Eur. J. Med. Chem. 36 (2001) 651–658

PII: S0223-5234(01)01256-9/FLA

Original article

Synthesis of novel tetrahydroimidazole derivatives and studies for their biological properties

Vibha Sharma*, M.S.Y. Khan

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Hamdard University, New Delhi, India

Received 19 June 2000; revised 18 June 2001; accepted 19 June 2001

Abstract – Ethylenediamine was reacted with suitable aromatic aldehydes in order to prepare their respective diSchiff bases. These compounds were then reduced to give the corresponding tetrahydrodiSchiff bases, which were low melting in nature. Finally, these derivatives were condensed with different aromatic aldehydes to give the desired tetrahydroimidazoles. The structures of all these compounds were established on the basis of spectral data. These novel tetrahydroimidazoles showed promising anti-inflammatory and analgesic activity. The compounds were also screened for their anti-bacterial property against *Staphylococcus aureus* and *Escherichia coli*. © 2001 Éditions scientifiques et médicales Elsevier SAS

diSchiff base / tetrahydrodiSchiff base / tetrahydroimidazole / anti-inflammatory / analgesic

1. Introduction

A diversity of useful biological effects is possessed by heterocyclic compounds containing the five-membered imidazole nucleus. A variety of drugs from anti-microbials (metronidazole, ketocanazole), cardiovascular (clonidine, naphazoline), centrally active (benperidol, fenmetozole) to anti-cancer (dacarbazine, misonidazole) are examples of this. The ring system itself is primarily a molecular scaffold upon which characteristic pharmacophores for various receptors are assembled. In view of the wide spectrum of useful biological activities of imidazole compounds further exploratory synthesis of compounds built up on imidazole skeleton was done. Present studies were devoted to the syntheses and pharmacological evaluation of tetrahydroimidazoles. These compounds have been an area of considerable recent research [1–8]. In the study, aromatic aldehydes were reacted with ethylenediamine to give their respective diSchiff bases, which were reduced with sodium borohydride to form tetrahydrodiSchiff bases, All tetrahydrodiSchiff bases except that derived from salicylaldehyde were semi-solid in character, Finally these derivatives were condensed with aromatic aldehydes to give new functional derivatives of *N*,*N*′-di-aryl-methyl-2-(4-diethylamino phenyl) tetrahydroimidazole and *N*,*N*′-di-4-diethylamino benzyl-2-(aryl) tetrahydroimidazole derivatives.

* Correspondence and reprints
E-mail address: vibhasharma@worldnet.att.net (V. Sharma).

2. Chemistry

The synthesis of *N*,*N*′-di-aryl-methyl-2-(4-diethylamino phenyl) tetrahydroimidazole and *N*,*N*′-di-4-diethylamino benzyl-2-(aryl) tetrahydroimidazole has been carried out following the steps shown in *figure 1*.

In the first step, aromatic aldehydes were reacted with ethylenediamine to give their respective diSchiff bases, **1**, **4**, **7**, **10**, **13**, **16**, **19**, **22**, **25**, **28** and **31**. Reduction of the diSchiff bases by sodium borohydride (step II) gave tetrahydrodiSchiff bases **2**, **5**, **8**, **11**, **14**, **17**, **20**, **23**, **26**, **29** and **32**. The compounds obtained were viscous in nature except the compound **29**, which was crystalline. The tetrahydrodiSchiff bases were condensed with different aromatic aldehydes in step III to obtain the desired tetrahydroimi-

dazole derivatives **3**, **6**, **9**, **12**, **15**, **18**, **21**, **24**, **27**, **30**, **33**, **34**, **35**, **36** and **37**. For step III, two methods were followed as described in Section 5. Physico-chemical data for the synthesized compounds are summarized in *tables I and II*.

3. Pharmacology

The synthesized tetrahydroimidazole derivatives were tested for their anti-inflammatory and analgesic potential. The anti-inflammatory activity of the compounds as measured by their ability to inhibit carrageenan-induced edema in rats, is given in *table III*. The compounds were evaluated for their analgesic activity by tail immersion method in mice at three time points. These derivatives were also casually tested for any hint of potential anti-bacterial activity against ATCC strains of *Staphylococcus aureus* and *Escherichia coli* at a dose of 100 μg mL^{-1}, as reported in *table III*.

4. Results and discussion

4.1. Anti-inflammatory activity

Fourteen compounds were screened for their anti-inflammatory activity. Percent inhibition was computed by comparing individual values in treatment groups to the mean value of the control group. The compound **21** showed maximum percentage reduction in edema volume followed by compounds **9** and **37**. Other compounds with significant activity were **6**, **15**, and **30**. These compounds were compared with the standard indomethacin at a dose of 20 mg kg^{-1} i.p.

4.2. Analgesic activity

The synthesized compounds were tested for their potential analgesic effect by comparing with aspirin at a dose of 25 mg kg^{-1} i.p. at three time points. Compound **21** showed maximum activity at 30 and 60 min. The compounds **35**, **12**, **18**, **9** and **37** showed significant good activity as compared to the standard.

4.3. Anti-bacterial activity

Twelve compounds of tetrahydroimidazole series were screened for their anti-bacterial activity against ATCC strains of both *S. aureus* and *E. coli* bacteria. Compound **36** showed good activity against both the strains while other tested compounds exhibited a degree of microbial inhibition against *S. aureus*. The compounds were compared with norfloxacin at the concentration of 100 μg mL^{-1} with dimethyl formamide (DMF) as control.

5. Experimental protocols

5.1. Chemistry

Melting points of all the compounds were taken on a liquid paraffin bath in open capillary tubes and are uncorrected. Purity of the compounds was tested on thin

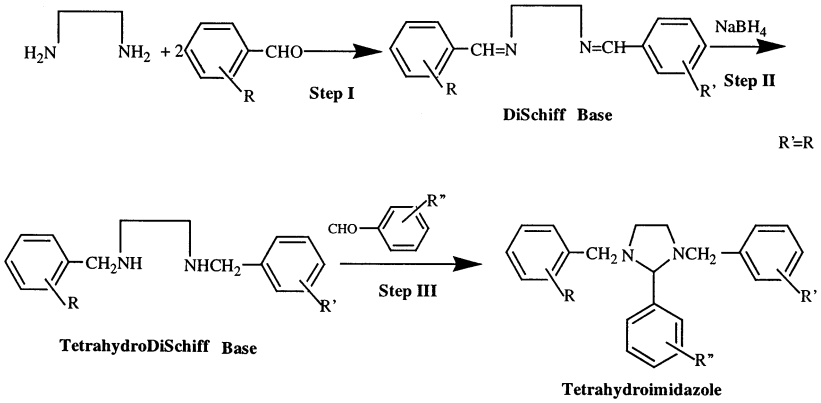
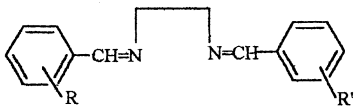
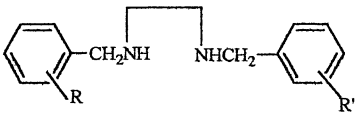


Figure 1. Steps involved in the synthesis of tetrahydroimidazole.

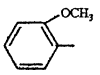
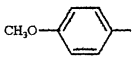
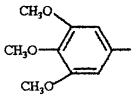
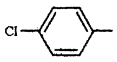
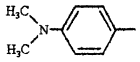
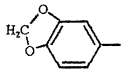
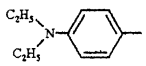
Table 1. Physico-chemical data of diSchiff and tetrahydrodiSchiff compounds.



DiSchiff Base

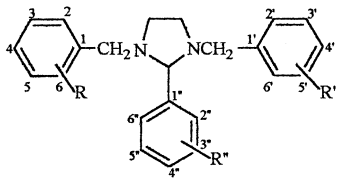


TetrahydroDiSchiff Base

Compound	R, R′	Yield (%)	M.P. (°C)	Formula	Compound	Yield (%)	M.P. (°C)	Formula
1		67	150-2	$C_{16}H_{16}N_2$	2	62	Semi solid	$C_{16}H_{20}N_2$
4		80	116-8	$C_{18}H_{20}N_2O_2$	5	75	Semi solid	$C_{18}H_{24}N_2O_2$
7		78	104	$C_{18}H_{20}N_2O_2$	8	78	Semi solid	$C_{18}H_{24}N_2O_2$
10		76	133-4	$C_{22}H_{28}N_2O_6$	11	84	Semi solid	$C_{22}H_{32}N_2O_6$
13		77	84-8	$C_{16}H_{14}N_2Cl_2$	14	70	Semi solid	$C_{16}H_{18}N_2Cl_2$
16		83	146-8	$C_{16}H_{14}N_2Cl_2$	17	72	Semi solid	$C_{16}H_{18}N_2Cl_2$
19		80	173-4	$C_{20}H_{26}N_4$	20	68	Semi solid	$C_{20}H_{30}N_4$
22		79	82-4	$C_{12}H_{12}N_2S_2$	23	75	Semi solid	$C_{12}H_{16}N_2S_2$
25		87	174-6	$C_{18}H_{16}N_2O_4$	26	72	Semi solid	$C_{18}H_{20}N_2O_4$
28		83	120-2	$C_{16}H_{16}N_2O_2$	29	70	114	$C_{16}H_{20}N_2O_2$
31		71	114-6	$C_{24}H_{34}N_4$	32	70	Semi solid	$C_{24}H_{38}N_4$

layer chromatography (TLC) plates (silica gel G.E. Merck) in the solvent system benzene–ethanol (8:2). The spots were located under UV light and/or by exposure to iodine vapors. ^{1}H-NMR spectra were recorded on 60, 90 or 300 MHz instruments using Me_4Si as an internal standard. The chemical shift values have been recorded in δ values. Mass spectra of the compounds were recorded on JEOL JMS-D 300 instruments.

Table II. Physico-chemical data of tetrahydroimidazoles.



Tetrahydroimidazole

Compound	R, R′	R″	Yield (%)	M.P. (°C)	Formula
3	Phenyl	4-diethylamino phenyl	65	80-2	$C_{27}H_{33}N_3$
6	2-methoxy phenyl	4-diethylamino phenyl	77	146	$C_{29}H_{37}N_3O_2$
9	4-methoxy phenyl	4-diethylamino phenyl	76	102	$C_{29}H_{37}N_3O_2$
12	3,4,5-trimethoxy phenyl	4-diethylamino phenyl	70	148	$C_{33}H_{45}N_3O_6$
15	2-chloro phenyl	4-diethylamino phenyl	78	126	$C_{27}H_{31}N_3Cl_2$
18	4-chloro phenyl	4-diethylamino phenyl	70	100	$C_{27}H_{31}N_3Cl_2$
21	4-dimethyl amino phenyl	4-diethylamino phenyl	79	140	$C_{31}H_{43}N_5$
24	2-thienyl	4-diethylamino phenyl	70	86	$C_{23}H_{29}N_3S_2$
27	3, 4-methylene dioxy phenyl	4-diethylamino phenyl	70	104	$C_{29}H_{33}N_3O_4$
30	2-hydroxy phenyl	4-diethylamino phenyl	62	156	$C_{27}H_{33}N_3O_2$
33	4-diethylamino phenyl	2-methoxy phenyl	69	60	$C_{32}H_{44}N_4O$
34	4-diethylamino phenyl	2-chloro phenyl	76	68	$C_{31}H_{41}N_4Cl$
35	4-diethylamino phenyl	4-chloro phenyl	78	98-102	$C_{31}H_{41}N_4Cl$
36	4-diethylamino phenyl	3, 4-methylene dioxy phenyl	76	80	$C_{32}H_{42}N_4O_2$
37	4-diethylamino phenyl	4-dimethyl amino phenyl	79	80	$C_{33}H_{47}N_5$

Table III. Anti-inflammatory, analgesic and anti-bacterial properties of tetrahydroimidazoles.

Compound	Anti-inflammatory activity Percentage inhibition against carrageenan induced edema		Analgesic activity Tail flick latency			Anti-bacterial activity Cup plate method	
	At 60 min	At 180 min	At 30 min	At 60 min	At 120 min	*Escherichia coli* (ATCC)	*Staphylococcus aureus* (ATCC)
3	0	4	3.25 ± 1.5	2.25 ± 0.5	2.8 ± 1.26	++	+++
6	60	75	3.33 ± 1.5	3.5 ± 1.3	2.75 ± 0.957	++	+++
9	90	82	5 ± 3.56	5 ± 3.37	3.1 ± 1.64	++	++
12	20	7	6.25 ± 0.96	3.5 ± 0.58	3.75 ± 1.5	+	+++
15	68	61	3.25 ± 0.95	2.5 ± 0.58	2.75 ± 1.26	+	+++
18	15	0	4.0 ± 0.82	5.0 ± 2.2	4.25 ± 0.95	NS	NS
21	93	96	5.25 ± 1.26	7.67 ± 6.66	3.75 ± 1.5	NS	NS
24	63	46	4.25 ± 0.96	3.5 ± 0.58	3.25 ± 1.26	++	++
27	15	10	4.5 ± 0.58	3.8 ± 1.7	3.75 ± 1.5	+	+++
30	65	64	3.25 ± 1.5	3.5 ± 1.73	3.0 ± 1.15	−	+++
33	50	50	3.25 ± 1.26	2.25 ± 1.5	2.25 ± 0.96	+	+++
35	47	7	5.0 ± 2.8	7.5 ± 2.08	4.25 ± 4.72	+	+++
36	48	77	3.5 ± 2.08	3.75 ± 1.5	2.75 ± 0.95	+++	+++
37	87	93	4.75 ± 0.96	4.25 ± 1.5	3.0 ± 0.82	+	+++
Standard	40	64	3.5 ± 0.58	4.0 ± 0.82	5.2 ± 1.3	+++	+++

Zone of inhibition observed (+); no zone of inhibition observed (−). Zone of inhibition: +, 7–9 cm; ++, 10–13 cm; +++, 14 cm and above; NS, not screened.

5.1.1. General procedure for the synthesis of diSchiff base from ethylenediamine and an appropriate aldehyde

A solution of an appropriate aromatic aldehyde (0.02 mol) and ethylenediamine (in slight excess of molar ratio) in dry benzene (50 mL)with a small quantity of molecular sieves (4 Å) was refluxed azeotropically with Dean–Stark apparatus. After complete removal of water the reaction mixture was refluxed for further 7 h or until TLC showed the reaction to be complete. On completion of reaction, excess benzene was distilled off. A solid mass so obtained was crystallized from methanol.

*5.1.1.1. Dibenzylidene ethylenediamine (**1**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 3.95 (s, 4H, $2\times CH_2$), 7.35(m, 6H, H aromatic), 7.67 (m, 4H, H aromatic), 8.25 (s, 2H, aldimine protons).

*5.1.1.2. Di-4-methoxy benzylidene ethylenediamine (**7**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 3.77(s, 6H, $2\times OCH_3$), 3.90 (s, 4H, $2\times CH_2$), 6.87 (d, 4H, A_2/B_2 pattern, H aromatic), 7.62 (d, 4H, A_2/B_2 pattern, H aromatic), 8.25(s, 2H, aldimine protons).

*5.1.1.3. Di-3,4,5-trimethoxy benzylidene ethylenediamine (**10**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 3.88 (s, 18H, $6\times OCH_3$), 3.94 (s, 4H, $2\times CH_2$), 6.95(s, 4H, H aromatic), 8.17(s, 2H, aldimine protons).

*5.1.1.4. Di-2-chloro benzylidene ethylenediamine (**13**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 4.03 (s, 4H, $2\times CH_2$), 7.9 (m, 8H, H aromatic), 8.72(s, 2H, aldimine protons).

*5.1.1.5. Di-4-chloro benzylidene ethylenediamine (**16**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 3.95(s, 4H, $2\times CH_2$), 7.34(d, 4H, H aromatic), 7.63 (d, $J=9$ Hz, 4H, H aromatic), 8.22(s, 2H, aldimine protons).

*5.1.1.6. Di-4-dimethylamino benzylidene ethylenediamine (**19**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 2.97(s, 12H, $4\times CH_3$), 3.66 (s, 4H, $2\times CH_2$), 6.64 (d, 4H, A_2/B_2 pattern, H aromatic), 7.56(d, 4H, $J=9$ Hz, A_2/B_2 pattern, H aromatic), 8.15 (s, 2H, aldimine protons).

*5.1.1.7. Di-2-thienylidene ethylenediamine (**22**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 3.88 (s, 4H, $2\times CH_2$), 6.9 (m, 2H, H-4,4′), 7.2(m, 2H, H-5,5′), 7.33(m, 2H, H-3,3′), 8.15 (s, 2H, aldimine protons).

*5.1.1.8. Di-3,4-methylene dioxy benzylidene ethylenediamine (**25**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 3.87(s, 4H, $2\times CH_2$), 6.0 (s, 4H, $2\times OCH_2O$), 6.8 (d, $J=8$ Hz, 2H, H-5,5′), 7.058 (dd, $J=1.5$, 9 Hz, 2H, H-6,6′), 7.58 (d, 2H, H-2,2′), 8.15 (s, 2H, aldimine protons).

*5.1.1.9. Di-2-hydroxy benzylidene ethylenediamine (**28**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 3.87 (s, 4H, $2\times CH_2$), 6.8 (dt, 2H, H-5,5′), 6.94 (dd, 2H, H-3,3′), 7.18 (dd, 2H, H-6,6′), 7.27 (m, 2H, H-4,4′), 8.3 (s, 2H, aldimine protons).

*5.1.1.10. Di-4-diethylamino benzylidene ethylenediamine (**31**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 1.13 (t, 12H, $4\times CH_2CH_3$), 3.34 (q, 8H, $4\times CH_2CH_3$), 3.85 (s, 4H, $2\times CH_2$), 6.61 (d, 4H, A_2/B_2 pattern, H aromatic), 7.56 (d, $J=9$ Hz, 4H, A_2/B_2 pattern, H aromatic), 7.56 (s, 2H, aldimine protons).

5.1.2. General procedure for synthesis of tetrahydrodiSchiff's base from diSchiff's base

DiSchiff base (1.0 g) was dissolved in a mixture of methanol (15 mL) and dichloromethane (10 mL). A solution of sodium borohydride (0.5 g) in 2 N NaOH (1 mL) after dilution with distilled water (6 mL) was added dropwise to the solution of diSchiff base with constant magnetic stirring under ice-cold conditions to keep the temperature of the reaction mixture below 18 °C. The contents were stirred for 7 h or until TLC showed the reaction to be complete. After completion of the reaction, the solvent was distilled off and the residue diluted with water and extracted with ether. The ethereal layer was dried over sodium sulfate, filtered to remove inorganic salt and ether was distilled off to give the expected compound. The compounds obtained were semi-solid in nature with the exception of tetrahydrodiSchiff base, *N*,*N*′-di-2-hydroxy benzyl ethylenediamine (**29**).

*5.1.2.1. N,N′-di-2-hydroxy benzyl ethylenediamine (**29**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 2.80 (s, 4H, $2\times CH_2$), 3.96 (s, 4H, $2\times NCH_2$), 6.7 (dt, 2H, H-5,5′), 6.83 (dd, 2H, H-3,3′), 6.97 (dd, 2H, H-6,6′), 7.16 (dt, 2H, H-4,4′).

5.1.3. General procedure for the synthesis of tetrahydroimidazole from tetrahydrodiSchiff's base

5.1.3.1. Method 1

TetrahydrodiSchiff base (2 mmol) was dissolved in ethanol (which had been purified by distilling over

NaOH) (15mL) in a test tube. To this solution was added an appropriate aromatic aldehyde (2 mmol). The test tube was shaken on a wrist action shaker till a solid mass separated out which was filtered and washed with ether. It was crystallized from ethanol.

5.1.3.2. Method 2

TetrahydrodiSchiff base (2 mmol) and an appropriate aldehyde (2 mmol) were taken in dry benzene (50 mL) in a round-bottom flask. A Dean–Stark apparatus was fitted on the flask along with an air condenser. The reaction mixture was refluxed to remove water azeotropically. The Dean–Stark apparatus was dismantled after complete removal of water and the reaction mixture was refluxed for further 7 h for completion of the reaction. Benzene was then distilled off and a solid mass so obtained was crystallized to give the expected tetrahydroimidazole derivative.

5.1.3.3. N,N′-dibenzyl-2-(4-diethylamino phenyl) tetrahydroimidazole ***(3)***

^{1}H-NMR ($CDCl_3$), δ ppm: 1.15 (t, 6H, $2\times CH_3CH_2$), 3.32 (q, 4H, $2\times CH_3CH_2$), 2.42 (m, 2H, CH_2 tetrahydroimidazole), 3.10 (m, 2H, CH_2 tetrahydroimidazole), 3.12 (d, 2H, CH_2 benzyl), 3.84 (d, 2H, CH_2 benzyl), 3.69 (s, H, CH tetrahydroimidazole), 6.67 (d, 2H, A_2/B_2 pattern, H aromatic), 7.44 (d, 2H, A_2/B_2 pattern, H aromatic), 7.22 (m, H aromatic). Molecular formula $C_{27}H_{33}N_3$ (M^+) 399, *m*/*z* 309, 252, 190, 163.

5.1.3.4. N,N′-di-2-methoxy benzyl-2-(4-diethylamino phenyl) tetrahydroimidazole ***(6)***

^{1}H-NMR ($CDCl_3$), δ ppm: 1.109 (t, 6H, $2\times CH_3CH_2$), 3.30 (m, 4H, $2\times CH_3CH_2$), 2.45, 3.30(m, 4H, $2\times CH_2$ tetrahydroimidazole), 3.4 (d, 2H, CH_2 benzyl), 3.67 (d, 2H, CH_2 benzyl), 3.7 (s, 6H, $2\times OCH_3$), 3.8 (s, H, CH tetrahydroimidazole), 6.62 (d, 2H, H-3,3′), 6.72 (d, 2H, *p*-disubst. phenyl ring), 6.68 (m, 2H, H-5,5′), 7.11(m, 2H, 4,4′), 7.42 (m, 4H, H-6,6′ and protons of *p*-disubst. phenyl ring). Molecular formula $C_{29}H_{37}N_3O_2$ (M^+) 459, *m*/*z* 338, 310, 189, 162, 121.

5.1.3.5. N,N′-di-4-methoxy benzyl-2-(4-diethylamino phenyl) tetrahydroimidazole ***(9)***

^{1}H-NMR ($CDCl_3$), δ ppm: 1.17 (t, 6H, $2\times CH_3CH_2$), 3.34 (q, 4H, $2\times CH_3CH_2$), 2.40 (m, 2H, CH_2 tetrahydroimidazole,), 3.11 (m, 2H, CH_2 tetrahydroimidazole), 3.08 (m, 2H, CH_2 benzyl), 3.75 (m, 2H, CH_2 benzyl), 3.8 (s, 6H, $2\times OCH_3$), 3.64 (s, 1H, CH of tetrahydroimidazole), 6.68 (d, 2H, A_2/B_2 pattern, H aromatic), 7.42 (d, 2H, A_2/B_2 pattern, H aromatic), 6.77 (d, 4H, A_2/B_2 pattern, *p*-anisidine moiety), 7.18 (d, 4H, A_2/B_2 pattern, *p*-anisidine moiety). Molecular formula $C_{29}H_{37}N_3O_2$ (M^+) 459, *m*/*z* 338, 310, 189, 162 and 121.

5.1.3.6. N,N′-di-3,4,5-trimethoxy benzyl-2-(4-diethylamino phenyl) tetrahydroimidazole ***(12)***

^{1}H-NMR ($CDCl_3$), δ ppm: 1.16 (t, 6H, $2\times CH_3CH_2$), 3.25 (q, 4H, $2\times CH_3CH_2$), 2.5, 3.2 (m, 4H, $2\times CH_2$ of tetrahydroimidazole), 3.14, 3.71 (d, 4H, $2\times CH_2$ benzyl), 3.79 (s, 19H, $6\times OCH_3$, CH tetrahydroimidazole), 6.48 (d, 4H, H-2,2′, 6,6′), 6.68, (d, 2H, A_2/B_2 pattern, H aromatic), 7.42 (d, 2H, A_2/B_2 pattern, H aromatic). Molecular formula $C_{33}H_{45}N_3O_6$ (M^+) 579, *m*/*z* 550, 431, 400 and 398.

5.1.3.7. N,N′-di-2-chloro benzyl-2-(4-diethylamino phenyl) tetrahydroimidazole ***(15)***

^{1}H-NMR ($CDCl_3$), δ ppm: 1.14 (t, 6H, $2\times CH_3CH_2$), 3.33 (q, 4H, $2\times CH_3CH_2$), 2.5, 3.2 (m, 4H, $2\times CH_2$ of tetrahydroimidazole), 3.45, 3.76 (d, 4H, $2\times CH_2$ benzyl), 3.87 (s, 1H, CH tetrahydroimidazole), 6.68 (d, 2H, A_2/B_2 pattern, H aromatic), 7.42 (d, 2H, A_2/B_2 pattern, H aromatic), 7.17 (m, 6H, H-4,4′, H-5,5′, H-6,6′), 7.53 (dd, 2H, H-3,3′).

Molecular formula: $C_{27}H_{31}N_3Cl_2$, a cluster of peaks were located at *m*/*z* 467, 469 and 471 due to the presence of two chlorine atoms in the molecule. The other peaks could be located at *m*/*z* 342, 323/321/319, 189 and 125/126.

5.1.3.8. N,N′-di-4-chloro benzyl-2-(4-diethylamino phenyl) tetrahydroimidazole ***(18)***

^{1}H-NMR ($CDCl_3$), δ ppm: 1.13 (t, 6H, $2\times CH_3CH_2$), 3.33 (q, 4H, $2\times CH_3CH_2$), 2.38, 3.09 (m, 4H, $2\times CH_2$ of tetrahydroimidazole), 3.74 (m, 4H, $2\times CH_2$ benzyl), 3.66 (s, 1H, CH of tetrahydroimidazole), 6.66, 7.39 (d, 4H, $J = 9$ Hz, A_2/B_2 pattern, H aromatic), 7.19 (s, 8H, protons of *p*-chloro phenyl ring).

5.1.3.9. N,N′-di-4-dimethylamino benzyl-2-(4-diethylamino phenyl) tetrahydroimidazole ***(21)***

^{1}H-NMR ($CDCl_3$), δ ppm: 1.17 (t, 6H, $2\times CH_3CH_2$), 3.36 (q, 4H, $2\times CH_3CH_2$), 2.89(s, 12H, $4\times CH_3$), 2.4–3.7 (m, 9H, $2\times CH_2$ benzyl, $2\times CH_2$, CH of tetrahydroimidazole), 6.65 (d, 8H, A_2/B_2 pattern, H aromatic), 6.69, 7.14 (d, 4H, A_2/B_2 pattern, H aromatic). Molecular formula $C_{31}H_{43}N_5$ (M^+) 485, *m*/*z* 364, 351, 203, 189, 162 and 134.

*5.1.3.10. N,N′-di-2-thienylmethyl-2-(4-diethylamino phenyl) tetrahydroimidazole (**24**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 1.13 (t, 6H, 2×CH_3CH_2), 3.30 (q, 4H, 2×CH_3CH_2), 2.54, 3.25 (m, 4H, 2×CH_2 of tetrahydroimidazole), 3.51, 3.87 (d, 4H, 2×CH_2 benzyl), 3.77 (s, 1H, CH of tetrahydroimidazole), 6.67, 7.42 (d, 4H, A_2/B_2 pattern, H aromatic), 6.86 (m, 4H, H-3,3′, H-4,4′), 7.14 (d, 2H, H-5,5′). Molecular formula $C_{23}H_{29}N_3S_2$ (M^+) 411, *m*/*z* 314, 263, 189, 162 and 97.

*5.1.3.11. N,N′-di-3,4-methylene dioxy benzyl-2-(4-diethylamino phenyl tetrahydroimidazole (**27**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 1.16 (t, 6H, 2×CH_3CH_2), 3.33 (q, 4H, 2×CH_3CH_2), 2.41, 3.13 (m, 4H, 2×CH_2 of tetrahydroimidazole), 3.05, 3.70 (d, 4H, 2×CH_2 benzyl), 3.62 (s, 1H, CH of tetrahydroimidazole), 5.87 (s, 4H, 2×OCH_2O), 6.65, 7.39 (d, 4H, A_2/B_2 pattern, H aromatic), 6.78 (d, 2H, H-2,2′), 6.67 (m, 4H, H-3,3′, 6,6′). Molecular formula $C_{29}H_{33}N_3O_4$ (M^+) 487, *m*/*z* 352, 339, 189, 162 and 77.

*5.1.3.12. N,N′-di-2-hydroxybenzyl-2-(4-diethylamino phenyl) tetrahydroimidazole (**30**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 1.13 (t, 6H, CH_3CH_2), 3.30 (q, 4H, CH_3CH_2), 2.58, 3.30 (m, 4H, 2×CH_2 of tetrahydroimidazole), 3.2, 4.07 (m, 4H, 2×CH_2 benzyl), 6.66, 7.3(d, 4H, A_2/B_2 pattern, H aromatic), 6.93 (dd, 2H, H-3,3′), 7.12 (dt, 2H, H-4,4′), 6.7 (dt, 2H, H-5,5′), 6.8(dd, H-6,6′). Molecular formula $C_{27}H_{33}N_3O_2$ (M^+) 431, *m*/*z*, 324, 283, 189, 162, 107 and 77.

*5.1.3.13. N,N′-di-4-diethylamino benzyl-2-(2-methoxy phenyl) tetrahydroimidazole (**33**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 1.11 (t, 12H, 4×CH_3CH_2), 3.26 (q, 8H, 4×CH_3CH_2), 2.49, 3.26 (m, 4H, 2×CH_2 of tetrahydroimidazole), 3.13, 3.64(d, 4H, 2×CH_2 benzyl), 3.61 (s, 1H, CH of tetrahydroimidazole), 3.80 (s, 3H, OCH_3), 6.54, 7.05 (d, 8H, A_2/B_2 pattern, H aromatic), 6.8 (dd, 1H, H-3″), 7.02 (m, 1H, H-5″), 7.24(dt, 1H, H-4″), 8.0 (dd, 1H, H-6″). Molecular formula $C_{32}H_{44}N_4O$ (M^+) 500, *m*/*z* 394, 352, 296, 204, 190, 162 and 118.

*5.1.3.14. N,N′-di-4-diethylamino benzyl-2-(2-chloro phenyl) tetrahydroimidazole (**34**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 1.11 (t, 12H, 4×CH_3CH_2), 3.28 (q, 8H, 4×CH_3CH_2), 2.53, 3.12 (m, 4H, 2×CH_2 of tetrahydroimidazole), 3.17, 3.67 (d, 4H, 2×CH_2 benzyl), 4.54 (s, 1H, CH of tetrahydroimidazole), 6.57, 7.04 (d, 8H, A_2/B_2 pattern, H aromatic), 7.30 (m, 3H, H-4″, H-5″, H-6″), 8.04(dd, 1H, H-3″).

*5.1.3.15. N,N′-di-4-diethylamino benzyl-2-(4-chloro phenyl) tetrahydroimidazole (**35**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 1.09 (t, 12H, 4×CH_3CH_2), 3.26 (q, 8H, 4×CH_3CH_2), 2.48, 3.17 (m, 4H, 2×CH_2 of tetrahydroimidazole), 3.15, 3.63 (d, 4H, 2×CH_2 benzyl), 3.7 (s, 1H, CH), 8.5, 7.02 (d, 8H, A_2/B_2 pattern, H aromatic), 7.31, 7.52 (d, 4H, A_2/B_2 pattern, H aromatic). Molecular formula $C_{31}H_{41}N_4Cl$ (M^+) 504, *m*/*z* 393, 355, 342, 189, 162, 147 and 118.

*5.1.3.16. N,N′-di-4-diethylamino benzyl-2-(3,4-methylene dioxy phenyl) tetrahydroimidazole (**36**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 1.12 (t, 12H, 4×CH_3CH_2), 3.28 (q, 8H, 4×CH_3CH_2), 4.49, 3.12 (m, 4H, 2×CH_2 of tetrahydroimidazole), 3.05, 3.68 (m, 4H, 2×CH_2 benzyl), 3.67 (s, 1H, CH of tetrahydroimidazole), 5.95 (s, 2H, OCH_2O), 6.56, 7.01 (d, 8H, A_2/B_2 pattern, H aromatic), 6.74(d, 1H, H-5″), 6.94(dd, 1H, H-6″), 7.26 (d, 1H, H-2″). Molecular formula $C_{32}H_{42}N_4O_2$ (M^+) 514, *m*/*z* 393, 379, 366, 352, 295, 203, 162, 147 and 118.

*5.1.3.17. N,N′-di-4-diethylamino benzyl-2-(4-dimethylamino phenyl) tetrahydroimidazole (**37**)*

^{1}H-NMR ($CDCl_3$), δ ppm: 1.07 (t, 12H, 4×CH_3CH_2), 3.27 (q, 8H, 4×CH_3CH_2), 2.43, 3.13 (m, 4H, 2×CH_2 of tetrahydroimidazole), 3.06, 3.6 (d, 4H, 2×CH_2 benzyl), 3.65 (s, 1H, CH of tetrahydroimidazole), 6.55, 7.06 (d, 8H, A_2/B_2 pattern, H aromatic), 6.75, 7.48 (d, 4H, H aromatic). Molecular formula $C_{33}H_{47}N_5$ (M^+) 513, *m*/*z* 393, 379, 364, 351, 295 and 162.

5.2. Biology

5.2.1. Study of the anti-inflammatory activity

Study of the anti-inflammatory activity was carried out according to Winter's method [9].

The studies were carried out on healthy rats of either sex, weighing between 120 and 200 g. All the test compounds and drugs were suspended in 2% gum acacia and were prepared on the day of experiment. The animals were weighed, numbered and divided into different groups comprising six rats in each group. A mark was made on the left hind paw to ensure constant paw volume. The initial paw volume of each animal was measured by the mercury displacement method. In one group, normal saline was injected which acted as control and to the other groups, the test compounds and stan-

dard drug indomethacin at the dose of 20 mg kg^{-1} were administered intraperitoneally. After 30 min, 0.1 mL of a 1% (w/v) carrageenan suspension in 0.9% saline solution was injected subcutaneously into the sub plantar region of the left hind paw of all the animals. The paw volume was determined plethysmographically at 60 and 180 min after carrageenan injection and the percent anti-inflammatory activity calculated in comparison to the standard drug at the same dose level. Results are expressed as percentage inhibition of the edema.

5.2.2. Study of the analgesic activity

The analgesic activity of the test compounds was evaluated by the tail immersion method [10]. Albino mice of either sex, weighing 25–30 g were selected for testing by immersing the tail in hot water at a temperature 55±5 °C and the basal reaction time was noted. The mice, which showed a positive response within a 2–5 s time duration for withdrawal of the tail clearly out of water, were taken for further studies. The time after which the mouse tried to remove the tail was taken as the end point. Any animal not responding within 2–5 s was rejected from the study. Each group was administered a different test compound and a standard drug, aspirin, as 2% acacia suspension intaperitoneally. To one group normal saline was injected which acted as a control. Immediately after administration of the drug and at intervals of 30, 60 and 120 min, the reaction time was recorded. As the reaction time reached 12 s, it was considered maximum analgesia and the tail was removed from the hot water to avoid tissue damage.

5.2.3. Study of the anti-bacterial activity

The microbiological testing of the synthesized compounds was done by cup plate method on ATCC bacterial strains of *S. aureus* and *E. coli*. Stock solutions of the compounds were freshly prepared (1 mg mL^{-1}) in DMF just before the experiment. Meat peptone agar medium was used for the experiment. Washed microorganisms were added into sterile and cooled media at 45 °C and these seeded media were poured into plates and allowed to solidify. A stainless steel cylinder of 8 mm diameter (pre-sterilized) was used to bore the cavities. All the synthesized compounds (100 μg mL^{-1}) mentioned in *table III* were placed serially in the cavities with the help of micropipettes and allowed to diffuse for 1 h. These plates were incubated at 37 °C for 24 h. DMF was poured as a control. The plates were observed after 24 h. The zone of inhibition observed is indicated by (+) sign, (−) sign indicates no zone of inhibition.

Acknowledgements

One of the authors (V.S.) is thankful to C.S.I.R., New Delhi, India, for the award of a senior research fellowship.

References

[1] Comley J.C.W., Court J.P., Gutteridge W.E., Hudson A.T., Jenkins D.C., Miller D.D., Nicol R.H., Randall A.W., Stables J.N., Thornton R., Eur. J. Med. Chem. 27 (1992) 503–509.

[2] Kalyanam N., Parthasarathy P.C., Ananthan L., Manjunatha S.G., Likhate M.A., Indian J. Chem. 31B (1992) 243–247.

[3] Klutchko S., Hodges J.C., Blankley C.., Colbry N.L., J. Heterocycl. Chem 28 (1991) 97–108.

[4] Besse R., Garratt P.J., Hobbs C.J., Rogers H.M., Sueleiman A.M., Walpole C.S.J., Wrigglesworth R., Tetrahedron 46 (1990) 7803–7812.

[5] Qing N., Colebrook L.D., Edward J.T., Kon A., Chubb F.L., Can. J. Chem. 67 (1989) 1560–1564.

[6] Bell A.S., Campbell S.F., Roberts D.A., Ruddock K.S., J. Med. Chem 32 (1989) 2042–2049.

[7] Jivespaa A.O., Jarumilinta R., Indian J. Chem. 21B (1982) 923–927.

[8] Cai J.-C., Pan J.-L., Ren Y.-F., Yao Hsueh Hsueh Pao 14 (1979) 52–54.

[9] Winter C.A., Riseley E.A., Nuss G.W., Proc. Soc. Exp. Biol. Med. 111 (1962) 544–547.

[10] Sewell R.D., Spencer P.S., Neuropharmacology 15 (1976) 683–688.