Regioselective synthesis of novel *N*-aminotriazolophanes

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Abstract: Bis-[4-amino-l,2,4-triazoles] were prepared by fusion of dibasic acids and thiosemicarbazide by condensation of aromatic acid hydrazides with hydrazine hydrate and carbon disulphide. Regioselective alkylation of these bis-[4-amino-1,2,4-triazoles] with 1,ω-dihaloalkanes in the presence of potassium hydroxide in aqueous methanol afforded novel *N*-aminotriazolophanes. The stereochemistry and antibacterial activity of these *N*-aminotriazolophanes were studied. In the case of the triazolophanes **5h**, **8d**, and **8f**, both N-NH_2 groups were observed trans to each other, whereas for case of other triazolophanes both N-NH_2 groups were observed cis to each other.

Key words: 4-amino-l,2,4-triazole, 1,ω-dihaloalkane, S-alkylation, regioselective, *N*-aminotriazolophanes.

Résumé : On a préparé des bis[4-amino-l,2,4-triazoles] par fusion d'acides dibasiques et de thiosemicarbazide, par condensation d'hydrazides d'acides aromatiques avec de l'hydrate d'hydrazine et du sulfure de carbone. L'alkylation régiosélective de ces bis-[4-amino-1,2,4-triazoles] avec des 1,ω-dihalogénoalcanes en présence d'hydroxyde de potassium, en solution dans le méthanol, fournit de nouveaux *N*-aminotriazolophanes. On a étudié la stéréochimie et l'activité antibactérienne de des *N*-aminotriazolophanes. Dans les cas des triazolophanes **5h**, **8d** et **8f**, on a observé que les deux groupes N–NH_2 sont trans l'un par rapport à l'autre alors que dans les autres cas les deux groupes N–NH_2 sont cis.

Mots-clés : 4-amino-l,2,4-triazole, 1,ω-dihalogénoalcane, S-alkylation, régiosélective, *N*-aminotriazolophanes.

[Traduit par la Rédaction]

Introduction

Crown compounds have generated considerable interest during the last three decades because of their ability to form stable complexes with variety of metal and organic cations and anions (1). They also have wide application in phase transfer catalysis (2). In recent years various structural changes have been made to the basic "crown ether" structure to enhance the selective activity of the ligands (3). These changes involve the insertion of aromatic and (or) heterocyclic ring systems into the macrocycles. The incorporation of a heterocyclic subunit provides rigidity to the macrocycle and assists in increasing the stability of complexes formed with both metals and organic cations (3). The development of crown compounds, especially macrocyclic compounds containing a heterocyclic subunit, has gained importance because of their wide range of applications. Many reviews and monographs have been published that highlight their synthesis and application in synthetic organic chemistry as phase transfer catalysts and in analytical chemistry as ligands for complexation (2, 4).

Received 19 April 2006. Accepted 8 November 2006. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 23 January 2007.

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In recent years, attention has been increasingly paid to the synthesis of bisheterocyclic compounds, which exhibit various biological activities (5) including antibacterial, antifungicidal, tuberculostatic, and plant growth regulative properties. Bisheterocyclic compounds displayed much better antibacterial activity than heterocyclic compounds (6). Various 1,2,4-triazoles are found to be associated with diverse pharmacological activities such as antiasthmatic (7), antiviral (ribavirin) (8), antifungal (fluconazole) (9), antimicrobial (10), antibacterial (11), insecticidal (12, 11*c*), amoebicidal (13), hypnotic (14), cytotoxic (15), and hypotensive (16) activities. This moiety was also found in potent agonist and antagonist receptor ligands (17) in HIV-1 protease inhibitors (18) and in thrombin inhibitors (19). Along with these significant pharmaceutical uses, 1,2,4-triazole derivatives are effectively used in polymers, dyestuff, photographic chemicals, and agricultural chemicals (20).

We have previously reported on the regioselective synthesis of novel oxadiazolophanes (21) and *N*-aminotriazolophanes (22). In continuation of this ongoing program in the synthesis of novel macrocyclic ligands (21, 22), their computational studies (21*b*), and their application as phase transfer catalysts (PTC) (22*c*), we now report a facile regioselective synthesis of novel *N*-aminotriazolophanes.

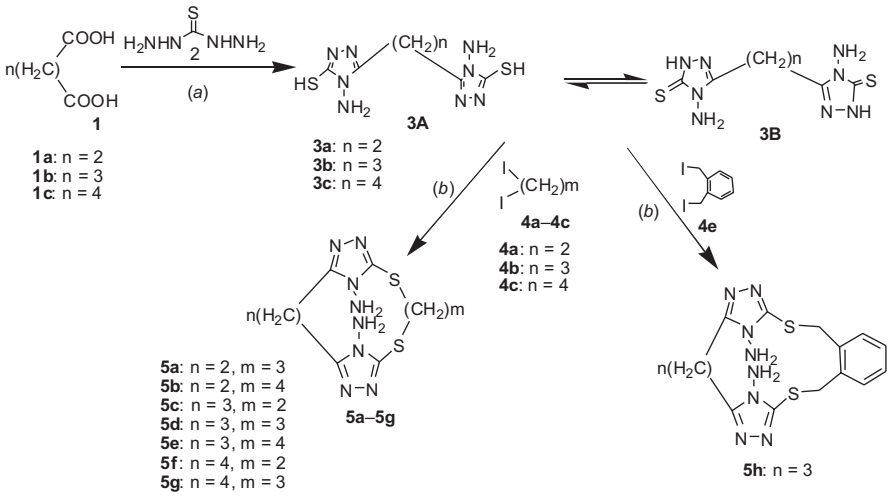
Results and discussion

Synthesis

The present work describes the versatile synthetic strategy for the regioselective synthesis of novel *N*-aminotriazolophanes

 doi:10.1139/V06-181

Scheme 1. Synthesis of *N*-aminotriazolophanes **5**. Reagents and conditions: (*a*) 170 °C, (*b*) KOH, aq. MeOH (80%), 80 °C.



that have been specially designed to study their stereochemistry.

Aminotriazole derivatives are well-known to be biologically active (23); e.g., 3-amino-1,2,4-triazole (amitrole) is known for its biological (24) and herbicidal (25) activities. 4-Amino-1,2,4-triazoles are potentially good corrosion inhibitors (26). Bisheterocyclic compounds prepared using 4-amino-1,2,4-triazoles derivatives exhibit significant biological activity (27, 5*f*). Hence, we decided to incorporate 4-amino-1,2,4-triazole as a basic unit in heterophane to further enhance heterophane's biological activity.

The obtained heterophanes (*N*-aminotriazolophanes) would be similar to lariat ether (28) with N-NH_2 groups as side arms. The study of the stereochemistry of these compounds is of interest because the two N-NH_2 groups would be either cis or trans to each other depending on the alkyl chain joining the two heterocyclic units and the thermodynamic stability of the molecule. This would in effect influence the properties of macrocycles such as cavity size.

There are many methods found in the literature for the synthesis of 3,5-disubstituted-4-amino-1,2,4-triazoles (29), but none of them concerns the synthesis of heterophanes. Bis-*N*-aminotriazoles **3a**–**3c** (30) were prepared in high yield by direct fusion of aliphatic diacids **1a**–**1c** with thiocarbohydrazine **2** (Scheme 1). The compound **3**, containing thioamido groups, has an amphoteric nature and can exist in tautomeric forms **3A** and **3B**. On alkylation of **3** with 1,ω-dihaloalkane, multiple products could form depending on the reaction condition.

The reaction of compounds **3a**–**3c** with diiodoalkanes **4a**–**4e** in aq. methanol (80%) in the presence of potassium hydroxide as base gave only products **5a**–**5h** regioselectively in good yield (Scheme 1, Table 1). The intramolecular alkylation, which regioselectively occurs at sulfur, is mainly due to the template formation, which is due to the presence of the hexadentate potassium ions where the two ligands are water molecules (31). The reaction was carried out in a large excess of solvent to ensure intramolecular cyclisation (high dilution condition). Reaction of compound **3** with dibromomethane was unsuccessful, perhaps because of the inability of the methyl group to link the two terminal thiol sulphur atoms.

The elucidation of the structures of **5a**–**5h** was accomplished on the basis of their spectral data and elemental analysis (Table 1). For example, the reaction of **3b** with 1,2 diiodoethane **4a** resulted in the formation of the desired *N*-aminotriazolophane **5c**, which was confirmed on the basis of NMR spectra. The ^{1}H NMR spectrum of the compound showed a triplet at δ: 3.37 for the S-CH_2 group in the ethane chain. The absence of a peak for C=S in the ^{13}C NMR spectrum confirmed the regioselectivity of S-alkylation. It showed a signal for S-CH_2 carbon at 29.6 ppm. From the above data, compound **5c** was identified as 1^4,5^4-diamino-6,9-dithia-1,5(3,5)-di-(1,2,4-triazola)cyclononaphane (32). The other *N*-aminotriazolophanes **5a**–**5h** were similarly synthesized and characterized.

To improve the solubility of the triazolophanes it was thought to incorporate a phenyl nucleus into the structure, which would also help in complexation or phase transfer catalyst (PTC) activity. Hence, the scope of the previous reaction was extended to the synthesis of benztriazolophane **8** (Scheme 2). Bistriazole **7** (33) was synthesized using the Reid and Heindel method [34] by the condensation of isophthalic acid dihydrazide **6** with hydrazine hydrate, carbon disulphide, and potassium hydroxide in methanol in high yield.

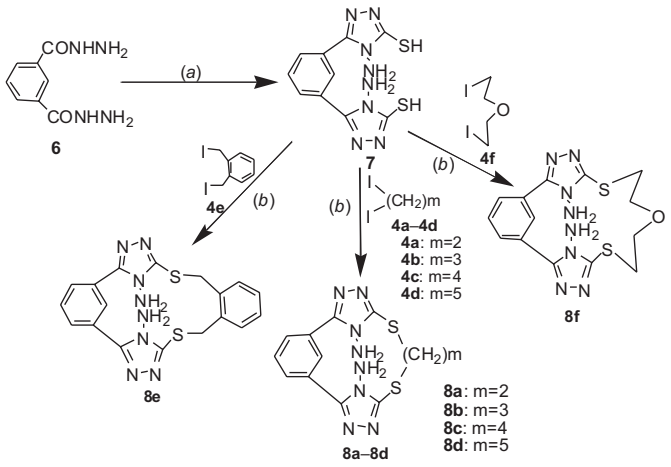
The reaction of **7** with **4a**–**4f** in aq. methanol (80%) in the presence of potassium hydroxide as a base gave the desired benztriazolophanes **8a**–**8f** regioselectively in moderate yield (Scheme 2, Table 1). The structure of the product was confirmed on the basis of spectral data and elemental analysis (Table 1). For example, the reaction of **7** with 1,2-diiodoethane **4a** resulted in the formation of the desired aminotriazolophane **8a**, which was confirmed on the basis of NMR spectra. The ^{1}H NMR spectrum of the compound showed a triplet at δ: 2.89 for the S-CH_2 group of the ethane chain. The absence of a peak for C=S in the ^{13}C NMR spectrum confirmed the regioselectivity of S-alkylation. It showed signals for S-CH_2 carbons at 27.9 and 30.0 ppm.

We have discussed in detail the regioselective N-alkylation (22*c*) and S-alkylation (21, 22*a*, 22*b*) for the synthesis of aminotriazolophanes. It was thought worthwhile to use O-alkylation for the synthesis of heterophane with an amino side arm. Hence, in continuation of this work on

Table 1. Preparation and analytical data of compounds.

Compound	Yield (%)	MP (°C)	Formulae	Found (required) (%)			
				C	H	N	S
3a	82	220	$C_6H_{10}N_8S_2$	—	—	—	—
3b	72	203	$C_7H_{12}N_8S_2$	—	—	—	—
3c	74	221	$C_8H_{14}N_8S_2$	—	—	—	—
5a	42	208	$C_9H_{14}N_8S_2$	36.23 (36.01)	4.73 (4.60)	37.55 (37.43)	21.49 (21.28)
5b	44	197	$C_{10}H_{16}N_8S_2$	38.44 (38.23)	5.16 (5.01)	35.87 (35.75)	20.53 (20.32)
5c	38	216	$C_9H_{14}N_8S_2$	36.23 (36.02)	4.73 (4.52)	37.55 (37.32)	21.49 (21.38)
5d	45	204	$C_{10}H_{16}N_8S_2$	38.44 (38.23)	5.16 (5.01)	35.87 (35.62)	20.53 (20.40)
5e	32	197	$C_{11}H_{18}N_8S_2$	40.47 (40.35)	5.56 (5.45)	34.33 (34.31)	19.65 (19.42)
5f	43	112	$C_{11}H_{18}N_8S_2$	40.47 (40.34)	5.56 (5.46)	34.33 (34.20)	19.65 (19.43)
5g	47	122	$C_{10}H_{16}N_8S_2$	38.44 (38.32)	5.16 (5.03)	35.87 (35.75)	20.53 (20.32)
5h	35	141	$C_{15}H_{18}N_8S_2$	48.11 (48.00)	4.84 (4.72)	29.92 (29.80)	17.13 (17.02)
7	82	>250	$C_{10}H_{14}N_8S_2$	39.22 (39.01)	3.27 (3.05)	36.60 (36.38)	20.91 (20.80)
8a	25	175	$C_{12}H_{12}N_8S_2$	43.37 (43.25)	3.61 (3.50)	33.74 (33.61)	19.28 (19.05)
8b	30	245	$C_{13}H_{14}N_8S_2$	45.09 (44.90)	4.05 (3.87)	32.37 (32.13)	18.49 (18.35)
8c	33	210	$C_{14}H_{16}N_8S_2$	46.67 (46.44)	4.44 (4.23)	31.11 (31.00)	17.78 (17.55)
8d	35	>250	$C_{15}H_{18}N_8S_2$	48.13 (48.01)	4.81 (4.58)	29.95 (29.72)	17.11 (17.00)
8e	47	235	$C_{18}H_{20}N_8S_2$	52.94 (52.71)	3.92 (3.78)	27.45 (27.31)	15.69 (15.46)
8f	44	>250	$C_{14}H_{20}N_8S_2O$	44.68 (44.55)	4.26 (4.12)	29.79 (29.56)	17.02 (16.80)
10	80	192	$C_8H_8N_4SO$	46.15 (46.02)	3.85 (3.72)	26.93 (26.72)	15.38 (15.15)
11	65	205	$C_{19}H_{20}N_8S_2O_2$	49.57 (49.46)	5.22 (5.10)	24.35 (24.23)	13.91 (13.78)
12a	35	>250	$C_{22}H_{24}N_8S_2O_2$	52.23 (52.11)	4.84 (4.60)	22.58 (22.36)	12.90 (12.66)
12b	36	220	$C_{23}H_{26}N_8S_2O_3$	52.08 (52.00)	5.66 (5.43)	21.13 (21.01)	12.08 (11.92)
14	80	>250	$C_8H_8N_4SO$	46.15 (46.01)	3.85 (3.62)	26.93 (26.70)	15.38 (15.24)
15	65	228	$C_{21}H_{24}N_8S_2O_2$	51.64 (51.51)	5.74 (5.62)	24.35 (24.23)	13.11 (13.00)
16	28	>250	$C_{26}H_{32}N_8S_2O_2$	56.52 (56.39)	5.78 (5.55)	20.29 (20.15)	11.59 (11.38)

Scheme 2. Synthesis of benztriazolophanes **8.** Reagents and conditions: (*a*) CS_2, $(NH_2)_2{\cdot}H_2O$, KOH, MeOH, 0–5 °C, (*b*) KOH, aq. MeOH (80%), 80 °C.



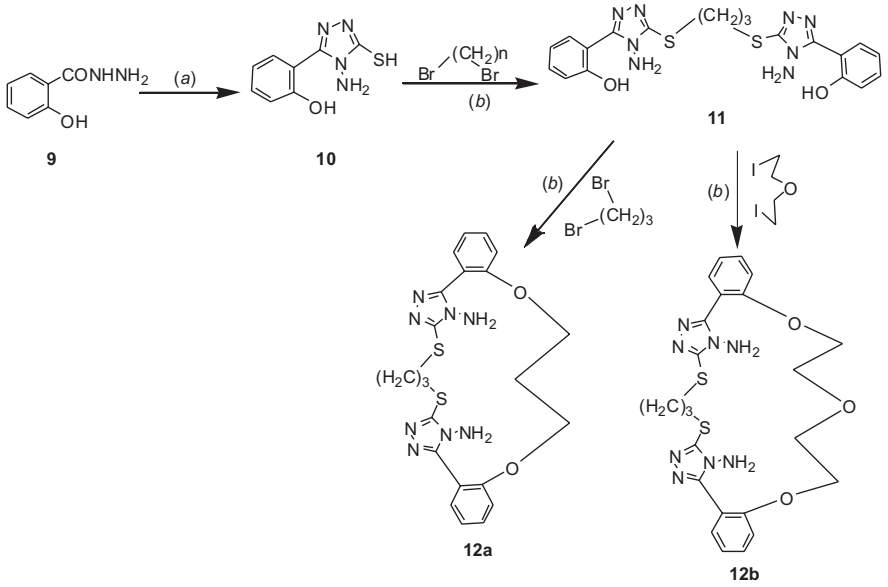
benztriazolophanes, salicylic acid hydrazide **9** was reacted with hydrazine hydrate, carbon disulphide, and potassium hydroxide in methanol to give compound **10** in high yield (Scheme 3). When **10** was reacted with 1,3-dibromopropane in methanolic potassium hydroxide, compound **11** was afforded regioselectively in good yield (Scheme 3, Table 1). The benztriazolophanes **12a** and **12b** were synthesized regioselectively as the only products in moderate yield by reacting **11** with dihaloalkanes in aq. methanol (80%) containing potassium hydroxide (Scheme 3, Table 1). The structure of the product was confirmed on the basis of spectral data and elemental analysis (Table 1). For example, reaction of **11** with 1,3-dibromopropane resulted in the formation of the desired compound **12a**, which was confirmed on the basis of NMR spectra. The ^{1}H NMR spectrum of the compound showed a triplet at δ: 3.66 for the S-CH_2 group of the propane chain and a triplet at δ: 4.08 for the O-CH_2 group of the propane chain. An M^+ peak at *m*/*z* 496 in the mass spectrum confirmed the formation of **12a**.

Similar reaction conditions were used to prepare compound **16** from *p*-hydroxy benzoic acid hydrazide **13**. When **13** was reacted with hydrazine hydrate, carbon disulphide, and potassium hydroxide in methanol, compound **14** was obtained in high yield. Compound **14** was reacted with 1,5-dibromopentane to afford **15** in moderate yield (Scheme 4, Table 1). Compound **15** was then reacted with 1,5-dibromopentane in methanolic potassium hydroxide to afford **16** in low yield (Scheme 4, Table 1).

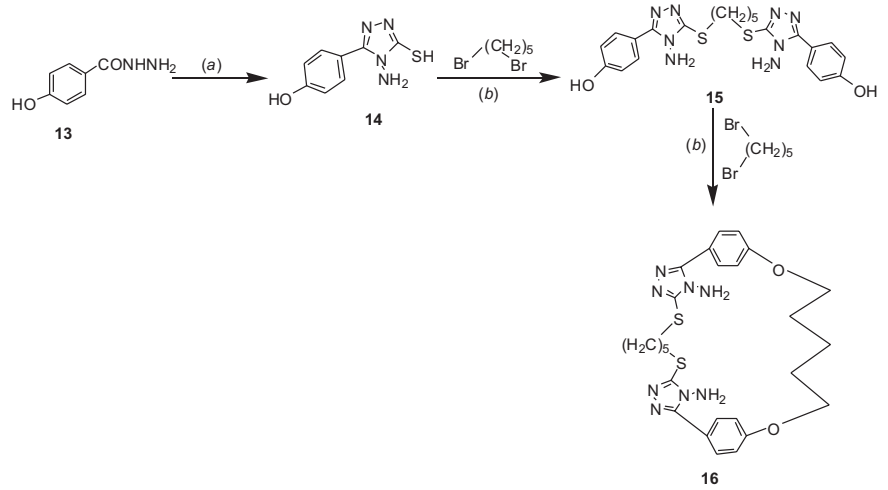
Stereochemistry

The stereochemistry of these *N*-aminotriazolophanes was studied using ^{1}H NMR spectral analysis and molecular modeling studies (35). It was observed that in compounds **5a**–**5g**,

Scheme 3. Synthesis of *N*-aminotriazolophanes **12.** Reagents and conditions: (*a*) CS_2, $(NH_2)_2{\cdot}H_2O$, KOH, MeOH, 0–5 °C, (*b*) KOH, aq. MeOH (80%), 80 °C.



Scheme 4. Synthesis of *N*-aminotriazolophanes **16.** Reagents and conditions: (*a*) CS_2, $(NH_2)_2{\cdot}H_2O$, KOH, MeOH, 0–5 °C, (*b*) KOH, aq. MeOH (80%), 80 °C.



8a–**8c**, and **8e** both N-NH_2 groups appeared as a single peak in the ^{1}H NMR, indicating that both N-NH_2 groups are cis to each other. This was also supported by the molecular modeling study. For compounds **5h**, **8d**, and **8f** (Fig. 1), two different peaks were observed for the N-NH_2 groups, indicating the presence of these groups in different magnetic environments. This showed that both N-NH_2 groups are trans to each other. The molecular model of **5h**, **8d**, and **8f** (Fig.1) showed that one of the NH_2 groups was hydrogen bonded to lone pairs of the ring nitrogen atoms, thus changing the magnetic environment.

Conclusion

In this paper, we have reported on a versatile and convenient route for the synthesis of novel *N*-aminotriazolophanes from aliphatic and aromatic acid hydrazides. For compounds **5h**, **8d**, and **8f**, both N-NH_2 groups are observed in different magnetic environments.

Experimental

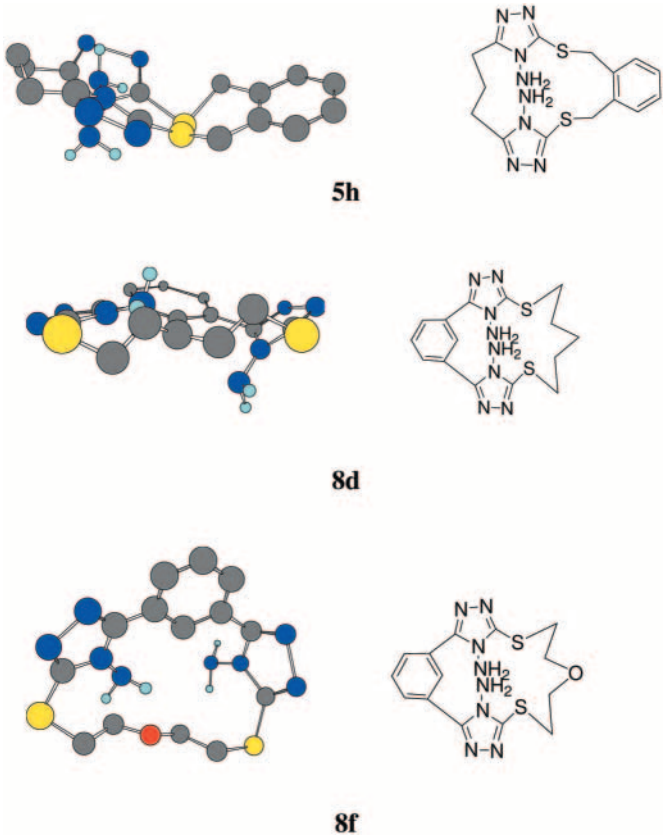
General procedure for the synthesis of bis-(4-amino-5-mercapto-1,2,4-triazol-3yl)alkanes (3a–3c)

Compounds **3a**–**3c** were synthesized using a method from the literature [31].

General procedure for the synthesis of 5a–5h, 8a–8f, 11, 12a-12c, 15, and 16

Compounds **3a**–**3c**, **7**, **10**, **11**, **14**, and **15** (for the synthesis of **5a**–**5h, 8a**–**8f, 11, 12a**–**12b, 15** and **16**, respectively) (0.01 mol) were dissolved in aq. methanol (methanol–water, 80:20, 200 mL) containing potassium hydroxide (0.02 mol). A solution of 1,ω-dihaloalkane (0.01 mol) in methanol was

Fig. 1. Stereochemistry of *N*-aminotriazolophanes.



added dropwise for 1 h. This reaction mixture was then refluxed with stirring on a magnetic stirrer for 8 h. On cooling to 10–15 °C, solid separated out. The obtained solid was then filtered, washed with cold water, and recrystallized from aq. dimethyl formamide (DMF).

$1^4,4^4$-Diamino-5,9-dithia-1,4(3,5)-di(1,2,4-triazola)cyclononaphane (5a)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.04 (p, 2H, CH_2), 3.21 (s, 4H, 2 × CH_2), 3.33 (t, 4H, 2 × S-CH_2), 5.95 (s, 4H, 2 × NH_2, D_2O exchangeable). ^{13}C NMR could not be scanned because of poor solubility.

$1^4,4^4$-Diamino-5,10-dithia-1,4(3,5)-di(1,2,4-triazola)cyclodecaphane (5b)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.78 (p, 4H, 2 × CH_2), 3.12 (s, 4H, 2 × CH_2), 3.33 (t, 4H, 2 × S-CH_2), 5.95 (s, 4H, 2 × NH_2, D_2O exchangeable). ^{13}C NMR (500 MHz, DMSO-d_6, ppm) δ: 21.0, 28.1 (4 × CH_2), 30.3 (2 × S-CH_2), 151.2 (2 × S-C=N), 155.3 (2 × C=N).

$1^4,5^4$-Diamino-6,9-dithia-1,5(3,5)-di(1,2,4-triazola)cyclononaphane (5c)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.38 (p, 2H, CH_2), 2.78 (t, 4H, 2 × CH_2), 3.37 (t, 4H, 2 × S-CH_2), 5.14 (s, 4H, 2 × NH_2, D_2O exchangeable). ^{13}C NMR (500 MHz, DMSO-d_6, ppm) δ: 22.1, 24.5, 29.7, (5 × CH_2), 148.7 (2 × S-C=N), 156.8 (2 × C=N).

$1^4,5^4$-Diamino-6,10-dithia-1,5(3,5)-di(1,2,4-triazola)cyclodecaphane (5d)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.75 (p, 2H, CH_2), 2.05 (p, 2H, CH_2), 2.75 (t, 4H, 2 × CH_2), 3.11 (t, 4H, 2 × S-CH_2), 5.87 (s, 4H, 2 × NH_2, D_2O exchangeable). ^{13}C NMR could not be scanned because of poor solubility.

$1^4,5^4$-Diamino-6,11-dithia-1,5(3,5)-di(1,2,4-triazola)cycloundecaphane (5e)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.74 (m, 4H, 2 × CH_2), 2.03 (p, 2H, CH_2), 2.70 (t, 4H, 2 × CH_2), 3.07 (t, 4H, 2 × S-CH_2), 5.80 (s, 4H, 2 × NH_2, D_2O exchangeable). ^{13}C NMR could not be scanned because of poor solubility.

$1^4,6^4$-Diamino-7,10-dithia-1,6(3,5)-di(1,2,4-triazola)cyclodecaphane (5f)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.88 (m, 4H, 2 × CH_2), 2.51 (m, 4H, 2 × CH_2), 2.89 (t, 4H, 2 × S-CH_2), 5.75 (s, 4H, 2 × NH_2, D_2O exchangeable). ^{13}C NMR could not be scanned because of poor solubility.

$1^4,6^4$-Diamino-7,11-dithia-1,6(3,5)-di(1,2,4-triazola)cycloundecaphane (5g)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.70 (m, 4H, 2 × CH_2), 2.02 (p, 2H, CH_2), 2.69 (m, 4H, 2 × CH_2), 3.33 (t, 4H, 2 × S-CH_2), 5.85 (s, 4H, 2 × NH_2, D_2O exchangeable). ^{13}C NMR could not be scanned because of poor solubility.

$1^4,5^4$-Diamino-8(1,2)-benzena-6,10-dithia-1,5(3,5)-di(1,2,4-triazola)cyclodecaphane (5h)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.02 (p, 2H, CH_2), 2.70 (t, 4H, 2 × CH_2), 4.45 (s, 4H, 2 × S-CH_2), 5.81(s, 2H, NH_2, D_2O exchangeable), 5.85(s, 2H, NH_2, D_2O exchangeable), 7.16–7.33 (d, 4H, aromatic H). ^{13}C NMR (500 MHz, DMSO-d_6, ppm) δ: 22.1, 24.0, 33.5 (5 × CH_2), 126.9, 130.8, 135.5 (aromatic C), 152.8 (2 × S-C=N), 160.7 (2 × C=N).

$1^4,3^4$-Diamino-2(1,3)-benzena-4,7-dithia-1,3(3,5)-di(1,2,4-triazola)cycloheptaphane (8a)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.89 (s, 4H, 2 × S-CH_2), 5.03 (s, 4H, 2 × NH_2, D_2O exchangeable), 6.84–7.56 (m, 4H, aromatic H). ^{13}C NMR (300 MHz, DMSO-d_6, ppm) δ: 30.0 (2 × S-CH_2), 127.1, 128.7, 130.1, 131.2 (aromatic C), 144.4 (2 × S-C=N), 153.7 (2 × C=N).

$1^4,3^4$-Diamino-2(1,3)-benzena-4,8-dithia-1,3(3,5)-di(1,2,4-triazola)cycloctaphane (8b)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.96 (p, 2H, CH_2), 3.86 (t, 4H, 2 × S-CH_2), 5.51 (s, 4H, 2 × N-NH_2, D_2O exchangeable), 7.63 – 8.57 (m, 4H, aromatic H). MS (DI) *m/z*: 346 (M^+), 322, 304, 284, 243, 202, 129, 102, 91, 76, 59.

$1^4,3^4$-Diamino-2(1,3)-benzena-4,9-dithia-1,3(3,5)-di(1,2,4-triazola)cyclononaphane (8c)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.06 (m, 4H, 2 × CH_2), 3.86 (t, 4H, 2 × S-CH_2), 6.18 (s, 4H, 2 × NH_2, D_2O exchangeable), 7.62 – 8.54 (m, 4H, aromatic H). ^{13}C NMR (500 MHz, DMSO-d_6, ppm) δ: 28.3 (2 × CH_2), 30.6, 30.7 (2 × S-CH_2), 127.1 – 134.3 (aromatic C), 141.3 (2 × S-C=N), 153.8 (2 × C=N). MS (DI) *m/z*: 360 (M^+), 330, 298, 256, 202, 171, 156, 143, 129, 102, 91, 77.

1^4,3^4-Diamino-2(1,3)-benzena-4,10-dithia-1,3(3,5)-di(1,2,4-triazola)cyclodecaphane (8d)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.29 (m, 2H, CH_2), 1.69 (m, 4H, 2 × CH_2), 3.13 (t, 4H, 2 × S-CH_2), 6.11 (s, 4H, 2 × NH_2, D_2O exchangeable), 7.38- 7.81 (m, 4H, aromatic H). MS (DI) *m/z*: 374 (M^+), 358, 324, 304, 182, 144, 128, 102, 91, 80, 77.

1^4,3^4-Diamino-2(1,3)-6(1,2)-dibenzena-4,8-dithia-1,3(3,5)-di(1,2,4-triazola)cyclooctaphane (8e)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.69 (t, 4H, 2 × S-CH_2), 6.21 (d, 4H, 2 × NH_2, D_2O exchangeable), 7.31- 8.61 (m, 8H, aromatic H). ^{13}C NMR (500 MHz, DMSO-d_6, ppm) δ: 32.6 (2 × S-CH_2), 127.1, 128.1, 128.8, 130.6, 131.2, 132.1, 135.6 (aromatic C), 147.5 (2 × S-C=N), 159.2 (2 × C=N). MS (DI) *m/z*: 408 (M^+), 322, 304, 288, 250, 220, 216, 192, 180, 128, 102, 90, 76.

1^4,3^4-Diamino-2(1,3)-benzena-7-oxa-4,10-dithia-1,3(3,5)-di(1,2,4-triazola)cyclodecaphane (8f)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.08 (t, 2H, S-CH_2), 3.54 (t, 2H, O-CH_2), 5.90 (s, 2H, NH_2, D_2O exchangeable), 5.94 (s, 2H, NH_2, D_2O exchangeable), 7.40- 8.55 (m, 4H, aromatic H). ^{13}C NMR (500 MHz, DMSO-d_6, ppm) δ: 31.2 (2 × S-CH_2), 69.2, 70.7 (O-CH_2), 127.6, 129.3, 129.6, 131.3 (aromatic C), 154.1 (2 × S-C=N), 163.2 (2 × C=N). MS (DI) *m/z*: 376 (M^+), 299, 267, 223, 208, 170, 128, 102, 91, 76, 66.

1,3-Di-[4-amino-5(2′-hydroxyphenyl)-1,2,4-triazol-3-yl]mercapto propane (11)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.22 (p, 2H, CH_2), 3.37 (t, 4H, 2 × S-CH_2) 6.06 (s, 4H, 2 × NH_2, D_2O exchangeable), 6.97–7.93 (m, 8H, aromatic H), 11.11 (s, 2H, 2 × OH, D_2O exchangeable). ^{13}C NMR (500 MHz, DMSO-d_6, ppm) δ: 29.5 (CH_2), 30.2 (2 × S-CH_2), 113.2, 116.9, 119.6, 129.7, 131.9, 156.2 (aromatic C), 153.9 (2 × S-C=N), 154.0 (2 × C=N).

1^4,9^4-Diamino-2,8(1,2)-dibenzena-3,7-dioxa-10,14-dithia-1(3,5)9(5,3)-di(1,2,4-triazola)cyclotetradecaphane (12a)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.73 (p, 2H, CH_2), 1.12 (p, 2H, CH_2), 3.66 (t, 4H, 2 × S-CH_2), 4.08 (t, 4H, 2 × O-CH_2), 5.17 (s, 4H, 2 × NH_2, D_2O exchangeable), 6.87 – 7.45 (m, 8 H, aromatic H). MS (DI) *m/z*: 496 (M^+), 480, 443, 405, 318, 209, 167, 91, 84, 77.

1^4,9^4-Diamino-2,8(1,2)-dibenzena-3,7-dioxa-10,14-dithia-1(3,5)9(5,3)-di(1,2,4-triazola)cyclotetradecaphane (12b)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.12 (p, 2H, CH_2), 3.66 (t, 4H, 2 × S-CH_2), 4.03 (t, 8H, 4 × O-CH_2), 5.62 (s, 4H, 2 × NH_2, D_2O exchangeable), 7.03–7.46(m, 8 H, aromatic H).

1,5-Di-[4-amino-5-(2′-hydroxyphenyl)-1,2,4-triazol-3-yl]mercapto pentane (15)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.56 (p, 2H, CH_2), 1.75 (p, 4H, 2 × CH_2), 3.16 (t, 4H, 2 × S-CH_2), 6.01 (s, 4H, 2 × NH_2, D_2O exchangeable), 6.86–7.80 (dd, 8 H, aromatic H), 9.89 (s, 2H, 2 × OH, D_2O exchangeable). ^{13}C NMR (500 MHz, DMSO-d_6, ppm) 27.1, 28.6 (3 × CH_2), 30.9 (2 × S-CH_2), 115.2, 117.7, 129.4, 138.7 (aromatic C), 152.7 (2 × S-C=N), 154.0 (2 × C=N).

1^4,11^4-Diamino-2,10(1,4)-dibenzena-3,9-dioxa-12,18-dithia-1(3,5)11(5,3)-di(1,2,4-triazola)cyclooctadecaphane (16)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.20 (p, 2H, CH_2), 1.43 (p, 2H, CH_2), 1.53 (p, 4H, 2 × CH_2), 3.12 (t, 4H, 2 × S-CH_2), 4.00 (t, 4H, 2 × O-CH_2), 6.00 (s, 4H, 2 × NH_2, D_2O exchangeable), 6.82–7.88 (dd, 8 H, aromatic H). MS (DI) *m/z*: 552 (M^+), 536, 520, 489, 446, 412, 396, 292, 239, 198, 137, 101, 91, 77.

General procedure for the synthesis of 7

Isophthalic acid dihydrazide **6** (0.01 mol) was dissolved in ethanol (20 mL) in the presence of potassium hydroxide (0.02 mol) and cooled to 5 °C. To this cold solution was added carbon disulphide (0.02 mol) under stirring. The potassium dithiacarbamate salt precipitated out and was filtered, washed with petroleum ether, and dried. This salt was fused with hydrazine hydrate (99%, 0.022 mol) at 90 °C for 4 h. The reaction mixture was poured onto cold water and filtered to remove traces of inorganic material. The filtrate was then treated with dilute hydrochloric acid until the pH of the solution became neutral. The obtained white product was then filtered, washed with cold water, and recrystallized from aq. DMF.

1,3-Bis-(4′-amino-5′-mercapto-1,2,4-triazol-3-yl)benzene (7)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.72 (s, 4H, 2 × NH_2, D_2O exchangeable), 7.65- 8.41 (m, 4H, aromatic H), 13.98 (s, 2H, 2 × NH, D_2O exchangeable). ^{13}C NMR (500 MHz, DMSO-d_6, ppm) δ: 126.1, 127.4, 128.6, 129.8 (aromatic C), 148.8 (2 × C=N), 167.1 (2 × C=S).

General procedure for the synthesis of 10 and 14

Salicylic acid hydrazide **9** and *p*-hydroxy benzoic acid hydrazide **13** (for **10** and **14,** respectively) (0.01 mole) were dissolved in ethanol (20 mL) in the presence of potassium hydroxide (0.02 mole) and cooled to 5 °C. To this cold solution was added carbon disulphide (0.01 mole) under stirring. The potassium dithiacarbamate salt precipitated out and was filtered, washed with petroleum ether, and dried. This salt was fused with hydrazine hydrate (99%, 0.011 mole) at 90 °C for 4 h. The reaction mixture was then poured onto cold water and filtered to remove traces of inorganic material. The filtrate was treated with dilute hydrochloric acid until the pH of the solution became neutral. The obtained white product was then filtered, washed with cold water, and recrystallized from aq. DMF.

4-Amino-5(2′-hydroxyphenyl)-3-meracpto-1,2,4-triazole (10)

^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.63 (s, 4H, 2 × NH_2, D_2O exchangeable) 6.92–7.44 (m, 4H, aromatic H), 10.37 (s, 1H, OH, D_2O exchangeable), 13.896 (s, 1H, S=C-NH, D_2O exchangeable). ^{13}C NMR (500 MHz, DMSO-d_6, ppm) 113.1, 116.2, 119.0, 130.9, 132.9, 156.1 (aromatic C), 149.2 (2 × C=N), 165.1 (2 × C=S).

4-Amino-5(4′-hydroxyphenyl)-3-meracpto-1,2,4-triazole (14)

^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.73 (s, 4H 2 × N-NH_2, D_2O exchangeable), 6.85, 7.84 (dd, 4H, aromatic H), 10.02 (s, 1H, OH, D_2O exchangeable), 13.76 (s, 1H, S=C-NH, D_2O exchangeable). ^{13}C NMR (300 MHz, DMSO-d_6, ppm) 115.3, 116.5, 129.7, 159.4 (aromatic C), 149.6 (2 × C=N), 166.4 (2 × C=S).

Acknowledgement

The help rendered by the Regional Sophisticated Instrumentation Centres (RSIC), the Indian Istitute of Technology (IIT), and the Tata Institute of Fundamental Research (TIFR), the Department of Chemistry, University of Pune, and the Department of Chemistry, Institute of Science, Mumbai, are gratefully acknowledged. We also thank "Lady Tata memorial trust" for their financial support.

References

1. (*a*) E. Graf and J.M. Lehn. Helv. Chim. Acta, **64**, 1040 (1981); (*b*) B. Dietrich, M.W. Hosseini, J.M. Lehn, and R.B. Session. Helv. Chim. Acta, **66**, 1262 (1983); (*c*) M.W. Hosseini, J.M. Lehn, and M.P. Mertes. Helv. Chim. Acta, **66**, 2444 (1983); (*d*) A. Kumar, S. Mageswaran, and I.O. Sutherland. Tetrahedron, **42**, 3291 (1986); (*e*) J.S. Bradshaw and R.M. Izatt. Acc. Chem. Res. **30**, 338 (1997).
2. (*a*) G.R. Newkome, J.G. Traynham, and G.R. Baker. *In* Crown ethers and cryptands in compendium of heterocyclic compounds. Vol. 5. *Edited by* A.R. Katritzky. Pergamon Press, London, U.K. 1984. p. 763; (*b*) Phase transfer catalysis, fundamentals, applications and industrial perspective. *Edited by* C.M. Stark, C. Liotta, and M. Halpern. Chapman and Hall, New York. 1994.
3. J.S. Bradshaw, R.M. Izzat, A.V. Bordunov, C.Y. Zhu, and J.K. Hathaway. *In* Comprehensive supramolecular chemistry. Vol. 1. *Edited by* G.W. Gokel. Pergamon Press, New York. 1996. p. 35.
4. C.J. Pedersen. J. Am. Chem. Soc. **89**, 2495 (1970).
5. (*a*) H. Singh, L.D.S. Yadav, and B.K. Bhattacharya. J. Indian Chem. Soc. **56**, 1013 (1979); (*b*) N.C. Desai. Indian J. Chem. Sect. B, **32**, 343 (1993); (*c*) X.M. Feng, R. Chen, X.C. Liu, and Z.Y. Zhang. Chin. J. Appl. Chem. **8**, 28 (1991); (*d*) P.S. Upadhyay, R.N. Vansdadia, and A.J. Baxi. Indian J. Chem. Sect. B, **29**, 793 (1990); (*e*) J. Mohan, G.S.R. Anjaneyula, S. Sudhir, and D.R. Arora. J. Indian Chem. Soc. **66**, 330 (1989); (*f*) M.M. Ghorab, Sh. A.M. El-Sharief, Y.A. Ammar, and Sh. I. Mohamed. Farmaco, **55**, 354 (2000).
6. Z.Y. Zhang, X.L. Chen, L. Wei, and Z.L. Ma. Chem. Res. Chin. Univ. **7**, 129 (1991).
7. Y. Naito, F. Akahoshi, S. Takeda, T. Okada, M. Kajii, H. Nishimura, M. Sugiura, C. Fukaya, and Y. Kagitani. J. Med. Chem. **39**, 3019 (1996).
8. (*a*) A.S. Narang and R. Vince. J. Med. Chem. **20**, 1684 (1977); (*b*) E. De Clercq. J. Clin. Virol. **30**, 115 (2004).
9. (*a*) X. Collin, A. Sauleau, and J. Coulon. Bioorg. Med. Chem. Lett. **13**, 2601 (2003); (*b*) B.S. Holla and B. Kalluraya. Indian J. Chem. Sect. B, **27**, 683 (1988); (*c*) S. Giri, H. Singh, L.D.S. Yadav, and R.K. Khare. J. Indian Chem. Soc. **55**, 168 (1978).
10. M. Kidwai, P. Sapra, P. Misra, R.K. Saxena, and M. Singh. Bioorg. Med. Chem. **9**, 217 (2001).
11. (*a*) T. George, D.V. Mehta, R. Tahilramani, J. David, and P.K. Talwalker. J. Med. Chem. **14**, 335 (1971); (*b*) S. Papakonstantinou-Garoufalias, N. Pouli, P. Marakos, and A. Chytyroglou-Ladas. Farmaco, **57**, 973 (2002); (*c*) A.K. Sengupta and H.K. Misra. J. Indian Chem. Soc. **58,** 508 (1981).
12. M.M. Ghorab, S.G. Abdel- Hamide, M.S.A. El-Gaby, and S.M. El- Sayed. Acta Pharm. **49**, 1 (1999).
13. C.S. Andotra and S.K. Sharma. Proc. Natl. Acad. Sci. India Sect. A, **58**, 215 (1988).
14. J.B. Hester, A.D. Rudzik, and B.V. Kamdar. J. Med. Chem. **14**, 1078 (1977).
15. N.G.N. Milton. Neurotoxicology, **22**, 767 (2001).
16. (*a*) G. Burell, J.M. Evans, M.S. Hadley, F. Hicks, and G. Stemp. Bioorg. Med. Chem. Lett. **4**, 1285 (1994); (*b*) M.M. Ghorab, S.G. Abdel-Hamide, G.M. Ali, El Sayed, and H. Shaurub. Pestic. Sci. **48**, 31 (1996); (*c*) M.K. Mody, A.R. Prasad, T. Ramalingham, and P.B. Suttur. J. Indian Chem. Soc. **59**, 769 (1982).
17. (*a*) J.H. Wadsworth, S.M. Jenkins, B.S. Orlek, F. Cassidy, M.S.G. Clark, F. Brown, G.J. Riley, D. Graves, J. Hawkins, and C.B. Naylor. J. Med. Chem. **35**, 1280 (1992); (*b*) S.M. Jenkins, H. Wadsworth, S. Bromidge, B.S. Orlek, P.A. Wyman, G.J. Riley, and J. Hawkins. J. Med. Chem. **35**, 2392 (1992); (*c*) C. Chen, R. Dagnino, C.Q. Huang, J.R. McCarthy, D.E. Grigoriadis. Bioorg. Med. Chem. Lett. **11**, 3165 (2001); (*d*) B. Neumann-Schultz, L. Unger, K. Blumbach, D. Starck, D. Schoebel, and H. Treiber. International Patent WO-2000-0042038, 20 August 2000.
18. S.K. Thompson, A.M. Eppley, J.S. Frazee, M.G. Darcy, R.T. Lum, T.A. Tomaszeck, L.A. Ivanoff, J.F. Morris, E.J. Sternberg, D.M. Lambert, A.V. Fernandez, S.R. Patteway, T.D. Meek, B.W. Metcalf, and J.G. Gleason. Bioorg. Med. Chem. Lett. **4**, 2441 (1994).
19. J.V. Duncia, J.B. Santella, C.A. Higley, M.K. VanAtten, P.C. Weber, R.S. Alexander, C.A. Kettner, J.R. Pruitt, A.Y. Liauw, M.L. Quan, R.M. Knabb, and R.R. Wexler. Bioorg. Med. Chem. Lett. **8**, 775 (1998).
20. K.T. Potts. Chem. Rev. **61**, 87 (1961).
21. (*a*) M.S. Chande, A.A. Godbole, and C. Sajithkumar. Heteroat. Chem. **14**, 273 (2003); (*b*) M.S. Chande, A.A. Godbole, E. Coutinho, and P. Desai. Indian J. Chem. Sect. B, **42**, 397 (2002).
22. (*a*) M.S. Chande and S.S. Athalye. Synth. Commun. **29**, 1711 (1999); (*b*) M.S. Chande, and S.S. Athalye. Synth. Commun. **30**, 1667 (2000); (*c*) M.S. Chande, S.S. Athalye, and A.A. Godbole. Indian J. Chem. Sect. B, **43**, 670 (2004); (*d*) M.S. Chande, M.H. Uchil, and P.A. Barve. Heteroat. Chem. **17**, 329 (2006).
23. A.R. Katritzky, B.V. Rogovoy, V.Y. Vvedensky, K. Kovalenko, P.J. Steel, V.I. Markov, and B. Forood. Synthesis, **6**, 897 (2001).
24. (*a*) L. Ventura, J.A. Perez-Gonzales, and D. Ramon. FEMS Microbiol. Lett. **149**, 207 (1997); (*b*) G. Stemp and G. Burrell. Eur. Patent Appl. EP399834, 28 November 1990; (*c*) J.W. Clitherow. Eur. Patent Appl. EP367484, 9 May 1990.
25. (*a*) K. Wermann, M. Hartmann, and H.J. Bauer. Z. Chem. **24**, 120 (1984); (*b*) M. Hartmann, H.J. Bauer, and K. Wermann. Polym. Bull. 195 (1985); (*c*) J.L. Hilton. J. Agric. Food Chem. **17**, 182 (1969); (*c*) S.A. Lang and B.L. Walworth. US. Patent 4-169-838, 2 October 1979.
26. (*a*) B. Mernari, H. Elattari, M. Traisnel, F. Bentiss, and M. Lagrenee. Corros. Sci. **40**, 391 (1998); (*b*) F. Bentiss, M. Lagrenee, M. Traisnel, and J.C. Hornez. Corros. Sci. **41**, 789 (1999).

27. (*a*) B.S. Holla, B.M. Veerendra, K. Shivananda, and N.S. Kumari. Indian J. Chem. Sect. B, **43**, 2010 (2003); (*b*) B.S. Holla and R. Gonsalves. Boll. Chem. Farm. **137**, 467 (1998); (*c*) B.S. Holla, R. Gonsalves, and S. Shenoy. Farmaco, **53**, 574 (1998).
28. G.W. Gokel, D.M. Dishang, and C.J. Dimond. J. Chem. Soc. Chem. Commun. 1053 (1980).
29. (*a*) E. Muller and L. Herrdegen. J. Prackt. Chem. **102**, 113 (1921); (*b*) F. Dallacker. Monatsh. Chem. **91**, 294 (1960); (*c*) W.W. Zajact, J.F. Siuda, M.J. Nolan, and T.M. Santossusso. J. Org. Chem. **36**, 3539 (1971); (*d*) M.O. Abdel-Rahman, M.A.M. Kira, and N. Tolba. Tetrahedron Lett. **9**, 3871 (1968); (*e*) R.A. Bowie, M.D. Gardner, D.G. Neilson, K.M. Watson, S. Mahmood, V.J. Ridd. J. Chem. Soc. Perkin Trans. 1, 2395 (1972); (*f*) J.F. Geldard and F.J. Lions. J. Org. Chem. **30**, 318 (1965); (*g*) K. Matsukawa, J. Setsune, K. Takagi, and T. Kitao. Dyes Pigm. **3**, 307 (1982); (*h*) F. Bentiss, M. Lagrenee, M. Traisnel, B. Mernari, and H. Elattari. J. Heterocycl. Chem. **36**, 149 (1999); (*i*) F. Bentiss, M. Lagrenee, and D. Barbry. Tetrahedron Lett. **41**, 1539 (2000).
30. P.-F. Xu, X.-W. Sun, L.-M. Zhang, and Z.-Y. Zhang. J. Chem. Res. Synop. **2**, 170 (1999).
31. (*a*) D.H. Busch. Rec. Chem. Prog. **25**, 107 (1965); (*b*) D.H. Busch and L.H. Lindoy. Preparative inorganic reactions. Vol. 6. *Edited by* W.L. Jolly. Wiley-Interscience, New York. 1971.
32. For nomenclature please see: (*a*) W.H. Powell. Pure Appl. Chem. **70**, 1513 (1998); (*b*) H.A. Favre, D. Hellwinkel, W.H. Powel, and H.A. Smith. Pure Appl. Chem. **74**, 809 (2002).
33. A. Dubey, S. Kumar, and K. Naresh. Indian J. Heterocycl. Chem. **3**, 277 (1994).
34. J.R. Reid and N.D. Heindel. J. Heterocycl. Chem. **13**, 925 (1976).
35. CS Chem 3D Pro [computer program]. Version 5. CambridgeSoft, Cambridge, Mass. 1999.