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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NOVAL DITHIOCARBAMATE SUBSTITUTED BENZIMIDAZOLO-QUINOLINES

PRIYA M. MADALAGERI and O. KOTRESH*

Department of Chemistry, Karnatak Science College, Karnatak University,
DHARWAD – 580003 (K.S.) INDIA

ABSTRACT

A series of substituted benzimidazolo-quinoline derivatives bearing a diverse dithiocarbamate moieties were designed and synthesized via a three-component reaction protocol. All these compounds were characterized by means of their IR, ^{1}H NMR and mass spectroscopic data. All the synthesized dithiocarbamate derivatives were screened for antimicrobial activities. Among antibactrial activity, four showed considerable activity of ciprofloxacin and other were found to be moderately active, especially compounds having methoxy and nitro group substitution at 6-position showed a moderate activity. Among fungicidal activity, compounds containing methoxy and methyl substituents at 6- position gave excellent activity and nearly equal to the standard amphotericin B.

Key words: Quinolines, Dithiocarbamates, Antibacterial, Antifungal.

INTRODUCTION

Quinolines and their derivatives form an important class of pharmacologically active synthetic compounds. The quinoline nucleus can also be frequently recognized in the structure of numerous naturally occurring alkaloids. They have been associated with a broad spectrum of biological activities[1]. The fusion of quinoline to the tetrazole ring is known to increase the biological activity[2].

The quinoline-containing polycyclic compounds are expected to have interesting biological activity. Pyrazoloquinoline derivatives are active agents for the treatment of cancer and herpes virus infections[3,4]. Quinolines and their derivatives are important constituents of pharmacologically active synthetic compounds, as these systems have been

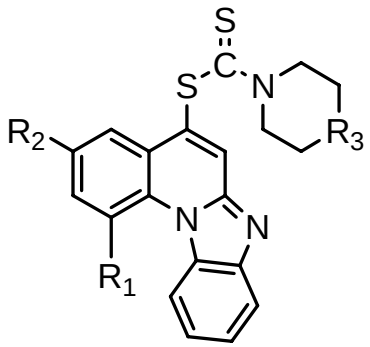
*Author for correspondence; E-mail: drokotresh@gmail.com; Mo.: 9448838665

associated with a wide spectrum of biological activities[5-8] such as DNA binding capability[9], antitumor activities[10,11], DNA-intercalating carrier[12] etc.

Benzimidazoles have potential and realized applications in pharmacology as bactericides[13], antihistamines, analgesics, antiviral compounds and antiulcer agents, among others[14]. Aside from the listed pharmacological applications, benzimidazoles have also found applications as fungicides[13] and as corrosion inhibitors[15].

Dithiocarbamate (DTC) derivatives are well known as organic intermediates, rubber additive, additive of polluted water, vulcanizing agents and fungicides[16]. Thiocarbonates (xanthates) and thiocarbamates[17] have received much attention due to their interesting technological[18], biological[19] and synthetic applications[20].

Dithiocarbamates have received considerable attention in recent times because of their occurrence in a variety of biologically active compounds[21]. They also play pivotal roles in agriculture[22] and they act as linkers in solid-phase organic synthesis[23]. In addition, functionalized carbamates are an important class of compounds and their medicinal and biological properties warrant study[21] and recently in the synthesis of ionic liquids[24]. Furthermore, dithiocarbamates are broadly employed in medicinal chemistry and have been used in cancer treatment[25].



3(a-o)

Fig. 1: Structure of dithiocarbamate substituted benzimidazolo-quinolines

Based on the above considerations, we proposed that benzimidazolo-quinolines bearing DTC moiety should display some interesting antimicrobial activity. Therefore, we designed compounds **3(a-o)** as shown in Fig. 1 with the aim to discover new structure with antimicrobial activity. Herein, we described the detailed synthetic route, screening results and structure–activity relationships of these designed compounds. Fortunately, methoxy and nitro compounds with promising broad-spectrum antimicrobial activity were identified.

EXPERIMENTAL

Chemicals and solvents were reagent grade and used with further purification. Melting points were determined on a capillary melting point apparatus and were uncorrected. IR spectra were recorded on Perkin-Elmer 298 instrument (KBr disk or liquid film). ^{1}H NMR spectra were performed on a VXR 300 (300 MHz) instrument in $DCCl_3$. Thin layer chromatography was carried out on pre-coated GF254 silica gel plates. The column chromatography was performed using G60 H silica gel.

Synthesis of 2, 4-dichloro-6, 8-disubstituted quinoline derivatives 1 (General method)

All the compounds were prepared by a reported method, and some of the compounds are well characterized in the literature[26].

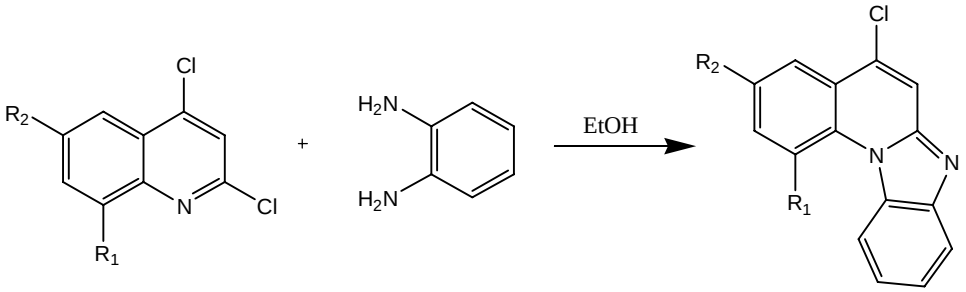
Synthesis of 4-chloro benzimidazolo[1,5-a] quinolines 2

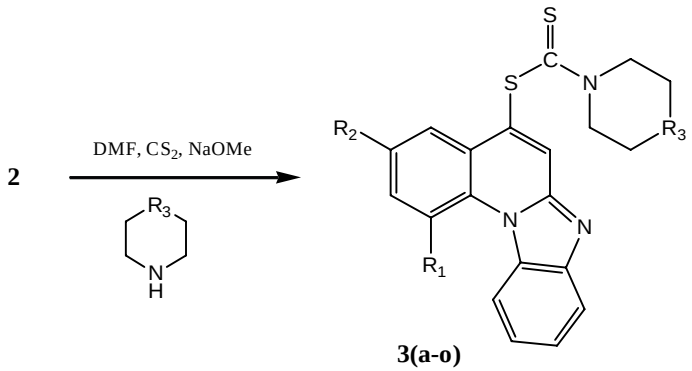
A mixture of **1** (2.48 g, 0.01 mol) and o-phenylenediamine (1.08 g, 0.01 mol) was refluxed in 50 mL of ethanol on water bath for 28 hr, the reaction mixture half concentrated and poured onto ice-HCl. The solid obtained was filtered, washed with water and crystallized from ethanol.

Synthesis of dithiocarbamate substituted benzimidazolo-quinolines 3(a-o)

To a solution of amine (1 mmol) in DMF (2 mL) was added dropwise carbon disulfide (2 mmol) and anhydrous sodium methoxide (1 mmol). The resulted mixture was stirred at room temperature for 30 min. Then chlorinated benzimidazolo-quinolines 2 (1 mmol) was added by one-portion and stirring was continued. After completion of the reaction (monitored by TLC), the mixture was diluted with ice-coldwater (20 mL) and the precipitate was filtered, and recrystallized from ethanol to give the target compound **3(a-o)**.

The chemical and spectral data of the compounds 3(a-o) are given in Tables 1 and 2.





3(a-o)

3a- R_1 = H, R_2 = CH_3, R_3 = CH_2 3f- R_1 = H, R_2 = CH_3, R_3 = O 3k- R_1 = H, R_2 = CH_3, R_3 = NH
3b- R_1 = CH_3, R_2 = H, R_3 = CH_2 3g- R_1 = CH_3, R_2 = H, R_3 = O 3l- R_1 = CH_3, R_2 = H, R_3 = NH
3c- R_1 = H, R_2 = NO_2, R_3 = CH_2 3h- R_1 = H, R_2 = NO_2, R_3 = O 3m- R_1 = H, R_2 = NO_2, R_3 = NH
3d- R_1 = H, R_2 = OCH_3, R_3 = CH_2 3i- R_1 = H, R_2 = OCH_3, R_3 = O 3n- R_1 = H, R_2 = OCH_3, R_3 = NH
3e- R_1 = CH_3, R_2 = CH_3, R_3 = CH_2 3j- R_1 = CH_3, R_2 = CH_3, R_3 = O 3o- R_1 = CH_3, R_2 = CH_3, R_3 = NH

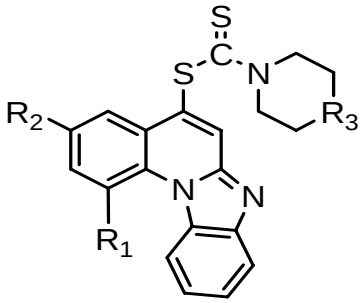
Scheme 1: Synthesis of dithiocarbamate substituted benzimidazolo-quinolines 3(a-o)

Table 1: Chemical data of the compounds 3(a-o)

Comp.	R_1	R_2	R_3	Formula[a]	m.p. (^oC)	Yield (%)
3a	-H	$-CH_3$	$=CH_2$	$C_{22}H_{21}N_3S_2$	134	87
3b	$-CH_3$	-H	$=CH_2$	$C_{22}H_{21}N_3S_2$	145	84
3c	-H	$-NO_2$	$=CH_2$	$C_{21}H_{18}N_4O_2S_2$	130	73
3d	-H	$-OCH_3$	$=CH_2$	$C_{22}H_{21}N_3OS_2$	156	82
3e	$-CH_3$	$-CH_3$	$=CH_2$	$C_{23}H_{23}N_3S_2$	149	76
3f	-H	$-CH_3$	-O-	$C_{21}H_{19}N_3OS_2$	153	89
3g	$-CH_3$	-H	-O-	$C_{21}H_{19}N_3OS_2$	130	85
3h	-H	$-NO_2$	-O-	$C_{20}H_{16}N_4O_3S_2$	145	76
3i	-H	$-OCH_3$	-O-	$C_{21}H_{19}N_3O_2S_2$	159	79
3j	$-CH_3$	$-CH_3$	-O-	$C_{22}H_{21}N_3OS_2$	162	81
3k	-H	$-CH_3$	=NH	$C_{21}H_{20}N_4S_2$	147	82
3l	$-CH_3$	-H	=NH	$C_{21}H_{20}N_4S_2$	152	78
3m	-H	$-NO_2$	=NH	$C_{20}H_{17}N_5O2S_2$	148	69
3n	-H	$-OCH_3$	=NH	$C_{21}H_{20}N_4OS_2$	139	75
3o	$-CH_3$	$-CH_3$	=NH	$C_{22}H_{22}N_4S_2$	158	71

[a]Elemental analysis for C, H, N are within ± 0.5% of the theoretical values.

Table 2: Spectral data of the compounds 3(a-o)



Compd.	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$, ppm)[a]
3a	1650 (C=N); 1610 (C=C); 1180 (C-N); 1352 (C=S)	2.34 (s, 3H, 6CH_3), 7.26-7.70 (m, 8H, Ar-H), 1.48-2.6 (m, 10H, pip CH_2's)
3b	1645 (C=N); 1611 (C=C); 1165 (C-N); 1359 (C=S)	2.30 (s, 3H, 8-CH_3), 7.15-7.62 (m, 8H, Ar-H) 1.46-2.50 (m, 10H, pip CH_2's)
3c	1634 (C=N); 1602 (C=C); 1156 (C-N) 1357 (C=S)	7.26-8.66 (m, 8H, Ar-H), 1.43-2.70 (m, 10H, pip CH_2's)
3d	1655 (C=N); 1598 (C=C); 1156 (C-N); 1357 (C=S)	3.67 (s, 3H, 6-OCH_3), 7.18-7.98 (m, 10H, pip CH_2's)
3e	1632 (C=N); 1595 (C=C); 1174 (C-N); 1345 (C=S)	2.38 (s, 3H, 6CH_3), 2.58 (s, 3H, 8CH_3), 7.14-7.75 (m, 7H, Ar-H), 1.78-2.76 (m, 10H, pip CH_2's)
3f	1649 (C=N); 1589 (C=C); 1153 (C-N); 1356 (C=S)	2.73 (s, 3H, 6-CH_3), 7.19-7.99 (m, 8H, Ar-H), 2.94-3.78 (m, 8H, mor CH_2's)
3g	1634 (C=N); 1620 (C=C); 1163 (C-N); 1359 (C=S)	2.74 (s, 3H, 8CH_3), 7.49-8.13 (m, 8H, Ar-H), 3.14-3.91 (m, 8H, mor CH_2's)
3h	1648 (C=N); 1611 (C=C); 1172 (C-N); 1354 (C=S)	7.70-8.94 (m, 8H, Ar-H), 3.14-3.84 (m, mor, CH_2's)
3i	1690 (C=N); 1600 (C=C); 1189 (C-N); 1358 (C=S)	3.79 (s, 3H, 6-OCH_3), 6.54-7.89 (m, 8H, Ar-H), 2.95-3.84 (m, 8H, mor CH_2's)
3j	1684 (C=N); 1576 (C=C); 1195 (C-N); 1353 (C=S)	2.85 (s, 3H, 6-CH_3), 2.94 (s, 3H, 8-CH_3), 7.48-8.14 (m, 7H, Ar-H), 3.11-3.97 (m, 8H, mor CH_2's)

Cont…

Compd.	IR (KBr, cm^{-1})	^1H NMR ($CDCl_3$, ppm)[a]
3k	1650 (C=N); 1589 (C=C); 1167 (C-N); 1354 (C=S), 3191 (NH)	2.45 (s, 3H, 6-CH_3), 7.48-7.99 (m, 8H, Ar-H), 2.66-2.94 (m, 8H, piz CH_2's), 1.76 (s, 1H, NH, disappeared with D_2O)
3l	1647 (C=N); 1598 (C=C); 1184 (C-N); 1357 (C=S); 3195 (NH)	2.54(s, 3H, 8-CH_3), 7.15-7.89 (m, 8H, Ar-H), 2.67-2.99 (m, 8H, piz CH_2's), 1.77 (s, 1H, NH, disappeared with D_2O)
3m	1690 (C=N); 1576 (C=C); 1165 (C-N); 1359 (C=S); 3194 (NH)	7.26-8.78 (m, 8H, Ar-H), 2.67-2.78 (m, 8H, piz CH_2's), 1.89 (s, 1H, NH, disappeared with D_2O)
3n	1678 (C=N); 1565 (C=C); 1176 (C-N); 1349 (C=S); 3197 (NH)	3.73 (s, 3H, 6-OCH_3), 6.64-7.43 (m, 8H, piz CH_2's), 1.92 (s, 1H, NH, disappeared with D_2O)
3o	1654 (C=N); 1567 (C=C); 1167 (C-N); 1357 (C=S); 3198 (NH)	2.48 (s, 3H, 6-CH_3), 2.54 (s, 3H, 8-CH_3), 7.12-7.94 (m, 7H, Ar-H), 2.73-3.11 (m, 8H, piz CH_2's), 1.84 (s, 1H, NH, disappeared with D_2O)

[a] s, singlet; m, multiplet

Pharmacology

Antibacterial assay

For the antimicrobial assay standard inoculums were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The discs measuring 8.0 mm in diameter were prepared from Whattman No. 1 filter paper and sterilized by dry heat at 120^{o}C for 1 h. The sterile discs previously soaked in a known concentration (100 mg/8 mm disc) of the test compounds were placed in nutrient agar medium. The plates were inverted and incubated for 24 h at 37^{o}C. The inhibition zones were measured and compared with the standard. The antimicrobial activity data of the test compounds are presented in Table 3.

Biological properties

Antibacterial activity

The newly synthesized compounds **3(a-o)** were tested for their *in vitro* antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli* by using the

agar disc diffusion method[27]. The results of the preliminary antimicrobial testing of the prepared compounds, the typical broad spectrum of antibacterial drug ciprofloxacin are shown in Table 3. Among the tested compounds, four compounds showed considerable activity almost equal to the activity of ciprofloxacin. The other compounds were found to be moderate or least effective. In order to get some meaningful results, the structure–activity relationship was carried out. From the bacterial screening results it has been observed that the compounds having methoxy and nitro groups at 6-position showed moderate effect on the growth of bacteria.

Table 3: Antimicrobial activity of compounds 3(a-o)

Compounds	Growth inhibition zone diameter (mm)					
	Antibacterial activity			Antifungal activity		
	S. aureus	***B. subtilis***	***E. coli***	***A. niger***	***A. nodulans***	***A. alternata***
3a	16	17	18	21	22	24
3b	9	8	8	---	9	8
3c	12	14	12	18	21	20
3d	20	21	22	19	21	18
3e	16	14	15	11	15	10
3f	14	17	13	12	16	15
3g	12	15	12	11	13	15
3h	21	20	19	20	21	19
3i	18	19	17	18	18	17
3j	15	13	12	9	13	12
3k	16	15	14	13	16	13
3l	9	11	10	11	13	14
3m	18	19	20	21	22	21
3n	13	15	13	13	12	12
3o	14	11	9	11	10	11
Ciprofloxacin	22	22	25	---	---	---
Amphotericin B	---	---	---	20	23	20

The compounds **3(a-o)** and the standards used were of 100 m g/8 mm discs.

Antifungal activity

All the newly synthesized compounds **3(a-o)** were also screened for their antifungal activity against *Aspergillus niger*, *Aspergillus nodulans* and *Alternaria alternate* by food poison technique[28]. The results of the preliminary antifungal testing of the prepared compounds, the typical broad spectrum of the potent antifungal drug amphotericin B are shown in Table 3. The antifungal activity data reveal that compounds containing methoxy and methyl substitutents at 6-position of quinoline ring, are showing excellent activity against the test fungi and nearly equal to the standard amphotericin B.

RESULTS AND DISCUSSION

In conclusion, a new series of dithiocarbamate substituted benzimidazolo-quinolines 3(a-o) has been synthesized and evaluated for their antimicrobial activity. Most of the new compounds showed appreciable antimicrobial activity. Among them, the compounds having methoxy and nitro substituted at 6-position of quinoline ring showed marked inhibition of bacterial and fungal growth nearly equal to the standards.

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REFERENCES

1. H. I. El-Subbagh, S. M. Abu-Zaid, M. A. Mahran, F. A. Badria and A. M. Alofaid, J. Med. Chem., **43**, 2915 (2000).
2. R.Gupta, A. K. Gupta and S. Paul, Ind. J. Chem., **39B**, 847 (2000).
3. M. P. Wentland, S. C. Aldous, M. D. Gruett and R. B. Perni, R. G. Powles, D. W. Danz and K. M. Klingbeil, A. D. Peverly, R. G. Robinson, T. H. Corbett, J. B. Rake and S. A. Coughlin, Bioorg. Med. Chem. Lett., **5**, 405 (1995).
4. J. M. Arif, M. Kunhi, M. P. Subramanian, A. A. Bekhit, O. A. El-Sayed, K. Al-Hussein and H. Y. Aboul-Enein, F. M. Al-Khodairy, Int. J. Biomed. Sci., **3**, 194 (2007).
5. H. I. El-Subbagh, S. M. Abu-Zaid, M. A. Mahran, F. A. Badria and A. M. Alofaid, J. Med. Chem., **43**, 2915 (2000).

6. A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux and R. J. Nugh, Phytochemistry, **56**, 265 (2001).

7. G. J. Richards, B. C. Juan, R. A. Macio and M. Roldan, C. R. Peinado and Fernando, Spen., **47**, 168 (1979).

8. B. R. Jerom and K. H. Spencer, Eur. Pat. Appl. EP, 277794 (1988).

9. G. J. Atwell, B. C. Baguley and W. A. Denny, J. Med. Chem., **32**, 396 (1989).

10. S. C. Kuo, H. Z. Lee, J. P. Juang, Y. T. Lin, T. S. Wu, J. J. Chang, D. Lednicer, K. D. Paull, C. M. Lin, E. Hamel and K. H. Lee, J. Med. Chem., **36**, 1146 (1993).

11. Y. Xia, Z. Y. Yang, P. Xia, K. F. Bastow, Y. Tachibana, S. C. Kuo, E. Hamel, T. Hackl and K. H. Lee, J. Med. Chem., **41**, 1155 (1998).

12. Y. L. Chen, I. L. Chen, C. C. Tzeng and T. C. Wang, Helv. Chim. Acta, **83**, 989 (2000).

13. (a) S. O. Zden, D. Atabey, S. Yıldız and H. Go¨ker, Bioorg. Med. Chem., **13**, 1587 (2005).

    (b) Z. Kazimierczuk, M. Andrzejewska, J. Kaustova and V. Klimesˇova´, Eur. J. Med. Chem., **40**, 203 (2005).

    (c) S. O. Zden, H. Karatasü, S. Yıldız and H. Go¨ker, Arch. Pharm. Pharm. Med. Chem., **337**, 556 (2004).

    (d) V. Klimesˇova´, J. Kocˇi, M. Pour, J. Stachel, K. Waisser and J. Kaustova´, Eur. J. Med. Chem., **37**, 409 (2002).

14. D. Lednicer, Strategies for Organic Drug Synthesis and Design, Wiley- Interscience: New York (1998).

15. (a) D. Zhang, L. Gao and G. Zhou, Corros. Sci., **46**, 3031 (2004).

    (b) A. Popova, M. Christov, S. Raicheva and E. Sokolova, Corros. Sci., **46**, 1333 (2004).

    (c) D. A. Lo´pez, S. N. Simison and S. R. de Sa´nchez, Electrochim. Acta, **48**, 845 (2003).

16. B. Cvek and Z. T. Dvorak, Curr. Pharm. Des., **30**, 3155-3167 (2007).

17. (a) S. R. Rao, Xanthates and Related Compounds; Marcel Dekker, New York (1971).

    (b) M. Yokoyama, T. Immamoto, Synthesis, 797 (1984).

    (c) W. Walter, K. D. Bode, Angew. Chem. Int. Ed. Engl., **6**, 281 (1967).

18. (a) K. Raichle, L. Rossing, H. Zorn, Ger. Pat. 840239, 1952 (Badische Anilin- & Soda-Fabrik); Chem. Abstr., **47**, 1732 (1953).

(b) American Cyanamid Co. Br. Pat. 700334, 1953; Chem. Abstr., **49**, 2492 (1955).

19. (a) B. H. Alexander, S. I. Gertler, T. A. Oda, R. T. Bown, R. W. Ihndris and M. J. Beroza, Org. Chem., **25**, 626 (1960).

(b) G. D. Thorn and R. A. Ludwig, The Dithiocarbamates and Related Compounds; Elsevier: Amsterdam (1962).

20. H. R. Nice, Org. React. and References Cited Therein, **12**, 57 (1962).

21. M. Dhooghe and N. De Kimpe, Tetrahedron and References Cited Therein, **62**, 513-535 (2006).

22. (a) C. Rafin, E. Veignie, M. Sancholle, D. Postel, C. Len, P. Villa and G. Ronco, J. Agric. Food Chem., **48**, 5283-5287 (2000).

(b) C. Len, D. Postel, G. Ronco, P. Villa, C. Goubert, E. Jeufrault, B. Mathon and H. Simon, J. Agric Food. Chem., **45**, 3-6 (1997).

23. P. Morf, F. Raimondi, H. G. Nothofex, B. Schnyder, A. Yasuda, J. M. Wessels and T. A. Jung, Langmuir and References Cited Therein, **22**, 658-663 (2006).

24. D. Zhang, J. Chen, Y. Liang and H. Zhou, Synth. Commun., **35**, 521 (2005).

25. (a) L. Ronconi, C. Marzano, P. Zanello, M. Corsini, G. Miolo, C. Macca, A. Trevisan and D. Fregona, J. Med. Chem., **49**, 1648 (2006).

(b) G. H. Elgemeie and S. H. Sayed, Synthesis, 1747 (2001).

(c) W. Walter and K. D. Bode, Angew. Chem. Int. Ed. Engl., **6**, 281 (1967).

26. E. A. Mohamed, M. M. Ismail, Y. Gabr and M. Abass, J. Serb. Chem. Soc., **59**, 715 (1994).

27. National Committee for Clinical Laboratory Standards (NCCLS), Standard Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria, Which Grow Aerobically, Nat. Comm. Lab. Stands, Villanova (1982) p. 242.

28. N. Ramchandran and G. N. Dake, Pest. Res., **25**, 538-542 (1989).

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