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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
E. S. D.

Respuesta a Oficio No. 13277 del 17 de octubre de 2008

REF: Expediente No. 04 022.003-A - Solicitud de patente de invención a favor de **ASTRAZENECA AB**.

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la Sociedad **ASTRAZENECA AB**, domiciliada en Södertälje, Suecia, según lo acredita el documento de poder presentado en esa División, atendiendo al requerimiento del señor Examinador, en relación con el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, según el concepto técnico No. 2658 notificado por fijación en lista de fecha 17 de octubre de 2008, me permito anexar al presente escrito los siguientes documentos:

- FORD, ROGER E. ET AL. "Synthesis and quantitative structure-activity relationships of antiallergic 2-hydroxy-N-(1H-tetrazol-5-yl) benzamides and N-(2-hydroxyphenyl)-1H-tetrazole-5-carboxamides". J.MED.CHEM (1986), 29(4), 538-49, XP001026086, formula 2, table 1.
- ZHANG, SANG-QI ET AL. "Synthesis based on affinity separation (SAS): Separation of products having barbituric acid tag from untagged compounds by using hydrogen bond interaction". SYNLETT (2001), (5), 590-596, XP001106577, page 591.

De la Señora Jefe,

Atentamente,

**JUAN PABLO CADENA SARMIENTO**
T.P. No. 57.492 del C.SJ.
C.C. 80.410.337 de Usaquén
Carrera 7 No. 71-21 Torre B - Oficina 402

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Anexos

# Synthesis and Quantitative Structure–Activity Relationships of Antiallergic 2-Hydroxy-*N*-1*H*-tetrazol-5-ylbenzamides and *N*-(2-Hydroxyphenyl)-1*H*-tetrazole-5-carboxamides

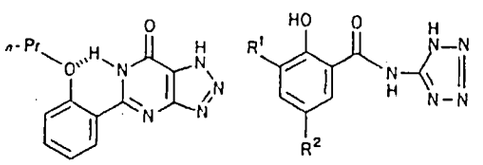
Roger E. Ford, Phillip Knowles, Edward Lunt, Stuart M. Marshall, Audrey J. Penrose, Christopher A. Ramsden,* Anthony J. H. Summers, Joyce L. Walker, and Derek E. Wright

*Research Laboratories, May & Baker Limited, Dagenham, Essex, England.* *Received May 6, 1985*

The synthesis and antiallergic activity of a series of 2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamides and isomeric *N*-(2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamides is described. A relationship between structure and intravenous antiallergic activity in the rat passive cutaneous anaphylaxis (PCA) test has been established using a Hansch/Free-Wilson model and used to direct studies toward potent derivatives. The contribution of physicochemical properties to activity is discussed. One member of this series, *N*-(3-acetyl-5-fluoro-2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamide (3f), which was selected for further evaluation, has an $ID_{50}$ value of 0.16 mg/kg po and is 130 times more potent than disodium cromoglycate (DSCG) on intravenous administration.

2-(o-Propoxyphenyl)-8-azapurin-6-one (Zaprinast; M&B 22,948) (1) is a potent inhibitor of reagin-mediated anaphylaxis and is superior to disodium cromoglycate (DSCG) in a number of test systems. Quantitative studies show that optimal antiallergic activity in 2-aryl-8-azapurin-6-ones (e.g., 1) is associated with coplanarity between the heterocyclic and aryl rings and that coplanarity in M&B 22,948 (1) is particularly favored as a result of intramolecular hydrogen bonding.[1] The planar structure of compound 1 has been confirmed by an X-ray study.[2] Comparison of the azapurinones with other potent antiallergic molecules reveals common features, and these qualitative structure–activity relationships have been discussed by E.L. in a recent review.[3] Important requirements for antiallergic activity appear to be (i) an extended planar (or quasi-planar) aromatic system that is associated with (ii) an acidic function in close proximity to (iii) a carbonyl group. Inspection of structure 1 demonstrates that these features are present.[3]

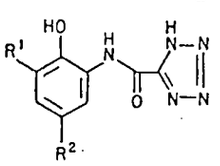
The promotion of an extended planar system by intramolecular hydrogen bonding is a particularly interesting feature of the azapurinone (1). In our search for orally



1 (Zaprinast)



2



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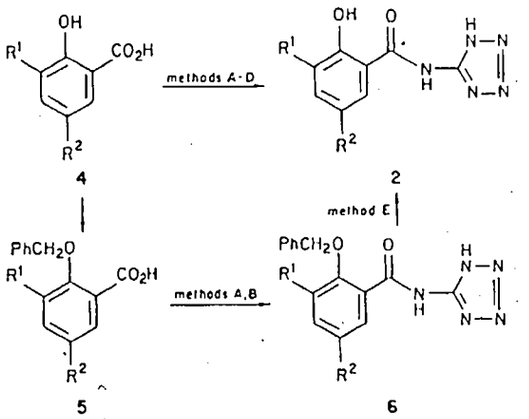
effective alternatives to DSCG we have been encouraged

Scheme I[a]




[a] Reagents: (method A) 5-aminotetrazole-DCC in pyridine; (method B) 5-aminotetrazole-$SiCl_4$; (method C) (i) $SOCl_2$, (ii) 5-aminotetrazole; (method D) (i) $PCl_5$, (ii) 5-aminotetrazole; (method E) $H_2$-Pd-C.

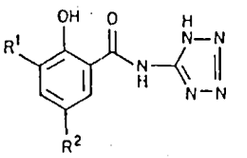
to investigate other molecules in which the requirement of extended planarity is facilitated by intramolecular hydrogen bonding. This paper describes how this approach led to the synthesis of two series of 5-substituted tetrazole derivatives, the 2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamides (2)[4] and the *N*-(2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamides (3),[5] many of which possess outstanding antiallergic activity.

**Chemistry.** *N*-1*H*-Tetrazol-5-ylbenzamides (2 and 6) are listed in Tables I and III and were prepared from the appropriate salicylic acid by methods summarized in Scheme I. The most convenient route involves condensation of a carboxylic acid (4 or 5) with anhydrous 5-aminotetrazole using dicyclohexylcarbodiimide (DCC) in pyridine (method A).[6] Alternatively, silicon tetrachloride was used as condensing agent (method B),[7] or the 5-aminotetrazole was reacted with the appropriate acid chloride generated in situ with either thionyl chloride

(1) (a) Broughton, B. J.; Chaplen, P.; Knowles, P.; Lunt, E.; Marshall, S. M.; Pain, D. L.; Wooldridge, K. R. H. *J. Med. Chem.* 1975, *18*, 1117. (b) Broughton, B. J.; Chaplen, P.; Knowles, P.; Lunt, E.; Pain, D. L.; Wooldridge, K. R. H.; Ford, R.; Marshall, S.; Walker, J. L.; Maxwell, D. R. *Nature* 1974, *251*, 650.
(2) Wilson, S. R.; Wilson, R. B.; Shoemaker, A. L.; Wooldridge, K. R. H.; Hodgson, D. J. *J. Am. Chem. Soc.* 1982, *104*, 259.
(3) Lunt, E. In "Progress in Pharmaceutical Research"; Wooldridge, K. R. H., Ed.; Blackwell Scientific Publications: Oxford, 1982; Vol. 4.
(4) Ramsden, C. A.; Knowles, P.; Lewis, E. J.; Lunt, E.; Wright, D. E. (May & Baker Ltd.) U.K. Patent 2006782, 1977; *Chem. Abstr.* 1979, *91*, 74626.
(5) Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Summers, A. J. H. (May & Baker Ltd.) U.K. Patent 1561350, 1976; *Chem. Abstr.* 1978, *89*, 109509*m*.
(6) Sheehan, J. C.; Goodman, M.; Hess, G. P. *J. Am. Chem. Soc.* 1956, *78*, 1367. Greenstein, J. P.; Winitz, M. "The Chemistry of the Amino Acids"; Wiley: New York, 1961; Vol. 2.
(7) Chan, T. H.; Wong, L. T. L. *J. Org. Chem.* 1969, *34*, 2766.

0022-2623/86/1829-0538$01.50/0 

Table I. 2-Hydroxy-*N*-1*H*-tetrazol-5-ylbenzamides 2



2

| no. | $R^1$ | $R^2$ | method (% yield) | cryst solvent | mp, °C | formula | anal.[a] | rel act. ($I$)[b] | log [$M_rI$] obsd | log [$M_rI$] calcd |
|---|---|---|---|---|---|---|---|---|---|---|
| 2a | $CH_3CO$ | H | A (49) | DMF-$H_2O$ | 291–292 dec | $C_{10}H_9N_5O_3$ | C, H, N | 1 | 2.393 | 2.596 |
| 2b | $CH_3CO$ | $CH_3$ | A (46), C(46) | DMF-$CH_3CO_2H$ | 279–281 dec | $C_{11}H_{11}N_5O_3$ | C, H, N | 1 | 2.417 | 2.240 |
| 2c | $CH_3CO$ | $C_2H_5$ | A (53) | DMF-$H_2O$ | 260–262 dec | $C_{12}H_{13}N_5O_3$ | C, H, N | 1 | 2.439 | 2.220 |
| 2d | $CH_3CO$ | $n$-$C_3H_7$ | A (40) | DMF-$H_2O$ | 257–258 | $C_{13}H_{15}N_5O_3$ | C, H, N | 2 | 2.762 | 2.137 |
| 2e | $CH_3CO$ | $i$-$C_4H_9$ | A (35) | $HCO_2H$-$H_2O$ | 239–241 dec | $C_{14}H_{17}N_5O_3$ | C, H, N | 0.2 | 1.783 | 1.973 |
| 2f | $CH_3CO$ | $t$-$C_4H_9$ | A (51) | $HCO_2H$-$H_2O$ | 258–260 dec | $C_{14}H_{17}N_5O_3$ | C, H, N | 0.4 | 2.084 | 1.798 |
| 2g | $CH_3CO$ | F | A (39) | DMF-$CH_3CO_2H$ | 268–270 dec | $C_{10}H_8FN_5O_3$ | C, H, N | 0.5 | 2.123 | 2.464 |
| 2h | $CH_3CO$ | Cl | A (14) | DMF-$CH_3CO_2H$ | 269–271 dec | $C_{10}H_8ClN_5O_3$ | C, H, Cl, N | 0.05 | 1.149 | 2.318 |
| 2i | $CH_3CO$ | Br | A (12) | DMF-$H_2O$ | 277–279 dec | $C_{10}H_8BrN_5O_3$ | C, H, Br, N | 0.05 | 1.212 | 2.263 |
| 2j | $CH_3CO$ | $CH_3O$ | A (60) | DMF-$H_2O$ | 288–290 dec | $C_{11}H_{11}N_5O_4$ | C, H, N | 2 | 2.743 | 2.438 |
| 2k | $CH_3CO$ | $NO_2$ | text (63) | $HCO_2H$ | 255–257 dec | $C_{10}H_8N_6O_5$ | H, N; C[d] | 1 | 2.465 | 1.873 |
| 2l | $CH_3CO$ | $SO_2NH_2$ | text (5) | DMF-$H_2O$ | >310 | $C_{10}H_{10}N_6O_5S$ | C, H, N | 0.2 | 1.814 | 1.844 |
| 2m | $CH_3CO$ | $NHCOCH_3$ | A (47) | $HCO_2H$ | 290 | $C_{12}H_{12}N_6O_4$ | C, H, N | 0.2 | 1.784 | 1.741 |
| 2n | $C_2H_5CO$ | $CH_3$ | A (40) | $HCO_2H$ | 280–281 | $C_{12}H_{13}N_5O_3$ | C, H; N[e] | 2 | 2.741 | 2.332 |
| 2o | $C_2H_5CO$ | $C_2H_5$ | A (40) | DMF-$H_2O$ | 262–263 | $C_{13}H_{15}N_5O_3$ | C, H, N | 0.75 | 2.336 | 2.312 |
| 2p | $CH_3O$ | H | A (69) | DMF-$CH_3CO_2H$ | 265–267 dec | $C_9H_9N_5O_3$ | C, H, N | 1 | 2.371 | 2.422 |
| 2q | $CH_3O$ | $CH_3$ | A (35) | DMF-$H_2O$ | 273–274 dec | $C_{10}H_{11}N_5O_3$ | C, H, N | 0.5 | 2.095 | 2.066 |
| 2r | $CH_3O$ | $C_2H_5$ | A (33) | DMF-$H_2O$ | 271–272 dec | $C_{11}H_{13}N_5O_3$ | C, H, N | 1 | 2.420 | 2.046 |
| 2s | $CH_3O$ | $t$-$C_4H_9$ | A (34) | DMF-$H_2O$ | 277 dec | $C_{13}H_{17}N_5O_3$ | C, H, N | 0.1 | 1.464 | 1.624 |
| 2t | $CH_3O$ | Br | A (40) | DMF-$H_2O$ | 257 | $C_9H_8BrN_5O_3$ | C, H, Br, N | 0.2 | 1.798 | 2.089 |
| 2u | $CH_3O$ | $CH_3O$ | A (27) | DMF | 278–279 | $C_{10}H_{11}N_5O_4$ | C, H, N | 0.5 | 2.122 | 2.264 |
| 2v | $CH_3O$ | $NO_2$ | A (34) | DMF-$H_2O$ | 257–258 | $C_9H_8N_6O_5$ | C, H, N | 1 | 2.447 | 1.699 |
| 2w | $CH_3O$ | CN | A (25) | DMF | 264–265 | $C_{10}H_8N_6O_3$ | C, H, N | 2 | 2.716 | 2.276 |
| 2x | $CH_3O$ | $NHCOCH_3$ | A (10) | DMF-$H_2O$ | 258–259 dec | $C_{11}H_{12}N_6O_4$ | C, H, N | 0.02 | 0.766 | 1.567 |
| 2y | H | H | E (87) | $CH_3CO_2H$ | 270–271 dec | $C_8H_7N_5O_2$ | C, H, N | 0.1 | 1.312 | 1.657 |
| 2z | H | $CH_3$ | E (63) | DMF-$H_2O$ | 289–291 dec | $C_9H_9N_5O_2$ | C, H, N | 0.1 | 1.340 | 1.301 |
| 2aa | H | $t$-$C_4H_9$ | B (20) | EtOH | 252–253 dec | $C_{12}H_{15}N_5O_2$ | C, H, N | 0.01 | 0.417 | 0.859 |
| 2ab | H | F | A (46) | DMF-$CH_3CO_2H$ | 274 dec | $C_8H_6FN_5O_2$ | C, H, N | 0.1 | 1.348 | 1.525 |
| 2ac | H | Cl | E (77) | EtOH | 266–269 dec | $C_8H_6ClN_5O_2$ | C, H, N | 0.1 | 1.380 | 1.378 |
| 2ad | H | Br | A (45) | $CH_3CO_2H$ | 272–274 dec | $C_8H_6BrN_5O_2$ | C, H, Br, N | 0.02 | 0.756 | 1.324 |
| 2ae | H | $CH_3O$ | D (12.5) | DMF-$H_2O$ | 272–274 dec | $C_9H_9N_5O_3$ | C, H, N | 0.2 | 1.672 | 1.499 |
| 2af | H | CN | A (27) | $CH_3CO_2H$ | 310–312 dec | $C_8H_6N_6O_4$ | C, H, N | 0.5 | 2.061 | 1.510 |
| 2ag | H | $NO_2$ | C (45) | $CH_3CO_2H$ | 271–272 dec | $C_8H_6N_6O_4$ | C, H, N | 0.5 | 2.097 | 0.933 |
| 2ah | H | $CF_3$ | E (40) | $i$-PrOH | 244–245 dec | $C_9H_6F_3N_5O_2$ | C, H, F, N | 0.02 | 0.737 | 0.968 |
| 2ai | H | $CH_3S$ | A (24) | DMF-$CH_3CO_2H$ | 261–262 dec | $C_9H_9N_5O_2S$ | C, H, N, S | 0.2 | 1.701 | 1.350 |
| 2aj | H | $CH_3SO_2$ | text (53) | $CH_3CO_2H$ | 291–292 dec | $C_9H_9N_5O_4S$ | C, H, N, S | 0.04 | 1.053 | 0.902 |
| 2ak | H | $(CH_3)_2NSO_2$ | text (32) | EtOH | 276–278 dec | $C_{10}H_{12}N_6O_4S$ | C, H, N, S | 0.05 | 1.193 | 0.905 |
| 2al | H | HO | E (66) | $H_2O$ | 299–300 dec | $C_8H_7N_5O_3$ | C, H, N | 0.1 | 1.345 | 1.499 |
| 2am | H | $C_6H_5$ | A (45) | DMF-$CH_3CO_2H$ | 277–278 dec | $C_{14}H_{11}N_5O_2$ | C, H, N | 0.01 | 0.449 | 0.560 |
| 2an | H | $CH_3CO$ | A (41) | DMF-$H_2O$ | 262–263 dec | $C_{10}H_9N_5O_3$ | C, H, N | 0.02 | 0.694 | 0.842 |
| 2ao | H | $NHCOCH_3$ | A (35) | DMF-$H_2O$ | 222–224 dec | $C_{10}H_{10}N_6O_3$ | H, N; C[f] | 0.01 | 0.418 | 0.801 |
| 2ap | $HON{=}CCH_3$ | $C_2H_5$ | text (67) | DMF-$H_2O$ | 249–250 dec | $C_{12}H_{14}N_6O_3$ | C, H, N | 10 | 3.462 | |
| 2aq | $CH_3ON{=}CCH_3$ | $C_2H_5$ | text (87) | DMF-$H_2O$ | 272–275 dec | $C_{13}H_{16}N_6O_3$ | C, H; N[g] | 3.5 | 3.025 | |

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed, except as shown in subsequent footnotes. [b] Activity relative to M&B 22,948 (=1) in the rat PCA test following iv administration. The dose of M&B 22,948 required for 100% inhibition was 0.1 μg/kg. See ref 1b. [c] Calculated by eq 1. [d] C: calcd, 41.1; found, 41.7. [e] N: calcd, 25.4; found, 25.9. [f] C: calcd, 45.8; found, 45.2. [g] N: calcd, 28.6; found, 28.1.

(method C) or phosphorus trichloride (method D).[8] In some preparations the phenolic function was protected by a benzyl group that was subsequently removed by catalytic reduction (method E). In addition to preparation by the general methods A–E (Scheme I), chemical modification of some *N*-1*H*-tetrazol-5-ylbenzamides (2) gave additional derivatives, and details of these procedures are given in the Experimental Section, as indicated in Table I.

Novel salicylic acid derivatives (4) are listed in Table VI. 3-Acetyl-2-hydroxybenzoic acid (**4a**) was obtained using the following sequence: (i) isomerization of 3-allyl-2-hydroxyacetophenone using bis(benzonitrile)palladous chloride;[9] (ii) ozonolysis to give 3-formyl-2-hydroxyacetophenones; (iii) oxidation to the carboxylic acid using argentous oxide. Other novel carboxylic acids and their precursors were prepared by standard procedures as indicated in the Experimental Section.

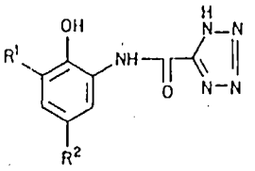
Synthetic routes to the *N*-(2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamides (3) (Table II) are summarized in Scheme II. Six of the routes (methods F–K) are variations of an approach that requires protection of the tetrazole ring by a benzyl substituent that is removed in the final stage. The 1-benzyltetrazoles (7; Ar = Ph, $R^3$ = H) were deprotected by catalytic hydrogenation using 5% Pd on charcoal (method F), and this procedure was also successful using 2-benzyltetrazoles (8; Ar = Ph) (method G). In some

(8) Taborsky, R. G. (Ben Venue Laboratories, Inc.) U.S. Patent 3 278 372, 1966; *Chem. Abstr.* 1966, *65*, 20068*d*.

(9) Golborn, P.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* 1973, 2870.

330

Table II. *N*-(2-Hydroxyphenyl)-1*H*-tetrazole-5-carboxamides 3



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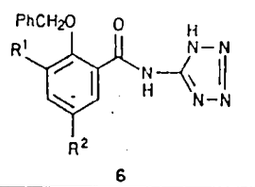
| no. | R¹ | R² | method (% yield) | cryst solvent | mp, °C | formula | anal.[a] | rel act. (*I*)[b] | log [*M*,*I*] obsd | log [*M*,*I*] calcd[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| 3a | $CH_3CO$ | H | J (84), L (41), N (48) | $CH_3CO_2H$ | 239–240 | $C_{10}H_9N_5O_3$ | C, H, N | 20 | 3.694 | 3.497 |
| 3b | $CH_3CO$ | $CH_3$ | F (17), J (94), L (26) | DMF–$H_2O$ | 245–247 dec | $C_{11}H_{11}N_5O_3$ | C, H, N | 10 | 3.417 | 3.142 |
| 3c | $CH_3CO$ | $C_2H_5$ | F (82), G (13), J (70), K (93), L (53) | DMF–$H_2O$ | 239–241 dec | $C_{12}H_{13}N_5O_3$ | C, H, N | 20 | 3.740 | 3.121 |
| 3d | $CH_3CO$ | *n*-$C_3H_7$ | L (40) | DMF–$H_2O$ | 179–180 | $C_{13}H_{15}N_5O_3$ | C, H, N | 10 | 3.461 | 3.038 |
| 3e | $CH_3CO$ | *t*-$C_4H_9$ | J (65) | *i*-PrOH | 246–247 dec | $C_{14}H_{17}N_5O_3$ | C, H, N | 0.5 | 2.170 | 2.700 |
| 3f | $CH_3CO$ | F | F (63), J (89), N (68) | MeCN | 237–239 dec | $C_{10}H_8FN_5O_3$ | C, H, F, N | 20 | 3.724 | 3.365 |
| 3g | $CH_3CO$ | Cl | J (67) | DMF–$H_2O$ | 242–244 dec | $C_{10}H_8ClN_5O_3$ | C, H, Cl, N | 7 | 3.295 | 3.219 |
| 3h | $CH_3CO$ | Br | J (84) | DMF–$H_2O$ | 252–254 dec | $C_{10}H_8BrN_5O_3$ | C, H, Br, N | 2 | 2.814 | 3.165 |
| 3i | $CH_3CO$ | $CH_3O$ | J (86) | DMF–$H_2O$ | 251–253 dec | $C_{11}H_{11}N_5O_4$ | C, H, N | 10 | 3.443 | 3.340 |
| 3j | $CH_3CO$ | CN | J (82), N (9) | DMF–$H_2O$ | 270–274 dec | $C_{11}H_8N_6O_3$ | C, H, N | 10 | 3.435 | 3.351 |
| 3k | $CH_3CO$ | $NO_2$ | J (62) | DMF–$H_2O$ | 239–240 dec | $C_{10}H_8N_6O_5$ | C, H, N | 5 | 3.164 | 2.774 |
| 3l | $CH_3CO$ | $CH_3SO_2$ | J (69) | DMF–$H_2O$ | 261–262 dec | $C_{11}H_{11}N_5O_5S$ | C, H, N, S | 2 | 2.813 | 2.743 |
| 3m | $CH_3CO$ | $CH_3CO$ | J (75) | DMF–$H_2O$ | 249–251 dec | $C_{12}H_{11}N_5O_4$ | C, H, N | 0.5 | 2.160 | 2.682 |
| 3n | $CH_3CO$ | $NHCOCH_3$ | J (64) | DMF–$H_2O$ | 270–271 dec | $C_{12}H_{12}N_6O_4$ | C, H, N | 0.5 | 2.189 | 2.642 |
| 3o | $C_2H_5CO$ | $CH_3$ | L (26) | EtOH | 230–232 dec | $C_{12}H_{13}N_5O_3$ | C, H, N | 5 | 3.139 | 3.233 |
| 3p | $C_2H_5CO$ | $C_2H_5$ | L (26) | $CH_3CO_2H$ | 225–227 dec | $C_{13}H_{15}N_5O_3$ | C, H, N | 5 | 3.160 | 3.213 |
| 3q | $C_2H_5CO$ | CN | J (80) | DMF–$H_2O$ | 257–259 | $C_{12}H_{10}N_6O_3$ | C, H, N | 5 | 3.156 | 3.443 |
| 3r | $CH_3O$ | H | I (47) | $H_2O$ | 218–220 dec | $C_9H_9N_5O_3$ | C, H, N | 5 | 3.070 | 3.323 |
| 3s | $CH_3O$ | $CH_3$ | I (22), M (17) | $H_2O$ | 222–223 | $C_{10}H_{11}N_5O_3$ | C, H, N[d] | 2.5 | 2.794 | 2.967 |
| 3t | $CH_3O$ | $C_2H_5$ | I (43) | $CH_3CO_2H$ | 233–235 | $C_{11}H_{13}N_5O_3$ | C, H, N | 10 | 3.420 | 2.947 |
| 3u | $CH_3O$ | Br | M (20) | $H_2O$ | 217–219 dec | $C_9H_8BrN_5O_3$ | C, H, N[e] | 2 | 2.798 | 2.990 |
| 3v | H | H | I (42), M (9) | $CH_3CO_2H$ | 220–223 | $C_8H_7N_5O_2$ | C, H, N | 1 | 2.312 | 2.558 |
| 3w | H | $(CH_3)_2NSO_2$ | J (92) | EtOH–$H_2O$ | 240 dec | $C_{10}H_{12}N_6O_4S$ | C, H, N | 0.25 | 1.892 | 1.806 |
| 3x | *n*-$C_3H_7CO$ | $CH_3$ | H (37) | DMF–$H_2O$ | 231–233 dec | $C_{13}H_{15}N_5O_3$ | C, H, N | 4 | 3.063 | |
| 3y | *i*-$C_3H_7CO$ | $CH_3$ | J (66) | MeOH–$H_2O$ | 224–225 dec | $C_{13}H_{15}N_5O_3$ | C, H, N | 5 | 3.160 | |
| 3z | *c*-$C_3H_5CO$ | $CH_3$ | J (95) | DMF–$H_2O$ | 261–263 dec | $C_{13}H_{13}N_5O_3$ | C, H, N | 5 | 3.157 | |
| 3aa | $C_6H_5CH_2CO$ | $CH_3$ | J (50) | EtOH | 202 | $C_{17}H_{15}N_5O_3$ | C, H, N | 0.1 | 3.528 | |
| 3ab | $CF_3CO$ | $CH_3$ | J (81) | $CH_3NO_2$ | 248–249 dec | $C_{11}H_8F_3N_5O_3$ | C, H, N | 0.2 | 1.800 | |
| 3ac | $NH_2CO$ | $CH_3$ | text (60) | DMF | 305–306 | $C_{10}H_{10}N_6O_3$ | C, H, N[f] | 5 | 3.118 | |
| 3ad | $(CH_3)_2NCO$ | $CH_3$ | H (58) | $CH_3NO_2$ | 235 | $C_{12}H_{14}N_6O_3$ | C, H, N | 1 | 2.463 | |
| 3ae | $CH_3OCO$ | $CH_3$ | H (18) | $CH_3NO_2$ | 238–240 | $C_{11}H_{11}N_5O_4$ | C, H, N | 2 | 2.744 | |
| 3af | $C_2H_5OCO$ | $CH_3$ | H (13) | $CH_3NO_2$ | 252–254 | $C_{12}H_{13}N_5O_4$ | C, H, N | 10 | 3.464 | |
| 3ag | HOCO | $CH_3$ | text (90) | DMF–$H_2O$ | 264 dec | $C_{10}H_9N_5O_4$ | C, H, N | 0.2 | 1.721 | |
| 3ah | $HN_4C$ | $CH_3$ | J (33) | DMF–$H_2O$ | 264 | $C_{10}H_7N_9O_2$ | C, H, N | 1 | 2.455 | |
| 3ai | $HON{=}CCH_3$ | $CH_3$ | text (38) | DMF–$H_2O$ | 245–247 | $C_{11}H_{12}N_6O_3$ | C, H, N | 35 | 3.985 | |
| 3aj | $CH_3ON{=}CCH_3$ | $CH_3$ | text (63) | DMF–$H_2O$ | 271–273 | $C_{12}H_{14}N_6O_3$ | C, H, N | 10 | 3.463 | |

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed, except as shown in subsequent footnotes. [b] Activity relative to M&B 22,948 (=1) in the rat PCA test following iv administration. The dose of M&B 22,948 required for 100% inhibition was 0.1 mg/kg. See ref 1b. [c] Calculated by eq 1. [d] N: calcd, 28.1; found, 27.5. [e] N: calcd, 22.3; found, 22.8. [f] N: calcd, 32.1; found, 31.4.

Table III. 2-(Benzyloxy)-*N*-1*H*-tetrazol-5-ylbenzamides 6

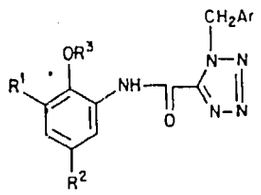


6

| no. | R¹ | R² | method | % yield | mp, °C | cryst solvent | formula | anal.[a] |
|---|---|---|---|---|---|---|---|---|
| 6a | H | H | D | 47 | 265–266 dec | DMF | $C_{15}H_{13}N_5O_2$ | H, N; C[b] |
| 6b | H | $CH_3$ | D | 54 | 259–260 | DMF–$H_2O$ | $C_{15}H_{15}N_5O_2$ | C, H, N |
| 6c | H | Cl | D | 20 | 256–257 dec | DMF–$H_2O$ | $C_{15}H_{12}ClN_5O_2$ | C, H, Cl, N |
| 6d | H | $CF_3$ | A | 70 | 248–249 | EtOH | $C_{16}H_{12}F_3N_5O_2$ | C, H, N |
| 6e | H | $PhCH_2O$ | D | 50 | 249–252 | DMF | $C_{22}H_{19}N_5O_3$ | C, H |

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed, except as shown in subsequent footnotes. [b] C: calcd, 61.0; found, 60.0.

Table IV. *N*-Aryl-1-benzyltetrazole-5-carboxamides 7

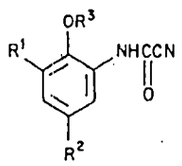


7

| no. | $R^1$ | $R^2$ | $R^3$ | Ar | % yield | mp, °C | cryst solvent | formula | anal.[a] |
|---|---|---|---|---|---|---|---|---|---|
| 7a | $CH_3CO$ | H | H | $p$-$CH_3OC_6H_4$ | 80 | 155–157 | MeCN | $C_{18}H_{17}N_5O_4$ | C, H, N |
| 7b | $CH_3CO$ | $CH_3$ | H | $C_6H_5$ | 93 | 183–184 | MeCN | $C_{18}H_{17}N_5O_3$ | C, H, N |
| 7c | $CH_3CO$ | $CH_3$ | H | $p$-$CH_3OC_6H_4$ | 84 | 182–185 | EtOH | $C_{19}H_{19}N_5O_4$ | C, H, N |
| 7d | $CH_3CO$ | $C_2H_5$ | H | $C_6H_5$ | 71 | 175–176 | $CH_3CO_2H$ | $C_{19}H_{19}N_5O_3$ | C, H, N |
| 7e | $CH_3CO$ | $C_2H_5$ | H | $p$-$CH_3OC_6H_4$ | 70 | 143–145 | MeCN | $C_{20}H_{21}N_5O_4$ | C, H, N |
| 7f | $CH_3CO$ | $t$-$C_4H_9$ | H | $p$-$CH_3OC_6H_4$ | 44 | 107–109 | MeOH | $C_{22}H_{25}N_5O_4$ | H, N; C[b] |
| 7g | $CH_3CO$ | F | H | $C_6H_5$ | 80 | 205–208 | MeCN | $C_{17}H_{14}FN_5O_3$ | C, H, F, N |
| 7h | $CH_3CO$ | F | H | $p$-$CH_3OC_6H_4$ | 56 | 180–182 | MeCN | $C_{18}H_{16}FN_5O_4$ | C, H, F, N |
| 7i | $CH_3CO$ | Cl | H | $p$-$CH_3OC_6H_4$ | 36 | 201–203 | MeCN | $C_{18}H_{16}ClN_5O_4$ | C, H, Cl, N |
| 7j | $CH_3CO$ | Br | H | $p$-$CH_3OC_6H_4$ | 59 | 202–204 | MeCN | $C_{18}H_{16}BrN_5O_4$ | H, Br, N; C[c] |
| 7k | $CH_3CO$ | $CH_3O$ | H | $p$-$CH_3OC_6H_4$ | 75 | 158–161 | MeCN–$Et_2O$ | $C_{19}H_{19}N_5O_5$ | C, H, N |
| 7l | $CH_3CO$ | CN | H | $p$-$CH_3OC_6H_4$ | 42 | 240–242 | MeCN | $C_{19}H_{16}N_6O_6$ | C, H, N |
| 7m | $CH_3CO$ | $NO_2$ | H | $p$-$CH_3OC_6H_4$ | 57 | 221–223 | MeCN | $C_{18}H_{16}N_6O_6$ | C, H, N |
| 7n | $CH_3CO$ | $CH_3SO_2$ | H | $p$-$CH_3OC_6H_4$ | 39 | 234–237 | MeCN | $C_{19}H_{19}N_5O_6S$ | H, N; C[d] |
| 7o | $CH_3CO$ | $CH_3CO$ | H | $p$-$CH_3OC_6H_4$ | 57 | 172–175 | MeCN | $C_{20}H_{19}N_5O_5$ | H; C; N[e] |
| 7p | $CH_3CO$ | $NHCOCH_3$ | H | $p$-$CH_3OC_6H_4$ | 10 | 170 | | $C_{20}H_{20}N_6O_5$ | H; C; N[f] |
| 7q | $C_2H_5CO$ | CN | H | $p$-$CH_3OC_6H_4$ | 72 | 214–216 | MeCN | $C_{20}H_{18}N_6O_4$ | H, N; C[g] |
| 7r | $CH_3O$ | H | $C_6H_5CH_2$ | $C_6H_5$ | 72 | 145–147 | EtOH | $C_{23}H_{21}N_5O_3$ | C, H, N |
| 7s | $CH_3O$ | $CH_3$ | $C_6H_5CH_2$ | $C_6H_5$ | 4 | 179–181 | EtOH | $C_{24}H_{23}N_5O_3$ | C, H, N |
| 7t | $CH_3O$ | $C_2H_5$ | $C_6H_5CH_2$ | $C_6H_5$ | 50 | 150–151 | $MeCO_2Et$ | $C_{25}H_{25}N_5O_3$ | H, N; C[h] |
| 7u | H | H | $C_6H_5CH_2$ | $C_6H_5$ | 50 | 140–142 | EtOH | $C_{22}H_{19}N_5O_2$ | C, H, N |
| 7v | H | $(CH_3)_2NSO_2$ | H | $p$-$CH_3OC_6H_4$ | 66 | 215 dec | EtOH–$H_2O$ | $C_{18}H_{20}N_6O_5S$ | C, H, N |
| 7w | $n$-$C_3H_7CO$ | $CH_3$ | H | $C_6H_5$ | 78 | 166–169 | $CHCl_3$–EtOH | $C_{20}H_{21}N_5O_3$ | C, H, N |
| 7x | $i$-$C_3H_7CO$ | $CH_3$ | H | $p$-$CH_3OC_6H_4$ | 79 | 144–145 | $CHCl_3$–EtOH | $C_{21}H_{23}N_5O_3$ | C, H, N |
| 7y | $c$-$C_3H_5CO$ | $CH_3$ | H | $p$-$CH_3OC_6H_4$ | 64 | 180–182 | $C_6H_6$ | $C_{21}H_{21}N_5O_4$ | H, N; C[i] |
| 7z | $C_6H_5CH_2CO$ | $CH_3$ | H | $p$-$CH_3OC_6H_4$ | 62 | 202–205 | $CHCl_3$–MeOH | $C_{25}H_{23}N_5O_4$ | C, H, N |
| 7aa | $CF_3CO$ | $CH_3$ | H | $p$-$CH_3OC_6H_4$ | 85 | 122–124 | petroleum (100–120 °C) | $C_{19}H_{16}F_3N_5O_4$ | H, F, N; C[j] |
| 7ab | $(CH_3)_2NCO$ | $CH_3$ | H | $C_6H_5$ | 64 | 224–225 | $CHCl_3$–MeOH | $C_{19}H_{20}N_6O_3$ | C, H, N |
| 7ac | $CH_3OCO$ | $CH_3$ | H | $C_6H_5$ | 70 | 168–170 | $CHCl_3$–MeOH | $C_{18}H_{17}N_5O_4$ | H, N; C[k] |
| 7ad | $C_2H_5OCO$ | $CH_3$ | H | $C_6H_5$ | 66 | 189–191 | $CHCl_3$–EtOH | $C_{19}H_{19}N_5O_4$ | C, H, N |
| 7ae | $HN_4C$ | $CH_3$ | H | $p$-$CH_3OC_6H_4$ | 24 | 220 | DMF–$H_2O$ | $C_{18}H_{17}N_9O_3$ | C, H, N |
| 7af | $p$-$CH_3OC_6H_4$-$CH_2NHCO$ | $CH_3$ | H | $p$-$CH_3OC_6H_4$ | 57 | 210 | $CHCl_3$–MeOH | $C_{26}H_{26}N_6O_5$ | C, H, N |

[a] Analytical results were within ±0.4% of the theoretical value for all elements listed, except as shown in subsequent footnotes. [b] C: calcd, 62.4; found, 61.8. [c] C: calcd, 48.4; found 49.0. [d] C: calcd, 51.2; found, 50.4. [e] C: calcd, 58.7; found, 58.2. N: calcd, 17.1; found, 16.5. [f] C: calcd, 56.3; found, 55.4. N: calcd, 20.2; found, 19.5. [g] C: calcd, 59.1; found, 59.6. [h] C: calcd, 67.7; found, 67.0. [i] C: calcd, 61.9; found, 61.2. [j] C: calcd, 52.4; found, 51.9. [k] C: calcd, 58.9; found, 58.1.

Table V. Cyanoformanilides 9



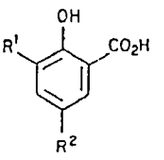
9

| no. | $R^1$ | $R^2$ | $R^3$ | % yield | mp, °C | formula | anal.[a] |
|---|---|---|---|---|---|---|---|
| 9a | $CH_3CO$ | H | H | 50 | 139–141 | $C_{10}H_8N_2O_3$ | na[b] |
| 9b | $CH_3CO$ | $CH_3$ | H | 48 | 155 | $C_{11}H_{10}N_2O_3$ | C, H, N |
| 9c | $CH_3CO$ | $C_2H_5$ | H | 56 | 125–127 | $C_{12}H_{12}N_2O_3$ | H, N; C[c] |
| 9d | $CH_3CO$ | $n$-$C_3H_7$ | H | 25 | 124–125 | $C_{13}H_{14}N_2O_3$ | H, N; C[d] |
| 9e | $C_2H_5CO$ | $CH_3$ | H | 37 | 145–150 dec | $C_{12}H_{12}N_2O_3$ | na[b] |
| 9f | $C_2H_5CO$ | $C_2H_5$ | H | 40 | 138–140 | $C_{13}H_{14}N_2O_3$ | C, H, N |
| 9g | $CH_3O$ | $CH_3$ | $C_6H_5CH_2$ | 45 | 94–95 | $C_{17}H_{16}N_2O_3$ | na[b] |
| 9h | $CH_3O$ | Br | $C_6H_5CH_2$ | 23 | 85 dec | $C_{16}H_{13}BrN_2O_3$ | C, H, Br, N |

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed, except as shown in subsequent footnotes. [b] The sample was pure by TLC and was used without analysis. [c] C: calcd, 62.1; found, 62.8. [d] C: calcd, 63.4; found, 62.9.

preparations the *N*-benzyl group was removed with aluminum chloride (method H). For some derivatives it was necessary to protect the phenolic function as a benzyl ether (7; Ar = Ph, $R^3$ = $CH_2Ph$) and subsequently both *O*- and *N*-benzyl groups were removed by catalytic reduction (method I). The *N*-(*p*-methoxybenzyl) group is an alternative protecting group that is conveniently removed by hot trifluoroacetic acid, and this method was successful for both 1-(*p*-methoxybenzyl) derivatives (7; Ar = 4-$CH_3OC_6H_4$, $R^3$ = H) (method J) and 2-(*p*-methoxybenzyl)

Table VI. 2-Hydroxybenzoic Acids 4

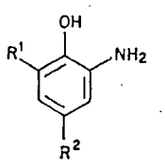


4

| no. | $R^1$ | $R^2$ | % yield | cryst solvent | mp, °C | formula | anal.[a] |
|---|---|---|---|---|---|---|---|
| 4a | $CH_3CO$ | H | 57 | $H_2O$ | 135–136 | $C_9H_8O_4$ | C, H |
| 4b | $CH_3CO$ | $C_2H_5$ | 67 | $CCl_4$ | 113–116 | $C_{11}H_{12}O_4$ | C, H |
| 4c | $CH_3CO$ | $n$-$C_3H_7$ | 56 | $CCl_4$–petrol | 95–96 | $C_{12}H_{14}O_4$ | C, H |
| 4d | $CH_3CO$ | $i$-$C_4H_9$ | 34 | $MeCO_2Et$ | 131–133 | $C_{13}H_{16}O_4$ | na[b] |
| 4e | $CH_3CO$ | $t$-$C_4H_9$ | 39 | $MeCO_2Et$ | 159–161 | $C_{13}H_{16}O_4$ | C, H |
| 4f | $CH_3CO$ | F | 9 | EtOH–$H_2O$ | 158–161 | $C_9H_7FO_4$ | C, H |
| 4g | $CH_3CO$ | $NO_2$ | 63 | $H_2O$ | 208–209 | $C_9H_7NO_6$ | C, H, N |
| 4h | $CH_3CO$ | $NHCOCH_3$ | 44 | $CH_3CO_2H$ | 256–258 dec | $C_{11}H_{11}NO_5$ | C, H, N |
| 4i | $C_2H_5CO$ | $C_2H_5$ | 45 | $CCl_4$ | 135–136 | $C_{12}H_{14}O_4$ | C, H |
| 4j | $CH_3O$ | $C_2H_5$ | 42 | $CH_3CO_2H$–$H_2O$ | 141–142 | $C_{10}H_{12}O_4$ | C, H |
| 4k | $CH_3O$ | $t$-$C_4H_9$ | 74 | $HCO_2H$ | 196–199 | $C_{12}H_{16}O_4$ | C, H |
| 4l | $CH_3O$ | CN | 41 | $CH_3OH$ | 228 dec | $C_9H_7NO_4$ | na[b] |
| 4m | $CH_3O$ | CHO | 37 | EtOH–$H_2O$ | 252–256 | $C_9H_8O_5$ | na[b] |
| 4n | HO | $t$-$C_4H_9$ | 38 | EtOH–$H_2O$ | 217–219 | $C_{11}H_{14}O_4$ | C, H |

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed. [b] The sample was not analyzed but was pure by TLC and NMR and was used immediately in the next stage.

Table VII. 2-Aminophenols 10



10

| no. | $R^1$ | $R^2$ | % yield | mp, °C | formula | anal.[a] |
|---|---|---|---|---|---|---|
| 10a | $CH_3CO$ | $CH_3$ | 48 | 55–57 | $C_9H_{11}NO_2$ | C, H, N |
| 10b | $CH_3CO$ | $C_2H_5$ | 60 | 48–51 | $C_{10}H_{13}NO_2$ | C, H, N |
| 10c | $CH_3CO$ | $n$-$C_3H_7$ | 77 | 42–43 | $C_{11}H_{13}NO_2$ | C, H, N |
| 10d | $CH_3CO$ | F | 99 | 113–114 | $C_8H_8FNO_2$ | C, H, F, N |
| 10e | $CH_3CO$ | Br | 31 | 99–102 | $C_8H_8BrNO_2$ | C, H, Br, N |
| 10f | $CH_3CO$ | CN | 65 | 152–156 | $C_9H_8N_2O_2$ | H, N; C[b] |
| 10g | $CH_3CO$ | $NO_2$ | 72 | 172–174 | $C_8H_8N_2O_4$ | C, H, N |
| 10h | $CH_3CO$ | $CH_3CO$ | 49 | 156–160 dec | $C_{10}H_{11}NO_3$ | H, N; C[c] |
| 10i | $C_2H_5CO$ | CN | 70 | 144–146 | $C_{10}H_{10}N_2O_2$ | H, N; C[d] |
| 10j | H | $(CH_3)_2NSO_2$ | 68 | 156–160 | $C_8H_{12}N_2O_3S$ | C, H, N |
| 10k | $n$-$C_3H_7CO$ | $CH_3$ | 77 | 79–81 | $C_{11}H_{15}NO_2$ | C, H, N |
| 10l | $i$-$C_3H_7CO$ | $CH_3$ | 89 | 41–42 | $C_{11}H_{15}NO_2$ | C, H, N |
| 10m | $c$-$C_3H_5CO$ | $CH_3$ | 74 | 79–80 | $C_{11}H_{13}NO_2$ | C, H, N |
| 10n | $C_6H_5CH_2CO$ | $CH_3$ | 74 | 74–76 | $C_{15}H_{15}NO_2$ | H, N; C[e] |
| 10o | $CF_3CO$ | $CH_3$ | 57 | 87–88 | $C_9H_8F_3NO_2$ | C, H, F, N |
| 10p | $(CH_3)_2NCO$ | $CH_3$ | 51 | 108 | $C_{10}H_{14}N_2O_2$ | C, H, N |
| 10q | $CH_3OCO$ | $CH_3$ | 58 | 65–68 | $C_9H_{11}NO_3$ | H, N; C[f] |
| 10r | $C_2H_5OCO$ | $CH_3$ | 89 | 92–93 | $C_{10}H_{13}NO_3$ | C, H, N |
| 10s | $NH_4C$ | $CH_3$ | 79 | 195 | $C_8H_9N_5O$ | C, H, N |
| 10t | $p$-$CH_3OC_6H_4CH_2NHCO$ | $CH_3$ | 56 | 116–116.5 | $C_{15}H_{18}N_2O_3$ | C, H, N |

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed except as shown in subsequent footnotes. [b] C: calcd, 61.4; found, 60.8. [c] C: calcd, 62.2; found, 61.1. [d] C: calcd, 63.2; found, 62.0. [e] C: calcd, 74.7; found, 73.9. [f] C: calcd, 59.7; found, 58.3.

derivatives (8; Ar = 4-$CH_3OC_6H_4$) (method K).

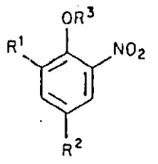
*N*-Aryl-1-benzyltetrazole-5-carboxamide intermediates (7) are shown in Table IV, and these, and also the *N*-aryl-2-benzyltetrazole-5-carboxamides (8), were prepared by reaction of an aromatic amine with the appropriately substituted benzyltetrazole-5-carbonyl chloride. These acid chlorides were formed by treatment of potassium 1- or 2-benzyltetrazole-5-carboxylates (13 and 14) with oxalyl chloride and were used immediately without characterization.

In the course of our studies we have found two preparative routes to the tetrazole-5-carboxamides (3) that do not require protection of the tetrazole ring (methods L–N). In one approach, a 2-aminophenol (10) was condensed with carbonyl dicyanide to give a cyanoformanilide (9; $R^3$ = H) (Table V), which upon treatment with aluminum azide ($AlCl_3$ + $NaN_3$) in tetrahydrofuran gave the desired product (3) (method L). A variation of this approach involved protection of the phenolic function as a benzyl ether (9; $R^3$ = $CH_2Ph$) and subsequent removal by catalytic hydrogenation (method M).

The most direct route to the 1*H*-tetrazole-5-carboxamides (3) involves activation of the dipotassium salt of tetrazole-5-carboxylic acid (11) using Vilsmeier's reagent ($Me_2N^+$=$CHOPOCl_2$·$Cl^-$)[10] followed by reaction of the

(10) Meth-Cohn, O.; Tarnowski, B. *Adv. Hetercycl. Chem.* 1982, *31*, 207.

Table VIII. 2-Nitrophenols and (2-Nitrophenyl)benzyl Ethers 14

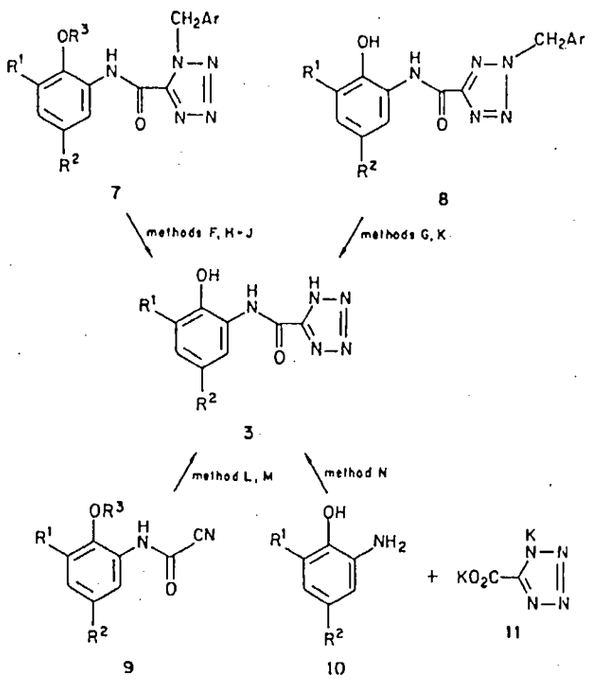


14

| no. | $R^1$ | $R^2$ | $R^3$ | % yield | mp or bp, °C | formula | anal.[a] |
|---|---|---|---|---|---|---|---|
| 14a | $CH_3CO$ | $C_2H_5$ | H | 44 | 118–120 | $C_{10}H_{11}NO_4$ | C, H, N |
| 14b | $CH_3CO$ | $n$-$C_3H_7$ | H | 42 | 67–68 | $C_{11}H_{13}NO_4$ | C, H, N |
| 14c | $CH_3CO$ | $t$-$C_4H_9$ | H | 2 | 80–81 | $C_{12}H_{15}NO_4$ | C, H, N |
| 14d | $CH_3CO$ | F | H | 46 | 87–89 | $C_8H_6FNO_4$ | C, H, F, N |
| 14e | $CH_3CO$ | CN | H | 59 | 142–143 | $C_9H_6N_2O_4$ | C, H, N |
| 14f | $CH_3CO$ | $CH_3SO_2$ | H | 50 | 189–191 | $C_9H_9NO_6S$ | C, H, N, S |
| 14g | $CH_3CO$ | $CH_3CO$ | H | 51 | 104–105 | $C_{10}H_9NO_5$ | H; C; N[b] |
| 14h | $C_2H_5CO$ | $C_2H_5$ | H | 25 | 86–87 | $C_{11}H_{13}NO_4$ | C, H, N |
| 14i | $C_2H_5CO$ | CN | H | 40 | 90 | $C_{10}H_8N_2O_4$ | C, H, N |
| 14j | $CH_3O$ | $C_2H_5$ | H | 23 | 60 | $C_9H_{11}NO_4$ | C, H, N |
| 14k | H | $(CH_3)_2NSO_2$ | H | 55 | 114–116 | $C_8H_{10}N_2O_5S$ | C, H, N |
| 14l | $n$-$C_3H_7CO$ | $CH_3$ | H | 55 | 72–74 | $C_{11}H_{13}NO_4$ | C, H, N |
| 14m | $i$-$C_3H_7CO$ | $CH_3$ | H | 76 | 75–77 | $C_{11}H_{13}NO_4$ | C, H, N |
| 14n | $c$-$C_3H_5CO$ | $CH_3$ | H | 68 | 122–125 | $C_{11}H_{11}NO_4$ | H, N; C[c] |
| 14o | $C_6H_5CH_2CO$ | $CH_3$ | H | 81 | 80–82 | $C_{15}H_{13}NO_4$ | C, H, N |
| 14p | $CF_3CO$ | $CH_3$ | H | 44 | 94–96 | $C_9H_6F_3NO_4$ | C, H, N |
| 14q | $(CH_3)_2NCO$ | $CH_3$ | H | 57 | 160–162 | $C_{10}H_{12}N_2O_4$ | C, H, N |
| 14r | $CH_3OCO$ | $CH_3$ | H | 24 | 145–147 | $C_9H_9NO_5$ | C, H, N |
| 14s | $C_2H_5OCO$ | $CH_3$ | H | 70 | 96–99 | $C_{10}H_{11}NO_5$ | C, H, N |
| 14t | $HN_4C$ | $CH_3$ | H | 42 | 243–245 dec | $C_8H_7N_5O_3$ | C, H, N |
| 14u | $p$-$CH_3OC_6H_4CH_2NHCO$ | $CH_3$ | H | 16 | 170–173 | $C_{16}H_{16}N_2O_5$ | C, H, N |
| 14v | $CH_3O$ | H | $C_6H_5CH_2$ | 93 | 178–181 (0.2 mm) | $C_{14}H_{13}NO_4$ | C, H, N |
| 14w | $CH_3O$ | $CH_3$ | $C_6H_5CH_2$ | 70 | 173–175 (0.4 mm) | $C_{15}H_{15}NO_4$ | C, H, N |
| 14x | $CH_3O$ | $C_2H_5$ | $C_6H_5CH_2$ | 62 | 184–186 (0.1 mm) | $C_{16}H_{17}NO_4$ | C, H, N |
| 14y | $CH_3O$ | Br | $C_6H_5CH_2$ | 81 | 74–76 | $C_{14}H_{12}BrNO_4$ | H, Br, N; C[d] |

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed, except as shown in subsequent footnotes. [b] C: calcd, 53.8; found, 52.5. N: calcd, 6.3; found, 7.2. [c] C: calcd, 59.7; found, 59.2. [d] C: calcd, 49.7; found, 49.0.

Scheme II[a]

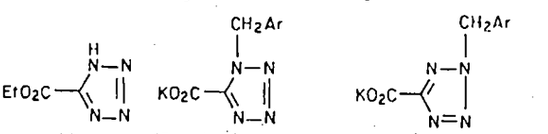


[a] Reagents: (methods F and G) $H_2$-Pd-C; (method H) $AlCl_3$; (method I) $H_2$-Pd-C; (methods J and K) $CF_3CO_2H$; (method L) $AlCl_3$-$NaN_3$; (method M) (i) $AlCl_3$-$NaN_3$, (ii) $H_2$-Pd-C; (method N) $Me_2N^+$=$CHCl^-OPOCl_2$.

active intermediate with an aromatic amine (10) (method N).

Aromatic amines (10) were obtained by reduction of the corresponding nitrobenzene; novel amines are listed in Table VII. Novel nitro derivatives, which were prepared by standard procedures, are listed in Table VIII.

Ethyl 1*H*-tetrazole-5-carboxylate (12),[11] which we have found convenient to prepare by treating a pyridine solution of ethyl cyanoformate with sodium azide and trifluoroacetic acid, is converted to the dipotassium salt (11) using aqueous ethanolic potassium hydroxide. Treatment of the ester (12) with benzyl chloride in the presence of sodium



12  13a, Ar = $C_6H_5$; 13b, Ar = $p$-$CH_3OC_6H_4$  14a, Ar = $C_6H_5$; 14b, Ar = $p$-$CH_3OC_6H_4$

hydride gives a mixture of the 1- and 2-benzyl esters, which were not isolated but were converted to the potassium salts (13a and 14a) with aqueous ethanolic potassium hydroxide and separated by fractional crystallization. A similar procedure gave the 1- and 2-(*p*-methoxybenzyl) salts (13b and 14b). Alternative routes to the 1-benzyl and 1-(*p*-methoxybenzyl) salts (13a and 13b) have recently been described.[12]

## Results

The role of hydrogen bonding in stabilizing a planar conformation of the azapurinone (1)[1,2] prompted us to

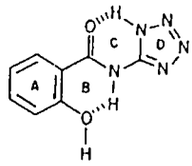
(11) Behringer, H.; Kohl, K. *Ber.* 1956, *89*, 2648.
(12) (a) Klaubert, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Bell, S. C.; Capetola, R. J. *J. Med. Chem.* 1981, *24*, 742. (b) Klaubert, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Capetola, R. J.; Bell, S. C. *J. Med. Chem.* 1981, *24*, 748.

Table IX. Parameter Values[a] Used in the Derivation of Equations 1–3

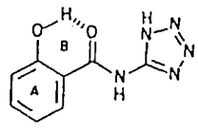
| subst | ES | MR | π | subst | ES | MR | π |
|---|---|---|---|---|---|---|---|
| H | 0.0 | 1.03 | 0.0 | $NO_2$ | −2.52 | 7.36 | −0.28 |
| $CH_3$ | −1.24 | 5.65 | 0.56 | CN | −0.51 | 6.33 | −0.57 |
| $C_2H_5$ | −1.31 | 10.30 | 1.02 | $CF_3$ | −2.40 | 5.02 | 0.88 |
| $n$-$C_3H_7$ | −1.60 | 14.96 | 1.55 | $NHCOCH_3$ | −2.98[b] | 14.93 | −0.97 |
| $i$-$C_4H_9$ | −2.17 | 19.59 | 2.03 | $CH_3S$ | −1.07 | 13.82 | 0.61 |
| $t$-$C_4H_9$ | −2.78 | 19.62 | 1.98 | $CH_3SO_2$ | −2.63[b] | 13.49 | −1.63 |
| F | −0.46 | 0.92 | 0.14 | $(CH_3)_2NSO_2$ | −2.62[b] | 21.88 | −0.78 |
| Cl | −0.97 | 6.03 | 0.71 | HO | −0.55 | 2.85 | −0.67 |
| Br | −1.16 | 8.88 | 0.86 | $C_6H_5$ | −3.82 | 25.36 | 1.96 |
| $CH_3O$ | −0.55 | 7.87 | −0.02 | $CH_3CO$ | −2.84[b] | 11.18 | −0.55 |

[a] Unless otherwise stated, parameter values were taken from the Pomona College Medicinal Chemistry Parameter Files.[18] [b] Calculated by Wooldridge[16] following the method of Charton.[19]

consider some hydrogen-bonded analogues. In particular our interest was directed toward 2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide (15), which in the hydrogen-bonded



15



16

form shown in structure 15 has important similarities with compound 1. In addition to the desirable acidic proton on the tetrazole ring, coplanarity between the phenolic ring (ring A) and the amide function is favored by hydrogen bonding (ring B), and additional hydrogen bonding (ring C) of the tetrazole fragment could mimic the pyrimidine ring of the azapurinone (1). Alternative hydrogen-bonded forms of the molecule (e.g., 16) are possible, and we do not wish to imply that structure 15 is necessarily the preferred geometry. However, the relationship between the hypothetical hydrogen-bonded structure (15) and the azapurinone (1) was the basis of the rationale that led to its synthesis and testing as a potential antiallergic compound.

The novel tetrazole derivative 15 (=2y) (Table I) was found to have one-tenth of the activity of the azapurinone (1) intravenously in the rat PCA test. This observation encouraged the examination of a series of derivatives, and the results of substitution at positions 3 and 5 are shown in Table I (compounds 2a–aq). The 3-acetyl (2a) and 3-methoxy (2p) derivatives of compound 15 showed a significant improvement in potency being equiactive with the azapurinone (1).

The effect of modification of the amide and tetrazole fragments of structure 15 was also investigated. The *N*-methyltetrazole derivatives had less than one-tenth of the activity of the free tetrazole (2y), suggesting an important contribution by the acidic tetrazole proton. Furthermore, the *v*- and *s*-triazole analogues of compound 2y had activity less than one-twentieth that of the tetrazole—a result that may be attributable to the weaker acidity of triazoles relative to tetrazoles.[13] These results suggested that manipulation of the tetrazole fragment was undesirable, and attention was directed toward the amide function. N-Methylation of the amido group of compound 2y resulted in a reduction of activity to one-tenth of that of the parent system (2y), and replacement of the amide function by a number of other functions resulted in either loss or deterioration of activity. However, a significant improvement in activity was achieved when the amide group in compound 2y was reversed to give *N*-(2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamide (3v) (Table II). Compound 3v is 10 times more potent than its isomer 2y. On the basis of the enhancement of activity by a 3-acetyl substituent in the isomeric 2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamides (2) (Table I), the 3-acetyl derivative (3a) (Table II) was synthesized and found to have 10 times the potency of compound 3v. In fact, compound 3a is 100 times more active than the original lead (2y) and 10 times more active than the azapurinone (1). This result led to the synthesis of a series of analogues of compound 3v. The results of modification at positions 3 and 5 are shown in Table II (compounds 3a–aj).

The high potency of several *N*-(3-acetyl-2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamides (3; $R^1 = CH_3CO$) made this series of special interest, and particular attention was paid to the preparation of a series of 5-substituted derivatives (compounds 3a–n) (Table II) from which a short list of candidates for further evaluation as clinically useful antiallergic agents could be selected.

On the basis of broader pharmacological evaluation, compound 3f was selected for further development. Compound 3f has an $ID_{50}$ value in the rat PCA test of 0.004 mg/kg, iv, and is approximately 13 times more potent than the azapurinone (1) ($ID_{50}$ = 0.05 mg/kg, iv) and 130 times more potent that DSCG ($ID_{50}$ = 0.5 mg/kg, iv). Upon oral administration compound 3f has a very flat dose–response curve with an $ID_{50}$ value of approximately 0.16 mg/kg.

## Structure–Activity Relationships

Using data for 64 derivatives described in Tables I and II (compounds 2a–ao, 3a–w), we have derived eq 1 to

$$\log (M_r I) = 1.657 + 0.940\ (\pm 0.138)[3\text{-}CH_3CO] + 1.031\ (\pm 0.226)[3\text{-}C_2H_5CO] + 0.765\ (\pm 0.158)[3\text{-}CH_3O] + 0.901\ (\pm 0.122)[NHCOCN_4H] + 0.287\ (\pm 0.055)ES \quad (1)$$

$$n = 64,\ r = 0.889,\ s = 0.430,\ F = 43.65,\ p < 0.00001$$

describe the intravenous activity in the rat PCA test. Equation 1 is statistically highly significant: the figures in parentheses are for construction of 95% confidence limits, $n$ is the number of data points, $r$ is the correlation coefficient, $s$ is the standard deviation from the regression equation, $F$ is the $F$ statistic, and $p$ is the probability of the relationship arising by chance. The function $\log (M_r I)$, where $M_r$ is the molecular weight of the test compound and $I$ is its activity relative to the reference compound 1, expresses the biological activity in molar terms. Equation 1 is a mixed Hansch/modified Free–Wilson linear multiple-regression model[14] and describes the effect of structural modification at three positions, each of which merits further discussion.

At position 3 of structures 2 and 3 (substituent $R^1$), a limited number of functional groups are of biological sig-

(13) Grimmett, M. R. In "Comprehensive Organic Chemistry"; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 4, p 365.

(14) Kubinyi, H. *J. Med. Chem.* 1976, *19*, 587.

nificance, and this situation is suited to description by Free–Wilson group increments. In deriving eq 1, substituents at position 3 have been restricted to functional groups ($R^1$) that are represented by five or more test compounds (i.e., $R^1$ = H, $CH_3CO$, $C_2H_5CO$, $CH_3O$). Inspection of eq 1 shows that group increments for 3-$CH_3CO$, 3-$C_2H_5CO$, and 3-$CH_3O$ substituents are large and highly significant. The ketone functions effectively increase potency ($I$) by a factor of 10, with a methoxy group making a slightly smaller contribution.

We believe that this high group activity may be attributable either to hydrogen bonding between the phenolic OH and the adjacent ketone or ether group or to chelation of a metal ion by the same substituents. This view is supported by the observation of even greater potency for acetoxime derivatives (compounds **2ap**, **2aq**, **3ai**, and **3aj**). The possible relationship between chelating activity and antiallergic potency has recently been discussed in a review.[3] A description of the chelating properties of some of these molecules will be the subject of a separate paper.[15]

Structural variation of the tetrazole fragment is limited to two groups. In eq 1 this difference is described by a Free–Wilson group increment for the tetrazole-5-carboxamide fragment [$NHCOCN_4H$] with the isomeric $N$-tetrazol-5-yl carbamoyl group [$CONHCN_4H$] taken as reference substituent. In eq 1 the relative contribution of the tetrazole-5-carboxamide group is highly significant. Reversal of the amide linkage (i.e., **2** → **3**) makes a substantial contribution to activity although the reason for the enhancement is not clear. We have produced evidence in the previous section to suggest that the acidity of the tetrazole group may be related to its biological activity and the relatively greater acidity of the tetrazole-5-carboxamide function [$NHCOCN_4H$] may be significant. The $pK_a$ values for the tetrazole groups in the isomers **2g** and **3f** are 4.20 ± 0.02 and 2.36 ± 0.06, respectively, at 25 °C. Both types of tetrazole function will be ionized at physiological pH. The difference in activity may well be associated with the significantly different charge distribution in the two types of tetrazole anion [$NHCOCN_4^-$ and $CONHCN_4^-$]. The charge distribution is, of course, closely related to the stability of the anions and, therefore, to the $pK_a$ values. The $pK_a$ values of the associated phenolic functions are 7.10 ± 0.02 (**2g**) and 8.69 ± 0.02 (**3f**). If phenolic acidity was related to the biological activity, then a variation of activity with the electronic structure of the substituents $R^2$ (**2** and **3**) would be expected but is not observed.

The $N$-phenyl-1$H$-tetrazole-5-carboxamides (**3**) are related to the $N$-phenyloxamic acids and esters, some derivatives of which are also potent antiallergic agents.[12] The electronic similarity between the carboxylate and tetrazole anions is clearly of significance in this context.[3]

A much wider range of substituents is significant at position 5 of structures **2** and **3** (substituent $R^2$), and this position is well suited to investigation by the Hansch method. In planning the synthesis of the derivatives in Tables I and II, substituents were selected to give a wide range of values of structural parameters ($\pi$, $\pi^2$, MR, $F$, $R$, ES) and to minimize interparameter correlation (see Chart I).[16] Note that ES is referenced to H = 0.[17] Equation 1 demonstrates a significant relationship between activity and the adjusted Taft steric parameter ES ($t_{ES}$ = 5.215; $p < 0.0001$). As might be expected from the high negative correlation between ES and molar refractivity (MR) (Chart I), a significant relationship is also obtained using MR (eq 2; $t_{MR}$ = 3.991; $p$ = 0.0002). We interpret these relationships to mean that a small group is required at position 5. Bulky groups possibly inhibit binding of the planar molecules at the receptor. We have also explored the use of more sophisticated steric parameters, including Verloop's Sterimol parameters, but on balance we believe that a closer scrutiny of the shape of the substituents $R^2$ leads to overinterpretation of the results.

**Chart I**

Squared Correlation Matrix ($r^2$) for Parameters Investigated in the Correlation Study (64 Compounds)

| | $\pi^2$ | MR | ES | F | R |
|---|---|---|---|---|---|
| $\pi$ | 0.181 | 0.052 | 0.000 | 0.343 | 0.066 |
| $\pi^2$ | | 0.573 | 0.349 | 0.089 | 0.009 |
| MR | | | 0.629 | 0.013 | 0.013 |
| ES | | | | 0.016 | 0.086 |
| F | | | | | 0.067 |

$$\log (M_r I) = 1.580 + 0.934\ (\pm 0.148)[3\text{-}CH_3CO] + 1.071\ (\pm 0.242)[3\text{-}C_2H_5CO] + 0.791\ (\pm 0.169)[3\text{-}CH_3O] + 0.928\ (\pm 0.131)[NHCOCN_4H] - 0.039\ (\pm 0.010)MR \quad (2)$$

$$n = 64,\ r = 0.871,\ s = 0.462,\ F = 36.34,\ p < 0.00001$$

Although there is no evidence of correlation with $\pi$, $F$, and $R$, a relationship between activity and $\pi^2$ has been found (eq 3; $t_{\pi^2}$ = 3.466; $p$ = 0.001). This probably arises from a chance correlation between $\pi^2$ and substituent size (see Chart I), but we cannot eliminate the possibility that the substituent $R^2$ has an optimum requirement of $\pi$ = 0.

$$\log (M_r I) = 1.331 + 1.023\ (\pm 0.154)[3\text{-}CH_3CO] + 1.145\ (\pm 0.248)[3\text{-}C_2H_5CO] + 0.851\ (\pm 0.173)[3\text{-}CH_3O] + 0.896\ (\pm 0.136)[NHCOCN_4H] - 0.176\ (\pm 0.051)\pi^2 \quad (3)$$

$$n = 64,\ r = 0.863,\ s = 0.474,\ F = 33.80,\ p < 0.00001$$

It is important to note that although a consideration of possible modes of hydrogen bonding of the benzamidotetrazole (e.g., **15** or **16**) was the reason for undertaking the initial investigation of this class of molecules, we have been unable to obtain spectroscopic evidence to support or reject the original hypothesis and we do not claim that biological activity is necessarily associated with any particular mode of intramolecular hydrogen bonding. The general significance of hydrogen bonding in antiallergic molecule has been discussed elsewhere.[3]

## Experimental Section

**Biological Methods.** In screening this series, the determination of $ID_{50}$'s in the rat passive cutaneous anaphylactic (PCA) reaction was less practicable because the variability of response would have necessitated the use of large numbers of animals to achieve meaningful results. Direct comparison with M&B 22,948 (Zaprinast) (**1**)[1] for ability to cause 100% inhibition of the rat PCA reaction following iv administration was more satisfactory and reproducible to within ±25%.[1] The relative activities ($I$) are given in Tables I and II.

The backs of male Sprague-Dawley rats weighing 100–150 g were shaved with electric clippers, and two skin sites diagonally opposite one another were sensitized by intradermal injection of 0.5 mL of a 1–20 dilution of *Nippostrongylus brasiliensis* antiserum. After 48 h each rat was injected intravenously with specific antigen (0.1–0.3 mL of *N. brasiliensis* worm extract, the required volume depending on the degree of sensitization of the rats and the potency of the antigen) and Evans Blue dye (0.2 mL of a 1.5% solution in saline). Each rat was killed 30 min after

(15) Bowden, K.; Sharma, R. K., unpublished results. Sharma, R. K. Ph.D. Thesis, University of Essex, 1979.
(16) Wooldridge, K. R. H. *Eur. J. Med. Chem.* **1980**, *15*, 63.
(17) Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, 91.
(18) Hansch, C.; Leo, A. J. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Wiley: New York, 1979.
(19) Charton, M. *J. Am. Chem. Soc.* **1969**, *91*, 615.

injection of antigen, the shaved area of skin was removed, and the responses were measured from the underside of the skin. The reactions were assessed subjectively by the amount of bluing, a score being allocated to each depending on its size and intensity.

Graded doses of the test compound in 3% aqueous triethanolamine were injected intravenously in groups of rats (at least two at each dose level) immediately before administration of the allergen and dye. The potency ($I$) relative to M&B 22,948 (1) (Zaprinast) was assessed by comparison with groups of rats treated with the graded doses of standard.

**Statistics.** Correlations were derived on a Wang 2200 MVP computer with a multiple-parameter regression analysis program written in BASIC.[20]

**Chemical Methods.** Melting points were determined on an Electrothermal instrument and are uncorrected. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.[21] All structural assignments were consistent with IR and NMR spectra.

For each general synthetic procedure a representative example of the experimental details is given.

**Preparation of *N*-1*H*-Tetrazol-5-ylbenzamides 2 and 6 (Tables I and III). Method A. 3-Acetyl-2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide (2a).** 3-Acetylsalicylic acid (4a) (3.0 g, 0.017 mol) and dicyclohexylcarbodiimide (3.8 g, 0.019 mol) were stirred in dry pyridine (30 mL) for 1 h. Anhydrous 5-aminotetrazole (1.6 g, 0.019 mol) was then added and the mixture stirred at 60 °C for 20 h. After cooling and filtration, the pyridine was removed under reduced pressure and the solid residue dissolved in 2 N ammonium solution with gentle heating. Undissolved solid was removed by filtration, and the cooled filtrate was acidified to pH 1 with concentrated HCl. The solid product was collected, boiled with 90% $HCO_2H$ (5 min), and finally recrystallized from DMF–$H_2O$ to give 2.0 g (49%) of **2a**.

**Method B. 2-(Benzyloxy)-*N*-1*H*-tetrazol-5-ylbenzamide (6a).** 2-(Benzyloxy)benzoic acid[22] (5.85 g, 0.025 mol) and anhydrous 5-aminotetrazole (2.18 g, 0.25 mol) were dissolved in dry pyridine (80 mL). Silicon tetrachloride (1.5 mL) was added dropwise, and stirring at room temperature was then continued (24 h). The mixture was poured onto iced water (300 mL) and stirred for 1 h. The solid product was collected, washed with water, and recrystallized from DMF to give 3.64 g (47%) of **6a**.

**Method C. 3-Acetyl-2-hydroxy-5-methyl-*N*-1*H*-tetrazol-5-ylbenzamide (2b).** 3-Acetyl-5-methylsalicylic acid[23] (1.94 g, 0.01 mol) was converted to the acid chloride by a standard procedure using $SOCl_2$. The acid chloride was dissolved in dry toluene (30 mL), anhydrous 5-aminotetrazole (1.7 g, 0.02 mol) was added, and the mixture was heated under reflux with stirring (18 h). After cooling, the mixture was diluted with light petroleum (bp 60–80 °C) (30 mL). The solid product was collected, stirred with 2 N HCl (30 mL) (30 min), washed with water, and recrystallized from DMF–$CH_3CO_2H$ to give 1.2 g (46%) of **2b**.

**Method D. 2-Hydroxy-5-methoxy-*N*-1*H*-tetrazol-5-ylbenzamide (2ae).** A mixture of 5-methoxysalicylic acid[24] (12.0 g, 0.07 mol), anhydrous 5-aminotetrazole (13.6 g, 0.16 mol), dry toluene (200 mL), and $PCl_3$ (5.2 mL) was heated under reflux with stirring (18 h). After cooling, the solid product was collected, washed with 2 N HCl (200 mL), extracted with hot EtOH (200 mL), and recrystallized from DMF–$H_2O$ to give 2.1 g (12.5%) of **2ae**.

**Method E. 2-Hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide (2y).** 2-(Benzyloxy)-*N*-1*H*-tetrazol-5-ylbenzamide (6a) (3.6 g, 0.012 mol) was added to *N*-methylpyrrolidin-2-one (130 mL), and 2 N NaOH was added dropwise with vigorous shaking until solution formed. The solution was then catalytically hydrogenated at 25 °C (70 psi) with 5% Pd on charcoal. The solvent was removed under reduced pressure and the residue treated with $H_2O$ (175 mL). After adjustment to pH 4.5 (concentrated HCl), the solid product was collected, washed with $H_2O$ and EtOH, and recrystallized from $CH_3CO_2H$ to give 2.2 g (87%) of **2y**.

**3-Acetyl-2-hydroxy-5-nitro-*N*-1*H*-tetrazol-5-ylbenzamide (2k).** Compound **2a** (6.0 g, 0.024 mol) was nitrated with 70% $HNO_3$ (1.62 mL, 0.029 mol) in concentrated $H_2SO_4$ (30 mL) at 0 °C. Conventional workup and recrystallization from $HCO_2H$ gave 5.0 g (63%) of **2k**.

**3-Acetyl-2-hydroxy-5-sulfamoyl-*N*-1*H*-tetrazol-5-ylbenzamide (21).** Compound **2a** (3.0 g, 0.012 mol) was dissolved in chlorosulfonic acid (21 mL). After standing at room temperature (24 h), the mixture was added to iced water (150 mL). The precipitate was collected and added to concentrated ammonia solution (25 mL). Conventional workup and recrystallization from DMF–$H_2O$ gave 0.2 g (5%) of **21**.

**2-Hydroxy-5-(methylsulfonyl)-*N*-1*H*-tetrazol-5-ylbenzamide (2aj).** Compound **2ai** (1.26 g, 0.005 mol) in glacial $CH_3CO_2H$ (10 mL) was stirred with 30% $H_2O_2$ (3 mL) at 100 °C (20 h). The cold mixture was poured onto water (70 mL), and the solid product was collected and recrystallized from glacial acetic acid to give 0.75 g (53%) of **2aj**.

**5-(*N*,*N*-Dimethylsulfamoyl)-2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide (2ak).** Compound **2y** (2.05 g, 0.01 mol) was slowly added to chlorosulfonic acid (15 mL), and the mixture was allowed to stand at room temperature (19 h). The solution was then poured onto iced water (100 mL). The resulting precipitate was collected and washed, and the damp solid was added to a solution of dimethylamine in ethanol (33% w/v) (60 mL). After standing overnight, the mixture was diluted with water (100 mL). Acidification with concentrated HCl and cooling in ice gave a solid that was washed with water and recrystallized from ethanol to give 1.0 g (32%) of **2ak**.

**3-Acetyl-5-ethyl-2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide Oxime (2ap).** A mixture of hydroxylamine hydrochloride (2.8 g, 0.04 mol) and anhydrous sodium carbonate (1.6 g, 0.02 mol) in *N*-methylpyrrolidin-2-one (40 mL) was stirred and heated at 80 °C (10 min). Compound **2c** (5.5 g, 0.02 mol) was then added, and heating (80 °C) and stirring were continued (15 h). After pouring into water (300 mL), the solution was adjusted to pH 1 (concentrated HCl), and the solid product was collected. Recrystallization from DMF–$H_2O$ gave 3.9 g (67%) of **2ap**.

**3-Acetyl-5-ethyl-2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide Methoxime (2aq).** This was prepared in a manner analogous to that for compound **2ap**, using compound **2c** (5.5 g, 0.02 mol), *O*-methylhydroxylamine hydrochloride (3.3 g, 0.04 mol), and sodium carbonate (1.6 g, 0.02 mol). Recrystallization from DMF–$H_2O$ gave 5.3 g (87%) of **2aq**.

**Preparation of 2-Hydroxybenzoic Acids 4 (Table VI).** Novel benzoic acid derivatives are shown in Table VI. Unless otherwise stated, the precursors to the acids in Table VI are known or were prepared by standard methods using readily available materials.

The acids **4b**, **4f**, and **4i** were prepared by Fries rearrangement of the appropriate 2-(acyloxy)benzoic acid using the general procedure described by Amin, Patel, and Patel,[23] and the acids **4c**, **4d**, and **4e** were prepared by standard Friedel–Crafts acylation of the appropriate 2-hydroxybenzoic acid in $CS_2$ solution. Methylation of the appropriate 2,3-dihydroxybenzoic acids using dimethyl sulfate under standard conditions gave the acids **4j** and **4k**. Nitration of compound **4a** using concentrated $H_2SO_4$/concentrated $HNO_3$ at 0–5 °C gave compound **4g**, which upon catalytic reduction in the presence of acetic anhydride gave compound **4h**.

**3-Acetyl-2-hydroxybenzoic Acid (4a).** 3-Formyl-2-hydroxyacetophenone (15.0 g, 0.09 mol) was added over a period of 1 h to a stirred suspension of argentous oxide (23.2 g, 0.10 mol) in 0.9 M NaOH solution (300 mL) at 5–10 °C. After further stirring (1 h), the mixture was filtered. The filtrate was clarified with charcoal and acidified to give the benzoic acid, which was recrystallized from $H_2O$ to give 9.4 g (57%) of **4a**.

**5-Formyl-2-hydroxy-3-methoxybenzoic Acid (4m).** 2-Hydroxy-3-methoxybenzoic acid[25] (21.0 g, 0.125 mol) was dissolved in $CF_3CO_2H$ (200 mL), and hexamethylenetetramine (17.5 g, 0.125 mol) was added with stirring. After heating under reflux (3 h),

(20) Basil, B.; Loveless, A. H.; Wooldridge, K. R. H., unpublished results.
(21) Microanalyses were performed by the Microanalytical Laboratories, May & Baker Ltd.
(22) Cohen, J. B.; Dudley, H. W. *J. Chem. Soc.* **1910**, 1745.
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(24) Tiemann, F.; Muller, W. H. M. *Ber.* **1881**, *14*, 1985.
(25) Perkin, W. H.; Stoyle, F. W. *J. Chem. Soc.* **1923**, 3171.

the $CF_3CO_2H$ was removed under diminished pressure and the residue poured into a mixture of 2 N HCl (250 mL) and ether (125 mL). This mixture was stirred at room temperature (2 h), and after standing overnight, the solid product was collected and recrystallized from EtOH–$H_2O$ to give 9.0 g (37%) of **4m**.

**5-Cyano-2-hydroxy-3-methoxybenzoic Acid (41).** Compound **4m** (1.96 g, 0.01 mol) was added to a solution of hydroxylamine hydrochloride (0.77 g, 0.011 mol) in DMF (10 mL), and the mixture was heated under reflux (15 min). After evaporation to dryness, the residue was triturated with 2 N HCl (6 mL), and the solid product was collected, washed with cold $H_2O$, and recrystallized from MeOH to give 0.8 g (41%) of **41**.

**2-(Benzyloxy)-5-methylbenzoic Acid (5; $R^1$ = H, $R^2$ = $CH_3$).** A mixture of methyl 5-methylsalicylate[26] (3.0 g, 0.018 mol), benzyl chloride (2.38 g, 0.019 mol), and anhydrous $K_2CO_3$ (2.5 g, 0.018 mol) in sulfolane (45 mL) was heated at 100 °C with stirring (21 h). The mixture was poured into ice water (300 mL) and adjusted to pH 6. The solid product was collected and heated under reflux with 2 N NaOH (100 mL) for 2 h. Upon cooling and acidification to pH 2, a colorless precipitate formed that was collected, washed with water (50 mL), and dried over $P_4O_{10}$ to give 2-(benzyloxy)-5-methylbenzoic acid (3.65 g, 85%), mp 98–100 °C. Anal. ($C_{15}H_{14}O_3$) C, H.

**3-Formyl-2-hydroxyacetophenone.** A solution of 2-hydroxy-3-propenylacetophenone (40.9 g, 0.23 mol) in dry ethyl acetate (600 mL) at −70 °C was treated with ozonized oxygen (2% $O_3$) until ozone uptake ceased. $Me_2S$ (60 mL) was added and the mixture allowed to warm to 25 °C (2 h). After standing at room temperature for a furthur 15 h, the volatile material was removed under diminished pressure and $H_2O$ (200 mL) was added to the residue. The resulting precipitate was extracted into $Et_2O$ (250 mL) and the ethereal solution washed (3 × 20 mL) and dried ($Na_2SO_4$). Evaporation gave a solid residue that was recrystallized from petroleum ether (bp 60–80 °C)–$CCl_4$ to give 3-formyl-2-hydroxyacetophenone (20.0 g, 54%), mp 67–69 °C. Anal. ($C_9H_8O_3$) C, H.

**2-Hydroxy-3-propenylacetophenone.** A solution of 3-allyl-2-hydroxyacetophenone[27] (100 g, 0.57 mol) and bis(benzonitrile)palladous chloride (5 g, 0.013 mol) in toluene (300 mL) was heated under reflux (20 h). After removal of the solvent, the resulting oil was distilled under reduced pressure to give 2-hydroxy-3-propenylacetophenone (90.0 g, 90%), bp 153–155 °C (18 mmHg). Anal. ($C_{11}H_{12}O_2$) C, H.

**Preparation of *N*-(2-Hydroxyphenyl)-1*H*-tetrazole-5-carboxamides 3. Table II. Method F. *N*-(3-Acetyl-5-ethyl-2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamide (3c).** Compound **7d** (65.0 g, 0.18 mol) in glacial acetic acid (1350 mL) was catalytically hydrogenated at 20 °C (60 psi) with 5% Pd on charcoal. The catalyst was thoroughly extracted with hot $CHCl_3$–$CH_2Cl_2$ (1:4) for 70 h. Evaporation of the mother liquor and extracts gave a solid product that was recrystallized from $CH_3CO_2H$ to give 40.0 g (82%) of **3c**.

**Method G.** The procedure was the same as for method F except that a 2-benzyltetrazole (8; Ar = $C_6H_5$) was employed as starting material.

**Method H. *N*-(3-Butanoyl-2-hydroxy-5-methylphenyl)-1*H*-tetrazole-5-carboxamide (3x).** $AlCl_3$ (3.0 g, 0.02 mol) was slowly added to a solution of compound **7x** (2.5 g, 0.007 mol) in dry methylene chloride (50 mL) and the mixture stirred and heated under reflux for a further 30 min. After cooling, 2 N HCl (30 mL) was added and the mixture heated (10 min) to destroy the complex. Upon cooling, the solid product was collected and the organic layer evaporated to give a solid residue. The combined solids were recrystallized from DMF–water to give 0.7 g (37%) of **3x**.

**Method I. *N*-(2-Hydroxy-3-methoxyphenyl)-1*H*-tetrazole-5-carboxamide (3r).** Compound **7r** (3.0 g, 0.007 mol) in glacial acetic acid (150 mL) was catalytically hydrogenated at 50 °C (60 psi) with 5% Pd on charcoal. The hot mixture was filtered and the catalyst washed with additional hot glacial acetic acid. Evaporation of the combined acid filtrates give a residue that was dissolved in 2 N $NH_4OH$ (50 mL) and acidified (concentrated HCl). The precipitate was recrystallized from water to give 0.8 g (47%) of **3r**.

**Method J. *N*-(3-Acetyl-2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamide (3a).** Compound **7a** (23.0 g, 0.063 mol) in $CF_3CO_2H$ (400 mL) was heated under reflux (30 min). Evaporation under reduced pressure gave a solid that was recrystallized from glacial acetic acid (300 mL) to give 13.0 g (84%) of **3a**.

**Method K.** The procedure was the same as for method J except that a 2-(*p*-methoxybenzyl)tetrazole (8; Ar = *p*-$CH_3OC_6H_4$) was employed as starting material.

**Method L. *N*-(3-Acetyl-2-hydroxy-5-*n*-propylphenyl)-1*H*-tetrazole-5-carboxamide (3d).** Anhydrous $AlCl_3$ (2.84 g, 0.022 mol) was carefully added to cold, dry THF (35 mL). When all the material had dissolved, sodium azide (4.14 g, 0.064 mol) was added with vigorous stirring followed by 3-acetyl-2-hydroxy-5-*n*-propylcyanoformanilide (**9d**) (1.7 g, 0.007 mol). The mixture was then heated under reflux (24 h) and poured onto a mixture of ice (75 g) and concentrated HCl (20 mL). The solid product was collected, washed with water, and recrystallized from ethanol–water to give 0.8 g (40%) of **3d**.

**Method M. *N*-(5-Bromo-2-hydroxy-3-methoxyphenyl)-1*H*-tetrazole-5-carboxamide (3u).** 2-(Benzyloxy)-5-bromo-3-methoxycyanoformanilide (**9h**) (1.9 g, 0.005 mol) was treated with $AlCl_3$ (2.17 g, 0.016 mol) and sodium azide (3.08 g, 0.047 mol) in dry THF (30 mL) according to the procedure of method L. The oily product was dissolved in 2 N ammonia solution (100 mL), extracted with ether (2 × 50 mL) and the alkaline solution, and then acidified (concentrated HCl) to pH 1. The resulting oil was dissolved in ethanol and catalytically hydrogenated at 20 °C (atmospheric pressure) with 5% Pd on charcoal. Evaporation gave a brown solid that upon recrystallization from water gave 0.3 g (20%) of **3u**.

**Method N. *N*-(3-Acetyl-5-fluoro-2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamide (3f).** Dry DMF (6.0 mL) in acetonitrile (13.8 mL) was stirred at −20 °C, and a solution of oxalyl chloride (2.1 mL) in acetonitrile (2.3 mL) was slowly added. After 15 min, compound **11** (4.56 g, 0.02 mol) was added, and after stirring for a further 20 min, a solution of the amine (**10d**) (2.04 g, 0.02 mol) and pyridine (8 mL) in acetonitrile (10 mL) was added dropwise (30 min). The stirred mixture was allowed to warm to room temperature (1 h) and finally heated under reflux (30 min). After cooling, the mixture was poured into water (100 mL) and the brown solution acidified to pH 1 (concentrated HCl). The solid product was recrystallized from acetonitrile to give 4.3 g (68%) of **3f**.

***N*-(3-Carbamoyl-2-hydroxy-5-methylphenyl)-1*H*-tetrazole-5-carboxamide (3ac).** Compound **7af** (4.8 g, 0.01 mol) and anisole (4.8 mL) in $CF_3CO_2H$ (100 mL) were heated under reflux on a steam bath (1 h). The solvent was removed under diminished pressure, and ether (100 mL) was added to the residue. The solid product was collected and recrystallized from DMF to give 1.5 g (60%) of **3ac**.

***N*-(3-Carboxy-2-hydroxy-5-methylphenyl)-1*H*-tetrazole-5-carboxamide (3ag).** Compound **3ae** (3.5 g, 0.013 mol) in 2 N NaOH (500 mL) was stirred at room temperature (30 min). Acidification gave a solid product that was recrystallized from DMF–$H_2O$ to give 3.0 g (90%) of **3ag**.

***N*-(3-Acetyl-2-hydroxy-5-methylphenyl)-1*H*-tetrazole-5-carboxamide Oxime (3ai).** A mixture of hydroxylamine hydrochloride (1.1 g, 0.016 mol), anhydrous sodium carbonate (0.6 g), $H_2O$ (1 mL), and *N*-methylpyrrolidin-2-one (10.5 mL) was stirred and heated to 90 °C (15 min). Compound **3b** (1.0 g, 0.004 mol) was then added, and heating (95–100 °C) and stirring were continued (21 h). After pouring into 2 N HCl (50 mL), the solid product was collected, washed, and recrystallized from DMF–$H_2O$ to give 0.4 g (38%) of **3ai**.

***N*-(3-Acetyl-2-hydroxy-5-methylphenyl)-1*H*-tetrazole-5-carboxamide Methoxime (3aj).** This was prepared in a manner analogous to that for compound **3ai** using compound **3b** (1.0 g, 0.004 mol), *O*-methyl hydroxylamine hydrochloride (0.96 g, 0.01 mol), $H_2O$ (2 mL), and sodium carbonate (1.09 g). Recrystallization from DMF–$H_2O$ gave 0.7 g (63%) of **3aj**.

**Preparation of *N*-Aryl-1-benzyltetrazole-5-carboxamides 7 (Table IV).** These derivatives were prepared from the appropriate aromatic amine (Table VII) and either potassium 1-benzyltetrazole-5-carboxylate (**13a**) or potassium 1-(4-methoxy-

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(27) Jakahashi, T.; Oshika, T. *J. Pharm. Soc.* **1954**, *74*, 48.

benzyl)tetrazole-5-carboxylate (13b). The following example gives typical conditions.

**N-(3-Acetyl-2-hydroxyphenyl)-1-(4-methoxybenzyl)tetrazole-5-carboxamide (7a).** A mixture of potassium 1-(4-methoxybenzyl)tetrazole-5-carboxylate (13b) (24.5 g, 1.1 mol) and pyridine (4.5 mL) in dry toluene (500 mL) was stirred and cooled to 10 °C. $SOCl_2$ (75 mL) was then added rapidly and the mixture stirred at 20 °C (1 h). The solid KCl was removed by filtration under vacuum, and evaporation of the filtrate gave the crude acid chloride.

The acid chloride in dry $CH_2Cl_2$ (350 mL) was added dropwise to a stirred solution of 2-acetyl-6-aminophenol[28] (12.4 g, 0.08 mol) and pyridine (7.0 mL) in dry $CH_2Cl_2$ (450 mL) maintained at 10 °C. The total mixture was then stirred at 20 °C (1 h), and $CH_2Cl_2$ (1500 mL) was then added. The solution was washed (2 × 500 mL of $H_2O$), dried ($MgSO_4$), and evaporated to give a crude yellow-orange product. Recrystallization from $CH_3CN$ (200 mL) gave 24.0 g (80%) of 7a.

**N-(3-Acetyl-5-ethyl-2-hydroxyphenyl)-2-benzyltetrazole-5-carboxamide (8; $R^1 = CH_3CO$, $R^2 = C_2H_5$, Ar = $C_6H_5$).** Using potassium 2-benzyltetrazole-5-carboxylate (14a) (0.9 g, 0.004 mol) and 2-acetyl-6-amino-4-ethylphenol (10b) (0.6 g, 0.003 mol) according to the procedure described for compound 7a, after recrystallization of the product from EtOH, gave 0.77 g (57%) of 8 ($R^1 = CH_3O$, $R^2 = C_2H_5$, Ar = $C_6H_5$), mp 160–162 °C. Anal. ($C_{19}H_{19}N_5O_3$) C, H, N.

**N-(3-Acetyl-5-ethyl-2-hydroxyphenyl)-2-(4-methoxybenzyl)tetrazole-5-carboxamide (8; $R^1 = CH_3CO$, $R^2 = C_2H_5$, Ar = $p$-$CH_3OC_6H_4$).** Using potassium 2-($p$-methoxybenzyl)-tetrazole-5-carboxylate (14b) (1.5 g, 0.006 mol) and 2-acetyl-6-amino-4-ethylphenol (10b) (0.9 g, 0.005 mol) according to the procedure described for compound 7a gave, after recrystallization from EtOH, 1.48 g (77%) of 8 ($R^1 = CH_3CO$, $R^2 = C_2H_5$, Ar = $p$-$CH_3OC_6H_4$), mp 159–161 °C. Anal. ($C_{20}H_{21}N_5O_4$) C, H, N.

**Preparation of Cyanoformanilides 9 (Table V).** The following example is representative of the method used to prepare the derivatives in Table V.

**3-Acetyl-2-hydroxy-5-methylcyanoformanilide (9b).** A solution of $Me_2S$ (14 mL) in dry ether (35 mL) was stirred at 0 °C, and tetracyanoethylene oxide (3.66 g, 0.025 mol) was added. After 1 h the solid product [$Me_2SC(CN)_2$] was collected and washed with ether (50 mL), and the combined filtrates, containing carbonyldicyanide, were cooled to 0 °C.

A solution of 3-acetyl-2-hydroxy-5-methylaniline (10a) (4.2 g, 0.025 mol) in dry ether (50 mL) was added dropwise to the chilled carbonyl dicyanide solution over a period of 15 min. Stirring at 0 °C was continued (1 h), and the solid product was then collected. Recrystallization from toluene gave 2.6 g (48%) of 9b.

**Preparation of 2-Aminophenols 10 (Table VII).** Novel fully characterized 2-aminophenols are shown in Table VII. In some cases the intermediate amines were used in subsequent stages without purification.

With the exception of compounds **10e** and **10g**, the amines were prepared by hydrogenation of the corresponding nitrophenol using 5% Pd/C catalyst in ethanol. Compound **10e** was prepared by reduction of 2-acetyl-4-bromo-6-nitrophenol[29] using 20% aqueous titanous chloride, and compound **10g** was prepared by reduction of 6-acetyl-2,4-dinitrophenol[30] using a mixture of ammonium chloride and sodium sulfide in hot MeOH.

**Preparation of 2-Nitrophenols and (2-Nitrophenol)benzyl Ethers. Table VIII.** Novel nitrobenzene derivatives are shown in Table VIII. These were prepared by nitration of the appropriate phenol at −20 °C using standard reagents and, where appropriate, alkylation using benzyl chloride. All precursors to the derivatives in Table VIII are known or were prepared by standard methods using readily available materials.

**Preparation of Tetrazole Intermediates. Ethyl 1*H*-Tetrazole-5-carboxylate.** A solution of ethyl cyanoformate (2.5 g, 0.025 mol) in dry pyridine (10 mL) was treated with a chilled mixture of $CF_3CO_2H$ (4.4 mL) and dry pyridine (15 mL). Sodium azide (1.8 g, 0.027 mol) was then added to the stirred solution, and the mixture was stirred at 60 ± 5 °C (48 h). After cooling, the product was poured into a mixture of ice (50 g) and concentrated HCl (20 mL) and the aqueous mixture extracted with ether (3 × 50 mL). Evaporation of the dried ($MgSO_4$) ethereal extracts gave an oil that was passed down a silica gel column [petroleum ether (bp 40–60 °C)–ether (1:1) as eluant] to give 1.57 g (44%) of product, mp 88–93 °C (lit.[11] mp 87–88 °C).

**Dipotassium 1*H*-Tetrazole-5-carboxylate (11).** A solution of KOH (0.22 g) in water (0.7 mL) was added to a solution of ethyl 1*H*-tetrazole-5-carboxylate (0.36 g, 0.0025 mol) in hot EtOH (7.5 mL). The solid product that formed immediately was collected and washed with cold EtOH to give 0.16 g (42%) of 11, mp >330 °C. Anal. ($C_2K_2N_4O_2$) C, N.

**Potassium 1- and 2-Benzyltetrazole-5-carboxylates (13a and 14a).** Sodium hydride (0.13 g, 0.006 mol) was added to dry sulfolane (10 mL), and after stirring (5 min), ethyl 1*H*-tetrazole-5-carboxylate (0.71 g, 0.005 mol) was added. After a further 20 min, benzyl chloride (0.7 g, 0.006 mol) was added and the mixture stirred at 60 °C (18 h). After pouring onto ice (25 g), the reaction product was extracted into ether (2 × 25 mL), washed with water (3 × 25 mL), dried ($MgSO_4$), and evaporated to give a pale yellow oil.

The oily product was dissolved in boiling EtOH (10 mL) and treated with a solution of KOH (0.27 g) in water (0.8 mL). The crystalline product was collected at 40–50 °C and washed with EtOH–ether to give 0.2 g (16%) of 14a, mp 272–273 °C. Anal. ($C_9H_7KN_4O_2 \cdot 0.5H_2O$) C, H, N.

Upon cooling, the filtrate gave a second crop of crystals that were collected and washed with EtOH–ether to give 0.16 g (13%) of 13a, mp 199–210 °C [lit.[12b] mp 200 °C dec]. Anal. ($C_9H_7KN_4O_2$) C, H, N.

**Potassium 1- and 2-($p$-Methoxybenzyl)tetrazole-5-carboxylates (13b and 14b).** A procedure identical with that described above starting with ethyl 1*H*-tetrazole-5-carboxylate (0.71 g, 0.005 mol) and $p$-methoxybenzyl chloride (0.9 g, 0.006 mol) gave 0.3 g (40%) of (14b), mp 273–275 °C dec [Anal. ($C_{10}H_9KN_4O_3 \cdot 0.5H_2O$) C, H, N], and 0.26 g (34%) of 13b, mp 192–194 °C dec (lit.[12b] mp 202–204 °C).

**p$K_a$ Measurements.** The p$K_a$ values of compound **2g** (4.20 ± 0.02; 7.10 ± 0.02) and compound **3f** (2.36 ± 0.06; 8.69 ± 0.02) in aqueous media at 25 °C were measured by using the spectroscopic method of Albert and Serjeant.[31] The values quoted are thermodynamic p$K_a$'s corrected for the ionic strength of the buffer solutions.

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**Registry No.** **2a**, 67127-97-3; **2aa**, 100245-51-0; **2ab**, 67127-05-3; **2ac**, 67127-15-5; **2ad**, 67127-15-5; **2ae**, 67127-23-5; **2af**, 67127-11-1; **2ag**, 67127-27-9; **2ah**, 67127-41-7; **2ai**, 67127-07-5; **2aj**, 67127-35-9; **2ak**, 67127-30-4; **2al**, 67127-17-7; **2am**, 67127-10-0; **2an**, 67127-12-2; **2ao**, 67127-01-9; **2ap**, 70986-17-3; **2aq**, 70986-17-3; **2b**, 67127-28-0; **2c**, 67127-42-8; **2d**, 67127-47-3; **2e**, 100245-40-7; **2f**, 67127-45-1; **2g**, 67324-88-3; **2h**, 67126-96-9; **2i**, 67127-46-2; **2j**, 100245-41-8; **2k**, 67127-62-2; **2l**, 67127-40-6; **2m**, 100245-42-9; **2n**, 67127-48-4; **2o**, 67127-49-5; **2p**, 67126-94-7; **2q**, 100245-43-0; **2r**, 100245-44-1; **2s**, 100245-45-2; **2t**, 100245-46-3; **2u**, 100245-47-4; **2v**, 100245-48-5; **2w**, 100245-49-6; **2x**, 100245-50-9; **2y**, 61745-70-8; **2z**, 67127-18-8; **3a**, 70977-58-1; **3aa**, 70977-65-0; **3ab**, 70977-64-9; **3ac**, 100245-60-1; **3ad**, 70977-54-7; **3ae**, 70977-55-8; **3af**, 70977-56-9; **3ag**, 70977-54-7; **3ah**, 100245-59-8; **3ai**, 70977-61-6; **3aj**, 70977-62-7; **3b**, 70977-39-8; **3c**, 70977-41-2; **3d**, 70977-57-0; **3e**, 100245-54-3; **3f**, 70977-46-7; **3g**, 100245-55-4; **3h**, 70977-47-8; **3i**, 70977-48-9; **3j**, 70977-44-5; **3k**, 70977-42-3; **3l**, 70977-66-1; **3m**, 100245-56-5; **3n**, 70977-63-8; **3o**, 70977-59-2; **3p**, 70977-49-0; **3q**, 70977-51-4; **3r**, 70977-67-2; **3s**, 70977-52-5; **3t**, 70977-68-3; **3v**, 70977-38-7; **3w**, 100245-58-7; **3x**,

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70977-53-6; 3y, 70977-43-4; 3z, 70977-45-6; 4 ($R^1$ = $CH_3CO$, $R^2$ = Cl), 1760-85-6; 4 ($R^1$ = $CH_3CO$, $R^2$ = Br), 1760-84-5; 4 ($R^1$ = $CH_3CO$, $R^2$ = $CH_3O$), 55008-13-4; 4 ($R^1$ = $C_2H_5CO$, $R^2$ = $CH_3$), 1760-86-7; 4 ($R^1$ = $R^2$ = $CH_3O$), 61637-60-3; 4 ($R^1$ = $CH_3O$, $R^2$ = $NO_2$), 20718-78-9; 4 ($R^1$ = $CH_3O$, $R^2$ = $NHCOCH_3$), 100245-39-4; 4 ($R^1$ = H, $R^2$ = Br), 89-55-4; 4 ($R^1$ = H, $R^2$ = CN), 10435-57-1; 4 ($R^1$ = H, $R^2$ = $CH_3S$), 32318-42-6; 4 ($R^1$ = H, $R^2$ = $C_6H_5$), 323-87-5; 4 ($R^1$ = H, $R^2$ = $CH_3CO$), 13110-96-8; 4 ($R^1$ = H, $R^2$ = $NHCOCH_3$), 51-59-2; 4 ($R^1$ = $CH_3CO$, $R^2$ = $CH_3$), 1760-83-4; 4 ($R^1$ = $CH_3CO$, $R^2$ = $CH_3$) ( acid chloride), 70986-26-4; 4 ($R^1$ = $CH_3O$, $R^2$ = $CH_3$), 4386-42-9; 4 ($R^1$ = H, $R^2$ = F), 345-16-4; 4 ($R^1$ = H, $R^2$ = $t$–$C_4H_9$), 16094-31-8; 4 ($R^1$ = H, $R^2$ = $CH_3O$), 2612-02-4; 4 ($R^1$ = H, $R^2$ = $NO^2$), 96-97-9; 4 ($R^1$ = H, $R^2$ = $NO_2$) (acid chloride), 3223-20-9; 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**7m**, 70977-90-1; **7n**, 70978-01-7; **7o**, 100245-26-9; **7p**, 70977-91-2; **7q**, 70977-99-0; **7r**, 70978-02-8; **7s**, 70978-17-5; **7t**, 70978-03-9; **7u**, 70977-73-0; **7v**, 100245-27-0; **7w**, 70978-14-2; **7x**, 70977-92-3; **7y**, 70977-94-5; **7z**, 70978-00-6; **8** ($R^1$ = $CH_3CO$, $R^2$ = $C_2H_5$, Ar = $C_6H_5$), 70978-21-1; **8** ($R^1$ = $CH_3CO$, $R^2$ = $C_{15}$, Ar = $P$–$CH_3OC_6H_4$), 70978-04-0; **9a**, 70978-25-5; **9b**, 100245-21-4; **9c**, 70978-26-6; **9d**, 70978-27-7; **9e**, 70978-18-6; **9f**, 70978-28-8; **9g**, 70978-30-2; **9h**, 70978-29-9; **10** ($R^1$ = $CH_3CO$, $R^2$ = Cl), 21312-85-6; **10** ($R^1$ = $CH_3CO$, $R^2$ = $CH_3O$), 55008-15-6; **10** ($R^1$ = $CH_3OCO$, $R^2$ = $NHCOCH_3$), 70978-63-1; **10** ($R^1$ = $CH_3OCO$, $R^2$ = H), 70977-72-9; **10** ($r^1$ = $CH_3CO$, $R^2$ = $t$–$C_{119}$), 100245-20-3; **10** ($R^1$ = $C_2H_5CO$, $R^2$ = $C_2H_5$), 70978-24-4; **10** ($R^1$ = $C_2H_5CO$, $R^2$ = $CH_3$), 70978-23-3; **10** ($R^1$ = $CH_3CO$, $R^2$ = $CH_3SO_2$), 70977-88-7; 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# Quantitative Evaluation of the $\beta_2$-Adrenoceptor Intrinsic Activity of *N-tert*-Butylphenylethanolamines†

Adriaan P. IJzerman, Teake Bultsma, and Hendrik Timmerman*

*Department of Pharmacochemistry, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands.*
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The extent of stimulation of the enzyme adenylate cyclase, and the concomitant production of cAMP, by a number of $\beta$-adrenoceptor agonists, all belonging to the class of the *N-tert*-butylphenylethanolamines, has been determined. The results have been used as direct measures for intrinsic sympathomimetic activity (ISA) and were correlated with various physicochemical parameters of the compounds. Significant correlations were established by means of the method of multiple regression analysis, and it was demonstrated that electronic effects only govern ISA. The use of $^{13}C$ NMR chemical shifts of the aromatic C atoms proved to be a valuable tool in this analysis.

In 1954, Ariëns[1] introduced the concept of intrinsic activity, as a necessary completion to the receptor-occupation theory, originally proposed by Clark.[2] Further refinements were made by Furchgott,[3] Nickerson,[4] and Stephenson,[5] and now it is generally believed that intrinsic activity does

† Dedicated to Jan van Dijk (Duphar, Weesp, The Netherlands) on the occasion of his retirement.

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# Synthesis Based on Affinity Separation (SAS): Separation of Products Having Barbituric Acid Tag from Untagged Compounds by Using Hydrogen Bond Interaction

San-Qi Zhang, Koichi Fukase,* Minoru Izumi, Yoshiyuki Fukase, Shoichi Kusumoto

Department of Chemistry, Graduate School of Science, Osaka University, Machikaneyama 1-1, Toyonaka, Osaka 560-0043, Japan
E-mail: koichi@chem.sci.osaka-u.ac.jp
*Received 6 March 2001*

**Abstract:** A new method is described for affinity purification of synthetic compounds based on molecular recognition between bis(2,6-diaminopyridine)amide of isophthalic acid and a barbituric acid derivative. The desired compounds possessing the barbituric acid derivative as a tag were readily isolated from the reaction mixture by the following procedure. After each reaction cycle, the reaction mixture was applied to the polystyrene column possessing bis(2,6-diaminopyridine)amide of isophthalic acid as an artificial receptor. The compound possessing the barbituric acid tag was selectively adsorbed on the column, whereas other impurities without the tag such as excess reagents and byproducts were washed off. Subsequent desorption with $CH_2Cl_2$-MeOH (1:1) afforded the desired compound with high purity. This new strategy was applied to the synthesis of a heterocycle, peptides, and oligosaccharides.

**Key words:** affinity purification, molecular recognition, molecular tag, oligosaccharide synthesis, high throughput synthesis

Polymer supported synthesis has greatly simplified work-up and purification procedure of organic reactions to establish combinatorial and parallel synthesis.[1] In solid-phase synthesis, the synthetic product at each step on solid support is immediately separated from a reaction mixture by filtration. Although utility of solid-phase synthesis has been confirmed, there still exist several disadvantages: i) some of conventional reaction conditions in solution are not compatible with reactions on solid-supports, ii) the reaction rates on solid-supports are generally lower than those of the corresponding reactions in solutions. In liquid-phase synthesis using soluble polymer support, the reactivity of compounds on the support is similar to that in solution but additional step, i.e., precipitation of the polymer-supported products, is required for their isolation.[1b] Polymer-supported reagents and scavenger resins have made solution synthesis efficient but this strategy is not always effective for multistep synthesis because of the limited availability of the reagents.[2]

Recently, "tag" methodology has been developed as a hybrid method of solid-phase and solution-phase synthesis.[3] In this methodology, a compound having a tag group is easily separated from untagged molecules by using the affinity of the tag with a respective specific functionality. Several tags such as fluorous affinity tags,[3a-c] hydrophobic tags,[3d-f] a 2-pyridylsilyl tag for acidic extraction,[3g] and an anthracene tag for Diels-Alder resin capture/release[3h] have been reported. The "tag" methodology has advantages over polymer-supported synthesis in the following points. Namely, monitoring of reaction is easy by simple and routine methods such as TLC and HPLC. Additional purification of tagged intermediates is possible by other methods after any reaction steps.

We previously reported a new "tag" strategy, termed "synthesis based on affinity separation (SAS)", in which the desired tagged compound was separated from the reaction mixture by solid-phase extraction using specific molecular recognition (Figure 1).[4] In that work, we employed the interaction between a crown ether (32-crown-10) and ammonium ion for SAS.

In the present study, we investigated a new SAS method by using interaction via multiple hydrogen bonds between a guest residue and its artificial receptor. From many artificial receptors reported, we employed Hamilton's receptor, i.e., bis(2,6-diaminopyridine)amide of isophthalic acid, which forms tight complex with barbituric acid via

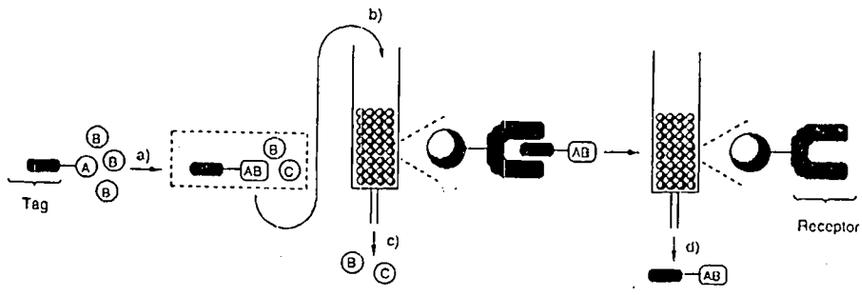



**Figure 1** Synthesis based on affinity separation. A: substrate, B: reagent, AB: product, C: byproduct. a) reaction in solution, b) adsorption of tagged product, c) elution of excess reagent and untagged byproduct, d) desorption of tagged product.

six hydrogen bonds.[5] A barbituric acid moiety was used as a tag and the receptor moiety was bound to polystyrene support (Figure 2).

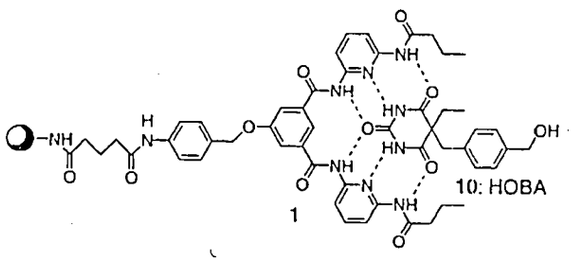
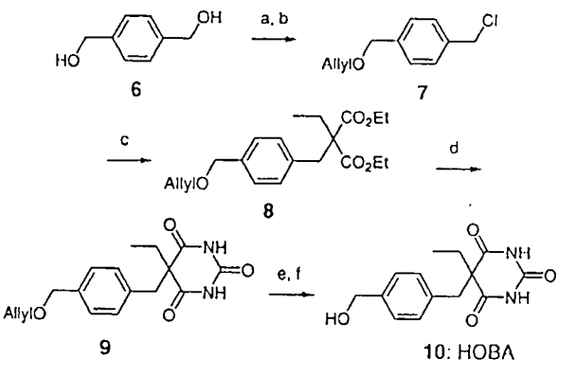



Figure 2 Host-guest interaction of a polymer-supported receptor with the barbituric acid tag.

Polymer-supported artificial receptor (**1**) was synthesized from 5-hydroxyisophthalic acid (**2**) as illustrated in Scheme 1.[6] A highly cross-linked macroporous polystyrene resin ArgoPore$^{TM}$–$NH_2$ (1.16 mmol/g) was used as a support since it gave better results than the usual 1% cross-linked gel-type polystyrene resin in the previous study. The barbituric acid tag **10** (HOBA) was synthesized as shown in Scheme 2.[7]

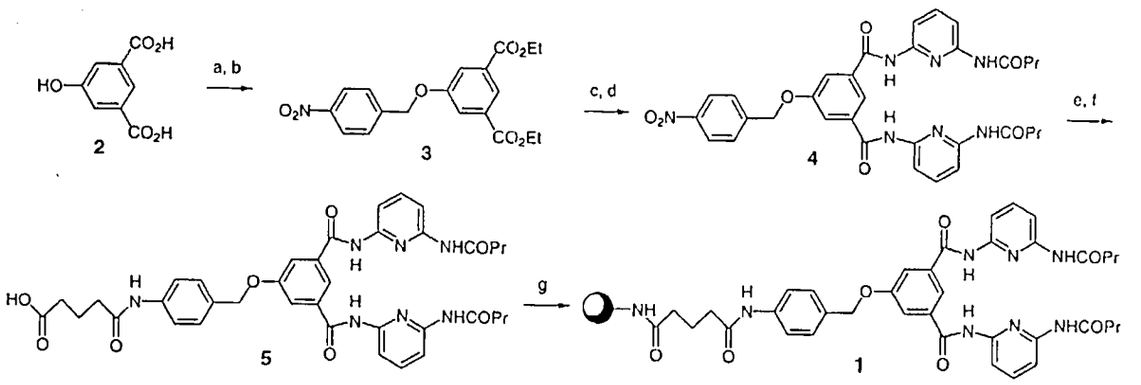
The tagged compounds were effectively retained in the resin column **1** by using nonpolar eluents such as $CH_2Cl_2$, $CHCl_3$, and toluene, which favors the formation of a complex through hydrogen bonds. Since polar solvents disfavor the complex formation, the tagged compounds were readily desorbed from the column by using $CH_2Cl_2$–methanol as an eluent. The separation scale was 0.1 mmol~0.2 mmol for peptides and heterocycle and 0.05 mmol~0.11 mmol for oligosaccharides with 7 g of the resin **1**.

This methodology was first applied to the synthesis of small peptides (Scheme 3).[8] The tag moiety **10** was coupled to the starting Fmoc amino acid **11** by using diisopro-



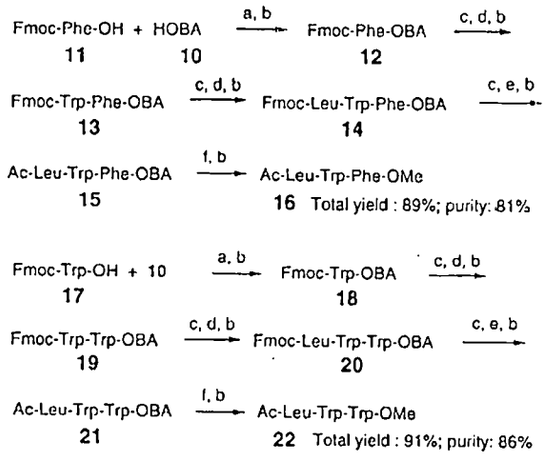

Scheme 2 Reagents and conditions: a) xylylene glycol (2.0 equiv.), NaH (2.2 equiv.), allylBr (1.0 equiv.), THF, 60°C, 7 h, 63%; b) $[Me_2NCl]^+Cl^-$ (1.3 equiv), MeCN, reflux, 30 min, 99%; c) diethyl ethylmalonate (1.06 equiv.), KOBu$^t$ (1.06 equiv.), toluene, reflux, 6.5h, 98%; d) urea (10 equiv.), NaH (4 equiv.), DMSO, rt, 14 h, 81%; e) $[Ir(COD)(PMePh_2)]^+PF_6^-$ (0.045 equiv.), $H_2$, THF, rt, 100 min, f) $I_2/H_2O$, rt, 30 min, 87%.

pylcarbodiimide (DIC) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in $CH_2Cl_2$. The reaction mixture was directly applied to the resin column **1**. The tagged **12** was retained in the column, whereas all untagged compounds such as excess **11**, DIC, DMAP, and *N,N'*-diisopropylurea were washed out from the column simply by elution with $CH_2Cl_2$. Elution of **12** with $CH_2Cl_2$-methanol (1:1) and concentration gave purified **12**. Fmoc group in **12** was then removed with 5% piperidine in DMF. Peptide condensation was carried out by the DIC method in $CH_2Cl_2$ to give dipeptide **13**, which was purified by the same affinity separation. After tripeptide **14** was formed in a similar manner, the removal of the Fmoc group, *N*-acetylation, and purification by the affinity separation afforded **15**. The tag moiety of **15** was then removed by transesterification to give **16**, which was separated from the barbituric acid tag **10** by the affinity separation: the desired compound **16** passed through the



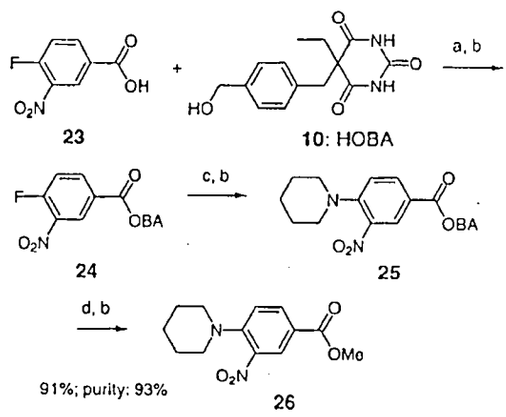

Scheme 1 Reagents and conditions: a) AcCl, EtOH, reflux, 4 h, 98%; b) *p*-nitrobenzyl bromide (1.12 equiv.), $K_2CO_3$, acetone, reflux, 2 h, 97%; c) n-BuLi (1.95 equiv.), 2,6-diaminopyridine (2.0 equiv.), THF, -78 °C to -60 °C, 8 h, 91%; d) PrCOCl (1.4 equiv.), DIEA, THF, rt, 4 h, 92%; e) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, THF, rt, 1.5 h; f) glutaric anhydride (2.0 equiv.), THF, rt, 5 h, 60% over two steps; g) ArgoPore$^{TM}$-$NH_2$ (1.16 mmol/g), DIC, DMAP, DMF, rt, 3 d.

column whereas **10** was adsorbed to the column. The overall yield of the tripeptide **16** was 89% (from HOBA (**10**)) with 81% purity (judged by HPLC analysis at 220 nm). Tripeptide Ac-Leu-Trp-Trp-OMe (**22**) (91% yield with 86% purity) was also synthesized by the same SAS strategy.




**Scheme 3** Reagents and conditions: a) Fmoc-amino acids (1.25 equiv.), DIC (2 equiv.), DMAP, $CH_2Cl_2$; b) affinity separation; c) 5% piperidine in DMF, rt, 8 min; d) Fmoc-amino acids (1.25 equiv.), DIC (2 equiv.), $CH_2Cl_2$; e) $Ac_2O$, TEA, $CH_2Cl_2$; f) 0.2 M NaOMe in MeOH, rt, 10 min.

This new synthetic protocol was then applied to synthesis of *N*-arylpiperidine (Scheme 4). Since 1-methyl-2-pyrrolidone (NMP), which reduces the interaction of the artificial receptor with the tag, was used as a solvent for the aromatic nucleophilic substitution of **24** with piperidine,[9] the reaction mixture was first diluted with $CH_2Cl_2$ and then subjected to the affinity separation. Purification of

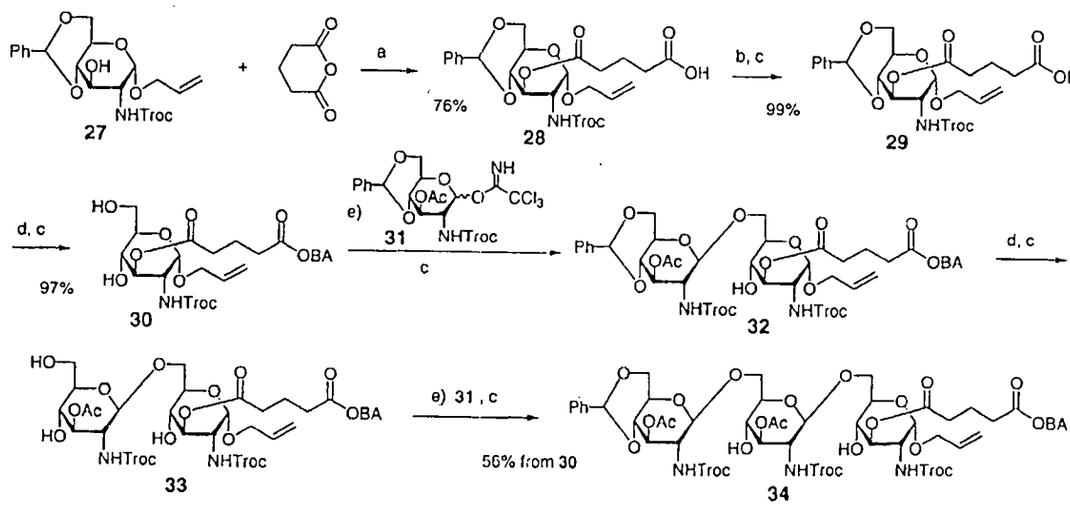



**Scheme 4** Reagents and conditions: a) DIC, DMAP, $CH_2Cl_2$; b) affinity separation; c) piperidine (1.5 equiv.), NMP, rt, 2h; d) 0.2 M MeONa in MeOH, rt, 10 min.

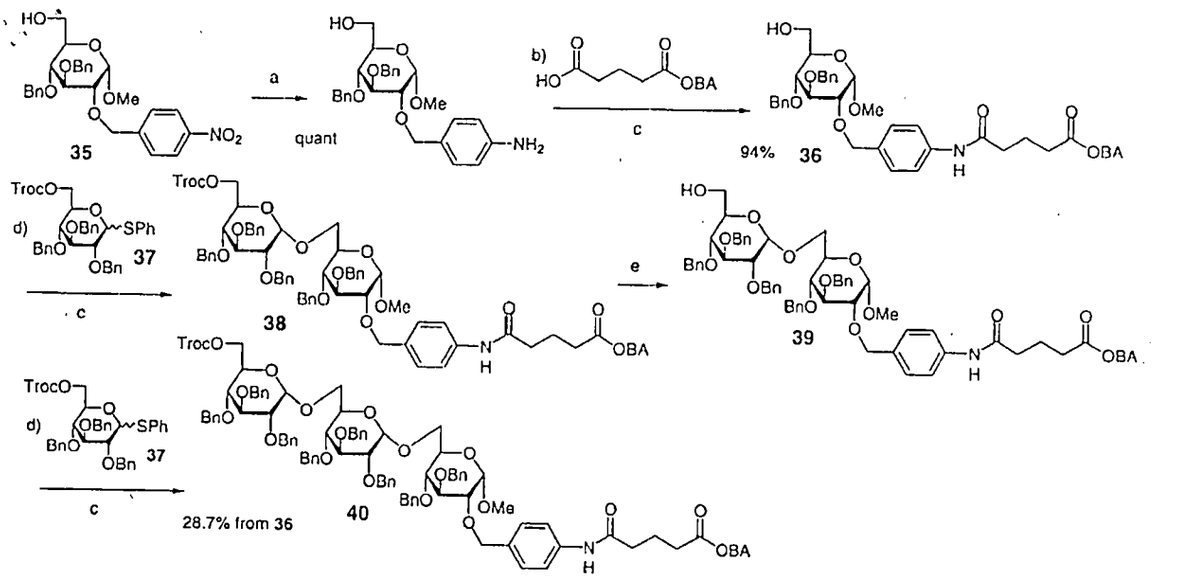
arylpiperidine **25** was thus effected without additional steps for the removal of NMP. Transesterification and isolation by affinity separation gave **26** in overall 91% yield.[10]

We then investigated oligosaccharide synthesis by the present SAS strategy (Scheme 5 and 6). The keys for the success were the following two points: i) the tag moiety was stable under glycosylation conditions and ii) oligosaccharides possessing many protective groups were effectively adsorbed on the resin.

The first example is synthesis of β-(1-6)oligoglucosamine (Scheme 5). The tag **10** was attached to the starting *N*-trichloroethoxycarbonyl (Troc) glucosamine **27** through a glutaric acid spacer. Removal of the benzylidene group of **29** gave a glycosyl acceptor **30**. β-Selective glycosylation of **30** with glycosyl trichloroacetimidate **31** (1.5 equiv. to **30**) was effected by using TMSOTf as a catalyst by virtue




**Scheme 5** Reagents and conditions: a) pyridine, DMAP, $CH_2Cl_2$, 3.5 h; b) HOBA (**10**), DIC, DMAP, $CH_2Cl_2$, 1.5 h; c) affinity separation; d) 5% TFA, 1% $H_2O$ in $CH_2Cl_2$, 0 °C; e) TMSOTf (0.1 equiv.), MS4A, $CH_2Cl_2$, -20 °C, 10 min.




Scheme 6 Reagents and conditions. a) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH; b) DIC, $CH_2Cl_2$; c) affinity separation; d) PhIO, TMSOTf, $Et_2O$/dioxane; e) Zn-Cu couple, AcOH.

of the neighboring participation of the *N*-Troc group to afford the disaccharide **32**.[11] Removal of the benzylidene from **32** followed by glycosylation with **31** (5 equiv.) gave trisaccharide **34**. After each reaction step, the product was rapidly separated from the reaction mixture by the affinity separation in this synthesis, too. Since there are two and three hydroxy groups in acceptors **30** and **33**, respectively, some undesired byproducts were formed by their glycosylation at more hindered 4-positions. These byproducts were not separated by affinity separation like solid-phase synthesis, since they had the tag moiety. The desired trisaccharide **34** was, however, readily purified by additional simple silica-gel chromatography. The purified **34** was thus obtained in 56% yield from **30** after silica-gel column chromatography.[12] In the case of solid-phase synthesis, purification is only possible after products are cleaved from solid-supports. By using the present SAS method, products can be purified by affinity separation as well as other purification methods. Purified synthetic intermediates can be subjected to next reaction. This is important feature of the present methodology.

As shown in Scheme 6, oligosaccharide synthesis was carried out under the conditions for α-selective glycosylation by virtue of the solvent effect of ether using 2-*O*-benzylated thioglycosyl donors. Since the solubilities of glycosyl acceptors having the barbituric acid tag in ether were low, a mixture of ether-dioxane was used as the reaction solvent.[13] We previously found combinations of iodosobenzene (PhIO) and various acids effectively promote glycosylation using thioglycosyl donors.[14] Among those found to be satisfactory, the combination of PhIO and TMSOTf was employed in the present study.[15]

The tagged acceptor **36** was prepared from 4-nitrobenzylglucoside **35** via reduction of the nitro group followed by coupling with the tag moiety (Scheme 6).[16] Glycosylation of the tagged acceptor **36** with excess phenyl 6-*O*-Troc-thioglycoside **37** (1.5 equiv.) using PhIO and TMSOTf gave disaccharide **38** (α:β = 10:1).[17] The 6-*O*-Troc group of **38** was removed and the resulting 6-*O*-free disaccharide **39** was then glycosylated with **37** to give the trisaccharide **40** (28.7% from **36**).[18] After each reaction step, the product was rapidly separated from the reaction mixture by the affinity separation. Since the acylaminobenzyl linker was partly cleaved at the glycosylation step, the final product **40** was purified by silica-gel column chromatography after the affinity separation.

In summary, we have developed a new synthetic strategy based on affinity separation. The present method can be applied to the synthesis of relatively large molecules such as protected oligosaccharides owing to the strong affinity of the barbituric acid tag with its artificial receptor, whereas previous tag strategies have been applied to synthesis of small molecules.[19] The strategy greatly facilitates the purification procedures in solution-phase synthesis and is expected to be particularly useful for multiple parallel synthesis and combinatorial library preparation where application of solid-phase synthesis is difficult.

## Acknowledgement

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(6) The experimental procedure for the preparation of the polymer supported receptor **1**.

Diethyl 5-(4-Nitrophenylmethyloxy)isophthalate (**3**). The mixture of diethyl 5-hydroxyisophthalate (7.68 g, 32.2 mmol), *p*-nitrobenzyl bromide (7.80 g, 36.0 mmol), and $K_2CO_3$ (8.0 g, 58 mmol) in acetone (100 ml) was refluxed for 2 h. After the mixture was cooled to room temperature, insoluble materials were removed by filtration and the filtrate was concentrated in vacuo. The crystalline residue was recrystallized from ethyl acetate and hexane to give **3** (11.6 g, 96.5%). ESI-MS (positive) m/z 396.1 [(M+Na)$^+$].

*N,N'*-Bis[2-(6-aminopyridyl)]-5-(4-nitrophenyl-methyloxy)isophthaldiamide. To a solution of 2,6-diaminopyridine (8.00 g, 73.3 mmol) in anhydrous THF (150 ml) was added 25.0 ml of n-butyl lithium in hexane (2.52 mol•l$^{-1}$) at −78 °C under $N_2$. After the mixture was stirred for 20 min, a solution of **3** (6.00 g, 16.1 mmol) in anhydrous THF (55 ml) was added dropwise. The mixture was stirred at −78 °C to −60 °C for 6 h and water (30 ml) was added to quench the reaction. After addition of EtOAc (200 ml), the organic layer was washed with water and brine, dried over $Na_2SO_4$. Parts of the desired product were crystallized from extracts. Filtration afforded 6.40 g of the product. The filtrate was concentrated in vacuo and the residue was purified by silica-gel column chromatography (EtOAc/hexane = 1:1) to give another 0.90 g of the product. Yield: 7.30 g (90.9%). ESI-MS (positive) m/z 500.2 [(M+H)$^+$].

*N,N'*-Bis[2-(6-butyrylaminopyridyl)]-5-(4-nitrophenylmethyloxy)isophthaldiamide (**4**). To a mixture of *N,N'*-bis[2-(6-aminopyridyl)]-5-(4-nitrophenyl-methloxy)-isophthaldiamide (3.32 g, 3.35 mmol) and *N,N*-diisopropylethylamine (2.5 ml, 14.4 mmol) in THF (80 ml) was added butanoyl chloride (2.0 ml, 19.3 mmol). The mixture was stirred at room temperature for 4 h under $N_2$. After addition of water (50 ml) and EtOAc (200 ml), the organic layer was washed with 0.5 M NaOH (50 ml × 1) and brine (100 ml × 2), dried over $Na_2SO_4$, and concentrated. The residue was purified by silica-gel column chromatography ($CHCl_3$/acetone = 10:1) to give **4** (3.8 g, 91.8%). ESI-MS (positive) m/z 662.3 [(M+Na)]$^+$. $^1$H NMR (600 MHz, DMSO), δ = 10.50 (2H, s, 2 × CONH), 10.09 (2H, s, 2 × CONH), 8.30 (2H, d, *J* = 8.5 Hz, $PhNO_2$), 8.16 (1H, s, Ph), 7.83~7.75 (10H, m, Ar-H), 5.47 (2H, s,-$OCH_2$-), 2.37 (4H, t, *J* = 7.3 Hz, 2 × -$COCH_2$-), 1.59 (4H, m, 2 × $CH_2$), 0.90 (6H, t, *J* = 7.3 Hz, 2 × $CH_3$).

*N,N'*-Bis[2-(6-butyrylaminopyridyl)]-5-[4-(4-carboxyl-butyryl)phenylmethyloxy]isophthaldiamide (**5**). To a solution of $NiCl_2$•$6H_2O$ (0.3 g, 1.26 mmol) in MeOH (80 ml) was added of $NaBH_4$ (0.1 g, 2.64 mmol) (the color of solution changed from green to black) and a solution of **4** (2.0 g, 3.13 mmol) in THF (40 ml) was added. $NaBH_4$ (4.0 g, 106 mmol) was then added to the mixture by portions for 1.5 h. After that 1M NaOH (20 ml) and EtOAc (80 ml) were added, the organic layer was washed with brine (60 ml × 3), dried over $Na_2SO_4$, and concentrated in vacuo. To the solution of the residue in THF (30 ml) was added glutaric anhydride (1.0 g, 8.77 mmol) and the mixture was stirred at room temperature for 5 h. The desired **5** precipitated was collected by filtration and washed with THF to give 1.10 g of **5**. The filtrate was concentrated and the residue was purified by silica-gel column chromatography ($CHCl_3$/MeOH = 20:1) to give another 0.25 g of the product. Yield 1.35 g (59.7%). ESI-MS m/z 722.3 (negative) [(M-H)$^-$]. $^1$H NMR (600 MHz, DMSO), δ = 10.49 (2H, s, 2 × CONH), 10.11 (2H, s, 2 × CONH), 10.00 (1H, s, CONH), 8.13(1H, s, Ph), 7.86-7.72 (5H, Ar-H),7.62 (2H, d, *J* = 7.7 Hz, *Ph*NHCO), 7.42 (2H, d, *J* = 7.7 Hz, *Ph*NHCO), 5.21(2H, s, -$OCH_2$-), 2.37 (6H, m, 3 x $CH_2CO$), 2.26 (2H, t, $CH_2CO$), 1.75 (4H, m, 2 × $CH_2$), 1.61 (4H, m, 2 × $CH_2$), 0.90 (6H, t, *J* = 6.9 Hz, 2 × $CH_3$).

Preparation of the polymer supported receptor **1**. To a suspension ArgoPore-$NH_2$-$^{TM}$ (1.16 mmol/g) (1.00 g, 1.16 mmol of $NH_2$ group), **5** (1.25 g, 1.73 mmol), and DMAP (5.0 mg, 0.04 mmol) in DMF (10 ml) was added DIC (545 µl, 3.48 mmol) at room temperature. After 3 d of agitation, the resin was washed with DMF (20 ml × 3), $CH_2Cl_2$-MeOH 1:1 (20 ml × 3), and $CH_2Cl_2$ (20 ml × 3) and dried under reduced pressure to give the receptor-bound resin (1.42 g, 50.2%).

(7) The experimental procedure for the preparation of the tag **10**.

4-Allyloxymethylbenzyl Alcohol. To a solution of *p*-xylylene glycol (**6**) (11.1 g, 80.3 mmol) in anhydrous THF (200 ml) was added NaH (60% oil suspension, 3.52 g, 88.0 mmol). The mixture was stirred at room temperature for 1 h. Allyl bromide (3.46 ml, 40.0 mmol) was added to the solution and the mixture was stirred at 60 °C for 7 h. After addition of EtOAc and aqueous saturated citric acid solution, the organic layer was washed with water and brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography ($CHCl_3$/acetone = 1:0 to 9:1) to give 5.64 g (63.4%) of the desired product. ESI-MS (positive) m/z 178.44 (M$^+$); 196.44 [(M+$H_2O$)$^+$].

4-Allyloxymethylbenzyl Chloride (**7**). To a solution of chloromethylenedimethylamimonium chloride (1.30 g, 10.2 mmol) in anhydrous $CH_3CN$ (10 ml) was added dropwise a solution of 4-allyloxyphenylmethanol (1.30 g, 7.29 mmol) in anhydrous $CH_3CN$ (10 ml) under $N_2$ and the mixture was refluxed for 40 min. After the mixture was cooled to room temperature, ice-cold water (10 ml) was added. The mixture was extracted with EtOAc and the organic layer was washed with water, dried over $K_2CO_3$, and concentrated in vacuo to give **7** (1.14 g, 98.6%).

Diethyl 2-(4-Allyloxymethylbenzyl)-2-ethylmalonate (**8**). To a solution of diethyl ethylmalonate (2.30 g, 12.2 mmol) in anhydrous toluene (40 ml) was added potassium t-butoxide (1.41 g, 12.6 mmol) under $N_2$. After the mixture was refluxed for 30 min, the solution of **7** (1.40 g, 7.12 mmol) in toluene (20 ml) was added. The mixture was refluxed for 6.5 h and then cooled to room temperature. After addition of water and EtOAc, the organic layer was washed with 0.5 M HCl, saturated $NaHCO_3$ solution, and brine, dried over $Na_2SO_4$, and

concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 20:1 to 10:1) to afford **8** (3.90 g, 97.7%). ESI-MS (positive) m/z 349.35 [(M+H)$^+$, 18%]; 366.35 [(M+$H_2O$)$^+$, 40%]; 371.30 [(M+Na)$^+$, 100%). $^1$H NMR (500 MHz, $CDCl_3$), δ = 7.22 (2H, d, *J* = 7.7 Hz, Ar-H), 7.07 (2H, d, *J* = 8.0 Hz, Ar-H), 5.94 (1H, m, $CH_2$=C*H*-$CH_2$-), 5.29 (1H, m, C*H*$_2$=CH-$CH_2$-), 5.19 (1H, m, C*H*$_2$=CH-$CH_2$-), 4.47 (2H, s, -OC*H*$_2$PhC$H_2$-), 4.18 (4H, m, 2 × -OC*H*$_2$C$H_3$), 4.01 (2H, m, $CH_2$=CH-C*H*$_2$-), 3.23 (2H, s, -OC$H_2$PhC*H*$_2$-), 1.82 (2H, q, *J* = 7.6 Hz, -C*H*$_2$C$H_3$), 1.24 (6H, t, *J* = 7.1 Hz, 2 × -OC$H_2$C*H*$_3$), 0.92 (3H, t, *J* = 7.6 Hz, -C$H_2$C*H*$_3$).

5-Ethyl-5-(4-allyloxymethylbenzyl)barbituric Acid (**9**). To a solution of urea (7.00 g, 117 mmol) in DMSO (25 ml) was added NaH (60% oil suspension, 2.0 g, 50 mmol) under $N_2$. After the mixture was stirred at room temperature for 30 min, **8** (4.10 g, 11.8 mmol) was added. The mixture was stirred at room temperature for 14 h and then poured into 20 g of ice. The mixture was acidified with 2M HCl and then extracted with EtOAc. The organic layer was washed with water, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 3:1 to 2:1) to give **9** (3.00 g, 80.6%). ESI-MS (positive) m/z 339.15 [(M+Na)$^+$]. $^1$H NMR (600 MHz, $CDCl_3$), δ = 7.86 (2H, s, NH), 7.22 (2H, d, *J* = 7.7 Hz, Ar-H), 7.08 (2H, d, *J* = 8 Hz, Ar-H), 5.93 (1H, m, $CH_2$=C*H*-$CH_2$-), 5.29 (1H, m, C*H*$_2$=CH-$CH_2$-), 5.20 (1H, m, C*H*$_2$=CH-$CH_2$-), 4.46 (2H, s, -OC*H*$_2$PhC$H_2$-), 4.00 (2H, m, $CH_2$=CH-C*H*$_2$-), 3.27(2H, s, -OC$H_2$PhC*H*$_2$-), 2.20 (2H, q, *J* = 7.6 Hz, -C*H*$_2$C$H_3$), 0.92 (3H, t, *J* = 7.6 Hz, -C$H_2$C*H*$_3$).

5-Ethyl-5-(4-hydroxymethylbenzyl)barbituric Acid (**HOBA**) (**10**). To a degassed solution of **9** (2. 89 g, 9.13 mmol) in anhydrous THF (100 ml) was added [Ir(COD)(PMePPh$_2$)]$^+$PF$_6^-$ (350 mg, 0.045 equiv) and the solution was stirred under $H_2$ at room temperature for 5 min (the color of the solution changed from red to yellow) and then for 100 min under $N_2$. Water (45 ml) and iodine (4.4 g) was added to the mixture successively. After the mixture was stirred for 30 min, aqueous 10% $Na_2S_2O_3$ solution (10 ml) was added to quench the reaction. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography ($CHCl_3$/MeOH = 20:1) to give **10** (2.20 g, 87.3%). ESI-MS (positive) m/z 575.3 [(2M+Na)$^+$]; 315.1 [(M+K)$^+$]; 299.2 [(M+Na)$^+$]. $^1$H NMR (600MHz, DMSO), δ = 7.18 (2H, d, *J* = 8 Hz, Ar-H), 6.94 (2H, d, *J* = 8 Hz, Ar-H), 5.15 (t, 1H, OH), 4.24 (2H, m, -OC*H*$_2$PhC$H_2$-), 3.07 (2H, s, -OC$H_2$PhC*H*$_2$-), 1.97 (2H, q, *J* = 7.6 Hz, -C*H*$_2$C$H_3$), 0.76 (3H, t, *J* = 7.6 Hz, -C$H_2$C*H*$_3$).

(8) General procedure for affinity separation. After completion of the reaction, the reaction mixture was directly applied to the resin **1** column (7.0 g: 1.5 cm × 7 cm, $CH_2Cl_2$) unless otherwise noted. After untagged compounds were washed off with $CH_2Cl_2$ (70 ml), the tagged compound was eluted with MeOH-$CH_2Cl_2$ (1:1) (30 ml). Evaporation of the solvents afforded the desired product having the tag.

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(10) The experimental procedure for the preparation of methyl 4-piperidino-3-nitrobenzoate (**26**). To a solution of HOBA (**10**) (27.6 mg, 0.100 mmol), 4-fluruo-3-nitrobenzoic acid (22.0 mg, 0.119 mmol), and DMAP (1mg, 8 μmol) in anhydrous $CH_2Cl_2$ (3 ml) was added DIC (30 μl, 0.19 mmol). The mixture was stirred at room temperature for 2 h and then applied to the affinity separation to give 5-ethyl-5-[4-(4-fluruo-3-nitrobenzoyl)oxymethylbenzyl]barbituric acid (**24**). To a solution of **24** in *N*-methylpyrrolidone (NMP) (0.8 ml) was added piperidine (20 μl, 0.20 mmol). The mixture was stirred at room temperature for 2 h, diluted with $CH_2Cl_2$ (8 ml), and then applied to the affinity separation. The desired 5-ethyl-5-[4-(4-piperidino-3-nitrobenzoyl)oxymethylbenzyl]barbituric acid (**25**) was eluted at both $CH_2Cl_2$ and $CH_2Cl_2$-MeOH (1:1) fractions. The $CH_2Cl_2$ fraction containing **25** was concentrated and then applied to the affinity separation again. The $CH_2Cl_2$-MeOH (1:1) fractions were combined and concentrated. Compound **25** thus obtained was dissolved in 0.2 M MeONa in MeOH (2.0 ml) and the mixture was stirred at room temperature for 30 min. After addition of AcOH (3 drops), the mixture was concentrated in vacuo. The residue was dissolved in $CHCl_3$ and then applied to the affinity separation. The desired **26** was eluted with $CHCl_3$, whereas HOBA (**10**) was eluted with $CH_2Cl_2$/MeOH (1:1). Evaporation of the solvent afforded **26** (24.0 mg, 90.9%): ESI-MS (positive) m/z 265.2 [(M+H)$^+$]. $^1$H NMR (600 MHz, $CDCl_3$), δ = 8.42 (1H, s, Ar-H), 8.02 (1H, d, *J* = 8.8 Hz, Ar-H), 7.05 (1H, d, *J* = 8.8 Hz, Ar-H), 3.90 (3H, s, $CH_3$), 3.15 (4H, t, $NCH_2$), 1.72 (4H, m, $CH_2$), 1.51 (2H, m, $CH_2$).

(11) Liu, W.-C.; Oikawa, M.; Fukase, K.; Suda, Y.; Kusumoto, S. *Bull. Chem. Soc., Jpn.* **1999**, *72*, 1377.

(12) The experimental procedure for the preparation of trisaccharide **34**. The mixture of the glycosyl acceptor **30** (69.2 mg, 0.09 mmol), the glycosyl donor **31** (85 mg, 0.135 mmol), and MS 4A in $CH_2Cl_2$ (4 ml) was stirred at room temperature for 1 h under $N_2$ atmosphere and then cooled to −20 °C. TMSOTf (4.0 μl, 22 μmol) was added and the mixture was stirred at the same temperature for 10 min. The mixture was directly applied to the affinity separation to give disaccharide **32**. Disaccharide **32** was dissolved in $CH_2Cl_2$ (4 ml) containing 5% TFA and 1% water. The mixture was stirred at 0 °C for 30 min, diluted with EtOAc (15 ml), washed with saturated $NaHCO_3$ solution and brine, dried over $Na_2SO_4$ and concentrated. The residue was applied to the affinity separation to afford disaccharide acceptor **33**. The mixture of **33** (59.2 mg, 0.0517 mmol), **31** (161 mg, 0.256 mmol), and MS 4A in $CH_2Cl_2$ (5 ml) was stirred at room temperature for 1 h under $N_2$, and then cooled to −20°C. TMSOTf (4.0 μl, 22 μmol) was added and the mixture was stirred at the same temperature for 10 min. The mixture was directly applied to the affinity separation to give 80.1 mg of the crude product, which was then purified by silica-gel column chromatography to afford the pure trisaccharide **34** (47.0 mg, 56.0%). ESI-MS m/z 1630.0 [(M+Na)$^+$]. $^1$H NMR (500 MHz, $CDCl_3$), δ = 8.45 (2H, NH: barbituric acid), 7.45 (2H, m, Ph-H), 7.34 (3H, m, Ph-H), 7.20 (2H, d, *J* = 7.6 Hz, Ph-H), 7.09 (2H, d, *J* = 8.1 Hz, Ph-H), 6.28 (1H, br s, 2-N*H*: $GlcN_C$), 5.92 (1H, m, $CH_2$=CH-$CH_2$-), 5.51 (1H, s, PhC*H*=), 5.43 (1H, d, *J* = 9.9 Hz, 2-N*H*: $GlcN_A$), 5.37 (1H, br s, 2-NH: $GlcN_B$), 5.33 (1H, m, $CH_2$=CH-$CH_2$-), 5.24 (1H, m, C*H*$_2$=CH-$CH_2$-), 5.18 (1H, t, *J* = 9.7 Hz, H-3: $GlcN_A$), 5.13 (1H, t, *J* = 9.9 Hz, H-3: $GlcN_C$), 5.05 (1H, H-3: $GlcN_B$), 5.02 (1H, d, *J* = 14 Hz, -OC*H*$_2$PhCH$_2$-), 4.97 (1H, d, *J* = 14 Hz, -OC*H*$_2$PhCH$_2$-). 4.90 (d, *J* = 3.7 Hz, 1H, H-1: $GlcN_A$), 4.79-4.65 (6H, $CCl_3CH_2$- × 3), 4.65 (1H, d, *J* = 8.3 Hz, H-1: $GlcN_C$), 4.63 (1H, d, *J* = 8.6 Hz, H-1: $GlcN_B$), 4.37 (1H, dd, *J* = 5.6 Hz, 10.6 Hz, H-6: $GlcN_C$), 4.22 (1H, m, $CH_2$=CH-C*H*$_2$-), 4.21 (1H, H-6: $GlcN_B$), 4.17 (1H, H-6: $GlcN_A$), 4.02 (1H, m, $CH_2$=CH-C*H*$_2$-), 3.96 (1H, H-5: $GlcN_A$), 3.95 (1H, H-2: $GlcN_A$), 3.84 (1H, H-6': $GlcN_A$), 3.82 (1H, H-6': $GlcN_C$), 3.80 (1H, H-2: $GlcN_C$), 3.79 (1H, H-6': $GlcN_B$), 3.71 (1H, H-4: $GlcN_C$), 3.70 (1H, H-4: $GlcN_A$), 3.62 (1H, H-2: $GlcN_B$), 3,53 (1H, H-5: $GlcN_B$), 3.52 (1H, H-5: $GlcN_C$), 3.51 (1H, H-4: $GlcN_B$), 3.26 (2H, m, -OC$H_2$PhC*H*$_2$-), 2.35-2.22 (4H, m, -COC*H*$_2$C*H*$_2$C*H*$_2$CO-), 2.18 (2H, q, *J* = 6.2 Hz, $CH_3$C*H*$_2$-), 2.10 (3H, s, C*H*$_3$CO-), 1.90 (2H, m, -

$COCH_2CH_2CH_2CO$-), (3H, t, $J$ = 6.2 Hz, $CH_3CH_2$-) (the saccharide residues are designated as $GlcN_A$, $GlcN_B$, and $GlcN_C$ (glucosamine residue) from reducing end).

(13) α-Promoting solvent effect of dioxane was reported. a) Demchenko, A. V.; Rousson, E.; Boons, G.-J. *Tetrahedron Lett.* **1999**, *40*, 6523. b) Rademann, J.; Schmidt, R. R. *J. Org. Chem.* **1997**, *62*, 3650.

(14) a) Fukase, K.; Kinoshita, I.; Kanoh, T.; Nakai, Y.; Hasuoka, A.; Kusumoto, S. *Tetrahedron* **1996**, *52*, 3897. b) Fukase, K.; Nakai, Y.; Kanoh, T.; Kusumoto, S. *Synlett* **1998**, 84.

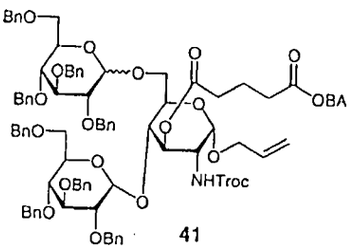
(15) α-Selectivity is expected to be increased by using combinations of PhIO with $SnCl_2$-$AgClO_4$, $SnCl_4$-$AgClO_4$, $BiCl_3$-$AgClO_4$, and $SbCl_3$-$AgClO_4$, though these reagents require careful handling.[14]

(16) An acylaminobenzyl linker, which can be cleaved by DDQ oxidation, was used for solid-phase oligosaccharide synthesis. Fukase, K.; Nakai, Y.; Egusa, K.; Porco Jr., J. A.; Kusumoto S. *Synlett* **1999**, 1074.

(17) We previously reported α-orienting effect of the 6-*O*-Troc group.[14] Fukase, K.; Yoshimura, T.; Kotani, S.; Kusumoto S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 473.

(18) The experimental procedure for the preparation of trisaccharide **40**. The mixture of the glycosyl acceptor **36** (97.4 mg, 0.114 mmol), phenyl thioglucoside **37** (122.8 mg, 0.171 mmol), PhIO (48 mg, 0.22 mmol), and MS 4A in diethyl ether (5.0 ml) and dioxane (4.0 ml) was stirred for 1 h at r.t. under $N_2$ then cooled to −10 °C. TMSOTf (20 µl, 0.110 mmol) was added and the reaction mixture was stirred for 1 h. The reaction was quenched by addition of aqueous saturated $NaHCO_3$ solution and ethyl acetate. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated. The residue was dissolved in $CH_2Cl_2$ and then subjected to the affinity separation. Since the product **38** contained small amount of the starting material **36**, the mixture of **38** and **36** was subjected repeatedly to glycosylation and then affinity separation to give **38** (α:β = 10:1). ESI-MS m/z 1480.4 [(M+Na)$^+$]; $^1$H NMR (600 MHz, $CDCl_3$), α-anomer: δ = 8.07 (2H, NH: barbituric acid), 4.95 (1H, d, $J$ = 3.6 Hz, H-1: $Glc_B$), 4.53 (1H, d, $J$ = 3.6 Hz, H-1: $Glc_A$), 4.32 (2H, d, $J$ = 3.3 Hz, H-6: $Glc_B$), 3.972 (1H, dd, $J$ = 9.3 Hz, 9.3 Hz, H-3: $Glc_A$), 3.966 (1H, dd, $J$ = 9.1 Hz, 9.1 Hz, H-3: $Glc_B$), 3.86 (m, 1H, H-5: $Glc_B$), 3.79 (1H, m, H-6, $Glc_A$), 3.77 (1H, m, H-5: $Glc_A$), 3.71 (1H, H-6': $Glc_A$), 3.64 (1H, dd, $J$ = 9.1 Hz, 9.3 Hz, H-4: $Glc_A$), 3.50 (1H, H-2: $Glc_B$), 3.50 (1H, H-4: $Glc_B$), 3.40 (1H, dd, $J$ = 3.6 Hz, 9.6 Hz, H-2: $Glc_A$), 3.34 (3H, s, -$OCH_3$), 3.257 (2H, s, -$OCH_2PhCH_2$-), 2.48-2.30 (4H, m, -$COCH_2CH_2CH_2CO$-), 2.19 (2H, $CH_3CH_2$-), 2.0 (2H, m, -$COCH_2CH_2CH_2CO$-), 0.92 (3H, $CH_3CH_2$-). β-anomer: δ = 4.60 (1H, H-1: $Glc_A$), 4.35 (1H, d, $J$ = 8.4 Hz, H-1: $Glc_B$), 3.44 (1H, H-2: $Glc_A$), 3.31 (3H, S, -$OCH_3$). To a solution of **38** in acetic acid (1 ml) was added Zn-Cu (260 mg) and the mixture was stirred at r.t. for 1 h. Ethyl acetate was added and the insoluble materials were removed by filtration. The filtrate was washed with aqueous saturated $NaHCO_3$ solution and brine, dried over $Na_2SO_4$, and concentrated. The residue was then subjected to the affinity separation to give **39**. The mixture of **39**, phenyl thioglucoside **37** (105.4 mg, 0.147 mmol), PhIO (48 mg, 0.22 mmol), and MS 4A in diethyl ether (4.0 ml) and dioxane (2.0 ml) was stirred at r.t. for 1 h under $N_2$ and then cooled to −10 °C. TMSOTf (20 µl, 0.110 mmol) was added and the reaction mixture was stirred for 1 h. The reaction was quenched by addition of aqueous saturated $NaHCO_3$ solution and ethyl acetate. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated. The residue was dissolved in $CH_2Cl_2$ and then subjected to the affinity separation to give 119.2 mg of the crude product. The product was purified by silica-gel column chromatography to afford compound **40** (62.0 mg, 28.7%). ESI-MS m/z 1912.6 [(M+Na)$^+$]; $^1$H NMR (600 MHz, $CDCl_3$), α(1-6)α(1-6)α: δ = 8.12 (2H, NH: barbituric acid), 4.98 (1H, d, $J$ = 3.3 Hz, H-1: $Glc_C$), 4.90 (1H, H-1: $Glc_B$), 4.54 (1H, H-1: $Glc_A$), 4.30 (2H, H-6: $Glc_C$), 3.96 (1H, dd, $J$ = 9.3Hz,9.3 Hz, H-3: $Glc_C$), 3.95 (1H, H-3: $Glc_A$), 3.94 (1H, H-3: $Glc_B$), 3.81 (m, 1H, H-5: $Glc_C$), 3.77 (1H, m, H-6, $Glc_A$), 3.76 (1H, m, H-6: $Glc_B$), 3.76 (1H, m, H-5: $Glc_B$), 3.72 (1H, H-5: $Glc_A$), 3.70 (1H, H-4: $Glc_B$), 3.66 (1H, H-4, $Glc_A$), 3.48 (1H, H-2: $Glc_C$), 3.48 (1H, H-4: $Glc_C$), 3.38 (1H, dd, $J$ = 3.0 Hz, 9.3 Hz, H-2: $Glc_A$), 3.37 (1H, dd, $J$ = 3.0 Hz, 9.3 Hz, H-2: $Glc_B$), 3.32 (3H, s, -$OCH_3$), 3.24 (2H, s, -$OCH_2PhCH_2$-), 2.48-2.30 (4H, -$COCH_2CH_2CH_2CO$-), 2.19 (2H, $CH_3CH_2$-), 2.01 (2H, m, -$COCH_2CH_2CH_2CO$-), 0.91 (3H, t, $J$ = 9.1 Hz, $CH_3CH_2$-).

(19) The trisaccharide **41** did not exhibit sufficiently strong affinity to the receptor and leaked from the resin column when $CH_2Cl_2$ was used as an eluent. Large hydrophobic moiety in **41** decreases the relative affinity of the barbituric acid tag with the receptor. When less polar toluene, in which the affinity is expected to increase, was used as an eluent, **41** was effectively retained in the column 1, which was then washed successively with toluene and $CH_2Cl_2$. Compound **41** was not eluted during the washing. Elution with $CH_2Cl_2$-methanol (1:1) afforded **41**.




**41**

Article Identifier:
1437-2096,E;2001,0,05,0590,0596,ftx,en;Y06601ST.pdf

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
**DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
**JUAN PABLO CADENA SARMIENTO**
Apoderado

| | | |
|---|---|---|
| ASUNTO | Radicación | 04022003-A |
| | Trámite | 011 |
| | Evento | 379 |
| | Actuación | 430 |
| | Oficio | 5158 |
| | Folios | 361 |

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap.I ☐ Cap. II ☒

No. Sol. Internacional PCT/GB02/03745
Fecha de Presentación Internal. 15/08/2002

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

**1. Documentos estudiados**

| | |
|---|---|
| Descripción: | Folios: 87 a 251 |
| Reivindicaciones: | Folios 252 a 259 como se radicó inicialmente<br>Folios 295 a 302 modificadas como respuesta al primer artículo 45.<br>Folios 353 a 357 modificadas como respuesta al segundo artículo 45. |
| Rta. del Solicitante: | Folios: 293 a 294<br>Folios 348 a 351 |
| Prioridad: | Fecha: 17/08/2001, País: SE, Número: 0102764-8 |

**2. Objeto de la invención**

- **Título sugerido para la solicitud:** Compuestos derivados de benzamida de formula IIB que afectan la glucocinasa.

**El problema planteado en esta solicitud** es la necesidad de compuestos útiles para tratar la obesidad y diabetes sin los episodios hipoglicémicos severos causados por una estimulación directa de la GLK o indirecta por inhibición de la interacción de GLKRP con GLK, lo cual es ventajoso ya que no causará hipoglicemia.

**Para solucionar este problema técnico** la solicitud en estudio proporciona compuestos de benzamida de formula (IIb).

Clasificación Internacional de Patentes (IPC.): A61K 31/425

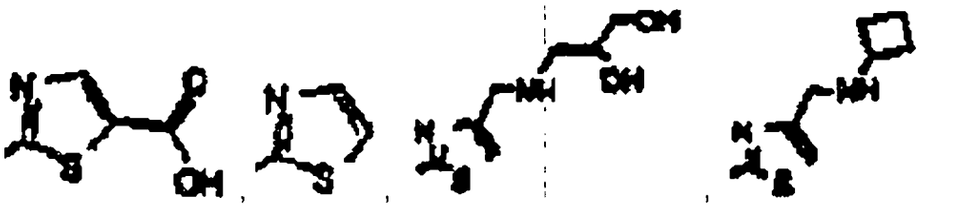
## 3. De la solicitud de Patente

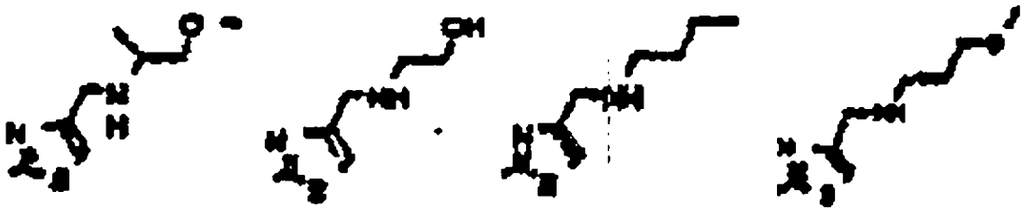
Reivindicaciones *(artículo 30 D 486)*

Una vez revisado el capitulo reivindicatorio esta dependencia encuentra:

- Se requiere al solicitante restringir la reivindicación 1 al tipo de compuesto que ha sido ejemplificado según los ensayos anexados en su respuesta, es decir, compuestos tipo II16, II18, II32, II54, II55, II57, II66, II67, II101, II120, II121, II122, II135, II137, II138.

  Donde:

R3= 



X= O

R4= Cl, F, alquilo, 

$Z^1$= enlace directo, $C_{2-6}$ alquenileno

## 4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 17/08/2001

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

| N° | Documento | Título | Fecha de publicación* |
|---|---|---|---|
| $D_1$ | US4146631 | BENZAMIDE DERIVATIVES | 27/03/1979 |
| $D_2$ | WO 0119788 | BENZAMIDES AND RELATED INHIBITORS OF FACTOR Xa | 22/03/2001 |

**5. Respuesta a los argumentos del solicitante:**

- El solicitante ha especificado aún más los compuestos objeto de la invención ya que se realizaron objeciones en cuanto al nivel inventivo de la solicitud en previos estudios de fondo y adicionalmente adjunta en su respuesta resultados de ensayos realizados; Sin embargo según el análisis del nuevo capítulo reivindicatorio se considera que se requiere más restricción en cuanto a la protección que se desea tomando en cuenta dichos ensayos ya que la reivindicación 1 es una generalización demasiado amplia de lo que realmente evidencia la solución al problema técnico.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

**ALIX CARMENZA CÉSPEDES DE VERGEL**
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 08 MAYO 2009

| CONCEPTO TÉCNICO<br>No. 324 | EXAMINADOR TÉCNICO<br>Código No. 202087 |
|---|---|

Industria y Comercio
SUPERINTENDENCIA

**REPUBLICA DE COLOMBIA**

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

**RESOLUCION** 43456

Por la cual se niega una patente de invención

Rad. PCT/04-22003A

**RESUELVE:**

**ARTICULO PRIMERO:** Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPUESTOS QUE AFECTAN LA GLUCOCINASA", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

**ARTICULO SEGUNDO:** Notificar personalmente el contenido de la presente resolución al doctor Juan Pablo Cadena Sarmiento, en su calidad de apoderado de AstraZeneca AB., o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

**NOTIFÍQUESE Y CUMPLASE**
Dada en Bogotá, D.C., a los 28 AGO. 2009

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

**GUSTAVO VALBUENA QUIÑONES**

Doctor
**JUAN PABLO CADENA SARMIENTO**
Carrera 7 Nº 71 – 21, Torre B, Piso 4.
Bogotá D.C.

202021

**REPUBLICA DE COLOMBIA**

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

**RESOLUCION** 43456

Por la cual se niega una patente de invención

Rad. PCT/04-22003A

**EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO**
en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 4, numeral 5 del decreto 2153 de 1992, y

**CONSIDERANDO:**

**PRIMERO:** Que la solicitud de patente de invención titulada "COMPUESTOS QUE AFECTAN LA GLUCOCINASA", que corresponde a la solicitud internacional PCT/GB 02/03745 de fecha 15 de agosto del 2002, fue radicada en esta Superintendencia el 10 de marzo del 2004 bajo el número 04022003A, para que se dé comienzo a la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

**SEGUNDO:** Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

**TERCERO:** Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un periodo de treinta días adicionales.(...) Si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente".*

**CUARTO:** Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 359 a 361 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del mismo, por lo cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.