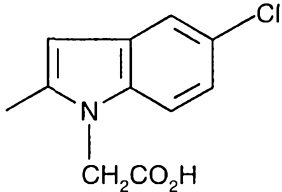
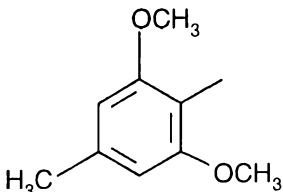
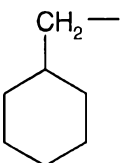
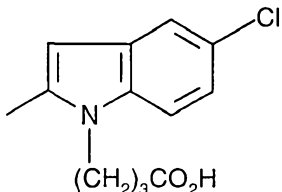
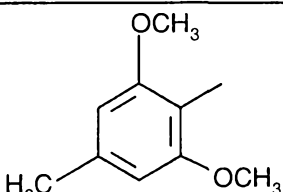
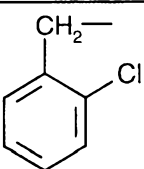
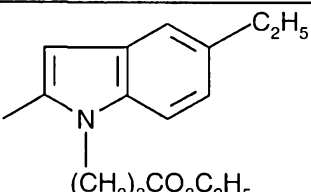
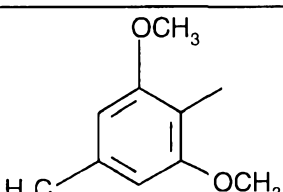
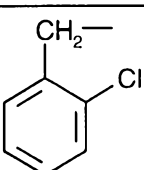
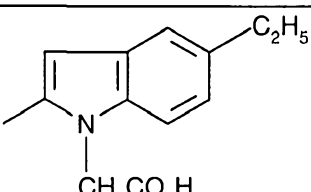
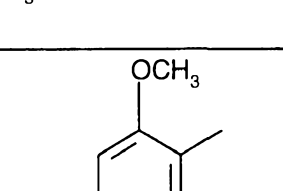
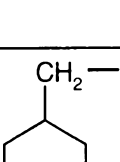
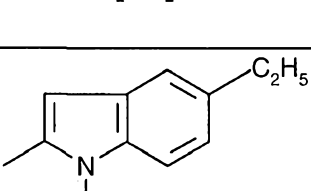
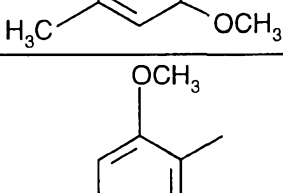
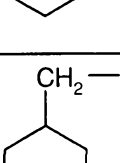
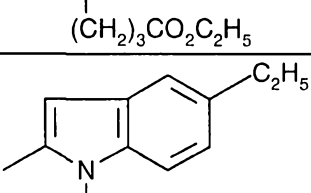
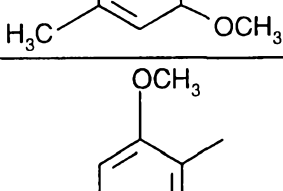
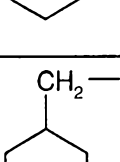
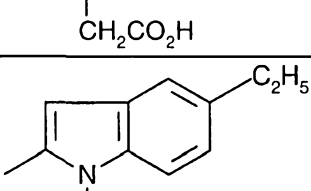
EXEMPLE N°		R ₁		F ; °C (sel)
113				205
114				191
115				154
116				233
117				82
118				257
119				181

TABLEAU VII (suite 5)

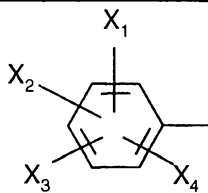
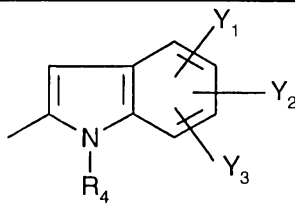
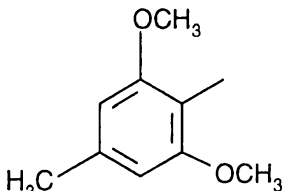
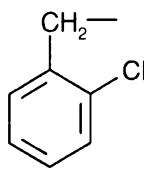
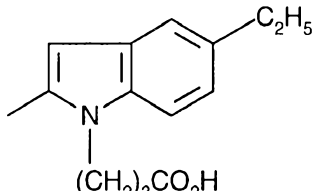
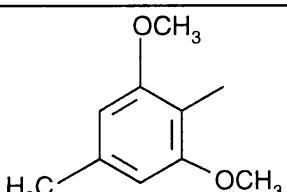
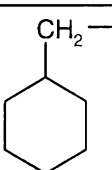
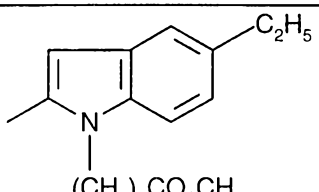
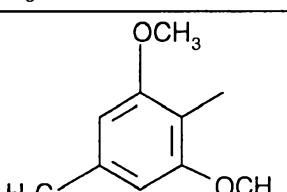
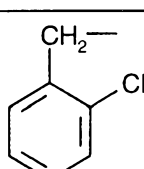
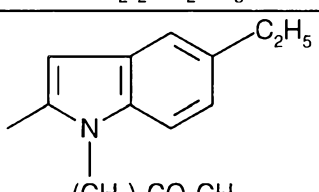
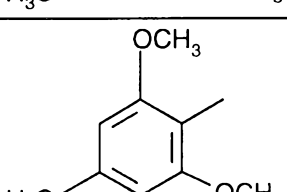
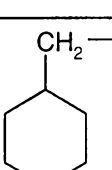
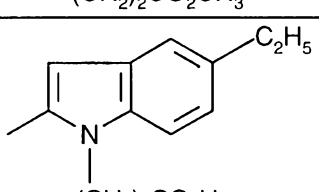
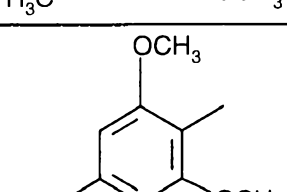
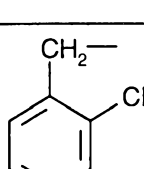
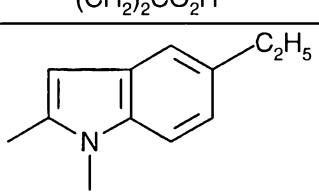
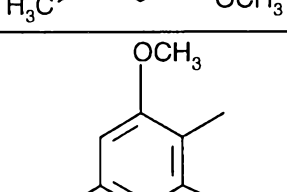
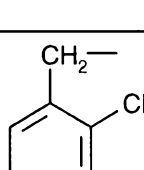
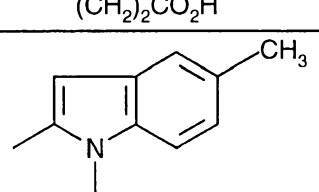
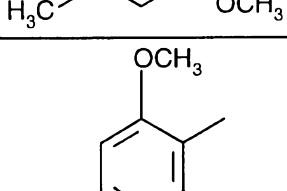
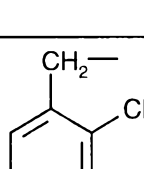
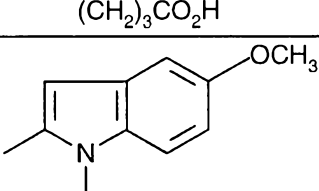
EXEMPLE N°		R ₁		F ; °C (sel)
120				275
121				132
122				135
123				263
124				250
125				154
126				184

TABLEAU VII (suite 6)

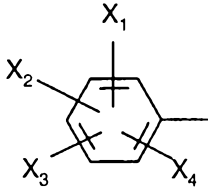
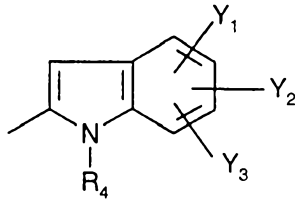
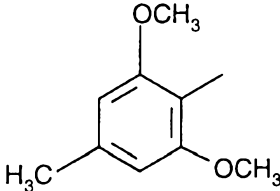
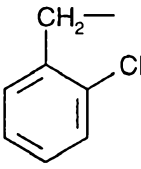
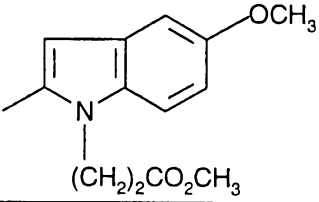
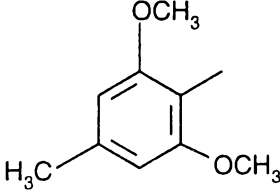
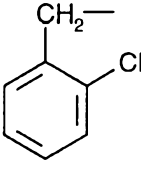
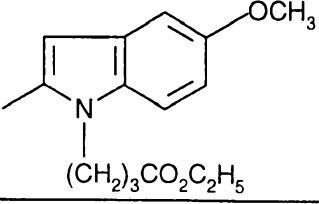
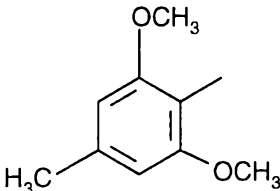
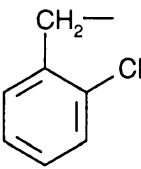
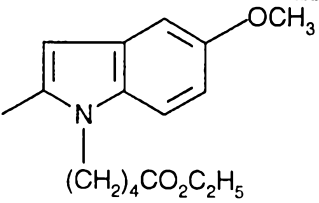
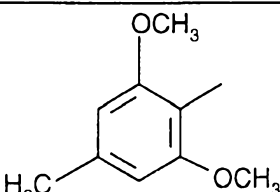
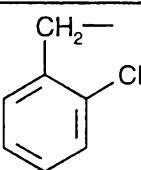
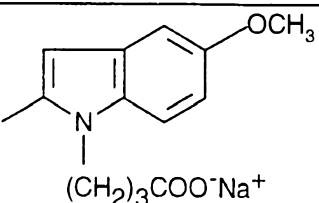
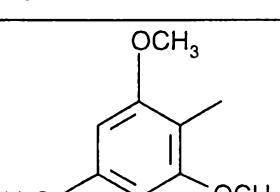
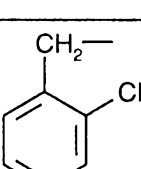
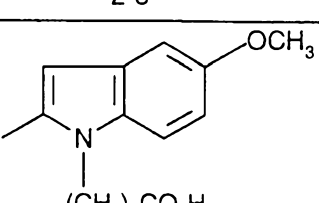
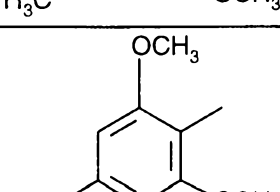
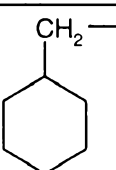
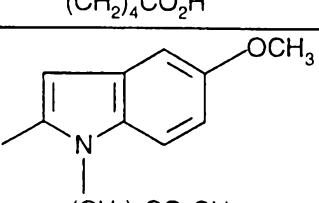
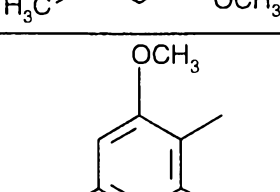
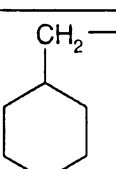
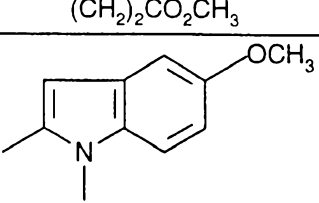
EXEMPLE N°		R ₁		F ; °C (sel)
127				207
128				179
129				175
130				188 (sel de Na)
131				235
132				177
133				141

TABLEAU VII (suite 7)

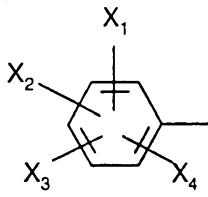
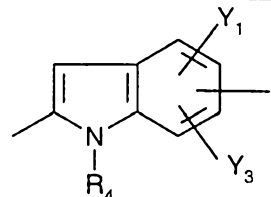
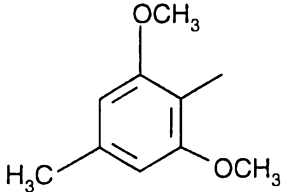
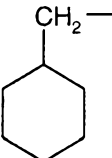
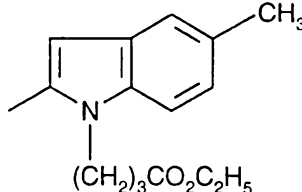
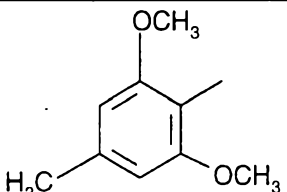
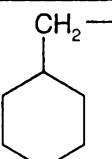
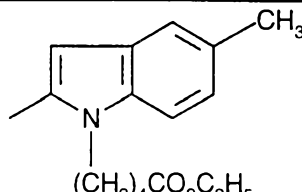
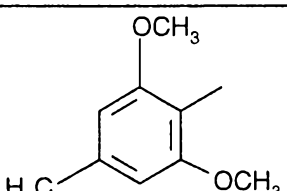
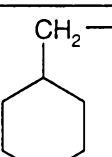
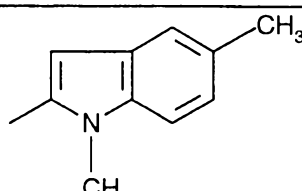
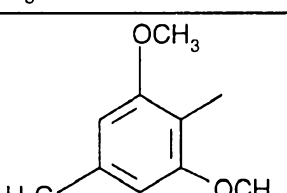
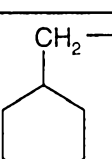
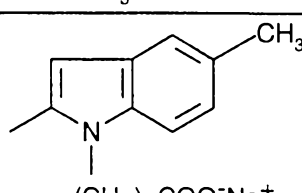
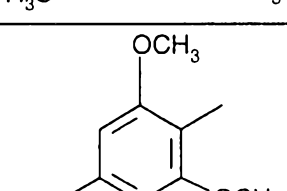
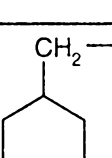
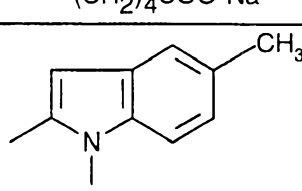
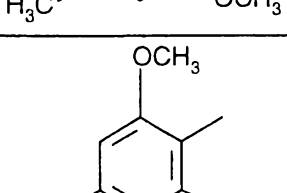
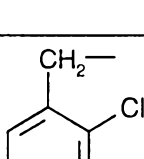
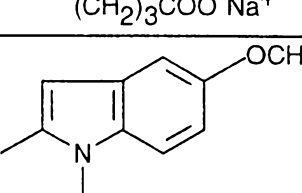
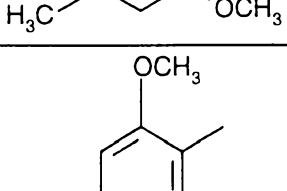
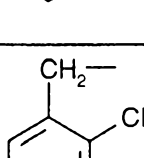
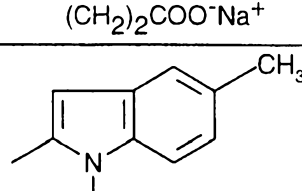
EXEMPLE N°		R ₁		F ; °C (sel)
134				108
135				144
136				196
137				249 (sel de Na)
138				176 (sel de Na)
139				198
140				212

TABLEAU VII (suite 8)

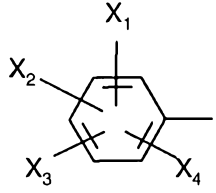
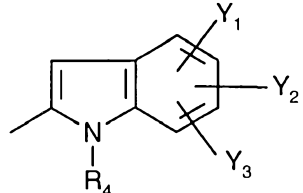
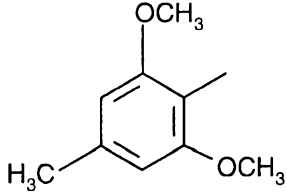
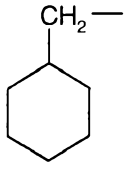
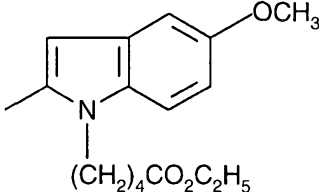
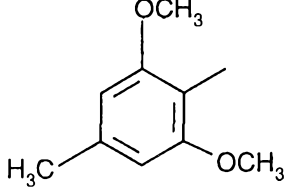
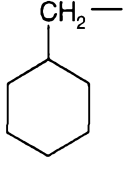
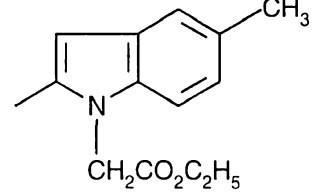
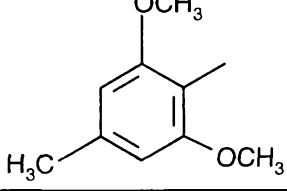
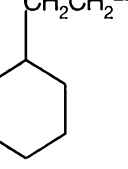
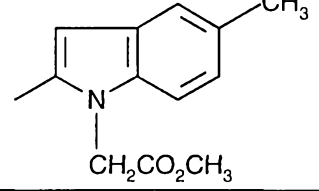
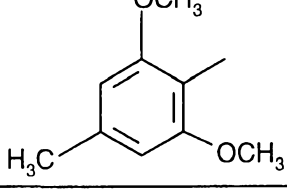
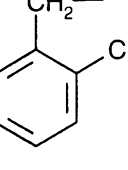
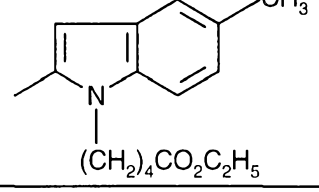
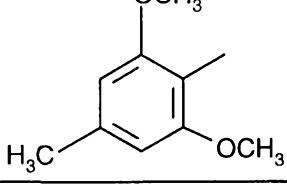
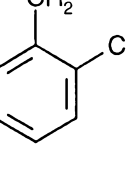
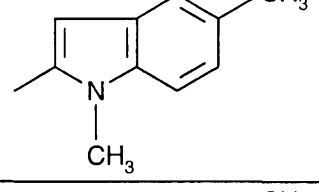
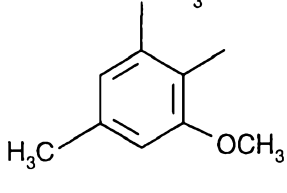
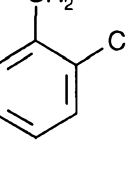
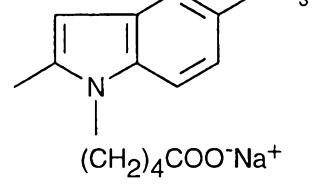
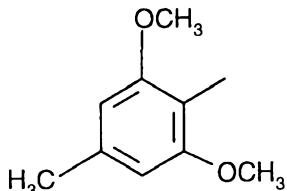
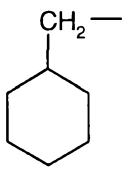
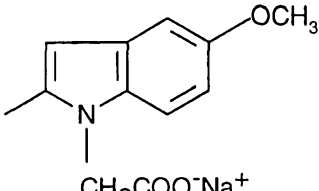
EXEMPLE N°		R ₁		F ; °C (sel)
141				140
142				159
143				121
144				158
145				220
146				266 (sel de Na)
147				206 (sel de Na)

TABLEAU VII (suite 9)

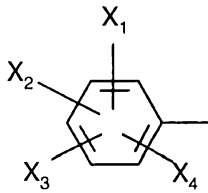
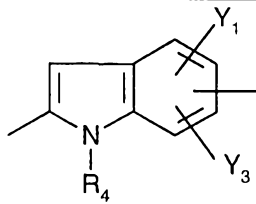
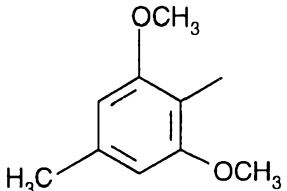
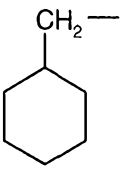
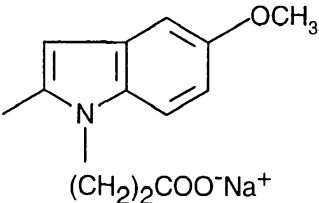
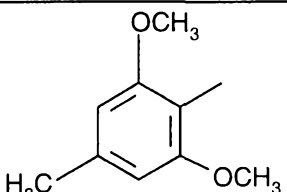
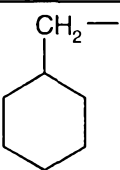
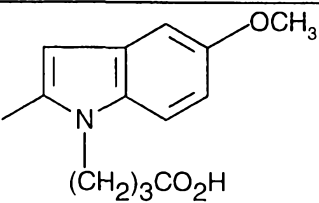
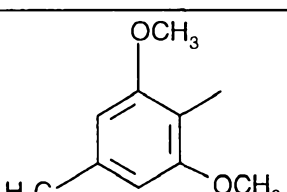
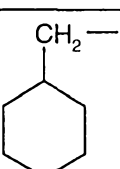
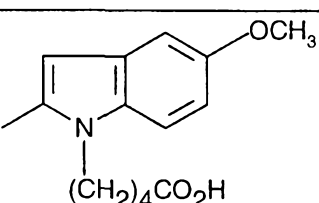
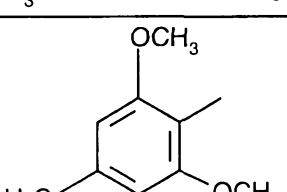
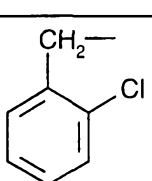
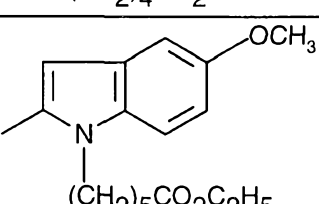
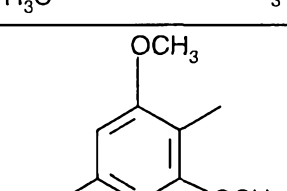
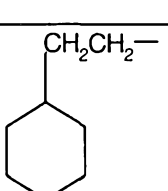
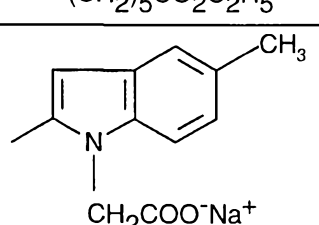
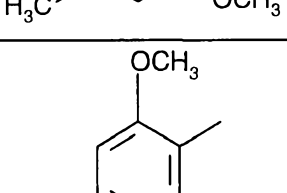
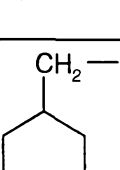
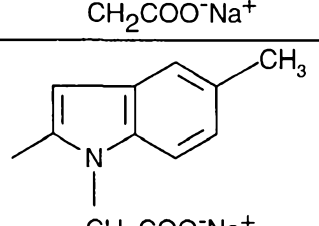
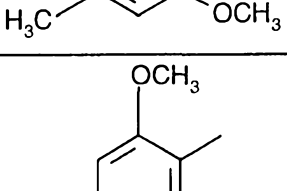
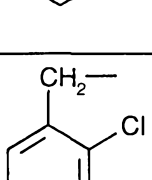
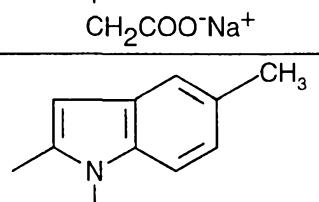
EXEMPLE N°		R ₁		F ; °C (sel)
148				210 (sel de Na)
149				213
150				247
151				163
152				230 (sel de Na)
153				252 (sel de Na)
154				132

TABLEAU VII (suite 10)

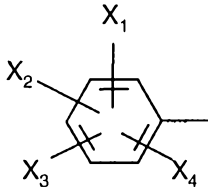
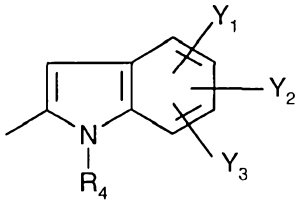
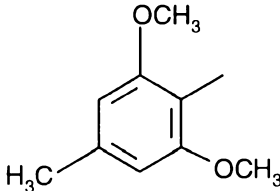
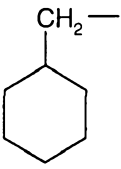
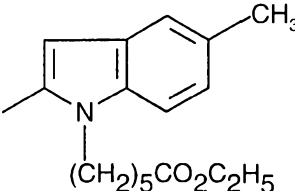
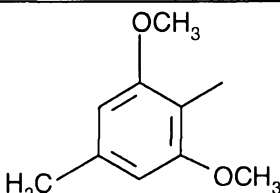
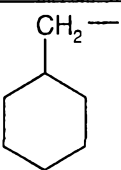
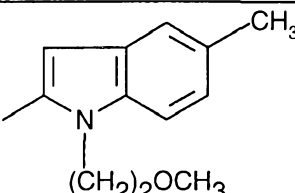
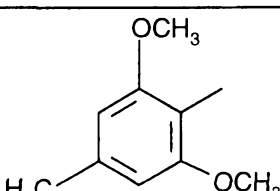
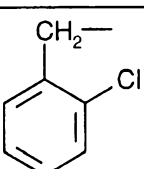
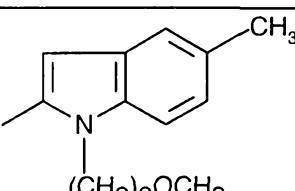
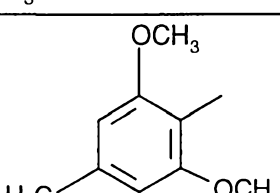
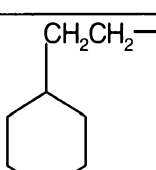
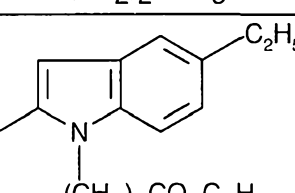
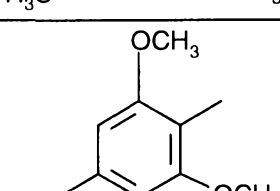
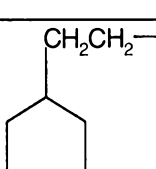
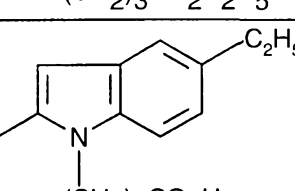
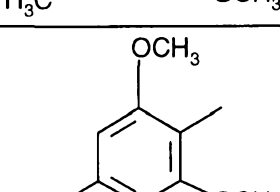
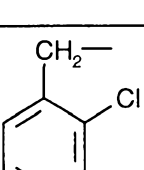
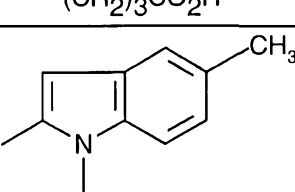
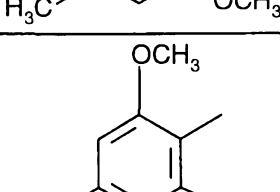
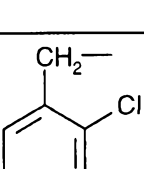
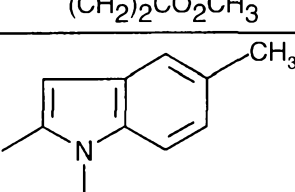
EXEMPLE N°		R ₁		F ; °C (sel)
155				138
156				188
157				196
158				82
159				215
160				177
161				233

TABLEAU VII (suite 11)

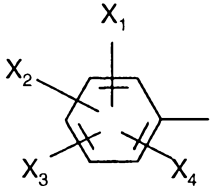
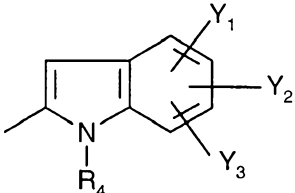
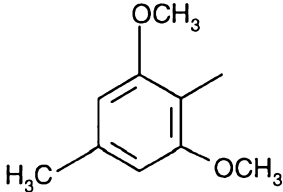
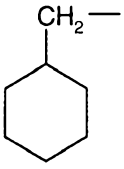
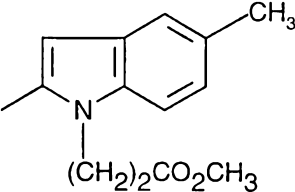
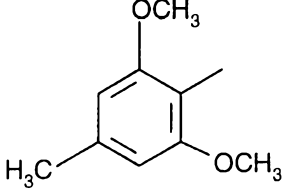
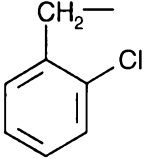
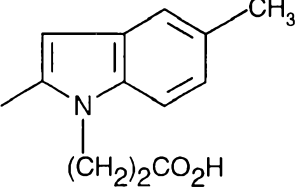
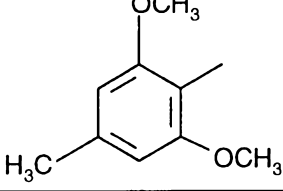
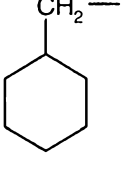
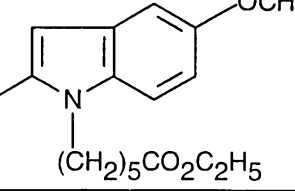
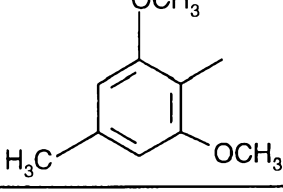
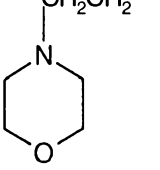
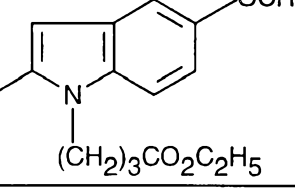
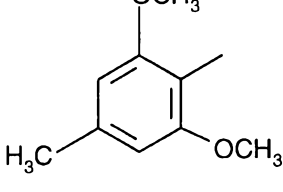
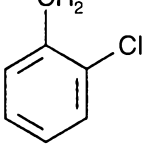
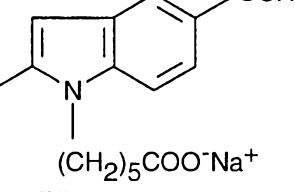
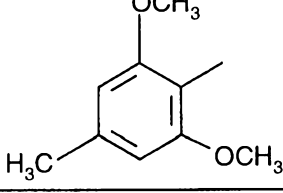
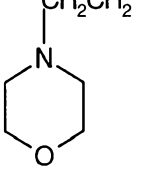
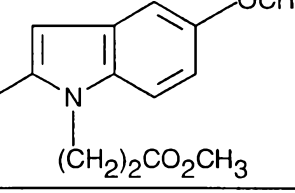
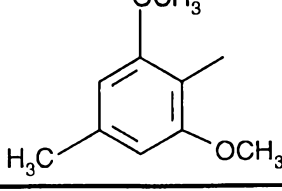
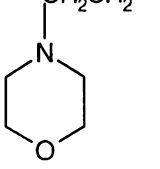
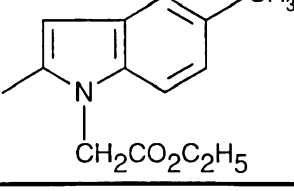
EXEMPLE N°		R ₁		F ; °C (sel)
162			 (CH ₂) ₂ CO ₂ CH ₃	131
163			 (CH ₂) ₂ CO ₂ H	241
164			 (CH ₂) ₅ CO ₂ C ₂ H ₅	120
165			 (CH ₂) ₃ CO ₂ C ₂ H ₅	145
166			 (CH ₂) ₅ COO ⁻ Na ⁺	144 (sel de Na)
167			 (CH ₂) ₂ CO ₂ CH ₃	114
168			 CH ₂ CO ₂ C ₂ H ₅	148

TABLEAU VII (suite 12)

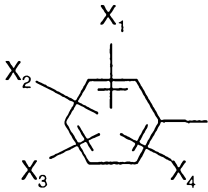
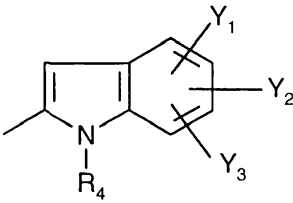
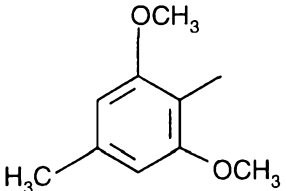
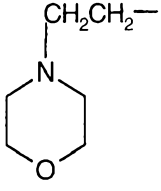
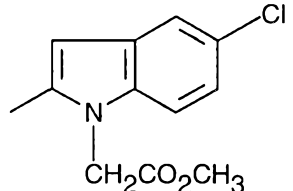
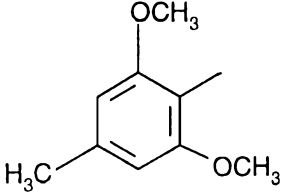
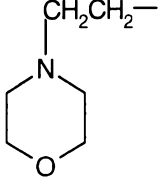
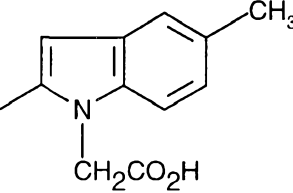
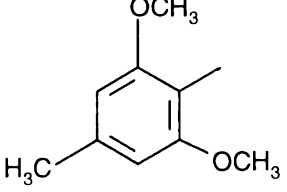
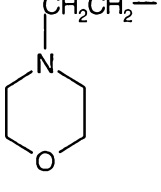
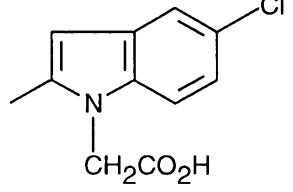
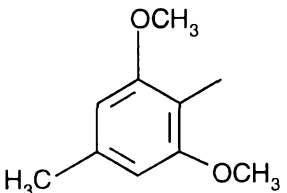
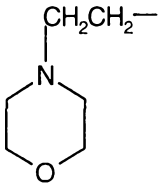
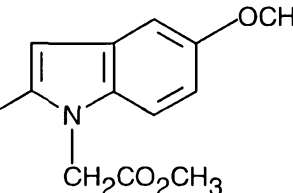
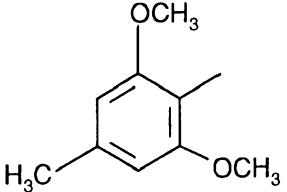
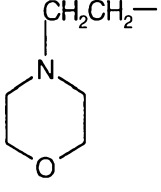
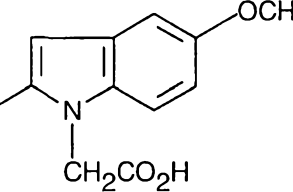
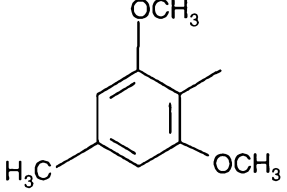
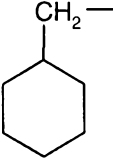
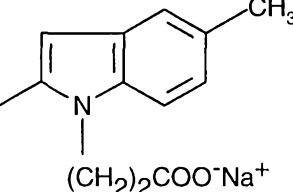
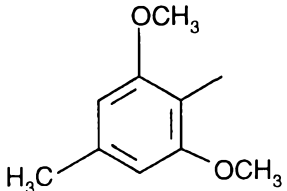
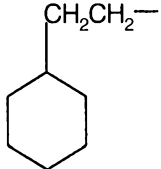
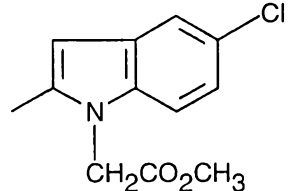
EXEMPLE N°		R ₁		F ; °C (sel)
169				202
170				231 (HCl)
171				237 (2HCl)
172				208
173				231 (2HCl)
174				268 (sel de Na)
175				195

TABLEAU VII (suite 13)

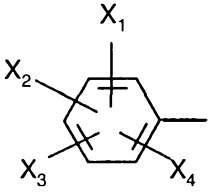
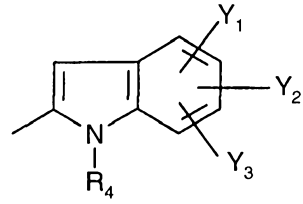
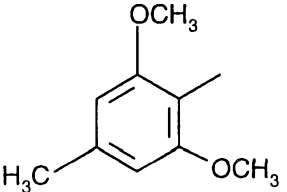
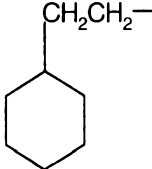
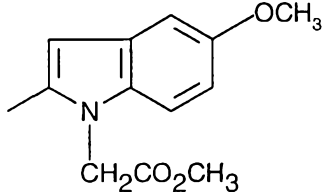
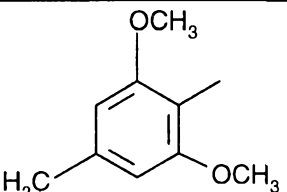
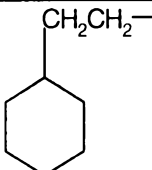
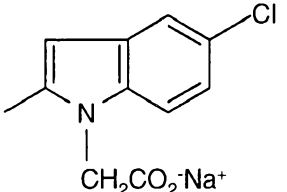
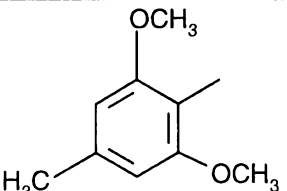
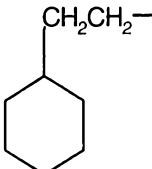
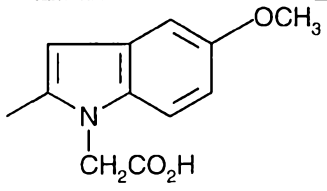
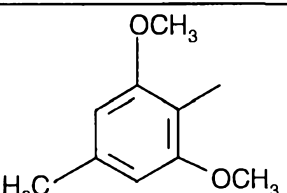
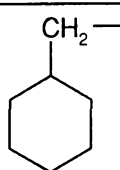
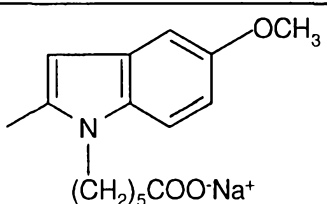
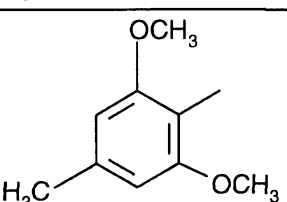
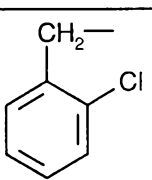
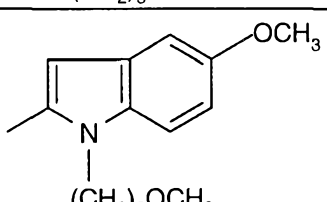
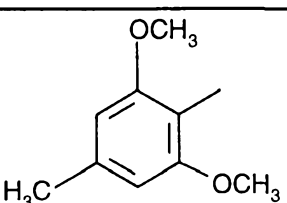
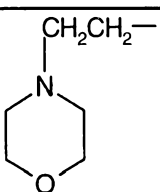
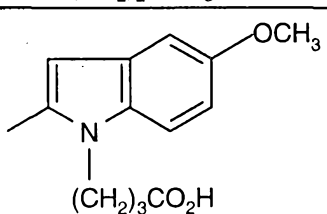
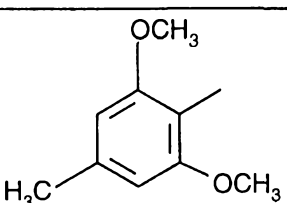
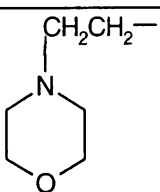
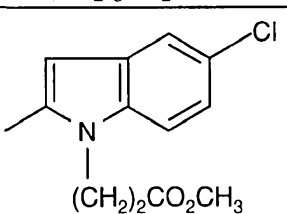
EXEMPLE N°		R ₁		F ; °C (sel)
176				164
177				215
178				232
179				200 (sel de Na)
180				199
181				233 (HCl)
182				101

TABLEAU VII (suite 14)

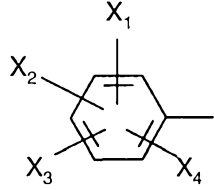
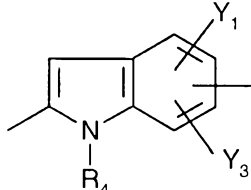
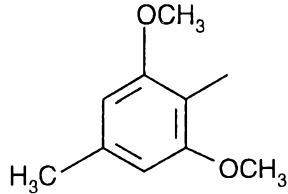
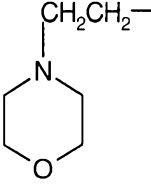
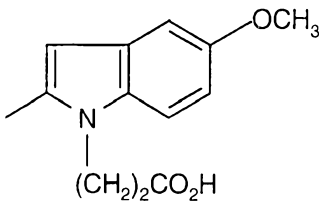
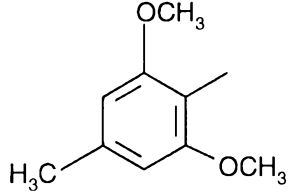
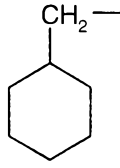
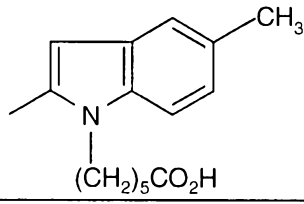
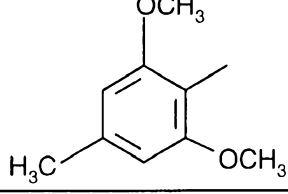
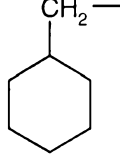
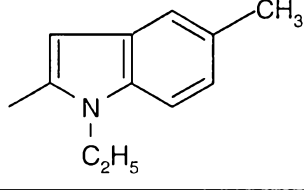
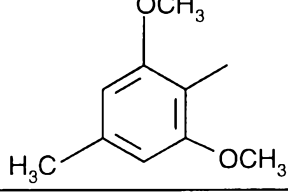
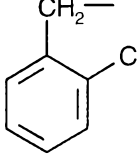
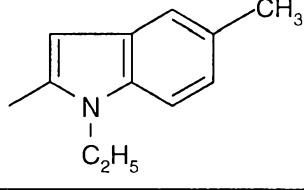
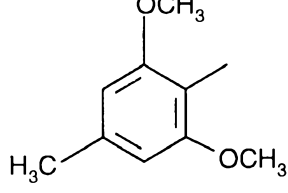
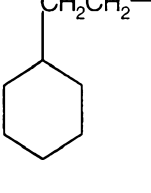
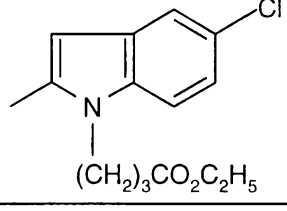
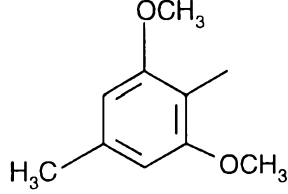
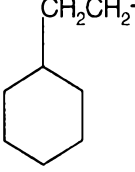
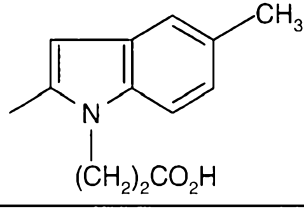
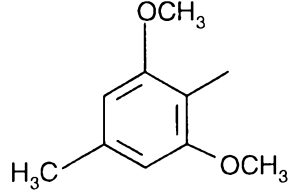
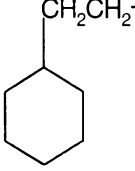
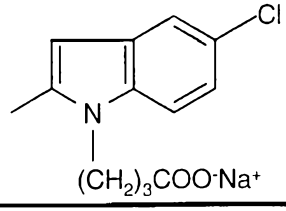
EXEMPLE N°		R ₁		F ; °C (sel)
183				246 (HCl)
184				217
185				108
186				219
187				87
188				263
189				184 (sel de Na)

TABLEAU VII (suite 15)

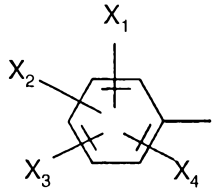
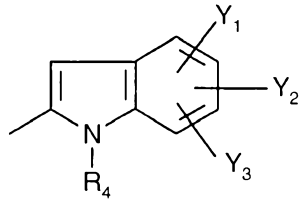
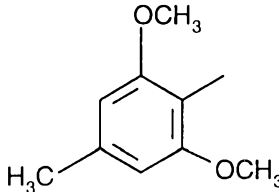
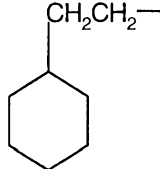
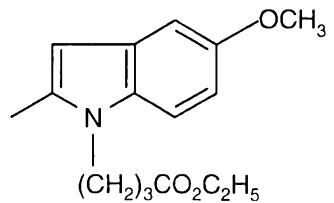
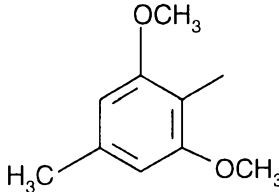
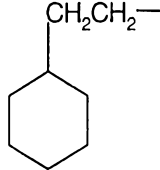
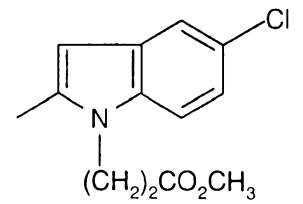
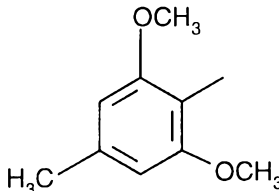
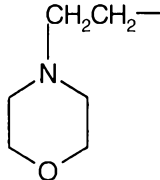
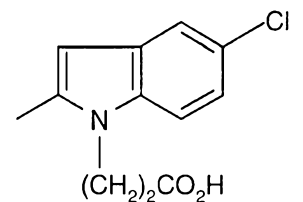
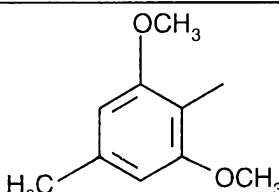
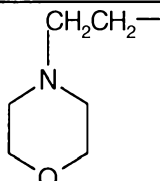
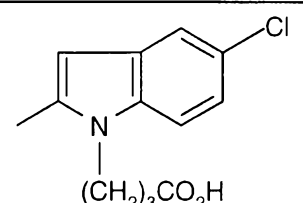
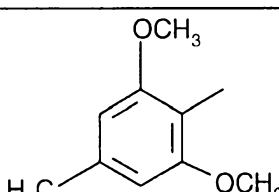
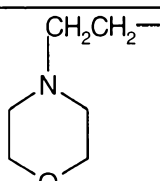
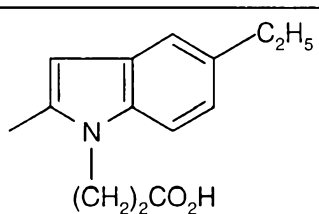
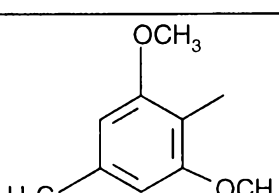
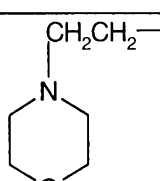
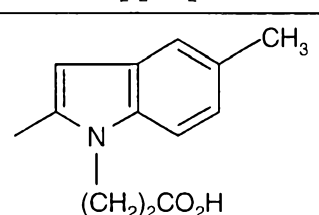
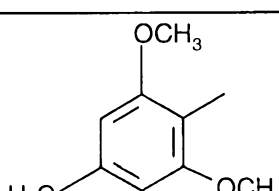
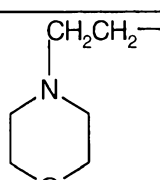
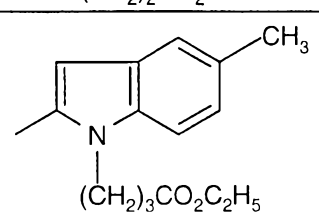
EXEMPLE N°		R ₁		F ; °C (sel)
190				140
191				187
192				208 (HCl)
193				200 (HCl)
194				197 (2HCl)
195				186 (2HCl)
196				148

TABLEAU VII (suite 16)

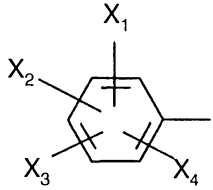
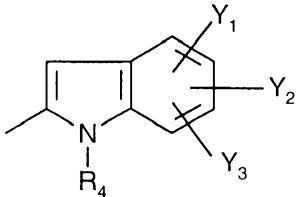
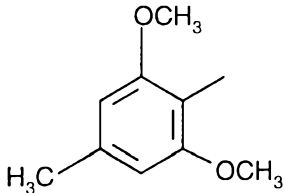
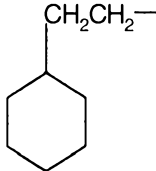
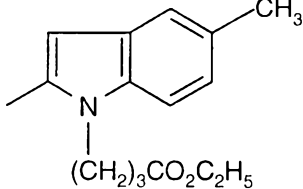
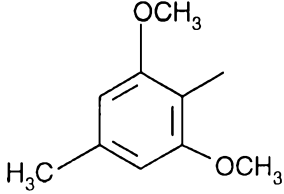
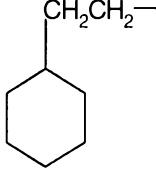
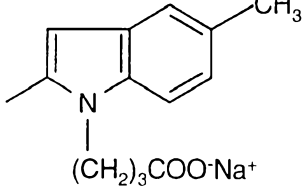
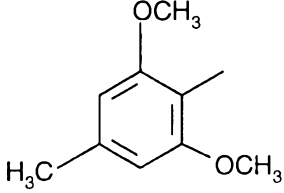
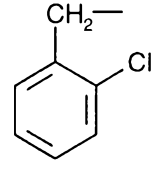
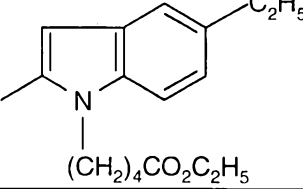
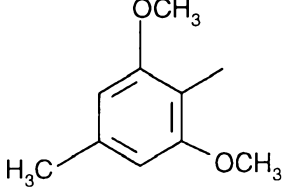
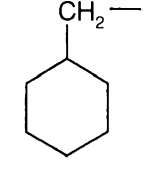
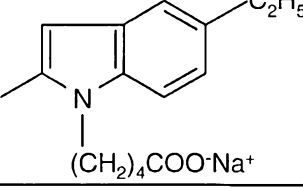
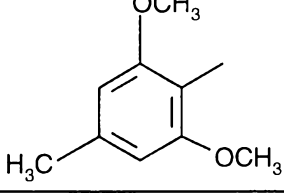
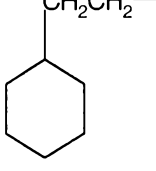
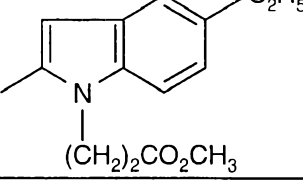
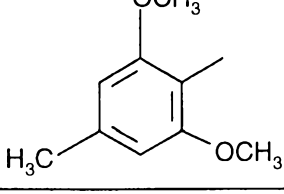
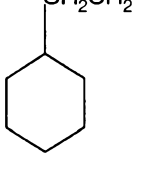
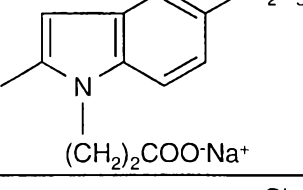
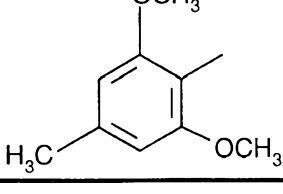
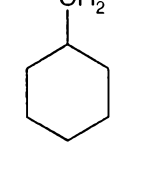
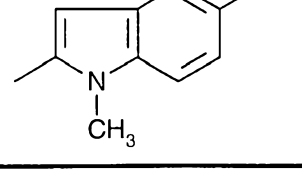
EXEMPLE N°		R ₁		F ; °C (sel)
197				136
198				170
199				130
200				282 (sel de Na)
201				101
202				273 (sel de Na)
203				231

TABLEAU VII (suite 17)

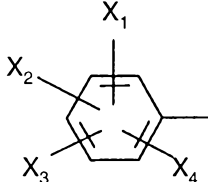
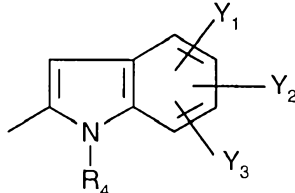
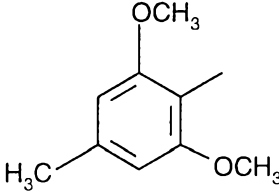
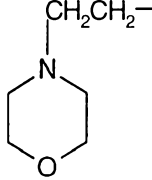
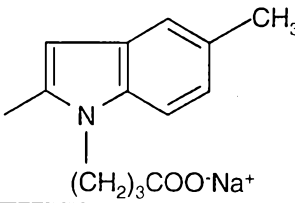
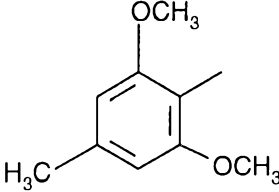
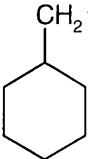
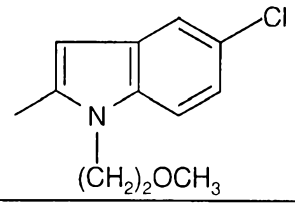
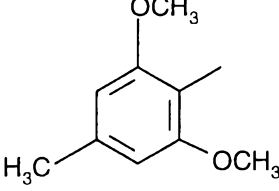
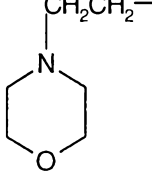
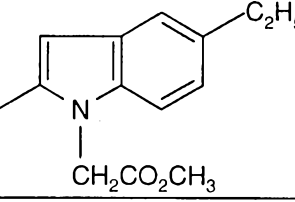
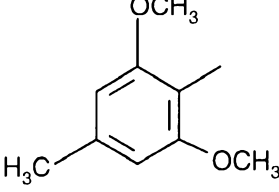
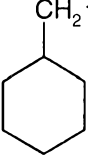
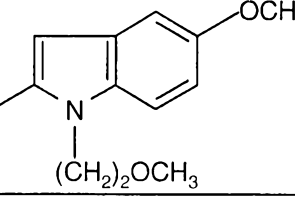
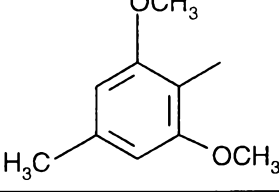
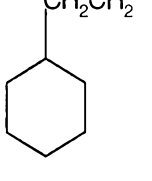
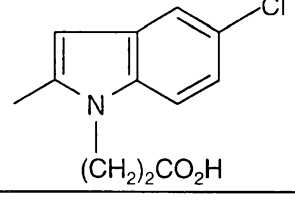
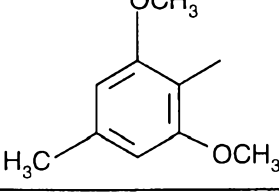
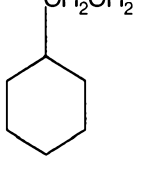
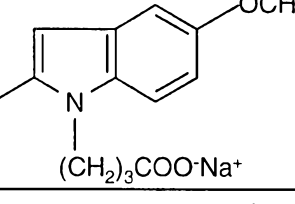
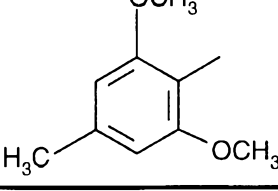
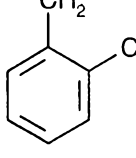
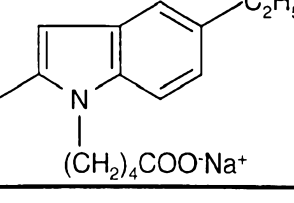
EXEMPLE N°		R ₁		F ; °C (sel)
204				225 (sel de Na)
205				112
206				108
207				122
208				155
209				162 (sel de Na)
210				225 (sel de Na)

TABLEAU VII (suite 18)

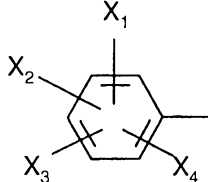
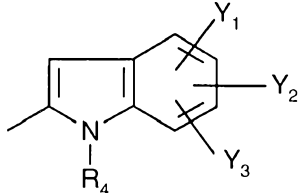
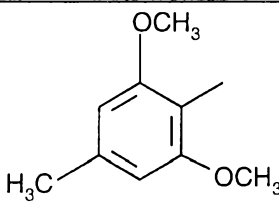
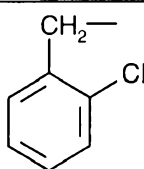
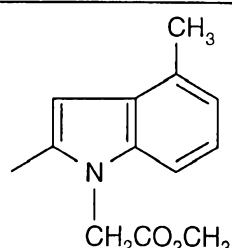
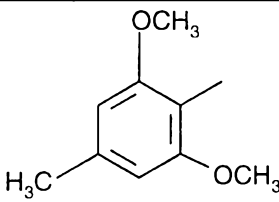
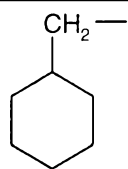
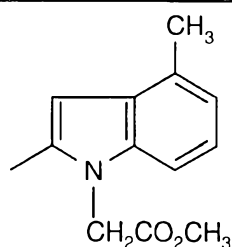
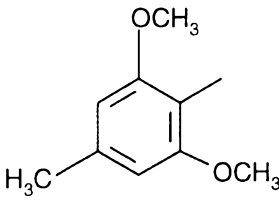
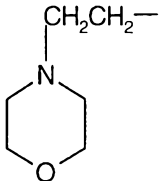
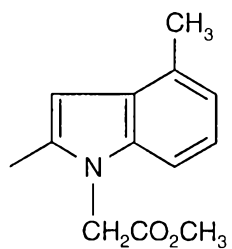
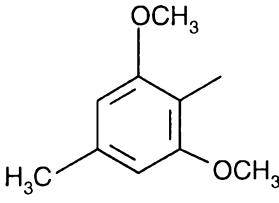
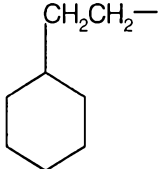
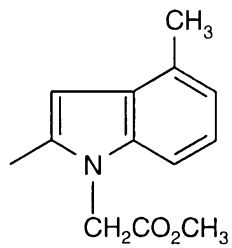
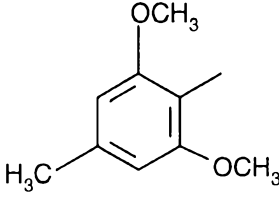
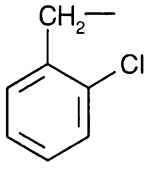
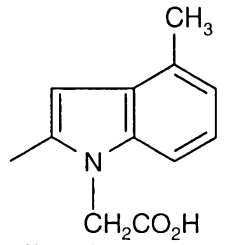
EXEMPLE N°		R ₁		F ; °C (sel)
211				130
212				141
213				177
214				126
215				213

TABLEAU VII (suite 19)

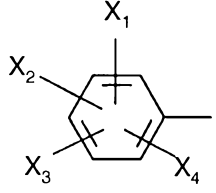
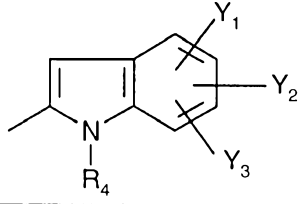
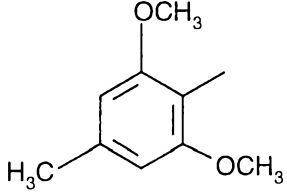
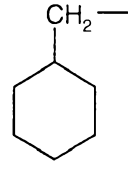
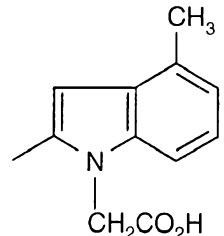
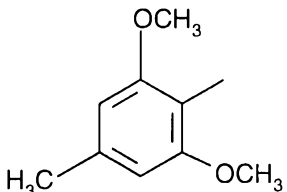
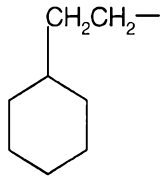
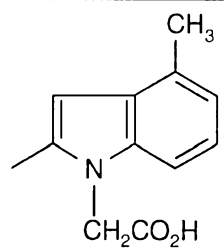
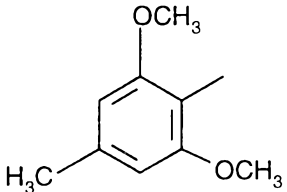
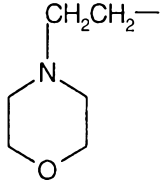
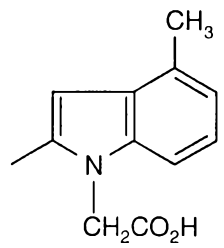
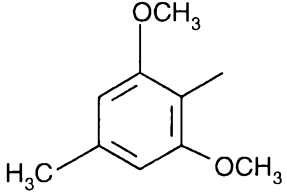
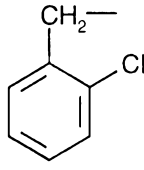
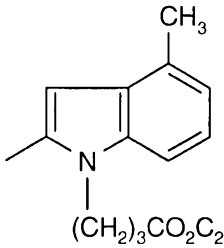
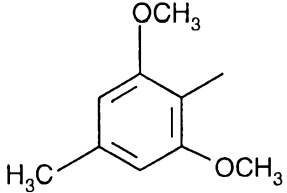
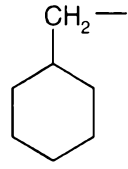
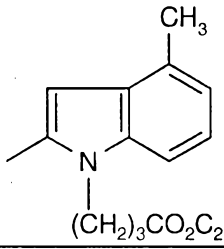
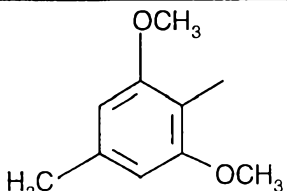
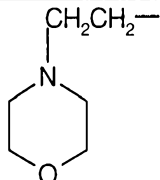
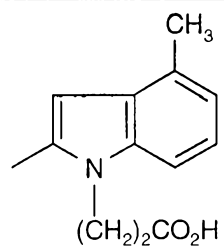
EXEMPLE N°		R ₁		F ; °C (sel)
216				241
217				257
218				221 (2HCl)
219				152
220				87
221				182 (2HCl)

TABLEAU VII (suite 20)

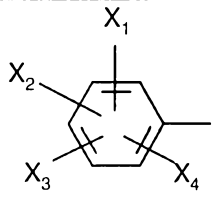
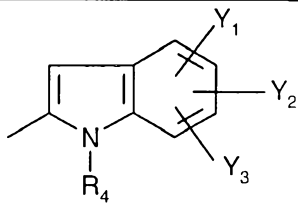
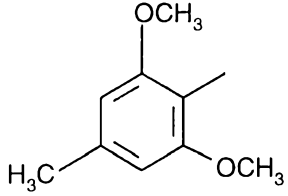
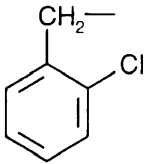
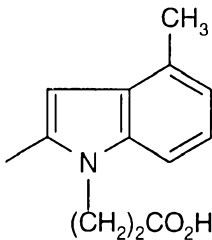
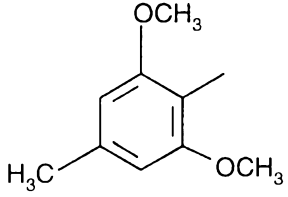
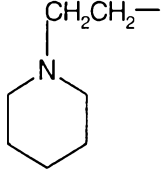
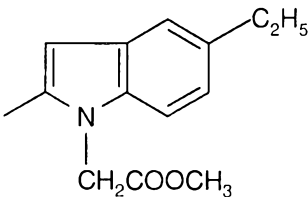
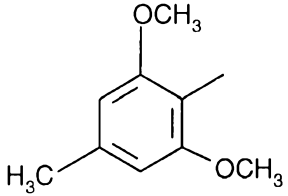
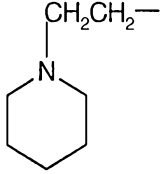
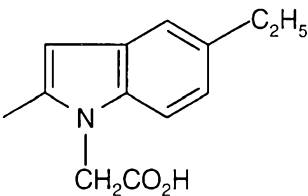
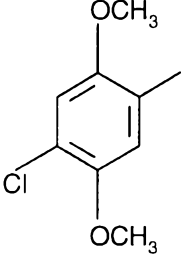
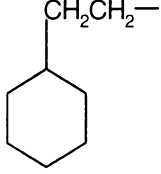
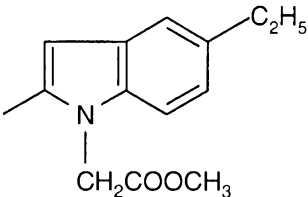
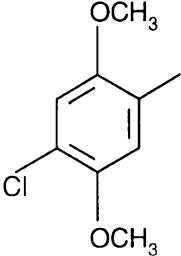
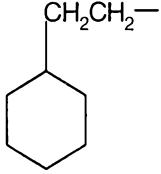
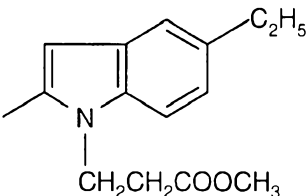
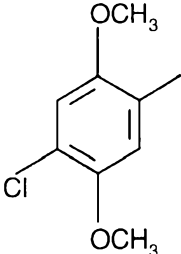
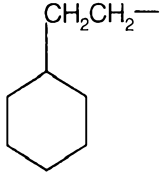
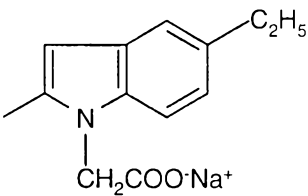
EXEMPLE N°		R ₁		F ; °C (sel)
222				168
223				205
224				256 (HCl)
225				198
226				95
227				198 (sel de Na)

TABLEAU VII (suite 21)

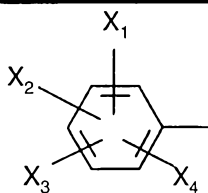
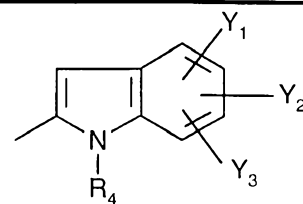
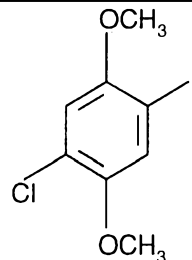
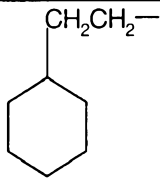
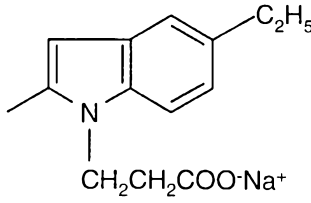
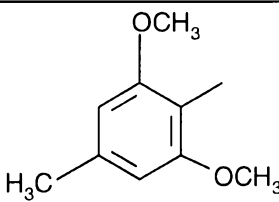
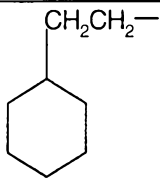
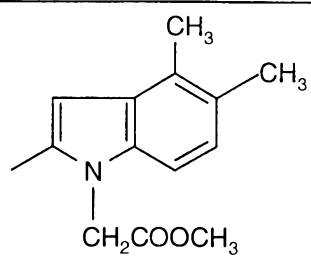
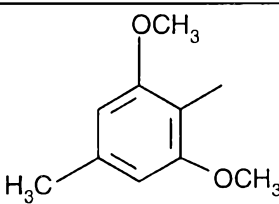
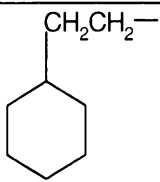
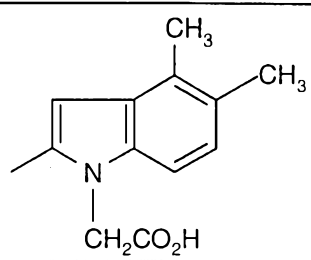
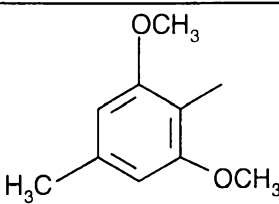
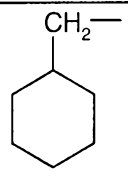
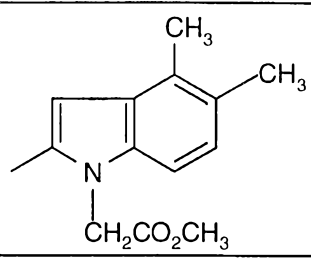
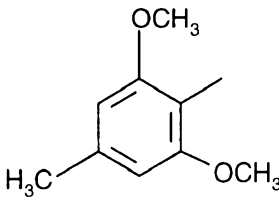
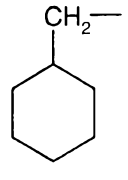
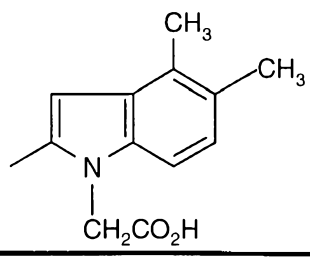
EXEMPLE N°		R ₁		F ; °C (sel)
228				200 (sel de Na)
229				145
230				256
231				157
232				265

TABLEAU VII (suite 22)

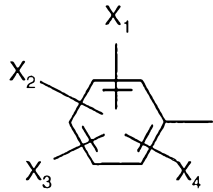
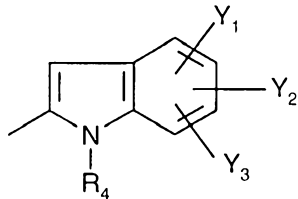
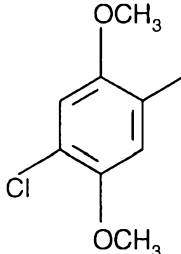
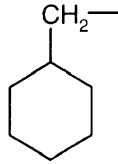
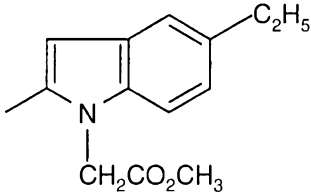
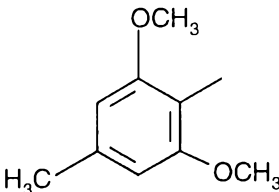
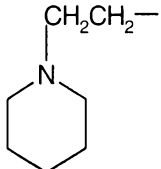
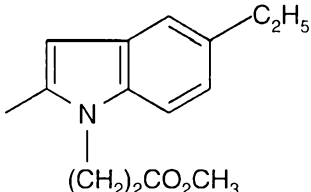
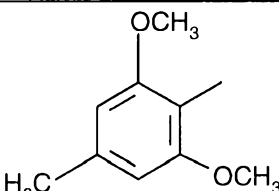
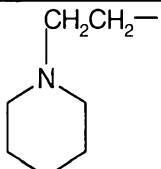
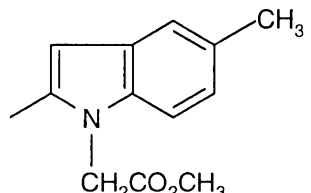
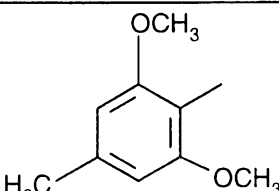
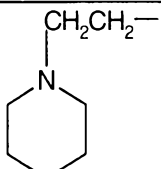
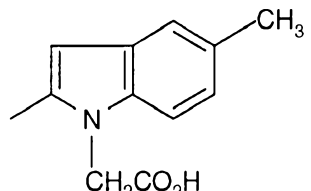
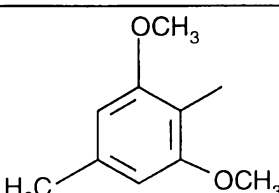
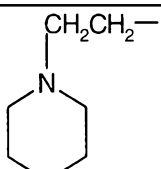
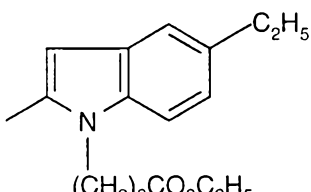
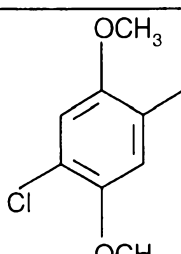
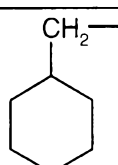
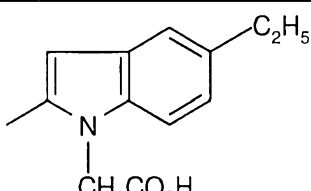
EXEMPLE N°		R ₁		F ; °C (sel)
233				157
234				211 (HCl)
235				209 (HCl)
236				222 (2HCl)
237				240 (HCl)
238				217

TABLEAU VII (suite 23)

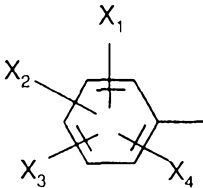
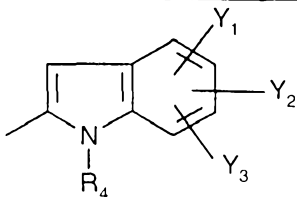
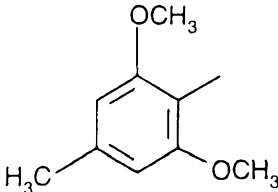
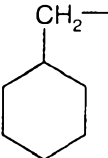
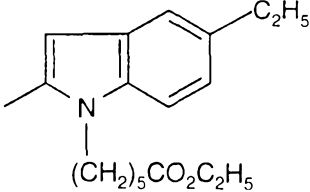
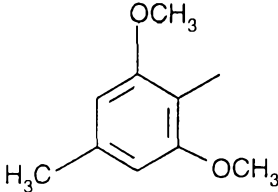
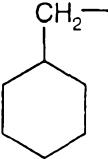
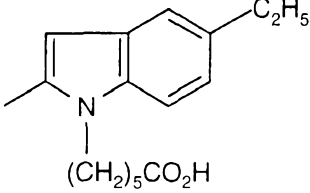
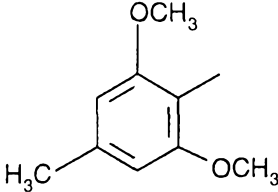
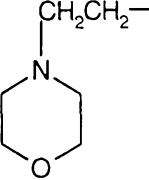
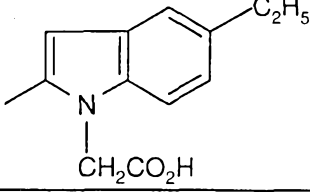
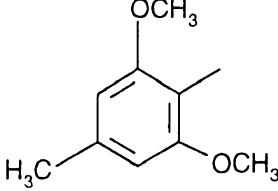
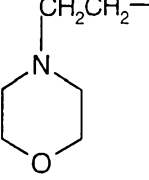
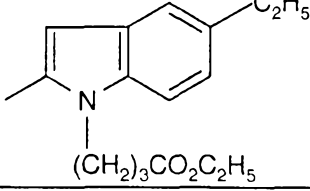
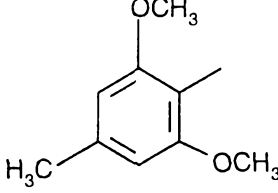
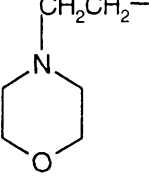
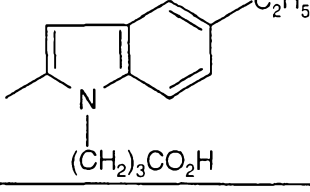
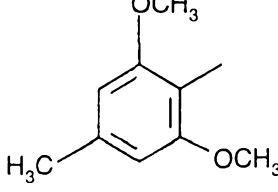
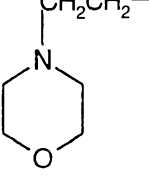
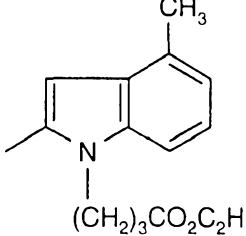
EXEMPLE N°		R ₁		F ; °C (sel)
239				129
240				138
241				215 (2HCl)
242				83
243				205 (2HCl)
244				125

TABLEAU VII (suite 24)

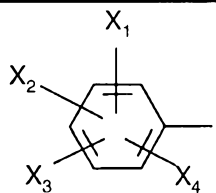
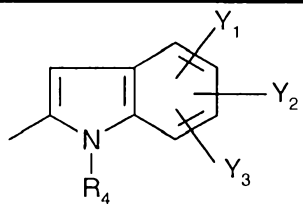
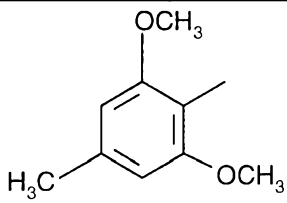
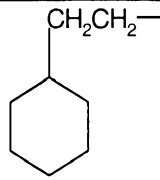
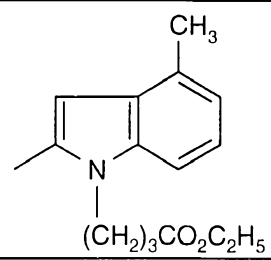
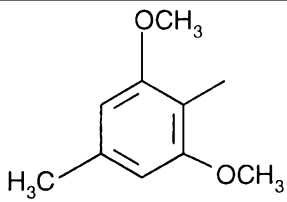
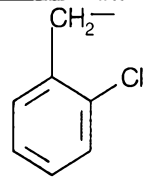
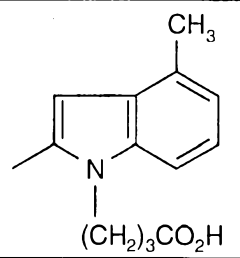
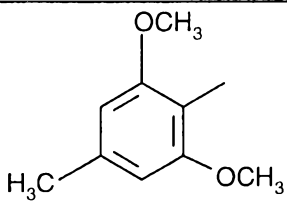
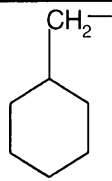
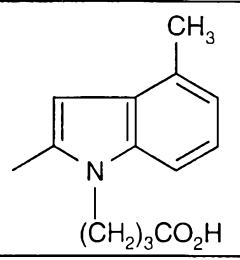
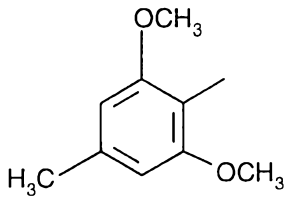
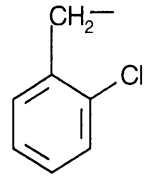
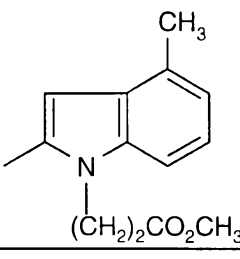
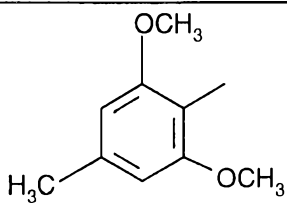
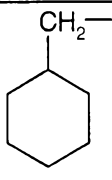
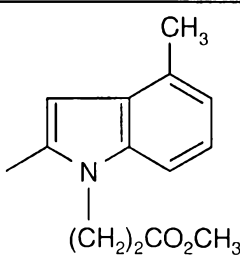
EXEMPLE N°		R ₁		F ; °C (sel)
245				94
246				234
247				170
248				143
249				107

TABLEAU VII (suite 25)

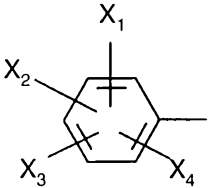
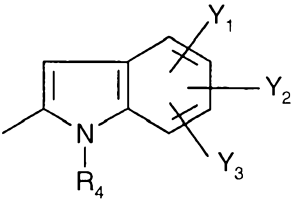
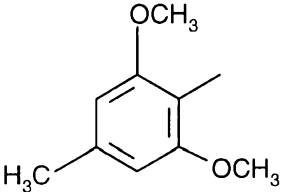
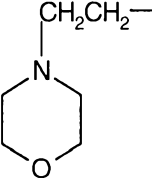
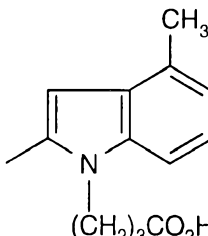
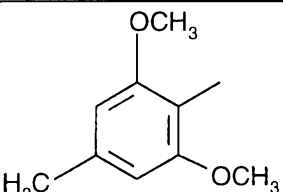
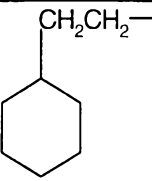
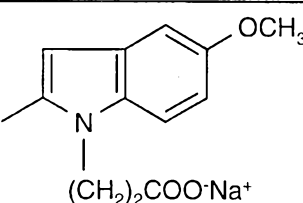
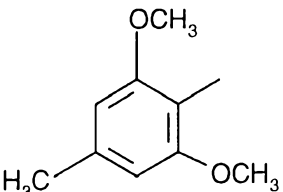
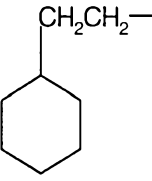
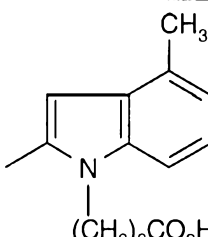
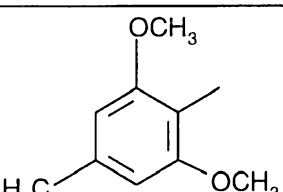
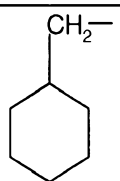
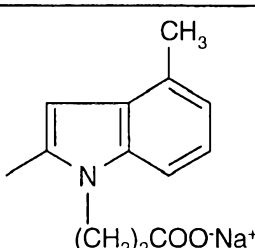
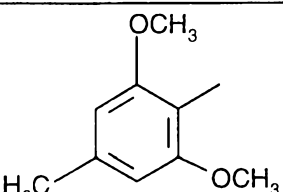
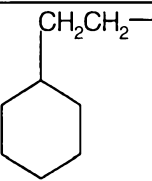
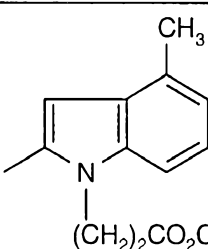
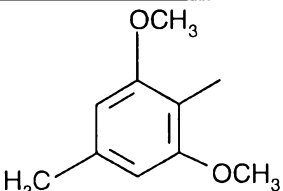
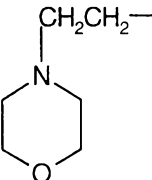
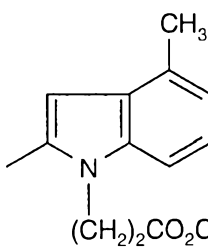
EXEMPLE N°		R ₁		F ; °C (sel)
250				206 (2HCl)
251				240 (sel de Na)
252				184
253				238 (sel de Na)
254				122
255				121

TABLEAU VII (suite 26)

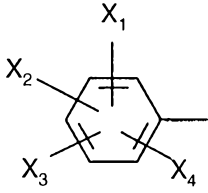
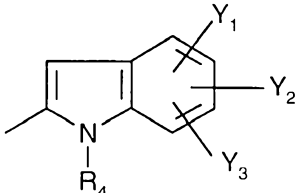
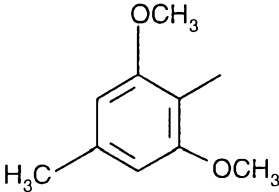
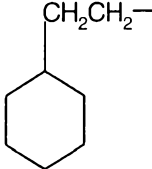
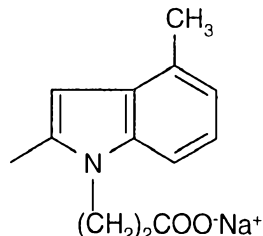
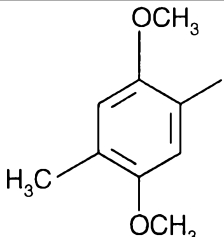
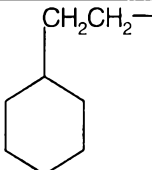
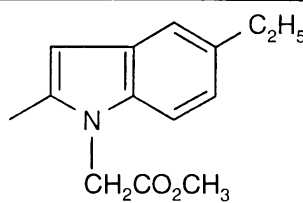
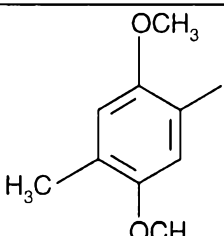
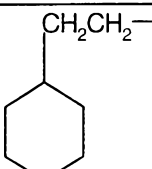
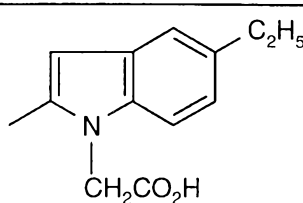
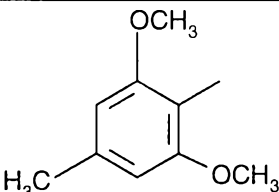
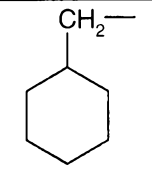
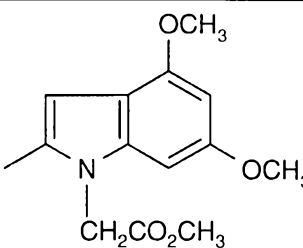
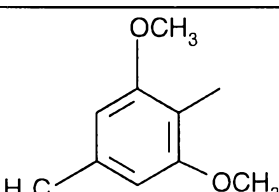
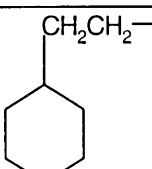
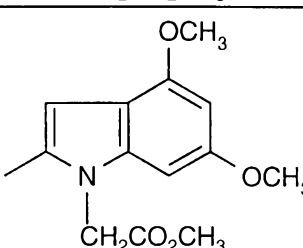
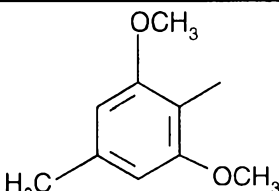
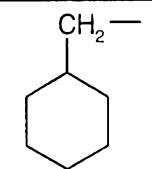
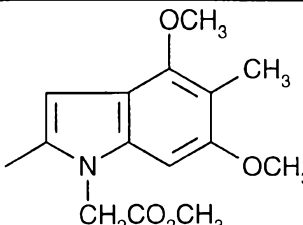
EXEMPLE N°		R ₁		F ; °C (sel)
256				251 (sel de Na)
257				200
258				151 (2HCl)
259				241
260				157
261				170

TABLEAU VII (suite 27)

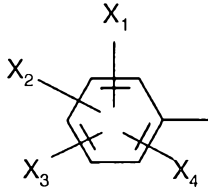
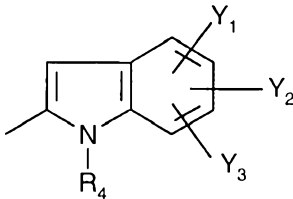
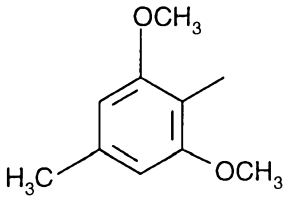
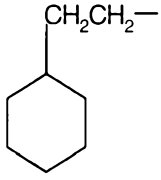
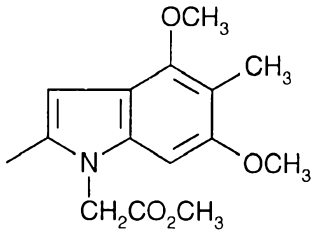
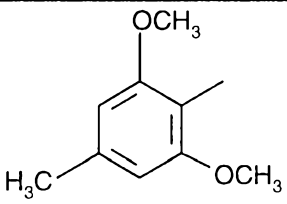
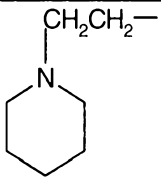
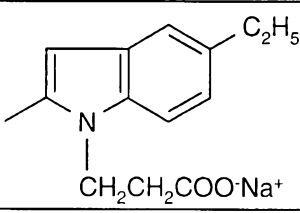
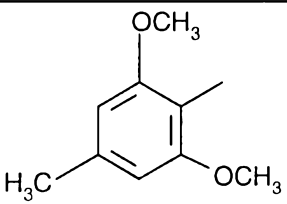
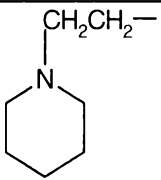
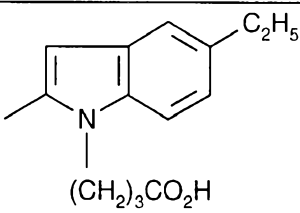
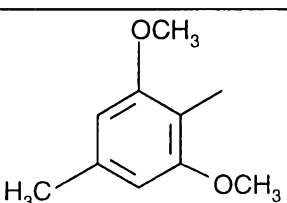
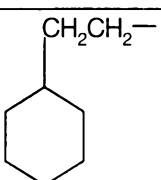
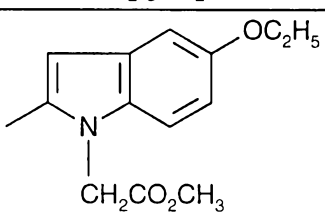
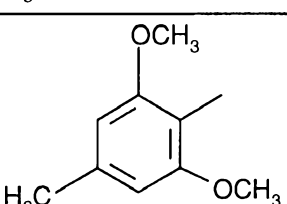
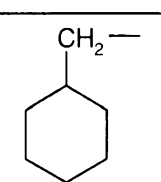
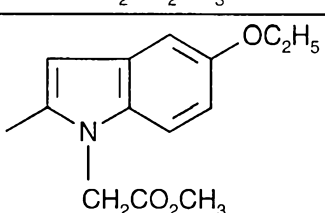
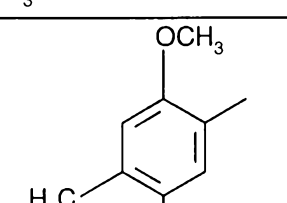
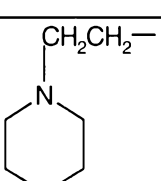
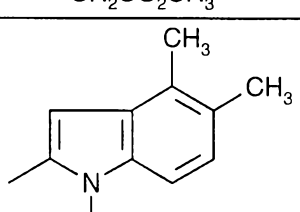
EXEMPLE N°		R ₁		F ; °C (sel)
262				191
263				193
264				198
265				163
266				205
267				114

TABLEAU VII (suite 28)

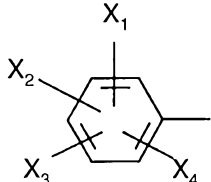
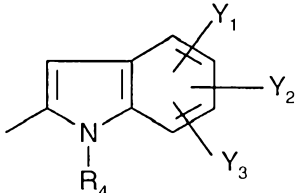
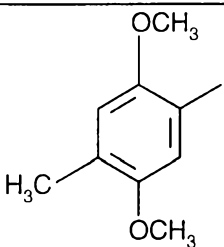
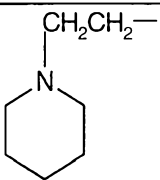
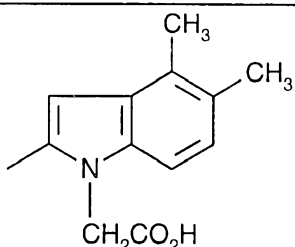
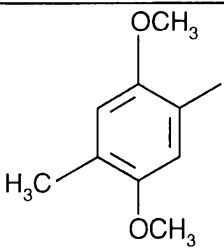
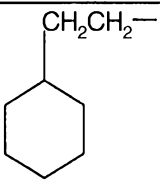
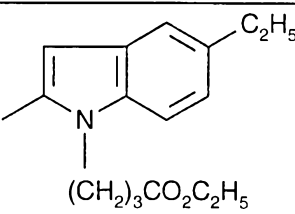
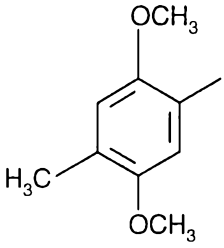
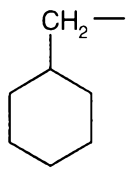
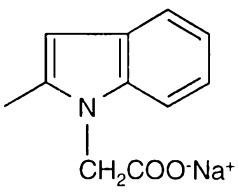
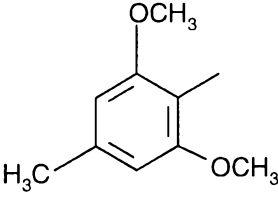
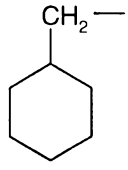
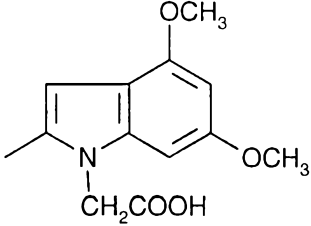
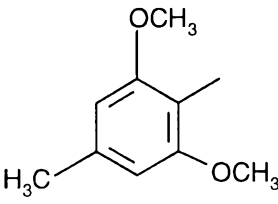
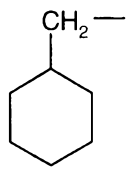
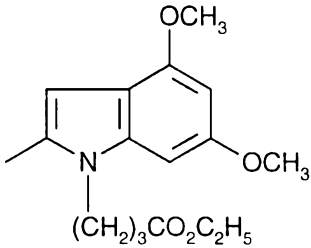
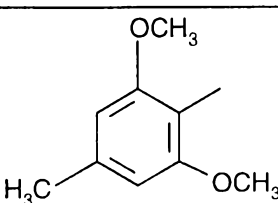
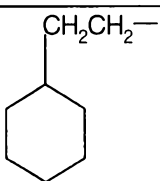
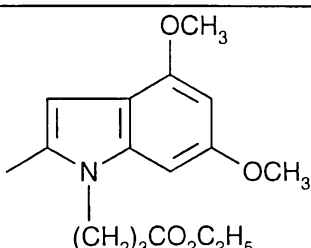
EXEMPLE N°		R ₁		F ; °C (sel)
268				223 (HCl)
269				159
270				295 (sel de Na)
271				227
272				102
273				162

TABLEAU VII (suite 29)

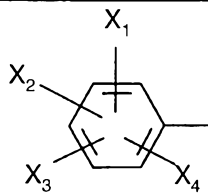
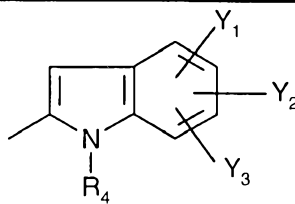
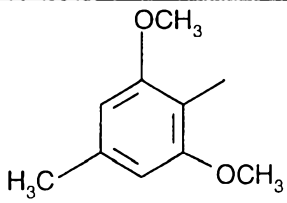
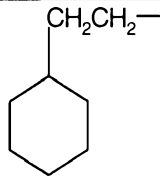
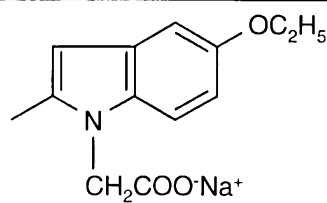
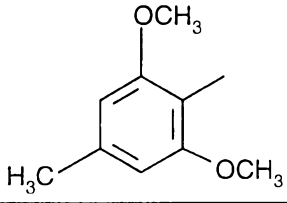
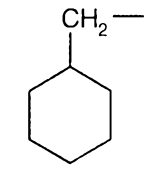
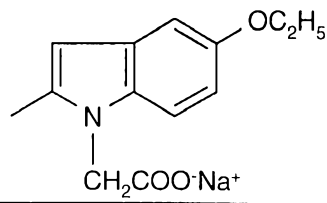
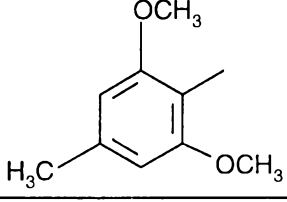
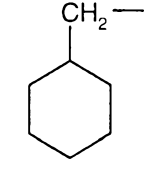
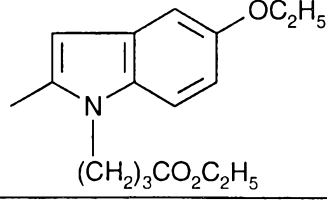
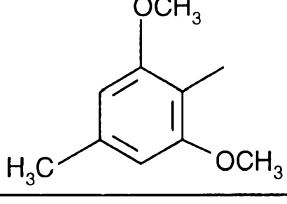
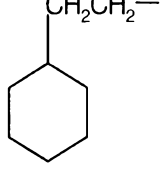
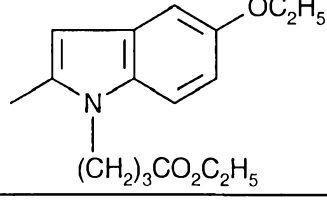
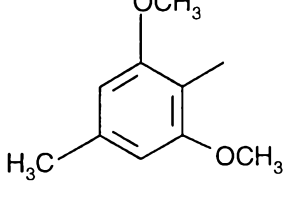
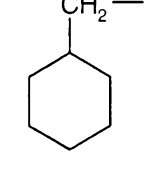
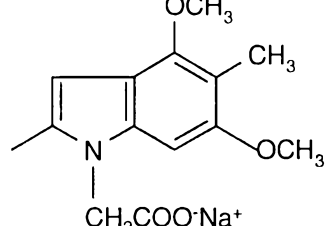
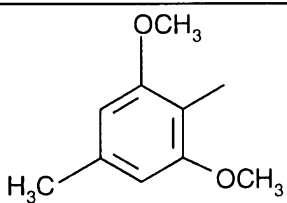
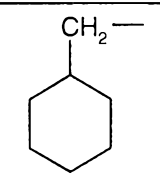
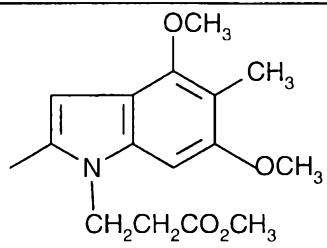
EXEMPLE N°		R ₁		F ; °C (sel)
274				240 (sel de Na)
275				250 (sel de Na)
276				161
277				177
278				297 (sel de Na)
279				127

TABLEAU VII (suite 30)

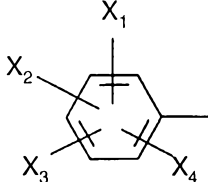
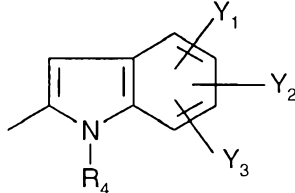
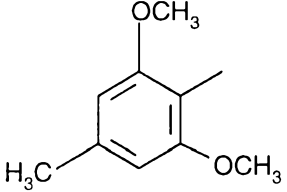
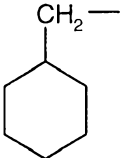
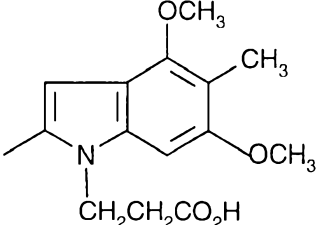
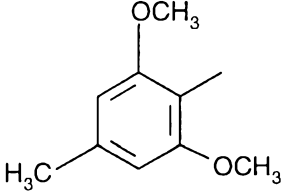
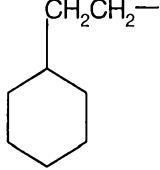
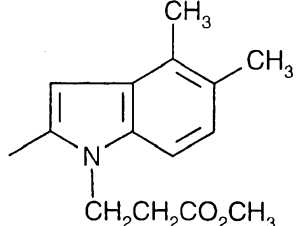
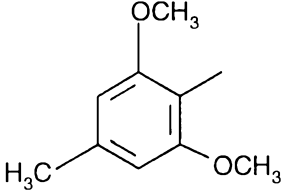
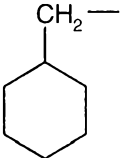
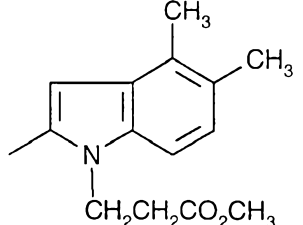
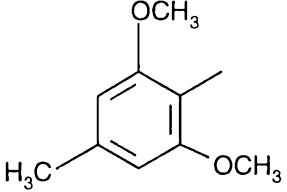
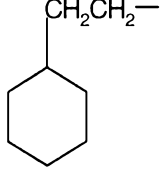
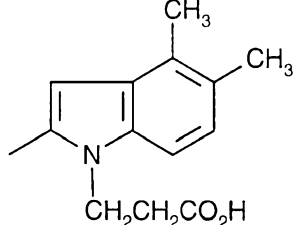
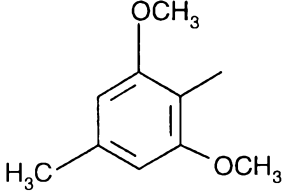
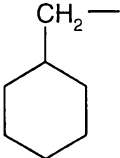
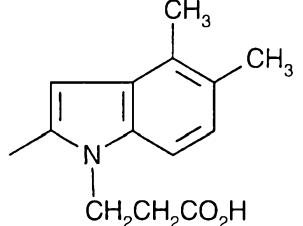
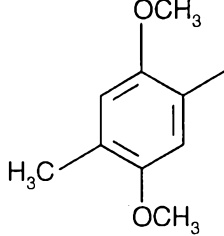
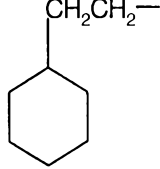
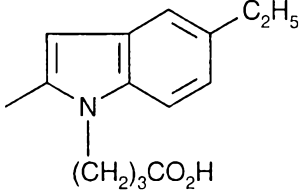
EXEMPLE N°		R ₁		F ; °C (sel)
280				303
281				111
282				191
283				289
284				273
285				131 (HCl)

TABLEAU VII (suite 31)

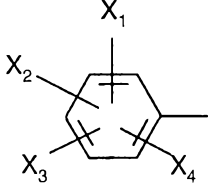
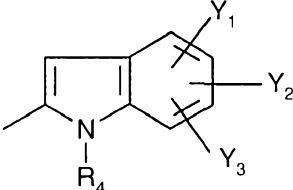
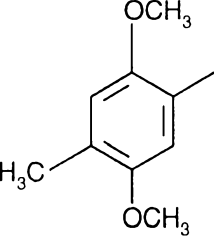
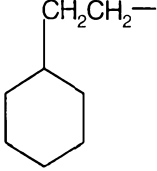
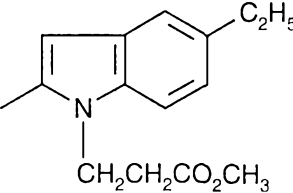
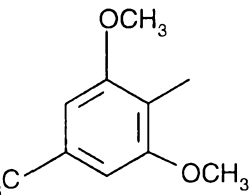
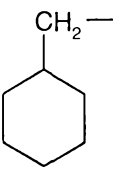
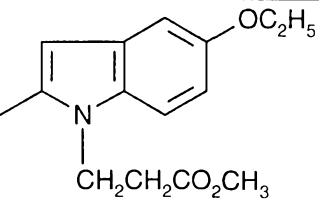
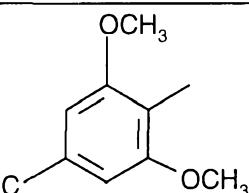
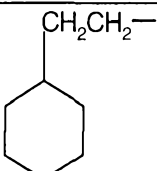
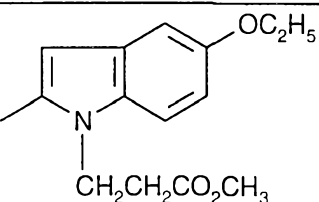
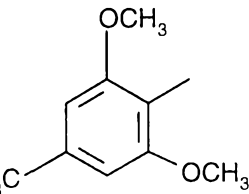
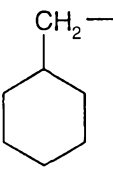
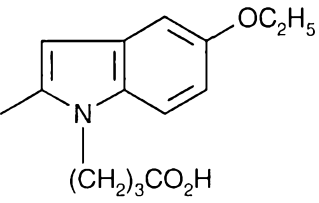
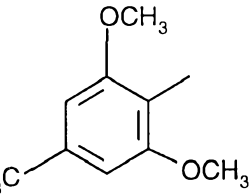
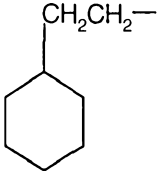
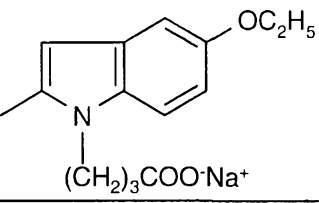
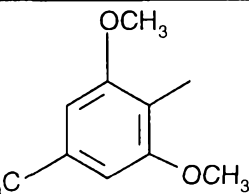
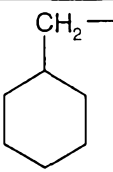
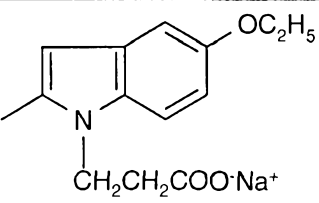
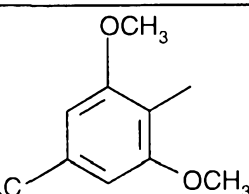
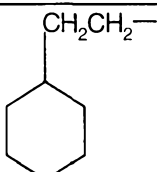
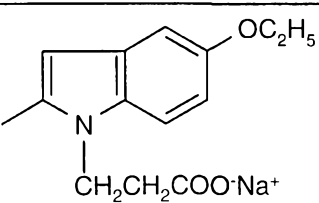
EXEMPLE N°		R ₁		F ; °C (sel)
286				156
287				160
288				181
289				157
290				140 (sel de Na)
291				174 (sel de Na)
292				170 (sel de Na)

TABLEAU (suite 32)

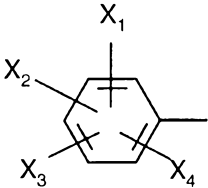
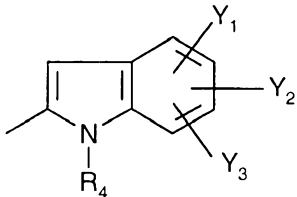
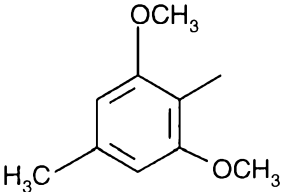
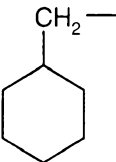
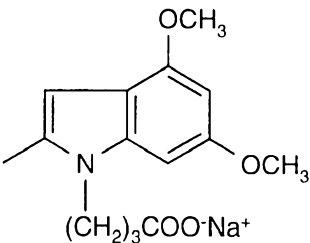
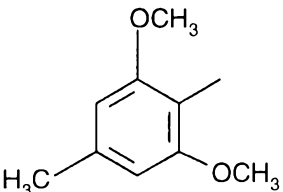
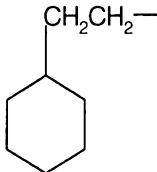
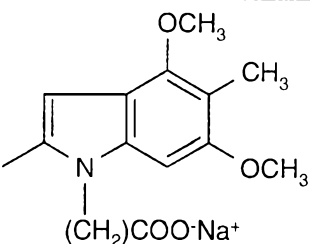
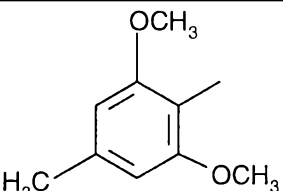
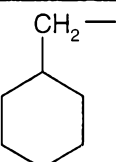
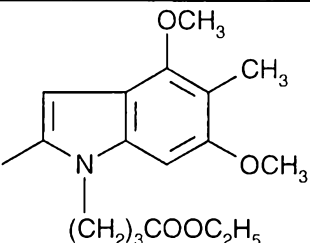
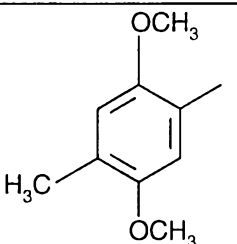
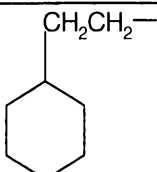
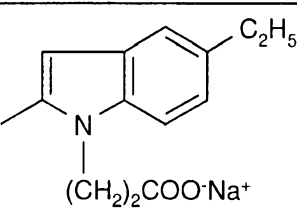
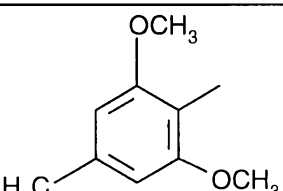
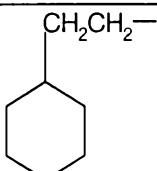
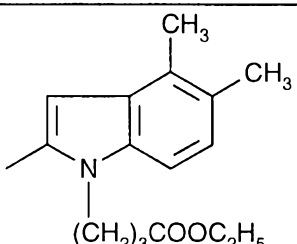
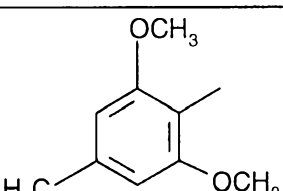
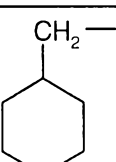
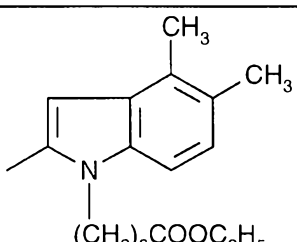
EXEMPLE N°		R ₁		F ; °C (sel)
293				247 (sel de Na)
294				220 (sel de Na)
295				151
296				216 (sel de Na)
297				104
298				111

TABLEAU VII (suite 33)

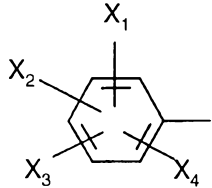
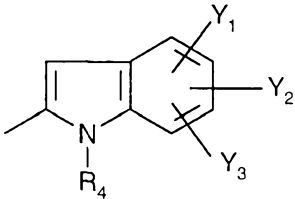
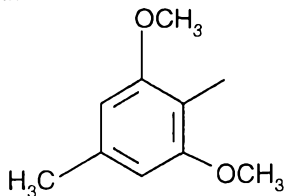
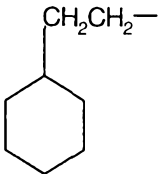
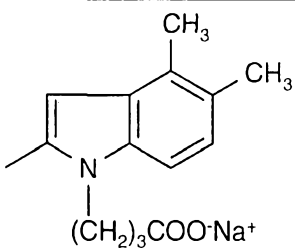
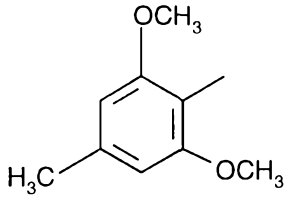
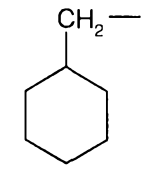
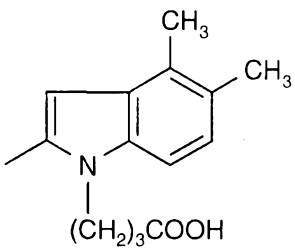
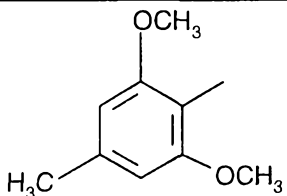
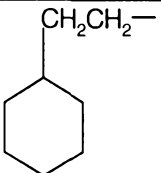
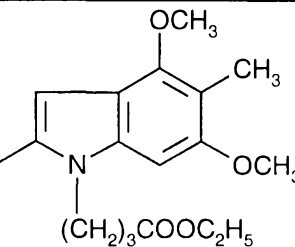
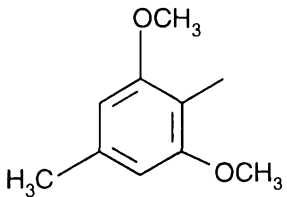
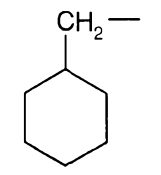
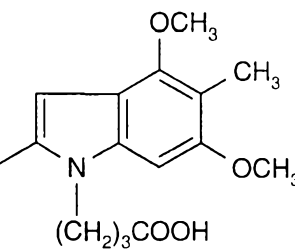
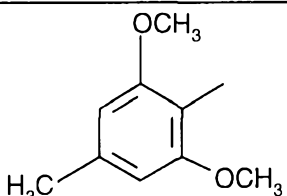
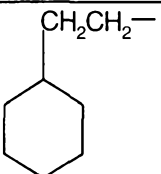
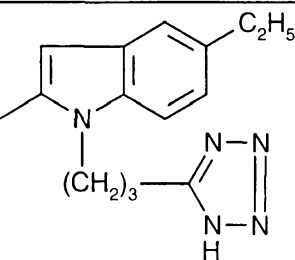
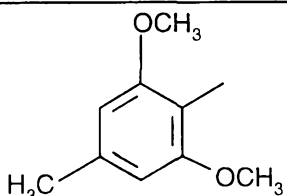
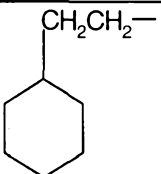
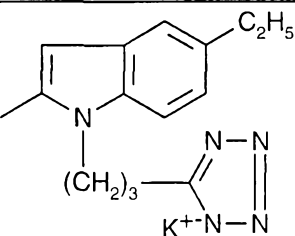
EXEMPLE N°		R ₁		F ; °C (sel)
299				159 (sel de Na)
300				218
301				142
302				254
303				240
304				204 (sel de K)

TABLEAU VII (suite 34)

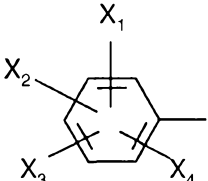
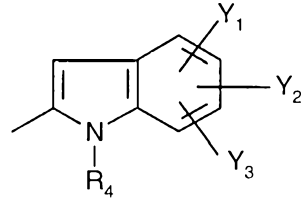
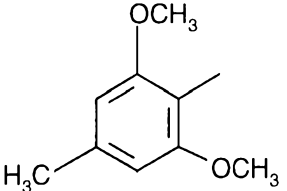
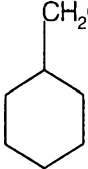
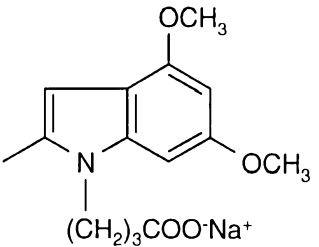
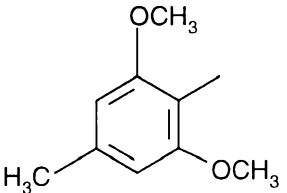
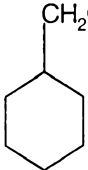
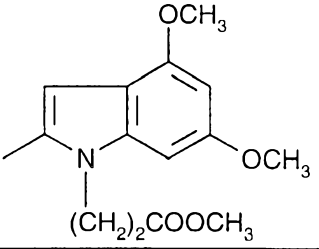
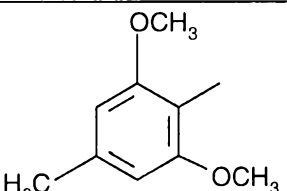
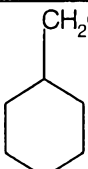
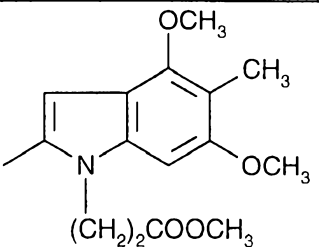
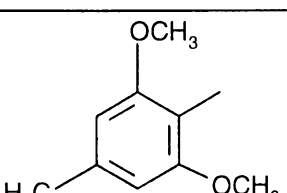
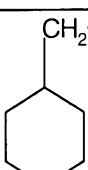
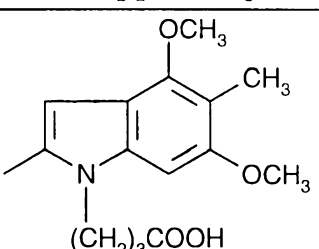
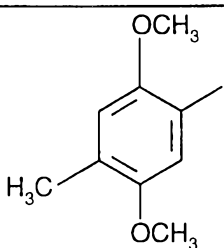
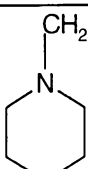
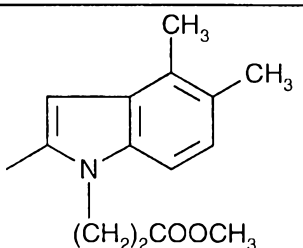
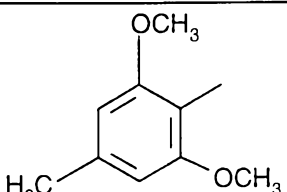
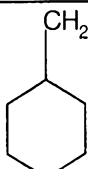
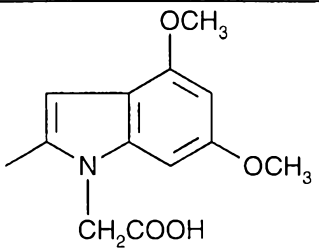
EXEMPLE N°		R ₁		F ; °C (sel)
305				262 (sel de Na)
306				169
307				103
308				242
309				104
310				235 (HCl)

TABLEAU VII (suite 35)

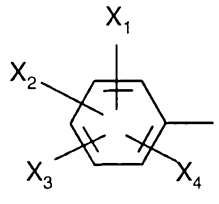
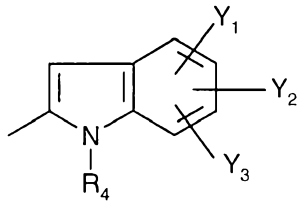
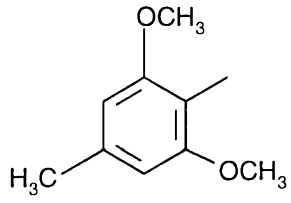
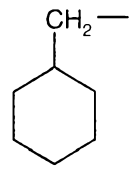
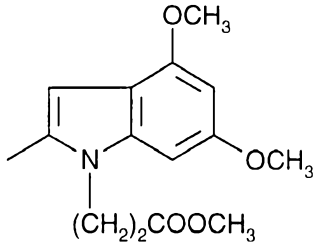
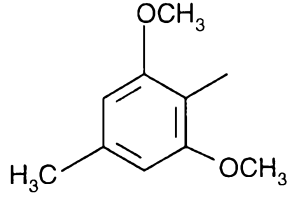
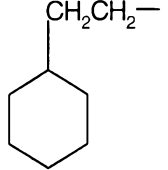
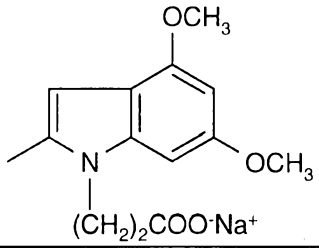
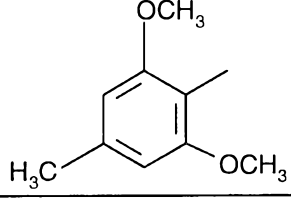
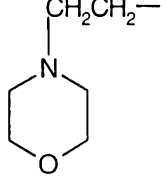
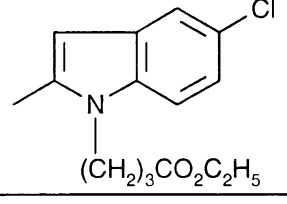
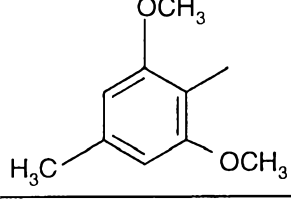
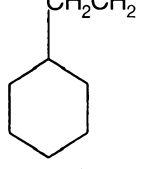
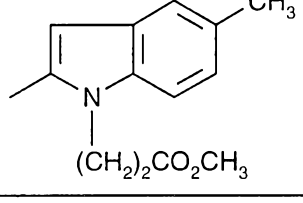
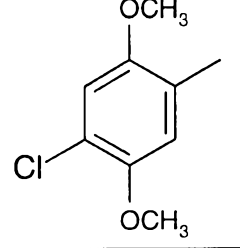
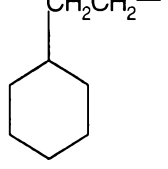
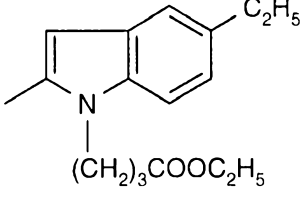
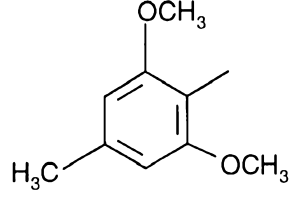
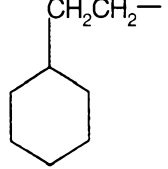
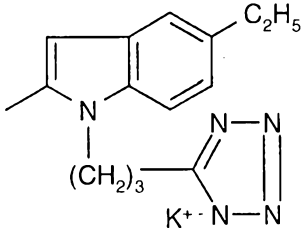
EXEMPLE N°		R ₁		F ; °C (sel)
311				196
312				259 (sel de Na)
313				130
314				92
315				170
316				187 (sel de K)

TABLEAU VII (suite 36)

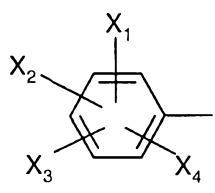
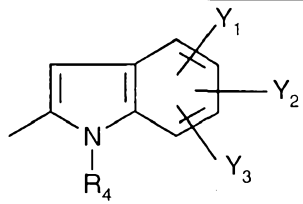
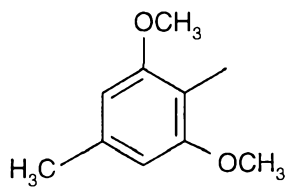
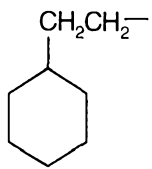
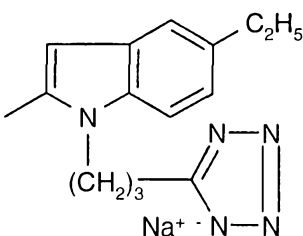
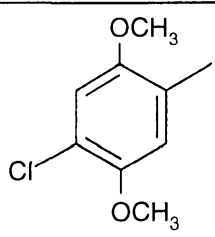
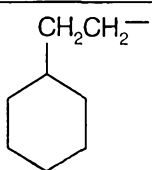
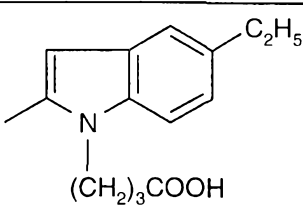
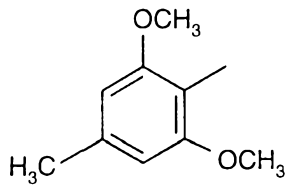
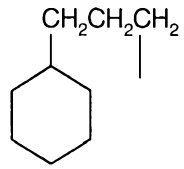
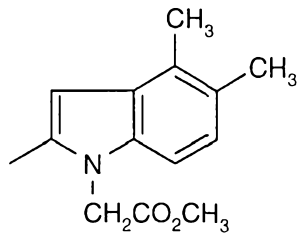
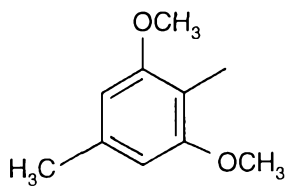
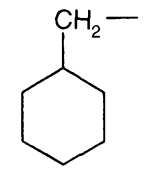
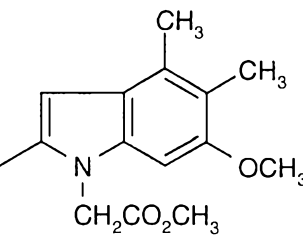
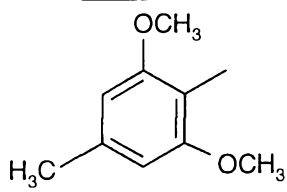
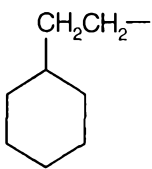
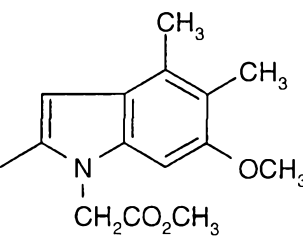
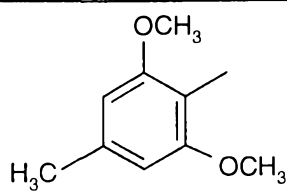
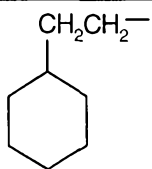
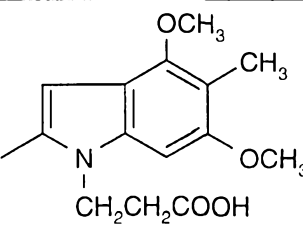
EXEMPLE N°		R ₁		F ; °C (sel)
317				260 (sel de Na)
318				132
319				112
320				258
321				188
322				293

TABLEAU VII (suite 37)

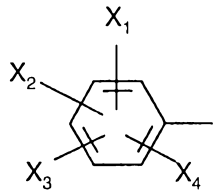
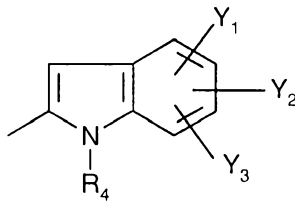
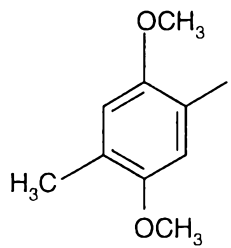
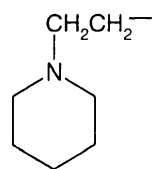
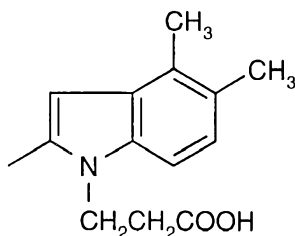
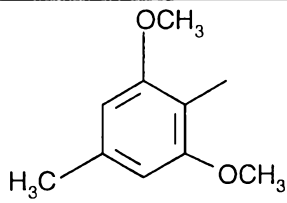
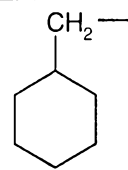
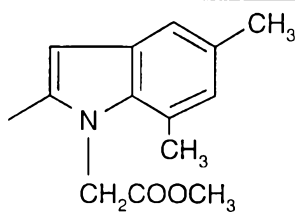
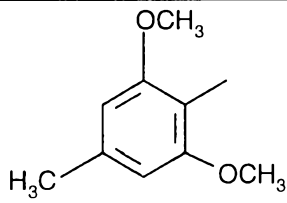
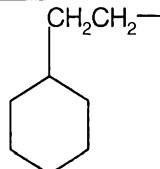
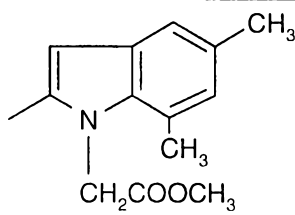
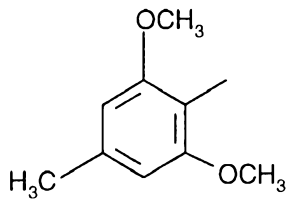
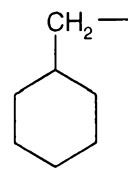
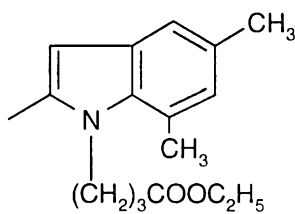
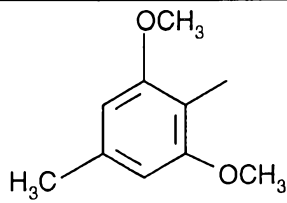
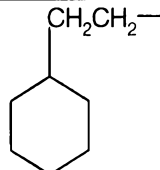
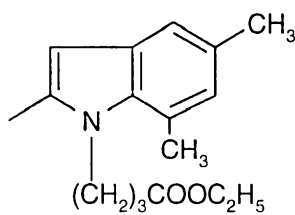
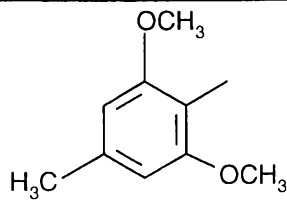
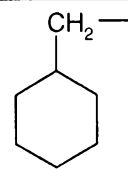
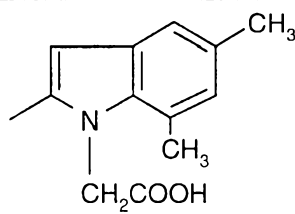
EXEMPLE N°		R ₁		F ; °C (sel)
323				258 2HCl
324				149
325				118
326				97
327				138
328				179

TABLEAU VII (suite 38)

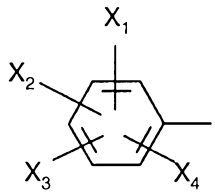
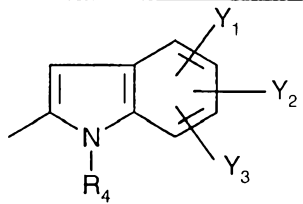
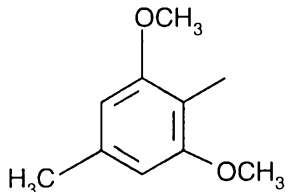
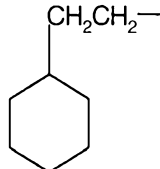
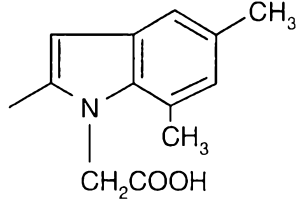
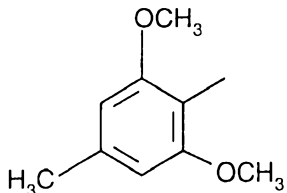
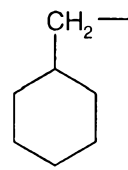
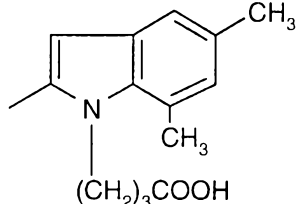
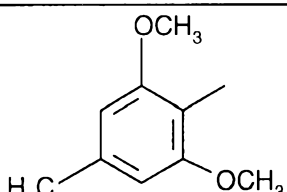
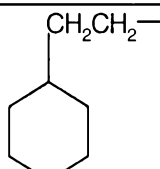
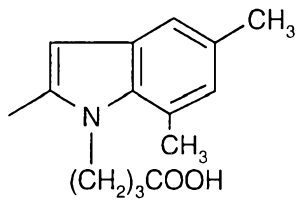
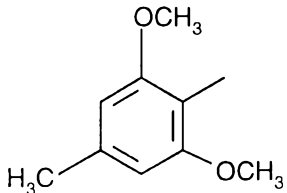
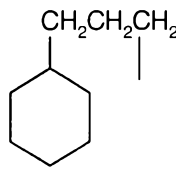
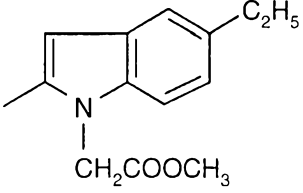
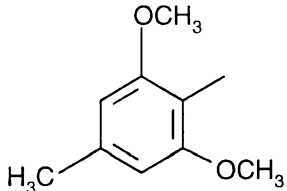
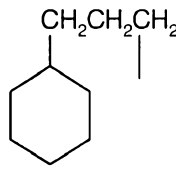
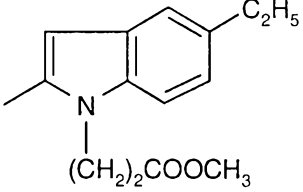
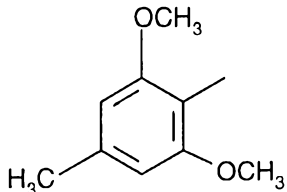
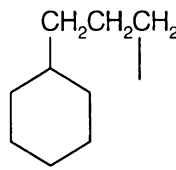
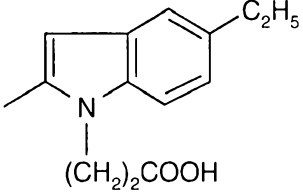
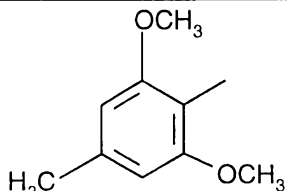
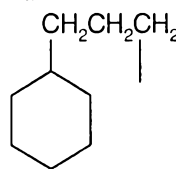
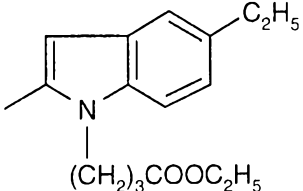
EXEMPLE N°		R ₁		F ; °C (sel)
329				189
330				200
331				151
332				119
333				102
334				143
335				135

TABLEAU VII (suite 39)

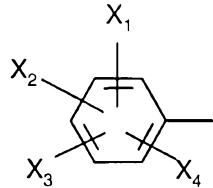
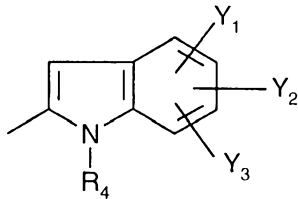
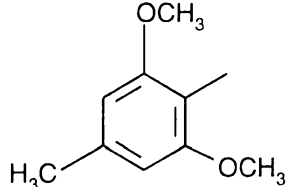
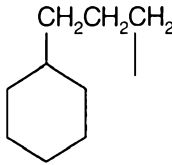
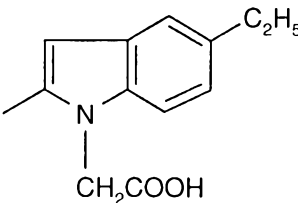
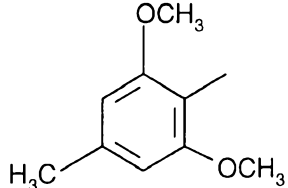
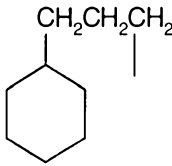
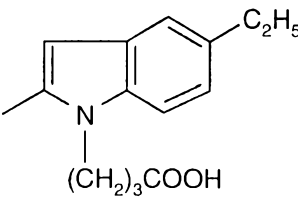
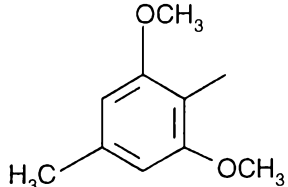
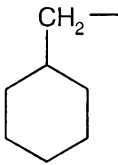
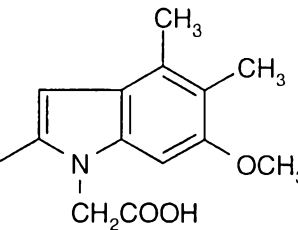
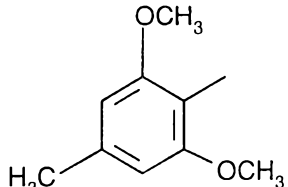
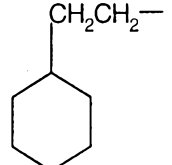
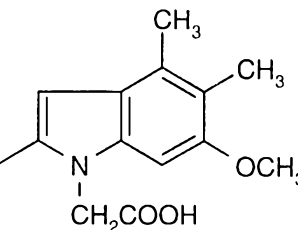
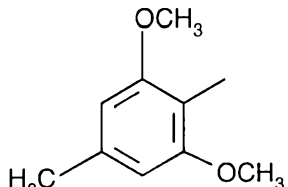
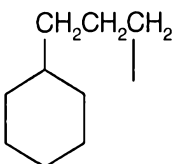
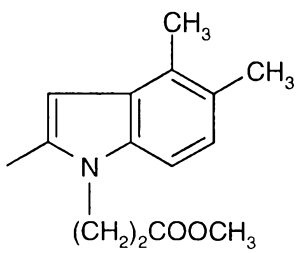
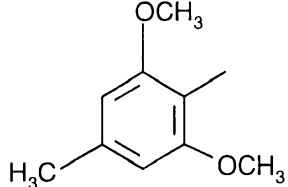
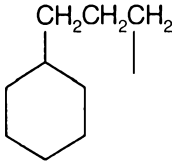
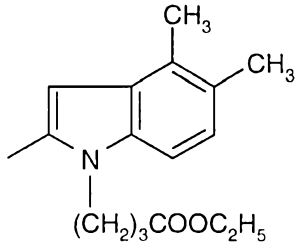
EXEMPLE N°		R ₁		F ; °C (sel)
336				151
337				138
338				195 (HCl)
339				185
340				116
341				98

TABLEAU VII (suite 40)

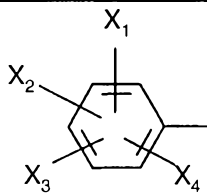
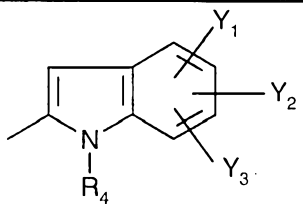
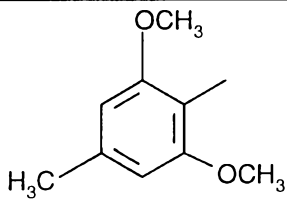
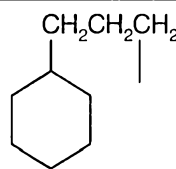
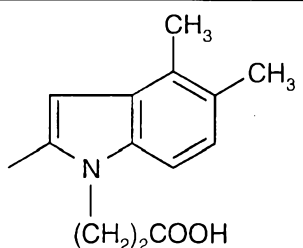
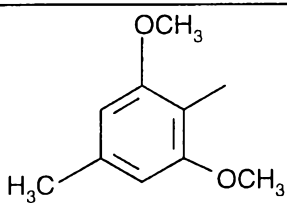
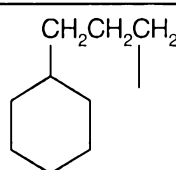
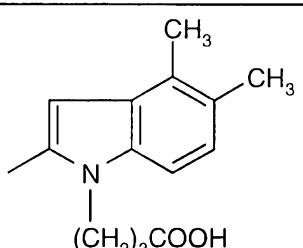
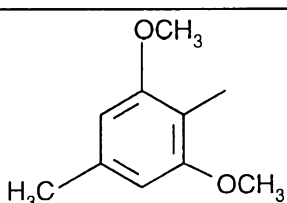
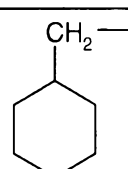
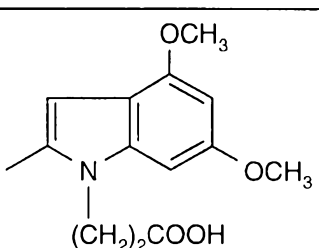
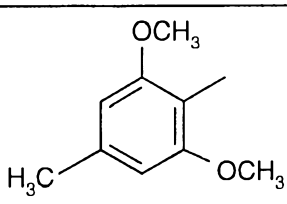
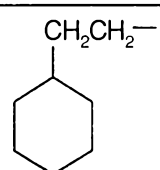
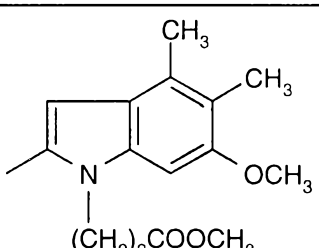
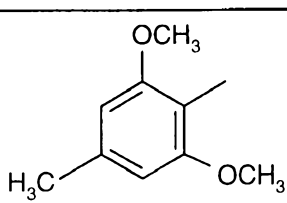
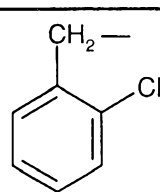
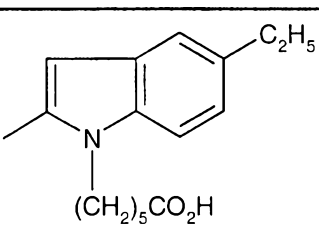
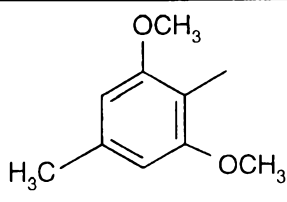
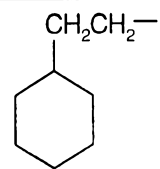
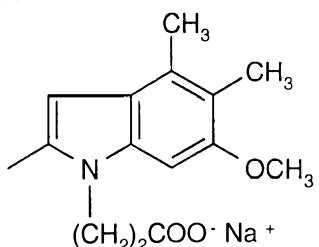
EXEMPLE N°		R ₁		F ; °C (sel)
342				149
343				146
344				273 (HCl)
345				202
346				167
347				279 (Sel de Na)

TABLEAU VII (suite 41)

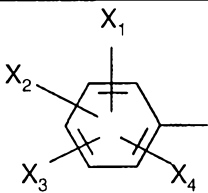
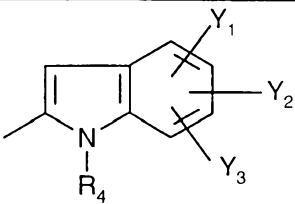
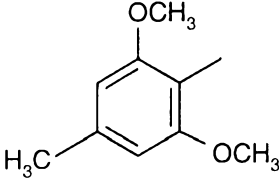
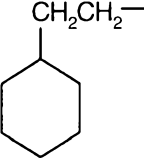
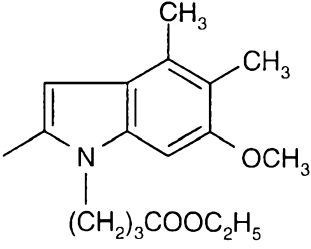
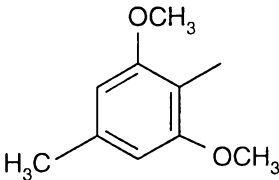
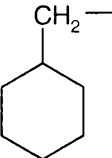
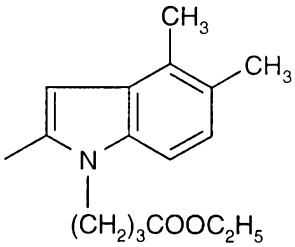
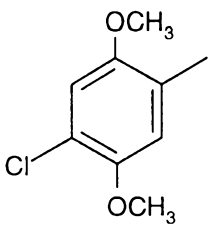
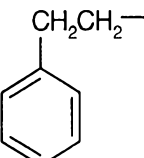
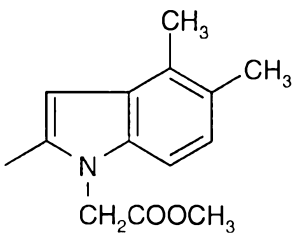
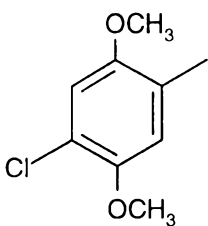
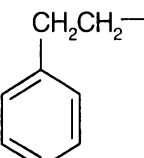
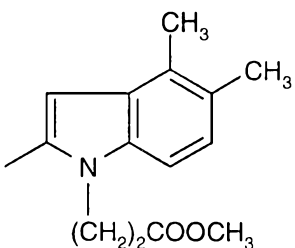
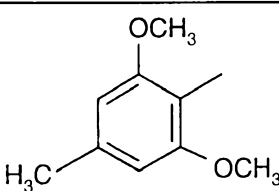
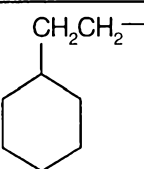
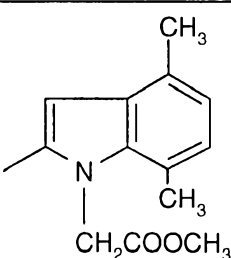
EXEMPLE N°		R ₁		F ; °C (sel)
348				80
349				134
350				130
351				122
352				99

TABLEAU VII (suite 42)

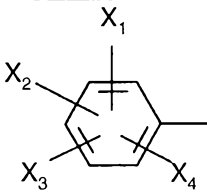
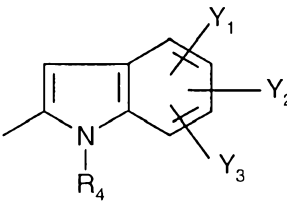
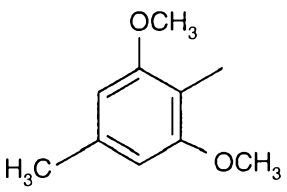
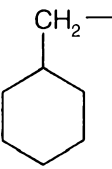
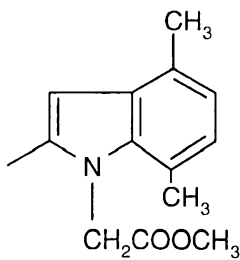
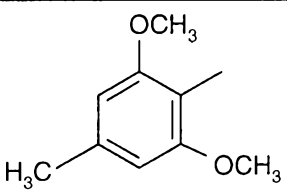
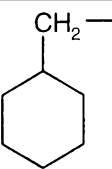
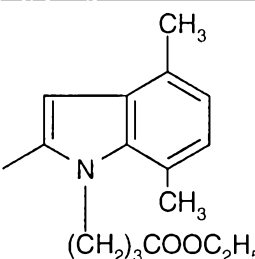
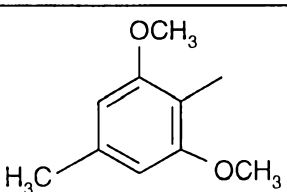
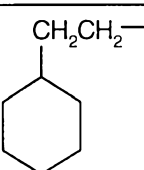
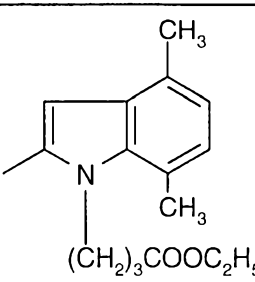
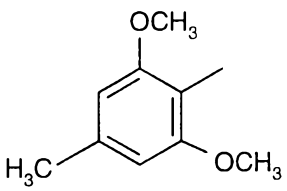
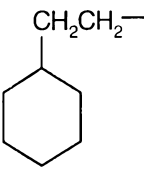
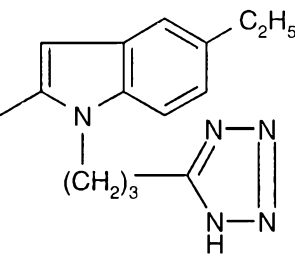
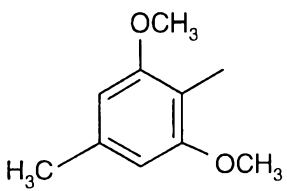
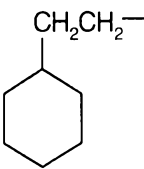
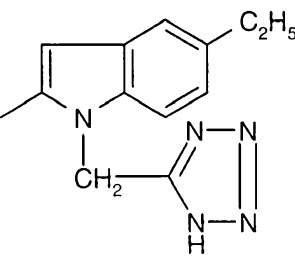
EXEMPLE N°		R ₁		F ; °C (sel)
353				218
354				96
355				168
356				248
357				196

TABLEAU VII (suite 43)

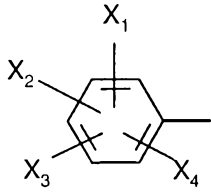
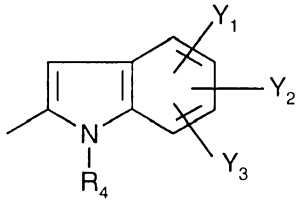
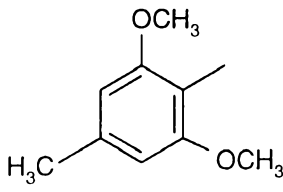
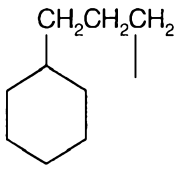
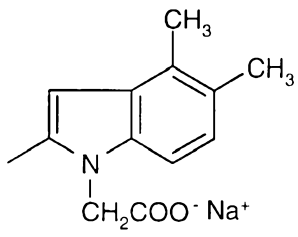
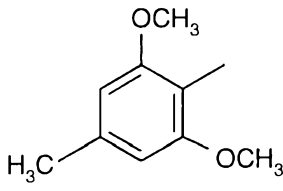
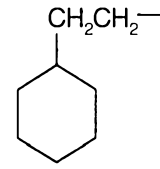
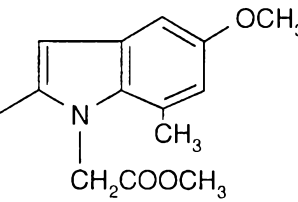
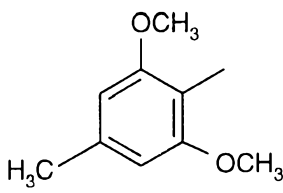
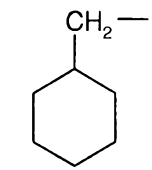
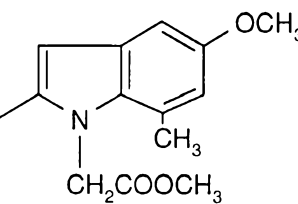
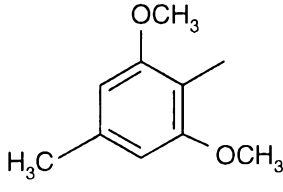
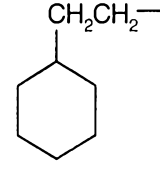
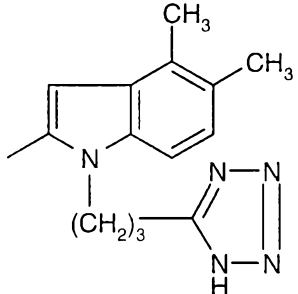
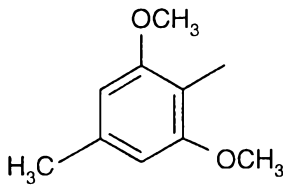
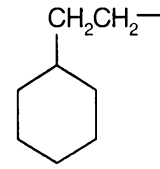
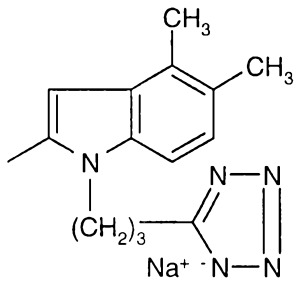
EXEMPLE N°		R ₁		F ; °C (sel)
358				174 (Sel de Na)
359				198
360				186
361				233
362				216 (Sel de Na)

TABLEAU VII (suite 44)

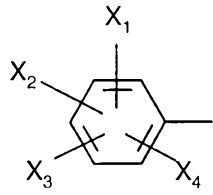
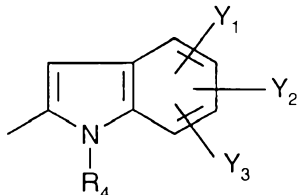
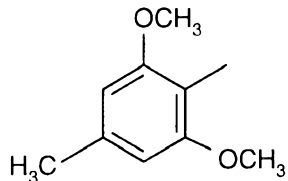
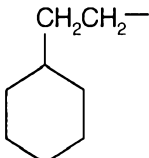
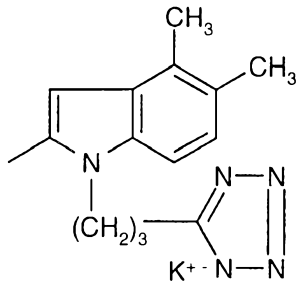
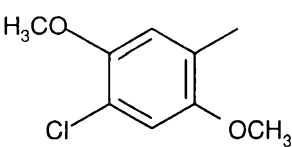
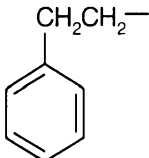
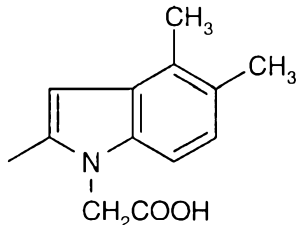
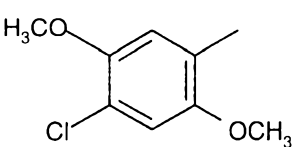
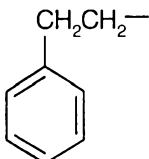
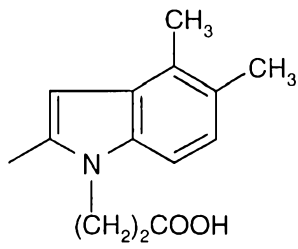
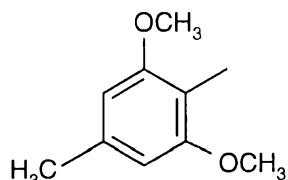
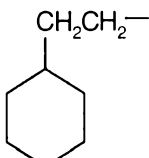
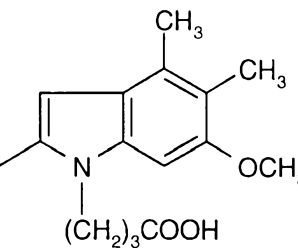
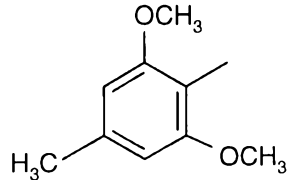
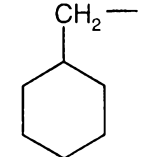
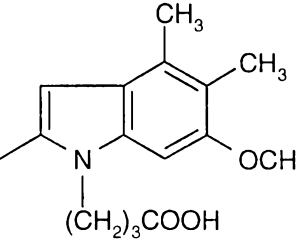
EXEMPLE N°		R ₁		F ; °C (sel)
363				191 (Sel de K)
364				240
365				198
366				247 (HCl)
367				185 (HCl)

TABLEAU VII (suite 45)

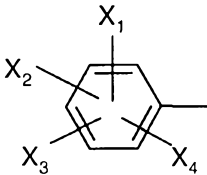
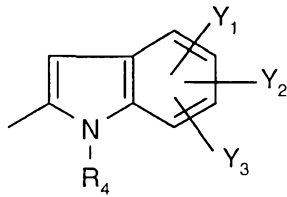
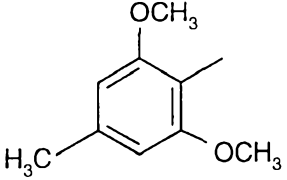
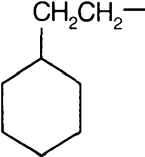
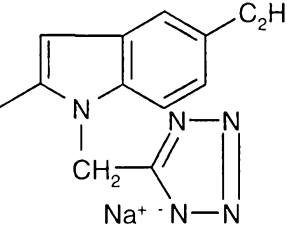
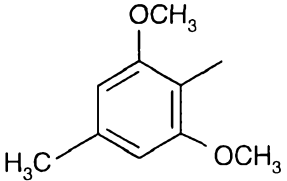
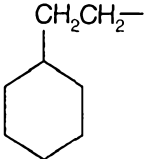
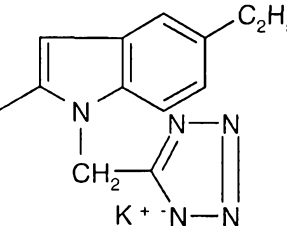
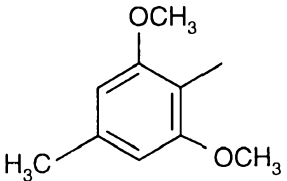
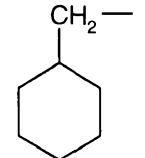
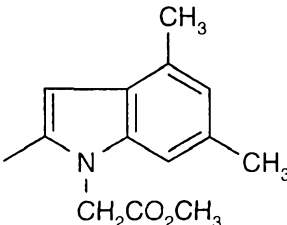
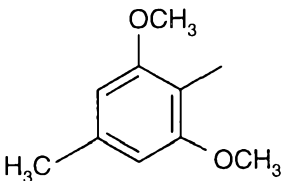
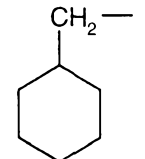
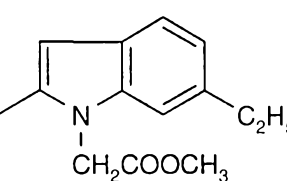
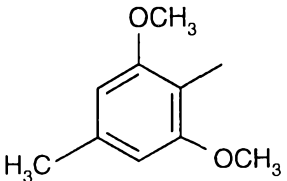
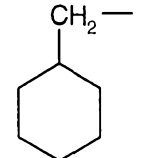
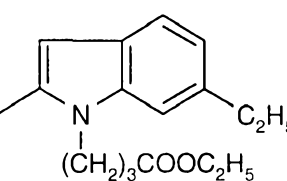
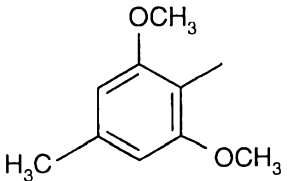
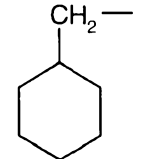
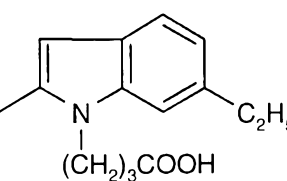
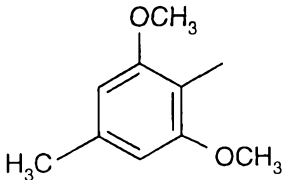
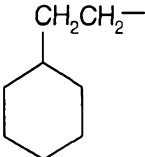
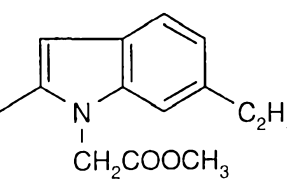
EXEMPLE N°		R ₁		F ; °C (sel)
368				165 (Sel de Na)
369				175 (Sel de K)
370				226
371				204
372				74
373				147
374				194

TABLEAU VII (suite 46)

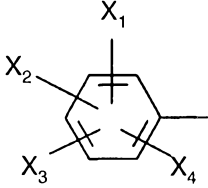
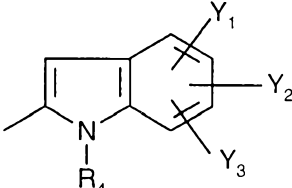
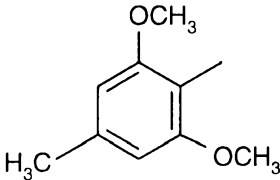
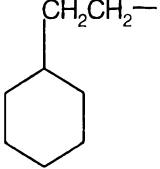
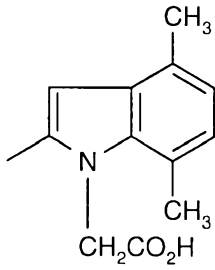
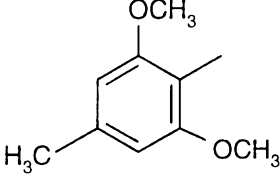
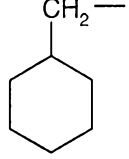
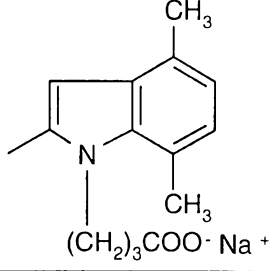
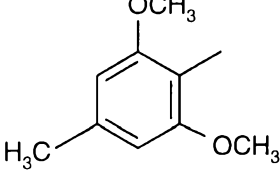
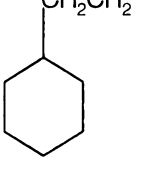
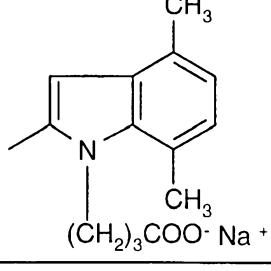
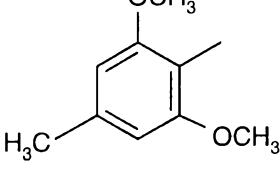
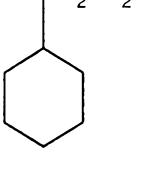
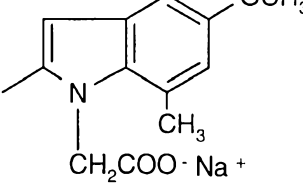
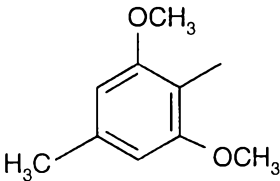
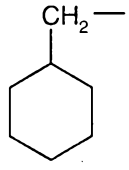
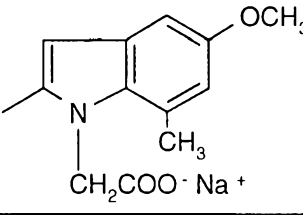
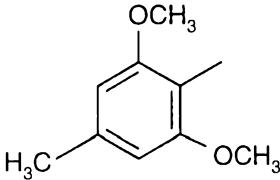
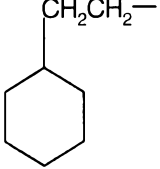
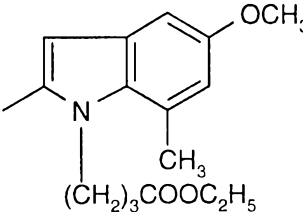
EXEMPLE N°		R ₁		F ; °C (sel)
375				199
376				214 (HCl et Sel de Na)
377				147 (HCl et Sel de Na)
378				156 (Sel de Na)
379				219 (Sel de Na)
380				131

TABLEAU VII (suite 47)

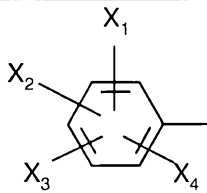
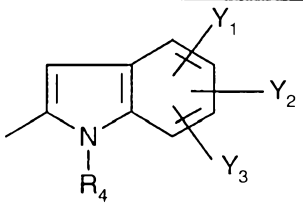
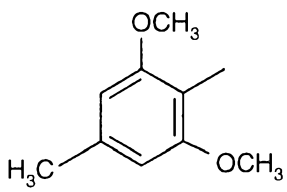
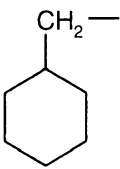
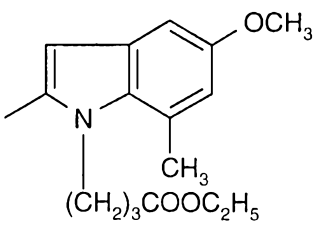
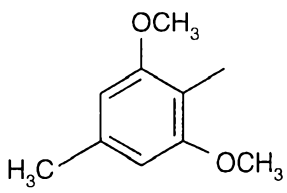
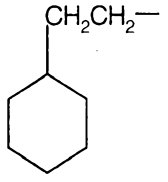
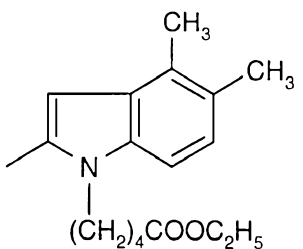
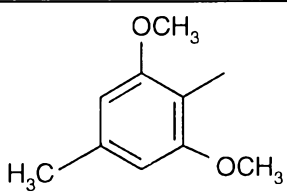
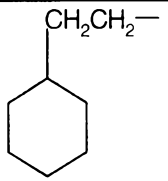
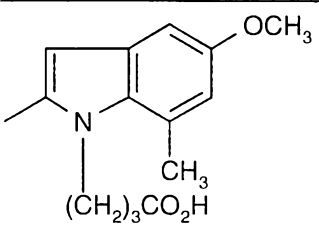
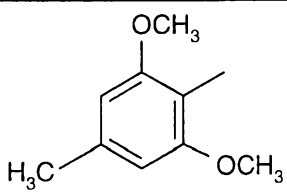
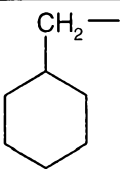
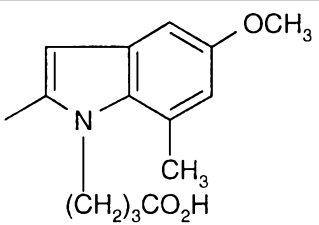
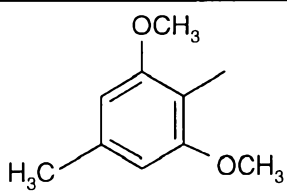
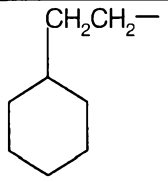
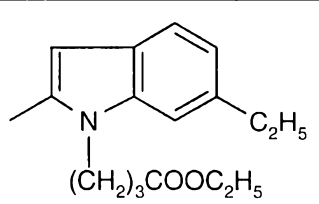
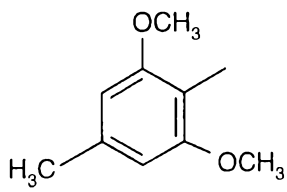
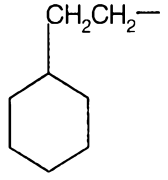
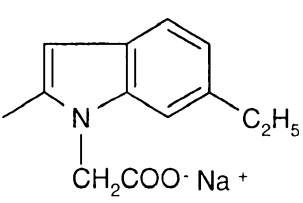
EXEMPLE N°		R ₁		F ; °C (sel)
381				148
382				85
383				141
384				161
385				151
386				268 (Sel de Na)

TABLEAU VII (suite 48)

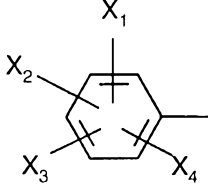
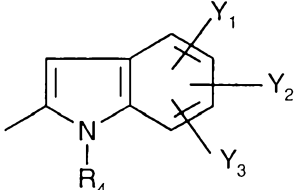
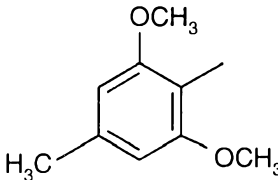
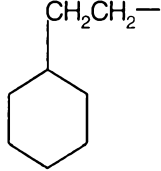
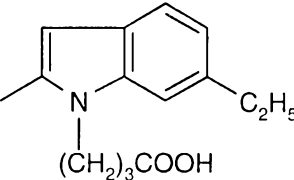
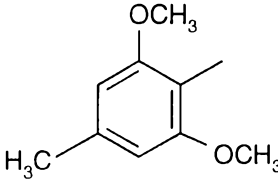
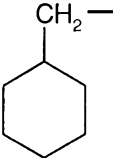
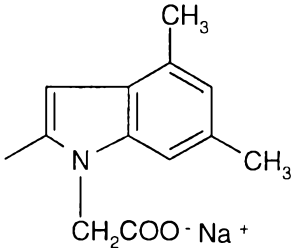
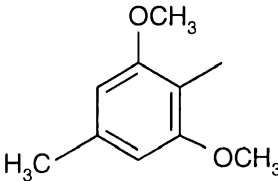
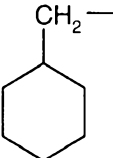
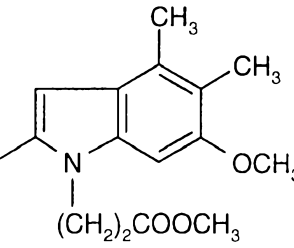
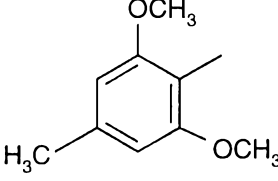
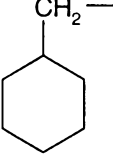
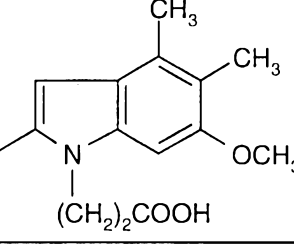
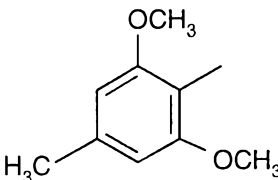
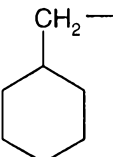
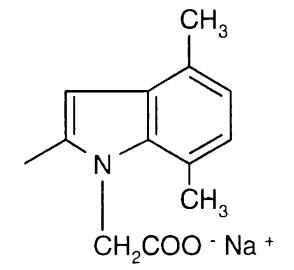
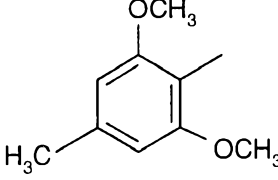
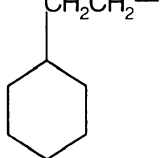
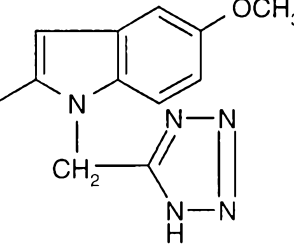
EXEMPLE N°		R ₁		F ; °C (sel)
387				155
388				195 (Sel de Na)
389				214
390				293 (HCl)
391				271
392				177

TABLEAU VII (suite 49)

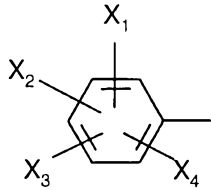
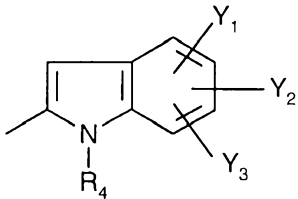
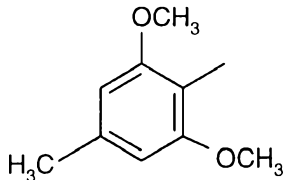
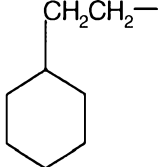
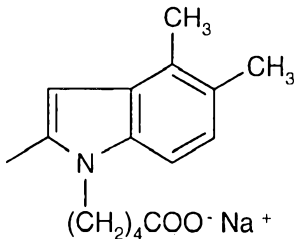
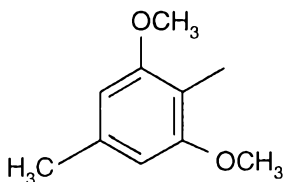
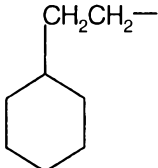
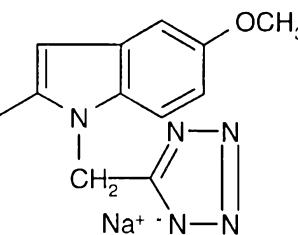
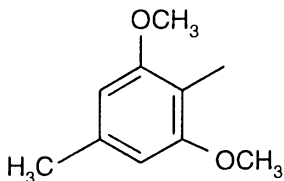
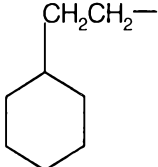
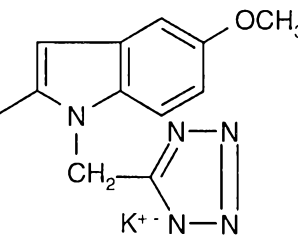
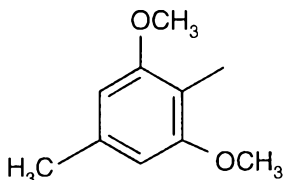
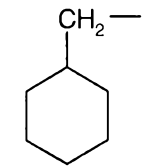
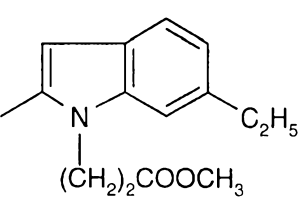
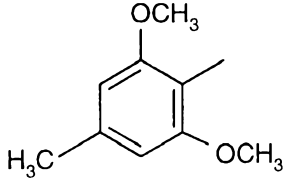
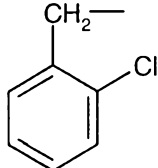
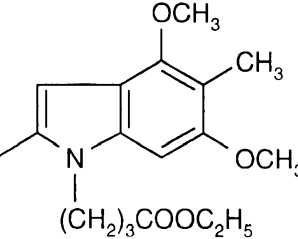
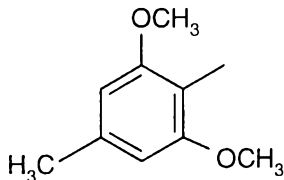
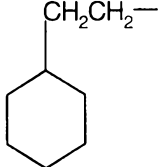
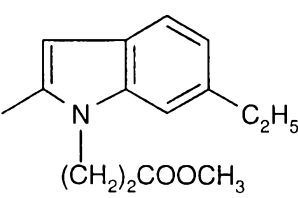
EXEMPLE N°		R ₁		F ; °C (sel)
393				264 (Sel de Na)
394				281 (Sel de Na)
395				257 (Sel de K)
396				107
397				124
398				166

TABLEAU VII (suite 50)

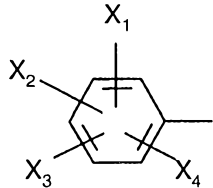
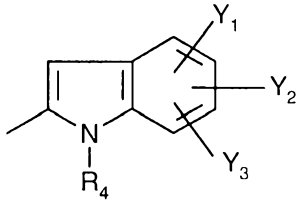
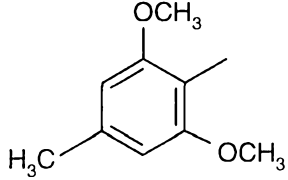
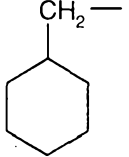
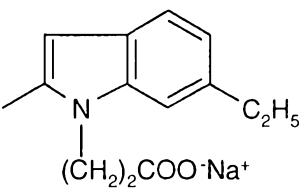
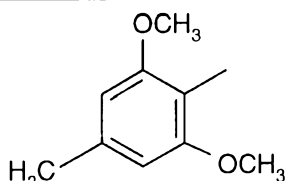
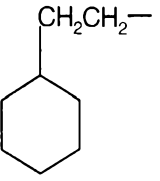
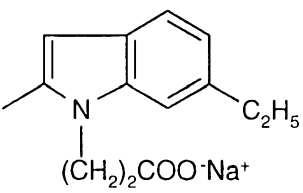
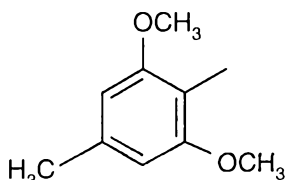
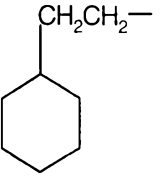
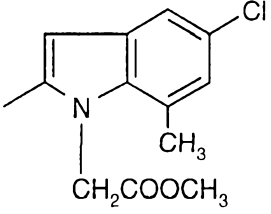
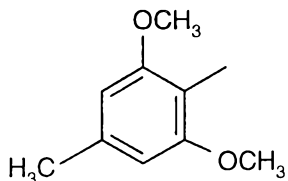
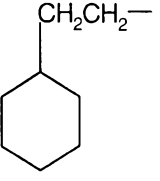
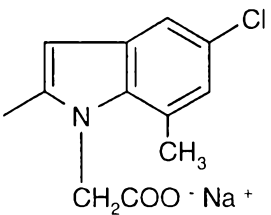
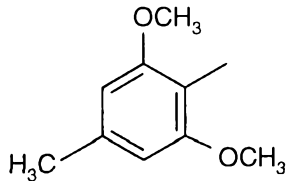
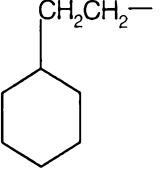
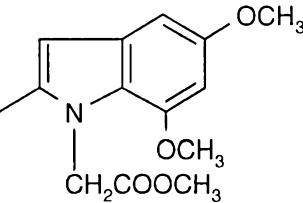
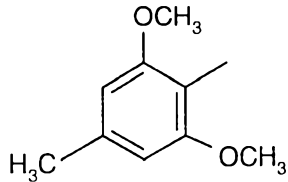
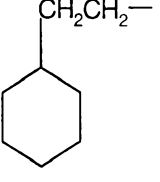
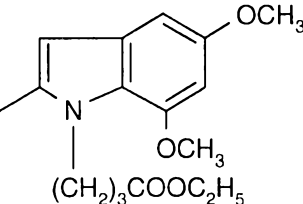
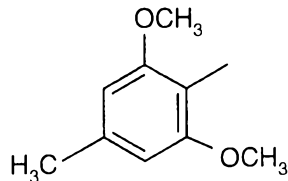
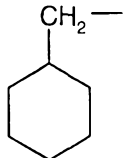
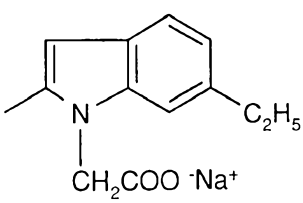
EXEMPLE N°		R ₁		F ; °C (sel)
399				220 (Sel de Na)
400				246
401				202
402				266 (Sel de Na)
403				128
404				144
405				224 (Sel de Na)

TABLEAU VII (suite 51)

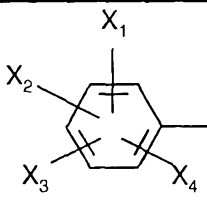
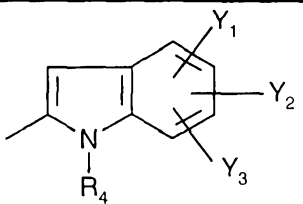
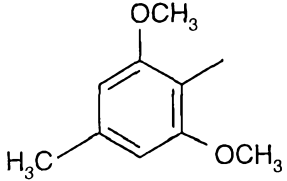
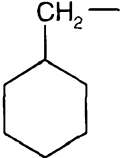
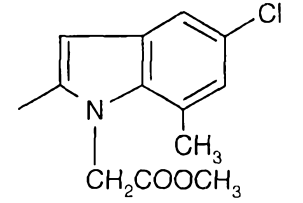
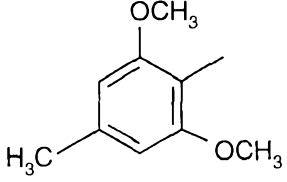
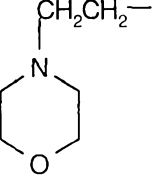
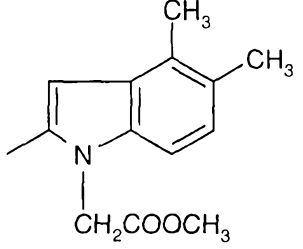
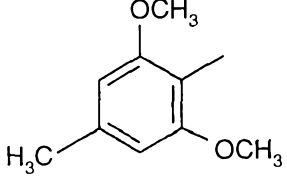
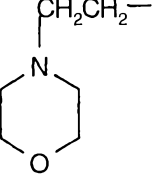
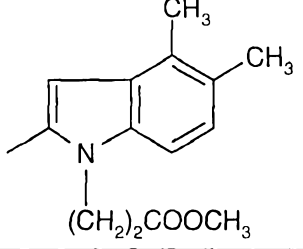
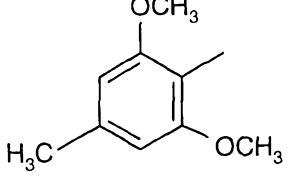
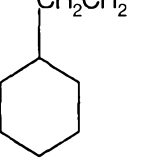
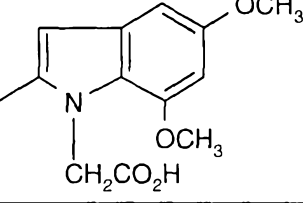
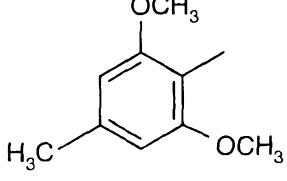
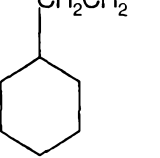
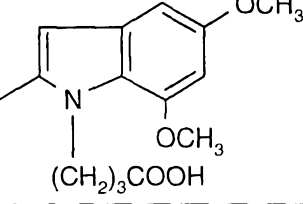
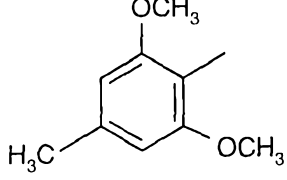
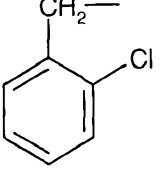
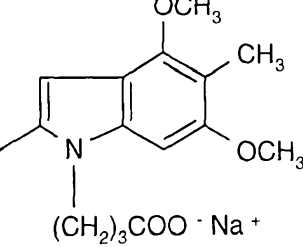
EXEMPLE N°		R ₁		F ; °C (sel)
406				158
407				117
408				134
409				185 (HCl)
410				144 (HCl)
411				178 (Sel de Na)

TABLEAU VII (suite 52)

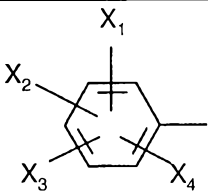
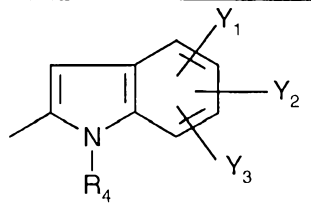
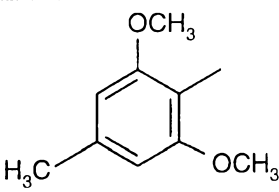
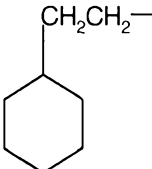
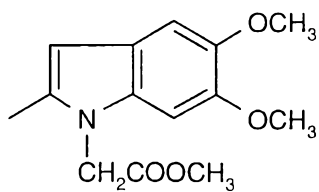
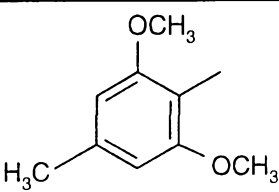
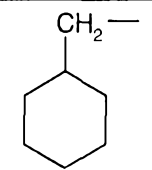
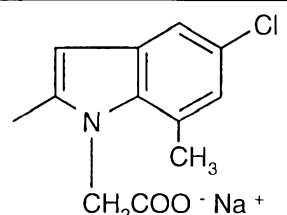
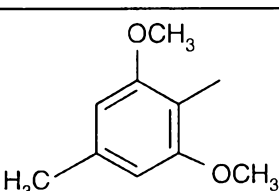
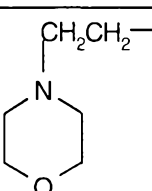
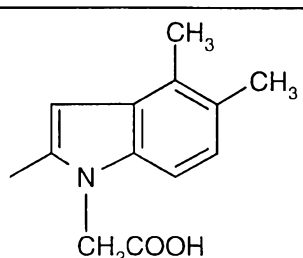
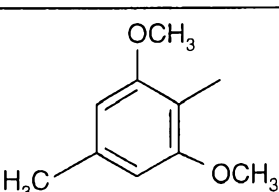
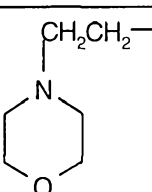
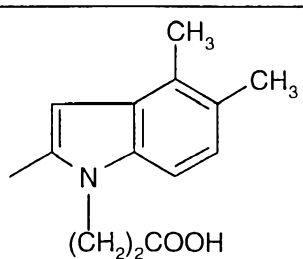
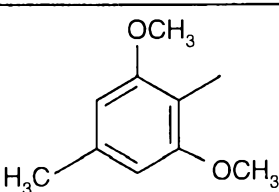
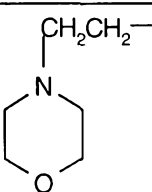
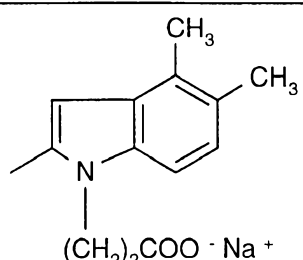
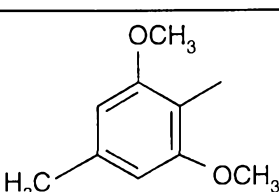
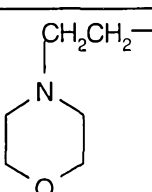
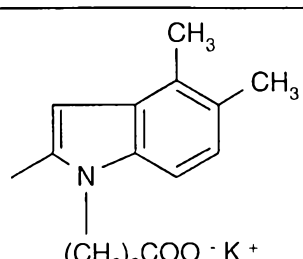
EXEMPLE N°		R ₁		F ; °C (sel)
412				207
413				191 (Sel de Na)
414				228 (2HCl)
415				203 (2HCl)
416				290 (Sel de Na)
417				257 (Sel de K)

TABLEAU VII (suite 53)

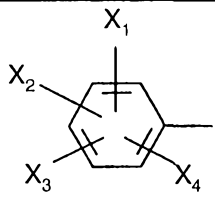
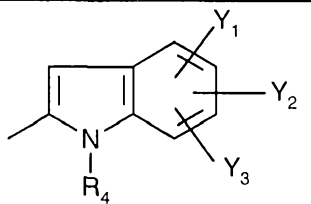
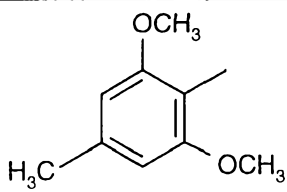
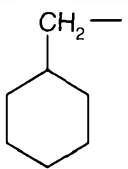
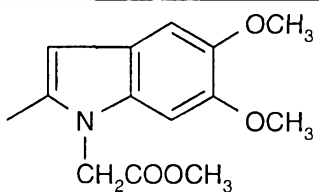
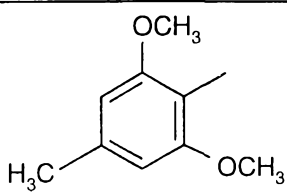
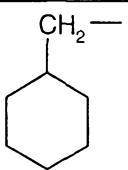
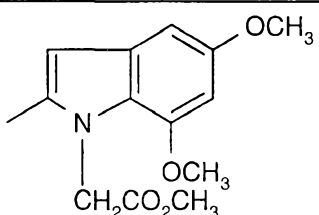
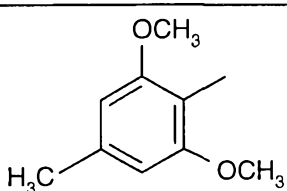
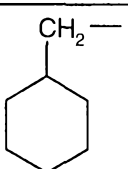
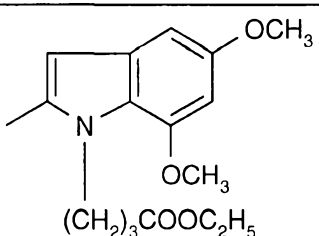
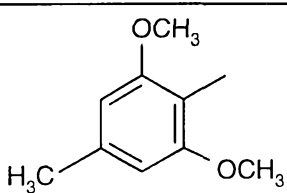
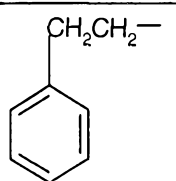
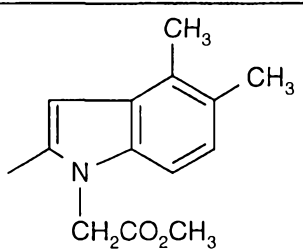
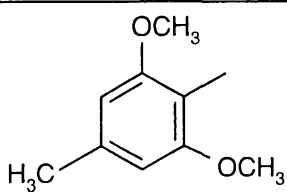
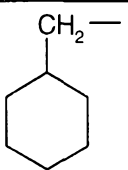
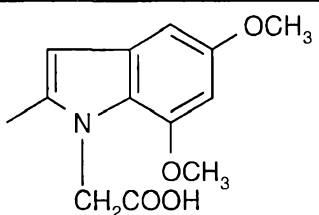
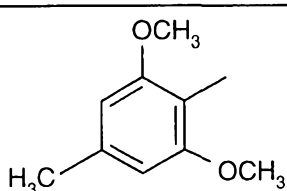
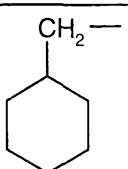
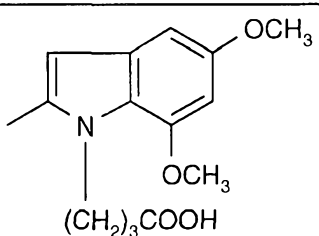
EXEMPLE N°		R ₁		F ; °C (sel)
418				228
419				217
420				168
421				113
422				201 (HCl)
423				146 (HCl)

TABLEAU VII (suite 54)

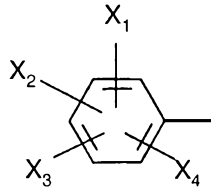
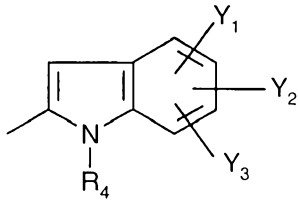
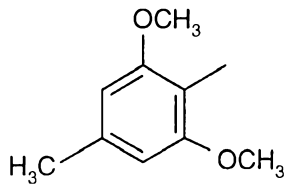
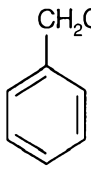
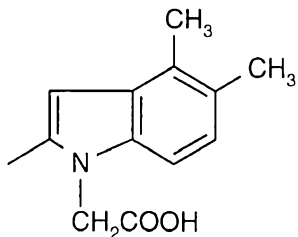
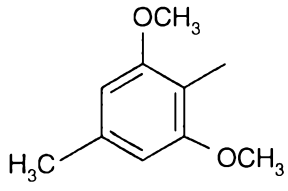
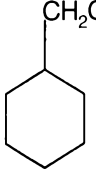
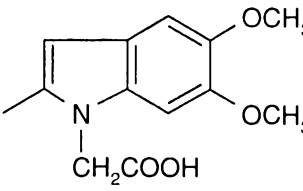
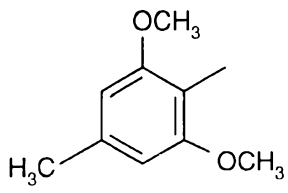
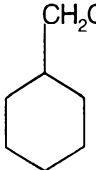
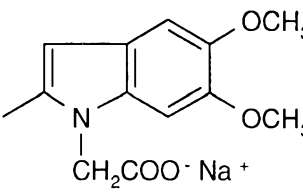
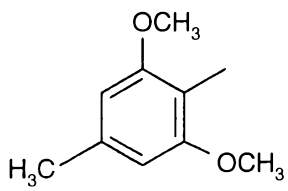
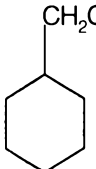
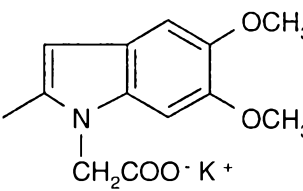
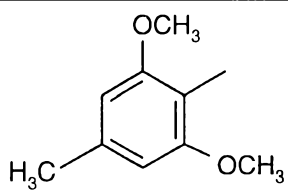
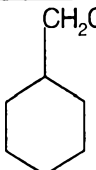
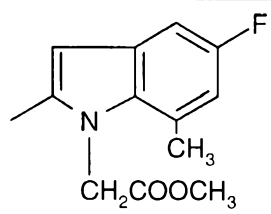
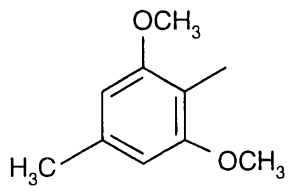
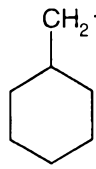
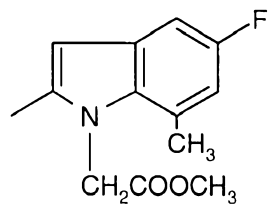
EXEMPLE N°		R ₁		F ; °C (sel)
424				198 (HCl)
425				167
426				244 (Sel de Na)
427				245 (Sel de K)
428				151
429				157

TABLEAU VII (suite 55)

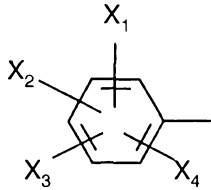
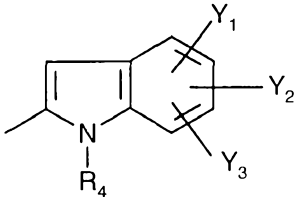
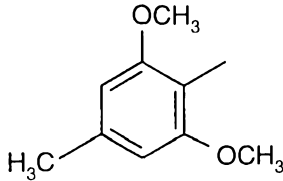
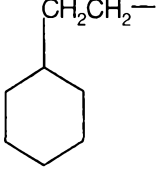
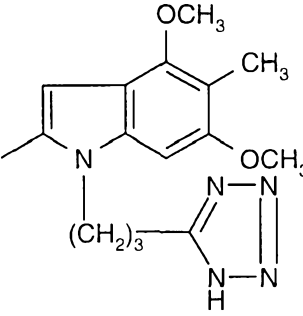
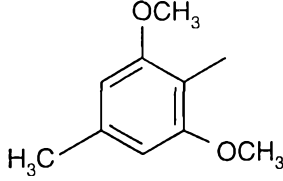
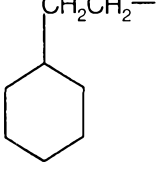
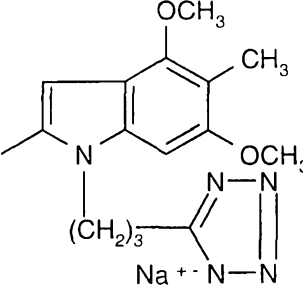
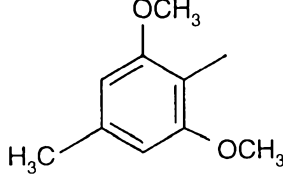
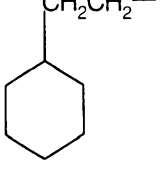
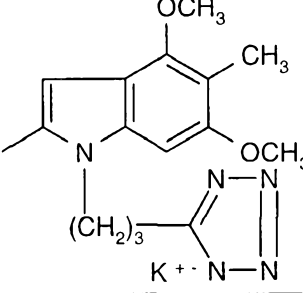
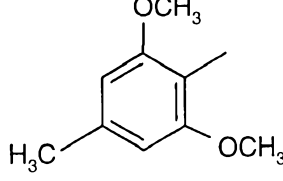
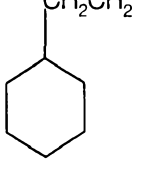
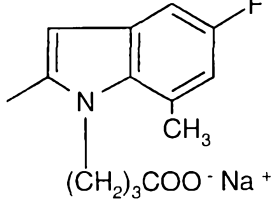
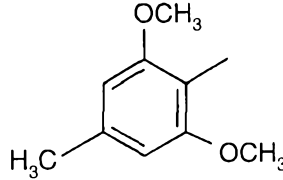
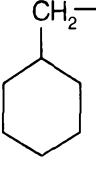
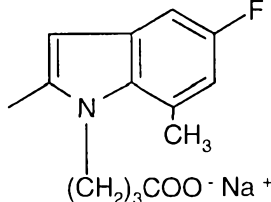
EXEMPLE N°		R_1		F ; °C (sel)
430				205
431				248 (Sel de Na)
432				240 (Sel de Na)
433				144 (Sel de Na)
434				220 (Sel de Na)

TABLEAU VII (suite 56)

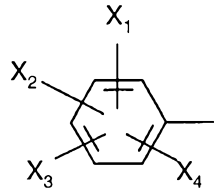
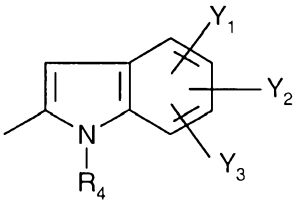
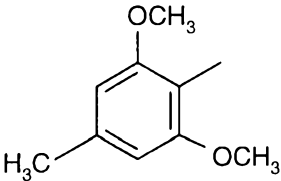
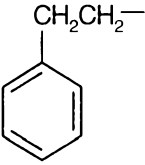
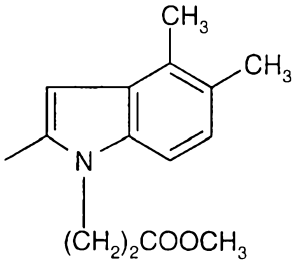
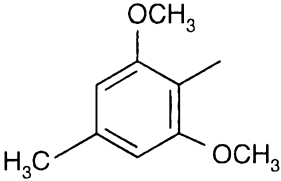
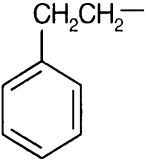
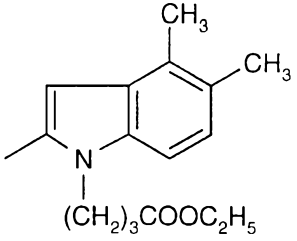
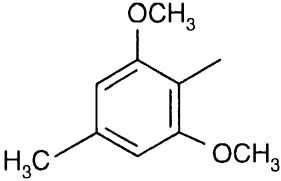
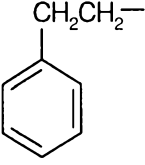
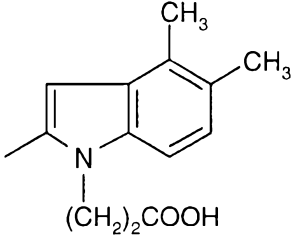
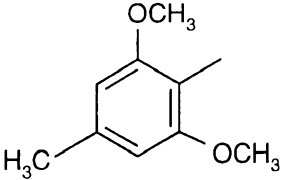
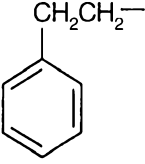
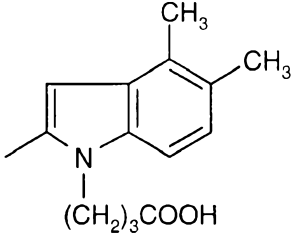
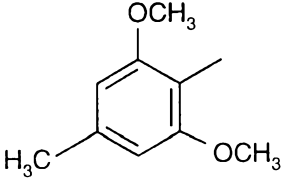
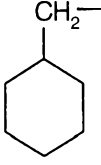
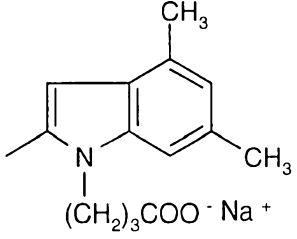
EXEMPLE N°		R ₁		F ; °C (sel)
435				108
436				77
437				270 (HCl)
438				278 (HCl)
439				179 (Sel de Na)

TABLEAU VII (suite 57)

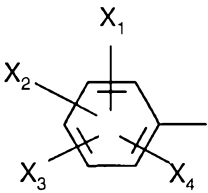
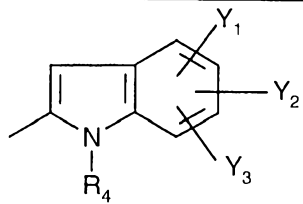
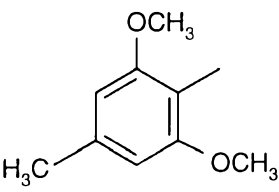
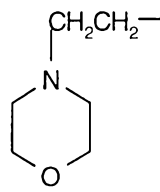
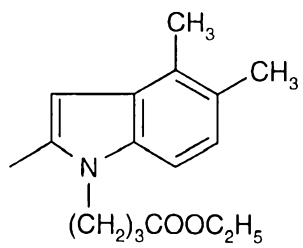
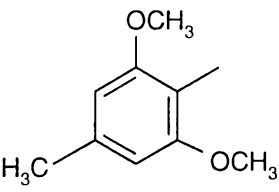
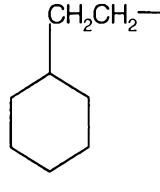
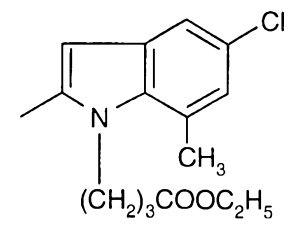
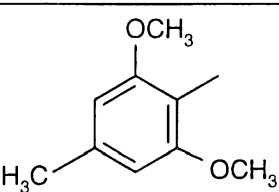
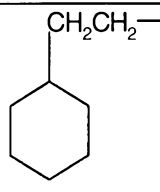
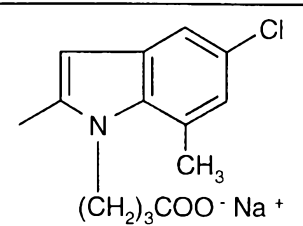
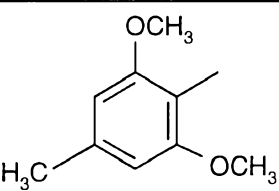
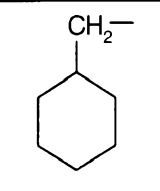
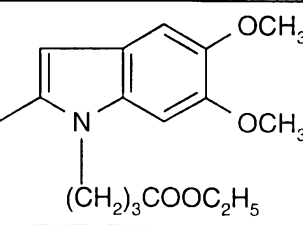
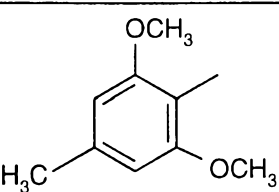
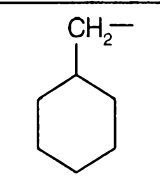
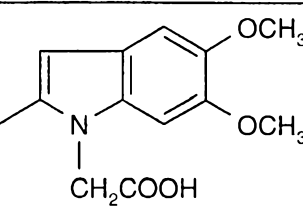
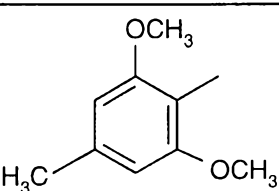
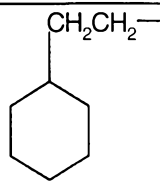
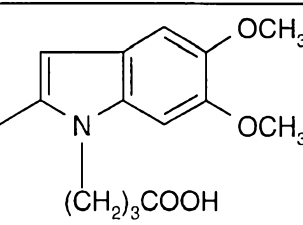
EXEMPLE N°		R ₁		F ; °C (sel)
440				167 (HCl)
441				164
442				150 (Sel de Na)
443				113
444				185
445				209

TABLEAU VII (suite 58)

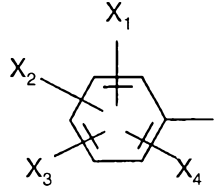
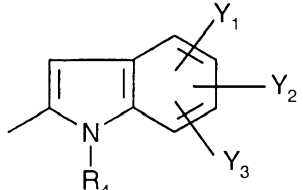
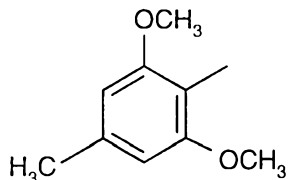
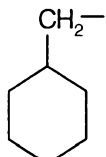
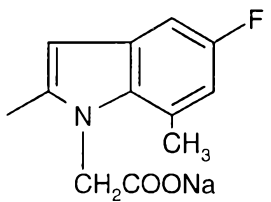
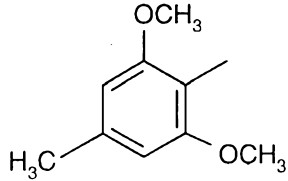
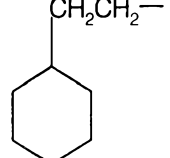
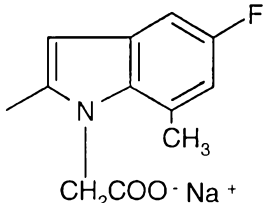
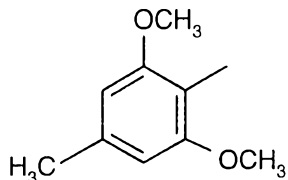
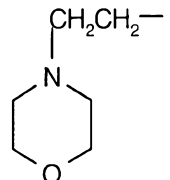
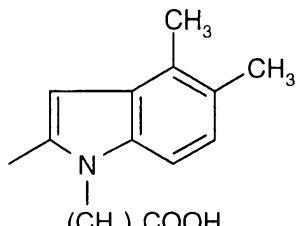
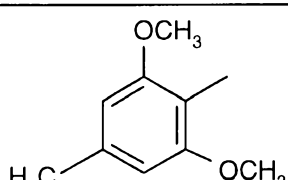
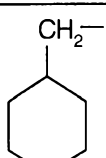
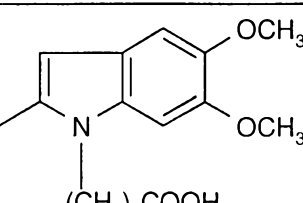
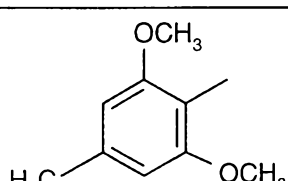
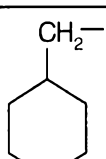
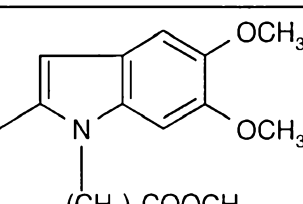
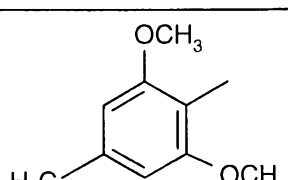
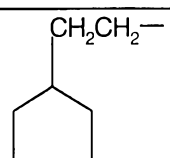
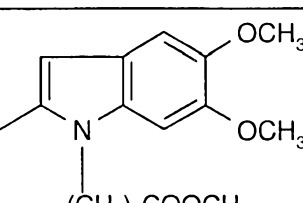
EXEMPLE N°		R ₁		F ; °C (sel)
446				296 (Sel de Na)
447				221 (Sel de Na)
448				190
449				246
450				196
451				139

TABLEAU VII (suite 59)

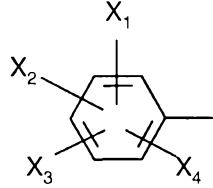
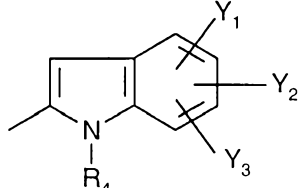
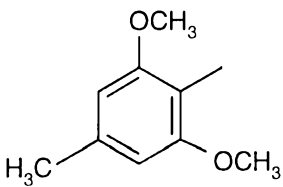
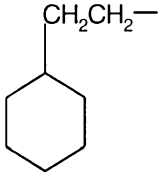
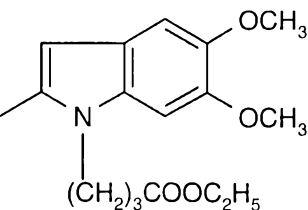
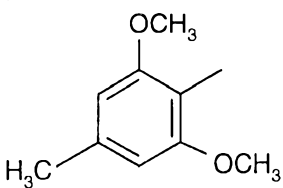
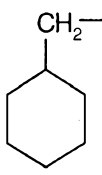
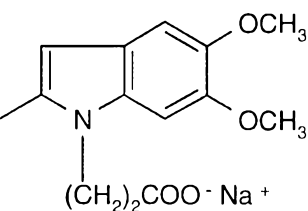
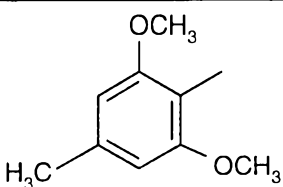
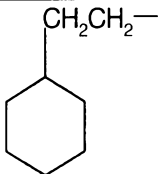
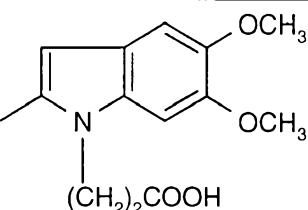
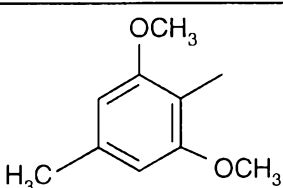
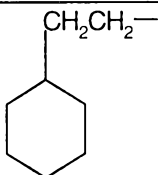
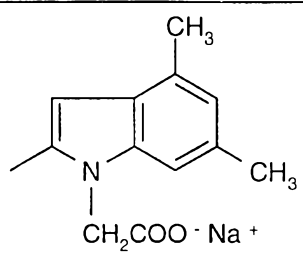
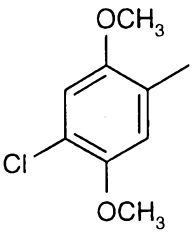
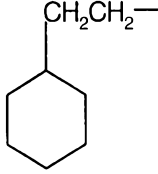
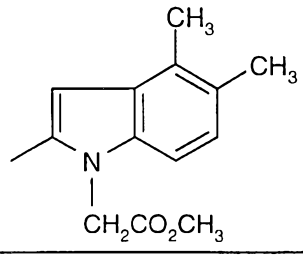
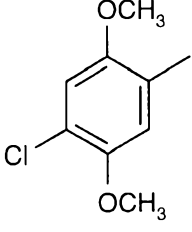
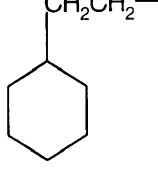
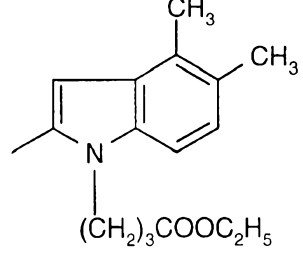
EXEMPLE N°		R ₁		F ; °C (sel)
452				109
453				217 (Sel de Na)
454				245
455				238 (Sel de Na)
456				173
457				169

TABLEAU VII (suite 60)

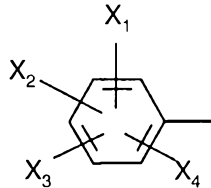
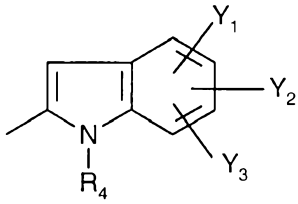
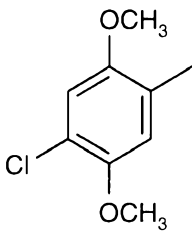
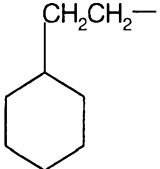
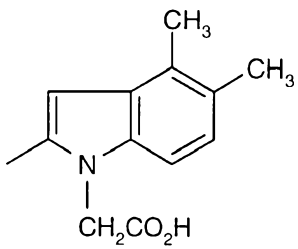
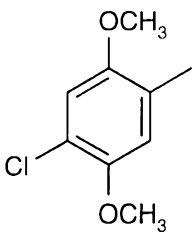
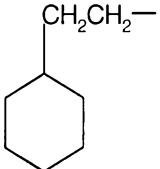
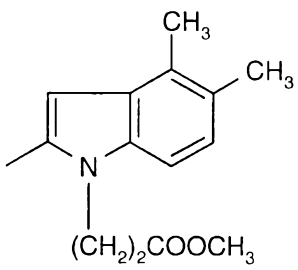
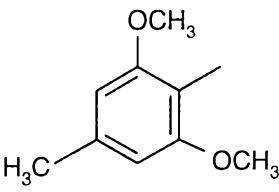
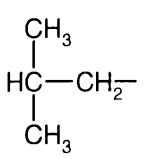
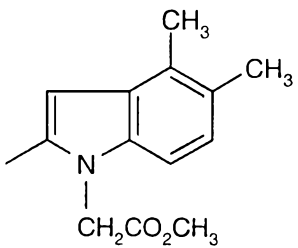
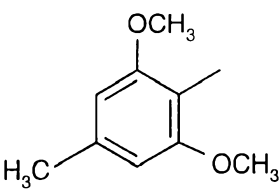
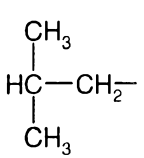
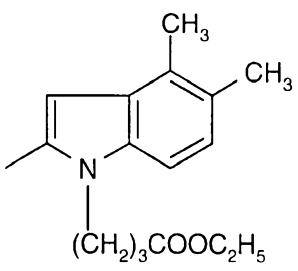
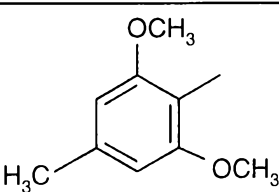
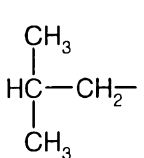
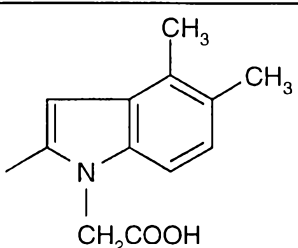
EXEMPLE N°		R ₁		F ; °C (sel)
458				164 (HCl)
459				116
460				243
461				159
462				227

TABLEAU VII (suite 61)

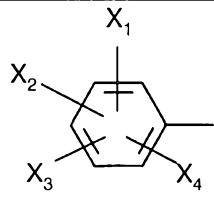
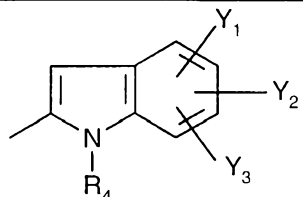
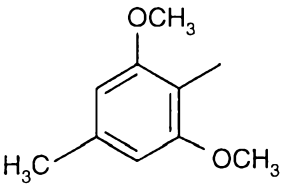
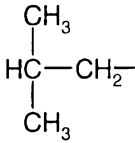
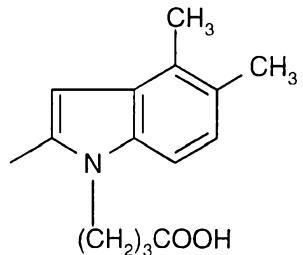
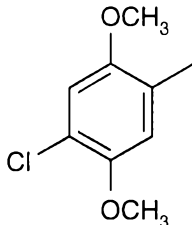
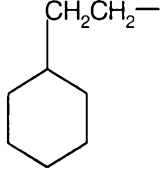
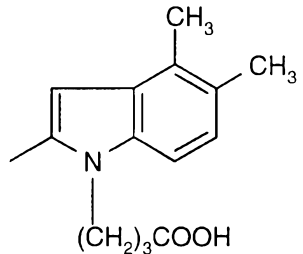
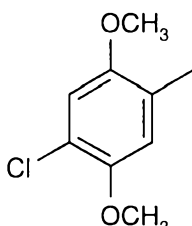
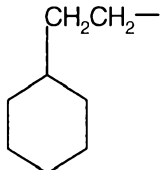
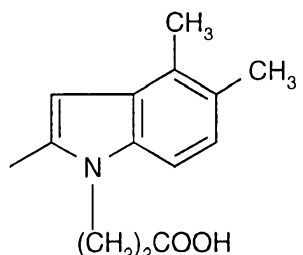
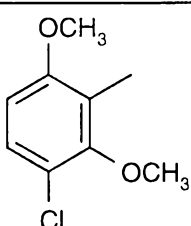
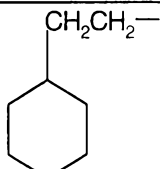
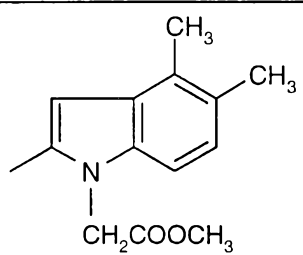
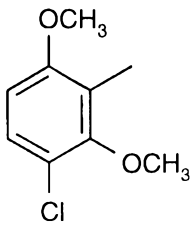
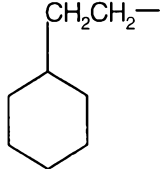
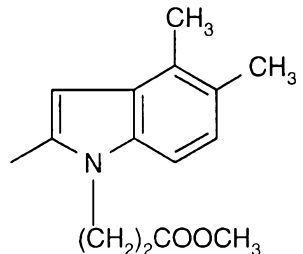
EXEMPLE N°		R ₁		F ; °C (sel)
463				150
464				208 (HCl)
465				254
466				108
467				91

TABLEAU VII (suite 62)

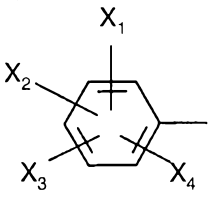
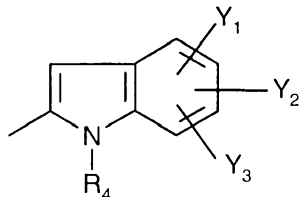
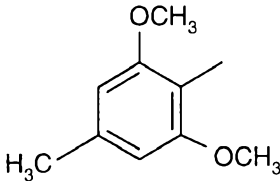
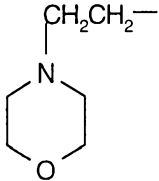
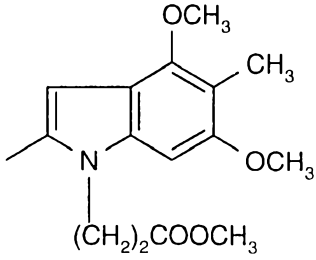
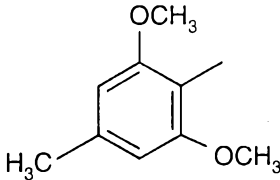
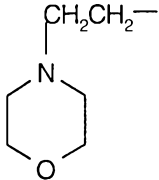
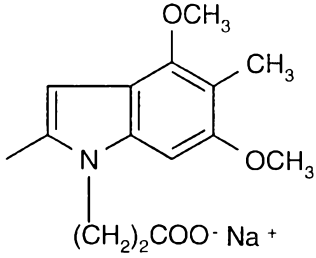
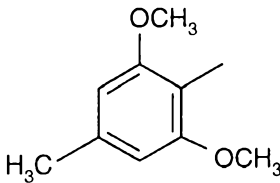
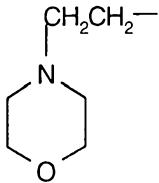
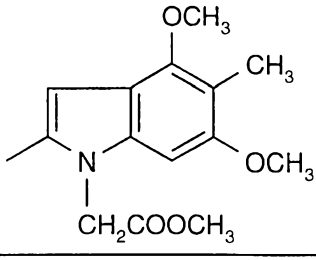
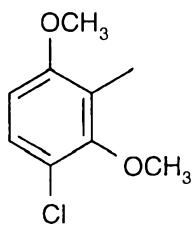
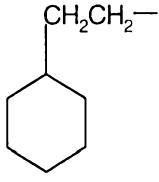
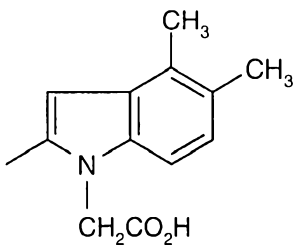
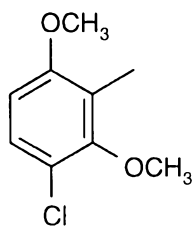
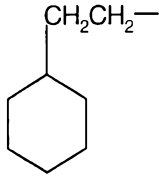
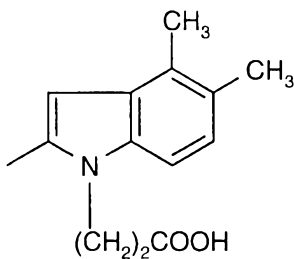
EXEMPLE N°		R_1		F ; °C (sel)
468				139
469				265 (Sel de Na)
470				188
471				190 (HCl)
472				243 (HCl)

TABLEAU VII (suite 63)

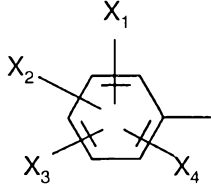
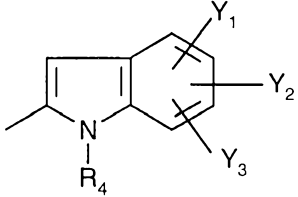
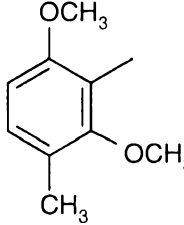
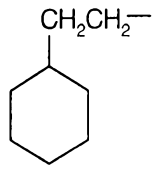
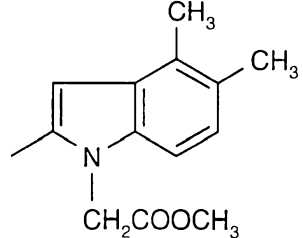
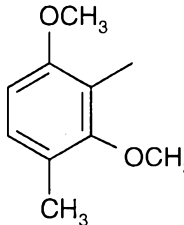
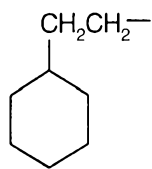
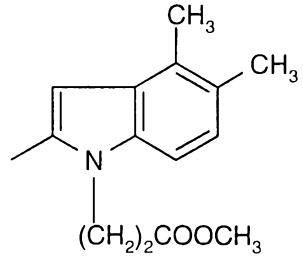
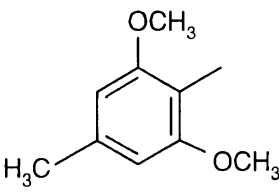
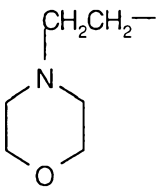
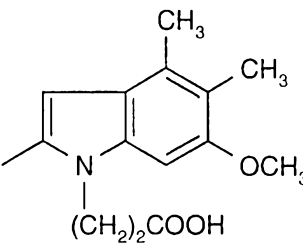
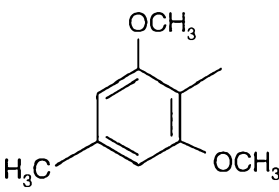
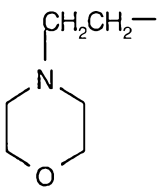
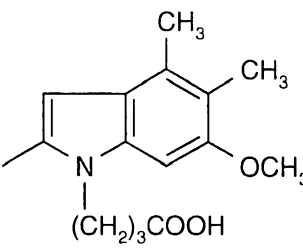
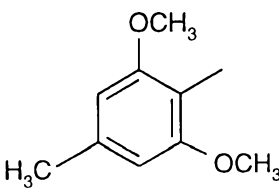
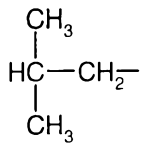
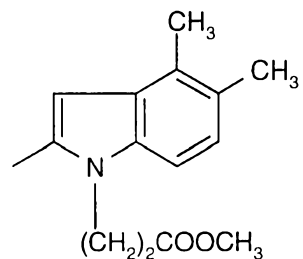
EXEMPLE N°		R ₁		F ; °C (sel)
473				98
474				86
475				275
476				175
477				205

TABLEAU VII (suite 64)

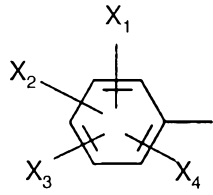
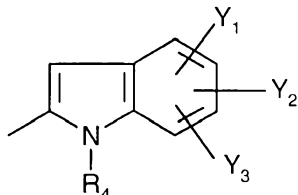
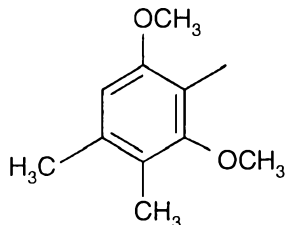
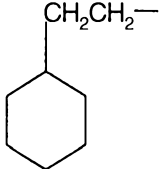
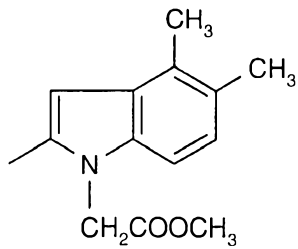
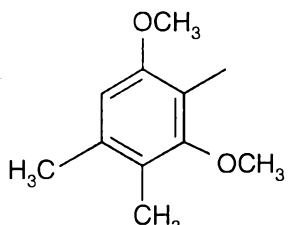
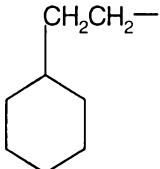
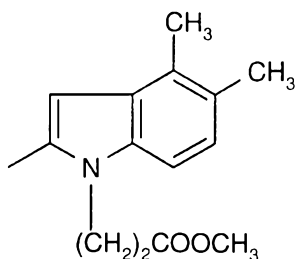
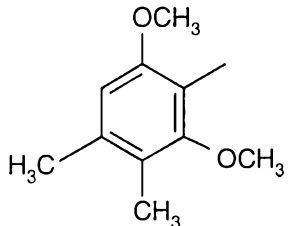
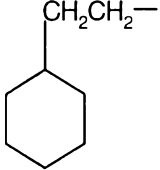
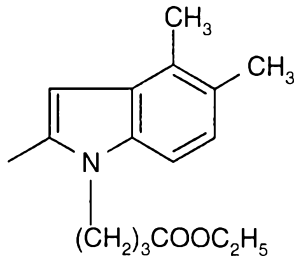
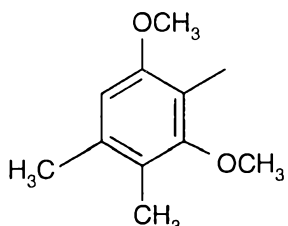
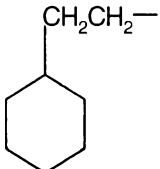
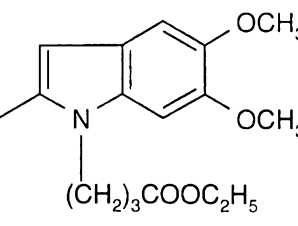
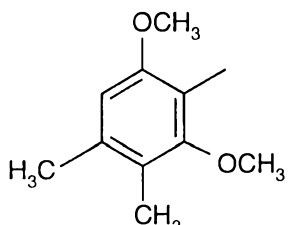
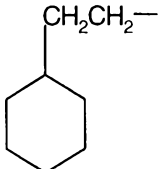
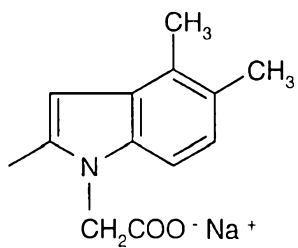
EXEMPLE N°		R ₁		F ; °C (sel)
478				132
479				83
480				97
481				82
482				274 (Sel de Na)

TABLEAU VII (suite 65)

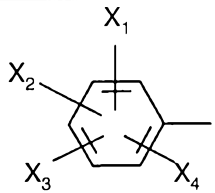
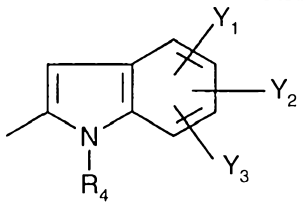
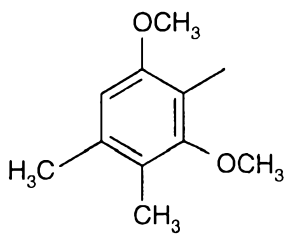
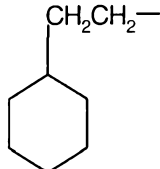
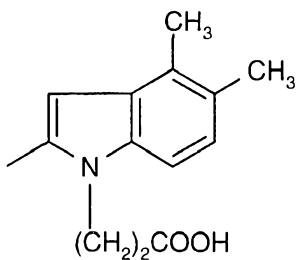
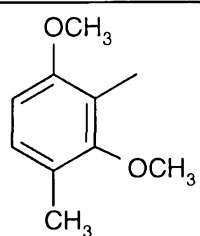
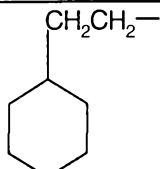
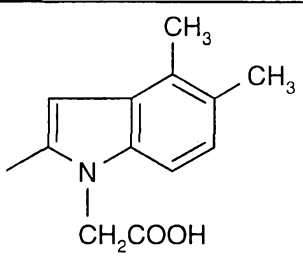
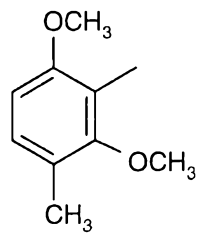
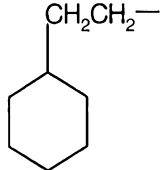
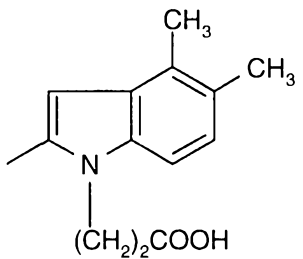
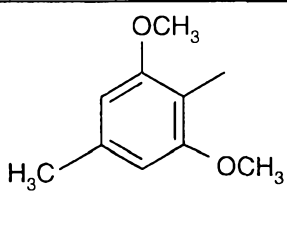
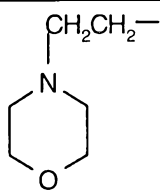
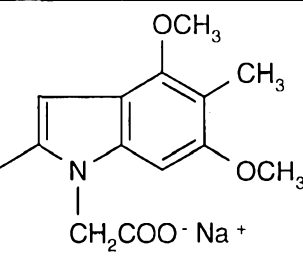
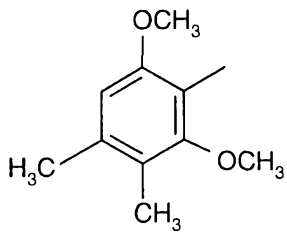
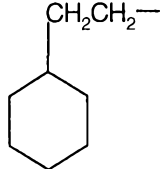
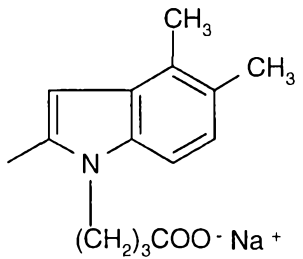
EXEMPLE N°		R ₁		F ; °C (sel)
483				271
484				237 (HCl)
485				144 (HCl)
486				228 (Sel de Na et HCl)
487				166 (Sel de Na)

TABLEAU VII (suite 66)

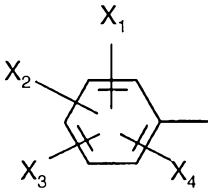
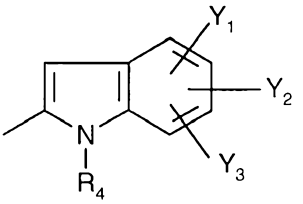
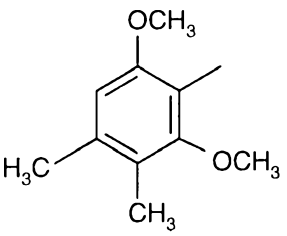
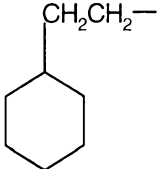
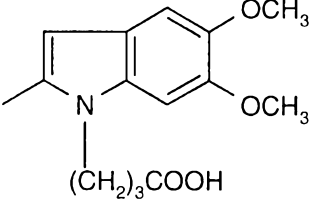
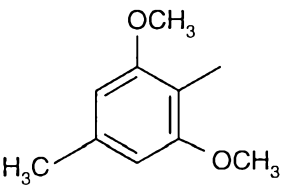
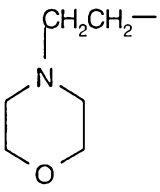
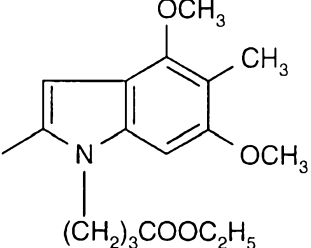
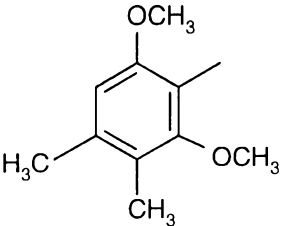
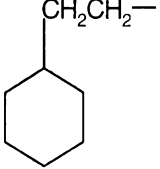
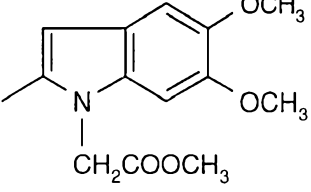
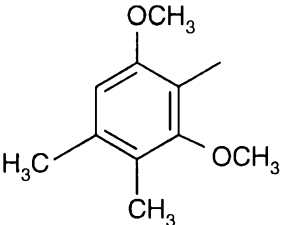
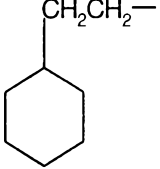
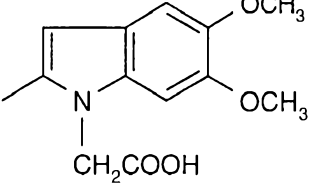
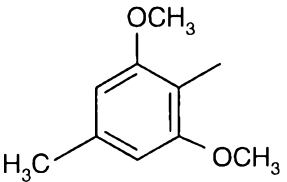
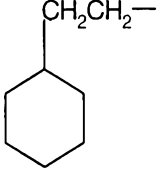
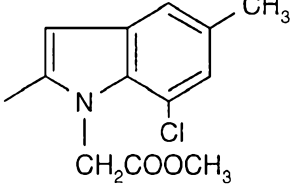
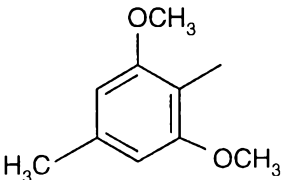
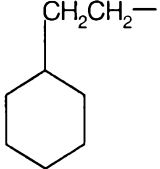
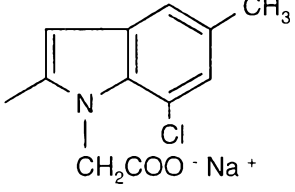
EXEMPLE N°		R ₁		F ; °C (sel)
488				138
489				124
490				138
491				224
492				197
493				210 (Sel de Na)

TABLEAU VII (suite 67)

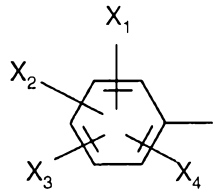
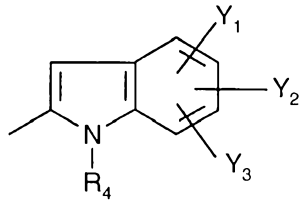
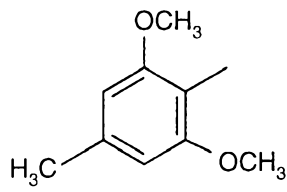
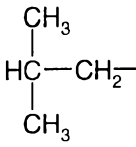
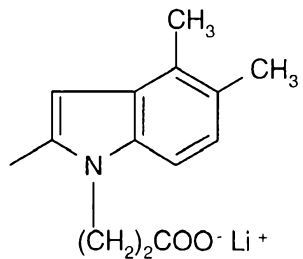
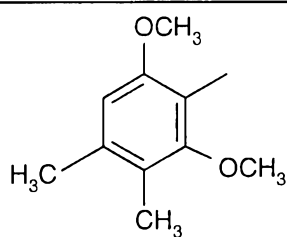
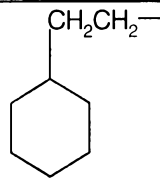
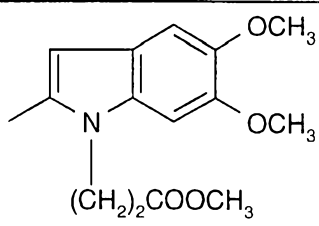
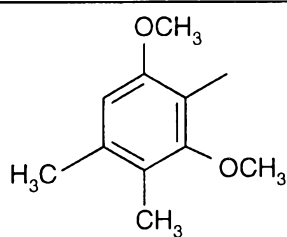
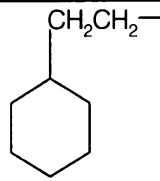
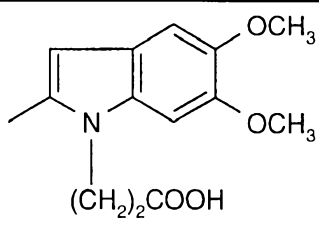
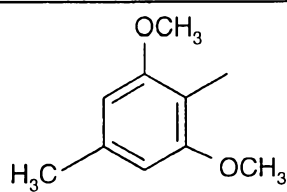
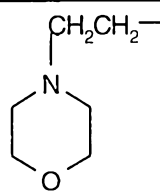
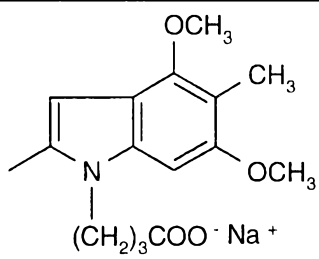
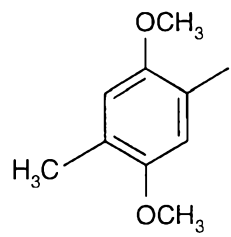
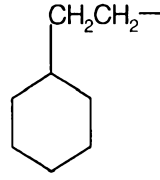
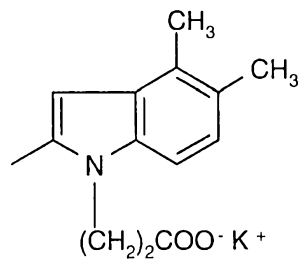
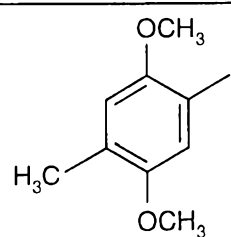
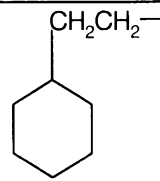
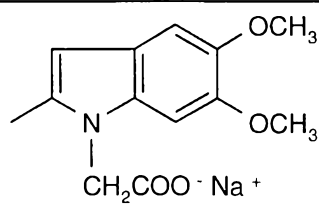
EXEMPLE N°		R ₁		F ; °C (sel)
494			 (CH ₂) ₂ COO ⁻ Li ⁺	274 (Sel de Li)
495			 (CH ₂) ₂ COOCH ₃	99
496			 (CH ₂) ₂ COOH	248
497			 (CH ₂) ₃ COO ⁻ Na ⁺	>300 (Sel de Na)
498			 (CH ₂) ₂ COO ⁻ K ⁺	148 (Sel de K)
499			 CH ₂ COO ⁻ Na ⁺	226 (Sel de Na)

TABLEAU VII (suite 68)

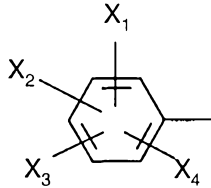
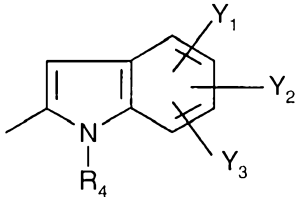
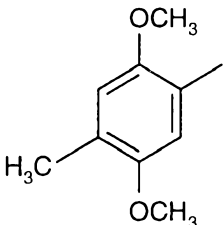
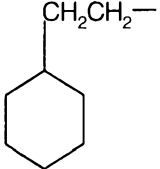
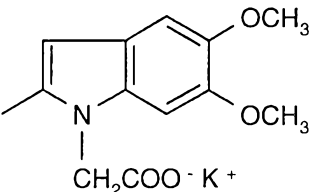
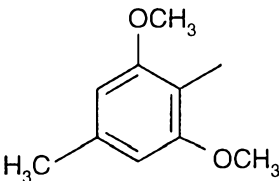
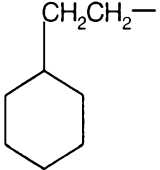
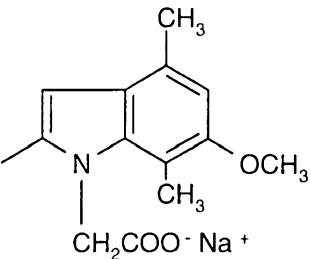
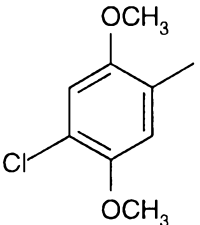
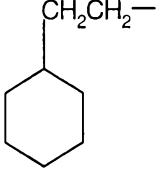
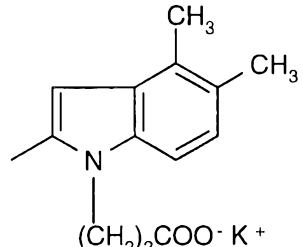
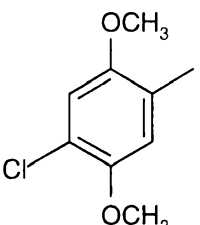
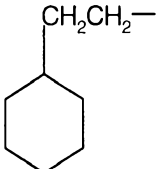
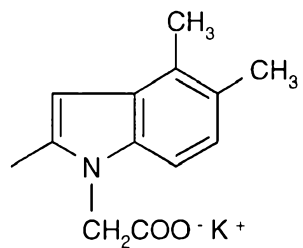
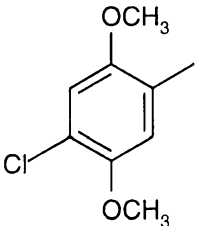
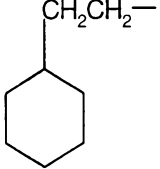
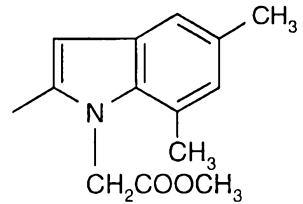
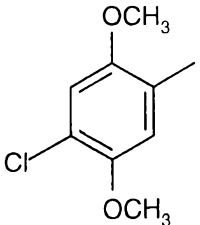
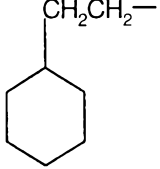
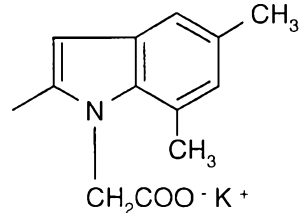
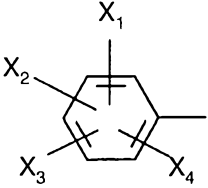
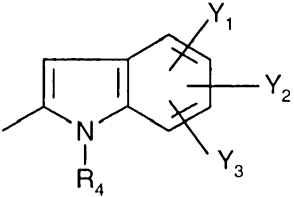
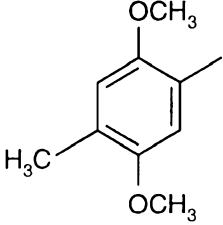
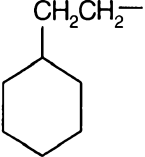
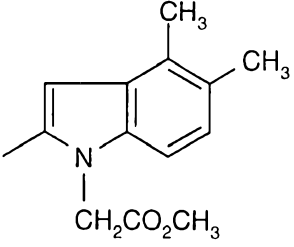
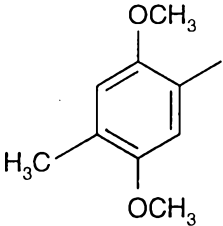
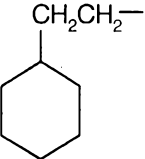
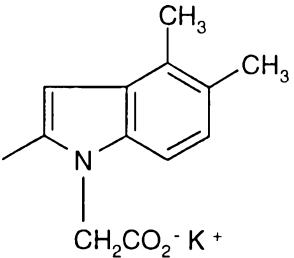
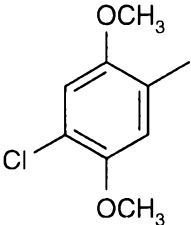
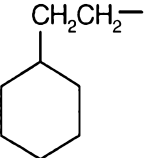
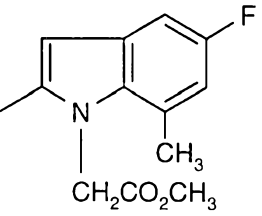
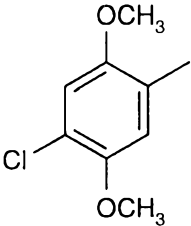
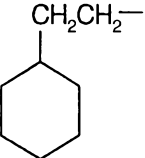
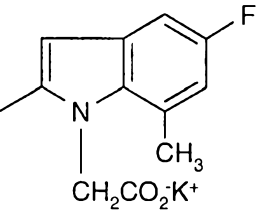
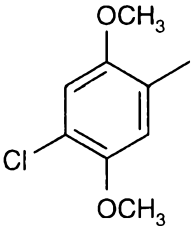
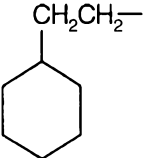
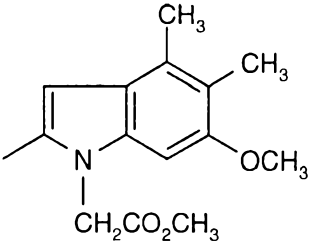
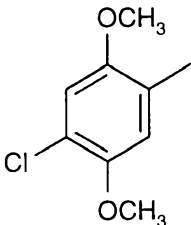
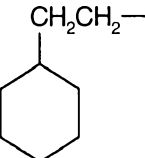
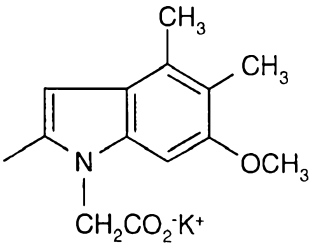
EXEMPLE N°		R ₁		F ; °C (sel)
500				139 (Sel de K)
501				190 (Sel de Na)
502				237 (Sel de K)
503				230 (Sel de K)
504				208
505				202 (Sel de K)

TABLEAU VII (suite 69)

EXEMPLE N°		R ₁		F ; °C (sel)
506				109
507				181 (Sel de K)
508				117
509				225 (Sel de K)
510				178
511				254 (Sel de K)

EXEMPLE 512 : N²-[5-(4-chloro-2,5-diméthoxyphényl)-1-(2-cyclohexyléthyl)-1H-1,2,4-triazol-3-yl]-4,5-diméthyl-1-[3-(2H-1,2,3,4-tétrazol-5-yl)propyl]-1H-2-indolecarboxamide.

Etape 1 : 4-[2-([1-(2-Cyclohexyléthyl)-5-(2,5-diméthoxy-4-chlorophényl)-1H-1,2,4-triazol-3-yl]amino)carbonyl]-4,5-diméthyl-1H-1-indolyl]butyronitrile

A 15 ml de dichlorométhane, on additionne successivement 1 ml de pyridine (0,013 mole) et 0,21 ml (0,0029 mole) de chlorure de thionyle. Après 15 minutes à 0°C, on introduit 0,615 g de l'acide 4,5-diméthyl-1-(3-cyanopropyl)-1H-2-indolecarboxylique (0,0024 mole), puis 0,9 g de chlorhydrate de 1-(2-cyclohexyléthyl)-5-(2,5-diméthoxy-4-chlorophényl)-1H-1,2,4-triazol-3-amine. On maintient le mélange réactionnel pendant 18 heures à température ambiante, puis on fait un lavage acide, puis un lavage basique. On sèche la phase organique sur sulfate de sodium anhydre et concentre sous pression réduite. Le résidu huileux est chromatographié sur une colonne de gel de silice, en éluant avec un mélange dichlorométhane/méthanol 98,5/1,5 (v/v) pour fournir une poudre blanche ; F=178°C ; Rendement = 87 %.

Etape 2 : N²-[5-(4-chloro-2,5-diméthoxyphényl)-1-(2-cyclohexyléthyl)-1H-1,2,4-triazol-3-yl]-4,5-diméthyl-1-[3-(2H-1,2,3,4-tétrazol-5-yl)propyl]-1H-2-indolecarboxamide.

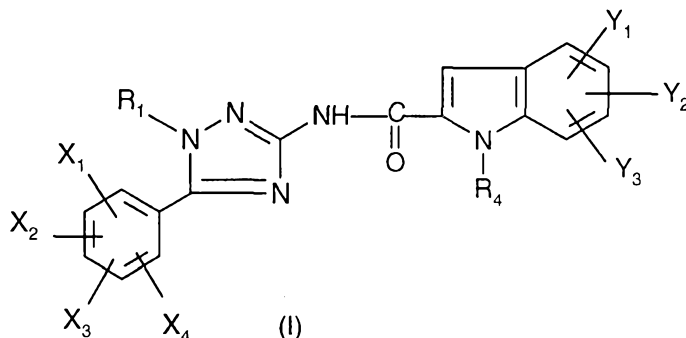
A 0,720 g (0,0012 mole) de 4-[2-([1-(2-cyclohexyléthyl)-5-(2,5-diméthoxy-4-chlorophényl)-1H-1,2,4-triazol-3-yl]amino)carbonyl]-4,5-diméthyl-1H-1-indolyl]butyronitrile en solution dans 15 ml de tétrahydrofurane, on additionne 0,5 ml d'azidotriméthylsilane, 0,030 g d'oxyde de dibutylétain et chauffe à reflux pendant 18 heures. On laisse revenir le mélange réactionnel à température ambiante, on élimine le tétrahydrofurane sous pression réduite et on chromatographie le résidu sur une colonne de gel de silice en éluant avec un mélange dichlorométhane/méthanol 95/5 (v/v). On obtient un solide blanc ; F = 233°C ; Rendement 78 %.

Ce mode opératoire décrit pour l'EXEMPLE 512 est également utilisé pour les EXEMPLES 303, 304, 316, 317, 356, 357, 361, 362, 363, 368, 369, 392, 394, 395, 430, 431, 432.

Les sels de potassium et de sodium de ces composés sont obtenus dans l'acétonitrile par addition d'un équivalent de base à température ambiante, suivie de l'évaporation sous pression réduite du solvant puis séchage.

REVENDICATIONS

1. Composé de formule :



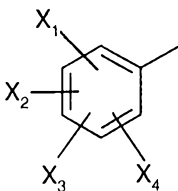
5 dans laquelle :

- R_1 représente un (C_2-C_6) alkyle ; un groupe $-(CH_2)_n-G$ avec n variant de 0 à 5 et G représentant un groupe hydrocarboné mono- ou polycyclique non aromatique en C_3-C_{13} éventuellement substitué par un ou plusieurs (C_1-C_3) alkyle; un phényl (C_1-C_3) alkyle dans lequel le groupe phényle est éventuellement substitué une ou plusieurs fois par un halogène, par un (C_1-C_3) alkyle ou par un (C_1-C_3) alcoxy ; un groupe $-(CH_2)_nNR_2R_3$ dans lequel n représente un nombre entier de 1 à 6 et R_2 et R_3 identiques ou différents représentent un (C_1-C_3) alkyle ou constituent avec l'atome d'azote auquel ils sont liés un groupe morpholino, pipéridino, pyrrolidinyle ou pipérazinyle ;
- X_1, X_2, X_3 ou X_4 représentent chacun indépendamment un atome d'hydrogène, d'halogène, un (C_1-C_6) alkyle, un (C_1-C_3) alcoxy ou un trifluorométhyle; étant entendu qu'un seul parmi X_1, X_2, X_3 et X_4 représente éventuellement un atome d'hydrogène ;
- R_4 représente l'hydrogène, un groupe $-(CH_2)_nCOOR_5$ dans lequel n est tel que défini précédemment et R_5 représente un atome d'hydrogène, un (C_1-C_6) alkyle ou un (C_6-C_{10}) aryl- (C_1-C_6) alkyle ; un (C_1-C_6) alkyle ; un groupe $-(CH_2)_nOR_5$ ou un groupe $-(CH_2)_nNR_2R_3$ dans lesquels n, R_2, R_3 et R_5 sont tels que définis précédemment ; un groupe $-(CH_2)_n$ tétrazolyle dans lequel n est tel que défini précédemment, ou R_4 représente l'un de ces groupes sous la forme de sel d'un métal alcalin ou alcalino-terreux ;
- Y_1, Y_2 et Y_3 , représentent indépendamment un hydrogène, un halogène, un (C_1-C_3) alkyle, un (C_1-C_3) alcoxy, un nitro, cyano, (C_1-C_6) acylamino, carbamoyle, trifluorométhyle, un groupe $COOR_6$ dans lequel R_6 représente l'hydrogène, ou (C_1-C_3) alkyle ;

ou un de ses sels ou solvates.

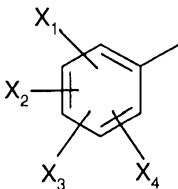
2. Composé de formule (I) selon la revendication 1, dans laquelle R_1 , R_4 , X_1 , X_2 , X_3 et X_4 sont tels que définis à la revendication 1 et Y_1 , Y_2 et Y_3 représentent l'hydrogène;
- 5 un de ses sels ou solvates.

3. Composé de formule (I) selon la revendication 1, dans laquelle R_1 et R_4 sont tels que définis à la revendication 1, Y_1 , Y_2 et Y_3 représentent l'hydrogène ; et



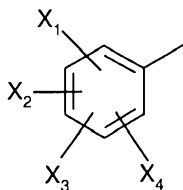
- 10 représente 2,6-diméthoxy-4-méthylphényle;
un de ses sels ou solvates.

4. Composé de formule (I) selon la revendication 1, dans laquelle R_1 , R_4 , Y_1 , Y_2 et Y_3 sont tels que définis à la revendication 1 et

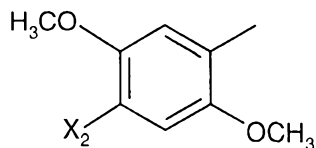


- 15 représente 2,6-diméthoxy-4-méthylphényle;
un de ses sels ou solvates.

5. Composé de formule (I) selon la revendication 1, dans laquelle R_1 , R_4 , Y_1 , Y_2 et Y_3 sont tels que définis à la revendication 1 et

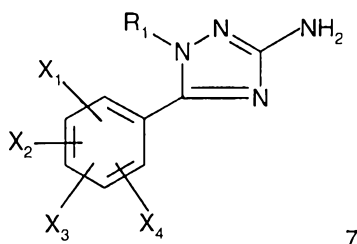


représente



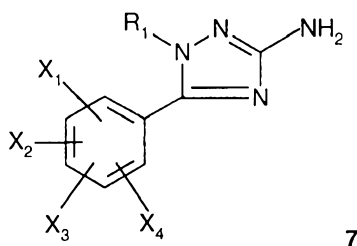
X_2 représentant un méthyle ou un atome de chlore ;
un de ses sels ou solvates.

6. Composé de formule :



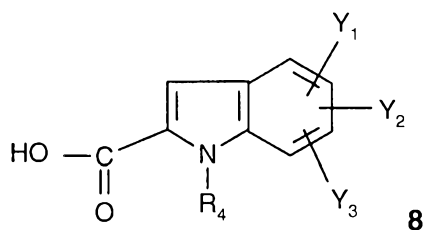
dans lequel R_1 , X_1 , X_2 , X_3 et X_4 sont tels que définis pour (I) à la revendication 1.

- 5 7. Procédé de préparation d'un composé de formule (I) selon l'une quelconque des revendications 1 à 5 comprenant l'étape consistant à faire réagir un aminotriazole de formule :



dans laquelle R_1 , X_1 , X_2 , X_3 et X_4 sont tels que définis pour (I) à la revendication 1, avec un dérivé acide indole carboxylique de formule 8 :

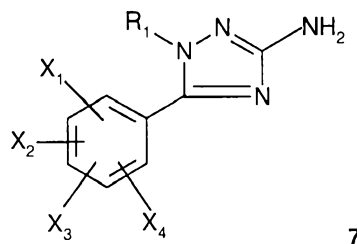
10



dans laquelle R_4 , Y_1 , Y_2 et Y_3 sont tels que définis pour (I) à la revendication 1, pour obtenir les composés de formule (I), un de leurs sels ou solvates.

15

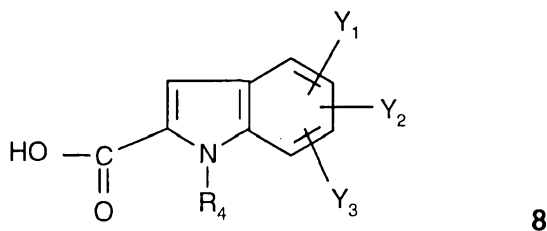
8. Procédé de préparation d'un composé de formule (I) selon l'une quelconque des revendications 1 à 5 comprenant la réaction d'un aminotriazole de formule :



20

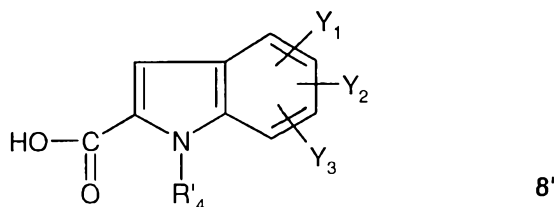
dans lequel R_1 , X_1 , X_2 , X_3 et X_4 sont tels que définis pour (I)

- soit avec un dérivé acide indole carboxylique de formule



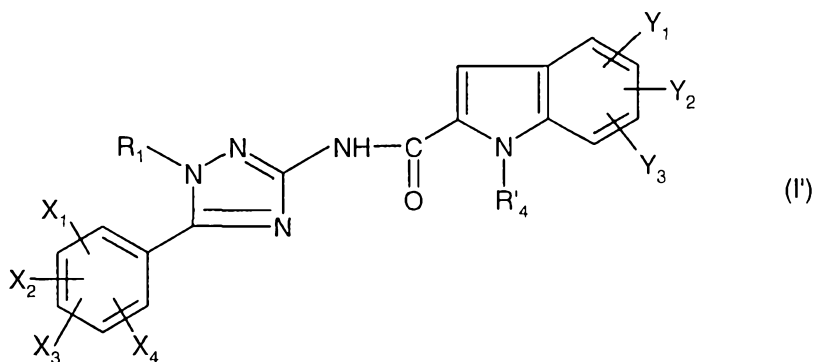
dans laquelle R_4 , Y_1 , Y_2 et Y_3 sont tels que définis ci-dessus pour (I) ;

- soit avec un dérivé acide indole carboxylique de formule :



5

dans laquelle Y_1, Y_2, Y_3 sont tels que définis ci-dessus pour (I) et R'_4 est un groupe précurseur de R_4 pour former intermédiairement le composé de formule :



dans laquelle $R_1, X_1, X_2, X_3, X_4, Y_1, Y_2$ et Y_3 sont tels que définis pour (I) et R'_4 est un groupe précurseur de R_4 , R_4 étant tel que défini pour (I)

10

9. Composition pharmaceutique contenant à titre de principe actif, un composé de formule (I) selon la revendication 1 ou un de ses sels pharmaceutiquement acceptables.

15

10. Composition pharmaceutique contenant, en tant que principe actif, un composé selon la revendication 2 ou un de ses sels pharmaceutiquement acceptables.

11. Composition pharmaceutique contenant, en tant que principe actif, un composé selon la revendication 3 ou un de ses sels pharmaceutiquement acceptables.

20

12. Composition pharmaceutique contenant, en tant que principe actif, un composé selon la revendication 4 ou un de ses sels pharmaceutiquement acceptables.
- 5 13. Composition pharmaceutique contenant, en tant que principe actif, un composé selon la revendication 5 ou un de ses sels pharmaceutiquement acceptables.
- 10 14. Utilisation d'un composé selon l'une quelconque des revendications 1 à 5 pour la préparation de médicaments destinés à traiter les désordres alimentaires, l'obésité et à réduire la prise de nourriture.
- 15 15. Utilisation d'un composé selon l'une quelconque des revendications 1 à 5 pour la préparation de médicaments destinés à traiter la dyskinésie tardive.
16. Utilisation d'un composé selon l'une quelconque des revendications 1 à 5 pour la préparation de médicaments destinés à traiter les troubles de la sphère gastrointestinale.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/FR 98/00905

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D403/12 C07D403/14 A61K31/41 C07D249/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 620 221 A (ELF SANOFI) 19 October 1994 cited in the application see the whole document	1-16
A	EP 0 611 766 A (ELF SANOFI) 24 August 1994 cited in the application see the whole document	1-16

☐

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 August 1998

Date of mailing of the international search report

04/09/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Allard, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. ational Application No

PCT/FR 98/00905

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 620221 A	19-10-1994	FR 2703995 A	21-10-1994
		AU 678208 B	22-05-1997
		AU 5945094 A	27-10-1994
		CA 2121425 A	17-10-1994
		CN 1100724 A	29-03-1995
		FI 941776 A	17-10-1994
		HU 70542 A	30-10-1995
		IL 109275 A	08-02-1998
		JP 6340663 A	13-12-1994
		NO 941374 A	17-10-1994
		NZ 260313 A	22-12-1994
		US 5534530 A	09-07-1996
		ZA 9402577 A	16-10-1995
EP 611766 A	24-08-1994	FR 2701708 A	26-08-1994
		AU 680213 B	24-07-1997
		AU 5516294 A	25-08-1994
		CA 2115805 A	20-08-1994
		CN 1107158 A	23-08-1995
		FI 940769 A	20-08-1994
		HU 70158 A	28-09-1995
		JP 6298761 A	25-10-1994
		MX 9401209 A	31-08-1994
		NO 940558 A	22-08-1994
		NZ 250907 A	26-01-1996
		US 5656648 A	12-08-1997
		ZA 9401128 A	18-08-1995

RAPPORT DE RECHERCHE INTERNATIONALE

L Recherche Internationale No
PCT/FR 98/00905

A. CLASSEMENT DE L'OBJET DE LA DEMANDE

CIB 6 C07D403/12 C07D403/14 A61K31/41 C07D249/14

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)

CIB 6 C07D A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	EP 0 620 221 A (ELF SANOFI) 19 octobre 1994 cité dans la demande voir le document en entier ---	1-16
A	EP 0 611 766 A (ELF SANOFI) 24 août 1994 cité dans la demande voir le document en entier -----	1-16



Voir la suite du cadre C pour la fin de la liste des documents



Les documents de familles de brevets sont indiqués en annexe

° Catégories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"&" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée

27 août 1998

Date d'expédition du présent rapport de recherche internationale

04/09/1998

Nom et adresse postale de l'administration chargée de la recherche internationale

Office Européen des Brevets, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Fonctionnaire autorisé

Allard, M

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

C .nde Internationale No

PCT/FR 98/00905

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
EP 620221 A	19-10-1994	FR 2703995 A	21-10-1994
		AU 678208 B	22-05-1997
		AU 5945094 A	27-10-1994
		CA 2121425 A	17-10-1994
		CN 1100724 A	29-03-1995
		FI 941776 A	17-10-1994
		HU 70542 A	30-10-1995
		IL 109275 A	08-02-1998
		JP 6340663 A	13-12-1994
		NO 941374 A	17-10-1994
		NZ 260313 A	22-12-1994
		US 5534530 A	09-07-1996
		ZA 9402577 A	16-10-1995
EP 611766 A	24-08-1994	FR 2701708 A	26-08-1994
		AU 680213 B	24-07-1997
		AU 5516294 A	25-08-1994
		CA 2115805 A	20-08-1994
		CN 1107158 A	23-08-1995
		FI 940769 A	20-08-1994
		HU 70158 A	28-09-1995
		JP 6298761 A	25-10-1994
		MX 9401209 A	31-08-1994
		NO 940558 A	22-08-1994
		NZ 250907 A	26-01-1996
		US 5656648 A	12-08-1997
		ZA 9401128 A	18-08-1995