

## SUBSTITUTED CARBOXAMIDE ANALOGUES AS A NEW CLASS OF LOCAL ANESTHETIC AGENTS: SYNTHESIS AND BIO-EVALUATION

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**Abstract:** A series of N-(2-oxo-2-(phenylamino) ethyl) substituted-4-carboxamide derivatives were synthesized as local anesthetic agents. The structures of carboxamide derivatives were established on the basis of IR, and <sup>1</sup>H spectral data. All the compounds were subjected to surface local anesthetic activity assay and infiltration local anesthetic activity assay. Among the tested compounds, N-(2-oxo-2-(p-tolylamino) ethyl) piperidine-1-carboxamide (**4h**) and N-(2-((4-methoxyphenyl) amino)-2-oxoethyl) piperidine-1-carboxamide (**4m**) were most promising compounds in terms of surface local anaesthetic and infiltration local anaesthetic activity on rats having considerably lower liver toxicity.

**Keywords:** Carboxamide, surface local anesthetic activity, infiltration local anesthetic activity, hepatotoxicity

Anesthetics are the drugs used to prevent pain during surgery. There are three main types of anaesthetic: general anaesthetic, regional anaesthetic and local anaesthetic (1). Local anaesthetics represent one of the most frequently used in daily medical practice groups of drugs (2). The first clinically available amide based local anaesthetic, lidocaine, was synthesized by Swedish chemist Nils Lofgren in 1943 (3). Lidocaine opened a new avenue for development of local anaesthetics and its structural features, such as tertiary amino group and arylamide moiety connected with one carbon atom, became a classical pattern for most of the modern local anaesthetics. In the process of development of new and more potent local anaesthetics, N, N-dialkyl derivatives of glycine evolved to N-alkyl substituted homoprolines and prolines. Thus homoprolin-

based mepivacaine, bupivacaine and ropivacaine were introduced as very potent local anaesthetics (4, 5). At the same time, effective anaesthetic derivatives of proline, namely cyclomecaine and pyromecaine were developed (6). However, therapeutic applications of these drugs are limited due to their substantial general toxicity (7) and associated side effects (8).

Although the main modern drug design and development inclines towards the search for various agents highly selective against one particular target, it looks that all clinically available anaesthetics are scarcely selective to any specific type and subtype of the ion channels. They all have been discovered on the basis of *in vitro* and *in vivo* tests assessing changes in the neuron functions. This can be attributed to incomplete knowledge of actual role of each type and subtypes of the ion channels in the activity. Therefore, it seems practical to conduct a search for new anaesthetic agents using assays based techniques to achieve the desired therapeutic outcome.

All local anesthetic molecules in clinical use have three parts: a lipophilic (aromatic) end, a hydrophilic (amine) end, and a link between the ends (Fig. 1). The link contains either an amino-ester or an amino amide bond, and local anesthetics are designated as belonging to one of two groups:

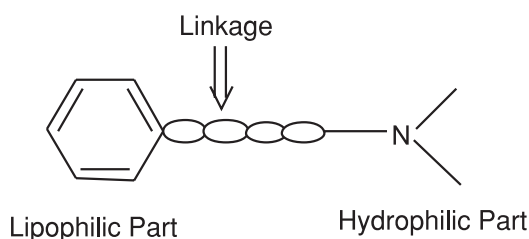


Figure 1. General structure of all local anesthetic molecules

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aminoester-linked local anesthetics or amino-amide-linked local anesthetics. Ester and amides have achieved popularity in clinical practice. Esters include cocaine, procaine, 2-chloroprocaine, tetracaine and benzocaine. Amides or carboxamides include lidocaine, bupivacaine, levobupivacaine, mepivacaine, etidocaine, prilocaine, ropivacaine and articaine.

In brief, the survey of the literature demonstrated that the amide derivatives such as butyramides, acetamides, anilides, oxazolidine etc., had exhibited potent local anesthetic agents (9-12).

Our previous research in the development of tetracaine pharmacokinetics studies (13, 14) encouraged me to design a series of carboxamide derivatives containing a lipophilic part which is further substituted with substituent such as Cl, methyl and methoxy groups. This lipophilic domain is linked to a diamide chain which is expected to impart more hydrogen bonding with sodium channels. The hydrophilic part is constituted by tertiary amines as cyclic or acyclic. The diamide function introduced between these two domains is the principle modification from the existing clinically used local anesthetics.

## EXPERIMENTAL

### Materials

All chemicals and reagents were obtained from various manufacturers (E. Merck, CDH, S. D. Fine Chem. Qualigens etc) and used without further purification. The reactions were monitored and the purity of the compounds was checked by thin layer chromatography (TLC) and spot being located under iodine vapors or UV-light. Melting points were determined by the open capillary method with electrical melting point apparatus and are uncorrected. IR spectra were recorded as KBr (pellet) on Bio Rad FT-IR spectrophotometer and  $^1\text{H}$  NMR spectra were recorded on Bruker DPX 300 MHz spectrophotometer using DMSO- $d_6$  or  $\text{CDCl}_3$  as a NMR solvent.

### Synthesis of 2-chloro-N-substituted phenyl acetamide (1)

Chloroacetyl chloride is added to mixture of appropriate substituted aniline in dimethylformamide (DMF) 20 mL containing (0.2 mol) of  $\text{K}_2\text{CO}_3$  and the mixture stirred for 8-12 h at room temperature. After completion of the reaction the content was poured in ice water, the precipitate obtained was filtered and washed with distilled water and dried in air.

### Synthesis of 2-amino-N-substituted phenyl acetamide (2)

To a mixture of compound (prepared in step 1) in absolute ethanol 25 mL, a saturated solution of ammonia 15 mL was added portion wise and the content of the flask refluxed for 5-8 h on water bath. On completion of the reaction a solid product, obtained was filtered and dried.

### Synthesis of carboxylate derivatives (3)

To a solution of appropriate amine (0.01 mol in 25 mL of pyridine), 0.015 mol of ethyl chloroformate was added dropwise and the content of the flask stirred at room temp for another 3-4 h. After that content of flask was poured into ice cold water, a precipitate was obtained which was filtered and washed with cold water and dried.

### Synthesis of N-(2-oxo-2-(phenylamino) ethyl) substituted-1/4-carboxamide (4a-t)

The product of step 2 and 3 in equimolar quantity are refluxed in absolute ethanol till the completion of the reaction monitored by TLC.

### N-(2-oxo-2-(phenylamino) ethyl) thiomorpholine-4-carboxamide (4a)

Yield: 67%; m.p.: 138-140°C; IR (KBr)  $\text{cm}^{-1}$ : 3156, 3268 (N-H), 1665 (C=O), 1632 (C=N), 1556 (C=C), 1024 (C-N).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ );  $\delta$  2.73 (m, 4H,  $2 \times \text{CH}_2$ ), 3.59 (m, 4H,  $2 \times \text{CH}_2$ ), 4.17 (s, 2H,  $\text{CH}_2\text{NH}$ ), 6.41 (bs, 1H,  $\text{CH}_2\text{NH}$ ,  $\text{D}_2\text{O}$  exchangeable), 7.17 (s, 1H, Ar-H), 7.49 (d, 2H, Ar-H), 7.73 (d, 2H, Ar-H), 10.83 (bs, 1H, CONH,  $\text{D}_2\text{O}$  exchangeable).

### N-(2-oxo-2-(phenylamino) ethyl) morpholine-4-carboxamide (4b)

Yield: 57%; m.p.: 144-146°C; IR (KBr)  $\text{cm}^{-1}$ : 3161 (N-H), 1676 (C=O), 1634 (C=N), 1550 (C=C), 1012 (C-N).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ );  $\delta$  3.33 (m, 4H,  $2 \times \text{CH}_2$ ), 3.61 (m, 4H,  $2 \times \text{CH}_2$ ), 4.19 (s, 2H,  $\text{CH}_2\text{NH}$ ), 6.43 (bs, 1H,  $\text{CH}_2\text{NH}$ ,  $\text{D}_2\text{O}$  exchangeable), 7.21 (s, 1H, Ar-H), 7.51 (d, 2H, Ar-H), 7.77 (d, 2H, Ar-H), 10.87 (bs, 1H, CONH,  $\text{D}_2\text{O}$  exchangeable).

### N-(2-oxo-2-(phenylamino) ethyl) piperidine-1-carboxamide (4c)

Yield: 60%; m.p.: 152-154°C; IR (KBr)  $\text{cm}^{-1}$ : 3153 (N-H), 1672 (C=O), 1631 (C=N), 1560 (C=C), 1022 (C-N).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ );  $\delta$  1.57 (m, 4H,  $2 \times \text{CH}_2$ ), 1.62 (m, 2H,  $\text{CH}_2$ ), 3.79 (m, 4H,  $2 \times \text{CH}_2$ ), 4.13 (s, 2H,  $\text{CH}_2\text{NH}$ ), 6.43 (bs, 1H,  $\text{CH}_2\text{NH}$ ,  $\text{D}_2\text{O}$  exchangeable), 7.18 (s, 1H, Ar-H),

7.49(d, 2H, Ar-H), 7.70 (d, 2H, Ar-H  $J = 7.6$  Hz), 10.87 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**4-methyl-N-[2-oxo-2-(phenylamino) ethyl]piperazine-1-carboxamide (4d)**

Yield: 66%; m.p.: 148–150°C; IR (KBr)  $\text{cm}^{-1}$ : 3132 (N-H), 1651 (C=O), 1628 (C=N), 1566 (C=C), 1021 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ );  $\delta$  3.03 (m, 11H, CH<sub>3</sub> and CH<sub>2</sub>), 4.17 (s, 2H, CH<sub>2</sub>NH), 6.41 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.21 (s, 1H, Ar-H), 7.49(d, 2H, Ar-H), 7.73 (d, 2H, Ar-H), 10.89 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**4-ethyl-N-[2-oxo-2-(phenylamino) ethyl]piperazine-1-carboxamide (4e)**

Yield: 62%; m.p.: 158–160°C; IR (KBr)  $\text{cm}^{-1}$ : 3172 (N-H), 1663 (C=O), 1638 (C=N), 1552 (C=C), 1028 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ );  $\delta$  1.21 (m, 3H, CH<sub>3</sub>), 2.28 (m, 10H, 5  $\times$  CH<sub>2</sub>), 3.37 (s, 2H, CH<sub>2</sub>NH), 7.40 (s, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.40 (s, 1H, Ar-H), 7.52 (d, 2H, Ar-H), 7.84 (d, 2H, Ar-H), 10.17 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-(2-oxo-2-(p-tolylamino) ethyl) thiomorpholine-4-carboxamide (4f)**

Yield: 58%; m.p.: 142–144°C; IR (KBr)  $\text{cm}^{-1}$ : 3170 (N-H), 2940, 2875 (–CH<sub>3</sub>), 1668 (C=O), 1628 (C=N), 1550 (C=C), 1024 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ );  $\delta$  2.34 (s, 3H, CH<sub>3</sub>), 2.71 (m, 4H, 2  $\times$  CH<sub>2</sub>), 3.55 (m, 4H, 2  $\times$  CH<sub>2</sub>), 4.15 (s, 2H, CH<sub>2</sub>NH), 6.41 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.29 (d, 2H, Ar-H), 7.61 (d, 2H, Ar-H), 10.83 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-(2-oxo-2-(p-tolylamino) ethyl)morpholine-4-carboxamide (4g)**

Yield: 70%; m.p.: 133–135°C; IR (KBr)  $\text{cm}^{-1}$ : 3166 (N-H), 2940, 2875 (–CH<sub>3</sub>), 1668 (C=O), 1638 (C=N), 1556 (C=C), 1024 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ );  $\delta$  2.39 (s, 3H, CH<sub>3</sub>), 3.37 (m, 4H, 2  $\times$  CH<sub>2</sub>), 3.69 (m, 4H, 2  $\times$  CH<sub>2</sub>), 4.19 (s, 2H, CH<sub>2</sub>NH), 6.45 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.23 (d, 2H, Ar-H), 7.59 (d, 2H, Ar-H), 10.83 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-(2-oxo-2-(p-tolylamino) ethyl)piperidine-1-carboxamide (4h)**

Yield: 63%; m.p.: 160–162°C; IR (KBr)  $\text{cm}^{-1}$ : 3165 (N-H), 3125 (–CH<sub>3</sub>), 1656 (C=O), 1619 (C=N), 1586 (C=C), <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>);  $\delta$  1.39 (m, 4H, 2  $\times$  CH<sub>2</sub>), 1.61 (m, 2H, CH<sub>2</sub>), 2.37 (s, 3H, CH<sub>3</sub>), 3.48 (m, 4H, 2  $\times$  CH<sub>2</sub>), 4.39 (s, 2H, CH<sub>2</sub>NH), 6.53 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.12 (d, 2H,

Ar-H), 7.52(d, 2H, Ar-H), 10.59 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**4-methyl-N-{2-[(4-methylphenyl) amino]-2-oxoethyl} piperazine-1-carboxamide (4i)**

Yield: 49%; m.p.: 130–132°C; IR (KBr)  $\text{cm}^{-1}$ : 3142 (N-H), 2946, 2873 (–CH<sub>3</sub>), 1668 (C=O), 1638 (C=N), 1556 (C=C), 1024 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ );  $\delta$  2.39 (s, 3H, CH<sub>3</sub>), 3.01 (m, 11H, CH<sub>3</sub> and CH<sub>2</sub>), 4.12 (s, 2H, CH<sub>2</sub>NH), 6.42 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.25 (d, 2H, Ar-H), 7.61 (d, 2H, Ar-H), 10.89 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**4-ethyl-N-{2-[(4-methylphenyl) amino]-2-oxoethyl} piperazine-1-carboxamide (4j)**

Yield: 47%; m.p.: 156–158°C; IR (KBr)  $\text{cm}^{-1}$ : 3172 (N-H), 2944, 2865 (–CH<sub>3</sub>), 1648 (C=O), 1628 (C=N), 1550 (C=C), 1010 (C-N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>);  $\delta$  1.72(m, 3H, CH<sub>3</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 3.97 (m, 10H, 5  $\times$  CH<sub>2</sub>), 4.67 (s, 2H, CH<sub>2</sub>NH), 6.45 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 6.71 (d, 2H, Ar-H), 7.20 (d, 2H, Ar-H), 9.45 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-(2-((4-methoxyphenyl) amino)-2-oxoethyl) thiomorpholine-4-carboxamide (4k)**

Yield: 61%; m.p.: 137–139°C; IR (KBr)  $\text{cm}^{-1}$ : 3176 (N-H), 1678 (C=O), 1637 (C=N), 1549 (C=C), 1244, 1043 (C-O-C), 1011 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ );  $\delta$  2.71 (m, 4H, 2  $\times$  CH<sub>2</sub>), 3.57 (m, 4H, 2  $\times$  CH<sub>2</sub>), 3.89 (s, 3H, CH<sub>3</sub>), 4.19 (s, 2H, CH<sub>2</sub>NH), 6.41 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 6.91 (d, 2H, Ar-H), 7.51 (d, 2H, Ar-H), 10.83 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-(2-((4-methoxyphenyl) amino)-2-oxoethyl) morpholine-4-carboxamide (4l)**

Yield: 58%; m.p.: 150–152°C; IR (KBr)  $\text{cm}^{-1}$ : 3179 (N-H), 1680 (C=O), 1641 (C=N), 1560 (C=C), 1254, 1051 (C-O-C), 1024 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ );  $\delta$  3.34 (m, 4H, 2  $\times$  CH<sub>2</sub>), 3.71 (m, 4H, 2  $\times$  CH<sub>2</sub>), 3.93 (s, 3H, CH<sub>3</sub>), 4.17 (s, 2H, CH<sub>2</sub>NH), 6.45 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.01 (d, 2H, Ar-H), 7.59 (d, 2H, Ar-H), 10.83 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-(2-((4-methoxyphenyl) amino)-2-oxoethyl) piperidine-1-carboxamide (4m)**

Yield: 63%; m.p.: 172–174°C; IR (KBr)  $\text{cm}^{-1}$ : 3121 (N-H), 1678 (C=O), 1631 (C=N), 1549 (C=C), 1257, 1062 (C-O-C), 1012 (C-N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>);  $\delta$  1.46 (m, 4H, 2  $\times$  CH<sub>2</sub>), 1.71 (m, 2H, CH<sub>2</sub>), 3.50 (m, 4H, 2  $\times$  CH<sub>2</sub>), 3.83 (s, 3H, CH<sub>3</sub>), 4.13

(s, 2H, CH<sub>2</sub>NH), 6.29 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 6.55(d, 2H, Ar-H), 6.93 (d, 2H, Ar-H), 9.63 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-{2-[(4-methoxyphenyl) amino]-2-oxoethyl}-4-methylpiperazine-1-carboxamide (4n)**

Yield: 52%; m.p.: 145-147°C; IR (KBr) cm<sup>-1</sup>: 3176 (N-H), 1658 (C=O), 1628 (C=N), 1552 (C=C), 1244, 1048 (C-O-C), 1024 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>); δ 3.01(m, 11H, CH<sub>3</sub> and CH<sub>2</sub>), 3.81 (s, 3H, CH<sub>3</sub>), 4.12 (s, 2H, CH<sub>2</sub>NH), 6.42 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 6.99 (d, 2H, Ar-H), 7.59 (d, 2H, Ar-H), 10.89 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**4-ethyl-N-{2-[(4-methoxyphenyl) amino]-2-oxoethyl} piperazine-1-carboxamide (4o)**

Yield: 49%; m.p.: 166-168°C; IR (KBr) cm<sup>-1</sup>: 3176 (N-H), 1680 (C=O), 1632 (C=N), 1551 (C=C), 1248, 1056 (C-O-C), 1032 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>); δ 1.41 (m, 3H, CH<sub>3</sub>), 3.89 (s, 3H, CH<sub>3</sub>), 3.99 (m, 10H, 5 × CH<sub>2</sub>), 4.19 (s, 2H, CH<sub>2</sub>NH), 6.43 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.05 (d, 2H, Ar-H), 7.61 (d, 2H, Ar-H), 10.87 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-(2-((4-chlorophenyl) amino)-2-oxoethyl) thiomorpholine-4-carboxamide (4p)**

Yield: 68%; m.p.: 147-149°C; IR (KBr) cm<sup>-1</sup>: 3167 (N-H), 1681 (C=O), 1633 (C=N), 1547 (C=C), 1243, 1046 (C-O-C), 1012 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>); δ 2.73 (m, 4H, 2 × CH<sub>2</sub>), 3.58 (m, 4H, 2 × CH<sub>2</sub>), 4.19 (s, 2H, CH<sub>2</sub>NH), 6.43 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.47(d, 2H, Ar-H), 7.83 (d, 2H, Ar-H), 10.83 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-(2-((4-chlorophenyl) amino)-2-oxoethyl) morpholine-4-carboxamide (4q)**

Yield: 64%; m.p.: 162-164°C; IR (KBr) cm<sup>-1</sup>: 3169 (N-H), 1682 (C=O), 1633 (C=N), 1591 (C=C), 1214, 1060 (C-O-C), 1019 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>); δ 3.33 (m, 4H, 2 × CH<sub>2</sub>), 3.79 (m, 4H, 2 × CH<sub>2</sub>), 4.16 (s, 2H, CH<sub>2</sub>NH), 6.47 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.49 (d, 2H, Ar-H), 7.82 (d, 2H, Ar-H), 10.81 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-(2-((4-chlorophenyl) amino)-2-oxoethyl) piperidine-1-carboxamide (4r)**

Yield: 70%; m.p.: 170-171°C; IR (KBr) cm<sup>-1</sup>: 3117 (N-H), 1693 (C=O), 1643 (C=N), 1547 (C=C), 1259, 101 (C-O-C), 1010 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>); δ 1.51 (m, 4H, 2 × CH<sub>2</sub>), 1.69 (m,

2H, CH<sub>2</sub>), 3.78 (m, 4H, 2 × CH<sub>2</sub>), 4.17 (s, 2H, CH<sub>2</sub>NH), 6.46 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.39 (d, 2H, Ar-H), 7.80 (d, 2H, Ar-H), 10.77 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-{2-[(4-chlorophenyl) amino]-2-oxoethyl}-4-methylpiperazine-1-carboxamide (4s)**

Yield: 61%; m.p.: 153-155°C; IR (KBr) cm<sup>-1</sup>: 3186 (N-H), 1658 (C=O), 1643 (C=N), 1557 (C=C), 1253, 1048 (C-O-C), 1014 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>); δ 3.10(m, 11H, CH<sub>3</sub> and CH<sub>2</sub>), 4.17 (s, 2H, CH<sub>2</sub>NH), 6.43 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.49 (d, 2H, Ar-H), 7.67 (d, 2H, Ar-H), 10.88 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**N-{2-[(4-chlorophenyl) amino]-2-oxoethyl}-4-ethylpiperazine-1-carboxamide (4t)**

Yield: 56%; m.p.: 169-170°C; IR (KBr) cm<sup>-1</sup>: 3179 (N-H), 1676 (C=O), 1637 (C=N), 1551 (C=C), 1254, 1043 (C-O-C), 1017 (C-N). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>); δ 1.47 (m, 3H, CH<sub>3</sub>), 3.81 (m, 10H, 5 × CH<sub>2</sub>), 4.19 (s, 2H, CH<sub>2</sub>NH), 6.44 (bs, 1H, CH<sub>2</sub>NH, D<sub>2</sub>O exchangeable), 7.41 (d, 2H, Ar-H), 7.79 (d, 2H, Ar-H), 10.82 (bs, 1H, CONH, D<sub>2</sub>O exchangeable).

**Biological activity**

**Surface local anaesthetic activity assay**

Surface anaesthetic activity was evaluated in white New Zealand rabbits using modified Regnier corneal reflex test (15). Briefly, aqueous solutions (1%, 0.25 mL) of compounds (**4a-t**) or reference drugs will be applied into the conjunctival sac of the animals during 30 s. The tactile stimulations of the rabbit cornea (up to 100 in a series) with the pointer will be applied in 8 min after the treatment and then in the define intervals (10, 12, 15 min and then every 5 min after that). The summation of numbers of the stimulations required to cause the corneal reflex during 1 h (13 series) provided the Regnier index. The duration of the anaesthesia was estimated as a time required for complete restoration of the corneal reflex. Each synthesized compound will be tested in 6 animals.

**Infiltration local anaesthetic activity assay**

Infiltration anaesthetic activity of the compounds will be evaluated in Wistar rats using modification of the reported method (16). Briefly, after identification of sensitive areas on the shaved skin of lumbar region of the rat back and determination of the electrical stimulation (rectangular pulses, 0.36-14.0 V, 0.3 ms, 50 Hz) threshold initiating the surface muscle contraction, the animals will be

injected with 0.5% solution of the tested compounds or reference drugs in saline (0.2 mL, intradermally and 0.2 mL, subcutaneously). The electrical stimulation required to cause the muscle contraction will be measured in 3 and 5 min after the injection; then the measurements will be continued with 5 min intervals until recovery to the initial threshold value. The depth of anaesthesia will be expressed as a percentage change in the stimulation threshold compare to the initial value. Increase of the stimulation threshold value more than 2 times will be considered as 100% anaesthesia. Each synthesized compound will be evaluated on 6 rats.

### Hepatotoxicity study

#### Liver Enzyme Estimation

Adult male albino rats (150-175 g) of Wistar strain were used to find out the toxic effects, if any, of the synthesized compounds on liver. The biochemical parameters such as serum glutamate oxaloacetate transaminase (SGOT) and serum gluta-

mate pyruvate transaminase (SGPT) were estimated by the Reitman and Frankel's method (17) while alkaline phosphatase (ALP) was measured by using King's method (18).

### *In-silico* bioactivity study

All the synthesized compounds were evaluated for their oral bioavailability, physicochemical properties, toxicity and online pharmacological activity by utilizing online Osiris Property Explorer, Molinspiration computational study. Lipophilicity (C logP), water solubility (C logS), molecular weight (MW), number of rotatable bonds (NROTB) of Lipinski's rule of five (19-21), drug likeness and toxicity were calculated using online Molinspiration property calculation toolkit and online OSIRIS Property explorer. With the help of Osiris Property Explorer software toxicities were predicted which indicated that the synthesized compounds would be free of mutagenicity, tumorigenicity, reproductive side effects and irritation.

Table 1. *In silico* physicochemical properties for oral bioavailability and bioactivity of the test compounds (**4a-t**) as evaluated utilizing computational predictive software.

Compd	X	Z	C LogP	C LogS	Mol.Wt.	Rotatable bonds	Drug likeness	Drug score	TPSA	Toxicity
<b>4a</b>	H	S	0.82	-2.3	279	3	3.52	0.92	86.74	NM, NC
<b>4b</b>	H	O	0.42	-1.61	263	3	2.6	0.92	70.67	NM, NC
<b>4c</b>	H	CH <sub>2</sub>	1.58	-2.5	261	3	1.55	0.84	61.44	NM, NC
<b>4d</b>	H	N-Me	0.44	-1.54	221	3	0.28	0.76	61.44	NM, NC
<b>4e</b>	H	N-Et	1.26	-2.14	249	5	3.78	0.93	61.44	NM, NC
<b>4f</b>	4-CH <sub>3</sub>	S	1.16	-2.64	293	3	3.78	0.90	86.74	NM, NC
<b>4g</b>	4-CH <sub>3</sub>	O	0.76	-1.95	277	3	2.85	0.91	70.67	NM, NC
<b>4h</b>	4-CH <sub>3</sub>	CH <sub>2</sub>	1.92	-2.84	275	3	1.78	0.83	61.44	NM, NC
<b>4i</b>	4-CH <sub>3</sub>	N-Me	1.60	-2.49	263	3	4.05	0.91	61.44	NM, NC
<b>4j</b>	4-CH <sub>3</sub>	N-Et	0.79	-1.89	235	5	0.57	0.78	61.44	NM, NC
<b>4k</b>	4-OCH <sub>3</sub>	S	0.75	-2.31	309	4	3.95	0.91	95.97	NM, NC
<b>4l</b>	4-OCH <sub>3</sub>	O	0.34	-1.63	293	4	3.0	0.92	79.90	NM, NC
<b>4m</b>	4-OCH <sub>3</sub>	CH <sub>2</sub>	1.51	-2.52	291	4	1.89	0.85	70.67	NM, NC
<b>4n</b>	4-OCH <sub>3</sub>	N-Me	1.19	-2.16	279	4	4.18	0.92	70.67	NM, NC
<b>4o</b>	4-OCH <sub>3</sub>	N-Et	0.37	-1.56	251	6	0.77	0.80	70.67	NM, NC
<b>4p</b>	4-Cl	S	1.42	-3.03	313	3	5.93	0.88	86.74	NM, NC
<b>4q</b>	4-Cl	O	1.02	-2.35	297	3	4.98	0.92	70.67	NM, NC
<b>4r</b>	4-Cl	CH <sub>2</sub>	2.18	-3.23	295	3	3.91	0.86	61.44	NM, NC
<b>4s</b>	4-Cl	N-Me	1.86	-2.88	283	3	6.18	0.89	61.44	NM, NC
<b>4t</b>	4-Cl	N-Et	1.05	2.28	255	5	2.93	0.91	61.44	NM, NC

C LogP: Lipophilicity, cLogS: Water solubility, TPSA: Topological polar surface area, NM: Non mutagenic, NC: Non carcinogenic, SM: Slightly mutagenic, NP: not predicted.

RESULTS

*In silico* physicochemical data of the synthesized compounds are given in Tables 1. In Table 2, surface anaesthetic activity data of the synthesized compounds are presented. Table 3 displays infiltration anesthesia activity data of compounds **4h**, **4i**, **4j**, **4m**, **4n** and **4o**. The results of hepatotoxicity study of aforementioned compounds are presented in Table 4.

DISCUSSION

Chemistry

As per the scheme outlined in Figure 2, N-(2-oxo-2-(phenylamino) ethyl) substituted-4-carboxamide derivatives were synthesized. Initially, on stirring of chloro acetyl chloride in substituted ani-

line in dimethyl formamide (DMF) in presence of K<sub>2</sub>CO<sub>3</sub> at room temperature, the 2-chloro-N-phenylacetamide (**1**) was attained. Further it was refluxed with ammonia in presence of absolute ethanol to get a 2-amino-N-phenylacetamide (**2**). In another step the different substituted amine was stirred at room temperature in the presence of pyridine and ethyl chloroformate, the ethyl substituted -4-carboxylate (**3**) was obtained. Finally, the equimolar mixture of compound (**2**) and (**3**) were refluxed in absolute alcohol to get a titled compounds N-(2-oxo-2-(phenylamino) ethyl) substituted-4-carboxamide (**4a-t**) (Figure 2). The structures of varied N-(2-oxo-2-(phenylamino) ethyl) substituted-4-carboxamide derivatives (**4a-t**) were elucidated by combined use of infrared (IR) and <sup>1</sup>H NMR data. In <sup>1</sup>H NMR spectra, the D<sub>2</sub>O exchangeable broad singlet peak was observed around δ 6.78 confirming NH protons of

Table 2. Surface anaesthetic activity data of the synthesized compounds (**4a-4t**).

Compound	X	Z	Surface anaesthesia (rabbit corneal reflex)	
			Regnier Index <sup>a</sup> ± SEM	Duration, Min ± SEM
<b>4a</b>	H	S	(-)	(-)
<b>4b</b>	H	O	(-)	(-)
<b>4c</b>	H	CH <sub>2</sub>	277.5 ± 51.7	14.7 ± 6.4
<b>4d</b>	H	N-Me	429.0 ± 37.9	20.3 ± 1.7
<b>4e</b>	H	N-Et	473.5 ± 91.3	21.8 ± 1.4
<b>4f</b>	4-CH <sub>3</sub>	S	434.8 ± 65.7	20.3 ± 3.7
<b>4g</b>	4-CH <sub>3</sub>	O	746.0 ± 38.9	43.4 ± 5.6
<b>4h</b>	4-CH <sub>3</sub>	CH <sub>2</sub>	1139.0 ± 57.1	69.7 ± 3.9
<b>4i</b>	4-CH <sub>3</sub>	N-Me	838.0 ± 53.9	41.4 ± 4.1
<b>4j</b>	4-CH <sub>3</sub>	N-Et	1083.0 ± 79.3	56.0 ± 4.9
<b>4k</b>	4-OCH <sub>3</sub>	S	743.6 ± 83.5	47.8 ± 3.2
<b>4l</b>	4-OCH <sub>3</sub>	O	879.7 ± 56.6	53.8 ± 7.3
<b>4m</b>	4-OCH <sub>3</sub>	CH <sub>2</sub>	1197.0 ± 34.2	77.5 ± 1.6
<b>4n</b>	4-OCH <sub>3</sub>	N-Me	834.5 ± 51.3	39.5 ± 3.7
<b>4o</b>	4-OCH <sub>3</sub>	N-Et	1069.0 ± 33.4	61.2 ± 5.9
<b>4p</b>	4-Cl	S	(-)	(-)
<b>4q</b>	4-Cl	O	(-)	(-)
<b>4r</b>	4-Cl	CH <sub>2</sub>	373.5 ± 53.8	16.7 ± 1.7
<b>4s</b>	4-Cl	N-Me	537.5 ± 67.0	23.7 ± 1.4
<b>4t</b>	4-Cl	N-Et	749.8 ± 67.5	31.3 ± 2.1
Lidocaine			791.7 ± 45.9	41.8 ± 4.3
Bupivacaine			1216.0 ± 39.7	93.0 ± 2.7

<sup>a</sup>Regnier index-Indicator of the anaesthesia depth during first 60 min after the compound application expressed as a sum of the threshold tactile stimuli needed to induce corneal reflex (13 series, up to 100 stimuli per one series). (-) indicates absent of anesthetic activity



Table 3. Duration of muscle contraction blockade (duration of anesthesia, Time in min) and % onset of depth of anesthesia in an experimental model of Infiltration anesthesia activity assay in Wistar rats.

Compound	Duration of anesthesia (time in min) and % Onset of depth of anesthesia											
	0	3	10	20	40	60	80	100	120	140		
4h	00 ± 00 100%	00 ± 00 100%	10.02 ± 0.1 (97.6 ± 3.1)	15.60 ± 4.10 (95.83 ± 6.1)	25.30 ± 7.21 (90.16 ± 8.1)	35.26 ± 10.20 (69.13 ± 11.2)	63.47 ± 12.41 (47.28 ± 6.1)	85.29 ± 15.2 (27.6 ± 3.1)	110.31 ± 45.23 (17.2 ± 6.12)	118.36 ± 51.20 (8.16 ± 1.63)		
4i	00 ± 00 100%	00 ± 00 100%	9.50 ± 0.20 (85.6 ± 6.1)	14.52 ± 3.12 (45.7 ± 8.13)	20.26 ± 4.13 (38.21 ± 4.16)	33.32 ± 6.52 (30.7 ± 6.13)	36.43 ± 8.47 (10.15 ± 1.20)	29.21 ± 1.02 (5.10 ± 3.15)	10.53 ± 3.15 (3.22 ± 0.22)	3.29 ± 2.03 (2.10 ± 1.0)		
4j	00 ± 00 100%	00 ± 00 100%	11.23 ± 1.0 (90.76 ± 4.83)	16.21 ± 2.20 (82.62 ± 5.12)	22.52 ± 6.10 (45.10 ± 9.10)	30.10 ± 5.13 (32.30 ± 6.7)	36.46 ± 6.32 (20.13 ± 1.21)	29.41 ± 10.2 (4.28 ± 0.12)	15.21 ± 6.03 (2.36 ± 1.13)	4.21 ± 1.80 (1.21 ± 1.20)		
4m	00 ± 00 100%	00 ± 00 100%	10.25 ± 2.1 (95.42 ± 6.12)	13.42 ± 6.10 (90.27 ± 8.41)	21.45 ± 5.19 (85.6 ± 14.2)	39.42 ± 11.02 (72.15 ± 11.6)	42.56 ± 4.96 (66.12 ± 15.2)	68.32 ± 12.1 (15.21 ± 4.1)	75.38 ± 17.21 (10.24 ± 1.25)	88.56 ± 10.25 (6.31 ± 3.10)		
4n	00 ± 00 100%	00 ± 00 100%	8.20 ± 3.10 (90.52 ± 5.63)	15.21 ± 5.31 (65.21 ± 8.10)	26.52 ± 9.11 (45.72 ± 4.16)	34.56 ± 8.41 (28.13 ± 2.85)	38.16 ± 11.3 (10.21 ± 1.6)	30.10 ± 11.45 (6.13 ± 1.52)	30.10 ± 11.45 (2.20 ± 0.12)	30.10 ± 11.45 (1.10 ± 0.16)		
4o	00 ± 00 100%	00 ± 00 100%	11.03 ± 4.10 (89.52 ± 3.15)	13.20 ± 5.21 (72.30 ± 6.25)	20.15 ± 8.2 (48.30 ± 7.82)	29.15 ± 9.10 (33.63 ± 4.89)	33.42 ± 2.17 (15.30 ± 7.63)	26.12 ± 8.10 (4.13 ± 2.31)	26.12 ± 8.10 (4.13 ± 2.31)	26.12 ± 8.10 (4.13 ± 2.31)		
Lidocaine	00 ± 00 100%	00 ± 00 100%	9.23 ± 1.0 (99.6 ± 4.2)	12.30 ± 3.16 (86.52 ± 10.2)	30.26 ± 9.32 (75.86 ± 15.32)	35.26 ± 10.20 (65.26 ± 16.3)	75.36 ± 14.32 (43.42 ± 5.32)	95.23 ± 18.10 (32.6 ± 8.32)	109.31 ± 33.25 (15.65 ± 7.10)	115.32 ± 66.32 (10.24 ± 1.63)		
Bupivacaine	00 ± 00 100%	00 ± 00 100%	8.32 ± 1.21 (99.32 ± 8.16)	16.85 ± 2.65 (96.21 ± 3.59)	28.34 ± 4.16 (90.23 ± 9.26)	46.16 ± 15.21 (88.63 ± 15.36)	50.23 ± 5.26 (67.25 ± 18.21)	80.53 ± 18.36 (43.28 ± 10.69)	100.85 ± 16.31 (20.37 ± 6.18)	120.26 ± 43.52 (11.26 ± 3.10)		

Values are expressed in Mean ± SEM, Number of animals used for each group is six. Values in parenthesis are (%) onset of depth of anesthesia

CONH group in 2-chloro-N-phenylacetamide (1) and it was also confirmed by IR spectra which exhibited two absorption bands in the region 3156 and 1668 cm<sup>-1</sup> characteristic peak of N-H and CO stretching which ascertained the presence of CONH group. In second step <sup>1</sup>H NMR spectra bears the D<sub>2</sub>O exchangeable broad singlet peak around δ 3.21 integrating two protons of NH<sub>2</sub> make certain of CH<sub>2</sub>NH<sub>2</sub> group in 2-amino-N-phenylacetamide (2). Disappearance of NH<sub>2</sub> and appearance of CONH which is attached with amine peak in <sup>1</sup>H NMR spectra was observed at δ 10.83 and IR spectra also revealed specific stretching vibrations of 3156, 3268 (N-H), 1665 (C=O), 1632 (C=N), 1556 (C=C), 1024 (C-N) cm<sup>-1</sup> were confirmed the titled compound.

Surface local anaesthetic activity

All the synthesized compounds were evaluated for their surface anaesthetic activity on white New Zealand rabbits using the corneal reflex test. Due to high sensitivity and relative simplicity, this test was used as the initial screening model for anaesthetic activity. Most of the synthesized compounds were found to retain surface anaesthetic activity at 1% concentration (Table 2). The structure activity relationship analysis revealed some important features were responsible for the anaesthetic effect of the compounds. Rigorous study of previously reported compounds bears classical substitution pattern in the aromatic ring for local anaesthetics of the arylamide classes of marketed drugs (Fig. 1). Characteristically the compounds possess one methyl group in the ortho-position (e.g. Prilocaine), two on meta (e.g. Bupivacaine, Lidocaine and Ropivacaine) and third one in para-position (e.g. Cyclomecaine, Trimecaine and Pyromecaine). In our series of compounds we found that either methyl or methoxy substituent at para position possess optimal anaesthetic activity. Slight change of methyl to methoxy on para position (4h) and (4m) group vividly increase surface local anaesthetic activity. Altering the methyl group to

chloro group at para position significantly decreased surface local anaesthetic activity and duration of the surface anaesthesia. Also without substitution on aryl ring, there was a substantial decrease of their activity (**4a**, **4b**). We also observed that the carboxamide extension of previously mentioned (e.g., lidocaine, bupivacaine, levobupivacaine, mepivacaine etc) compounds must be responsible for the anaesthetic activity. Coincidentally, our synthetic compounds also possess carboxamide extension and substitution of secondary amine for better local anaesthetic activity. Replacement of cyclic amine with S and O in case of morpholine and thiomorpholine (**4f**, **4g**, **4k** and **4l**) kept least activity in comparison of substituted piperidines (**4h** and **4m**) which hold potent surface local anaesthetic activity. The compounds (**4i**, **4j**, **4n** and **4o**) possess significant surface local anaesthetic activity whereas, compounds (**4c**, **4d**, **4e**, **4r**, **4s** and **4t**) displayed least activity. Compounds (**4a**, **4b**, **4p** and **4q**) showed absent of surface local anaesthetic activity. All these above explanations were found to be promising for

the further development of this class of local anaesthetics.

#### Infiltration local anaesthetic activity

All active compounds from surface local anaesthesia study were evaluated for infiltration local anaesthetic activity on rats. The anaesthetic activity was considered by the duration of blocking of muscle contraction as onset, depth and duration. The electric current (0.3 ms, 50 Hz, 0.36-14.0V) were used for stimulation of contractions. Anaesthetic activity was expressed as percentage increase of stimulation threshold; if stimulation threshold value increases more than two from initial then it was reflected as complete (100%) anaesthesia (Table 3).

After the administration of potent compounds (**4h**, **4i**, **4j**, **4m**, **4n** and **4o**) and reference drugs to the animals, these agents showed fast onset of action in blocking the muscle contractions within 3 min. The duration of anaesthesia caused by the tested compounds (**4h**, **4i**, **4j**, **4m**, **4n** and **4o**) and reference

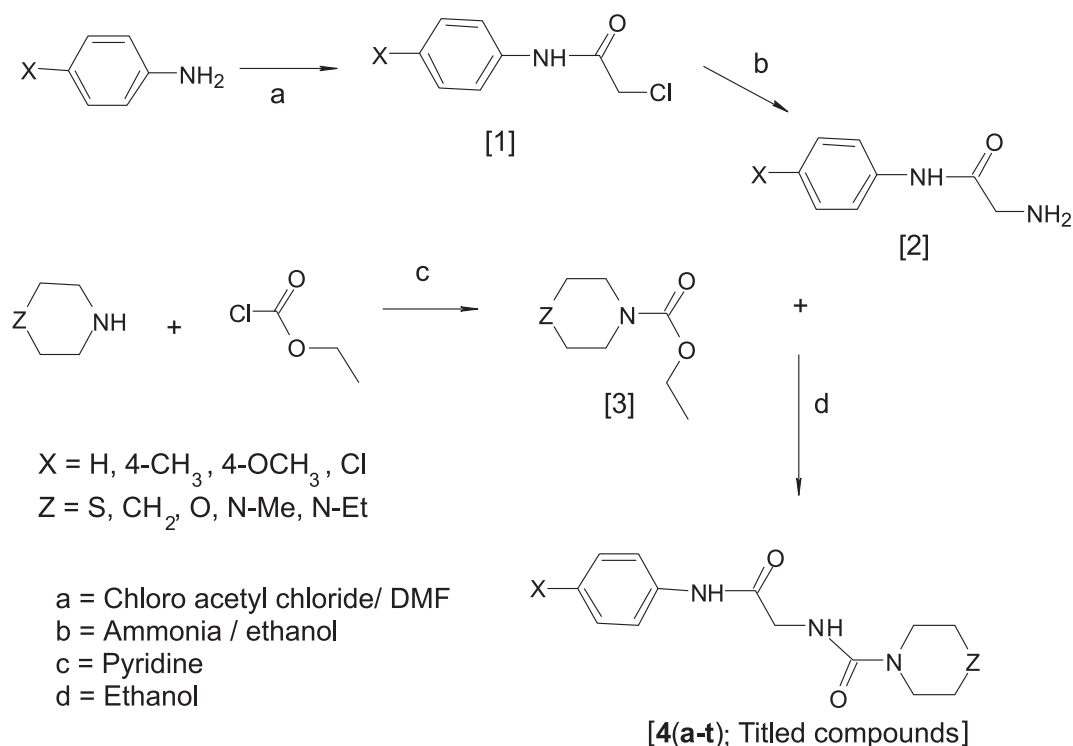


Figure 2. Route of synthesis of Substituted N-(2-oxo-2-(phenylamino) ethyl) thiomorpholine-4-carboxamide derivatives (**4a-t**). Reagent and conditions: (a) Chloroacetylchloride/DMF refluxes (b) Ammonia / Ethanol, Stirring with reflux. (c) Pyridine, Stirring at room temperature (d) Absolute Ethanol, reflux



Table 4. Enzyme estimation of the most active compounds.

Compound	ALP (KA unit/dL) (Mean $\pm$ SEM )	SGOT (IU/L) (Mean $\pm$ SEM )	SGPT (IU/L) (Mean $\pm$ SEM )
<b>4h</b>	28.05 $\pm$ 1.02	32.95 $\pm$ 1.21	36.35 $\pm$ 1.25
<b>4i</b>	36.26 $\pm$ 1.32**	35.21 $\pm$ 1.55	39.37 $\pm$ 1.64
<b>4j</b>	25.97 $\pm$ 1.18	32.84 $\pm$ 1.48	35.22 $\pm$ 1.28
<b>4m</b>	26.43 $\pm$ 0.98	33.05 $\pm$ 1.17	37.94 $\pm$ 1.06
<b>4n</b>	35.54 $\pm$ 1.09*	44.31 $\pm$ 2.07**	38.06 $\pm$ 1.93
<b>4o</b>	28.05 $\pm$ 1.21	32.09 $\pm$ 1.13	39.50 $\pm$ 1.70*
Control	24.42 $\pm$ 1.09	29.87 $\pm$ 1.88	34.28 $\pm$ 1.05

The concentrations of SGPT and SGOT are expressed in international unit per liter whereas for alkaline phosphatase, the concentration is expressed KA unit per deciliter. Number of animals tested (n = 6). \*Indicate significant difference from control (P < 0.05), \*\* indicate significant difference from control (P < 0.005). Mean  $\pm$  SEM values were calculated using ANOVA followed by Dunnett's multiple comparison test

compound were ranged. Then reactions from 35  $\pm$  5.3 to 119  $\pm$  18.4 min were carried out (Table 3). The muscle contraction was completely blocked by the test and reference compound and the action was immediate after the administration. The compounds (**4h**, **4i**, **4j**, **4m**, **4n** and **4o**) which completely block the stimulated muscle contraction and the duration of action were found maximum as compared with reference drug. The depth of anaesthesia for compounds **4i**, **4j**, **4m**, **4n** and **4o** were decreases abruptly and the threshold values return to the normal in 38.42  $\pm$  5.32 min after application. The compounds **4h** and **4m** (with lidocaine and bupivacaine) completely blocked the muscle contraction at beginning of time, as the duration of complete anaesthesia for **4h** and **4m** was smaller (69.7  $\pm$  3.9 and 77.5  $\pm$  1.6 min) as compared with bupivacaine (93.0  $\pm$  2.7 min). The duration of complete anaesthesia of compound **4i** and **4o** was comparable with lidocaine. Over-all the compounds **4h** and **4m** were more potent than lidocaine and equivalent to bupivacaine for inducing surface anaesthesia, however, the duration of their effects was slightly lower than that of bupivacaine. These compounds were also less compelling than in infiltration anaesthesia assay of bupivacaine and appeared to be less beneficial.

#### Liver toxicity test

Compounds (**4h**, **4m**, **4i**, **4j** **4n** and **4o**) were selected for the liver enzyme analysis as these compounds were found potent in local anesthetic tests. Liver enzyme estimation of these compounds was carried out and the results are shown in Table 4.

Results are expressed in international unit per liter (as mean  $\pm$  SEM) for SGOT and SGPT and KA unit per deciliter for alkaline phosphatase, with six animals in each group. Single asterisk (\*) indicates significant difference from control (P < 0.05), whereas double asterisk (\*\*) indicates significant difference from control (P < 0.005). It was observed that all the values were comparable to the control and the changes seen, were not significant except in case of compounds **4i** and **4n** that showed an elevated alkaline phosphatase value (\*P < 0.05 and \*\*P < 0.005), respectively. Hence it can be concluded that except compounds **4i** and **4n**, the other tested compounds do not possess any adverse effect on liver.

#### In-silico studies

For elaboration of anesthetic drug is a big challenge nowadays for improving of pharmacological profile and the prediction of physicochemical properties. Increased lipophilicity and deprived water solubility is one of the significant parameters for local anesthesia. With the help of online Osiris Property explorer and Molinspiration property calculation toolkit, the drug-likeness characters such as lipophilicity (C logP), water-solubility (C logS), molecular weight (MW), number of rotatable bonds (NROTB), and drug-likeness score of Lipinski's rule of five (19-21) were calculated for the targeted synthesized compounds (**4a-t**) (Table 1). The solubility (C logS), of synthesized compounds were found in an acceptable range (< -4). The lipophilicity-related C logP quantifying target-oriented drug-likeness properties, drug potency, pharmacokinetics

and toxicity analyses were used. Compounds with C logP value < 5 have more favorable drug-likeness profile (22, 23). All the synthesized compounds were found < 5 C logP value which signify their applicability for oral route of administration. Compounds with TPSA values > 60 Å are commonly picked for oral drug molecules (24). All synthesized compounds (**4a-f**) of present series the TPSA values were found in the range of 61.44-95.67 Å which fascinated the structural optimization for development of new derivatives. In distinction of all synthesized compounds influencing drug-likeness scores > 0, all compounds except **4p** and **4s** showed likeness score in between 0.77-5.00 as shown in Table-1. This online prediction software helped in fast recognizing a set of feasible compounds and also suitable for selection of compounds for biological activities.

## CONCLUSION

N-(2-oxo-2-(phenylamino) ethyl) substituted-4-carboxamide derivatives were synthesized and evaluated for local anesthetic activity and liver toxicity. Among the tested compounds, N-(2-oxo-2-(phenylamino) ethyl) piperidine-1-carboxamide (**4h**) and N-(2-((4-methoxyphenyl) amino)-2-oxoethyl) piperidine-1-carboxamide (**4m**) were most promising compounds in terms of surface local anaesthetic and infiltration local anaesthetic activity on rats having considerably lower toxicity than the reference drugs. All these experimental data revealed that these compounds might serve as candidates for local anaesthetic agents as lead compounds for further design and development as local anaesthetic agents with low toxicity profile.

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