Heteroatom Chemistry
Volume 13, Number 3, 2002

Naproxen in Heterocyclic Chemistry: Novel Syntheses of Triazoles, Triazolothiadiazines, Triazolothiadiazoles, and Triazolothiadiazepine Bearing an Asymmetric Carbon Atom and Radiostability of the Biologically Active Compounds

Y. A. Ammar,[1] M. M. Ghorab,[2] A. M. Sh. El-Sharief,[1] and Sh. I. Mohamed[1]

[1]*Department of Chemistry, Faculty of Science, Al-Azhar University, Nasr City, P.O. Box 11884, Cairo, Egypt*

[2]*Department of Drug Radiation Research, National Center for Radiation Research and Technology, P.O. Box 29, Nasr City, Cairo, Egypt*

Received 17 April 2001; revised 18 August 2001

ABSTRACT: *Several s-triazoles* **2, 7a, 10, 12***; s-triazolo[3,4-b][1,3,4]thiadiazines (***3–5***); s-triazolo[3,4-b][1,3,4]thiadiazoles (***6, 8, 11, 15***); and s-triazolo[3,4-b][1,3,4]thiadiazepine (***14***) were synthesized starting from 2-(6-methoxy-2-naphthyl)propanoic acid (***1***) (Naproxen). The structures of the synthesized compounds were elucidated by elemental analyses and spectral data. Compounds* **2, 5, 11, 12, 14***, and* **15** *exhibited a remarkable antifungal activity compared with the standard fungicide Mycostatine. Radiosterilization of the biologically active compounds* **2, 5, 11***, and* **14** *in the dry state may prove to be applicable (retaining their structures unchanged up to 40 kGy).* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:199–206, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10019

Correspondence to: Y. A. Ammar; e-mail: yossry@yahoo.com.

INTRODUCTION

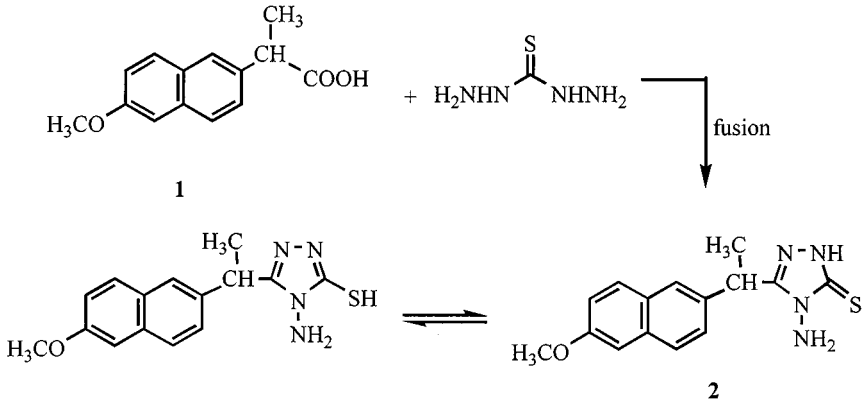
Various *s*-triazoles, *s*-triazolo[3,4-*b*][1,3,4]thiadiazoles, and thiadiazines have been reported to possess diverse biological activities, such as antifungal [1], antibacterial [2], insecticidal [3], herbicidal [4], and plant growth regulative [5] effect. Encouraged by the above observations and as a further probe in this direction, we undertook a study in which the aromatic system (naphthyl) with a small lipophilic group (OCH_3) at the 6-position and a moiety containing an asymmetric carbon atom [6] has been incorporated into an *s*-triazolothiadiazole or thiadiazine and/or a thiadiazepine, all present in one molecule, with a view to explore the possibility of achieving better antifungal effects. In recent years, considerable interest has developed regarding the radiation sensitivity of various antibiotics [7–10] and synthetic biologically active heterocyclic compounds [11,12]. Studies, for the most part, have focused on the correlation between chemical structure and biological function. Generally, data of these compounds indicate that, even at a dose of 25 kGy, the radiosterilization may be feasible [13–15].

CHEMISTRY

The starting material, 1-(6-methoxy-2-naphthyl)-1-(5′-amino-4′-mercapto-s-triazol-3-yl)ethane **(2)** was prepared in good yield by fusion of 2-(6-methoxy-2-naphthyl)propanoic acid (Naproxen) **(1)** with thiocarbohydrazide. The IR spectrum of **2** showed bands at 3330, 3250 (NH_2), 3100 (CH arom.), 2930 (CH aliph.), 1600 cm^{-1} (C=N). Its ^1H NMR spectrum (DMSO-d_6) exhibited signals at δ 1.6 [d, 3H, CH_3], 3.9 [s, 3H, OCH_3], 4.3 [q, 1H, CH], 5.4 [s, 2H, NH_2], 7.1–7.8 [m, 6H, Ar-H], 13.6 [s, 1H, NH]. The mass spectrum of **2** revealed a molecular ion peak *m/z* at 300 (M^+, 0.1%), with a base peak at 185 (100%); other significant peaks appeared at 284 (0.12%), 230 (62.66%), 170 (32.69%), 141 (30.25%), 115 (27.29%), 77 (3.04%).

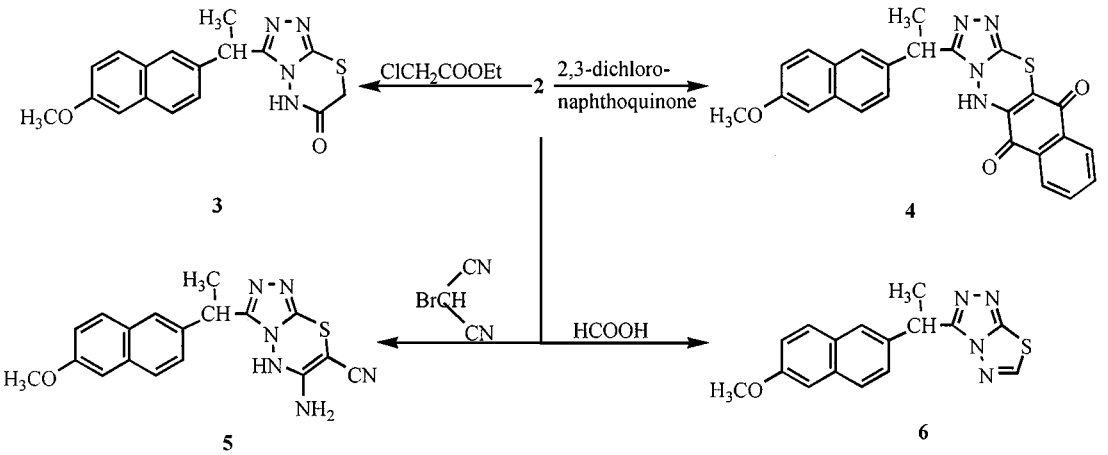
In addition, reaction of **2** with 2,3-dichloronaphthoquinone effected cyclization to furnish the corresponding triazolothiadiazine derivative **4** through elimination of 2 mol of HCl. Its IR spectrum showed bands at 3392 (NH), 3094 (CH arom), 2927 (CH aliph), 1690 cm^{-1} (C=O). The mass spectrum of **4** revealed a molecular ion peak *m/z* 454 (M^+, 24.03%), with a base peak at 55 (100%); other significant peaks appeared at 330 (22.85%), 272 (26.68%), 217 (35.77%), 105 (22.14%), 91 (27.10%), 73 (44.98%).

Furthermore, the triazolothiadiazine derivative **5** was also prepared by reaction of **2** with bromomalononitrile. The structure of **5** was established through microanalyses and its IR spectrum, which showed bands at 3355, 3298 (NH, NH_2), 2208 cm^{-1} (C≡N). The mass spectrum of **5** exhibited a molecular ion peak *m/z* 364 (M^+, 13.29%), with a base peak at 232 (100%); other significant peaks appeared at 309 (25.25%), 266 (69.44%), 185 (44.85%), 149 (71.10%), 97 (70.43%), 57 (75.75%).

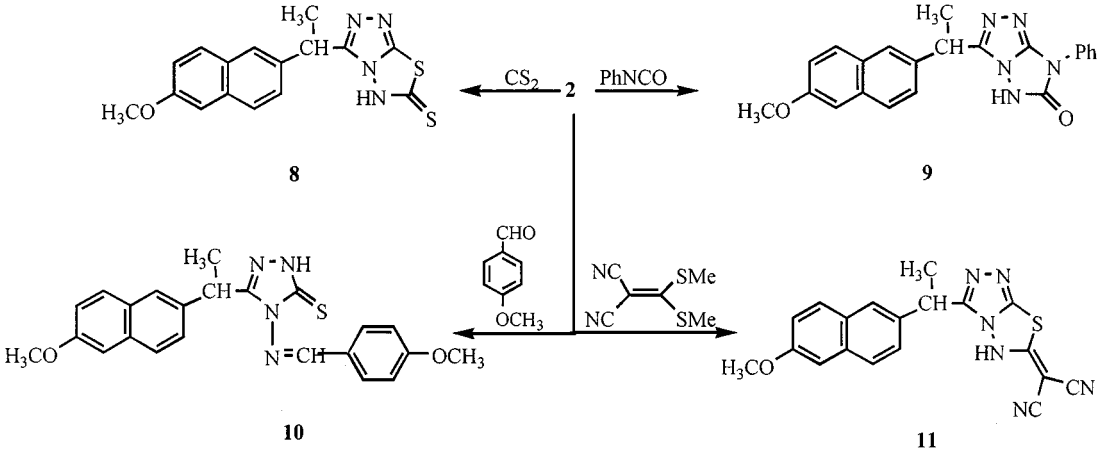


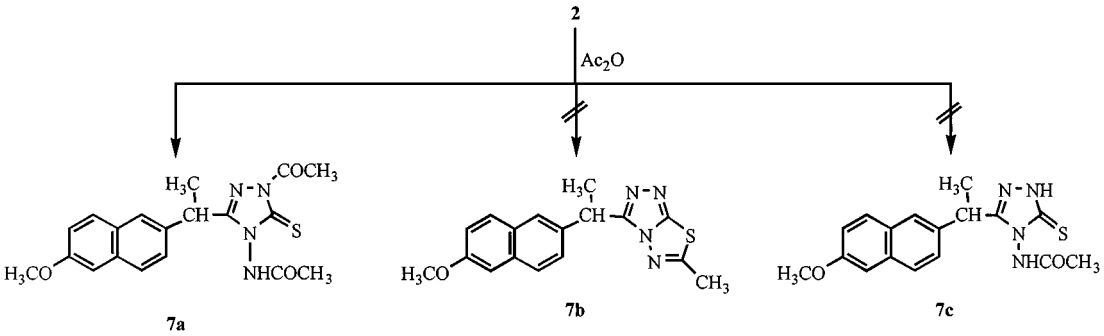
The reactivity of compound **2** towards halogenated reagents is discussed herein. Thus, reaction of **2** with ethyl chloroacetate yielded the triazolothiadiazine derivative **3**. The IR spectrum of **3** showed bands at 3320 (NH), 2933 (CH aliph), 1693 (C=O), 1610 cm^{-1} (C=N). Its ^1H NMR spectrum (DMSO-d_6) showed signals at δ 1.6 [d, 3H, CH_3], 3.8 [s, 3H, OCH_3], 4.5 [q, 1H, CH], 6.0 [s, 2H, CH_2CO], 7.2–7.7 [m, 6H, Ar-H].

The behaviour of compound **2** towards acid derivatives was also investigated. Thus, heating compound **2** with formic acid caused cyclization by elimination of 2 mol of H_2O to give the



triazolothiadiazole derivative **6**. The IR spectrum of **6** exhibited bands at 3100 (CH arom), 2950 cm^{-1} (CH aliph). The mass spectrum of **6** showed a molecular ion peak *m/z* 310 (M^+, 1.75%), with a base peak at 255 (100%); other significant peaks appeared at 225 (11.00%), 192 (24.00%), 130 (22.00%), 85 (6.50%), 70 (9.25%). When compound **2** was made to react with acetic anhydride, the diacetyl derivative **7a** was isolated, and the fused system **7b** or monoacetyl **7c** was eliminated from consideration on the basis of elemental analyses and ^{1}H NMR spectroscopy. The IR spectrum of **7a** showed bands at 3425 (NH), 2910 (CH aliph), 1710 (2C=O), 1605 cm^{-1} (C=N). Its ^{1}H NMR spectrum (DMSO-d_6) exhibited signals at δ 1.6 [d, 3H, CH_3], 2.6, 2.7 [2s, 6H, $2COCH_3$], 3.8 [s, 3H, OCH_3], 4.4 [q, 1H, CH], 7.1–7.8 [m, 6H, Ar-H], 10.9 [s, 1H, NH].





Reaction of **2** with carbon disulfide gave a product which was formulated as the triazolothiadiazole derivative **8**. The IR spectrum of **8** showed bands at 3315 (NH), 2932 (CH aliph), 1600 (C=N), 1265 cm^{-1} (C=S). Its ^{1}H NMR spectrum (DMSO-d_6) revealed signals at δ 1.6 [d, 3H, CH_3], 3.8 [s, 3H, OCH_3], 4.5 [q, 1H, CH], 7.1–7.7 [m, 6H, Ar-H], 13.8 [s, 1H, NH].

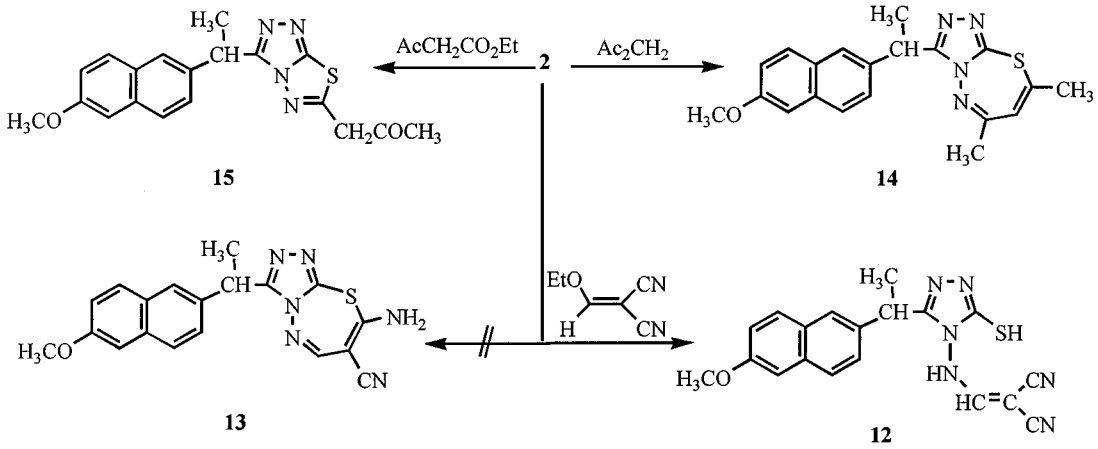
Reaction of **2** with phenyl isocyanate yielded the triazolotriazole derivative **9**, through elimination [16] of 1 mol of H_2S. The obtained product **9** was found to be sulfur free. The IR spectrum of **9** showed bands at 3387 (NH), 1660 (C=O), 1600 cm^{-1} (C=N). Its ^{1}H NMR spectrum (DMSO-d_6) exhibited signals at δ 1.6 [d, 3H, CH_3], 3.8 [s, 3H, OCH_3], 4.5 [q, 1H, CH], 7.0–7.9 [m, 11H, Ar-H], 13.6 [s, 1H, NH]. The mass spectrum of **9** revealed a molecular ion peak *m/z* 385 (M^+, 0.3%), with a base peak at 93 (100%); other significant peaks appeared at 306 (0.28%), 236 (4.83%), 212 (20.33%), 152 (4.01%), 111 (10.40%), 69 (25.96%).

Reaction of **2** with 4-anisaldehyde in acetic acid afforded the Schiff's base **10**. The IR spectrum of **10** showed the absence of (NH_2) bands and the presence of bands at 3174 (NH), 2934 (CH aliph), 1600 cm^{-1} (C=N). Its ^{1}H NMR spectrum (DMSO-d_6) showed signals at δ 1.6 [d, 3H, CH_3], 3.4, 3.8 [2s, 6H, $2OCH_3$], 4.0 [q, 1H, CH], 7.1–7.8 [m, 10H, Ar-H], 10.1 [br, 2H, N=CH + NH].

The dicyanotriazolothiadiazole derivative **11** was obtained by reaction of **2** with [bis(methylsulfanyl)methylidene]malononitrile. The IR spectrum of **11** showed bands at 3319 (NH), 3100 (CH arom.), 2935 (CH aliph), 2210 (C≡N), 1608 cm^{-1} (C=N). Its ^{1}H NMR spectrum (DMSO-d_6) exhibited signals at

δ 1.6 [d, 3H, CH_3], 3.8 [s, 3H, OCH_3], 4.4 [q, 1H, CH], 7.1–7.7 [m, 6H, Ar-H], 13.6 [s, 1H, NH]. The mass spectrum of **11** revealed a molecular ion peak *m/z* 374 (M^+, 1.85%), with a base peak at 55 (100%); other significant peaks appeared at 300 (35.52%), 247 (42.89%), 185 (38.01%), 97 (61.63%).

Also, reaction of **2** with ethoxymethylenemalononitrile yielded the dicyano derivative **12** rather than the thiadiazepine derivative **13**, on the basis of its IR spectrum which showed the presence of bands at 3317, 3214 (2NH), 3105 (CH arom), 2937 (CH aliph) and two bands at 2223, 2172 cm^{-1} corresponding to two cyano groups. The mass spectrum of **12** revealed a molecular ion peak *m/z* 376 (M^+, 0.71%), with a base peak at 300; other significant peaks appeared at 236 (12.99%), 172 (57.96%), 97 (22.13%), 73 (19.14%).



Finally, reaction of **2** with acetylacetone and/or ethyl acetoacetate furnished the corresponding triazolothiadiazepine **14** or triazolothiadiazole **15**, respectively. The IR spectrum of **14** exhibited bands at 3100 (CH arom), 2929 (CH aliph), 1608 cm^{-1} (C=N). Its ^{1}H NMR (DMSO-d_6) revealed signals at δ 1.7 [d, 3H, CH_3], 2.3, 2.4 [2s, 6H, $2CH_3$], 3.8 [s, 3H, OCH_3], 4.4 [q, 1H, CH], 7.1–7.9 [m, 6H, Ar-H], 7.4 [s, 1H, CH, thiadiazepine]. The IR spectrum of **15** showed bands at 2933 (CH aliph), 1700 (C=O), 1600 cm^{-1} (C=N). Its ^{1}H NMR spectrum (DMSO-d_6) exhibited signals at δ 1.2 [s, 3H, CH_3], 1.6 [d, 3H, CH_3], 3.8 [s, 3H, OCH_3], 4.2 [q, 1H, CH], 4.5 [s, 2H, CH_2CO], 7.2–7.9 [m, 6H, Ar-H].

EXPERIMENTAL

Melting points are uncorrected and were determined on a Stuart melting point apparatus. IR spectra were recorded on a Pye-Unicam SP 3-100 spectrophotometer using the KBr Technique. ^{1}H NMR spectra were recorded on a 90 MHz Varian EM-390 NMR spectrometer in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as an internal standard. Mass spectra were run on a HP MODEL MS-5988. Elemental analyses were determine on a Perkin-Elmer 240 (microanalyser). The samples were irradiated with gamma radiation (^{60}Co) at the National Center for Radiation Research and Technology. Powder sample was irradiated at room temperature conditions in polycarbonate vials at a dose rate (10 kGy/h). UV spectra were recorded using a ATI UNICAM-UV/VIS AURORA SCAN.

*1-[(6-Methoxy-2-naphthyl)-1-(5′-amino-4′-mercapto-s-triazol-3′-yl]ethane (**2**)*

A mixture of thiocarbohydrazide (1.06 g, 0.01 mol) and 2-(6-methoxy-2-naphthyl)propanoic acid (**1**) (2.30 g, 0.01 mol) was fused at 180°C in an oil bath for 15 min. After cooling, the reaction mixture was triturated with ethanol to give **2** (Table 1).

*1-[(6-Methoxy-2-naphthyl)-1-(6′-oxo-5H-s-triazolo[3,4-b][1,3,4]thiadiazin-3-yl)]ethane (**3**)*

To a solution of **2** (3 g, 0.01 mol) in dioxane (50 ml) and triethylamine (1.01 g, 0.01 mol), ethyl chloroacetate (1.22 g, 0.01 mol) was added. The reaction mixture was refluxed for 2 h. The precipitate that had formed was filtered off, washed with water, dried, and recrystallized from dioxane to give **3**.

*1-[(6-Methoxy-2-naphthyl)-1-(6′,11′-dioxo (naphtho[5,6:2,3][1,3,4]thiadiazino-[2,3-c]-s-triazol-3-yl)]ethane (**4**)*

A mixture of **2** (3 g, 0.01 mol) and 2,3-dichloronaphthoquinone (2.27 g, 0.01 mol) in dimethylformamide (20 ml) containing (1.01 g, 0.01 mol) triethylamine was refluxed for 12 h. The solid that had formed was collected and recrystallized from ethanol to give **4**.

TABLE 1 Characterization Data for Newly Synthesized Compounds 2–15

Compound	M.P. (°C)	Yield (%)	Mol. Formula (Mol. Wt)	Elemental Analyses Calculated/Found (%)		
				C	H	N
2	208–210	89	$C_{15}H_{16}N_4OS$	60.00	5.33	18.66
			(300)	59.80	5.10	18.40
3	>300	63	$C_{17}H_{16}N_4O_2S$	60.00	4.70	16.47
			(340)	60.30	4.50	16.20
4	>300	76	$C_{25}H_{18}N_4O_3S$	66.08	3.96	12.33
			(454)	66.40	3.60	12.60
5	>300	66	$C_{18}H_{16}N_6OS$	59.34	4.39	23.07
			(364)	59.10	4.70	23.20
6	130–132	54	$C_{16}H_{14}N_4OS$	61.93	4.51	18.06
			(310)	61.70	4.30	18.40
7a	112–114	71	$C_{19}H_{20}N_4O_3S$	59.37	5.20	14.58
			(384)	59.70	5.40	14.30
8	277–279	81	$C_{16}H_{14}N_4OS_2$	56.14	4.09	16.37
			(342)	56.40	4.30	16.10
9	235–237	78	$C_{22}H_{19}N_5O_2$	68.57	4.93	18.18
			(385)	68.30	4.60	18.50
10	260–262	69	$C_{23}H_{22}N_4O_2S$	66.02	5.26	13.39
			(418)	66.20	5.40	13.60
11	280–282	73	$C_{19}H_{14}N_6OS$	60.96	3.74	22.46
			(374)	61.20	3.50	22.60
12	232–234	61	$C_{19}H_{16}N_6OS$	60.63	4.25	22.34
			(376)	60.40	4.50	22.60
14	>300	75	$C_{20}H_{20}N_4OS$	65.93	5.49	15.38
			(364)	66.20	5.70	15.10
15	150–152	74	$C_{19}H_{18}N_4O_2S$	62.29	4.91	15.30
			(366)	62.10	4.70	15.50

*1-[(6-Methoxy-2-naphthyl)-1-(6′-amino-7′-cyano-5H-s-triazolo[3,4-b][1,3,4]-thiadiazin-3-yl)]ethane (**5**)*

A mixture of **2** (3 g, 0.01 mol), bromomalononitrile (1.45 g, 0.01 mol), and potassium hydroxide (0.56 g, 0.01 mol) in ethanol (50 ml) was refluxed for 1 h. The solid obtained was collected and recrystallized from ethanol to give **5**.

*1-[(6-Methoxy-2-naphthyl)-1-(s-triazolo[3,4-b]-[1,3,4]thiadiazol-3-yl]ethane (**6**)*

A solution of **2** (3 g, 0.01 mol) in formic acid (10 ml) was refluxed for 6 h. The obtained solid was recrystallized from dioxane to give **6**.

*1-[(6-Methoxy-2-naphthyl)-1-(1′-acetyl-4-acetylamino-5-thioxo-s-triazol-3-yl)]ethane (**7a**)*

A solution of **2** (3 g, 0.01 mol) in acetic anhydride (20 ml) was heated under reflux for 10 h. After the solution had cooled, the excess acetic anhydride was removed under reduced pressure. The obtained solid was recrystallized from acetic acid to give **7a**.

*1-[(6-Methoxy-2-naphthyl)-1-(5H-6-thioxo-s-triazolo[3,4-b][1,3,4]thiadiazol-3-yl)]ethane (**8**)*

A mixture of **2** (3 g, 0.01 mol), carbon disulphide (0.92 g, 0.012 mol), and potassium hydroxide (0.56 g, 0.01 mol) in ethanol (50 ml) was refluxed until the evolution of H_2S had ceased (10 h). The reaction mixture was concentrated, cooled, poured into ice water (100 ml) and acidified with dil. HCl. A solid product was filtered off and recrystallized from dioxane to give **8**.

*1-[(6-Methoxy-2-naphthyl)-1-(6′-oxo-5H-s-triazolo[3,4-b][1,2,4]triazol-3-yl)]ethane (**9**)*

A solution of **2** (3 g, 0.01 mol), phenyl isocyanate (1.19 g, 0.01 mol) in dry pyridine (30 ml) was refluxed until the evolution of H_2S had ceased (12 h). The reaction mixture was poured into ice cold water (100 ml), the solid product that formed was filtered off and recrystallized from ethanol to give **9**.

*1-[(6-Methoxy-2-naphthyl)-1-(4′-(4-methoxybenzylidineamino)-5′-thioxo-1H-s-triazole-3-yl]ethane (***10***)*

A mixture of **2** (3 g, 0.01 mol) and 4-anisaldehyde (1.24 g, 0.01 mol) in glacial acetic acid (10 ml) was refluxed for 2 h. The solvent was evaporated under reduced pressure, and the solid product was collected and recrystallized from acetic acid to give **10**.

*1-[(6-Methoxy-2-naphthyl)-1-(5H-s-triazolo-[3,4-b][1,3,4]thiadiazol-2-dicyano-ethylidine-3-yl)]ethane (***11***); 1-(6-Methoxy-2-naphthyl)-1-(5′-aminomethylene-malononitrile-4′-mercapto-s-triazol-3-yl)ethane (***12***); 1-[(6-methoxy-2-naphthyl)-1-(6′,8′-dimethyl-s-triazolo[3,4-b]-[1,3,4]thiadiazepin-3-yl)]ethane (***14***) and 1-[(6-methoxy-2-naphthyl)-1-(6-acetonyl-s-triazolo[3,4-b][1,3,4]thiadiazol-3-yl)]ethane (***15***)*

A mixture of **2** (3 g, 0.01 mol), [bis(methylsulfanyl)-methylidene]malononitrile or ethoxymethylenemalononitrile or acetylacetone and/or ethyl acetoacetate (0.01 mol) and triethylamine (1.01 g, 0.01 mol) in dimethylformamide (20 ml) was refluxed for 12 h. The obtained solid was recrystallized from ethanol to give compounds **11, 12, 14**, and **15**, respectively.

ANTIFUNGAL ACTIVITY

The antifungal activity of some of the synthesized compounds were determined against four species of fungi, namely *Aspergillus ochraceus* Wilhelm (AUCC-230), *Aspergillus flavus* Link (AUCC-164); *Penicillium chrysogenum* Thom (AUCC-530), and *Candida albicans (*Robin*)* Berkho (AUCC-1720), by using a cup plate agar method [17] at a concentration of 1 mg/ml in DMF as a solvent, which showed no inhibition zones. Fungi were grown on sabovraud's dextrose agar containing (g/l): glucose, 40; peptone, 10 and agar 20. Inhibition zones were measured in (mm) at the end of an incubation period of 48 h at 28°C. Mycostatine was used as a standard reference. The minimal inhibitory concentrations (MIC) of the active compounds were measured using the serial dilution method [17]. The data obtained are summarized in Table 2. The triazole derivative **2** which containing amino and mercapto groups and the triazolothiadiazine (5) bearing amino and cyano groups were found to be the most active compounds against all the fungi under investigation whereas triazoles containing either thiadiazole **11** or dicyano group **12** and thiadiazepine 14 showed higher activity against *A. flavus* and *P. chrysogenum*. Also, compound **15** exhibited higher activity against *C. albicans*. From these results it can be concluded that the biologically active compounds **2, 5, 11, 12, 14**, and **15** (MIC values were <50 μg/ml) are more active than the starting material Naproxen and nearly as active as the standard Mycostatine (30 μg/ml).

RADIOSTABILITY OF THE BIOLOGICALLY ACTIVE COMPOUNDS

The aim of the present work is to investigate the stability of the chemical structure of the biologically active compounds **2, 5, 11**, and **14** before sterilization. These compounds, in the dry state, were exposed to doses of gamma irradiation ranging from 5–40 kGy. Ultraviolet measurements (UV spectra) and thin layer chromatography (TLC) were run before and after irradiation to probe any changes after irradiation. The UV spectra of unirradiated (control) and irradiated compounds in DMF as solvent are listed in Table 3.

TABLE 2 Antifungal Activity of Some Newly Synthesized Compounds (Inhibition Zones, mm)

Compound	*Aspergillus Ochraceus Wilhelm (AUCC-230)*	*Aspergillus Flavus Link (AUCC-164)*	*Penicillium Chrysogenum Thom (AUCC-530)*	*Candida Albicans (Robin) Berkho (AUCC-1720)*
1	18	10	20	14
2	40	36	36	24
3	20	20	12	18
4	18	14	18	10
5	34	36	24	24
6	14	18	10	14
8	30	12	12	18
9	20	10	20	12
11	18	34	36	10
12	18	34	34	14
14	12	36	34	18
15	18	18	30	34
Mycostatine[a]	40	40	38	40

[a]Manufactured by Bristol-Myers Squibb, Giza, Egypt.

TABLE 3 UV and Visible Data of Biologically Active Compounds Before and After Gamma-Irradiation

Compound	*Dose (kGy)*	*Conc. (Mol)*	λ_{max} *(1)*	*Abs. (O.D)*	λ_{max} *(2)*	*Abs. (O.D)*
2	Control	1×10^{-4}	270	0.584	–	–
	5		270	0.816	–	–
	10		270	0.836	–	–
	15		270	0.917	–	–
	20		270	0.926	–	–
	25		270	0.975	–	–
	30		270	0.988	–	–
	40		270	1.024	–	–
5	Control	1×10^{-4}	280	0.288	320	0.231
	5		280	0.335	320	0.255
	10		280	0.421	320	0.282
	15		280	0.484	320	0.296
	20		280	0.499	320	0.367
	25		280	0.508	320	0.427
	30		280	0.522	320	0.681
	40		280	0.569	320	0.949
11	Control	1×10^{-4}	275	0.619	330	0.144
	5		275	0.802	330	0.163
	10		275	0.905	330	0.169
	15		275	0.916	330	0.177
	20		275	0.949	330	0.208
	25		275	0.964	330	0.291
	30		275	0.969	330	0.296
	40		275	0.983	330	0.317
14	Control	1×10^{-4}	275	0.475	480	0.133
	5		275	0.734	480	0.140
	10		275	0.967	480	0.261
	15		275	0.990	480	0.273
	20		275	1.214	480	0.279
	25		275	1.301	480	0.301
	30		275	1.361	480	0.325
	40		275	1.381	480	0.346

Abs. = absorbance.

The results showed that all of the biologically active compounds **2, 5, 11**, and **14** remain radioresistant, retaining their structure unchanged up to 40 kGy (Table 3).

Further, thin layer chromatographic analyses (R_f) were made on precoated silica gel G sheets 1B-F and were detected by use of a UV lamp at 254 nm. The R_f values of the unirradiated compounds **2, 5, 11**, and **14** were 0.30, 0.45, 0.85, and 0.50, respectively [eluent ethyl acetate/petrolum ether 2:1]. After irradiation, the irradiated compounds gave identical R_f values as before irradiation. This means that the structures of these compounds remain radioresistant, and sterilization of these compounds in dry form by gamma irradiation may prove to be applicable.

ACKNOWLEDGMENTS

We thank Dr. M. M. Afifi, Microbiology Department, Faculty of Science, Al-Azhar University at Assiut, Egypt for doing the antifungal activity.

REFERENCES

[1] Bianchi, D.; Cesti, P.; Spezia, S.; Garavaglia, C.; Mirenna, L. J Agric Food Chem 1991, 39, 197–201.
[2] Holla, B. S.; Akberali, P. M. J Indian Chem Soc 1991, 68, 341–343.
[3] Ghorab, M. M.; Abdel-Hamide, S. G.; Ali, G. M.; Shaurub, E. H. Pestic Sci 1996, 48, 31–35.
[4] Xiao, W. S.; Yan, Z.; Zi, Y. Z. J Chinese Chem Soc 1998, 45, 535–538.
[5] Zi, Y. Z.; Xiao, W. S.; Chang, H. C.; Lan, Z. J Chinese Chem Soc 1997, 44, 535–538.
[6] Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolouis, A.; Fried, J. H. J Med Chem 1970, 13, 203–205.
[7] Boess, C.; Bogl, K. W. Drug Dev Ind Pharm 1996, 22, 495–529.
[8] CiranniSignoretti, E.; Onori, S.; Valvo, L.; Fattibene, P.; Savella, A. L.; DeSena, C.; Alimonti, S. Drug Dev Ind Pharm 1993, 19, 1693–1708.
[9] Jacobs, G. P. J Biomed Appl 1995, 10, 59–96.
[10] Miyazaki, T.; Kaneko, T.; Yoshimura, T.; Crucq, A. S.; Tilquin, B. J Pharm Sci 1994, 83, 68–71.
[11] Ghorab, M. M.; Mohamed, Y. A.; Mohamed, S. A.; Ammar, Y. A. Phosphorus Sulfur Silicon 1996, 108, 249–256.

[12] Ghorab, M. M. Egypt J Radiat Sci Appl 1995, 8(2), 179–190.
[13] Ghorab, M. M.; Shihab, A.; Heiba, H. I. Egypt J Radiat Sci Appl 1995, 8(2), 191–198.
[14] Basly, J. P.; Basly, I.; Bernard, M. Int J Radiat Biol 1999, 75(2), 259–263.
[15] Basly, J. P.; Basly, I.; Bernard, M. Int J Radiat Biol 1998, 74(4), 521–528.
[16] El-Saraf, G. A. Indian J Chem 1992, 31B, 167–171.
[17] Reeves D. S.; White, L. O. Principles of Methods of Assaying Antibiotic in Pharmaceutical Microbiology, 3rd Ed.; Blackwell Scientific Publications: Oxford, 1983; pp. 140–162.