Pentacyclic Triazolodiazepines as PAF-Antagonists

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The syntheses of two novel pentacyclic ring systems, the thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepino-[4,5-*a*]benzimidazole and the indazolo[2,3-*d*][1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine are described. Attachment of a propargyl linked quinolinone resulted in compounds **6** and **16** which showed PAF-antagonist activity by the intravenous route of administration in guinea pigs. The more potent compound **16** also exhibited good oral activity with an ID_{50} of 0.2 mg/kg in the bronchoconstriction assay.

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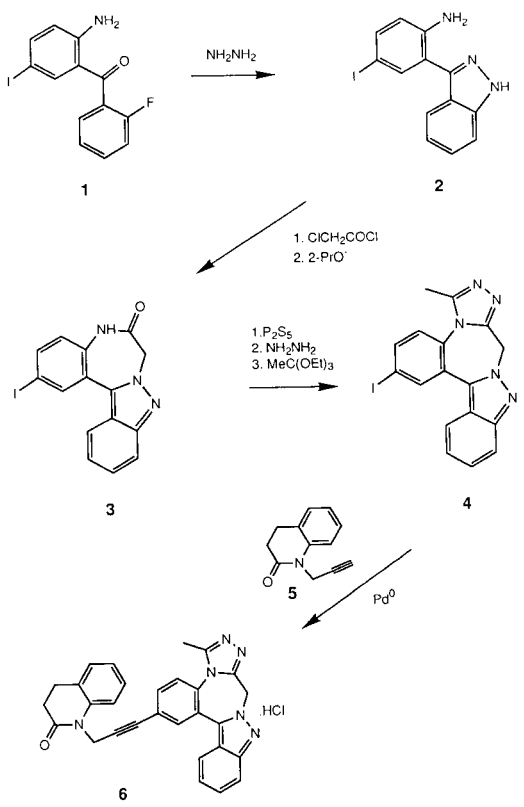
The discovery of the platelet activating factor (PAF) antagonist activity of triazolobenzodiazepines [1,2], well known for their anxiolytic effects [3], prompted the syntheses of analogs which would not affect the cental nervous system, but retain PAF-antagonist activity. Several groups of researchers [4,5,6] have been successful in this endeavor. In our laboratory, we found that attachment of a propargylic side chain to the 8-position of triazolobenzodiazepines or to the equivalent 2-position of the isosteric thienotriazolodiazepines resulted in very potent PAF-antagonists devoid of CNS-effects [7]. In search for other patentable compounds we explored the structure-activity relationship of these triazolodiazepines and synthesized, in this context, the pentacyclic compounds **6** and **16**.

Scheme I

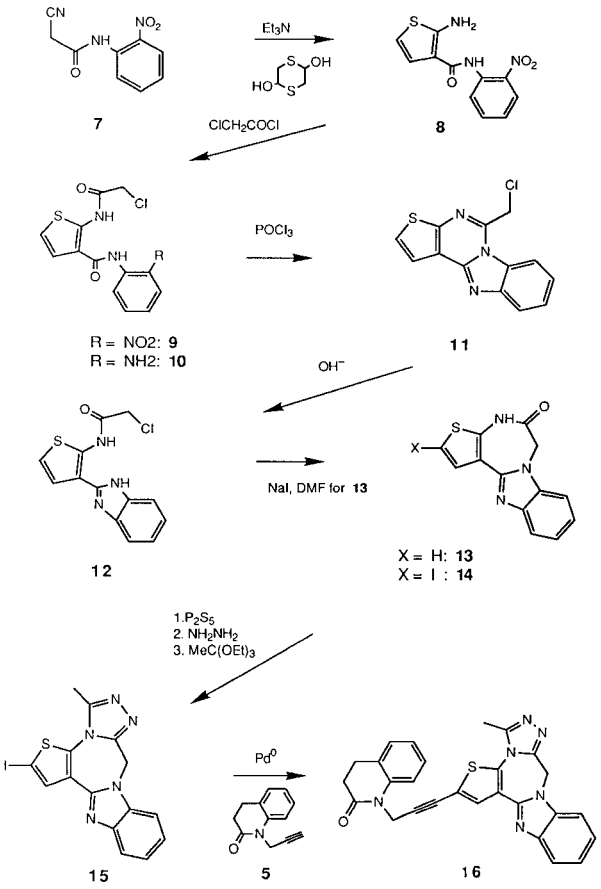


The synthesis of the indazolobenzodiazepine **6** was straightforward and is outlined in Scheme I. Reaction of the 2-fluorobenzophenone **1** [8] with hydrazine at reflux led in analogy with previously published work [9] to the indazole **2** in good yield. The standard chloroacetylation followed by treatment with potassium isopropoxide resulted in the tetracyclic compound **3**. The triazolo derivative **4** was built up as described previously [3,7], by first converting the lactam to the thione and reacting the latter with hydrazine and subsequently with triethyl orthoacetate. The palladium catalyzed coupling of **4** with the *N*-propargylquinolinone, **5**, [10] afforded the desired target compound **6**, crystallized, characterized and tested as a hydrochloride salt.

The preparation of the thienodiazepinobenzimidazole ring system **12** (Scheme II) was more cumbersome. The anilide **7**, obtained by acylation of 2-nitroaniline with cyanoacetic acid by means of dicyclohexylcarbodiimide, was converted to the 2-aminothiophene **8** following literature procedures [11]. After chloroacetylation to **9**, the nitro group was reduced catalytically over palladium on carbon to yield the aniline **10**. A double dehydration with hot phosphorus oxychloride then led to the tetracyclic compound **11**. Treatment of this thienopyrimidine with hydroxide effected ring opening to the chloroacetate **12**. We were not able to cyclize this chloride under the conditions successfully used for ring closure of the chloroacetate of the indazole **2**. Compound **12** was thus converted to the corresponding iodide which cyclized *in situ* (warm DMF) to the diazepinone **13** without the addition of a strong base. Iodination of **13** with iodine monochloride in methanol/acetic acid/sodium acetate gave compound **14** which was converted to the triazolo derivative **15** in the usual fashion *via* thione and hydrazino derivative. The palladium catalyzed coupling of **15** with the acetylene **5** yielded the desired target compound **16**.

The difference in conformational mobility of the diazepine ring in compounds **4** and **6** *versus* **15** and **16** was evident from the proton nmr data. The methylene protons in the triazolobenzodiazepine systems **4** and **6** show up as AB-patterns with a coupling constant of 14.5 Hz, while the

Scheme II



equivalent protons in the thienodiazepine system appear as singlets. The triazolobenzodiazepines are less flexible because of steric interaction of the methyl group on the triazole ring with the neighboring aromatic proton.

Biological Data.

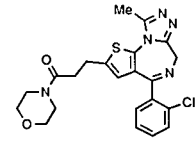
The compounds listed below were evaluated *in vitro* and *in vivo* in tests established to screen PAF-antagonists [7, 12]. The *in vitro* binding assay measured the ability of the compounds to inhibit the binding of radiolabelled PAF to its receptors on dog platelets. The *in vivo* testing determined the amount of compound needed to antagonize the PAF-induced bronchoconstriction in anesthetized guinea pigs. The drug was given both by the intravenous and oral route. The data obtained for the Boehringer Ingelheim compound WEB 2086 [4] and our related triazolodiazepines, **17** and **18** [7], are given for comparison.

Compound **16** is an order of magnitude more potent than **6** and equipotent to WEB 2086 by the intravenous route. Orally, it was superior to WEB 2086, while compound **6** was inactive at the testing dose. The fusion of additional rings at the d-side of the diazepine ring thus led to active PAF-antagonists, but the activity of these polycyclic compounds did not reach that of the related phenylsubstituted imines **17** and **18**. Compound **16** appears to have better oral bioavailability than **6**. This could be attributed to the thieno *versus* benzo or the imidazole *versus* indazole substitution. Based on our experience [7] we believe that the thieno *versus* benzo substitution is mainly responsible for this observation, since many thieno analogs had better oral potency than the corresponding benzodiazepines. This is illustrated by the difference in the p.o. to i.v. ratio for compounds **17** and **18**.

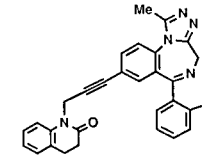
Table

Compound	Binding assay IC_{50} (nM)	Guinea pig bronchoconstriction test ID_{50} (mg/kg)	
		i.v.	p.o.
6	1000	0.25	inact[a]
15	>1000	inact[a]	NT[b]
16	120	0.03	0.3
17 [7]	20	0.02	0.4
18 [7]	0.2	0.004	0.02
WEB 2086 [4]	200	0.03	1.2

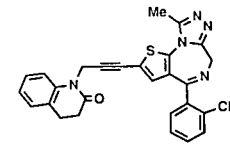
[a] inact = no significant inhibition at 1 mg/kg i.v. or 3 mg/kg p.o.
[b] NT = not tested



WEB 2086



17



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EXPERIMENTAL

Melting points were taken on a Thomas Hoover capillary melting apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian XL-200 spectrometer. Silica gel Merck 70-230 mesh was used for preparative column chromatography. Organic layers were dried over anhydrous sodium sulfate.

3-(2-Amino-2-iodophenyl)indazole, **1**.

A mixture of 10 g of (2-amino-5-iodophenyl)(2-fluorophenyl)-methanone [8] and 35 ml of hydrazine (95%) was heated at reflux under nitrogen for two hours. The cooled reaction mixture was diluted with ice and water. The precipitated product was collected and sucked dry. The crude product was dissolved in THF. The solution was dried and evaporated after addition of xylene. Crystallization of the residue from THF/hexane yielded 7.3 g (74%) of crystals. The analytical sample was purified by chromatography over silica gel using 10% of ethyl acetate in methylene

chloride for elution. Crystallization from THF/hexane gave colorless crystals with mp 157-159°; ^{1}H-nmr (deuteriochloroform): δ *ca.* 5.2 (very br s, 2, NH_2), 6.58 (d, 1, J = 8 Hz, $C_{3'}$-H), 7.1-7.6 (m, 4, aromatic H), 7.92 (d, 1, J = 8 Hz, C_4-H), 7.99 (d, 1, J = 2 Hz, $C_{6'}$-H), *ca.* 10.3 (br s, 1, NH).

Anal. Calcd. for $C_{13}H_{10}IN_3$: C, 46.59; H, 3.01; N, 12.54. Found: C, 46.52; H, 2.90; N, 12.49.

2-Iodo-5*H*-indazolo[2,3-*d*][1,4]benzodiazepin-6-one, **2**.

Chloroacetyl chloride, 4.8 ml (0.06 mole), was added to a solution of 6.7 g (0.02 mole) of **1** in 250 ml of ether. The solution was layered with 250 ml of saturated aqueous sodium bicarbonate solution and the two-phase system was stirred for 30 minutes. The organic layer was separated, dried and evaporated. The residue was dissolved in 100 ml of THF and 100 ml of 2-propanol and the solution was treated with 7.8 g (0.07 mole) of potassium *t*-butoxide. After stirring for 30 minutes, the reaction mixture was acidified with acetic acid and the product was precipitated by dilution with water. It was collected, washed with water, sucked dry and recrystallized from THF/ethanol to yield 6.4 g (85%) of colorless crystals with mp 345-347°; ^{1}H-nmr (DMSO-d_6): δ 5.12 (s, 2, CH_2), 7.1-8 (m, 6, aromatic H), 8.17 (d, 1, J = 2 Hz, C_1-H), 10.78 (s, 1, NH).

Anal. Calcd. for $C_{15}H_{10}IN_3O$: C, 48.02; H, 2.69; N, 11.20. Found: C, 48.01; H, 2.54; N, 11.08.

2-Iodo-6-methyl-9*H*-indazolo[2,3-*d*][1,2,4]triazolo[4,3-*a*][1,4]diazepine, **3**.

Compound **2**, 3.75 g (0.01 mole), was dissolved in 350 ml of diglyme by warming to *ca* 120°. After cooling to 100°, 2.5 g of phosphorus pentasulfide and 3 g of sodium bicarbonate were added and the mixture was stirred and heated for 1 hour at 90-100°. The cooled reaction mixture was then diluted with ice and water and the precipitated product was collected, washed with water and sucked dry. This thione was suspended in 500 ml of THF and treated with 2.5 ml of hydrazine. After stirring at room temperature for 30 minutes the solvent was evaporated under reduced pressure and the residue was stirred with 50 ml of methylene chloride and 50 ml of water. The insoluble product was filtered off and washed with water and ether to leave 3.6 g (95%) of hydrazino derivative which was used without further purification.

This material, 3.6 g, was heated to reflux for 30 minutes with 400 ml of ethanol, 15 ml of triethyl orthoacetate and 0.1 g of *para*-toluenesulfonic acid. The solvent was evaporated and the crystalline residue was collected with ethyl acetate to yield 3.2 g (84%) of colorless crystals with mp 337-340°. The analytical sample was recrystallized from ethyl acetate and had the same mp; ^{1}H-nmr (deuteriochloroform): δ 2.58 (s, 3, CH_3), 5.2 (d, 1) and 6.13 (d, 1)(AB-system, J = 14.5 Hz, CH_2), 7.1-7.4 (m, 3, aromatic H), 7.75 (d, 2, J = 8 Hz, aromatic H), 7.91 (dd, 1, J = 8 and 2 Hz, C_3-H), 8.31 (d, 1, J = 2 Hz, C_1-H).

Anal. Calcd. for $C_{17}H_{12}IN_5$: C, 49.41; H, 2.93; N, 16.95. Found: C, 49.22; H, 3.00; N, 16.98.

3,4-Dihydro-1-{3-(6-methyl-9*H*-indazolo[2,3-*d*][1,2,4]triazolo[4,3-*a*]-[1,4]benzodiazepin-2-yl)-2-propynyl}-2(1*H*)-quinolinone Hydrochloride, **6**.

A mixture of 0.41 g (1 mmole) of **4**, 0.24 g (1.3 mmoles) of 3,4-dihydro-1-(2-propynyl)-2(1*H*)-quinolinone, **5** [10], 40 mg of triphenylphosphine, 10 mg of cuprous iodide, 1 ml of triethylamine and 40 ml of DMF was stirred and degassed with argon for 10 minutes. Palladium acetate, 15 mg, was then added and stirring under argon was continued for 2 days at room temperature. The solvent was removed under reduced pressure and the residue was partitioned between methylene chloride and water. The organic layer was dried and evaporated and the residue was chromatographed over 30 g of silica gel using 5% (v/v) of ethanol in methylene chloride for elution. The combined clean fractions were dissolved in ethanol and treated with ethanolic hydrogen chloride. The crystalline hydrochloride was collected and washed with ethyl acetate and ether to leave 0.25 g (49%) of colorless crystals with mp 223-226°; ^{1}H-nmr (deuteriochloroform): δ 2.75 (m, 2, CH_2), 2.98 (m, 5, CH_3, CH_2), 5.01 (s, 2, NCH_2), 5.53 (d, 1) and 6.21 (d, 1) (AB-system, J = 14.5 Hz, CH_2-diazepine), 7.0-8.2 (m, 11, aromatic H).

Anal. Calcd. for $C_{29}H_{22}N_6O$·HCl: C, 68.70; H, 4.57; N, 16.58. Found: C, 68.55; H, 4.58; N, 16.59.

2-Cyano-*N*-(2-nitrophenyl)acetamide, **7**.

A solution of 22.7 g (0.11 mole) of dicyclohexylcarbodiimide in 75 ml of DMF was added within 10 minutes to a solution of 13.8 g (0.1 mole) of 2-nitroaniline and 9 g (0.105 mole) of cyanoacetic acid in 150 ml of DMF. The mixture was stirred at room temperature for 1 hour. The precipitated urea was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken into methylene chloride. The insoluble material was removed by filtration and the solution was diluted with ethyl acetate and concentrated on the steam bath to distill off all the methylene chloride. The crystals that separated after cooling were collected to leave 15.3 g (74%) of colorless material with mp 154-156°; ^{1}H-nmr (deuteriochloroform): δ 3.68 (s, 2, CH_2), 7.3 (dt, 1, J = 8 Hz and 2 Hz, $C_{4'}$-H), 7.71 (dt, 1, J = 8 Hz and 2 Hz, $C_{5'}$-H), 8.28 (dd, 1, J = 8 Hz and 2 Hz, $C_{3'}$-H), 8.7 (dd, 1, J = 8 Hz and 2 Hz, $C_{6'}$-H), 10.94 (br s, 1, NH).

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.69; H, 3.44; N, 20.48. Found: C, 52.75; H, 3.33; N, 20.62.

2-Amino-*N*-(2-nitrophenyl)thiophene-3-carboxamide, **8**.

A mixture of 8.2 g (0.04 mole) of **7**, 3.3 g (0.0217 mole) of 1,4-dithiane-2,5-diol, 3 ml of triethylamine and 150 ml of ethanol was stirred under nitrogen and heated to 70° for 1.5 hours. The cooled reaction mixture was diluted with water to precipitate the product. It was collected by filtration, sucked dry and dissolved in methylene chloride. The solution was dried and evaporated and the residue was crystallized from methylene chloride/ethanol to give 8.4 g (79%) of orange crystals. The analytical sample was recrystallized from the same solvents and had mp 142-144°; ^{1}H-nmr (deuteriochloroform): δ *ca* 6.3 (s, 2, NH_2), 6.33 (d, 1, J = 5 Hz, C_4-H), 7.03 (d, 1, J = 5 Hz, C_5-H), 7.15 (dt, 1, J = 8 Hz and 2 Hz, $C_{4'}$-H), 7.65 (dt, 1, J = 8 and 2 Hz, $C_{5'}$-H), 8.26 (dd, 1, J = 8 and 2 Hz, $C_{3'}$-H), 8.9 (dd, 1, J = 8 and 2 Hz, $C_{6'}$-H).

Anal. Calcd. for $C_{11}H_9N_3O_3S$: C, 50.18; H, 3.45; N, 15.96. Found: C, 49.93; H, 3.26; N, 15.98.

2-(2-Chloroacetyl)amino-*N*-(2-nitrophenyl)thiophene-3-carboxamide, **9**.

A mixture of 7.9 g (0.03 mole) of **8**, 8 g of potassium carbonate, 10.7 ml of chloroacetyl chloride and 150 ml of dioxane was stirred at room temperature for 3 hours. With cooling in ice-water, the mixture was made basic by slowly adding 10% aqueous sodium carbonate solution followed by 300 ml of water.

After stirring in the cold for 15 minutes, the precipitated product was filtered off and sucked dry to yield 9 g (88%) of crystals. Recrystallization from methylene chloride/ethanol gave colorless crystals with mp 204-206°; ^{1}H-nmr (deuteriochloroform): δ 4.32 (s, 2, CH_2), 6.97 (d, 1, J = 5 Hz, C_4-H), 7.24 (dt, 1, J = 8 and 2 Hz, $C_{4'}$-H), 7.3 (d, 1, J = 5 Hz, C_5-H), 7.73 (dt, 1, J = 8 and 2 Hz, $C_{5'}$-H), 8.3 (dd, 1, J = 8 and 2 Hz, $C_{3'}$-H), 8.95 (dd, 1, J = 8 and 2 Hz, C_6-H),, 11.26 (br s, 1, NH) 12.58 (br s, 1, NH).

Anal. Calcd. for $C_{13}H_{10}ClN_3O_4S$: C, 45.96; H, 2.97; N, 12.37. Found: C, 45.88; H, 2.72; N, 12.53.

N-(2-Aminophenyl)-2-[(2-chloroacetyl)amino]thiophene-3-carboxamide, **10**.

A mixture of 7.5 g of **9**, 1.5 g of palladium on carbon (5%), 4.5 ml of concentrated hydrochloric acid and 225 ml of ethanol was hydrogenated at atmospheric pressure until hydrogen uptake ceased (3 hours). Methylene chloride, 300 ml, was added and the suspension was stirred for 5 minutes. The catalyst was filtered off and the filtrate was evaporated. The resulting solid hydrochloride was converted to the base by partitioning between methylene chloride containing 10% (v/v) of ethanol and aqueous sodium carbonate solution. The organic layer was dried and evaporated and the residue was crystallized from methylene chloride/ethanol to give 6.2 g (90%) of colorless crystals with mp 167-169°; ^{1}H-nmr (deuteriochloroform): δ 3.83 (br s, 2, NH_2), 4.26 (s, 2, CH_2), 6.8-7.4 (m, 6, aromatic H), 7.6 (br s, 1, NH), 12.67 (br s, 1, NH).

Anal. Calcd. for $C_{13}H_{12}ClN_3O_2S$: C, 50.40; H, 3.90; N, 13.57. Found: C, 49.98; H, 3.89; N, 13.26.

10-(Chloromethyl)thieno[2,3-*d*]pyrimido[3,4-*a*]benzimidazole, **11**.

A mixture of 6 g of **10** and 40 ml of phosphorus oxychloride was heated to reflux for 15 minutes. The resulting clear solution was evaporated under reduced pressure, at the end azeotropically with toluene. The residue was dissolved in dioxane, cooled and diluted with water to crystallize the product (4.7 g or 88%). The analytical sample was chromatographed over silica gel using methylene chloride/ethyl acetate 1:1 for elution. Crystallization from these solvents gave colorless crystals with mp 220-221°; ^{1}H-nmr (deuteriochloroform): δ 5.26 (s, 2, CH_2), 7.4-8.2 (m, 6, aromatic H).

Anal. Calcd. for $C_{13}H_8ClN_3S$: C, 57.04; H, 2.95; N, 15.35. Found: C, 56.93; H, 2.88; N, 15.49.

N-[3-(1*H*-Benzimidazol-2-yl)-2-thienyl]-2-chloroacetamide, **12**.

A mixture of 6.9 g (0.025 mole) of **11**, 50 ml of dioxane and 30 ml of 1*N* sodium hydroxide solution was stirred at room temperature for 30 minutes. The product was precipitated by addition of water, was filtered off, washed with water and sucked dry. It was dissolved in THF and the solution was passed over a plug of silica gel using THF. The solution was evaporated and the residue was crystallized from a small amount of ethyl acetate to yield 6.9 g (93%) of crystals with mp 183-185°; ^{1}H-nmr (deuteriochloroform): δ 4.37 (s, 2, CH_2), 7.0 (d, 1, J = 5 Hz, C_4-H, thiophene), 7.1-7.8 (m, 5, aromatic H), 9.18 (br s, 1, NH), 13.75 (br s, 1, NH).

Anal. Calcd. for $C_{13}H_{10}ClN_3OS$: C, 53.52; H, 3.45; N, 14.40. Found: C, 54.03; H, 3.61; N, 14.04.

10,12-Dihydrothieno[3,2-*f*][1,4]diazepino[4,5-*a*]benzimidazol-11-(11*H*)-one, **13**.

A solution of 2 g of **12** in 20 ml DMF was added over a period of 10 minutes to a mixture of 2 g of sodium iodide and 40 ml of DMF heated to 80°. Following the addition, the mixture was heated at 100-105° for 30 minutes. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride containing 10% of ethanol and aqueous sodium bicarbonate solution. The organic layer was dried and evaporated and the residue was crystallized from ethanol to give 1.2 g (68%) of crystals with mp 290-293°. For analysis the product was recrystallized from methylene chloride/ethanol to give colorless crystals with mp 292-293°; ^{1}H-nmr (deuteriochloroform + DMSO-d_6): δ 4.7 (s, 2, CH_2), 6.9-7.8 (m, 6, aromatic H), 10.9 (br s, 1, NH).

Anal. Calcd. for $C_{13}H_9N_3OS$: C, 61.16; H, 3.55; N, 16.46. Found: C, 60.93; H, 3.42; N, 16.39.

10,12-Dihydro-2-iodothieno[3,2-*f*][1,4]diazepino[4,5-*a*]benzimidazol-11(11*H*)-one, **14**.

Compound **13**, 1.1 g (4 mmoles), was dissolved in 50 ml of methanol and 30 ml of acetic acid. Iodine monochloride, 0.66 g (4 mmoles), and 0.33 g (4 mmoles) of sodium acetate were then added and the mixture was stirred at room temperature for 30 minutes. It was poured into ice-water containing sodium bisulfite. The crystals which separated were collected and sucked dry. Recrystallization from methanol yielded 0.9 g (72%) of product which was recrystallized for analysis from ethanol to give colorless crystals with mp 258-260° dec; ^{1}H-nmr (deuteriochloroform + DMSO-d_6): δ 4.75 (s, 2, CH_2), 7.2-7.9 (m, 5, aromatic H), 10.97 (br s, 1, NH).

Anal. Calcd. for $C_{13}H_8IN_3OS$: C, 40.96; H, 2.12; N, 11.02. Found: C, 41.10; H, 2.09; N, 11.07.

2-Iodo-13-methyl-10*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepino[4,5-*a*]benzimidazole, **15**.

A mixture of 1.52 g (4 mmoles) of **14**, 1 g of phosphorus pentasulfide and 1 g of sodium bicarbonate in 75 ml of diglyme was heated to 85-90° for 5 hours. It was poured into ice-water and stirred to crystallize. The solids were collected by filtration, washed with water and sucked dry. This crude thione (1.2 g) was stirred in 40 ml of THF and 40 ml of 2-propanol with 0.7 ml of hydrazine for 30 minutes at room temperature. The solvents were evaporated under reduced pressure without heating and the residue was filtered over silica gel with THF. The filtrate was evaporated and the residue was combined with 40 ml of ethanol, 40 ml of ethyl acetate, 2.5 ml of triethyl orthoacetate and 0.1 g of *para*-toluenesulfonic acid. This mixture was heated to reflux for 30 minutes and evaporated. The residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic layer was separated, dried and evaporated. The residue was chromatographed over 50 g of silica gel using THF/hexane 3:2 for elution. Crystallization of the combined clean fractions from ethanol gave 0.65 g (39%) of colorless with mp 256-258°; ^{1}H-nmr (deuteriochloroform): δ 2.73 (s, 3, CH_3), 5.46 (s, 2, CH_2), 7.3-7.9 (m, 4, aromatic H), 7.97 (s, 1, C_3-H).

Anal. Calcd. for $C_{15}H_{10}IN_5S$: C, 42.97; H, 2.40; N, 16.71. Found: C, 43.13; H, 2.31; N, 16.63.

3,4-Dihydro-1-{3-(13-methyl-10*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepino[4,5-*a*]benzimidazol-2-yl)-2-propynyl}-2(1*H*)-quinolinone, **16**.

A mixture of 204 mg (0.5 mmole) of **15**, 185 mg of **5** [10], 23 mg of triphenylphosphine, 5 mg of cuprous iodide, 0.5 ml of triethylamine and 20 ml of DMF was degassed for 10 minutes by argon.

Palladium acetate, 8 mg, was added and stirring under argon was continued for 24 hours. The reaction mixture was poured into saturated sodium bicarbonate solution and the precipitated product was collected by filtration, washed with water and sucked dry. It was dissolved in methylene chloride and the solution was dried and evaporated. The residue was chromatographed over 15 g of silica gel using 3% of ethanol in methylene chloride (v/v) for elution. The combined clean fractions were evaporated and the residue was crystallized from ethanol to give 130 mg (53%) of colorless crystals with mp 280-282°; ^{1}H-nmr (deuteriochloroform): δ 2.71 (s, 3, CH_3), 2.73 (t, 2, J = 6 Hz, CH_2), 2.97 (t, 2, J = 6 Hz, CH_2), 4.98 (s, 2, N-CH_2), 5.44 (s, 2, CH_2), 7-7.9 (m, 9, aromatic H).

Anal. Calcd. for $C_{27}H_{20}N_6OS \cdot 0.5\ H_2O$: C, 66.78; H, 4.36; N, 17.31. Found: C, 66.92; H, 4.24; N, 17.09.

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REFERENCES AND NOTES

[1] E. Kornecki, Y. H. Ehrlich and R. H. Lenox, *Science*, **226**, 1454 (1984).

[2] J. Casals-Stenzel and K. H. Weber, *Brit. J. Pharmacol.*, **90**, 139 (1987).

[3a] K. Meguro and Y. Kuwada, *Tetrahedron Letters*, 4039 (1970); [b] J. B. Hester, Jr., D. J. Duchamp and C. G. Chidester, *Tetrahedron Letters*, 1609 (1971); [c] J. B. Hester, Jr., A. D. Rudzik and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971).

[4a] K. H. Weber, G. Walther, A. Harreus, J. Casals-Stenzel, G. Muacevic and W. Troeger, German Offen. DE 3'502'392 A1, July 1986; *Chem. Abstr.*, **106**, 156502b (1987); [b] K. H. Weber and H. O. Heuer, *Med. Res. Rev.*, **9**, 181 (1989).

[5] T. Tahara, M. Moriwaki, M. Abe and S. Yuasa, EP 0268242 A1, May 1988; *Chem. Abstr.*, **109**, 211096t (1988).

[6] S. H. Cheon and W. J. Houlihan, EP 0338993 A1, October 1989; *Chem Abstr.*, **112**, 216976b (1990).

[7] A. Walser, T. Flynn, C. Mason, H. Crowley, C. Maresca, B. Yaremko and M. O'Donnell, *J. Med. Chem.*, **34**, 1209 (1991).

[8] G. F. Field and L. H. Sternbach, Swiss patent 561706, May 1975; *Chem. Abstr.*, **83**, 97407n (1975).

[9] A. Walser, W. Zally and R. I. Fryer, *J. Heterocyclic Chem.*, **11**, 863 (1974).

[10] A. Lindquist, P.-O. Lagerstroem and R. Dahlbom, *Acta Pharm. Suecica*, **9**, 99 (1972).

[11a] J. Hellerbach, P. Zeller, D. Binder and O. Hromatka, US patent 4,155,913, May 1979; [b] K.-H. Weber, A. Langbein, E. Lehr, K. Boeke and F.-J. Kuhn, German Offen. 2'701'752, July 1978; *Chem. Abstr.*, **90**, 23126t (1979).

[12] J. W. Tilley, J. W. Clader, S. Zawoiski, M. Wirkus, R. A. LeMahieu, M. O'Donnell, H. Crowley and A. F. Welton, *J. Med. Chem.*, **32**, 1814 (1989).