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Bioorganic & Medicinal Chemistry Letters 14 (2004) 5013–5017
Bioorganic & Medicinal Chemistry Letters

Pyridazine derivatives and related compounds. Part 13: Synthesis and antimicrobial activity of some pyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazines☆

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Received 17 March 2004; accepted 22 June 2004
Available online 18 August 2004

Abstract—A general method for the preparation of substituted pyridazinopyrazolotriazines is reported. 3-Aminopyrazolo[3,4-*d*]pyridazine was diazotized and coupled with active methylene reagents to afford the tricyclic pyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazines with substituents such as methyl, phenyl, ethoxycarbonyl, acetyl or benzoyl, depending on the methylene reagent used. In addition several condensation reactions with hydrazines gave the corresponding acid hydrazide and/or hydrazones. Reactions of **3** with aromatic aldehydes afforded hydrazones. The products were screened for their antimicrobial activity against five microorganisms.

1. Introduction

Heterocyclic diazo compounds represent an interesting class of reactive substrates[2] and their stability depends mainly on charge delocalization through the heterocyclic ring. Recently we have described the reaction between the stable 3-diazo-4,5-diphenylpyrazolo[3,4-*c*]pyridazine **1** and reactive methylene compounds.[3] We now report similar reactions with further examples of active methylene reagents and the confirmation of their product structures. Moreover, several pyridazine ring systems are associated with diverse biological activities[4] as well as the biological activities of pyrazolopyridazine and pyrazolotriazine ring systems are well documented.[5,6] Therefore, it was thought of interest to combine the above mentioned biolabile rings together in a molecular framework to see the additive effect of these rings toward the biocidal activities.

2. Chemistry

The required 3-diazo-4,5-diphenylpyrazolo[3,4-*d*]-pyridazine **1** was prepared following the literature method.[7] As a route for the synthesis of pyridazino-[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazines; the reaction of compound **1** with different β-bifunctional reagents seemed to be a logical method for preparation of these compounds. Thus when compound **1** treated with ethyl acetoacetate a product **2** was obtained. Structure **2** was established for this product based on its analytical and spectral data. The mass spectrum showed the expected molecular ion peak M^+ at *m/e* 410 (100%), and a characteristic fragmentation pattern, where the most abundant peaks at *m/e* 381 ($M-C_2H_5$) and at *m/e* 337 ($M-COOC_2H_5$).

Addition of hydrazine hydrate to compound **2** gave 3-carboxylic acid hydrazide **3** in high yield. The assignment of structure **3** was based on an analytical and spectral data. The IR spectrum displaying bands at 3450–3275 (NH), 1660 (C=O) and 1592 cm^{-1} (C=N).

The carbohydrazide **3** was reacted with aromatic aldehydes in ethanol to give the corresponding carbohydrazones **4a–l**. The structure of compound **4a–l** was elucidated on the basis of their analytical and IR data. The IR absorption spectra showed the disappearance of the broad band at 3450 cm^{-1} (NH_2) and the existence of small band at 3220 cm^{-1} (NH). Also the reaction of **2** with phenylhydrazine and semicarbazide was carried out in refluxing ethanol to yield the corresponding carbohydrazide derivatives **5**, **6**.

☆See Ref. 1.
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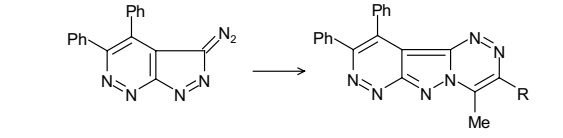
doi:10.1016/j.bmcl.2004.06.102

The hydrolysis of **2** was possible by heating under reflux with ethanolic potassium hydroxide. The identification of the resulting product as 3-carboxylic acid derivative **7** was based on spectral data and its subsequent reaction product. The IR spectrum exhibited absorption band at 3424 (OH), and at 1703 cm^{-1} (C=O). Compound **7** underwent ready decarboxylation to give **8** on heating above its melting point. By analogy with ethyl acetoacetate, acetylacetone, benzoylacetone and ethyl benzoylacetate react readily with compound **1** to give the corresponding substituted pyridazino[3′,4′:3,4]-pyrazolo-[5,1-*c*]-1,2,4-triazine derivatives **9**, **13** and **17**, respectively. The structure of compound **9** was elucidated on the basis of their analytical and spectral data. The mass spectrum showed the expected molecular ion peak M^+ at *m/e* 380 (73.6%), and a characteristic fragmentation pattern where the most abundant peaks at *m/e* 337 ($M-COCH_3$) (100%). The ^1H NMR spectrum revealed presence of multiplet at δ 7.9–7.2 due to 10H (phenyl protons), singlet at δ 3.8 due to 3H ($-COCH_3$) and singlet at 3.2 due to 3H (CH_3) and chemical evidence. The reaction of **9** with hydrazine hydrate, phenyl hydrazine and semicarbazide yielded the expected hydrazones **10**–**12**. The structures of products **10**–**12** follow their method of preparation and their physical data (see Experimental section). The oxidation of acetyl group in compound **9** using hypobromite yielded the corresponding carboxylic acid derivative which underwent ready decarboxylation on heating above its melting point. Structure of these compounds were assigned by comparison with authentic samples **8** and **9**, respectively.

The structure of compound **13** instead of the anticipated product **13a** was elucidated on the basis of their analytical and spectral data. The mass spectrum showed the expected molecular ion peak M^+ at *m/e* 442, and a characteristic fragmentation pattern where the most abundant peaks at *m/e* 337 (M−COPh) shows the presence of benzoyl group and not acetyl group. The hydrazinolysis of **13** with hydrazine hydrate, phenyl hydrazine and semicarbazide give the hydrazones **14**–**16**, the structures were established based on their analytical and spectral data.

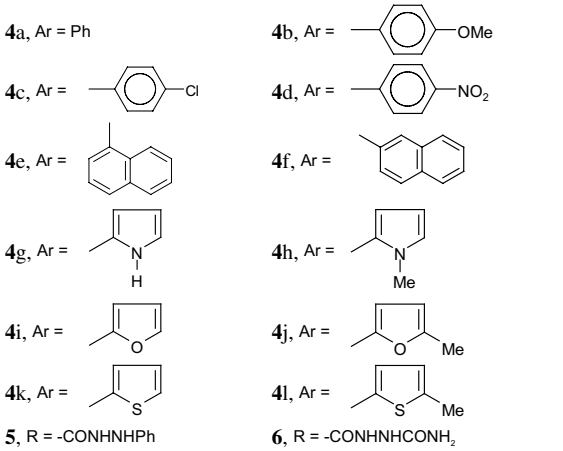
Structural elucidation of compound **17** was accomplished from analytical, spectral data, and chemical evidence. The mass spectrum showed the expected molecular ion peak M^+ at *m/e* 472 (100%). The reaction of the ester **17** with hydrazine hydrate, phenylhydrazine and semicarbazide yielded the expected hydrazides **18**–**20**. The ester **17** was saponified with potassium hydroxide to give the expected acid **21**, which underwent ready decarboxylation on heating above its melting point and yielded **22**. The most salient features of IR and ^1H NMR are given under Experimental.



1 **2**, R = COOEt

3, R = $CONHNH_2$

4a-l, R = CONHN=CHAr



4a, Ar = Ph **4b**, Ar = OMe

4c, Ar = Cl **4d**, Ar = NO_2

4e, Ar = **4f**, Ar =

4g, Ar = **4h**, Ar =

4i, Ar = **4j**, Ar =

4k, Ar = **4l**, Ar =

5, R = -CONHNHPh **6**, R = $-CONHNHCONH_2$

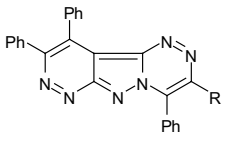
7, R = -COOH **8**, R = -H

9, R = -COMe **10**, R = $-C(Me)=NNH_2$

11, R = $-C(Me)=NNHPh$ **12**, R = $-C(Me)=NNHCONH_2$

13, R = -COPh **14**, R = $-C(Ph)=NNH_2$

15, R = $-C(Ph)=NNHPh$ **16**, R = $-C(Ph)=NNHCONH_2$



13a, R = COMe **17**, R = COOEt

18, R = $CONHNH_2$ **19**, R = CONHNHPh

20, R = $CONHNHCONH_2$ **21**, R = COOH

22, R = H

3. Antimicrobial activity

The in vitro antimicrobial activities for some of the synthesized compounds at different applied concentrations, (1000, 5000, and 10,000 ppm) against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* and also antifungal activity against *Candida albicans* were determined.

The bacteria under investigation were cultivated on nutrient agar medium, whereas yeast were cultivated on malt extract agar.

The antimicrobial activity of the studied compounds were assayed by measuring the inhibition zone of microbial growth caused by known volume of water soluble compounds, the method was essentially as follows.

Hold glass microfiber discs (0.6 cm) with saturated known volume (0.2 mL) of different concentrations of aqueous solution of the compounds synthesized were put on the surface of the specific agar medium seeded with the test organisms. Then the plates were incubated at 37 °C for 48 h for bacteria and at 28 °C for 96 h for yeast, and the diameter of inhibition zone in millimeters were measured.

Table 1.

Compound[b]	Organism[a]			
	A	B	C	D
4b	3	—	—	—
4d	—	5	—	—
4g	—	2	—	—
4i	—	2	—	—
4k	2	2	—	—
4l	—	—	—	2
9	4	—	—	3
16	4	3	2	—

[a] A, *S. aureus*; B, *E. coli*; C, *P. aeruginosa*; D, *C. albicans*; (—) = no inhibition zones.
[b] No significant inhibition caused by compounds: **2**, **4a**, **4c**, **4f**, **4h**, **4j**, **5**–**8**, **12**, **14**, **15**, **17**–**22**.

The in vitro antimicrobial activity of the 27 compounds screened is summarized in Table 1. The only significant inhibition caused on the growth of all tested microorganisms by the water soluble pure compounds at the highest concentration (10,000 ppm). Among the variously substituted derivatives of the pyridazino-pyrazolotriazines studied, eight had antimicrobial activity. The acetyl derivative **9** had activity against the yeast *C. albicans* and inhibited *S. aureus*. This activity was lost on hydrazinolysis. The antibacterial activity of these hydrazides again increased by the condensation with aromatic aldehydes compounds **4b**, **4d**, **4g**, **4i**, **4k**, and **4l** had activity against *S. aureus* and *E. coli*. Finally, compound **16** had anti *S. aureus*, *E. coli*, and *P. aeruginosa* activity. It is of interest to mention the antifungal activity of the products with regard to the agricultural importance of the fungi used.

4. Experimental

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra of the compounds were recorded on a Perkin–Elmer spectrophotometer model 1430 as potassium bromide pellets and frequencies are reported in cm^{-1}. The ^1H NMR spectra were observed on a Perkin–Elmer R12B spectrometer and chemical shifts (δ) are in ppm relative to internal TMS, and mass spectra were recorded on a Mass Spectrometer HP model MS 5988 El 70 ev. Reactions were routinely followed by thin layer chromatography (TLC) on silica gel F_{254} aluminum sheets (Merck). The spots were detected by UV irradiation at 254–365 nm.

4.1. General procedure for the preparation of coupling products from 3-diazo-4,5-diphenylpyrazolo[3,4-*c*]pyridazine 1 and active methylene compounds

A solution of compound **1** (0.6 g, 2 mmol) in ethanol (20 mL) was treated with the corresponding active methylene compounds (2 mmol). The reaction mixture was refluxed for 30 min. The separated product was filtered off and crystallized. In this manner the following compounds were prepared.

4.1.1. Ethyl 4-methyl-9,10-diphenylpyridazino[3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazine-3-carboxylate 2. Prepared from ethyl acetoacetate, yellow crystals in 92.6% yield, mp 248–250 °C (ethanol); MS: *m/e* 410 (M^+, 100%), 381 (4.4%), 337 (56.3%), 310 (40.5%), IR: 1728 (C=O), 1620 (C=N) and 1540 (C=C); ^1H NMR (DMSO-d_6): 7.8–7.2 (m, 10H, 2Ph), 4.4 (q, 2H, CH_2CH_3), 3.6 (s, 3H, CH_3) and 1.4 (t, 3H, CH_2CH_3). Anal. Calcd for $C_{23}H_{18}N_6O_2$: C, 67.30; H, 4.42; N, 20.48. Found: C, 67.10; H, 4.20; N, 20.20.

4.1.2. 3-Acetyl-4-methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine 9. Prepared from acetyl acetone, yellow crystals in 90.2% yield, mp 268–270 °C (ethanol); MS: *m/e* 380 (M^+, 73.7%), 337 (M^+–$COCH_3$, 100%), 310 (26.4%), 271 (35.3); IR: 1695 (C=O), 1625 (C=N), 1540 (C=C); ^1H NMR (CF_3COOH): 7.9–7.2 (m, 10H, 2Ph), 3.8 (s, 3H, $COCH_3$), and 3.2 (s, 3H, CH_3). Anal. Calcd for $C_{22}H_{16}N_6O$: C, 69.46; H, 4.24; N, 22.10. Found: C, 69.20; H, 4.00; N, 22.00.

4.1.3. 3-Benzoyl-4-methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine 13. Prepared from benzoylacetone, orange crystals in 81% yield, mp 277–279 °C (ethanol); MS: *m/e* 442 (M^+, 10%), 337 (M−COPh, 0.12%), 214 (17–5%), 105 (90%), 77 (100%); IR: 1700 (C=O), 1610 (C=N), 1540 (C=C). Anal. Calcd for $C_{27}H_{18}N_6O$: C, 73.29; H, 4.10; N, 19.00. Found: C, 73.0; H, 3.90; N, 19.10.

4.1.4. Ethyl 4-phenyl-9,10-diphenylpyridazino[3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazine-3-carboxylate 17. Prepared from ethyl benzoylacetate, orange crystals in 97% yield, mp 225–227 °C (ethanol); MS: *m/e* 472 (M^+, 100%), 400 (65.5%), 373 (46%); IR: 1735 (C=O), 1625 (C=N), 1580 (C=C). Anal. Calcd for $C_{28}H_{20}N_6O_2$: C, 71.17; H, 4.27; N, 17.79. Found: C, 70.90; H, 4.00; N, 17.80.

4.1.5. 4-Methyl-9,10-diphenyl and 4,9,10-triphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine-3-carbohydrazide 3 and 18. A solution of ethyl carboxylate derivatives **2** and/or **17** (1.0 mmol) in ethanol (30 mL) was treated with hydrazine hydrate 85% (3 mL). The reaction mixture was refluxed for 3 h, then it was concentrated under reduced pressure and left to cool. The precipitate was filtered and recrystallized from ethanol.

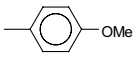
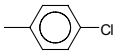
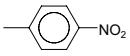
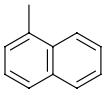
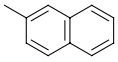
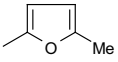
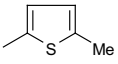
Compound **3**. Yellow crystals, mp 252–253 °C, yield 97%; IR: 3441, 3161, 1674, 1425. Anal. Calcd for $C_{21}H_{16}N_8O$: C, 63.63; H, 4.07; N, 28.27. Found: C, 63.40; H, 3.90; N, 28.0.

Compound **18**. Red crystals, mp 240–241 °C, yield 95%; IR: 3420, 1667, 1585, 1118, 698. Anal. Calcd for $C_{26}H_{18}N_8O$: C, 68.11; H, 3.96; N, 24.44. Found: C, 67.90; H, 3.80; N, 24.10.

4.2. Reaction of 3 with aromatic aldehydes. Formation of 4a–l. General procedure

A mixture of the hydrazine derivative **3** (0.4 g, 1.0 mmol) and aromatic aldehyde (1.0 mmol) in ethanol (20 mL) was refluxed for 5 h and then allowed to cool. The solid

Table 2. 4-Methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazin-3-yl)carbohydrazones (**4a–l**)

Compd No.	Ar	Mp (C°)	Yield (%)	Molecular formula	Analysis calcd/found (%)		
					C	H	N
4a	Ph	286–288	95	$C_{28}H_{20}N_8O$	69.41 69.20	4.16 3.90	23.13 22.80
4b		240–241	91	$C_{29}H_{22}N_8O_2$	67.69 67.40	4.31 4.00	21.78 21.50
4c		292–294	90	$C_{28}H_{19}ClN_8O$	64.80 64.50	3.69 3.40	21.59 21.30
4d		308–310	90	$C_{28}H_{19}N_9O_3$	63.51 63.30	3.62 3.40	23.81 23.60
4e		302–304	85	$C_{32}H_{22}N_8O$	71.89 71.70	4.15 4.00	20.96 20.80
4f		286–288	91	$C_{32}H_{22}N_8O$	71.89 71.60	4.15 3.90	20.96 20.70
4g		253–254	86	$C_{26}H_{19}N_9O$	65.95 65.80	4.04 3.90	26.63 26.40
4h		244–246	80	$C_{27}H_{21}N_9O$	66.52 66.40	4.34 4.10	25.86 25.70
4i		260–261	85	$C_{26}H_{18}N_8O_2$	65.81 65.60	3.82 3.60	23.62 23.40
4j		254–255	88	$C_{27}H_{20}N_8O_2$	66.38 66.10	4.13 4.00	22.94 22.70
4k		284–285	90	$C_{26}H_{18}N_8OS$	63.66 63.40	3.70 3.50	22.84 22.70
4l		289–290	91	$C_{27}H_{20}N_8OS$	64.27 64.00	3.99 3.70	22.21 22.00

product was collected and recrystallized from ethanol. The results are summarized in Table 2.

4.3. Reaction of ethyl carboxylate derivatives 2 and 17 with phenylhydrazine and with semicarbazide. General procedure

A mixture of ethyl carboxylate derivatives **2** and/or **17** (1.0 mmol) and phenyl hydrazine and/or semicarbazide hydrochloride (1.0 mmol) in ethanol (20 mL) was refluxed for 3 h, and then it was concentrated under reduced pressure and left to cool. The precipitate was filtered and recrystallized from ethanol.

Compound **5**. Orange crystals in 65% yield; mp 316–317 °C; IR: 3446, 3144, 1672, 1555, 1333, 1113, 659. Anal. Calcd for $C_{27}H_{20}N_8O$: C, 68.63; H, 4.27; N, 23.72. Found: C, 68.40; H, 4.00; N, 23.40.

Compound **6**. Orange crystals in 70% yield; mp 314–315 °C; IR: 3414, 3342, 3194, 1713, 1680, 1554, 1231. Anal. Calcd for $C_{22}H_{17}N_9O_2$: C, 60.13; H, 3.90; N, 28.69. Found: C, 60.00; H, 3.80; N, 28.40.

Compound **19**. Brown crystals in 85% yield; mp 219–220 °C; IR: 3379, 1632, 1598, 1495, 696. Anal. Calcd for $C_{32}H_{22}N_8O$: C, 71.89; H, 4.15; N, 20.96. Found: C, 71.60; H, 4.00; N, 20.80.

Compound **20**. Red crystals in 95% yield; mp 332–333 °C; IR: 3430, 3366, 3310, 1687, 1587; Anal. Calcd for $C_{27}H_{19}N_9O_2$: C, 64.66; H, 3.82; N, 25.14. Found: C, 64.40; H, 3.60; N, 25.00.

4.4. Reaction of 3-acetyl(benzoyl) derivatives 9 and 13 with hydrazines. General procedure

A mixture of compound **9** and/or **13** (1.0 mmol) and hydrazines namely hydrazine hydrate 85%, phenylhydrazine, and/or semicarbazide hydrochloride (1.0 mmol) in ethanol (20 mL) was refluxed for 3 h, and then it was concentrated under reduced pressure and left to cool. The precipitate was filtered and recrystallized from ethanol.

Compound **10**. Brown crystals in 65% yield; mp 238–239 °C; IR: 3445, 3325, 3155, 1612, 1567, 703; Anal. Calcd for $C_{22}H_{18}N_8$: C, 66.99; H, 4.60; N, 28.41. Found: C, 66.70; H, 4.40; N, 28.10.

Compound **11**. Brown crystals in 85% yield, mp 188–190 °C; IR: 3202, 3057, 1595, 1559, 696; Anal. Calcd

for $C_{28}H_{22}N_8$: C, 71.47; H, 4.71; N, 23.82. Found: C, 71.20; H, 4.50; N, 23.60.

Compound **12**. Brown crystals in 95% yield, mp 273–274 °C; IR: 3399, 3184, 3099, 1686, 1572, 699; Anal. Calcd for $C_{23}H_{19}N_9O$: C, 63.15; H, 4.38; N, 28.82. Found: C, 62.90; H, 4.10; N, 28.70.

Compound **14**. Yellow crystals in 70% yield, mp 253–254 °C; IR: 3445, 3390, 3324, 1612, 1423, 705. Anal. Calcd for $C_{27}H_{20}N_8$: C, 71.04; H, 4.42; N, 24.55. Found: C, 70.80; H, 4.20; N, 24.20.

Compound **15**. Brown crystals in 80% yield, mp 182–183 °C; IR: 3181, 3057, 1598, 1499, 761; Anal. Calcd for $C_{33}H_{24}N_8$: C, 74.42; H, 4.54; N, 21.04. Found: C, 74.10; H, 4.20; N, 20.90.

Compound **16**. Orange crystals in 95% yield, mp 264–265 °C; IR: 3398, 3183, 3105, 1669, 1571, 698. Anal. Calcd for $C_{28}H_{21}N_9O$: C, 67.32; H, 4.24; N, 25.24. Found: C, 67.10; H, 4.00; N, 25.10.

4.5. Hydrolysis of ethyl carboxylates 2 and 17

To a stirred solution of compounds **2** and/or **17** (1.0 mmol) in ethanol (50 mL) a 1 N potassium hydroxide solution (30 mL) was added. The mixture was refluxed for 1 h and the solvent evaporated. The residue was dissolved in water (20 mL) and acidified with hydrochloric acid. The solid thus formed was filtered, washed with water, dried and recrystallized from ethanol.

Compound **7**. Brown crystals in 65% yield, mp 242–243 °C; IR: 3424, 2922, 1703, 1631, 1599, 699. Anal. Calcd for $C_{21}H_{14}N_6O_2$: C, 65.96; H, 3.69; N, 21.98. Found: C, 65.70; H, 3.40; N, 21.70.

Compound **21**. Yellow crystals in 55% yield, mp 264–265 °C; IR: 3420, 3160, 1624, 1541, 698. Anal. Calcd for $C_{26}H_{16}N_6O_2$: C, 70.26; H, 3.63; N, 18.91. Found: C, 70.00; H, 3.40; N, 18.70.

4.6. Decarboxylation of carboxylic acids 7 and 21

The carboxylic acid **7** and/or **21** (1 g) was heated above their melting points in an oil-bath until the evolution of carbon dioxide subsided (about 5 min). The product which solidified on cooling was treated with aqueous sodium bicarbonate, filtered and recrystallized from ethanol.

Compound **8**. Brown crystals in 85% yield mp 340–341 °C; IR: 3361, 3164, 1599, 1561, 697. Anal. Calcd for $C_{20}H_{14}N_6$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.70; H, 4.00; N, 24.60.

Compound **22**. Brown crystals in 70% yield, mp 344–345 °C; IR: 3055, 1536, 1476, 1375, 693. Anal. Calcd for $C_{25}H_{16}N_6$: C, 74.98; H, 4.03; N, 20.99. Found: C, 74.80; H, 3.90; N, 20.80.

Acknowledgements

The author acknowledges the help of Prof. Dr. Y. El-Zawahry, Department of Microbiology for carrying out the antimicrobial activity.

References and notes

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