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9. J. R. VAN NORDEN, *INDUSTRIAL WAYS OF OBTAINING*
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 06.037.930

Solicitud de patente a nombre de **Ortho-McNeil-Janssen Pharmaceuticals, Inc.**

Yo, DILIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **Ortho-McNeil-Janssen Pharmaceuticals, Inc.**, domiciliada en Titusville, New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, en respuesta al oficio No. 6178 notificado por fijación en lista el 7 de mayo de 2010, relacionado con el concepto técnico de fondo No. 1632, me permito acompañar los siguientes documentos solicitados por ese despacho:

- 1 A. Rosowsky. "One step synthesis of novel 2,4-diamino-pyrimidine antifolates" Journal Heterocyclic Chemistry. Vol. 39, 1999, pages 723-728, XP002270518.
- 2 Kandeel, E.M. "Synthesis of new 1,2-dihydro-4-amino-2-thioxo-5H-indeno-1,2-D-pyrimidin-5-one derivatives". Pakistan Journal of Scientific and Industrial Research, XX, XX, vol 29, no. 6, December 1986 (1986-12), pages 424-426, XP009025178. ISN:0030-9885.
- 3 Goerlitzer K. et al. "Indenoä 1,2-düpyrimidin-4-yl-amine indenoä 1,2, üpyrimidin-2-4-yl-amines". Pharmazie, Veb Verlag volk und gesundheit. Berlin, DD, vol. 52, no. 9, 1997, pages 670-672, XP001179310. ISSN:0031-7144

Espero con esto haber dado cabal cumplimiento a lo solicitado por ese despacho y de conformidad con lo indicado en los artículos 3º, inciso 3, 35 inciso 2 y 59 inciso 2 del CCA, al analizar este memorial, atentamente solicito se traten todas las cuestiones planteadas con motivo del mismo.

Señor Superintendente,

DILIA RODRIGUEZ D'ALEMAN
CC. 41.654.882 de Bogotá
TP 20824
Cód. 008

Andre Rosowsky* [a], Andrew T. Papoulis [a], and Sherry R. Queener [b]

[a] Dana-Farber Cancer Institute and Department of Biological Chemistry
and Molecular Pharmacology, Harvard Medical School,
Boston, Massachusetts 02115[b] Department of Pharmacology and Toxicology, Indiana University School of
Medicine, Indianapolis, Indiana 46202

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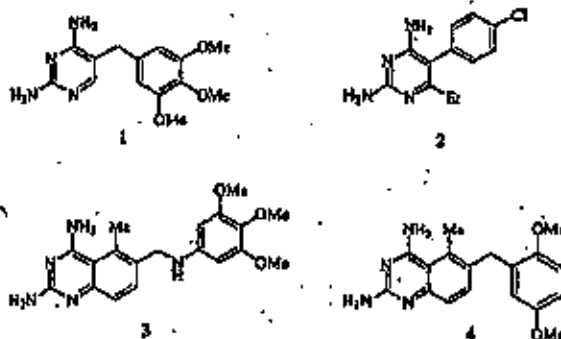
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A convenient one-step reaction with cyanoguanidine was used to convert alicyclic ketones to previously undescribed 2,4-diamino-5,6,7,8-tetrahydroquinazolines with a one-, two-, or three-carbon bridge in the carbocyclic ring. Although the yields of the desired products were modest, the principal advantage of this one-step process was that it provided easy access to a variety of novel bridged heterocyclic ring systems whose synthesis from sterically hindered ketones by other methods would have required multiple steps with an even lower overall yield. The products were tested as inhibitors of dihydrofolate reductases from *Pneumocystis carinii*, *Toxoplasma gondii*, and rat liver with a view to examining the effect of a space-filling bridge on binding. The most potent and selective compound in the group was 4,6-diamino-3,5-diazatetracyclo[7.2.1.0^{2,7}.0^{3,6}]undeca-2,4,6-triene (13), whose potency and selectivity approached those of trimethoprim, a drug commonly used to treat *P. carinii* and *T. gondii* infection. 3,5-Diamino-4,6-diazatetracyclo[6.2.1.0^{2,7}.0^{3,6}]undeca-2,4,6-triene (14), the analog of 13 with a one-carbon rather than a two-carbon bridge showed similar potency and selectivity against the *T. gondii* enzyme, but was a weak and nonselective inhibitor of *P. carinii* dihydrofolate reductase. The other compounds tested were likewise weak and nonselective.

J. Heterocyclic Chem., 36, 723 (1999).

Lipophilic antifolates that bind tightly and selectively to dihydrofolate reductase from the opportunistic pathogens *Pneumocystis carinii* and *Toxoplasma gondii* have been actively sought for a number of years [reviewed in 1-3]. However, especially in the case of inhibitors of the *Pneumocystis carinii* enzyme, the combination of high potency and high selectivity has remained elusive. Classical antifolates such as methotrexate bind very tightly to the *P. carinii* and *T. gondii* dihydrofolate reductase, but cannot be used clinically against these organisms because they lack the membrane-bound active transport protein which is responsible for concentrative methotrexate uptake by mammalian cells [4]. Thus, standard antifolate prophylaxis and therapy of *P. carinii* and *T. gondii* infection relies on the permeability of these organisms to lipophilic molecules (like trimethoprim, (1) [5,6] or pyrimethamine (2) [7,8], generally in combination with a sulfa drug such as sulfamethoxazole. Trimethoprim exhibits a high degree of species selectivity for *P. carinii* and *T. gondii* versus mammalian dihydrofolate reductase, but is not very potent. Pyrimethamine is somewhat more potent but less selective. Two other lipophilic antifolates, trimetrexate (3) and piritoxim (4), are extremely potent but non-selective, and therefore have to be given together with leucovorin ((6R,6S)-5-formyl-5,6,7,8-tetrahydrofolate) in order to prevent the hematopoietic toxicity which would otherwise ensue [9,10]. The success of leucovorin as a protective agent is due in this case to its ability to be actively transported by the cells of the host as opposed to those of the pathogen. Controlled clinical comparison of trimetrexate-leucovorin with standard trimethoprim-sulfamethoxazole showed no dramatic difference, though it was

suggested that the trimetrexate-leucovorin combination would be appropriate in patients who experience unacceptable side effects from sulfa drugs. Taken together, the frequent inability of patients to tolerate sulfa drugs and the relatively high cost of leucovorin have prompted attempts in several laboratories to try to design a new generation of lipophilic dihydrofolate reductase inhibitors potent enough to be used without a sulfa drug and yet selective enough to not require co-administration of leucovorin [11-14]. However this has proved to be a daunting task, as most such attempts have been thwarted by what seems to be, at least empirically, an inverse correlation between potency and selectivity [15].



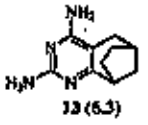
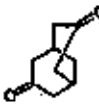
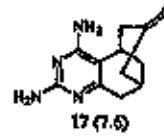
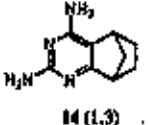
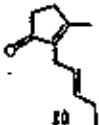
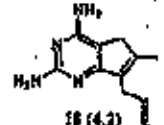
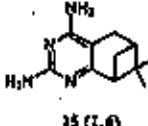
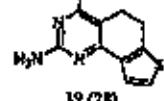
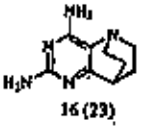
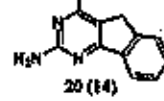
A possible approach to enhancing the selective binding of inhibitors to the active site of dihydrofolate reductase

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from different species might be to take advantage of differences in steric bulk in the part of the molecule directly adjacent to the diaminopyrimidine moiety of trimethoprim and pyrimethamine. According to this view, inspired by elegant recent work on *Candida albicans* dihydrofolate reductase [16], the ability of a dihydrofolate reductase inhibitor with space-filling alkyl substituents in this region to make effective van der Waals contacts with hydrophobic residues in the active site would vary according to the topology of the cavity formed by these residues. In other words, if the pocket into which this part of the inhibitor fits is either too narrow or too wide allow effective hydrophobic interaction, binding will be weaker than if the pocket has precisely the right volume and contour to allow a tight fit. To test this hypothesis we thought it might be useful to examine the binding to *P. carinii*, *T. gondii*, and mammalian (rat liver) dihydrofolate reductase of bicyclic diaminopyrimidine derivatives with a fused carbocyclic moiety that contains a bulky hydrophobic bridge while lacking the substituted aryl group of conventional trimethoprim and pyrimethamine analogues. The synthesis and activity of a small group of such compounds as dihydrofolate reductase inhibitors are the subject of this paper.

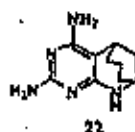
Thermal condensation of cyclic ketones with cyanoguanidine under fusion conditions or in a high-boiling inert solvent affords a convenient one-step route to condensed diaminopyrimidine derivatives [17], and has been used to prepare a variety of nonbridged ring systems [18-22]. The largest number of these have been tetrahydroquinazolines, and dihydrobenzo[*f*]quinazolines, though others have also been made by this route. In contrast, there have been few attempts to extend this reaction to bridged cyclic ketones. In the present study, cyanoguanidine was condensed with bicyclo[3.2.1]octan-2-one (5), norcamphor (6), (*R*)-(+)-nopinone (7), 3-quinucillinone (8), and bicyclo[3.3.1]nonan-3-one (9). Three non-bridged ketones, *cis*-jasmonone (10), 4-keto-1,2,3,4-thianaphthene (11), and 1-indanone (12) were also used for comparison. The structures of 5-12, along with those of their respective cyanoguanidine fusion products, 13-20, which represent some very unusual heterocyclic ring systems, are shown in Table 1. Compound 18 is, to our knowledge, the first reported example of the reaction of cyanoguanidine with a substituted cyclopentenone. Compound 16 can be viewed as a bridged 2,4-diamino-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine, and is notable because of its bioisosteric relationship to the bridged

Table 1
Synthesis of Condensed 2,4-Diaminopyrimidines from Cyclic Ketones and Cyanoguanidine

Ketone	Fusion Conditions	Product (% Yield) (a)	Ketone	Fusion Conditions	Product (% Yield) (a)
	200°C 1 hour	 13 (6.3)		200°C 1 hour	 17 (7.6)
	190-200°C 2.5 hours (sealed tube)	 14 (1.3)		220°C 1.5 hours	 18 (4.2)
	200-210°C 1 hour	 15 (1.4)		200°C 1 hour	 19 (28)
	210°C 1.5 hours	 16 (23)		200-205°C 1 hour	 20 (14)

(a) Compounds 14 and 16 were purified by preparative thin-layer chromatography on silica gel using 92:8 and 85:15 chloroform-methanol, respectively. The other products were purified by column chromatography on silica gel using 85:15 chloroform-methanol. Yields are not corrected for recovered starting material.

2,4-diamino-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine 22, which was recently discussed as being of potential interest as a dihydrofolate reductase ligand (24).



A general procedure for the cyanoguanidine fusion reaction is given in the experimental section. Reaction conditions and non-optimized yields obtained for individual reactions summarized in Table 1; systematic chemical and names and physical data for the products are given in Table 2. Briefly, the ketone and an equimolar amount of recrystallized cyanoguanidine were heated under a stream of nitrogen at 190-230° for 1.0-2.5 hours; the mixture was

allowed to cool, and the solidified melt was pulverized and thoroughly extracted with an 85:15 mixture of chloroform and methanol. The insoluble residue, assumed to consist of melamine-type polymers resulting from the thermal breakdown and polymerization of cyanoguanidine (23), was discarded, and the organic extract was chromatographed on silica gel using 85:15 chloroform-methanol as the eluent. The yield of purified product varied considerably, from a low of 1.3% (15) to a high of 28% (19). Among the compounds with a bridged carbocyclic ring, the one that formed in highest yield was 16 (23%). However yields were higher when they were corrected for recovered starting material. For example, the adjusted yield in the synthesis of 13 was 18%, rather than 6.3%. Substantial amounts of unchanged starting ketones were generally recovered from all the reactions, along with many byproducts assumed to arise via self-condensation reactions of the ketones.

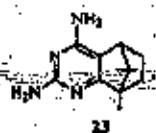
Both the degradative polymerization of cyanoguanidine, and the self-condensation of ketones appear to be unavoidable

Table 2
Chemical Names and Physical Data for Compounds 13-20

Compound	Molecular Formula	Chemical Name	¹ H-NMR Data (s)	Microanalysis and/or Mass Spectral Data
13	C ₁₀ H ₁₄ N ₄	4,6-Diamino-3,5-diazatriacyclo-[7.2.1.0 ^{2,7}]dodeca-2,4,6-triene	δ 1.0-3.0 (complex m, 10H, 4 CH ₂ , 2H), 4.8 (br s, 4H, 2- and 4-NH ₂)	m/z (M+1) ⁺ 191.25, expected 191.26
14	C ₉ H ₁₃ N ₄	3,5-Diamino-4,6-diazatriacyclo-[6.2.1.0 ^{2,7}]undeca-2,4,6-triene	δ 1.3-3.2 (complex m, 8H, 3 CH ₂ , 2 CH), 4.6 (br s, 2H, 4-NH ₂), 5.0 (br s, 2H, 2-NH ₂)	m/z (M) ⁺ 176.21, expected 176.22
15	C ₁₁ H ₁₆ N ₄	4,6-Diamino-3,5-diaza-10,15-dimethyltricyclo[7.1.1.0 ^{2,7}]undeca-2,4,6-triene	δ 0.9-2.6 (complex m, 10H, 2 CH ₃ , 2 CH ₂ , 2 CH), 4.7 (br s, 4H, 2- and 4-NH ₂)	Calcd. for C ₁₁ H ₁₆ N ₄ O ⁺ 0.15H ₂ O: C, 63.92; H, 7.68; N, 27.11. m/z (M+1) ⁺ 203.16, expected 203.28
16	C ₉ H ₁₃ N ₅	3,5-Diamino-1,4,6-triazatriacyclo-[6.2.2.0 ^{2,7}]dodeca-2,4,6-triene	δ 1.6-3.2 (complex m, 9H, 4 CH ₂ , 1 CH), 4.8 (br s, 2H, 4-NH ₂), 5.2 (br s, 2H, 2-NH ₂)	Calcd. C, 56.51; H, 6.86; N, 26.62. Found: C, 56.54; H, 6.68; N, 26.65
17	C ₉ H ₁₄ N ₄ O	4,6-Diamino-3,5-diazatriacyclo-[7.3.1.0 ^{2,7}]trideca-2,4,6-trien-10-one	δ 1.6-3.6 (complex m, 10H, 4 CH ₂ , 2 CH), 3.2 (br s, 4-NH ₂), 6.1 (s, 2H, 2-NH ₂)	m/z (M+1) ⁺ 219.10, expected 219.13
18	C ₁₃ H ₁₃ N ₄	2,4-Diamino-6-methyl-7-(trans-pent-2-en-1-yl)-6-methyl-5H-cyclopenta[2,1-d]pyrimidine	δ 1.0-3.3 (complex m, 10H, 2 CH ₃ , 2 CH ₂), 5.0 (br s, 4H, 2- and 4-NH ₂), 5.4 (m, 2H, CH=CH)	m/z (M+1) ⁺ 231.31, expected 231.33
19	C ₁₀ H ₁₀ N ₄ S	6,8-Diamino-4,5-dihydrothieno-[7.3-d]quinoxalines	δ 2.9 (m, 4H, CH ₂ CH ₂), 4.8 (br s, 4H, 2- and 4-NH ₂), 7.1 (d, 1H, 2-thienyl), 7.6 (d, 1H, 3-thienyl)	Calcd. for C ₁₀ H ₁₀ N ₄ S ⁺ 0.4 H ₂ O: C, 53.13; H, 4.64; N, 24.79. Found: C, 53.13; H, 4.46; N, 24.80
20	C ₁₁ H ₁₀ N ₄	2,4-Diamino-5H-indeno[3,2-c]pyrimidine	δ 3.6 (m, 2H, CH ₂), 5.9 (br s, 2H, 4-NH ₂), 6.4 (br s, 2H, 2-NH ₂), 7.3 (m, 4H, 1,7,9)	Calcd. for C ₁₁ H ₁₀ N ₄ ⁺ 0.25H ₂ O: C, 63.48; H, 5.23; N, 27.64. Found: C, 63.27; H 5.04; N, 27.80. m/z (M+1) ⁺ 199.23, expected 199.24

(s) The spectra of 13-16, 18, and 19 were obtained in deuteriochloroform solution, whereas those of 17 and 20 were obtained in *d*₂-dimethylsulfoxide.

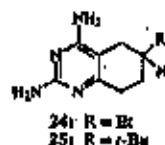
features of this high-temperature process. However, despite its low yield, the reaction is not without merit when one considers that other routes to sterically hindered 2,4-diamino-5,6-cycloalkanopyrimidines require several steps whose overall yield may not be any higher. For example, in a multistep synthesis of the bridged analog 23 from camphor via 3-cyano-2-methoxycamph-2-ene (25) the yield in just the final step, involving reaction of the cyano enol ether with guanidine in an autoclave at 160–170°, is reported to be only 4%.



It may be noted that since the cyanoguanidine reaction only works with ketones that contain a free CH₂ group, and the ketones in Table 1 either contain only one such group or contain a plane of symmetry (as in 9), all the reactions can only give a single diaminopyrimidine product. However, because 13–17 are chiral, the products from these ketones are assumed to be racemic. As a result, bioassay data obtained with the racemates, will reflect the combined effect of two enantiomers that may or may not have the same potency. Obviously, if the inhibitory effect of the racemic mixture against dihydrofolate reductase were due entirely to one enantiomer, the potency of this species would not vary from that of the racemic mixture by more than twofold.

The ability of the bridged analogs 13–17 and the non-bridged analogs 18–20 to inhibit dihydrofolate reductase from *P. carinii*, *T. gondii*, and rat liver was determined spectrophotometrically as described earlier [26,27]. This method depends on the change in ultraviolet absorbance which occurs at 254 nm when dihydrofolate is reduced to tetrahydrofolate and the 1,4-dihydropyridine ring of the nicotinamide adenine nucleotide cofactor is oxidized. The concentration of each compound required to inhibit the enzyme-catalyzed reaction by 50%, defined as the IC₅₀, is shown in Table 3, along with the previously determined IC₅₀ values of reference compounds 1–4. As noted above, 1 and 2 are examples of selective but relatively weak inhibitors whereas 3 and 4 are very potent but completely nonselective. Also shown for comparison are recently published IC₅₀ values for two additional examples of non-bridged analogs, namely 2,4-diamino-6-ethyl-5,6,7,8-tetrahydroquinazoline (24) and 2,4-diamino-6-*tert*-butyl-5,6,7,8-tetrahydroquinazoline (25). Like the other compounds in the series, 24 and 25 were synthesized from the thermal reaction of appropriate ketones with cyanoguanidine [22].

Comparison of the IC₅₀ values for compounds 13–17 as dihydrofolate reductase inhibitors suggests that a space-filling hydrophobic group in the B-ring region may indeed influence



binding in a species-specific manner. However, this type of substitution unfortunately also seems to lead to a sharp decrease in potency. The most active of the bridged compounds was 13, with an IC₅₀ of 6.1 μM against *P. carinii* dihydrofolate reductase and 5.1 μM against *T. gondii* dihydrofolate reductase. Its selectivity index for the *P. carinii* enzyme was 9.7, and this was similar to that of trimethoprim but substantially greater than that of pyrimethamine, trimetrexate, or pirarixin. The selectivity index of 13 for the *T. gondii* enzyme was 12, a value somewhat lower than that of trimethoprim, but still significant in comparison with the other reference drugs. While the selectivity of 13 was somewhat greater than that of the nonbridged analogs 23 and 24, its potency, especially in comparison with 24, was reduced. Thus it appears that bulky substitution may actually be tolerated better when it lies in the region just beyond the B-ring, rather than being part of a bridge spanning the ring.

Decreasing the number of CH₂ groups in the bridge, as in 14, resulted in little change in binding to *T. gondii* dihydrofolate reductase but a 20-fold loss of binding to *P. carinii* dihydrofolate reductase, suggesting that the active site of the *P. carinii* enzyme is more sensitive to a small change in size and geometry of the hydrophobic bridge. The selectivity index of 14 for *T. gondii* dihydrofolate reductase, while a little lower than that of 13, was still significant in comparison with trimetrexate and pirarixin. Interestingly, when the bridge spanned C6 and C8, as in 15, and additional bulk was introduced in the form of geminal dimethyl groups, there was a loss of binding to both the *T. gondii* enzyme and the rat liver enzyme. Moreover, selectivity for the *T. gondii* enzyme was nearly abolished. When the bridge spanned C5 and C7 and was extended to three carbons, as in 17, there was a sharp loss of potency against both *P. carinii* and *T. gondii* dihydrofolate reductase. The presence of a polar carbonyl group on the bridge may have been detrimental for binding to the enzyme. The solubility of this compound was also a problem, preventing it from being tested at concentrations greater than 46 μM. Compounds 18–20 were very weak inhibitors, and were also nonselective.

In summary, we have shown that the condensation reaction between cyanoguanidine and bicycloalkanones provides a reasonable route to sterically hindered 2,4-diamino heterocyclic systems whose synthesis would otherwise be uneconomical and extremely laborious. Although the yields in this reaction are low, they provided enough material to allow these novel and otherwise difficultly accessible bridged compounds to be tested *in vitro*.

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Table 3
Dihydrofolate Reductase Inhibition by Compounds 13-20 and Other Lipophilic 2,4-Diaminopyrimidines

Compound	IC ₅₀ (μM) (a)		Rat Liver	Selectivity Index (b)	
	<i>P. carinii</i>	<i>T. gondii</i>		<i>P. carinii</i>	<i>T. gondii</i>
1 (rimethoprim)	12	2.7	130	11	48
2 (pyrimethamine)	2.4	0.39	1.3	0.62	3.9
3 (methotrexate)	0.042	0.01	0.003	0.07	0.30
4 (pirarubicin)	0.031	0.017	0.0015	0.048	0.018
13	6.1	3.1	59	9.7	12
14	117	5.5	43	0.37	7.7
15	77	39	112	1.5	2.9
16	26% @ 45 μM	46	27% @ 45 μM	ND	ND
17	260	34	237	0.91	7.0
18	176	30	101	0.57	3.2
19	43% @ 352 μM	191	30	ND	0.3
20	18% @ 203 μM	20	29	ND	1.5
24 (c)	6.9	1.1	3.0	0.43	2.7
25 (c)	0.18	0.018	0.065	0.36	3.6

(a) Enzyme activity was determined at 340 nm according to a standardized and highly reliable method [26,27] which has been in continuous use in this program for a number of years. Each concentration of drug was tested in triplicate. As an example of the reproducibility of the assay, the IC₅₀ value (mean ± standard error) obtained in Dr. Queener's laboratory over a five-year period using the reference compound pyrimethamine (2) against *P. carinii*, *T. gondii*, and rat liver dihydrofolate reductase has been 2.39 ± 0.42, 0.50 ± 0.23, and 1.52 ± 0.32 μM, respectively. (b) Selectivity Index = IC₅₀ (rat liver)/IC₅₀ (*P. carinii*) or IC₅₀ (rat liver)/IC₅₀ (*T. gondii*). (c) Data from reference 22.

EXPERIMENTAL

The ¹H-NMR spectra were recorded on a Varian Model EM360L spectrometer with tetramethylsilane as the reference. Analytical thin-layer chromatography was on Quercus Baker S1250F silica gel plates, with spots being visualized under ultraviolet light at 254 nm. Column chromatography was on Baker 70-230 mesh silica gel or Baker flash-grade silica gel (40 μm particle size). Melting points (uncorrected) were obtained on a Fisher-Johns hot-stage apparatus. Microanalyses were by Robertson Laboratory, Madison, NJ, or QTI Laboratories, Whitehouse, NJ. Mass spectral data were supplied by the Mass Spectrometry Core Facility, University of California/Riverside, and the Molecular Biology Core Facility, Dana-Farber Cancer Institute. Chemicals and solvents were purchased from Aldrich (Milwaukee, WI) or Fisher (Boston, MA). Cyanoguanidine was recrystallized from water before being used.

General Procedure.

An equimolar mixture of the ketone and cyanoguanidine was finely pulverized and placed in a round-bottom flask which was heated at 230-230° in an oil bath for 1.0 or 1.5 hour under a gentle stream of nitrogen. In the case of the volatile ketone nortamphor (2) the reaction was carried out in a sealed tube at 190-200° for 2.5 hours. At the end of the reaction, the dark molten mixture was allowed to come to room temperature, and the contents of the flask were scraped out with a strong spatula and triturated with a large volume of 85:15 chloroform-methanol. The insoluble portion, assumed to contain polymeric by-products derived from the breakdown of cyanoguanidine, was discarded. Because the fused melt typically solidified as a glass, care had to be taken not to break the flask during this operation. The extract was washed with water, then dried over anhydrous sodium sulfate and evaporated, or was dried and evaporated directly. The product was purified by column chromatography on silica gel with 85:15% chloroform-methanol

as the eluent, or on a preparative thin-layer chromatography plate with the same eluent or one containing a little less methanol (e.g., 8%). Significant amounts of unreacted ketone always eluted from the column ahead of the product. Fractions were monitored by thin-layer chromatography, and only those containing a single spot were pooled and evaporated. Despite being homogeneous by thin-layer chromatography and giving the expected spectral and/or microanalytical results, the product typically had a very poorly defined decomposition point starting above 200°.

1,5-Diamino-1,4,6-triazinecyclo[6.2.2.0^{2,7}]dodeca-2,4,6-triene (16).

As the best example of the general procedure, 3-quinuclidinone (1 g, 8 mmole) was thoroughly mixed with powdered cyanoguanidine (0.679 g, 8 mmole) and the mixture was heated for 1.5 hour at 210° under a gentle flow of nitrogen. The reaction mixture was cooled to room temperature and the fused melt was thoroughly extracted with 85:15 chloroform-methanol (200 ml). The insoluble portion (0.22 g) showed no absorption at 254 nm and was discarded. The solution was washed with water, the water layer was extracted with 85:15 chloroform-methanol, and the combined organic extracts were dried over anhydrous sodium sulfate and evaporated. Column chromatography on silica gel with 85:15 chloroform-methanol as the eluent yielded 16 as a pale yellow solid (0.33 g, 23%). Chemical formulas and yields of the other diaminopyrimidines prepared by this method, 13-15 and 17-20, are shown in Table 1, and their spectral and microanalytical data are given in Table 2.

Dihydrofolate Reductase Inhibition Assays.

The ability of 13-20 to inhibit *P. carinii*, *T. gondii*, and rat liver dihydrofolate reductase was determined spectrophotometrically as previously reported [26,27]. The results of these assays are presented in Table 3, along with previously reported data for reference compounds 1-4 and the nonbridged analogs 24 and 25 [22].

Acknowledgments

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Institut für Pharmazeutische Chemie¹ der Technischen Universität Braunschweig und Bernhard-Nocht-Institut für Tropenmedizin, Abteilung Biochemie², Hamburg

Indeno[1,2-*d*]pyrimidin-4-yl-amine³

K. GÖRLTZER¹, S. HERBIG¹ und R. D. WALTER²

Herrn Prof. Dr. P. Nuhn, Halle, zum 60. Geburtstag gewidmet

Die 2-Acyl-3-aminoindene 1 und 2 reagieren mit Formamidinacetat zu den Indeno[1,2-*d*]pyrimidinen 3 und 4. Das 4-Chlorpyrimidin 5, aus 4 mit Phosphoroxychlorid dargestellt, reagiert mit *N*-Nucleophilen zu den Titelverbindungen 6–8. Nur 8 zeigt eine schwache Antimalaria-Aktivität.

Indeno[1,2-*d*]pyrimidin-4-yl-amines

The 2-acyl-3-aminoindenes 1 and 2 react with formamidine acetate to yield the indeno[1,2-*d*]pyrimidines 3 and 4. The 4-chloropyrimidine 5, synthesized from 4 with phosphorous oxychloride, reacts with *N*-nucleophiles to form the title compounds 6–8. Only 8 shows a weak antimalaria activity.

1. Einleitung

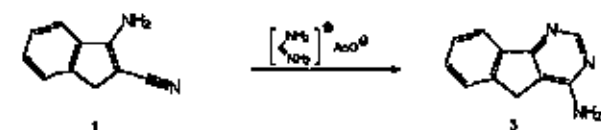
Nachdem Chloroquin- und Amodiaquin-ähnliche Substanzen, bei denen der Chinolinring durch Indeno[1,2-*b*]pyridine ersetzt wurde, eine Wuchshemmung sowohl auf Chloroquin-sensitive wie auch auf Chloroquin-resistente *Plasmodium-falciparum*-Stämme ausübten, war es interessant, das Indeno[1,2-*b*]pyridin-System durch das stärker basische Indeno[1,2-*d*]pyrimidin-System zu ersetzen. Hierdurch könnten eventuelle Wechselwirkungen mit aciden Zentren, wie sie in der Interkalationstheorie nach O'Brien et al. [1] postuliert wurden, verstärkt werden. Wenn aber die Hemmung einer Polymerase, wie später von Slater und Cerami [2] angegeben, die Antimalariawirkung ausmacht, sollte die starke Veränderung der Elektronenverteilung des Moleküls die Bindung an das Enzym beeinflussen. Ziel der vorliegenden Arbeit war die Synthese und biologische Prüfung von Indeno[1,2-*d*]pyrimidin-4-yl-aminen, die die Chloroquin- und Amodiaquin-analogen Seitenketten enthalten.

2. Untersuchungen, Ergebnisse und Diskussion

2.1. Synthese der Verbindungen

Das 4-Aminopyrimidin 3 ließ sich nach der Methode von Taylor [3] durch Erhitzen des Enaminonitrils 1 [4] mit Formamidinacetat in Ethylenglycolmonoethylether darstellen (Schema 1).

Schema 1



Um die substituierten 4-Aminoverbindungen 6–8 zu erhalten, wurde zuerst das 4-Pyrimidin 4 hergestellt. Dies gelang analog zu 3 durch Reaktion des 3-Aminoindeno-2-carbonsäureethylesters [4] mit Formamidinacetat. 4 wurde dann mit Phosphoroxychlorid zum 4-Chlorpyrimidin 5

umgesetzt. Die Reaktion von 5 mit aromatischen Aminen verläuft schnell mit guten Ausbeuten unter Bildung von 6 und 7. Für die Darstellung des Chloroquin-Analogen 8 war die Durchführung einer Phenolschmelze von 5 unter Zusatz von Natriumiodid mit der Novaldiamin-Base nach Andersag [5] notwendig (Schema 2).

2.2. Biologische Untersuchungen

2.2.1. Wirkung gegen Malaria

Die Substanzen 3, 4 und 6–8 wurden *in vitro* auf Wachstumshemmung gegen *Plasmodium-falciparum*-Stämme geprüft [6–9]. Getestet wurde gegen den drogenempfindlichen Stamm FCH-5 und den multiresistenten Stamm K-1. Als Vergleich diente Chloroquin. Die Substanzen 4, 6 und 7 zeigten keine Aktivität in einer Konzentration von 100 ng/ml. Substanz 8 wies in der gleichen Konzentration einen schwachen Effekt mit 10–20% Wachstumshemmung auf.

2.2.2. Antimikrobielle Aktivität

Die Substanzen 6 und 8 wurden in einem Agar-Diffusionstest gegen *Aspergillus niger*, *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa* und *Staphylococcus aureus* eingesetzt und zeigten keine Wachstumshemmung in einer Konzentration von 10 mg/ml.

3. Experimenteller Teil

3.1. Allgemeine Angaben

Vgl. [10].

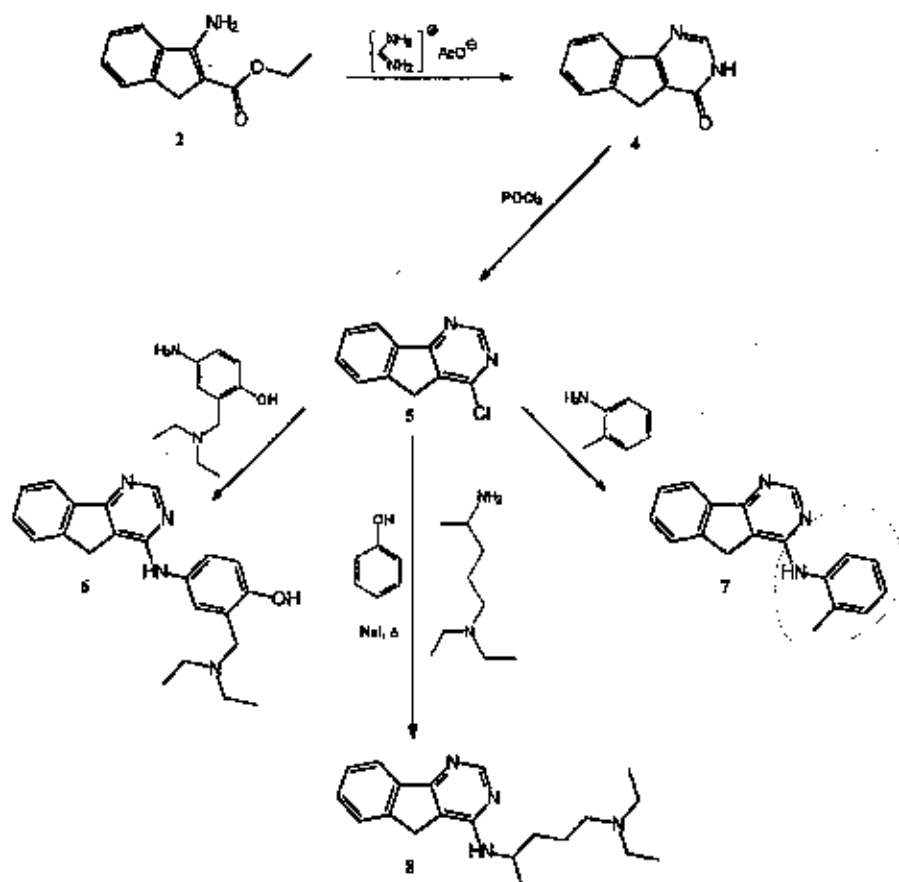
3.2. 4-Amino-5*H*-indeno[1,2-*d*]pyrimidin (3)

1,10 g (7 mmol) 1 und 2,25 g (21 mmol) Formamidinacetat werden in 25 ml Ethylenglycolmonoethylether gelöst. Es wird 6 h unter Rückfluß erhitzt. Nach 3 h werden nochmals 0,75 g (7 mmol) Formamidinacetat zugegeben. Das Lösungsmittel wird im Vakuum abdestilliert, der Rückstand mit H₂O gewaschen und fe gereinigt (Lösung: EtOAc). Farbloser Fktz, Schmp. 230–245 °C Zers. (EtOH). Ausb. 0,51 g (40%). IR (KBr, cm⁻¹): ν = 3381, 3335 (NH), 1661, 1585 (C=N, C=C). UV (Dioxan, nm): λ_{max} (lg ϵ) = 240 (4,36), 284 (3,90), 290 (3,95). ¹H-NMR (DMSO, ppm): δ = 3,72 (s, 3-H₂); 7,02 (s, NH₂); 7,46 (t, 1 = 6 Hz, 7-H); 7,50 (t,

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Schema 2



$J = 6$ Hz, 8-H); 7,68 (d, $J = 6$ Hz, 6-H); 7,88 (d, $J = 6$ Hz, 9-H); 8,45 (s, 2-H). MS: m/z (%) = 183 ($[M]^+$, 100). HPLC (2): $t_r = 1,89$. $C_{11}H_9N_3$ (183,2)

3.3. 4,5-Dihydroindeno[1,2-d]-4(3H)-pyrimidinon (4)

4,06 g (20 mmol) 2 werden nach Zugabe von 4,16 g (40 mmol) Formamidinacetat in 65 ml Ethylenglycolmonoäthylether gelöst und unter Rückfluß 9 h zum Sieden erhitzt, wobei nach 3 h und 6 h nochmals 2,08 g (20 mmol) Formamidinacetat zugegeben werden. Im Vakuum wird der Ansatz auf die Hälfte eingeengt. Das ausgefallene Produkt wird abfiltriert und mit EtOH gewaschen. Oranger Flaum, Schmp. 150–170 °C Zers. (Ethylenglycolmonoäthylether). Ausbeute: 0,35 g (27%). IR (KBr, cm^{-1}): $\tilde{\nu} = 3439$ (NH), 1669 (CO), 1615 (C=N, C=C). UV (Dioxan, nm): λ_{max} (lg ϵ) = 246 (4,38), 287 (3,82), 295 (3,86), 311 (3,72), 325 (3,40). ^1H -NMR ($[D_6]$ DMSO, ppm): $\delta = 3,75$ (s, 5-H₂); 7,46–7,52 (m, 7-H, 8-H); 7,66 (d, $J = 6$ Hz, 6-H); 7,84 (d, $J = 6$ Hz, 9-H); 8,29 (s, 2-H); 12,54 (br. s, NH). MS: m/z (%) = 184 ($[M]^+$, 16), 149 (100). HPLC (2): $t_r = 1,46$. $C_{11}H_9N_3O$ (184,2)

3.4. 4-Chlor-5H-Indeno[1,2-d]pyrimidin (5)

1,30 g (7 mmol) 4 werden 1 h in 30 ml POCl₃ unter Rückfluß erhitzt. Nach dem Abkühlen wird filtriert und in 300 ml Eiswasser eingerührt. Es wird mit 50% KOH-Lösung neutralisiert und der erhaltene Niederschlag abfiltriert. Das Produkt wird so gereinigt (Eluent: Petroläther/EtOAc = 50:50). Braune Nadeln, Schmp. 137 °C (EtOH/H₂O). Ausbeute: 0,64 g (45%). IR (KBr): $\tilde{\nu} = 1588, 1576$ cm^{-1} (C=N, C=C). UV (Dioxan, nm): λ_{max} (lg ϵ) = 257 (3,96), 283 (4,25), 291 (4,24), 300 (4,20). ^1H -NMR ($[D_6]$ DMSO, ppm): $\delta = 4,07$ (s, 5-H₂); 7,37 (t, $J = 7$ Hz, 7-H); 7,66 (t, $J = 7$ Hz, 7-H); 7,77 (d, $J = 7$ Hz, 6-H); 8,05 (d, $J = 7$ Hz, 9-H); 9,02 (s, 2-H). MS: m/z (%) = 202 ($[M]^+$, 100). HPLC (2): $t_r = 0,68$. $C_{11}H_7ClN_2$ (202,6)

3.5. 4-((5H-Indeno[1,2-d]pyrimidin-4-yl)amino)-2-(diethylaminoethyl)-phenoldihydrochloridmonohydrat (6)

0,20 g (0,7 mmol) 5 werden mit 0,19 g (0,7 mmol) 4-Amino-2-diethylaminophenoldihydrochlorid in 20 ml Ethylenglycolmonoäthylether gelöst und 2 h bei 120 °C gerührt. Der Ansatz wird im Vakuum eingeengt. Gelbes Pulver, Schmp. 185 °C Zers. (EtOH). Ausbeute: 0,24 g (77%). IR (KBr, cm^{-1}): $\tilde{\nu} = 3453$ (OH), 3385 (NH), 1630, 1604 (C=N, C=C). UV (Dioxan, nm): λ_{max} (lg ϵ) = 259 (3,43), 284 (3,22), 294 (3,25), 323 (3,24). ^1H -NMR ($[D_6]$ DMSO, ppm): $\delta = 1,30$ (t, $J = 7$ Hz, $N(CH_2CH_3)_2$); 3,13–3,14 (m, $N(CH_2CH_3)_2$); 4,05 (s, CH_2N); 4,23 und 4,25 (s, 5-H₂); 7,13 (d, $J = 9$ Hz, 6'-H); 7,55–7,61 (m, 7-H, 6-H); 7,67 (t, $J = 7$ Hz, 8-H); 7,78–7,81 (m, 3'-H, 5'-H); 8,41 (d, $J = 7$ Hz, 9-H); 8,88 (s, 2-H); 9,95 (s, OH); 10,71 (s, NH); 11,00 (s, NH^+). MS: m/z (%) = 360 ($[M]^+$, 100). HPLC (2): $t_r = 1,58$. $C_{21}H_{24}N_4O \cdot 2 HCl \cdot H_2O$ (451,4)

3.6. (5H-Indeno[1,2-d]pyrimidin-4-yl)-(2-methylphenyl)aminohydrochlorid (7-HCl)

0,50 g (2,5 mmol) 5 werden mit 0,54 g (5 mmol) o-Toluidin 5 min unter Rühren zum Sieden erhitzt. Nach dem Abkühlen wird der Ansatz in EtOH aufgenommen und das Produkt durch Zusatz von Petroläther ausgefällt. Gelbliche Kristalle, Schmp. 160 °C (Et₂O/Petroläther). Ausbeute: 0,34 g (44%). IR (KBr, cm^{-1}): $\tilde{\nu} = 3441, 3383$ (NH), 1628, 1608 (C=N, C=C). ^1H -NMR ($[D_6]$ DMSO, ppm): $\delta = 2,24$ (s, CH_3); 3,97 (s, br., 5-H₂); 7,31–7,38 (m, 3'-H, 4'-H, 5'-H, 6'-H); 7,60 (t, $J = 7$ Hz, 8-H); 7,68 (t, $J = 7$ Hz, 7-H); 7,80 (d, $J = 7$ Hz, 6-H); 8,38 (d, $J = 7$ Hz, 9-H); 8,84 (s, 2-H); 10,80 (s, NH). MS: m/z (%) = 273 ($[M]^+$, 100). $C_{18}H_{16}N_2 \cdot HCl$ (309,8)

3.7. (5H-Indeno[1,2-d]pyrimidin-4-yl)-(2-methylphenyl)amin (7)

1,86 g (6 mmol) 7-HCl werden mit 50 ml 12% NaOH-Lösung versetzt und mit Et₂O ausgeschüttelt. Nach Trocknen der organischen Phase über Na₂SO₄ wird das Lösungsmittel abdestilliert. Farbloses Pulver, Schmp. 158 °C (EtOAc). Ausbeute: 0,47 g (25%). IR (KBr, cm^{-1}): $\tilde{\nu} = 3211$

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(NH), 1593, 1571 (C=N, C=C). UV (Dioxan, nm): λ_{max} (lg ϵ) = 252 (4,43), 283 (4,01), 291 (4,06), 308 (4,11). ¹H-NMR (D₂O, ppm): δ = 2,23 (s, CH₃); 3,76 (s, 5-H₂); 7,19 (t, J = 7 Hz, 5'-H); 7,24 (t, J = 7 Hz, 4'-H); 7,30 (d, J = 7 Hz, 6'-H); 7,39 (d, J = 7 Hz, 3'-H); 7,48 (t, J = 7 Hz, 8-H); 7,52 (t, J = 7 Hz, 7-H); 7,58 (d, J = 7 Hz, 6-H); 7,92 (d, J = 7 Hz, 9-H); 8,52 (s, 2-H); 8,93 (s, NH). HPLC (2): t_r = 0,92. C₂₀H₁₃N₃ (273,3)

3.8. (R,S)-N¹-(5-H-Indeno[1,3-d]pyrimidin-4-yl)-N¹,N¹-diethyl-1,4-pentandiamin (8)

0,30 g (1,5 mmol) 5 werden mit 0,48 g (3 mmol) N¹,N¹-Diethyl-1,4-pentandiamin, 0,15 g (1,5 mmol) Phenol und 0,01 g NaI unter N₂ 1 h auf 180 °C erhitzt. Der Ansatz wird in 15% H₂SO₄ aufgenommen und mit EtOAc ausgeschüttelt. Die EtOAc-Phase wird verworfen, die H₂O-Phase mit 12% NaOH alkalisiert und erneut ausgeschüttelt. Die organische Phase wird über Na₂SO₄ getrocknet und im Vakuum eingeengt. Schwach gelblicher Fleum, Schmp. 157 °C (Cyclohexan). Ausbeute: 0,27 g (56%). IR (KBr, cm⁻¹): ν = 3235 (NH), 1598 (C=N, C=C). UV (Dioxan, nm): λ_{max} (lg ϵ) = 247 (4,52), 283 (3,88), 290 (3,97), 307 (4,00). ¹H-NMR (D₂O, ppm): δ = 0,92 (t, J = 7 Hz, N(CH₂CH₃)₂); 1,20 (d, J = 6,5 Hz, CH₃); 1,40–1,66 (m, CH₂CH₂); 2,41 (t, J = 7 Hz, CH₂N); 2,45 (q, J = 7 Hz, N(CH₂CH₃)₂); 3,72 (s, 5-H₂); 4,33 (m-sept, CH); 7,05 (d, J = 8 Hz, NH); 7,42–7,50 (m, 7-H, 8-H); 7,66 (d, J = 6 Hz, 6-H); 7,86 (d, J = 6 Hz, 9-H); 8,48 (s, 2-H). MS: m/z (%) = 324 (M)⁺, 34, 86 (0). HPLC (2): t_r = 1,02. C₂₂H₂₆N₄ (324,5)

3.9. Wachstumshemmung der Plasmodium-falciparum-Sämlinge FCH-5 und K-1

Vgl. [10].

3.10. Antitumorische Aktivität

Vgl. [10].

¹ Aus der geplanten Dissertation von S. Herbig, TU Braunschweig

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Prof. Dr. K. Gödtitzer
 Institut für Pharmazeutische Chemie
 Beethovenstraße 55
 D-38106 Braunschweig

Pharmazeutisches Institut der Universität Leipzig, Germany

PAF-Antagonisten mit Lipidstruktur

6. Mitt.: 1-Alkylpropandiol-Lipide mit Ester- bzw. Etherstrukturen in C-3-Position und heterocyclischen Kopfgruppen; Synthese, Charakterisierung und Struktur-Wirkungs-Betrachtungen

H.-P. KERTSCHER

Herrn Prof. Dr. P. Nuhn, Halle, mit besten Wünschen zum 60. Geburtstag gewidmet

Eine Serie von 14 Analoga des plättchenaggregierenden Faktors (PAF) mit einfacher Lipidstruktur und heterocyclischen Kopfgruppen wurden synthetisiert. Ihre PAF-inhibitorische Wirkung an Human-Blutplättchen wurde *in vitro* geprüft. Struktur-Wirkungs-Untersuchungen zeigten, daß die PAF-antagonistische Aktivität streng durch den Abstand zwischen C-3-Position des Grundgerüsts und Oniumzentrum sowie von der Struktur des Heterocyclus bestimmt wird. Die stärkste Wirkung wurde beim 3,5-Dimethylpyridinium-Derivat mit einer Distanz von 5 Methylengruppen beobachtet (IC₅₀ = 0,8 µmol/l).

PAF-antagonists with lipid structure

Part 6: Alkylpropandiol lipids with acyl and ether structure in position C-3 of the backbone and heterocyclic head groups; synthesis, characterization and structure-activity relationships

A series of 14 PAF-analogues with simple lipid structure and heterocyclic head groups were synthesized, and the PAF-inhibitory potencies on human blood platelets was evaluated *in vitro*. Structure-activity relationships revealed that the PAF-antagonist activity is strongly influenced by the distance between position C-3 of the backbone and onium center and the structure of the heterocycle. The best activity showed the 3,5-dimethylpyridinium derivative with a distance of 5 methylene groups (IC₅₀ = 0,8 µmol/l).

1. Einleitung

Neben zahlreichen Phospholipidanaloga [1–3] inhibieren auch synthetisch abgewandelte einfache Lipide [4–11] den plättchenaggregierenden Faktor (PAF). Voraussetzung ist,

daß am Grundgerüst in C-1-Position eine langkettige Ether- bzw. Alkylcarbamoyl-Struktur und in C-2-Position ein kurzketziger Alkylrest erhalten bleibt. Des weiteren muß eine quaternäre Stickstoffstruktur mit einem sehr präzisen Abstand zur C-3-Position des Grundgerüsts vorhanden sein.

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**SYNTHESIS OF SOME NEW FUNCTIONALIZED PYRIDINES,
5-OXOINDENO[1,2-b]PYRIDINES AND RELATED COMPOUNDS
OF POTENTIAL PHARMACEUTICAL INTEREST**

Ez-el-din M. Kandeel

Chemistry Department, Faculty of Science, Mansoura University,
Mansoura, Egypt.

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ABSTRACT

This study is directed towards the utility of the electrophilic cyanoolefines 1 and 3 as well as the 2-(arylmethylene)-indan-1,3-dione 9 to synthesize the polyfunctionalized pyridines 2, 4, 6 and 5-oxoindeno[1,2-b]pyridines 10, 13 and some related compounds of potential pharmaceutical interest. Unambiguous syntheses and/or spectral analyses of the products confirmed the suggested structures.

INTRODUCTION

In the light of the reported important biological activity of some pyridines [Comprehensive Heterocyclic Chemistry, 1984; Essentials of Medicinal Chemistry, 1998; Principles of Medicinal Chemistry, 1995 and The Merck Index, (1996)], indenopyridines [Bisenieks et al., 1982 and Rose (1990)], and benzofurans [Hishmat et al., 1977 and Hishmat et al. (1982)], and in continuation of our program aiming to synthesize polyfunctionally substituted heterocycles of potential biological interest [El-Desoky et al. 1988; Kandeel et al., 1996 and El-Desoky et al., (1999)], it was interesting to study the utility of activated cyanoolefines as well as 2-(arylmethylene)-indan-1,3-diones to synthesize polyfunctionally pyridines and indenopyridines, and some related compounds having a benzofuranyl pharmacophore, of potential pharmaceutical interest.

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RESULTS AND DISCUSSION

The reaction of α -cyano- β -(2,3-diphenyl-5-methoxybenzofuran-6-yl)-acrylonitrile (1) with β -amino- β -ethoxyacrylonitrile hydrochloride (A) in an equimolecular ratio in the presence of ammonium acetate, in boiling ethanol afforded 2,6-diamino-4-(2',3'-diphenyl-5'-methoxybenzofuran-6'-yl)-pyridine-3,5-dinitrile (2). The structure of 2 was elucidated by studying its ¹H NMR spectrum which showed a singlet at δ 3.8 for OCH₃ group, and a multiplet at δ 7.1-8.1 ppm for the two symmetrical -NH₂ groups and the aromatic protons and its mass spectrum showed the molecular ion, M⁺, as the base peak, at m/e 457. Formation of 2 can be explained via initial Michael addition of 2-cyano-1,1-diaminoethene, which was generated *in situ* [Coda et al. (1996)], to the ylidenic bond in 1 followed by cyclization through a nucleophilic attack of an -NH₂ group on a cyano carbon, tautomerization and aromatization via dehydrogenation. Autoxidation of dihydropyridines under comparable conditions has been reported [Shams et al. (1988)], [Scheme 1]).

It was worthy to apply the above given reaction as a synthetic route to 2-amino-4-(2',3'-diphenyl-5'-methoxybenzofuran-6'-yl)-6-phenylpyridine-3,5-dinitrile (4) as the expected product of the reaction of α -benzoyl- β -(2,3-diphenyl-5-methoxybenzofuran-6-yl)acrylonitrile (3) with 2-cyano-1,1-diaminoethene. The analytical and spectral data of the product were not in agreement with structure 4 and confirmed the formation of 2 rather than 4, because a retro-aldol reaction occurs in enones such as 3 generating the aldehyde 5 which combines with A to form 2. This is in agreement with previously reported cases [Sofan et al., 1989 and Kandeel (1999)].

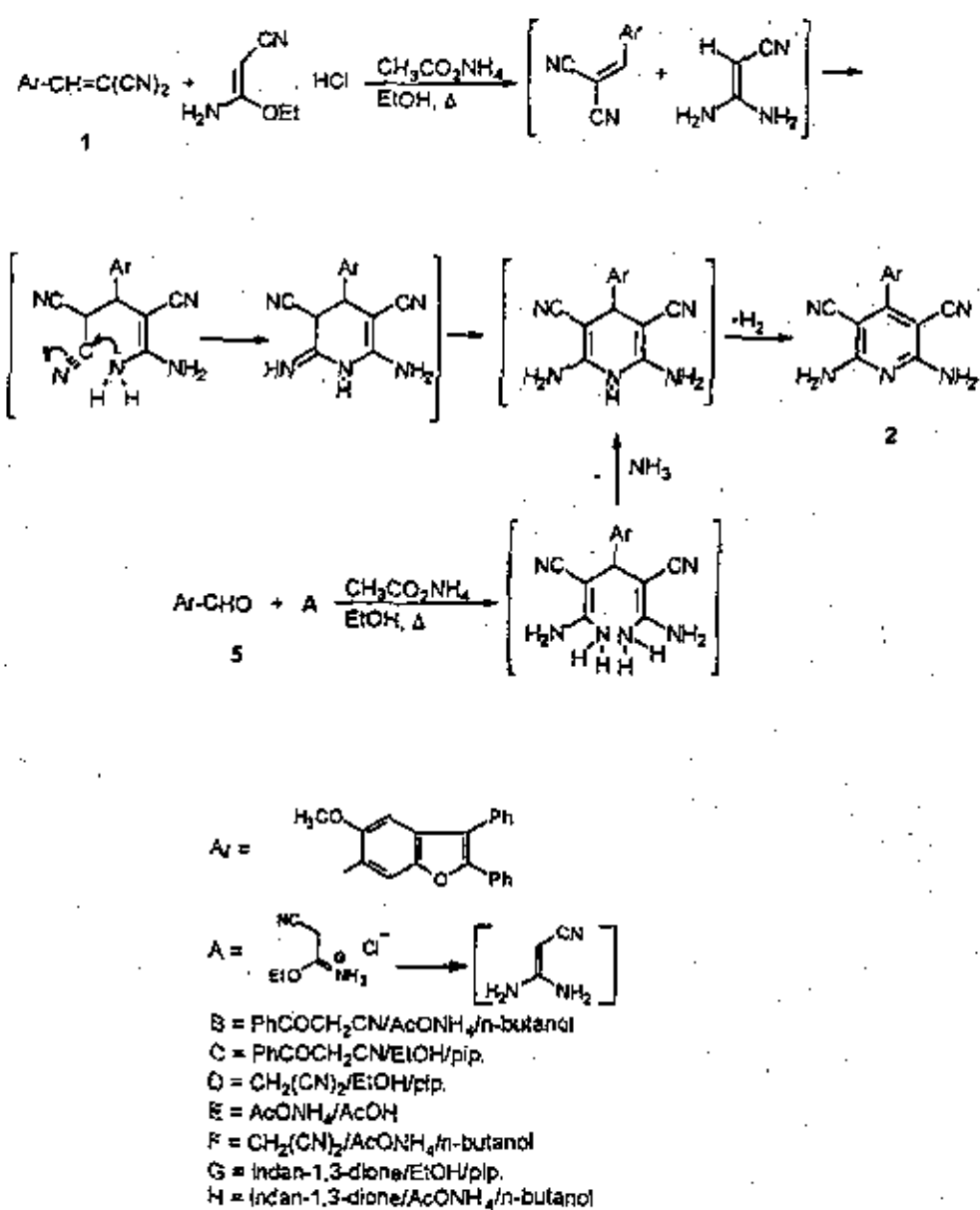
A further confirmation of the structure 2 was obtained unambiguously via a direct condensation of the aldehyde 5 with A in a molar ratio of 1:2. In this case one molecule of the aldehyde condenses with two molecules of A at the highly nucleophilic site C₂, with the elimination of a water molecule, to afford an acyclic intermediate which cyclized into a dihydropyridine via intramolecular elimination of an ammonia molecule, then aromatized to 2 [Scheme 1].

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Scheme 1



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Cyclocondensation of 1 with benzoylacetonitrile in the presence of ammonium acetate (B) seemed to be a convenient route to 4. The analytical and spectral data of the product elucidated the formation of 4-(2',3'-diphenyl-5'-methoxybenzofuran-6'-yl)-2,6-diphenyl-1,4-dihydropyridine-3,5-dinitrile (6) rather than 4. Further synthesis of 6 either *via* reaction of 5 with benzoylacetonitrile and ammonium acetate in acetic acid (Hantzsch pyridine synthesis) or by cyclocondensation of 3 with B confirmed the structure of 6 [Scheme 2].

As a result of the unsuccessful attempts to synthesize 4, I felt obligated to introduce an alternative route to it. Thus, either refluxing 1 with benzoylacetonitrile or 3 with malononitrile, in ethanol containing a catalytic amount of piperidine (C and D), afforded the 4H-pyran derivative 7. Ring transformation of 2-amino-4H-pyrans into the corresponding pyridines is possible via the reaction with ammonium acetate in acetic acid [Seoane et al. (1981)]. By this way 7 could be converted to the target molecule 4. A trial to produce 4 directly through the reaction of 3 with malononitrile in the presence of ammonium acetate (F) furnished the naphthyridine derivative 8 [Scheme 2].

Substituted 5-oxo-indeno[1,2-b]pyridines have been synthesized *via* condensation of arylideneindandiones with enaminocsters [Vigante et al. (1980)]. This prompted the author to introduce a facile one-pot synthesis of 2-amino-4-heteryl-5-oxo-indeno[1,2-b]pyridine-3-nitrile (10) *via* condensation of the 2-arylidene-indan-1,3-dione (9) with A. Unfortunately, compound 10 has not been obtained and 2 was formed instead. This is in accordance with the formation of 2 through the reaction of 3 with A.

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An alternative route to 10 seemed possible by reacting 1 with indan-1,3-dione and ammonium acetate (H) but the desired compound was not obtained and instead the diindenopyridine derivative 11 was formed. Such related skeletons have been previously synthesized using different methods [Zimaity et al., 1979 and Afsah et al. (1990)]. Formation of 11 has been also supported by its independent synthesis from 5 [Scheme 3].

Another attempt to have 10 through a one-pot synthesis was the reaction of 9 with F and this was unsuccessful and the spectral data of the product were in agreement with the formation of the indenonaphthyridine derivative 12.

The unsuccessful trials to achieve 10 has prompted the synthesis of the 2-phenyl analogue 13 which was obtained via a one pot synthetic route by reacting 9 with B. However, an attempt to obtain this compound through cyclocondensation of 3 with H afforded 11 instead of 13.

Since indenopyrans could be used as precursors for the indenopyridines 10 and 13, and in view of the reported formation of indenopyrans via the reaction of indan-1,3-dione with arylidenemalononitrile or ethyl arylidenecyanoacetate [Mashaly (1993)], however, the arylideneindandione 9 was the sole product from the reaction of 1 and/or 3 with G rather than the expected indenopyrans 14 and 15. These transformations of 1 or 3 to 9 is in line with the formation of 11 via the reaction of these cyanoolefines with H. Alternatively, the reaction of 9 with C afforded 15 whereas 16 was formed instead of 14 on reacting 9 with D.

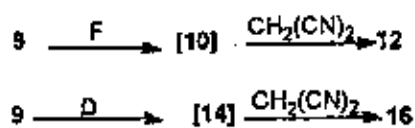
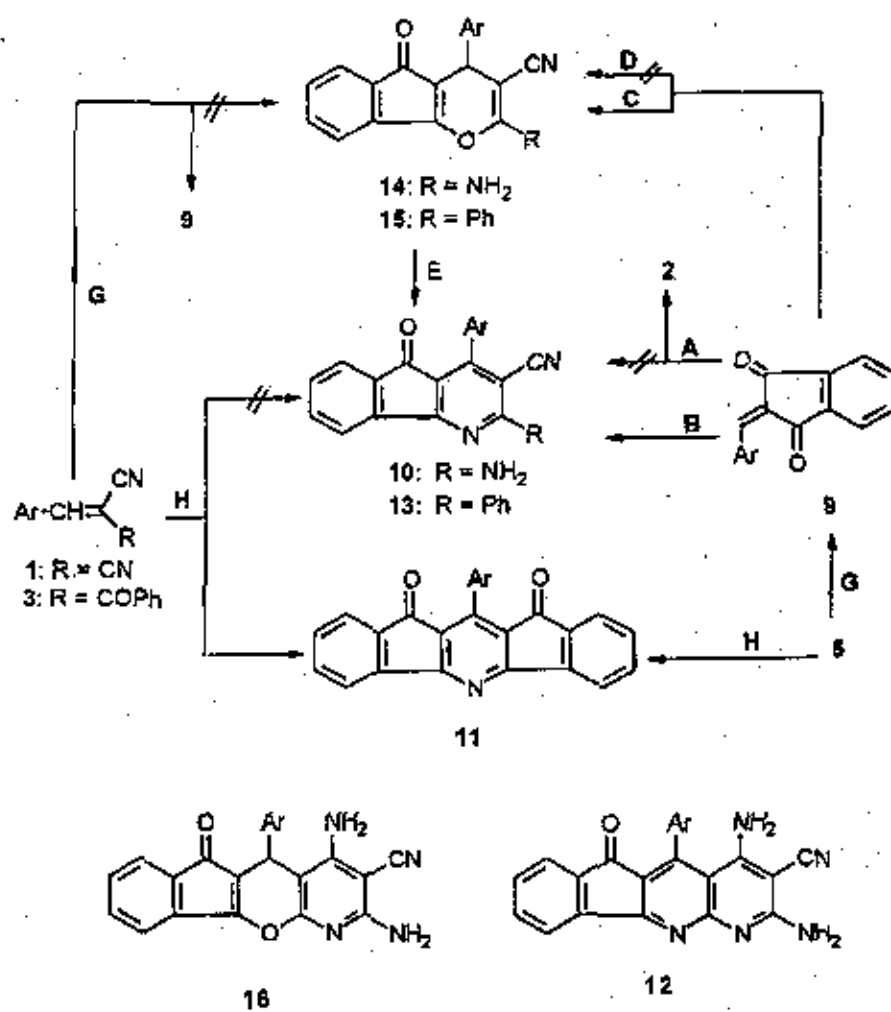
The reaction of ammonium acetate in acetic acid (E) with 15 and 16 led to the formation of the indeno-condensed systems 13 and 12, respectively.

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Scheme 3



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EXPERIMENTAL

Melting points were uncorrected. The IR spectra were recorded on Matheson 5000 FTIR spectrometer as KBr discs (ν in cm^{-1}). $^1\text{H-NMR}$ spectra were obtained on Bruker AC250 spectrometer with TMS as an internal standard and DMSO-d_6 as solvent. Chemical shifts were expressed as δ ppm. Electron impact mass spectra were recorded on a GC-MSQP-1000 Ex Shimadzu instrument, at 70 eV. The new compounds gave satisfactory elemental analysis.

2,6-Diamino-4-(2',3'-diphenyl-5'-methoxybenzofuran-6'-yl)pyridine-3,5-dinitrile (2):

Procedure a: A solution of ethyl cyanoiminoacetate hydrochloride (A) (1 g, 0.0067 mole), 1 [Hishmat et al., 1987] (2.52 g, 0.0067 mole) and ammonium acetate (3.2 g) in absolute ethanol (20 ml) was refluxed for 2 h. The solid product deposited was filtered off, washed with water (3 x 10 ml) to get rid of ammonium chloride, dried and crystallized from ethanol to give 2 as colourless crystals, yield 85%, m.p. 302°C .

Procedure b: A solution of A (1g, 0.0067 mol), 3 (3 g, 0.0067 mol) and ammonium acetate (3.2 g) in absolute ethanol (20 ml) was worked up as in procedure a to give 2 in 45% yield.

Procedure c: A solution of A (1 g, 0.0067 mol), 2,3-diphenyl-6-formyl-5-methoxybenzofuran (5) (1.1 g, 0.0034 mol) and ammonium acetate (3.2 g) in absolute ethanol (20 ml) was worked up as in procedures a and b to give 2 in 85% yield.

Procedure d: A solution of A (1g, 0.0067 mol), 9 (3 g, 0.0067 mol) and ammonium acetate (3.2 g) was worked up as in procedures a-c to give 2 in 40% yield.

IR(cm^{-1}): 3463, 3338, 3219 (NH_2), 2211 (CN). $^1\text{H-NMR}$: δ 3.8 (s, 3H, OCH_3), 7.1-8.1 ppm [m, 16H, (12H, aromatic protons) and (4H, 2NH_2)]. MS: M^+ at $m/e = 457$.

α -Benzoyl- β -substitutedbenzofuranylacrylonitrile (3):

A solution of 5 (3.28 g, 0.01 mol) and benzoylacetonitrile (1.46 g, 0.01 mol) in ethanol (30 ml) containing a catalytic amount of piperidine

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was refluxed for 15 min. The crystalline solid formed was filtered off and recrystallized from ethanol to give 3 as yellow crystals, yield 90%, m.p. 210°C.

IR(cm^{-1}): 2212 (CN), 1646 (C=O).

2-Amino -4-heteryl-6-phenylpyridine-3,5-dinitrile (4):

A solution of 7 (0.52 g, 0.001 mol) and ammonium acetate (0.1 g) in glacial acetic acid (10 ml) was refluxed for 3 h. The solid separated after cooling and dilution with water was filtered off, washed with water, dried and crystallized from ethanol to give 4 as pale brown crystals, yield 65%, m.p. 171°C.

IR(cm^{-1}): 3455, 3356, 3248 (NH_2), 2210 (CN). $^1\text{H-NMR}$: δ 3.2 (s, 2H, NH_2), 3.85 (s, 3H, OCH_3), 7.1-8.2 ppm (m, 17H, aromatic protons).

2,6-Diphenyl-4-heteryl-1,4-dihydropyridine-3,5-dinitrile (6):

Procedure a: A solution of 1 (0.94 g, 0.0025 mol), benzoylacetonitrile (0.36 g, 0.0025 mol) and ammonium acetate (0.2 g) in n-butanol (30 ml) was refluxed for 5 h then left to cool. The solid that precipitated after concentrating the solvent was filtered off, washed with water, dried and crystallized from ethanol to give 6 as colourless crystals, yield 40%, m.p. 230°C.

Procedure b: A solution of 3 (1.1 g, 0.0025 mol), benzoylacetonitrile (0.36 g, 0.0025 mol) and ammonium acetate (0.2 g) in n-butanol (20 ml) was worked up as in procedure a to give 6 in 70% yield.

Procedure c: A solution of 5 (0.82 g, 0.0025 mol), benzoylacetonitrile (0.73 g, 0.005 mol) and ammonium acetate (0.2 g) in acetic acid (10 ml) was refluxed for 2 h then left to cool. The solid that separated by dilution with water was filtered off, washed with water, dried and crystallized from ethanol to give 6 in 80% yield.

IR(cm^{-1}): 3293 (NH), 2201 (CN). $^1\text{H-NMR}$: δ 3.9 (s, 3H, OCH_3), 5.1 (s, 1H, 4-H), 7.0-8.15 (m, 22H, aromatic protons) and 10.1 ppm (s, 1H, NH). MS: M^+ at m/e = 581.

2-Amino-3,5-dicyano-4-heteryl-5-phenyl-4H-pyran (7):

Procedure a: A solution of 1 (0.94 g, 0.0025 mol) and benzoylacetonitrile (0.36 g, 0.0025 mol) in ethanol (50 ml) containing a

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catalytic amount of piperidine was refluxed for 5 h then left to cool. The solid that separated after concentrating the solvent was filtered off and crystallized from ethanol to give 7 as yellow crystals; yield 70%, m.p. 158°C.

Procedure b: A solution of 3 (1.1 g, 0.0025 mol) and malononitrile (0.17 g, 0.0025 mol) in ethanol (30 ml) containing a catalytic amount of piperidine was worked up as in procedure a to give 7 in 75% yield. IR(cm^{-1}): 3343, 3248 (NH_2), 2196 (CN). $^1\text{H-NMR}$: δ 3.2 (s, 2H, NH_2), 3.8 (s, 3H, OCH_3), 4.8 (s, 1H, pyran 4-H), 7.0-8.0 ppm (m, 17H, aromatic protons).

Synthesis of the naphthyridine derivative (8):

A solution of 3 (0.45 g, 0.001 mol), malononitrile (0.07 g, 0.001 mol) and ammonium acetate (0.1 g) in n-butanol (20 ml) was refluxed for 2 h. The solid that separated by concentrating the solvent and cooling was filtered off, washed with water, dried and crystallized from ethanol to give 8 as deep yellow in 40% yield, m.p. 162°C. IR(cm^{-1}): 3414, 3337, 3282 (NH_2), 2200 (CN). MS: M^+ at m/e = 584.

2-Arylidene-indan-1,3-dione (9):

Procedure a: A solution of 5 (3.28 g, 0.01 mol) and indan-1,3-dione (1.46 g, 0.01 mol) in ethanol (30 ml) was refluxed for 30 min. The solid formed was filtered off and crystallized from ethanol/acetone mixture to give 9 as deep yellow crystals, yield 90%, m.p. 242°C.

Procedure b: A mixture of 1 or 3 (0.0025 mole), indandione (0.379 g, 0.0025 mole) in ethanol (50 ml) containing a catalytic amount of piperidine was refluxed for 2 h to give 9 in 70% yield. IR(cm^{-1}): 1673 (C=O).

Synthesis of the substituted diindenopyridine (11):

Procedure a: A mixture of 1 or 3 (0.0025 mol), indan-1,3-dione (0.37 g, 0.0025 mole) and ammonium acetate (0.2 g) in n-butanol (20 ml) was refluxed for 3 h then left to cool. The solid obtained was filtered off, washed with water, dried and crystallized from ethanol to give 11 as deep yellow powder, m.p. > 300°C in 45% yield.

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Procedure b: A solution of 5 (0.82 g, 0.0025 mol), indan-1,3-dione (0.73g, 0.005 mol) and ammonium acetate (0.2 g) in n-butanol (20 ml) was worked up as in procedure a to give 11 in 80% yield.
IR(cm^{-1}): 1715 (C=O). $^1\text{H-NMR}$: insoluble in commonly used NMR solvents. MS: M^+ at $m/e = 581$.

Synthesis of the indenonaphthyridine derivative (12):

Procedure a : A solution of 9 (1.14 g, 0.0025 mol), malononitrile (0.12 g, 0.0025 mol) and ammonium acetate (0.2 g) in n-butanol (20 ml) was worked up as in usual to give 12 from ethanol as brown crystals, m.p. 220°C in 35% yield.

Procedure b: A solution of 16 (1.3 g, 0.0025 mol) and ammonium acetate (0.2 g) in glacial acetic acid (10 ml) was refluxed for 3 h then left to cool. The solid formed after cooling and dilution with water was filtered off, dried and crystallized from ethanol to give 12 in 70% yield.
IR(cm^{-1}): 3560, 3430, 3380 (NH_2), 2191 (CN), 1705 (C=O). $^1\text{H-NMR}$: δ 3.9 (s, 3H, OCH_3), 7.0-8.6 ppm [m, 20H (16H, aromatic protons) and (4H, 2NH_2)].
MS: M^+ at $m/e = 585$.

The indenopyridine derivative (13):

Procedure a: A solution of 9 (1.14 g, 0.0025 mol), benzoylacetonitrile (0.36 g, 0.0025 mol) and ammonium acetate (0.2 g) in n-butanol (20 ml) was worked up as usual to give 13 as brown crystals, from ethanol in 70% yield, m.p. 181°C .

Procedure b: A solution of 15 (1.5 g, 0.0025 mol) and ammonium acetate (0.2 g) in glacial acetic acid (10 ml) was worked up as in case of 12 (procedure b) to give 13 in 65% yield.
IR(cm^{-1}): 2215 (CN), 1714 (C=O). $^1\text{H-NMR}$: δ 3.85 (s, 3H, OCH_3), 7.1-8.5 ppm (m, 21H, aromatic protons).

Formation of the 2-phenylindeno-4H-pyran derivative (15):

A solution of 9 (1.14 g, 0.0025 mol) and benzoylacetonitrile (0.36 g, 0.0025 mol) in ethanol (20 ml) containing a catalytic amount of

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piperidine was worked up as usual to give 15 as yellow crystals from ethanol, yield 70%, m.p. 162°C.

IR(cm^{-1}): 2221 (CN), 1710 (C=O). ^1H NMR: δ 3.9 (s, 3H, OCH_3), 4.7 (s, 1H, pyran 4-H), 7.1-8.4 ppm (m, 21H aromatic protons).

Formation of compound 16

A solution of 9 (1.14 g, 0.0025 mol) malononitrile (0.17 g, 0.0025 mol) in ethanol (20 ml) and a catalytic amount of piperidine was worked up as in case of 15 to give 16 as yellow crystals from ethanol, m.p. 205°C in 40% yield.

IR(cm^{-1}): 3561, 3441, 3392 (NH_2), 2201 (CN), 1705 (C=O).

MS: M^+ at $m/e = 588$.

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تخليق بعض مشتقات البيريدين و 5 - أوكسوايندينو [1,2- b] بيريدين ومركبات
مشابهة ذات نشاط دوائي متوقع

عز الدين محمد قنديل

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أوكسوايندينو [1,2- b] بيريدين (10, 13) وبعض المركبات المشابهة ذات النشاط
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