Synthesis and Biological Activity of (3,5-Disubstituted-1*H*-1,2,4-triazol-1-yl)benzophenone Derivatives (1)

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Received May 12, 1982

The synthesis of (5-acylaminomethyl-3-carbamoyl-1*H*-1,2,4-triazol-1-yl)benzophenone derivatives **4a-i**, **14a-d**, **15a-d**, **16a-c**, is described. Acylation of the key intermediate, 1-benzoylphenylazo-1-aminoacetamide **7**, followed by cyclization in the presence of acid afforded 1*H*-1,2,4-triazole derivatives. These compounds were evaluated for their central nervous system (CNS) activity. Some of these compounds exhibited high activities in anti-pentylene tetrazole and rotarod test in mice when orally administered.

J. Heterocyclic Chem., **19**, 1363 (1982).

Dipeptidoaminobenzophenones **1** were synthesized as ring opened derivatives of 1,4-benzodiazepine **2** and exhibited pharmacologically potent CNS activities (2).

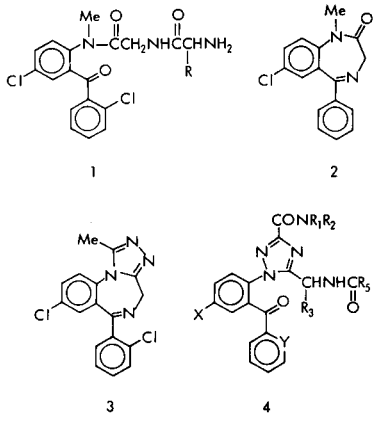


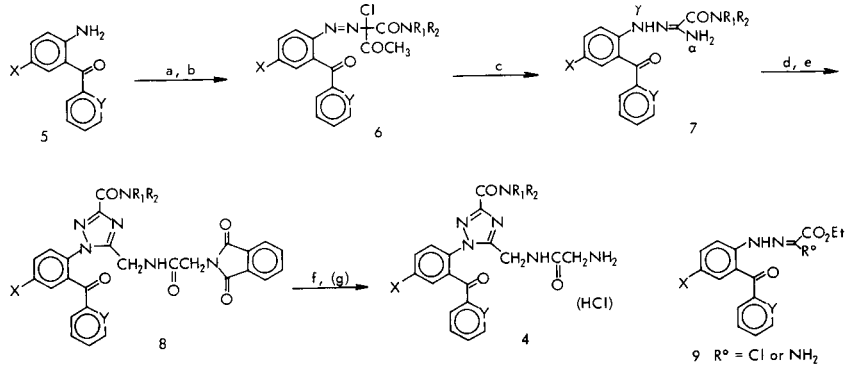
Figure 1

Introduction of a heterocyclic ring to the amide moiety in **2** is often used for chemically modifying **2**, *e.g.*, for obtaining triazolam **3** (3). In order to enhance the pharmacological activity of **1**, we tried synthesizing 1*H*-1,2,4-triazole-1-ylbenzophenone derivatives **4** in which the tertiary amide moiety in **1** was converted into a carbamoyltriazole ring.

Chemistry.

The synthetic approach to the title compound **4** is shown in Scheme I. In the typical synthetic procedure for compound **4c**, 2',5-dichloro-2-aminobenzophenone **5a** was diazotized with sodium nitrite in aqueous hydrochloric acid-acetic acid at 5°, and then reacted *N,N*-dimethyl-2-chloroacetoacetamide (4) and aqueous potassium carbonate solution at 5° in a one-pot Japp-Klingemann reaction to obtain the diazo derivatives **6c** in 73% yield. Ammonolysis and concurrent deacylation of **6c** in aqueous ammonia and ethyl acetate at room temperature provided the key intermediate **7c** almost quantitatively. Intermediate **7** can also be obtained by aminolysis of **9** (R° = NH_2, X = Cl, Y = C-Cl), (5) with the corresponding amine in alcohol (Table I). Coupling of **7c** with pthalylglycylglycyl chloride in tetrahydrofuran-hexamethylphosphoramide (10:1 v/v) at room temperature in the absence of base yielded a mix-

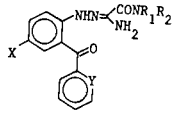
Scheme I (a)



(a) a, $NaNO_2$/aq HCl-AcOH, 5°. b, $ClCOCOCH_2CONR_1R_2$/aq K_2CO_3, 5°. c, aq NH_3-AcOEt, rt. d, Pht-Gly-Gly-Cl/HMPA-THF, rt. e, AcOH, reflux. f, $H_2NNH_2 \cdot H_2O$/EtOH, reflux. g, HCl/EtOH

Table I

1-Amino-1-benzoylphenylazoacetamides **7a-i**

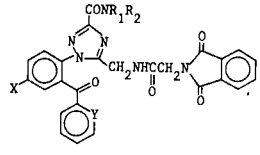


							Analysis %							
							Calcd.				Found			
7	X	Y	NR_1R_2	Mp °C	Yield % (a)	Formula	C	H	N	Cl	C	H	N	Cl
7a	Cl	C-H	NMe_2	167-169	41	$C_{17}H_{17}ClN_4O_2$	59.22	4.97	16.25	10.28	59.21	5.02	16.36	10.50
7b	Cl	C-F	NMe_2	151-153	75	$C_{17}H_{16}ClFN_4O_2$	56.28	4.45	15.44	9.77 5.24 (c)	55.94	4.70	15.51	9.99 5.05 (c)
7c	Cl	C-Cl	NMe_2	150-151	86	$C_{17}H_{16}Cl_2N_4O_2$	53.84	4.25	14.77	18.70	53.64	4.21	14.82	18.65
7d	Cl	C-Cl	pyrrol-idino	172-174	87	$C_{19}H_{18}Cl_2N_4O_2$	56.31	4.48	13.82	17.50	56.06	4.50	13.68	17.64
7e	Cl	C-Cl	morpho-lino	186-187	67	$C_{19}H_{18}Cl_2N_4O_3$	54.17	4.31	13.30	16.83	54.32	4.14	13.03	16.96
7f	Cl	C-F	NHMe	168-169	99	$C_{16}H_{14}ClFN_4O_2$	55.10	4.05	16.06	10.17 5.45 (c)	55.17	4.15	16.15	10.28 5.66 (c)
7g	Cl	C-Cl	NHMe	162-164	96	$C_{16}H_{14}Cl_2N_4O_2 \cdot 1/4(C_2H_5)_2O$	53.28	4.21	14.62	18.50	53.12	4.09	14.90	18.84
7h	Cl	C-Cl	NH_2	217-219	88 (b)	$C_{15}H_{12}Cl_2N_4O_2$	51.30	3.44	15.95	20.19	51.39	3.37	15.92	20.19
7i	Br	N	pyrrol-idino	212-213	22	$C_{18}H_{16}BrN_5O_2$	51.94	4.36	16.82	19.19 (d)	52.11	4.34	16.65	18.95 (d)

(a) Based on **9** (R° = NH_2). (b) Based on **9** (R° = Cl). (c) Value for F. (d) Value for Br.

Table II

2',5-Disubstituted-2-(3-carbamoyl-5-pthalylglycylaminomethyl-1*H*-1,2,4-triazolyl-1-yl)benzophenones **8a-i**



							Analysis %							
							Calcd.				Found			
8	X	Y	NR_1R_2	Mp °C	Yield % (a)	Formula	C	H	N	Cl	C	H	N	Cl
8a	Cl	C-H	NMe_2	214-216	25	$C_{29}H_{23}ClN_6O_5$	61.00	4.06	14.72	6.21	60.75	4.18	14.77	6.41
8b	Cl	C-F	NMe_2	224-226	22	$C_{29}H_{22}ClFN_6O_5$	59.14	3.76	14.27	6.03 3.23 (b)	59.15	4.01	14.36	6.15 3.46 (b)
8c	Cl	C-Cl	NMe_2	152-154	59	$C_{29}H_{22}Cl_2N_6O_5 \cdot H_2O$	55.87	3.88	13.48	11.37	55.35	4.18	13.10	11.41
8d	Cl	C-Cl	pyrrol-idino	160-165	49	$C_{31}H_{24}Cl_2N_6O_5$	58.96	3.83	13.31	11.23	59.27	4.20	12.86	11.24
8e	Cl	C-Cl	morpho-lino	204-205	29	$C_{31}H_{24}Cl_2N_6O_6$	57.51	3.74	12.98	10.95	57.28	4.03	12.54	11.15
8f	Cl	C-F	NHMe	209-213	14	$C_{28}H_{20}ClFN_6O_5$	58.49	3.51	14.62	6.17 3.30 (b)	58.36	3.76	14.54	6.32 3.57 (b)
8g	Cl	C-Cl	NHMe	204-206	12	$C_{28}H_{20}Cl_2N_6O_5$	56.87	3.41	14.21	11.99	56.66	3.42	13.99	11.86
8h	Cl	C-Cl	NH_2	259-264	22	$C_{27}H_{28}Cl_2N_6O_5$	56.17	3.14	14.56	12.88	56.06	3.06	14.54	12.42
8i	Br	N	pyrrol-idino	252-254	60	$C_{30}H_{24}BrN_7O_5$	56.09	3.77	15.26	12.44 (c)	56.00	4.06	14.83	12.61 (c)

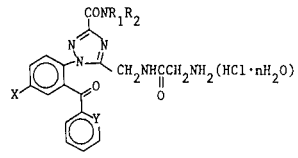
(a) Based on **7**. (b) Value for F. (c) Value for Br.

ture of the α and/or γ nitrogen acylated product, which was subjected, without purification, to cyclization in refluxing acetic acid (5), giving 1*H*-1,2,4-triazole **8c** in 76% yield based on **7c** (Table II). Acylation in the presence of base, such as the potassium carbonate, seemed to lower its yield. Deprotection was accomplished by refluxing **8c** with hydrazine hydrate in ethanol and subsequent treatment with hydrochloric acid in ethanol afforded **4c** in 78% yield (based on **8c**) after recrystallization from 95% ethanol.

Triazolylbenzophenones **4a-h** were prepared by the above method, and the results are summarized in Table III.

Table III

2',5-Disubstituted-2-(3-carbamoyl-5-glycylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenones **4a-i**

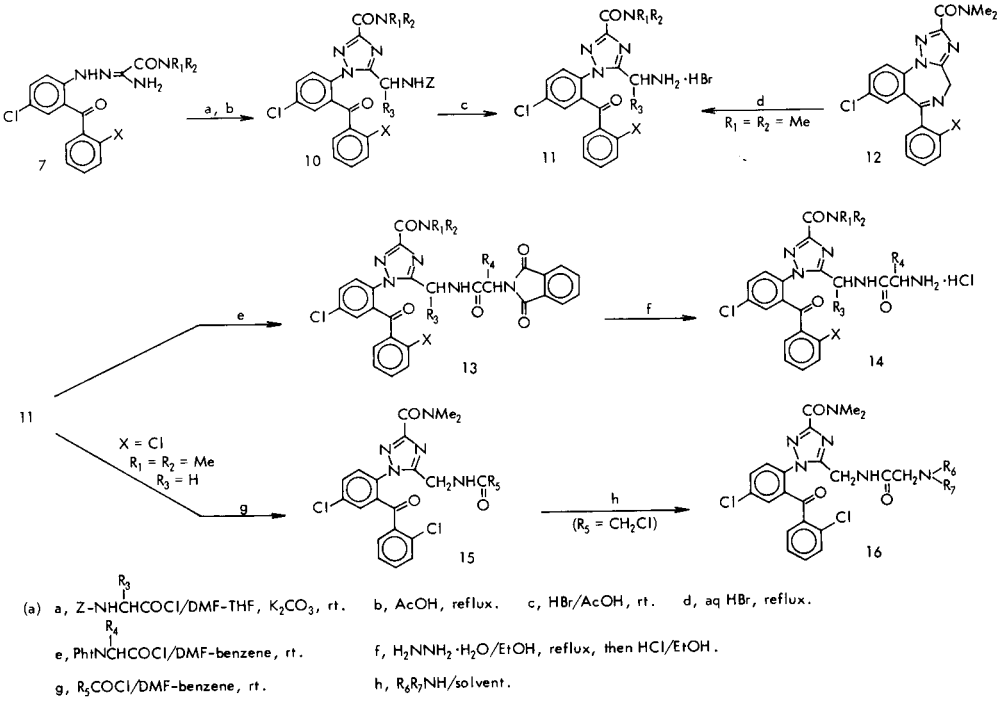


							Analysis %							
							Calcd.					Found		
4	X	Y	NR_1R_2	Mp °C	Yield % (a)	Formula	C	H	N	Cl		C	H	N	Cl	
4a	Cl	C-H	NMe_2	247-250	70	$C_{21}H_{21}ClN_6O_3 \cdot HCl$	52.84	4.65	17.61	14.85		52.68	4.78	17.61	14.97	
4b	Cl	C-F	NMe_2	220-222	82	$C_{21}H_{20}ClFN_6O_3 \cdot HCl$	50.92	4.27	16.97	14.31	3.84 (b)	50.89	4.45	16.97	14.30	4.09 (b)
4c	Cl	C-Cl	NMe_2	107	83	$C_{21}H_{20}Cl_2N_6O_3 \cdot HCl \cdot 2H_2O$	46.04	4.60	15.34	19.41		46.31	4.71	15.30	19.67	
4d	Cl	C-Cl	pyrrolidino	130-132	90	$C_{23}H_{22}Cl_2N_6O_3 \cdot 1/2H_2O$	54.12	4.54	16.47	13.89		53.92	4.50	16.46	14.37	
4e	Cl	C-F	morpholino	150	34	$C_{23}H_{22}Cl_2N_6O_4 \cdot HCl \cdot 1.5H_2O$	47.56	4.51	14.47			47.58	4.93	14.20		
4f	Cl	C-F	NHMe	155-157	79	$C_{20}H_{18}ClFN_6O_3 \cdot 1/4H_2O$	53.45	4.15	18.70	7.89	4.22 (b)	53.42	4.38	18.82	8.03	4.38 (b)
4g	Cl	C-Cl	NHMe	188-190	42	$C_{20}H_{18}Cl_2N_6O_3$	52.07	3.93	18.22	15.37		52.15	3.88	18.27	15.49	
4h	Cl	C-Cl	NH_2	209-211	77	$C_{19}H_{16}Cl_2N_6O_3$	51.02	3.61	18.79	15.85		51.14	3.58	18.75	15.99	
4i	Br	N	pyrrolidino	166-168	35	$C_{22}H_{22}BrN_7O_3 \cdot 1/4H_2O$	51.12	4.38	18.96	15.46	(c)	51.39	4.25	18.84	15.41	(c)

(a) Based on **8**. (b) Based for F. (c) Value for Br.

In order to replace the glycyl moiety in **4** with another acyl group, stepwise acylation of **7** was carried out, as shown in Scheme II. Aminomethyltriazole **11** was obtained by treatment of **7** with *N*-carbobenzoxyamino acid chloride in dimethylformamide-tetrahydrofuran in the presence of base at room temperature followed by cyclization in refluxing acetic acid to give **10** (Table IV) and subsequent deprotection with hydrobromic acid in acetic

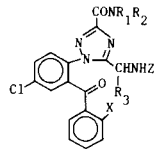
Scheme II (a)



(a) a, Z-NHCHCOCl/DMF-THF, K_2CO_3, rt. b, AcOH, reflux. c, HBr/AcOH, rt. d, aq HBr, reflux.
e, PhtNCHCOCl/DMF-benzene, rt. f, $H_2NNH_2 \cdot H_2O$/EtOH, reflux, then HCl/EtOH.
g, R_5COCl/DMF-benzene, rt. h, R_6R_7NH/solvent.

Table IV

2',5-Disubstituted-2-(3-carbamoyl-5-carbobenzoxyaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenones **10a-c**

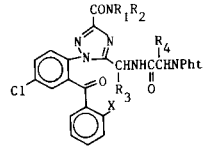


								Analysis %							
						Yield		Calcd.				Found			
10	R_1	R_2	X	R_3	Mp °C	% (a)	Formula	C	H	N	Cl	C	H	N	Cl
10a	Me	Me	H	Me	oil	26									
10b	Me	Me	Cl	H	131-133	47	$C_{27}H_{23}Cl_2N_5O_4$	58.71	4.20	12.68	12.84	58.82	4.33	12.80	12.56
10c	H	H	Cl	H	175-177	17	$C_{25}H_{19}Cl_2N_5O_4$	57.26	3.65	13.36	13.52	57.22	3.54	13.37	13.71

(a) Based on **7**.

Table V

2',5-Disubstituted-2-(3-carbamoyl-5-pthalylaminoacetylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenones **13a-d**

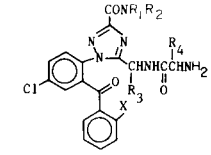


									Analysis %							
							Yield		Calcd.				Found			
13	R_1	R_2	X	R_3	R_4 (a)	Mp °C	% (b)	Formula	C	H	N	Cl	C	H	N	Cl
13a	Me	Me	H	Me	H	120	31	$C_{30}H_{25}ClN_6O_5$	61.59	4.31	14.37	6.06	61.30	4.78	14.00	5.80
13b	Me	Me	Cl	H	i-Bu	161-164	33	$C_{33}H_{30}Cl_2N_6O_5$	59.91	4.57	12.70	10.72	60.10	4.61	12.71	10.68
13c	Me	Me	Cl	H	CH_2Ph	162-166	40	$C_{36}H_{28}Cl_2N_6O_5$	62.16	4.06	12.08	10.19	61.85	4.09	12.07	10.30
13d	H	H	Cl	H	CH_2Ph	270-273	72	$C_{34}H_{24}Cl_2N_6O_5$	61.18	3.62	12.59	10.62	61.06	3.59	12.69	10.84

(a) L-Amino acid was used. (b) Based on **10**.

Table VI

2',5-Disubstituted-2-(3-carbamoyl-5-aminoacetylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenones **14a-d**



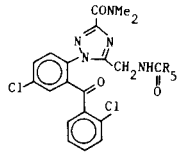
									Analysis %							
							Yield		Calcd.				Found			
14	R_1	R_2	X	R_3	R_4 (a)	Mp °C	%	Formula	C	H	N	Cl	C	H	N	Cl
14a	Me	Me	H	Me	H	155	80	$C_{22}H_{23}ClN_6O_3 \cdot HCl \cdot 1/2H_2O$	52.81	5.04	16.80	14.17	52.50	5.27	16.47	14.01
14b	Me	Me	Cl	H	i-Bu	120	85	$C_{25}H_{28}Cl_2N_6O_3 \cdot HCl$	52.87	5.15	14.80	18.73	52.81	5.41	14.30	18.20
14c	Me	Me	Cl	H	CH_2Ph	135	93	$C_{28}H_{26}Cl_2N_6O_3 \cdot HCl \cdot H_2O$	54.24	4.72	13.56	17.16	54.42	4.68	13.35	17.03
14d	H	H	Cl	H	CH_2Ph	145-147	58	$C_{25}H_{22}Cl_2N_6O_3(CO_2H)_2 \cdot H_2O$	52.10	4.06	13.02	10.99	52.15	4.36	13.25	11.06

(a) L-Amino acid was used.

acid. Alternatively, **11** (R_3 = H) could be obtained from acid hydrolysis of **12** (5,6). Crude hydrobromide salt **11** was further allowed to react with pthalylamino acid chloride in dimethylformamide-benzene at room temperature in the absence of base to produce **13** (Table V). Little cyclization of **11** to **11** was observed under these conditions. Deblocking of **13** with hydrazine hydrate in refluxing ethanol followed by quarternization with hydrochloric acid in ethanol yielded **14a-d** in an overall yield of 10-15% on the basis of **7** (Table VI).

Table VII

2',5-Disubstituted-2-(3-dimethylcarbamoyl-5-acylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenones **15a-c**

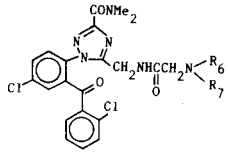


15	R_5	Mp °C	Yield % (a)	Formula	Analysis % Calcd. C	H	N	Cl	Found C	H	N	Cl
15a	CH_2Cl	80-82	90	$C_{21}H_{18}Cl_3N_5O_3$	50.98	3.67	14.15	21.50	50.54	3.80	14.02	21.29
15b	Ph	180-183	21	$C_{26}H_{21}Cl_2N_5O_3$	59.78	4.05	13.41	13.57	59.49	4.22	13.42	13.44
15c	i-Pr	180-182	31	$C_{23}H_{23}Cl_2N_5O_3$	56.57	4.75	14.34	14.52	56.28	4.91	14.25	14.61
15d	Me	118-120	22	$C_{21}H_{19}Cl_2N_5O_3$	54.79	4.16	15.21	15.40	54.66	4.25	15.27	15.49

(a) Based on **10**.

Table VIII

2',5-Dichloro-2-(3-dimethylcarbamoyl-5-(substitutedamino)acetylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenones **16a-c**



16	NR_6R_7	Mp °C	Yield % (a)	Formula	Analysis % Calcd. C	H	N	Cl	Found C	H	N	Cl
16a	NMe_2	122-124	39	$C_{23}H_{23}Cl_2N_6O_3$	54.88	4.61	16.19	14.09	55.05	4.99	16.45	13.91
16b	Pyrrolidino	119-122	75	$C_{25}H_{26}Cl_2N_6O_3$	56.72	4.95	15.87	13.39	56.70	5.05	15.93	13.43
16c	NHMe	124-125	38	$C_{22}H_{22}Cl_2N_6O_3$	54.00	4.53	17.17	14.49	54.07	4.63	17.02	14.57

(a) Based on **15**.

Alkyl and aryl acyl chlorides also react similarly with **11**, giving **15a-d** (Table VII). Compound **15a** readily underwent substitution reaction with amine in an appropriate solvent at room temperature to afford terminal *N*-substituted aminoacetylaminomethyl derivatives **16a-c** (Table VIII).

Biological Screening Results.

The triazolylbenzophenones were submitted to pharmacological tests in mice by oral adminsitration. Anti anxiety activity was tested by antagonism of pentylenetetrazole-induced convulsion and muscle relaxation by the rotarod performance test. Table IX shows these results for all tested compounds along with the comparative data for diazepam.

Compounds **4** and **14** which have aminoacetylaminomethyl substituent at C-5 in triazole showed generally higher activity than **15** and **16** did. The latter compounds had no rotarod activity. Introduction of methyl group at R_3 decreased both anti pentylenetetrazole and rotarod activities in comparison with R_3-unsubstituted derivatives. Replacement of glycyl group with another amino acid residue slightly enhanced both activities. An interesting en-

Table IX

Pharmacological Activity in Mice (a)

Compound	ED_{50} (mg/kg) (b) A-PTZ (c)	Rotarod
4c	0.11	236.9
4e	6.7	>100
4d	6.0	52.17
4a	1.13	12.7
4b	0.25	20.7
14b	0.22	10.72
14c	0.25	32.64
14a	4.77	
15a	22.0	>100
15b	>100	>100
15c	11.3	>100
15d	30.0	>100
16a	47.8	>100
16b	19.9	>100
16c	19.9	>100
4i	12.6	>100
4g	0.145	
4f	0.19	3.31
4h	0.18	21.7
14d	0.16	15.8
Diazepam	0.76	17.7

(a) All samples were administered orally and estimated at 60 minutes after dosing. (b) ED_{50} values were obtained by graphical interpolation. (c) Anti pentylenetetrazole.

hancement in activity was observed in the substituent of carbamoyl group. The anti anxiety activity increased with decrease in bulkyness of secondary amino moiety of carbamoyl substituent. Introduction of halogen group at Y position produced increase in anti anxiety activity, which is the same effect observed in diazepam derivatives.

Among the compounds tested, **4c** showed strong activity in anti pentylenetetrazole test, while it was almost inactive for rotarod test. This indicates that anti anxiety and muscle relaxation activities are well separated in **4c**.

EXPERIMENTAL

Melting points were determined in a Yamato capillary melting point apparatus and are uncorrected. Infrared spectra (ν max in cm^{-1}) were recorded on a JASCO DS-403G spectrometer and nmr spectra were determined in deuteriochloroform unless otherwise indicated on a Varian T-60A spectrometer using TMS as the internal standard. Anhydrous sodium sulfate was used for drying the extract. Solvents used for recrystallization are indicated in parentheses next to the melting point.

N,N-Dimethyl 2-Chloro-2-(2-(2-chlorobenzoyl)-5-chlorophenylazo)acetoacetamide **6c**.

To a cooled solution (5°) of **5c** (44.0 g, 165 mmoles) in acetic acid (130 ml) and concentrated hydrochloric acid (45 ml) was added dropwise sodium nitrite (12.0 g, 174 mmoles) in water (60 ml) over 15 minutes. After addition of sodium nitrite, the mixture was stirred for 5 minutes at 5°, then *N,N*-dimethyl 2-chloroacetoacetamide (34.0 g, 208 mmoles) in acetone (50 ml) added all at once at the same temperature followed by dropwise addition of potassium carbonate (168 g) in water (500 ml). The mixture was stirred for 50 minutes at room temperature. The brown suspended mixture was separated by filtration. The residue was dissolved in chloroform and washed with water. The organic layer was separated, dried, and evaporated *in vacuo*. The remaining oil was triturated with ethanol to give 53.3 g (73.2%) of **6c**, mp 170-172 (methanol); ir: 1735 cm^{-1}, 1650 cm^{-1}; nmr: δ 2.35 (s, 3H, COMe), 2.75 and 3.00 (broad s × 2, 6H, NMe_2), 7.3-7.7 (m, 7H, aromatic).

Anal. Calcd. for $C_{19}H_{16}Cl_3N_3O_3$: C, 51.78; H, 3.66; N, 9.53; Cl, 24.13. Found: C, 51.67; H, 3.55; N, 9.64; Cl, 24.21.

N,N-Dimethyl 2-Amino-2-(2-(2-chlorobenzoyl)-5-chlorophenylazo)acetamide (**7c**).

A mixture of **6c** (53.3 g, 121 mmoles) in ethyl acetate (250 ml) and aqueous ammonia (28%, 30 ml) was stirred for 2 hours at room temperature. The organic layer was separated, dried and evaporated *in vacuo*. The residue was triturated with methanol followed by filtration to afford 34.4 g of **7c**. The mother liquor was concentrated and the resulting oil triturated with methanol to give 3.50 g **7c** (combined yield, 84.8%), mp 150-151° (methanol) ir: 3430 cm^{-1}, 3330 cm^{-1}, 3180 cm^{-1}, 1620 cm^{-1}; nmr: δ 3.13 and 3.50 (s × 2, 6H, NMe_2), 5.10 (broad s, 2H, NH_2), 7.2-7.7 (m, 7H, aromatic).

N,N-Dimethyl 2-Amino-2-(2-benzoyl-5-chlorophenylazo)acetamide **7a**, **7a-g**, **7i** (Table I).

A mixture of ethyl 2-amino-2-(2-benzoyl-5-chlorophenylazoacetate **9** (R° = NH_2, X = Cl, Y = C-H) (5) (5.5 g, 16 mmoles) and dimethylamine (9.0 g) in methanol (150 ml) was left at room temperature for 4 days. The precipitate was filtered to give 1.8 g of **7a**. The filtrate was concentrated *in vacuo* and the residue triturated with ethanol to afford 0.5 g of **7a**. Combined yield was 2.3 g (41%), mp 167-169° (methanol); ir: 3430 cm^{-1}, 3330 cm^{-1}, 1620 cm^{-1}; nmr: δ 3.23 and 3.45 (s × 2, 6H, NMe_2), 5.03 (broad s, 2H, NH_2), 7.3-7.7 (m, 8H, aromatic), 10.74 (broad s, 1H, NH).

2-Amino-2-(2-(2-chlorobenzoyl)-5-chlorophenylazo)acetamide (**7h**).

To a solution of ethyl 2-chloro-2-(2-(2-chlorobenzoyl)-5-chlorophenylazo)acetate **9** (R° = Cl, X = Cl, Y = C-Cl) (5) (12 g, 30 mmoles) in ethanol (200 ml) and chloroform (200 ml) was added aqueous ammonia (28%, 120 ml). The mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residual material filtered followed by washing with water and ethanol to give 9.3 g (88%) of **7h**, mp 217-219° (ethanol); ir: 3440 cm^{-1}, 3260 cm^{-1}, 3060 cm^{-1}, 1690 cm^{-1}, 1620 cm^{-1}, 1600 cm^{-1}; nmr: δ 6.23 (broad s, 2H, NH_2), 7.0-8.1 (m, 9H, aromatic and NH_2), 10.9 (broad s, 1H, NH).

2′,5-Dichloro-2-(3-dimethylcarbamoyl-5-pthalylglycylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenone **8c**, **8a-i** (Table II).

To a solution of **7c** (38.9 g, 103 mmoles) in tetrahydrofuran (400 ml) and hexamethylphosphoramide (36 ml) was added pthalylglycylglycyl chloride (35.0 g). The mixture was stirred for 4 hours at room temperature then left at the same temperature overnight. After the mixture was neutralized with aqueous potassium carbonate solution, it was concentrated *in vacuo* and the residual oil dissolved in ethyl acetate and water. The organic layer was separated and the aqueous layer again extracted with ethyl acetate. The combined organic layer was washed with water, separated and concentrated without drying. The residue was triturated with ethyl acetate and filtered to give yellow solid (about 41 g). The filtrate was washed with water, separated, dried and concentrated to give oily residue (about 32 g).

The above yellow solid and the oily residue were suspended in acetic acid (150 ml) and the mixture was refluxed for about an hour and a half. The solvent was removed *in vacuo* and the remaining oil dissolved in chloroform and the aqueous potassium carbonate solution. The organic layer was separated, dried and concentrated. The residue was triturated with ethyl acetate to afford 54.2 g (76.2% based on **7c**) of **8c**, mp 153° (ethanol); ir 3260 cm^{-1}, 1770 cm^{-1}, 1710 cm^{-1}, 1690 cm^{-1}, 1660 cm^{-1}, 1620 cm^{-1}; nmr: δ 3.05 and 3.12 (s × 2, 6H, NMe_2), 4.42 (s, 2H, CH_2), 4.53 (d, 2H, J = 6 Hz, CH_2NH), 7.4-8.0 (m, 11H, aromatic), 8.2 (broad t, 1H, J = 6 Hz, NH).

The coupling of **7** with pthalylglycylglycyl chloride can also be carried out in dimethylformamide-tetrahydrofuran (about 10:1 v/v) in the presence of potassium carbonate at room temperature, however, the yield decreased slightly.

2′,5-Dichloro-2-(3-dimethylcarbamoyl-5-glycylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenone Hydrochloride Dihydrate **4c**, **4a-i** (Table III).

A mixture of **8c** (1.30 g, 2.09 mmoles) and hydrazine hydrate (0.30 ml) in ethanol (25 ml) was refluxed for 1 hour. After the mixture cooled, the precipitated solid was separated by filtration. The filtrate was concentrated and the remaining oil dissolved in chloroform and aqueous sodium bicarbonate solution. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by chromatography on silica gel with methanol as eluant. The crude product was treated with excess 16% hydrochloric acid in ethanol. The solid product was filtered followed by recrystallization from 95% ethanol to give 3.20 g (82.5%) of **4c**, mp 107° (95% ethanol); ir: 1680 cm^{-1}, 1662 cm^{-1}, 1603 cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 2.90 and 2.97 (s × 2, 6H, NMe_2), 3.62 (broad s, 2H, CH_2NH_2), 4.42 (broad d, 2H, J = 5 Hz, CH_2NH), 7.3-8.0 (m, 7H, aromatic), 9.27 (broad t, 1H, J = 5 Hz, NH).

2′,5-Dichloro-2-(3-dimethylcarbamoyl-5-benzyloxycarbonylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenone **10b**, **10a-c** (Table IV).

To a solution of **7c** (0.95 g, 2.5 mmoles) and potassium carbonate (0.35 g) in tetrahydrofuran (20 ml) and dimethylformamide (2 ml) was added freshly prepared carbobenzoxyglycyl chloride, which was prepared from carbobenzoxyglycine (6.3 g, 30 mmoles) and phosphorous pentachloride (6.9 g, 3.3 mmoles) in ether (38 ml) at room temperature, in tetrahydrofuran (6.5 ml). The mixture was stirred overnight at room temperature, it was neutrallized with aqueous sodium bicarbonate solution followed by evaporation of the solvent. The residue was dissolved in ethyl cacetate and water. The organic layer was separated, dried and concentrated *in vacuo*. The remaining product was chromatographed on silica gel using ethyl acetate as eluant to give 0.65 g (47%) of **10b**, mp 131-133° (ethyl

acetate); ir: 3260 cm^{-1}, 1730 cm^{-1}, 1670 cm^{-1}, 1630 cm^{-1}; nmr: δ 3.07 (s, 6H, NMe_2), 4.43 (d, 2H, J = 6 Hz, CH_2NH), 5.07 (s, 2H, CH_2), 5.82 (t, 1H, J = 6 Hz, NH), 7.2-7.6 (m, 12H, aromatic).

2',5-Dichloro-2-(3-dimethylcarbamoyl-5-pthalylphenylalanylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenone **13c**, **13a-d** (Table V).

A mixture of pthalylphenylalanine (1.33 g, 4.50 mmoles) and thionyl chloride (0.42 ml) was refluxed for 40 minutes. After excess thionyl chloride was removed *in vacuo*, the residue was suspended in benzene (20 ml).

A mixture of **10b** (1.65 g, 2.99 mmoles) in 30% hydrobromic acid in acetic acid (5 ml) was stirred for 2 hours at room temperature. Excess ether was added and the mixture decanted to remove the supernatant (three times). The resulting precipitate was suspended in benzene (10 ml), then the above benzene solution of acid chloride and dimethylformamide (10 ml) were added. The solution was stirred for 4 hours and diluted with ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was separated, dried and evaporated. The crude product was chromatographed on silica gel with ethyl acetate as eluant to give 0.83 g (40%) of **13c**, mp 162-166° (ethanol); ir: 3260 cm^{-1}, 1775 cm^{-1}, 1720 cm^{-1}, 1685 cm^{-1}, 1640 cm^{-1}; nmr: δ 3.02 (broad s, 6H, NMe_2), 3.53 (d, 2H, J = 8 Hz, CH_2CH), 4.57 (d, 2H, J = 5 Hz, CH_2NH), 5.13 (t, 1H, J = 8 Hz, CH), 7.1-7.9 (m, 16H, aromatic).

Hydrazinolysis of **13** (Table VI).

Hydrazinolysis of **13** was carried out by the same procedure described for **4c**, and the results were summarized in Table VI.

2',5-Dichloro-2-(3-dimethylcarbamoyl-5-chloroacetylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenone **15a**, **15a-d** (Table VII).

2',5-Dichloro-2-(3-dimethylcarbamoyl-5-aminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenone hydrobromide **11** was synthesized by the same procedure described for **13c** from **10b** (3.60 g, 6.52 mmoles). A mixture of crude salt **11** and chloroacetyl chloride (1.20 g) in benzene (40 ml) and dimethylformamide (20 ml) was stirred for 3 hours, then diluted with ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was separated, washed with water, dried and concentrated to give yellow oil. Trituration with ethyl acetate-*n*-hexane afforded 2.90 g (90%) of **15a**, mp 80-82 (ethyl acetate); ir: 3240 cm^{-1}, 1730 cm^{-1}, 1680 cm^{-1}, 1640 cm^{-1}, 1585 cm^{-1}; nmr: δ 3.08 and 3.13 (s × 2, 6H, NMe_2), 4.03 (s, 2H, CH_2Cl), 4.55 (d, 2H, J = 6 Hz, CH_2NH), 7.3-7.9 (m, 7H, aromtic), 8.23 (broad t, 1H, NH).

2',5-Dichloro-2-(3-dimethylcarbamoyl-5-dimethylaminoacetylaminomethyl-1*H*-1,2,4-triazol-1-yl)benzophenone **16a**, **16a-c** (Table VIII).

To a solution of **15a** (500 mg, 1.01 mmoles) in chloroform (6 ml) and methanol (3 ml) was added 50% aqueous dimethylamine solution (200 mg). The mixture was left for 3 days at room temperature. The solvent was removed *in vacuo* and the resulting oil dissolved in methylene chloride and water. The organic layer was separated, dried and concentrated. The oily product was chromatographed on silica gel with ethyl acetate-methanol (4:1 v/v) as eluant. The viscous oil was triturated with ethyl acetate-*n*-hexane to afford 200 mg (39%) of **16a**, mp 122-124° (ethyl acetate); ir: 3210 cm^{-1}, 1685 cm^{-1}, 1640 cm^{-1}, 1590 cm^{-1}; nmr: δ 2.27 (s, 6H, CH_2NMe_2), 2.93 (s, 2H, CH_2N), 3.10 (s, 6H, $CONMe_2$), 4.55 (d, 2H, J = 6 Hz, CH_2NH), 7.3-7.8 (m, 7H, aromatic), 7.90 (broad, t, 1H, NH).

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