Triazolotriazines as Potential Chemotherapeutic Agents. VI

Vishnu J. Ram† and (Mrs) Vidyohama Dube

Department of Chemistry, S. C. College,
Ballia, India

A. J. Vlietinck*

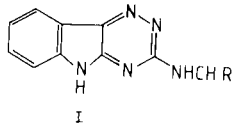
Department of Pharmaceutical Sciences, University of Antwerp,
B-2610 Antwerp, Belgium

Received February 2, 1987

Several new 1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indoles were prepared in anticipation that they would have better chemotherapeutic activities, but in the screening test none of the compounds was found to be active.

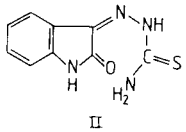
J. Heterocyclic Chem., **24**, 1435 (1987).

Azoles and azines such as pyrazoles, triazoles, thiadiazoles, triazines, pyrazines, pyridazines, and thiazines are well known for diverse biological activities in isolated as well as fused states. Sometimes the fusion of heterocyclic nuclei enhances the pharmacological activities many-fold more than its parent nucleus. The importance of the indole nucleus is well established in pharmaceutical chemistry, as its corresponding derivatives are used as antipyretic, anticonvulsant, analgesic and antidepressant agents [1-3]. Several *as*-triazines fused with an indole nucleus **I** have been considered as potential drugs for the treatment of common cold infections caused by different rhino virus strains [4-7]. These compounds were active *in vitro*, not only against rhinoviruses but also against Coxsackie, Echo, herpes, polio, pseudorabies and vaccinia viruses [5]. The clinical efficacy of *as*-triazines [8] and methisazone [9] **(II)** prompted us to prepare novel compounds **III** in which the triazole, triazine and indole nuclei are fused together in anticipation of better pharmacological activities.

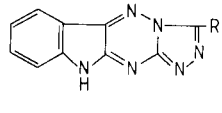


I

R = CH_2CH_2OH
= $CH_2C(CH_3)_2OH$
= $C(CH_3)_2CH_2OH$



II



III

Figure 1

The intermediate 3-hydrazino-*as*-triazino[5,6-*b*]indole **(4)** was prepared by refluxing the thione **3** with hydrazine as reported earlier [11,12]. Compound **3** was obtained in excellent yield by base cyclization of isatin-3-thiosemicarbazone **(2)**. The ir spectrum of **3** did not show any peaks around 2600 cm^{-1} but showed peaks at 1100-1250 cm^{-1}, which clearly indicated that **3** exists in the thione **3a** rather than the thiol **3b** form in the solid state. Interaction of **4** with carbon disulfide in pyridine provided 3-mercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole, which was alkylated to 3-alkyl-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indoles **6a-l** with different alkyl halides in DMF using potassium carbonate as base. 3-Alkyl-1,2,4-triazolo[4,3-*b*]-triazino[7,6-*b*]indole was obtained by refluxing a mixture of hydrazine **4** with aliphatic acid. Reaction of hydrazine **4** with aromatic aldehydes yielded the corresponding hydrazones, which were cyclized to 3-aryl-1,2,4-triazolo[4,3-*b*]-triazino[7,6-*b*]indoles **9** with bromine in acetic acid.

All the compounds synthesized were evaluated for insecticidal, fungicidal, bactericidal and virucidal activities according to methods described earlier [13]; but none of the test chemicals exhibited significant activity.

EXPERIMENTAL

All the melting points are uncorrected. The ir and mass spectra of the compounds were recorded on a Perkin Elmer spectrophotometer model 137 E and a MS 312 Finnigan respectively.

1,2,4-Triazino[5,6-*b*]indole-3-thione **(3)**.

This compound was prepared from the base cyclization of isatin-3-thiosemicarbazone **(2)** in 56% yield by the procedure reported earlier [10,11], mp >300°.

3-Hydrazino-1,2,4-triazino[5,6-*b*]indole **(4)**.

Refluxing a mixture of **3** and hydrazine in alcohol by following the procedure described earlier [11,12] gave the title compound.

3-Mercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole **(5)**.

This compound was prepared by refluxing a solution of **4** (1.0 g, 5 mmoles) with carbon disulfide (0.4 g) in 10 ml of pyridine for 5 hours. Excess pyridine was removed and the reaction mixture was diluted with water. The precipitate thus obtained was filtered off and crystallized from water:DMF, 40%, mp 295°; ms: 242.

Anal. Calcd. for $C_{10}H_6N_6S$: C, 49.59; H, 2.48; N, 34.70. Found: C, 49.32; H, 2.32; N, 34.67.

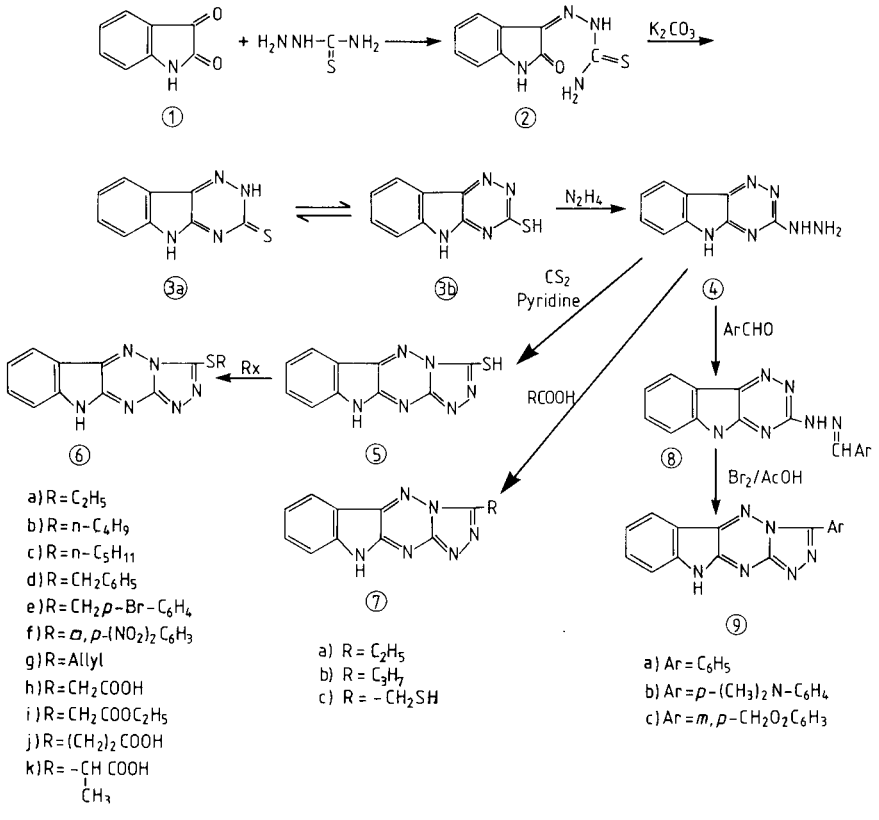


Figure 2

3-Ethylmercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6a**).

This compound was prepared by stirring a solution of **5** (0.25 g, 1 mmole) in DMF with ethyl bromide (0.12 g) using potassium carbonate as the base for 4 hours at room temperature. Dilution of the reaction mixture with water provided a solid, which was filtered off, washed with water and crystallized from DMF, 58%, mp 282°; ms: M^+ 270.

Anal. Calcd. for $C_{12}H_{10}N_6S$: C, 53.33; H, 3.70; N, 31.11. Found: C, 53.68; H, 3.56; N, 30.96.

3-*n*-Butylmercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6b**).

The title was obtained by stirring on equimolar mixture of **5** (0.24 g, 1 mmole), *n*-butyl bromide (0.15 g, 1.1 mmoles) and potassium carbonate (0.28 g) in DMF and isolated as described in the preceding experiment, 0.2 g, mp >300°; ms: M^+ 298.

Anal. Calcd. for $C_{14}H_{14}N_6S$: C, 56.37; H, 4.70; N, 28.19. Found: C, 56.58; H, 4.35; N, 28.54.

3-*n*-Amylmercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6c**).

This compound was synthesized from **5** and *n*-amyl iodide as described above in 35% yield, mp 185°; ms: M^+ 312.

Anal. Calcd. for $C_{15}H_{16}N_6S$: C, 57.69; H, 5.12; N, 26.92. Found: C, 57.58; H, 4.92; N, 26.66.

3-Benzylmercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6d**).

The title compound was prepared from the reaction of benzyl chloride and **5** in 60% yield, mp 229°; ms: M^+ 332.

Anal. Calcd. for $C_{17}H_{12}N_6S$: C, 61.45; H, 3.61. Found: C, 61.83; H, 3.43.

3-(**p**)-Bromobenzylmercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6e**).

This compound was obtained from **5** and *p*-bromobenzyl bromide in 40% yield, mp 285°; ms: M^+ 411.

Anal. Calcd. for $C_{17}H_{11}BrN_6S$: C, 49.63; H, 2.68. Found: C, 49.32; H, 2.94.

3-(2′4′-Dinitrophenyl)mercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6f**).

This compound was prepared from **5** and 2,4-dinitrochlorobenzene in 45% yield, mp >300°; ms: M^+ 408.

Anal. Calcd. for $C_{16}H_8N_8O_4S$: C, 47.06; H, 1.96. Found: C, 47.34; H, 2.22.

3-Allylmercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6g**).

This compound was synthesized from the reaction of **5** with allyl bromide in 35% yield, mp >300°; ms: M^+ 282.

Anal. Calcd. for $C_{13}H_{10}N_6S$: C, 55.32; H, 3.55. Found: C, 55.62; H, 3.45.

3-Carboxylmethylmercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6h**).

This compound was obtained in 40% yield from **5** and chloroacetic acid, mp >300°.

Anal. Calcd. for $C_{12}H_8N_6O_2S$: C, 48.00; H, 2.67. Found: C, 48.35; H, 2.53.

3-Carbethoxymethylmercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6i**).

The title compound was obtained from the reaction of **5** with ethyl chloroacetate in 38% yield, mp 287°; ms: M^+ 328.

Anal. Calcd. for $C_{14}H_{12}N_6O_2S$: C, 51.22; H, 3.66. Found: C, 51.35; H, 3.83.

β-Carboxylethylmercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6j**).

This compound was prepared from **5** and β-chloropropionic acid in 32% yield, mp >300°.

Anal. Calcd. for $C_{13}H_{10}N_6O_2S$: C, 49.68; H, 3.18. Found: C, 49.58; H, 3.25.

α-Carboxylethylmercapto-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**6k**).

Reaction of α-chloropropionic acid with **5** yielded the title compound in 35% yield, mp 258°.

Anal. Calcd. for $C_{13}H_{10}N_6O_2S$: C, 49.68; H, 3.18. Found: C, 49.88; H, 3.33.

3-Ethyl-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**7a**).

A mixture of **4** (0.2 g) and propionic acid (7 ml) was heated under reflux for 5 hours. Excess of acid was removed under reduced pressure and the residue was treated with water. The precipitate thus obtained was filtered off and crystallized from DMF:water, 45%, mp 295°; M^+ 238.

Anal. Calcd. for $C_{12}H_{10}N_6$: C, 60.50; H, 4.20. Found: C, 60.23; H, 4.56.

3-*n*-Propyl-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**7b**).

This compound was prepared by refluxing **4** in *n*-butyric acid for 5 hours and isolated as usual, mp 299°; ms: M^+ 252.

Anal. Calcd. for $C_{13}H_{12}N_6$: C, 61.90; H, 4.76. Found: C, 61.65; H, 4.58.

3-Mercaptomethyl-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**7c**).

This compound was synthesized by refluxing **4** in mercaptoacetic acid for 5 hours in 35% yield; ms: M^+ 256.

Anal. Calcd. for $C_{11}H_8N_6S$: C, 51.56; H, 3.13. Found: C, 51.85; H, 3.18.

3-Benzalhydrazino-1,2,4-triazino[5,6-*b*]indole (**8a**).

A mixture of **4** (0.2 g) and benzaldehyde (0.12 g) in ethanol (15 ml) was refluxed for 2-3 hours. After this period, the precipitate obtained was filtered off and crystallized from DMF:water 95%, mp >300°.

Anal. Calcd. for $C_{16}H_{12}N_6$: C, 66.67; H, 4.17. Found: C, 66.45; H, 4.28.

3-(*p*)-Dimethylaminobenzalhydrazino-1,2,4-triazino[5,6-*b*]indole (**8b**).

The title compound was obtained from **4** and *p*-dimethylaminobenzaldehyde as described above in 75% yield, mp >300°; ms: M^+ 331.

Anal. Calcd. for $C_{18}H_{17}N_7$: C, 65.26; H, 5.13. Found: C, 65.38; H, 4.92.

3-(3'4'-Methylenedioxybenzal)hydrazino-1,2,4-triazino[5,6-*b*]indole (**8c**).

Condensation of piperonal with **4** in equimolar quantities yielded the title compound in 85% yield, mp >300°.

Anal. Calcd. for $C_{17}H_{12}N_6O_2$: C, 61.44; H, 3.61. Found: C, 61.28. H, 3.85.

3-Phenyl-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**9a**).

A solution of **8a** (0.29 g, 1 mmole) in glacial acetic acid was treated with bromine (0.2 g, 1.2 mmoles) in acetic acid and stirred at ambient temperature for 5 hours. The reaction mixture was diluted with water and filtered. The crude product was crystallized from DMF:water, 45%, mp >300°; ms: M^+ 286.

Anal. Calcd. for $C_{16}H_{10}N_6$: C, 67.13; H, 3.49. Found: C, 67.24; H, 3.57.

3-(*p*)-Dimethylaminophenyl-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**9b**).

This compound was obtained in 38% yield from the oxidative ring closure of **8b** as described above, mp 220°; ms: M^+ 329.

Anal. Calcd. for $C_{18}H_{15}N_7$: C, 65.65; H, 4.56. Found: C, 65.33; H, 4.86.

3-(3'4'-Methylenedioxyphenyl)-1,2,4-triazolo[4,3-*b*]triazino[7,6-*b*]indole (**9c**).

This compound was prepared from the cyclization of **8c** with bromine-acetic acid in 35% yield, mp 245°.

Anal. Calcd. for $C_{17}H_{10}N_6O_2$: C, 61.82; H, 3.03. Found: C, 61.65; H, 3.25.

Chemotherapeutic Activities.

All the compounds synthesized were screened for antibacterial, antifungal, antiviral and insecticidal activities, but none of the test chemicals showed any significant activities in a primary screening.

Acknowledgement.

The authors are thankful to the authorities of the S. C. College, Ballia for providing necessary facilities.

REFERENCES AND NOTES

† Present address: Medicinal Chemistry Division, C.D.R.I., Lucknow 220061, India.

[1] M. R. Bell, A. R. Zalay, R. Oesterlin, S. D. Clemans, D. J. Dum, J. C. Bradford and J. Rozitis, Jr., *J. Med. Chem.*, **20**, 537 (1977).

[2] F. D. Popp, *J. Heterocyclic Chem.*, **21**, 1641 (1984).

[3] K. C. Joshi, V. N. Pathak and S. K. Jain, *Pharmazie*, **35**, 677 (1980).

[4] J. M. Z. Gladych, J. H. Hunt, D. Jack, R. F. Haff, J. J. Boyle, and R. C. Stewart, *Nature*, **221**, 286 (1969).

[5] J. J. Boyle, W. G. Raupp, F. J. Stanfield, F. R. Haff, E. C. Dick, D. D'Allessio and C. Dick, *Ann. N. Y. Acad. Sci.*, **173**, 477 (1970).

[6] J. M. Gwaltney, *Proc. Soc. Exp. Biol. Med.*, **133**, 1148 (1970).

[7] R. F. Haff, W. B. Flagg, J. J. Gallo, J. R. E. Hoover, J. A. Miller, C. A. Printo and J. F. Pegano, *Proc. Soc. Exp. Biol. Med.*, **141**, 475 (1975).

[8] T. Ueda and I. Nakata, *Yakugaku Zasshi*, **80**, 1068 (1960); *Chem. Abstr.*, **55**, 562 (1961).

[9] D. J. Bauer and F. W. Sheffield, *Nature*, **184** 1496 (1959).

[10] J. M. Z. Gladych, R. Hornby, J. H. Hunt and D. Jack, *J. Med. Chem.*, **15**, 277 (1972).

[11] V. J. Ram, *Arch. Pharm.* (Weinheim), **313**, 108 (1980).

[12] I. S. Ioffe, A. B. Tomchin and E. N. Zhukova, *Zh. Org. Khim.*, **7**, 173 (1971).

[13] V. J. Ram and A. J. Vlietinck, *J. Heterocyclic Chem.*, **23**, 1367 (1986).