Synthesis of *N*-Substituted Piperazinyl Carbamoyl and Acetyl Derivatives of Tetrahydropapaverine: Potent Antispasmodic Agents

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The synthesis and structure–activity-relationship (SAR) for a series of *N*-substituted piperazinyl carbamoyl 7—15 and piperazinyl acetyl 18—26 derivatives of tetrahydropapaverine have been carried out. The general synthetic methods of carbamoyl tetrahydropapaverine analogues involve *N*-substituted piperazines and carbamoyl imidazole tetrahydropapaverine as starting materials. Another route for synthesizing these compounds, involving the formation of carbamoyl imidazole piperazine has also been explored. Acylation of tetrahydropapaverine followed by substitution with various piperazinyl moities afforded the acetyl tetrahydropapaverine derivatives. Variously substituted piperazines have been used to monitor the effect of electron releasing and electron withdrawing substituents upon the antispasmodic activity of the molecules. Effect of varying electron densities on the antispasmodic activity, by altering the position of these groups on the benzene ring has also been monitored. Pharmacological methods involve the *in vitro* antispasmodic activity studies on a freshly removed guinea pig ileum using a force displacement transducer amplifier connected to a physiograph. Among the analogues synthesized in the present study, a promising compound 7, a potent muscle relaxant as compared to papaverine has been obtained.

Key words isoquinoline; antispasmodic; piperazine; papaverine; urea

An abnormal spasm in gastrointestinal, uretral and utrine smooth muscles is the most frequent cause of abdominal discomfort. The causative factor for the spasm is not clearly understood. Generally, drugs like anticholinergics and nonspecific smooth muscle relaxants have been used clinically to relieve the symptoms. Atropine-like antispasmodics do not show selectivity towards a particular muscarinic receptor subtype and thereby they also show several side effects. Their ready penetration of the central nervous system (CNS) can give rise to undesireable CNS effects. Synthesis of quaternary ammonium salts of the free bases serves as a useful technique to avoid or minimise these side effects.[1] However, absorption after oral administration is greatly reduced in spasmolytics containing the quaternary ammonium group.

Few drugs, chemically unrelated to atropine show a direct relaxant effect on various smooth muscle types, *e.g.* papaverine, a benzylisoquinoline alkaloid, is a well known smooth muscle relaxing agent with multiple activities such as cyclic nucleotide phosphodiesterase (PDE) inhibitor and Ca^{2+} channel blocker *via* specific binding to the benzothiazepine receptor site in the Ca^{2+} channel.[2—6] Because of these multiple mechanisms it is useful as a non-specific spasmolytic agent but cannot be put to more specific use in cardiovascular and abdominal disorders.[7] However, if we take the chemical structure of papaverine as a model, we may find that small structural differences could lead to more useful compounds.

Tetrandrine, a bis-benzyltetrahydroisoquinoline alkaloid, blocks inward calcium current most likely by acting at the benzothiazepine site of L-channel.[8] It inhibits [^{3}H]-diltiazem binding competitively, partly inhibits [^{3}H]-verapamil binding and stimulates [^{3}H]-nitrendipine binding to cardiac sarcolemmal membranes. It is reported that substituted tetrahydroisoquinolines which are active in inhibiting specific [^{3}H]-nitrendipine binding to rat cerebral cortical membranes, are also able to inhibit the KCl-induced contraction of rat aorta. Also increase in the size of *N*-alkyl substituents from acetyl to propionyl, nicotinyl and finally 2-(1-piperidine)-acetyl and presence of carbonyl functionality increases the antispasmodic activity.[9] It is reported that 4-aminopiperidine ureas act as potent selective agonists of the human β_3-adrenergic receptor.[10] Substituted ureas[11] have also been of recent interest due to appearance of this functionality in drug candidates such as human immunodeficiency virus (HIV) protease inhibitors,[12—14] FKBP12 inhibitors,[15] CCKB-receptor antagonists[16,17] and endothelin antagonists.[18] Recently, Okuyama *et al.* have reported a novel Ca^{2+} channel blocker T-477 [(*R*)-(+)-2-(4-chlorophenyl)-2,3-dihydro-4-diethylaminoacetyl-4*H*-1,4-benzothiazine hydrochloride] which prevents brain edema in rats.[19] We envisaged that the two spasmophoric groups *i.e.* the tetrahydroisoquinoline moiety and the urea/amide functionality, if brought together in a single molecule can produce very good antispasmodic agents. Considering these factors and in continuation to our earlier efforts[20] to find out potent smooth muscle relaxants, we synthesized the *N*-substituted piperazinyl carbamoyl **7**—**15** and *N*-substituted piperazinyl acetyl **18**—**26** derivatives of tetrahydopapaverine and evaluated them for their antispasmodic activity.

Results and Discussion

Compounds **7**—**15** and **18**—**26** were synthesized using tetrahydropapaverine **5** as the starting material. Tetrahydropapaverine efficiently displaced one of the imidazole rings of carbonyldiimidazole to give Tetrahydropapaverine carbamoyl imidazole **6** on refluxing it with carbonyldiimidazole (CDI) in tetrahydrofuran (THF) for 24 h. The carbamoyl imidazole **6** obtained, did not require furthur purification for use in subsequent steps. Stirring of **6** with MeI (4 molar eq) in dichloromethane for 12 h at room temperature produced the imidazolium salt quantitatively. This imidazolium salt again required no additional purification for final conversion to ureas. Although the salt is hygroscopic in nature, but it could be stored for several days without detectable decomposition. Addition of 1-substituted piperazines, morpholine to a solution of imidazolium salt in dichloromethane with triethyl-

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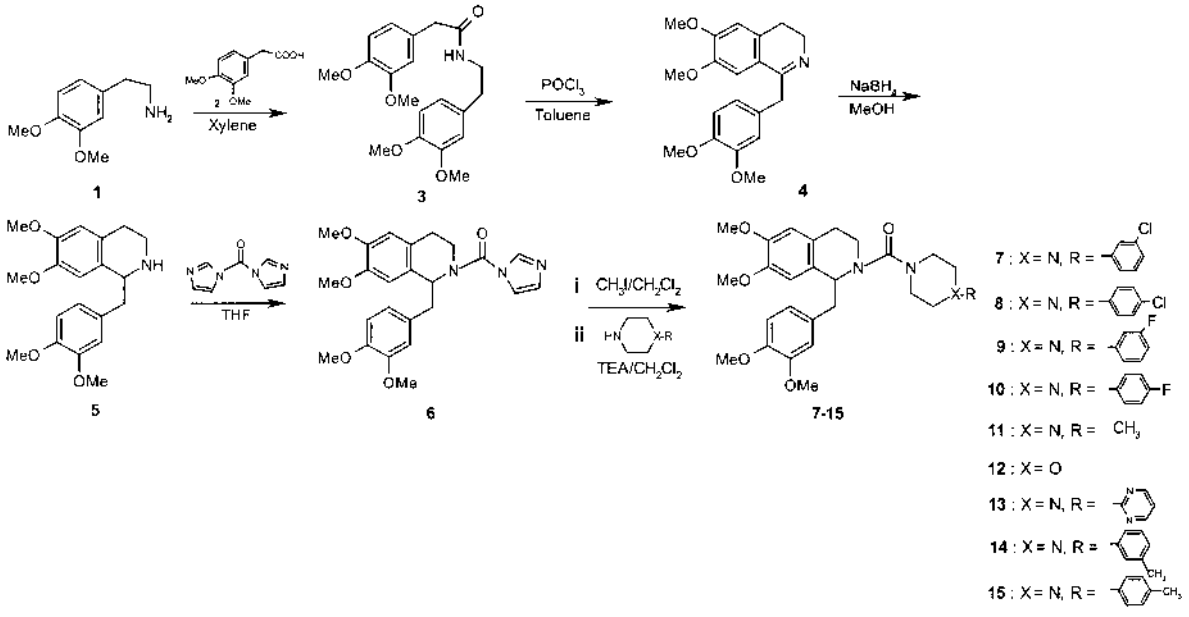


Chart 1

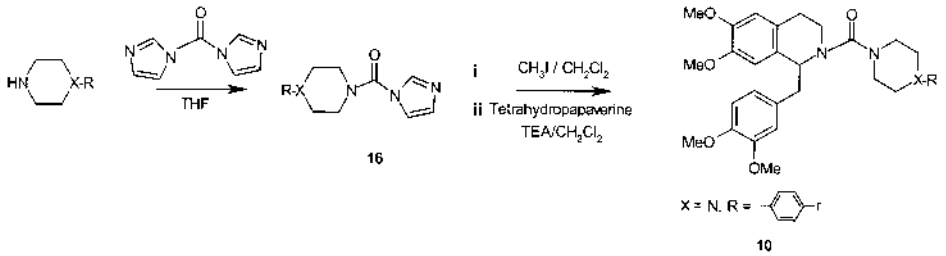


Chart 2

amine at room temparature afforded tetrasubstituted ureas **7**—**15** (Chart 1). These compounds were purified by column chromatography and obtained in 75—85% yield. The activation of the leaving imidazole ring was found to be necessary for the formation of desired ureas since the carbamoyl imidazoles were unreactive towards piperazines even under refluxing conditions for prolonged periods. Addition of triethylamine (1 molar eq) resulted in improved yields of ureas.

Another route, where the imidazole ring of carbonyldimidazole is displaced by piperazine [1-(4-fluorophenyl)piperazine] instead of tetrahydropapaverine was also tried. Cationic carbamoyl imidazolium salt of piperazine carbamoyl imidazole **16** on reaction with tetrahydropapaverine gave **10** (Chart 2) in equally good yield as obtained by the method reported in Chart 1. However, this approach was not utilized for the synthesis of other derivatives in the series as it included the formation of separate cationic carbamoyl imidazolium salt for each derivative.

Reaction of tetrahydropapaverine with chloroacetylchloride and triethylamine in dichloromethane at zero degree centigrade lead to the formation of *N*-acetylchloride tetrahydropapaverine **17**. It was purified by column chromatography and was obtained as a white crystalline solid. Stirring **17** with different piperazines, morpholine in dimethylformamide and potassium carbonate at 60 °C yielded derivatives **18**—**26** (Chart 3). These were purified by column chromatography and obtained in 70—80% yield. The compounds **7**—**15** and **18**—**26** were characterized on the basis of their ^{1}H-NMR, mass spectral data, IR absorption methods and elemental analysis. The biological data obtained for these compounds is reported in Table 1.

Amide **3** was prepared by the condensation of homoveratryl amine **1** and homoveratric acid **2** in xylene with azeotropic removal of water. Cyclization of **3** to 3,4-dihydroisoquinoline **4** was achieved in Bischler–Napierlaski fashion, in refluxing toluene with phosphorous oxychloride. Reduction of 3,4-dihydroisoquinoline with sodium borohydride in methanol resulted in the formation of tetrahydropapaverine[20,21] **5** (Chart 1).

Antispasmodic activity studies of compounds **7**—**15** and **18**—**26** were performed on guinea pig ileum. Acetylcholine was used to induce sustained contraction in guinea pig ileum. When the contraction response to acetylcholine reached a steady level, papaverine was added cumulatively. Papaverine inhibited the acetylcholine induced contraction in a concentration dependent manner. Similarly, acetylcholine induced contraction inhibition by tetrahydropapaverine derivatives **7**—**15** and **18**—**26** was studied. Dose–response curves were obtained for papaverine and the derivatives. The results showed that the test compounds **7**—**15** and **18**—**26** more potently inhibited the acetylcholine induced contractions than papaverine. Table 1 summarizes the concentration of pa-

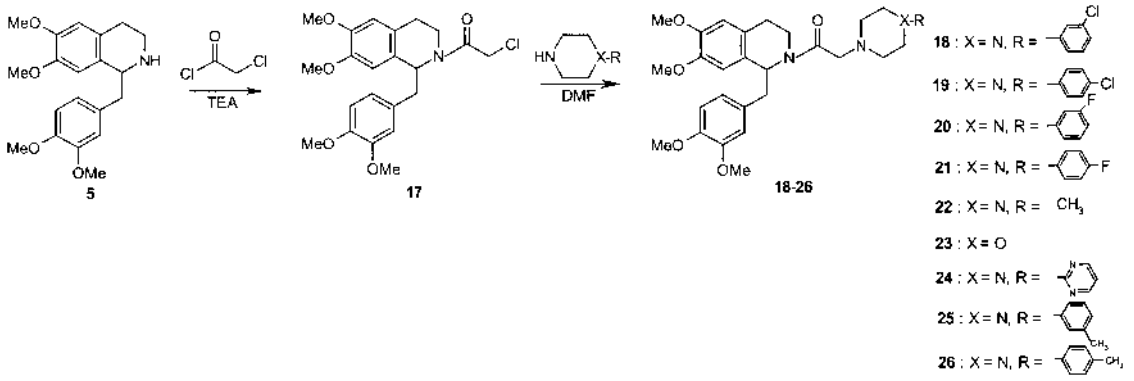
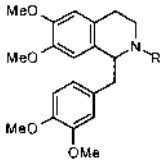
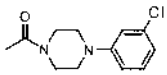
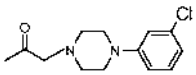
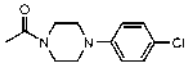
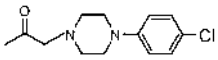
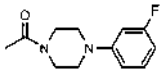
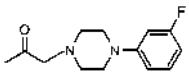
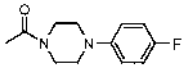
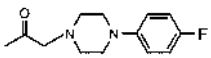
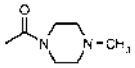
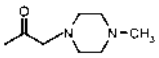
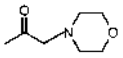
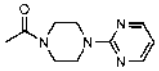
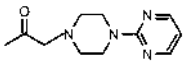
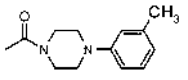
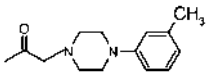
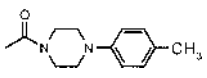
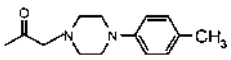


Chart 3

Table 1. Structural Formula of Tetrahydropapaverine Derivatives and Their IC_{50} in Inhibiting Acetylcholine Induced Contraction in Guinea Pig Ileum



Compound	R	IC_{50} (μM)[a]	Compound	R	IC_{50} (μM)[a]
7		0.30	**18**		0.75
8		0.35	**19**		0.81
9		0.39	**20**		1.07
10		0.41	**21**		1.13
11		2.81	**22**		3.95
12		2.76	**23**		5.11
13		1.48	**24**		4.96
14		3.06	**25**		6.21
15		3.01	**26**		6.10

a) IC_{50} of papaverine = 7.31 μM. IC_{50}s were calculated using a mean of at least 3 measurements (all duplicates) for 6 concentrations in the range 0.1—20 μM.

paverine and test compounds producing 50% relaxation (IC_{50}) of acetylcholine induced contraction. IC_{50} values were determined graphically from dose–response curves obtained by measuring antispasmodic activity at different concentrations of the compounds in duplicate of triplicates.

As compared to papaverine the *N*-substituted carbamoyl **7**—**15** and acetyl **18**—**26** derivatives of tetrahydropapaverine exhibited better antispasmodic activities. Tetrasubstituted

ureas **7**—**15** were found to be more potent as compared to amides **18**—**26**. Among the tetrasubstituted ureas, the presence of electron withdrawing groups chloro and fluoro at *meta* or *para* position of their respective phenyl rings in compounds **7**—**10** lead to more potent compounds as compared to **14** and **15** having electron releasing methyl group at *meta* and para position of phenyl ring. The compounds not having aromatic ring on *N*-substituent **11** and **12** decreased the antispasmodic activity in comparison to compounds possessing aromatic ring like **7**—**10**. Among the compounds having electron withdrawing substituents at the *meta* and *para* positions, the *meta* isomers **7** and **9** exhibited better activity in comparison to the corresponding *para* isomers **8** and **10**. However, compound **14** having electron releasing methyl group at *meta* position was found to be less active than **15** having the methyl group at *para* position.

Considering the structure of T-477 and pirenzipine[1)] (a cholinomimetic, selective to M_1 receptors), we envisaged that the addition of a CH_2 spacer in the tetrasubstituted urea molecules **7**—**15** may improve upon the muscle relaxation properties of these compounds. Correspondingly, compounds **18**—**26** with CH_2 spacer were synthesized. Though these compounds showed better antispasmodic activity in comparison to papaverine but in comparison to urea derivatives **7**—**15**, these compounds exhibited a decline in the antispasmodic activity. However, similar internal trends regarding the IC_{50} values were observed in the series of amide derivatives **18**—**26** as were found for urea derivatives **7**—**15**. Compound **7** was found to be the most potent antispasmodic agent.

Conclusion

N-Substituted tetrahydropapaverine derivatives showed better antispasmodic activity in comparison with papaverine in guinea pigs in preliminary screenings. Tetrasubstituted ureas were found to be more active than trisubstituted urea derivatives. Presence of electron withdrawing groups and aromatic ring in the *N*-substituents increased the activity. Structure activity relationship studies revealed the importance of chloro and fluro group at the 3 or 4 positions of phenyl ring. Compound **7** was found to be the most potent compound among the series.

Experimental

Melting points are recorded in open capillary tubes on Büchi melting point B-540 instrument and are uncorrected. Solvent system used throughout the experimental work for running TLC plates was ethylacetate–hexane. The ^{1}H-NMR spectra were recorded in $CDCl_3$ as solvent (using TMS as internal standard) on a Bruker Avance Spectrospin 300 instrument at 300 MHz. Mass spectra were run on a MALDI Kratos Analytical Kompact SEQ mass spectrometer using α-cyano-4-hydroxycinnamic acid (4-HCCA) as matrix under positive linear reflectance mode and JEOL JMS-DX 303 mass spectrometer. IR spectra were recorded using KBr discs on a Shimadzu FTIR-8300 spectrophotometer. Elemental analysis was carried out on Heraeus Rapid CHN analyser.

1-(3,4-Dimethoxybenzyl)-2-carbamoylimidazol-1-yl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6) To a suspension of CDI (9.73 g, 60 mmol) in THF (100 ml) was added tetrahydropapaverine **5** (18.86 g, 55 mmol). The mixture was refluxed for 24 h before cooling to room temperature. Removal of solvent under vacuum gave a viscous oil which was dissolved in CH_2Cl_2 (100 ml), and washed twice with 100 ml portions of water. The organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to yield the carbamoyl imidazole **6** and it was used in the next step without further purification (20.66 g, 83%), mp: 95—97 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.89 (2H, m), 3.25 (4H, m), 3.56 (3H, s), 3.71 (6H, s), 3.80 (3H, s), 5.15 (1H, t, J=6.0 Hz), 6.29 (1H, s), 6.56 (1H, s), 6.72 (3H, m), 7.05 (2H, m), 7.52 (1H, s). IR (KBr) cm^{-1}: 1687. MS (*m*/*z*): 438 $(M+H)^+$. *Anal.* Calcd for $C_{24}H_{27}N_3O_5$: C, 65.88; H, 6.22; N, 9.60. Found: C, 65.81; H, 6.25; N, 9.67.

1-(3,4-Dimethoxybenzyl)-2-[4-(3-chlorophenyl)piperazine-1-yl]carbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7) To a solution of **6** (3 g, 6.8 mmol) in dichloromethane (15 ml) was added methyl iodide (1.57 ml, 25.2 mmol). The mixture was stirred at room temperature for 12 h. Solvent was removed in vacuum to yield cationic carbamoyl imidazolium salt which was dissolved without purification in CH_2Cl_2 (20 ml) and mixed with 1-(3-chlorophenyl)piperazine (1.33 g, 6.8 mmol) and triethylamine (0.95 ml, 6.8 mmol). The mixture was stirred at room temperature for 12 h, then washed with 1.0 M HCl (10 ml), the organic layer dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield the required tetrasubstituted urea as an oil which was column chromatographed (ethylacetate–hexane) to obtain pure **7** (3.14 g, 84%) mp: 125—127 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.75 (8H, m), 2.97 (2H, m), 3.21 (4H, m), 3.60 (3H, s), 3.81 (6H, s), 3.83 (3H, s), 5.10 (1H, t, J=6.0 Hz), 6.29 (1H, s), 6.56 (1H, s), 6.73 (3H, m), 6.88 (4H, m). IR (KBr) cm^{-1}: 1680. MS (*m*/*z*): 566 $(M+H)^+$. *Anal.* Calcd for $C_{31}H_{36}N_3O_5Cl$: C, 65.77; H, 6.40; N, 7.42. Found: C, 65.81; H, 6.41; N, 7.45.

1-(3,4-Dimethoxybenzyl)-2-[4-(4-chlorophenyl)piperazine-1-yl]carbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8) Synthesized in a manner similar to that described for **7**. The product was obtained as a viscous oil (83%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.71 (8H, m), 2.95 (2H, m), 3.23 (4H, m), 3.64 (3H, s), 3.80 (6H, s), 3.83 (3H, s), 5.12 (1H, t, J=6.0 Hz), 6.28 (1H, s), 6.59 (1H, s), 6.72 (3H, m), 6.90 (4H, m). IR (KBr) cm^{-1}: 1675. MS (*m*/*z*): 566 $(M+H)^+$. *Anal.* Calcd for $C_{31}H_{36}N_3O_5Cl$: C, 65.77; H, 6.40; N, 7.42. Found: C, 65.80; H, 6.43; N, 7.46.

1-(3,4-Dimethoxybenzyl)-2-[4-(3-fluorophenyl)piperazine-1-yl]carbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9) Synthesized in a manner similar to that described for **7**. The product was obtained as a gummy material (82%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.75 (8H, m), 2.94 (2H, m), 3.25 (4H, m), 3.71 (3H, s), 3.87 (6H, s), 3.91 (3H, s), 5.13 (1H, t, J=6.0 Hz), 6.29 (1H, s), 6.53 (1H, s), 6.75 (3H, m), 6.89 (4H, m). IR (KBr) cm^{-1}: 1639. MS (*m*/*z*): 550 $(M+H)^+$. *Anal.* Calcd for $C_{31}H_{36}N_3O_5F$: C, 67.74; H, 6.60; N, 7.64. Found: C, 67.76; H, 6.63; N, 7.69.

1-(3,4-Dimethoxybenzyl)-2-[4-(4-fluorophenyl)piperazine-1-yl]carbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (10) Synthesized in a manner similar to that described for **7**. The product was obtained as yellow powder (81%) mp: 164—165 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.77 (8H, m), 2.98 (2H, m), 3.24 (4H, m), 3.70 (3H, s), 3.83 (6H, s), 3.85 (3H, s), 5.11 (1H, t, J=6.0 Hz), 6.29 (1H, s), 6.59 (1H, s), 6.72 (3H, m), 6.91 (4H, m). IR (KBr) cm^{-1}: 1634. MS (*m*/*z*): 550 $(M+H)^+$. *Anal.* Calcd for $C_{31}H_{36}N_3O_5F$: C, 67.74; H, 6.60; N, 7.64. Found: C, 67.71; H, 6.65; N, 7.67.

1-(3,4-Dimethoxybenzyl)-2-(4-methylpiperazine-1-yl)carbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (11) Synthesized in a manner similar to that described for **7**. The product was obtained as white solid (85%) mp 78—79 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.18 (3H, s), 2.62 (8H, m), 2.96 (2H, m), 3.17 (4H, m), 3.50 (3H, s), 3.66 (6H, s), 3.68 (3H, s), 5.00 (1H, t, J=6.0 Hz), 6.18 (1H, s), 6.47 (1H, s), 6.62 (3H, m). IR (KBr) cm^{-1}: 1633. MS (*m*/*z*): 470 $(M+H)^+$. *Anal.* Calcd for $C_{26}H_{35}N_3O_5$: C, 66.50; H, 7.51; N, 8.94. Found: C, 66.51; H, 7.48; N, 8.91.

1-(3,4-Dimethoxybenzyl)-2-(morpholin-1-yl)carbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (12) Synthesized in a manner similar to that described for **7**. The product was obtained as white solid (80%) mp 110—112 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.47 (8H, m), 3.31 (2H, m), 3.56 (4H, m), 3.75 (3H, s), 3.84 (6H, s), 3.85 (3H, s), 5.09 (1H, t, J=6.0 Hz), 6.28 (1H, s), 6.58 (1H, s), 6.72 (3H, m). IR (KBr) cm^{-1}: 1632. MS (*m*/*z*): 457 $(M+H)^+$. *Anal.* Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.06; N, 6.13. Found: C, 65.80; H, 7.09; N, 6.21.

1-(3,4-Dimethoxybenzyl)-2-[4-(pyrimidin-1-yl)piperazine-1-yl]carbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13) Synthesized in a manner similar to that described for **7**. The product was obtained as gummy material (78%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.43 (8H, m), 3.02 (2H, m), 3.13 (4H, m), 3.68 (3H, s), 3.78 (6H, s), 3.85 (3H, s), 5.11 (1H, t, J=6.0 Hz), 6.25 (1H, s), 6.51 (1H, t, J=6.0 Hz), 6.59 (1H, s), 6.72 (3H, m), 8.34 (2H, d, J=6.0 Hz). IR (KBr) cm^{-1}: 1639. MS (*m*/*z*): 534 $(M+H)^+$. *Anal.* Calcd for $C_{29}H_{35}N_5O_5$: C, 65.27; H, 6.61; N, 13.12. Found: C, 65.55; H, 6.50; N, 13.22.

1-(3,4-Dimethoxybenzyl)-2-[4-(3-methylphenyl)piperazine-1-yl]carbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (14) Synthesized in a manner similar to that described for **7**. The product was obtained as pale yellow solid (80%) mp 90—91 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.38 (3H, s), 2.59 (8H, m), 2.90 (2H, m), 3.08 (4H, m), 3.82 (3H, s), 3.85 (6H, s), 3.86

(3H, s), 5.65 (1H, t, J=6.0 Hz), 6.28 (1H, s), 6.50 (1H, s), 6.62 (3H, m), 6.70 (4H, m). IR (KBr) cm^{-1}: 1640. MS (*m/z*): 546 $(M+H)^+$. *Anal.* Calcd for $C_{32}H_{39}N_3O_5$: C, 70.43; H, 7.20; N, 7.70. Found: C, 70.55; H, 7.31; N, 7.67.

1-(3,4-Dimethoxybenzyl)-2-[4-(4-methylphenyl)piperazine-1-yl]carbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15) Synthesized in a manner similar to that described for **7**. The product was obtained as gummy material (82%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.40 (3H, s), 2.64 (8H, m), 2.89 (2H, m), 3.11 (4H, m), 3.84 (3H, s), 3.86 (6H, s), 3.87 (3H, s), 5.65 (1H, t, J=6.0 Hz), 6.29 (1H, s), 6.46 (1H, s), 6.57 (3H, m), 6.69 (4H, m). IR (KBr) cm^{-1}: 1640. MS (*m/z*): 546 $(M+H)^+$. *Anal.* Calcd for $C_{32}H_{39}N_3O_5$: C, 70.43; H, 7.20; N, 7.70. Found: C, 70.51; H, 7.19; N, 7.65.

4-(4-Fluorophenyl)piperazine-1-carbamoylimidazole (16) To a suspension of CDI (5.18 g, 32 mmol) in THF (50 ml) was added 1-(4-florophenyl)piperazine (5 g, 27.7 mmol). The mixture was refluxed for 24 h before cooling to room temperature. Removal of solvent under vacuum gave a viscous oil which was dissolved in CH_2Cl_2 (100 ml), and washed twice with 100 ml portions of water. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to yield a light yellow solid. The carbamoyl imidazole **16** (6.46 g, 85%) mp 92—93 °C obtained was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.17 (4H, t, J=6 Hz), 3.78 (4H, t, J=6 Hz), 6.89 (2H, m), 6.95 (2H, m), 7.13 (2H, m), 7.91 (1H, s). IR (KBr) cm^{-1}: 1695. MS (*m/z*): 274 $(M)^+$. *Anal.* Calcd for $C_{14}H_{15}N_4OF$: C, 61.30; H, 5.51; N, 20.42. Found: C, 61.21; H, 5.59; N, 20.53.

1-(3,4-Dimethoxybenzyl)-2-[4-(4-fluorophenyl)piperazine-1-yl]carbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (10) Using 16 To a solution of **16** (1.86 g, 6.8 mmol) in dichloromethane (15 ml) was added methyl iodide (1.57 ml, 25.2 mmol). The mixture was stirred at room temperature for 12 h. Solvent was removed in vacuum to yield its cationic carbamoyl imidazolium salt, which was dissolved without purification in CH_2Cl_2 (20 ml). To this solution added 1-(4-fluorophenyl)piperazine (1.22 g, 6.8 mmol) and triethylamine (0.95 ml, 6.8 mmol). The mixture was stirred at room temperature for 24 h, then washed with 1.0 M HCl, the organic layer dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield the required tetrasubstituted urea as an oil which was column chromatographed (ethylacetate–hexane) to obtain pure **10** (3.05 g, 82%).

1-(3,4-Dimethoxybenzyl)-2-chloroacetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (17) To a solution of tetrahydropapaverine **5** (18.86 g, 55 mmol) and triethylamine (11.5 ml, 82 mmol) in dry dichloromethane (50 ml), chloroacetylchloride (7.24 g, 64 mmol)) was added slowly. During addition the reaction mixture was kept in ice. On addition the mixture was stirred at room temperature for 4 h. After the completion (TLC) of the reaction, evaporated off the solvent, diluted the residue with water (150 ml) and extracted with ethylacetate (3×50 ml). The collective organic portion was washed with brine and dried over Na_2SO_4. It was finally concentrated and chromatographed on silica gel using ethylacetate–hexane as eluent. A final recrystallization from ethylacetate–hexane (20 : 70) afforded the product as a white solid (18.74 g, 81%) mp 98—100 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.76 (2H, m), 3.19 (4H, m), 3.55 (2H, s), 3.68 (3H, s), 3.87 (6H, s), 3.91 (3H, s), 5.56 (1H, t, J=6.0 Hz), 6.24 (1H, s), 6.53 (1H, s), 6.75 (3H, m). IR (KBr) cm^{-1}: 1642.9. MS (*m/z*): 420 $(M+H)^+$. *Anal.* Calcd for $C_{22}H_{26}NO_5Cl$: C, 62.92; H, 6.24; N, 3.34. Found: C, 62.91; H, 6.04; N, 3.27.

1-(3,4-Dimethoxybenzyl)-2-[4-(3-chlorophenyl)piperazine-1-yl]acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (18) A solution of 1-(3-chlorophenyl)piperazine (0.97 g, 5 mmol) in DMF (10 ml) was added slowly to a solution of **17** (2 g, 4.7 mmol) and activated K_2CO_3 (2 g, 14.4 mmol) in DMF (15 ml). The mixture was stirred for 3 h at 60 °C. After the completion (TLC) of reaction, diluted the reaction mixture with water (500 ml) and extracted with ethylacetate (3×50 ml). The collective organic portion was washed with brine and dried over Na_2SO_4. It was finally concentrated and chromatographed on silica gel using ethylacetate–hexane as eluent to obtain pure **18** as a gummy material (2.26 g, 82%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.60 (8H, m), 2.87 (2H, m), 3.02 (4H, m), 3.25 (2H, s), 3.65 (3H, s), 3.86 (6H, s), 3.87 (3H, s), 5.66 (1H, t, J=6.0 Hz), 6.22 (1H, s), 6.46 (1H, s), 6.61 (3H, m), 6.81 (4H, m). IR (KBr) cm^{-1}: 1685. MS (*m/z*): 580 $(M+H)^+$. *Anal.* Calcd for $C_{32}H_{38}N_3O_5Cl$: C, 66.25; H, 6.60; N, 7.24. Found: C, 66.17; H, 6.54; N, 7.29.

1-(3,4-Dimethoxybenzyl)-2-[4-(4-chlorophenyl)piperazine-1-yl]acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19) Synthesized in a manner similar to that described for **18**. The product was obtained as gummy material (83%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.52 (8H, m), 2.82 (2H, m), 3.13 (4H, m), 3.27 (2H, s), 3.71 (3H, s), 3.79 (6H, s), 3.85 (3H, s), 5.63 (1H, t, J=6.0 Hz), 6.21 (1H, s), 6.56 (1H, s), 6.67 (3H, m), 6.89 (4H, m). IR (KBr) cm^{-1}: 1679. MS (*m/z*): 580 $(M+H)^+$. *Anal.* Calcd for $C_{32}H_{38}N_3O_5Cl$: C, 66.25; H, 6.60; N, 7.24. Found: C, 66.31; H, 6.51; N, 7.31.

1-(3,4-Dimethoxybenzyl)-2-[4-(3-fluorophenyl)piperazine-1-yl]acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (20) Synthesized in a manner similar to that described for **18**. The product was obtained as gummy material (80%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.63 (8H, m), 2.77 (2H, m), 3.12 (4H, m), 3.29 (2H, s), 3.70 (3H, s), 3.82 (6H, s), 3.89 (3H, s), 5.59 (1H, t, J=6.0 Hz), 6.25 (1H, s), 6.51 (1H, s), 6.63 (3H, m), 6.82 (4H, m). IR (KBr) cm^{-1}: 1644. MS (*m/z*): 564 $(M+H)^+$. *Anal.* Calcd for $C_{32}H_{38}N_3O_5F$: C, 68.18; H, 6.79; N, 7.45. Found: C, 68.05; H, 6.61; N, 7.59.

1-(3,4-Dimethoxybenzyl)-2-[4-(4-fluorophenyl)piperazine-1-yl]acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (21) Synthesized in a manner similar to that described for **18**. The product was obtained as gummy material (83%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.67 (8H, m), 2.87 (2H, m), 3.02 (4H, m), 3.25 (2H, s), 3.66 (3H, s), 3.84 (6H, s), 3.86 (3H, s), 5.69 (1H, t, J=6.0 Hz), 6.26 (1H, s), 6.43 (1H, s), 6.61 (3H, m), 6.80 (4H, m). IR (KBr) cm^{-1}: 1634. MS (*m/z*): 564 $(M+H)^+$. *Anal.* Calcd for $C_{32}H_{38}N_3O_5F$: C, 68.18; H, 6.79; N, 7.45. Found: C, 68.25; H, 6.71; N, 7.49.

1-(3,4-Dimethoxybenzyl)-2-(4-methylpiperazine-1-yl)acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (22) Synthesized in a manner similar to that described for **18**. The product was obtained as gummy material (78%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.38 (3H, s), 2.65 (8H, m), 2.87 (2H, m), 2.98 (4H, m), 3.22 (2H, s), 3.64 (3H, s), 3.79 (6H, s), 3.85 (3H, s), 5.64 (1H, t, J=6.0 Hz), 6.23 (1H, s), 6.45 (1H, s), 6.61 (3H, m). IR (KBr) cm^{-1}: 1637. MS (*m/z*): 484 $(M+H)^+$. *Anal.* Calcd for $C_{27}H_{37}N_3O_5$: C, 67.05; H, 7.71; N, 8.68. Found: C, 67.23; H, 7.63; N, 8.56.

1-(3,4-Dimethoxybenzyl)-2-(morpholin-1-yl)acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (23) Synthesized in a manner similar to that described for **18**. The product was obtained as gummy material (79%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.26 (8H, m), 2.59 (2H, m), 2.90 (4H, m), 3.66 (2H, s), 3.71 (3H, s), 3.83 (6H, s), 3.88 (3H, s), 5.67 (1H, t, J=6.0 Hz), 6.26 (1H, s), 6.51 (1H, s), 6.60 (3H, m). IR (KBr) cm^{-1}: 1633. MS (*m/z*): 471$(M+H)^+$. *Anal.* Calcd for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.45; H, 7.13; N, 5.83.

1-(3,4-Dimethoxybenzyl)-2-[4-(pyrimidin-1-yl)piperazine-1-yl]acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24) Synthesized in a manner similar to that described for **18**. The product was obtained as gummy material (81%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.49 (8H, m), 2.85 (2H, m), 3.10 (4H, m), 3.24 (2H, s), 3.64 (3H, s), 3.82 (6H, s), 3.85 (3H, s), 5.67 (1H, t, J=6.0 Hz), 6.24 (1H, s), 6.43 (1H, s), 6.46 (1H, t, J=6.0 Hz), 6.61 (3H, m), 8.29 (2H, d, J=6.0 Hz). IR (KBr) cm^{-1}: 1632. MS (*m/z*): 548 $(M+H)^+$. *Anal.* Calcd for $C_{30}H_{37}N_5O_5$: C, 65.79; H, 6.80; N, 12.78. Found: C, 65.55; H, 6.96; N, 12.83.

1-(3,4-Dimethoxybenzyl)-2-[4-(3-methylphenyl)piperazine-1-yl]acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (25) Synthesized in a manner similar to that described for **18**. The product was obtained as light yellow solid (81%) mp 104—105 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.31 (3H, s), 2.55 (8H, m), 2.89 (2H, m), 3.07 (4H, m), 3.25 (2H, s), 3.80 (3H, s), 3.84 (6H, s), 3.86 (3H, s), 5.69 (1H, t, J=6.0 Hz), 6.25 (1H, s), 6.41 (1H, s), 6.60 (3H, m), 6.69 (4H, m). IR (KBr) cm^{-1}: 1640. MS (*m/z*): 560 $(M+H)^+$. *Anal.* Calcd for $C_{33}H_{41}N_3O_5$: C, 70.81; H, 7.38; N, 7.50. Found: C, 70.69; H, 7.56; N, 7.32.

1-(3,4-Dimethoxybenzyl)-2-[4-(4-methylphenyl)piperazine-1-yl]acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (26) Synthesized in a manner similar to that described for **18**. The product was obtained as gummy material (82%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.26 (3H, s), 2.65 (8H, m), 2.85 (2H, m), 3.17 (4H, m), 3.29 (2H, s), 3.78 (3H, s), 3.81 (6H, s), 3.84 (3H, s), 5.63 (1H, t, J=6.0 Hz), 6.29 (1H, s), 6.40 (1H, s), 6.67 (3H, m), 6.69 (4H, m). IR (KBr) cm^{-1}: 1645. MS (*m/z*): 560 $(M+H)^+$. *Anal.* Calcd for $C_{33}H_{41}N_3O_5$: C, 70.81; H, 7.38; N, 7.50. Found: C, 70.61; H, 23; N, 7.31.

Pharmacological Methods Antispasmodic activity: isolated guinea pig ileum. Guinea pigs of both sexes (300—500 g) were killed by cervical dislocation and exsanguinated. The abdomen was opened and the terminal ileum carefully dissected, repeatedly washed and the connective tissue removed. Intestinal segments of 1.0 to 1.5 cm length were set up under 1 g resting tension in a 10 ml organ bath with Tyrode's solution: (mM: NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 1.05, $NaHCO_3$ 11.9, NaH_2PO_4 0.42, glucose 5.6). The bath temperature was maintained at 37 °C and aerated with compressed air. Tension changes in the tissues were monitored using force displacement transducer amplifier connected to physiograph (Polyrite, Recorders and Medicare System).

After 30 min of equilibration period, concentration–response curves to the cumulative addition of acetylcholine (ACh) (0.1 nM—0.1 mM) were constructed every 30 min. After constant responses had been obtained, concen-

tration–response were repeated in the presence of increasing concentrations of the standard antagonist papaverine (0.1—20 μM). After a further control experiment (concentration-response curve of Ach) the test compounds **7**—**15** and **18**—**26** were measured. All substances were incubated 3 min prior to the cumulative addition of Ach; after each experiment all substances were carefully washed out. For each test substance a new ileum preparation was used. Test compounds were dissolved in 46% EtOH to yield solutions (0.1—20 μM). The antispasmodic activity was assessed as a percent reduction over the initial value. The IC_{50} values were obtained from individual experiments with 3 to 5 different concentrations of test compounds. As EtOH in the concentration used also inhibits ACh-induced contractions the antispasmodic activity of EtOH was measured and subtracted from the values obtained with test compounds.

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