Full Paper

Synthesis and Local Anesthetic Activity of Some Novel *N*-[5-(4-Substituted)phenyl-1,3,4-oxadiazol-2-yl]-2-(Substituted)-Acetamides

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A novel series of acetamides carrying substituted-1,3,4-oxadiazole moiety were synthesized from reaction of 5-aryl-2-chloroacetamido-1,3,4-oxadiazoles with different secondary amines. The local anesthetic potential of the compounds was investigated using rabbit corneal reflex method and guinea pig's wheal derm method. The present work is the only one of its kind reporting local anesthetic activity in acetamide system combined with 1,3,4-oxadiazole nucleus. Lidocaine was selected as standard drug in evaluation of local anesthetic activity of synthesized oxadiazole analogues. Compound **19** was found to possess significant local anesthetic activity in both the models employed for evaluation of local anesthetic activity. Compound **20, 23, 28, 29** and **35** also demonstrated marked local anesthetic activities. Structure-activity relationships among synthesized compounds were also established.

Keywords: Corneal anesthesia in rabbits / Infiltration anesthesia in guinea pigs / Local anesthetic activity / Oxadiazoles

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Introduction

A local anesthetic agent is a drug that, when given either topically or parenterally to a localized area, produces a state of local anesthesia by reversibly blocking the conduction of neural messages in sensory, motor, and autonomic nerves to produce temporary loss of consciousness. It prevents both the generation and conduction of the nerve impulses in a circumscribed area by binding to the sodium channel and blocking sodium entry into neuron [1]. Local anesthetics are widely used clinically in dentistry and in other minor surgery for temporary relief from pain. Amides (lidocaine, bupivacaine) along with esters (procaine, tetracaine) are the major classes of local anesthetic drugs.

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The success of lidocaine as a local anesthetic agent has speeded up the synthesis and pharmacological evaluation of its numerous analogues and homologues. Modifications of the aminoacyl portion of this structure and the effect of these modifications on biological activity have been studied extensively [2 – 5].

1,3,4-Oxadiazoles are well known for their variety of biological activities including anti-inflammatory [6 – 8], hypoglycemic [9, 10], anticonvulsant [11, 12], anti-anxiety and antidepressant [13] activities.

Considering the importance of acetamides as local anesthetic agents, we were encouraged to synthesize some novel *N*-[5-(4-substituted)phenyl-1,3,4-oxadiazol-2-yl]-2-(substituted)-acetamides, hitherto unreported for their local anesthetic property. The aim behind this was to search for a better local anesthetic agent and to observe the effect of combining 1,3,4-oxadiazole nucleus to the acetamide system. The present work is unique in the sense that the possession of local anesthetic activity in compounds containing 1,3,4-oxadiazole as structural unit has not been reported so far.

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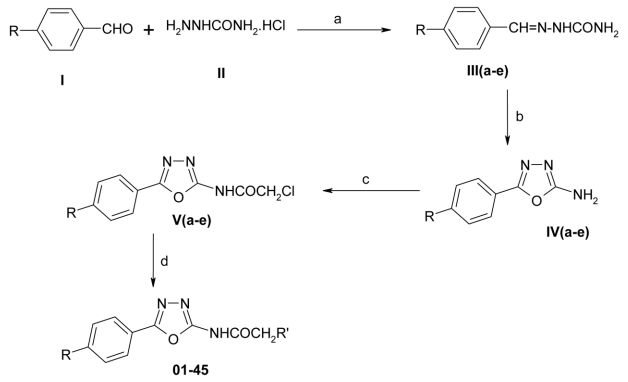

Compound Code	R	Compound Code	R	Compound Code	R	Compound Code	R	Compound Code	R
IIIa	Cl	**IIIb**	NO_2	**IIIc**	CH_3	**IIId**	F	**IIIe**	OH
IVa	Cl	**IVb**	NO_2	**IVc**	CH_3	**IVd**	F	**IVe**	OH
Va	Cl	**Vb**	NO_2	**Vc**	CH_3	**Vd**	F	**Ve**	OH

Reagents and conditions: (a) CH_3COONa, distilled water, rt; (b) CH_3COONa, CH_3COOH, Br_2, 30 min stirring, rt; (c) $ClCH_2COCl$, C_6H_6, reflux, 3 h; (d) secondary amine, C_2H_5OH, dry pyridine, reflux, 6 h.

Scheme 1. Synthesis of 1,3,4-oxadiazole analogues 1–45.

Results and discussion

Chemistry

The title compounds were prepared using the scheme described in Scheme 1. The title compounds, i. e. 2-(substituted)-ethanoylamino-5-(*p*-substituted)phenyl-1,3,4-oxadiazoles were prepared by the reaction of 5-aryl-2-chloroacetamido-1,3,4-oxadiazoles with various secondary amines. The first step of the synthetic strategy involves preparation of semicarbazones **IIIa–e** by reaction of semicarbazide hydrochloride with different aromatic aldehydes. Semicarbazones **IIIa–e** were cyclized to 2-amino-5-aryl-1,3,4-oxadiazoles **IVa–e** by oxidative cyclization with bromine. 2-Amino-5-aryl-1,3,4-oxadiazoles **IVa–e** were acetylated with chloroacetyl chloride to give 5-aryl-2-chloroacetamido-1,3,4-oxadiazoles **Va–e**, from which title compounds **1–45** were synthesized.

The yield of the final compounds, their melting points, and elemental analysis (percentage C, H and N analysis) found are given in Table 1. The structures of the title compounds were elucidated on the basis of elemental analysis, IR, ^{13}C-NMR, and mass spectral data. The rationale for using ^{13}C-NMR rather than ^{1}H-NMR spectroscopy for characterization of compounds is that the nucleus of the title compounds, i. e. oxadiazole does not possess any proton(s), thus to confirm the formation of nucleus, ^{13}C-NMR is more essential than ^{1}H-NMR spectroscopy.

IR data of the synthesized oxadiazole analogues clearly show C=N stretching and C–O absorption bands around 1660 cm^{-1} and around 1090 cm^{-1}, respectively, which indicates ring closure of 1,3,4-oxadiazole ring. All the final compounds have a strong absorption around 3060 cm^{-1} which is evidence for the presence of aromatic C–H bonds. Presence of aromatic C–C bonds was confirmed by presence of absorption bands around 1602 and 1501 cm^{-}. IR data also confirm the presence of specific functional groups present in the final synthesized compounds. In ^{13}C-NMR spectra, C-2 and C-5 of the oxadiazole nucleus were seen around 171 and 168 ppm, respectively. The chemical shift of all other carbons of final compounds was seen as expected. The mass spectra of the title compounds were in conformity with the assigned structure. The mass spectra of these compounds showed molecular ion peaks corresponding to their molecular formula (Table 2).

Local anesthetic activity

All the compounds were found to possess diverse local anesthetic properties, in both the models selected, in the present local anesthetic studies. In the rabbit corneal reflex method, the onset of local anesthesia and the duration of anesthesia were 6 to 10 min and 18 to 27 min, respectively. On the other hand, in the guinea pig wheal derm method, the onset of action and the duration of action were 8 to 14 min and 24 to 37 min, respectively (Table 3).

A result of the rabbit corneal reflex method indicates that among the synthesized compounds, maximum local anesthetic activity was exhibited by compound **19** with the onset of action and the duration of action lasting for 6 and 27 min, respectively. Minimum activity was shown by compound **36** with the onset of action and the duration of action lasting for 10 and 18 min, respectively. Other compounds showing considerable activity were **20**, **23**, **28**, **32**, and **38**.

In order to evaluate the local anesthetic potential of the synthesized oxadiazoles, test compounds were also subjected to the guinea pig wheal derm method. Almost similar results were observed in these studies. Maximum activity was shown by compound **19** with the onset of action and the duration of action lasting for 8 and 37 min, respectively. Minimum activity was exhibited by compound **36** with the onset of action and duration of action that lasted for 13 and 25 min, respectively. Other compounds showed moderate local anesthetic activity.

The result of structure-activity studies among the synthesized oxadiazole analogues showed that local anesthetic activity is sensitive to structural changes. Among all the synthesized oxadiazole analogues, the most active compound was **19**, which possesses a methyl group on the benzene ring attached to C-2 of the oxadiazole nucleus and a diethylamino moiety attached to the acetamido group. The other striking point to be considered is

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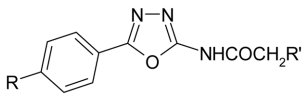
Table 1. Physical data of the synthesized oxadiazoles

.



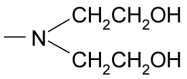
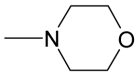
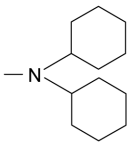
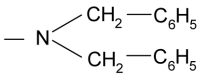
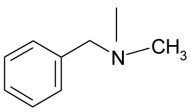
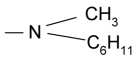
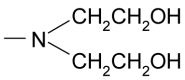
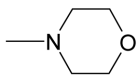
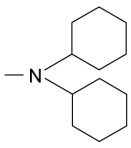
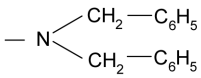
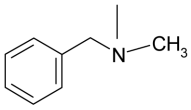
Compound Code	R	R′	Mol. formula (Mol. Wt.)	Mp. (°C)	Yield (%)
1	-Cl	$-N(CH_2CH_3)_2$	$C_{14}H_{17}N_4O_2Cl$ (308.76)	232	68
2	-Cl	$-N(CH_2CH_2CH_3)_2$	$C_{16}H_{21}N_4O_2Cl$ (336.81)	257	68
3	-Cl	$-N(CH_2CH_2CH_2CH_3)_2$	$C_{18}H_{25}N_4O_2Cl$ (364.86)	244	70
4	-Cl		$C_{14}H_{17}N_4O_4Cl$ (340.76)	272	65
5	-Cl		$C_{14}H_{15}N_4O_3Cl$ (322.74)	190	68
6	-Cl		$C_{22}H_{29}N_4O_2Cl$ (416.94)	237	69
7	-Cl		$C_{24}H_{21}N_4O_2Cl$ (432.90)	203	62
8	-Cl		$C_{18}H_{17}N_4O_2Cl$ (356.80)	248	64
9	-Cl		$C_{17}H_{21}N_4O_2Cl$ (348.82)	252	60
10	$-NO_2$	$-N(CH_2CH_3)_2$	$C_{14}H_{17}N_5O_4$ (319.32)	179	67
11	$-NO_2$	$-N(CH_2CH_2CH_3)_2$	$C_{16}H_{21}N_5O_4$ (347.36)	189	68
12	$-NO_2$	$-N(CH_2CH_2CH_2CH_3)_2$	$C_{18}H_{25}N_5O_4$ (375.42)	207	66
13	$-NO_2$		$C_{14}H_{17}N_5O_6$ (351.31)	236	62
14	$-NO_2$		$C_{14}H_{15}N_5O_5$ (333.29)	228	65
15	$-NO_2$		$C_{22}H_{29}N_5O_4$ (427.49)	240	64
16	$-NO_2$		$C_{24}H_{21}N_5O_4$ (443.45)	256	62
17	$-NO_2$		$C_{18}H_{17}N_5O_4$ (367.35)	244	60

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Table 1. Continued.

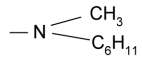
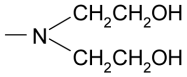
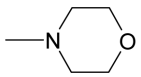
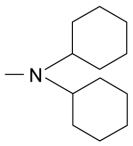
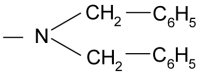
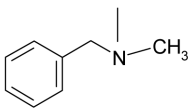
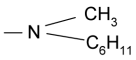
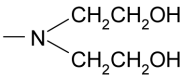
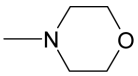
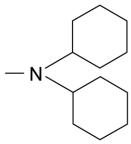
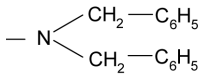
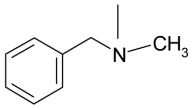
Compound Code	R	R′	Mol. formula (Mol. Wt.)	Mp. (°C)	Yield (%)
18	-NO_2		$C_{17}H_{21}N_5O_4$ (359.37)	268	58
19	-CH_3	-$N(CH_2CH_3)_2$	$C_{15}H_{20}N_4O_2$ (288.34)	161	64
20	-CH_3	-$N(CH_2CH_2CH_3)_2$	$C_{17}H_{24}N_4O_2$ (316.39)	152	62
21	-CH_3	-$N(CH_2CH_2CH_2CH_3)_2$	$C_{19}H_{28}N_4O_2$ (344.45)	166	64
22	-CH_3		$C_{15}H_{20}N_4O_4$ (320.34)	220	60
23	-CH_3		$C_{15}H_{18}N_4O_5$ (302.32)	185	56
24	-CH_3		$C_{23}H_{32}N_4O_2$ (396.52)	237	57
25	-CH_3		$C_{25}H_{24}N_4O_2$ (412.48)	188	54
26	-CH_3		$C_{19}H_{20}N_4O_2$ (336.38)	207	60
27	-CH_3		$C_{18}H_{24}N_4O_2$ (328.40)	214	56
28	-F	-$N(CH_2CH_3)_2$	$C_{14}H_{17}N_4O_2F$ (292.30)	210	56
29	-F	-$N(CH_2CH_2CH_3)_2$	$C_{16}H_{21}N_4O_2F$ (320.36)	218	54
30	-F	-$N(CH_2CH_2CH_2CH_3)_2$	$C_{18}H_{25}N_4O_2F$ (348.11)	229	55
31	-F		$C_{14}H_{17}N_4O_4F$ (324.30)	234	53
32	-F		$C_{14}H_{15}N_4O_3F$ (306.29)	241	54
33	-F		$C_{22}H_{29}N_4O_2F$ (400.48)	213	55
34	-F		$C_{24}H_{21}N_4O_2F$ (416.44)	232	57
35	-F		$C_{18}H_{17}N_4O_2F$ (340.42)	212	53

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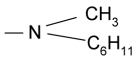
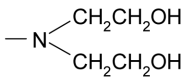
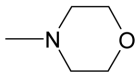
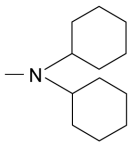
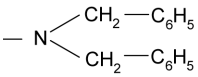
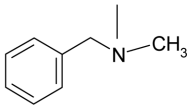
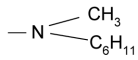
Table 1. Continued.

Compound Code	R	R′	Mol. formula (Mol. Wt.)	Mp. (°C)	Yield (%)
36	-F		$C_{17}H_{21}N_4O_2F$ (332.37)	222	52
37	-OH	$-N(CH_2CH_3)_2$	$C_{14}H_{18}N_4O_3$ (290.31)	207	64
38	-OH	$-N(CH_2CH_2CH_3)_2$	$C_{16}H_{22}N_4O_3$ (318.37)	212	62
39	-OH	$-N(CH_2CH_2CH_2CH_3)_2$	$C_{18}H_{26}N_4O_3$ (346.42)	256	60
40	-OH		$C_{14}H_{18}N_4O_5$ (322.31)	242	59
41	-OH		$C_{14}H_{16}N_4O_4$ (304.30)	225	57
42	-OH		$C_{22}H_{30}N_4O_3$ (398.49)	163	60
43	-OH		$C_{24}H_{22}N_4O_3$ (414.45)	155	56
44	-OH		$C_{18}H_{18}N_4O_3$ (338.36)	232	59
45	-OH		$C_{17}H_{22}N_4O_3$ (330.38)	183	55

that among all the compounds **8**, **15**, **17**, **26**, **36**, and **39** possess very weak local anesthetic activity. The compounds with a methyl group, i. e. **19**, **20**, and **23** possess considerably more activity in comparison to the compounds carrying a hydroxy group, i. e. **39, 44**, and **45**. Replacement of the methyl group with other groups on the aryl moiety, i. e. hydroxy, chloro, or nitro groups resulted in clearly decreased local anesthetic activities in both local anesthetic models. A *N*-substituted moiety present on the right side of molecules also appears to contribute to the local anesthetic activity. Compounds with appreciable local anesthetic activity, i. e. **1**, **19**, **20**, **23**, **28**, **32**, **37**, and **41** were found to possess *N,N*-diethylamino, morpholino, *N,N*-dipropylamino, *N,N*-diethanolamino moieties. On other hand, compounds with weak local anesthetic activity, like **8**, **15**, **16**, **26**, **30**, **35**, **36**, **39**, and **42** were found to possess *N*-methyl benzylamino, *N,N*-dibutylamino, and *N,N*-dicyclohexylamino groups. Thus, by going through the structure-activity relationship among the synthesized oxadiazole analogues, it can be said that methyl, fluoro, *N,N*-diethylamino, morpholino, *N,N*-dipropylamino, and *N,N*-diethanolamino groups are responsible for imparting local anesthetic activity to the oxadiazole nucleus in the present studies.

Structures of the presently studied compounds with different interesting substitutents around 1,3,4-oxadiazole nucleus were found to possess all essential structural features [14–16] i. e., a lipophilic moiety usually of aromatic nature, an intermediate amide chain, and a hydrophilic part, often a substituted amino group, required for the local anesthetic activity. Comparison of the structural features of lidocaine with compound **19** as a local anesthetic agent is to be seen in Fig. 1.

Presence of local anesthetic activity in the presently studied oxadiazoles may be due to the presence of lipophilic portions. A high lipophilic nature of oxadiazole analogues appears to play an important role in the binding of local anesthetics to the channel receptor resulting in appearance of local anesthetic activity. Thus, confirm-

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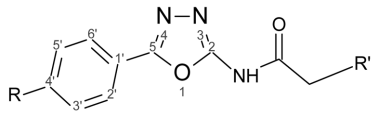
Table 2. Spectral data of the synthesized oxadiazole analogues.



Compound Code	IR (cm^{-1}) (KBr)	^{13}C-NMR δ (ppm) (DMSO-d_6, TMS)	ESMS (Methanol) m/z Molecular ion peak & Fragment
1	3065.1 (Aromatic C-H str), 1091.6 (C-O of 1,3,4-oxadiazole nucleus), 1659.8 (C=N of 1,3,4-oxadiazole nucleus), 1602.5 & 1509.6 (Aromatic C-C str), 1304.2 (C-N str tertiary amino group), 1687.0 (C=O str of amide), 3356.4 (N-H str of amide), 2935.4 (aliphatic C-H str), 1433.5 (aliphatic C-H def), 829.9 (C-H def disubstituted benzene ring), 709.8 (C-Cl str).	128.4 (C-2′ & C-6′), 129.6 (C-3′ & C-5′), 133.6 (C-4′), 134.8 (C-1′), 171.4 (C-2), 169.1 (C-5), 174.5 NH*C*OCH$_2$N), 13.3 (*C*H$_3$CH$_2$N), 45.8 (CH$_3$*C*H$_2$N), 57.3 (NHCO*C*H$_2$N).	309, 86
2	3068.3 (Aromatic C-H str), 1094.0 (C-O of 1,3,4-oxadiazole nucleus), 1658.0 (C=N of 1,3,4-oxadiazole nucleus), 1603.8 & 1509.5 (Aromatic C-C str), 1303.2 (C-N str tertiary amino group), 1687.4 (C=O str of amide), 3360.1 (N-H str of amide), 2931.8 (aliphatic C-H str), 1434.1 (aliphatic C-H def), 831.6 (C-H def di-substituted benzene ring), 708.4 (C-Cl str).	128.2 (C-2′ & C-6′), 129.7 (C-3′ & C-5′), 133.9 (C-4′), 134.3 (C-1′), 171.3 (C-2), 168.5 (C-5), 174.7 NH*C*OCH$_2$N), 11.6 (*C*H$_3$CH$_2$CH$_2$N), 21.4 (CH$_3$*C*H$_2$CH$_2$N), 55.8 (CH$_3$CH$_2$*C*H$_2$N), 57.6 (NHCO*C*H$_2$N).	353, 114
3	3068.3 (Aromatic C-H str), 1092.0 (C-O of 1,3,4-oxadiazole nucleus), 1657.8 (C=N of 1,3,4-oxadiazole nucleus), 1604.2 & 1509.1 (Aromatic C-C str), 1302.7 (C-N str tertiary amino group), 1687.8 (C=O str of amide), 3362.6 (N-H str of amide), 2932.6 (aliphatic C-H str), 1433.0 (aliphatic C-H def), 832.4 (C-H def di-substituted benzene ring), 705.8 (C-Cl str).	128.3 (C-2′ & C-6′), 129.6 (C-3′ & C-5′), 133.7 (C-4′), 134.2 (C-1′), 171.5 (C-2), 168.2 (C-5), 174.4 (NH*C*OCH$_2$N), 13.8 (*C*H$_3$CH$_2$CH$_2$CH$_2$N), 20.5 (CH$_{3C}$H$_2$CH$_2$CH$_2$N), 31.1 (CH$_3$CH$_2$*C*H$_2$CH$_2$N), 53.5 (CH$_3$CH$_2$CH$_2$*C*H$_2$N), 57.6 (NHCO*C*H$_2$N).	365, 142
4	3062.3 (Aromatic C-H str), 1093.2 (C-O of 1,3,4-oxadiazole nucleus), 1658.3 (C=N of 1,3,4-oxadiazole nucleus), 1602.8 & 1599.0 (Aromatic C-C str), 1305.0 (C-N str tertiary amino group), 1691.4 (C=O str of amide), 3372.6 (N-H str of amide), 2922.9 (aliphatic C-H str), 1432.7 (aliphatic C-H def), 830.5(C-H def di-substituted benzene ring), 708.3 (C-Cl str), 3459.3 (O-H str of alcoholic group), 1164.0 (C-O str of alcoholic group).	128.2 (C-2′ & C-6′), 129.5 (C-3′ & C-5′), 133.8 (C-4′), 134.4 (C-1′), 171.2 (C-2), 168.4 (C-5), 174.6 (NH*C*OCH$_2$N), 57.4 (NHCO*C*H$_2$N), 62.3 (OH*C*H$_2$CH$_2$N), 56.1 (OHCH$_2$*C*H$_2$N).	341, 118
5	3059.4 (Aromatic C-H str), 1091.3 (C-O of 1,3,4-oxadiazole nucleus), 1662.1 (C=N of 1,3,4-oxadiazole nucleus), 1597.5, 1499.3 (Aromatic C-C str), 1306.2 (C-N str tertiary amino group), 1698.7 (C=O str of amide), 3372.4 (N-H str of amide), 831.5 (C-H def di-substituted benzene ring), 709.6 (C-Cl str).	128.4 (C-2′ & C-6′), 129.9 (C-3′ & C-5′), 133.5 (C-4′), 134.6 (C-1′), 171.6 (C-2), 168.2 (C-5), 174.8 (NH*C*OCH$_2$N), 57.5 (NHCO*C*H$_2$N), 55.4 (C-a & C-d of morpholine), 72.3 (C-b & C-c of morpholine).	323, 100
6	3060.4 (Aromatic C-H str), 1086.9 (C-O of 1,3,4-oxadiazole nucleus), 1662.6 (C=N of 1,3,4-oxadiazole nucleus), 1596.7 & 1498.2 (Aromatic C-C str), 1298.0 (C-N str tertiary amino group), 1692.5 (C=O str of amide), 3358.1 (N-H str of amide), 832.6 (C-H def di-substituted benzene ring), 710.3 (C-Cl str).	128.6 (C-2′ & C-6′), 129.9 (C-3′ & C-5′), 133.7 (C-4′), 134.5 (C-1′), 171.1 (C-2), 168.4 (C-5), 174.3 (NH*C*OCH$_2$N), 55.3 (NHCO*C*H$_2$N), 27.8 (C-c, C-e, C-c′ & C-e′ of dicyclohexylamine), 30.6 (C-b, C-f, C-b′ & C-f′ of dicyclohexylamine), 23.4 (C-d & C-d′ of dicyclohexylamine), 51.2 (C-a & C-a′ of dicyclohexylamine).	417, 194
7	3065.2 (Aromatic C-H str), 1087.4 (C-O of 1,3,4-oxa diazole nucleus), 1656.9 (C=N of 1,3,4-oxadiazole nucleus), 1604.7 & 1500.2 (Aromatic C-C str), 1304.1 (C-N str tertiary amino group), 1688.6 (C=O str of amide), 3363.7 (N-H str of amide), 831.6 (C-H def di-substituted benzene ring), 709.5 (C-Cl str).	128.2 (C-2′ & C-6′), 129.3 (C-3′ & C-5′), 133.8 (C-4′), 134.5 (C-1′), 171.4 (C-2), 168.6 (C-5), 174.5 (NH*C*OCH$_2$N), 57.2 (NHCO*C*H$_2$N), 58.4 [N(CH$_2$C$_6$H$_5$)], 128.5 (C-c, C-e, C-c′ & C-e′ of dibenzylamine), 129.2 (C-b, C-f, C-b′ & C-f′ of dibenzylamine), 127.1 (C-d & C-d′ of dibenzylamine), 136.5 (C-a & C-a′ of dibenzylamine).	433, 210

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Table 2. Continued

Compound Code	IR (cm^{-1}) (KBr)	^{13}C-NMR δ (ppm) (DMSO-d_6, TMS)	ESMS (Methanol) m/z Molecular ion peak & Fragment
8	3063.4 (Aromatic C-H str), 1092.0 (C-O of 1,3,4-oxadiazole nucleus), 1662.0 (C=N of 1,3,4-oxadiazole nucleus), 1598.3 & 1501.5 (Aromatic C-C str), 1302.2 (C-N str tertiary amino group), 1693.6 (C=O str of amide), 3363.8 (N-H str of amide), 832.3 (C-H def di-substituted benzene ring), 707.4 (C-Cl str), 2882.1 (C-H str in CH_3, CH_2), 1434.7 (aliphatic C-H def), 745.2 (C-H def mono-substituted benzene).	128.6 (C-2′ & C-6′), 129.7 (C-3′ & C-5′), 133.9 (C-4′), 134.4 (C-1′), 171.2 (C-2), 168.7 (C-5), 174.6 (NH*C*O-CH_2N), 58.6 (NHCO*C*H_2N), 38.2 (N(*C*H_3)$CH_2C_6H_5$), 61.3 (N(CH_3)*C*$H_2C_6H_5$), 128.5 (C-c, C-e of *N*-methylbenzylamine), 129.3 (C-b, C-f of *N*-methylbenzylamine), 136.6 (C-a of *N*-methylbenzylamine), 127.1 (C-d of *N*-methylbenzylamine).	357, 134
9	3059.6 (Aromatic C-H str), 1092.7 (C-O of 1,3,4-oxadiazole nucleus), 1660.1 (C=N of 1,3,4-oxadiazole nucleus), 1598.6 & 1498.8 (Aromatic C-C str), 1304.3 (C-N str tertiary amino group), 1694.6 (C=O str of amide), 3362.1 (N-H str of amide), 836.7 (C-H def di-substituted benzene ring), 709.5 (C-Cl str), 2921.6 (C-H str in CH_3), 2950.1 (C-H str cyclohexane), 1440.7 (C-H def CH_3 group).	128.5 (C-2′ & C-6′), 129.6 (C-3′ & C-5′), 133.7 (C-4′), 134.2 (C-1′), 171.5 (C-2), 168.4 (C-5), 174.2 (NH*C*O-CH_2N), 57.8 (NHCO*C*H_2N), 36.4 (N(*C*H_3)C_6H_{11}), 27.3 (C-c & C-e of *N*-methylcyclohexylamine), 30.8 (C-b, C-f of *N*-methylcyclohexylamine), 55.5 (C-a of *N*-methylcyclohexylamine), 23.9 (C-d of *N*-methylcyclohexylamine).	349, 126
10	3065.2 (Aromatic C-H str), 1092.5 (C-O of 1,3,4-oxadiazole nucleus), 1658.3 (C=N of 1,3,4-oxadiazole nucleus), 1603.6 & 1503.2 (Aromatic C-C str), 1303.1 (C-N str tertiary amino group), 1688.6 (C=O str of amide), 3360.0 (N-H str of amide), 2936.7 (aliphatic C-H str), 1433.6 (aliphatic C-H def), 830.8 (C-H def di-substituted benzene ring), 1548.0 & 1357.5 (N=O str in Ar-NO_2 group).	129.2 (C-2′ & C-6′), 123.4 (C-3′ & C-5′), 148.6 (C-4′), 142.0 (C-1′), 171.1 (C-2), 168.0 (C-5), 174.4 (NH*C*O-CH_2N), 57.6 (NHCO*C*H_2N), 13.2 (*C*H_3CH_2N), 45.9 (CH_3*C*H_2N).	319, 86
11	3064.4 (Aromatic C-H str), 1093.6 (C-O of 1,3,4-oxadiazole nucleus), 1659.8 (C=N of 1,3,4-oxadiazole nucleus), 1602.8 & 1505.1 (Aromatic C-C str), 1304.2 (C-N str tertiary amino group), 1688.0 (C=O str of amide), 3359.1 (N-H str of amide), 2932.6 (aliphatic C-H str), 1432.4 (aliphatic C-H def), 829.6 (C-H def di-substituted benzene ring), 1548.2 & 1356.7(N=O str in Ar-NO_2 group).	129.5 (C-2′ & C-6′), 123.4 (C-3′ & C-5′), 148.8 (C-4′), 142.2 (C-1′), 171.2 (C-2), 168.4 (C-5), 174.6 (NH*C*O-CH_2N), 57.7 (NHCO*C*H_2N), 11.8 (*C*$H_3CH_2CH_2$N), 22.5 (CH_3*C*H_2CH_2N), 55.3 (CH_3CH_2*C*H_2N).	347, 114
12	3065.3 (Aromatic C-H str), 1094.1 (C-O of 1,3,4-oxadiazole nucleus), 1661.3 (C=N of 1,3,4-oxadiazole nucleus), 1601.3 & 1503.6 (Aromatic C-C str), 1301.9 (C-N str tertiary amino group), 1688.3 (C=O str of amide), 3361.5 (N-H str of amide), 2933.5 (aliphatic C-H str), 1434.8 (aliphatic C-H def), 830.7 (C-H def di-ubstituted benzene ring), 1548.4 & 1355.8 (N=O str in Ar-NO_2 group).	128.8 (C-2′ & C-6′), 123.1 (C-3′ & C-5′), 148.3 (C-4′), 142.0 (C-1′), 171.4 (C-2), 168.7 (C-5), 174.5 (NH-*C*OCH_2N), 53.3 (NHCO*C*H_2N), 13.9 (*C*$H_3CH_2CH_2CH_2$N), 20.9 (CH_3*C*$H_2CH_2CH_2$N), 31.7 (CH_3CH_2*C*H_2CH_2N), 53.3 ($CH_3CH_2CH_2$*C*H_2N).	375, 142
13	3062.4 (Aromatic C-H str), 1090.6 (C-O of 1,3,4-oxadiazole nucleus), 1663.2 (C=N of 1,3,4-oxadiazole nucleus), 1598.6 & 1499.1 (Aromatic C-C str), 1303.8 (C-N str tertiary amino group), 1692.5 (C=O str of amide), 3370.4 (N-H str of amide), 2921.6 (aliphatic C-H str), 1437.4 (aliphatic C-H def), 833.2 (C-H def di-substituted benzene ring), 3460.1 (O-H str of alcoholic group), 1162.7 (C-O str of alcoholic group), 1547.6 & 1355.2 (N=O str in Ar-NO_2 group).	129.7 (C-2′ & C-6′), 123.5 (C-3′ & C-5′), 148.6 (C-4′), 142.4 (C-1′), 171.3 (C-2), 168.1 (C-5), 174.5 (NH*C*O-CH_2N), 57.5 (NHCO*C*H_2N), 62.8 (OH*C*H_2CH_2N), 56.9 (OHCH_2*C*H_2N).	351, 118
14	3058.3 (Aromatic C-H str), 1092.5 (C-O of 1,3,4-oxadiazole nucleus), 1664.0 (C=N of 1,3,4-oxadiazole nucleus), 1601.3 & 1499.6 (Aromatic C-C str), 1304.1 (C-N str tertiary amino group), 1698.5 (C=O str of amide), 3370.6 (N-H str of amide), 832.2 (C-H def di-substituted benzene ring), 1549.3 & 1356.9 (N=O str in Ar-NO_2 group).	129.2 (C-2′ & C-6′), 123.8 (C-3′ & C-5′), 148.3 (C-4′), 142.0 (C-1′), 171.3 (C-2), 168.7 (C-5), 174.1 (NH*C*OCH$_2$N), 57.5 (NHCO*C*H_2N), 55.6 (C-a & C-d of morpholine), 71.9 (C-b & C-c of morpholine).	333, 100

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Table 2. Continued

Compound Code	IR (cm^{-1}) (KBr)	^{13}C-NMR δ (ppm) (DMSO-d_6, TMS)	ESMS (Methanol) m/z Molecular ion peak & Fragment
15	3061.6 (Aromatic C-H str), 1089.1 (C-O of 1,3,4-oxadiazole nucleus), 1661.4 (C=N of 1,3,4-oxadiazole nucleus), 1598.9 & 1499.4 (Aromatic C-C str), 1299.8 (C-N str tertiary amino group), 1691.0 (C=O str of amide), 3360.3 (N-H str of amide), 833.5 (C-H def disubstituted benzene ring), 1548.0 & 1356.8 (N=O str in Ar-NO_2 group).	129.4 (C-2′ & C-6′), 123.7 (C-3′ & C-5′), 148.5 (C-4′), 142.6 (C-1′), 171.3 (C-2), 168.2 (C-5), 174.7 (NH*C*O-CH_2N), 57.9 (NHCO*C*H_2N), 27.3 (C-c, C-e, C-c′ & C-e′ of dicyclohexylamine), 31.8 (C-b, C-f, C-b′ & C-f′ of dicyclohexylamine), 23.2 (C-d & C-d′ of dicyclohexylamine), 51.4 (C-a & C-a′ of dicyclohexylamine).	427, 194
16	3066.4 (Aromatic C-H str), 1088.5 (C-O of 1,3,4-oxadiazole nucleus), 1658.2 (C=N of 1,3,4-oxadiazole nucleus), 1602.1 & 1500.3 (Aromatic C-C str), 1303.6 (C-N str tertiary amino group), 1689.7 (C=O str of amide), 3355.2 (N-H str of amide), 830.2 (C-H def disubstituted benzene ring), 1549.6 & 1355.7 (N=O str in Ar-NO_2 group).	129.6 (C-2′ & C-6′), 123.9 (C-3′ & C-5′), 148.4 (C-4′), 142.5 (C-1′), 171.3 (C-2), 168.6 (C-5), 174.2 (NH*C*O-CH_2N), 57.3 (NHCO*C*H_2N), 58.9 [N($CH_2C_6H_5$)], 128.7 (C-c, C-e, C-c′ & C-e′ of dibenzylamine), 129.4 (C-b, C-f, C-b′ & C-f′ of dibenzylamine), 127.2 (C-d & C-d′ of dibenzylamine), 136.8 (C-a & C-a′ of dibenzylamine).	443, 210
17	3064.2 (Aromatic C-H str), 1091.4 (C-O of 1,3,4-oxadiazole nucleus), 1664.5 (C=N of 1,3,4-oxadiazole nucleus), 1599.0 & 1501.2 (Aromatic C-C str), 1301.6 (C-N str tertiary amino group), 1692.3 (C=O str of amide), 3361.8 (N-H str of amide), 831.1 (C-H def disubstituted benzene ring), 2883.0 (C-H str in CH_3, CH_2), 1436.4 (aliphatic C-H def), 746.7 (C-H def mono-substituted benzene), 1548.1 & 1356.9 (N=O str in Ar-NO_2 group).	129.5 (C-2′ & C-6′), 123.6 (C-3′ & C-5′), 148.9 (C-4′), 142.4 (C-1′), 171.5 (C-2), 168.3 (C-5), 174.7 (NH*C*O-CH_2N), 57.4 (NHCO*C*H_2N), 38.3 [N(CH_3)$CH_2C_6H_5$], 61.6 [N(CH_3)$CH_2C_6H_5$], 128.5 (C-c, C-e of N-methylbenzylamine), 129.3 (C-b, C-f of *N*-methylbenzylamine), 136.7 (C-a of *N*-methylbenzylamine), 127.1 (C-d of of *N*-methylbenzylamine).	367, 134
18	3064.4 (Aromatic C-H str), 1094.5 (C-O of 1,3,4-oxadiazole nucleus), 1662.3 (C=N of 1,3,4-oxadiazole nucleus), 1600.2 & 1501.7 (Aromatic C-C str), 1304.2 (C-N str tertiary amino group), 1692.5 (C=O str of amide), 3361.0 (N-H str of amide), 834.6 (C-H def disubstituted benzene ring), 2925.3 (C-H str in CH_3), 1442.4 (C-H def in CH_3), 2952.9 (C-H str cyclohexane), 1548.0 & 1356.4 (N=O str in Ar-NO_2 group).	127.6 (C-2′ & C-6′), 123.3 (C-3′ & C-5′), 148.6 (C-4′), 142.5 (C-1′), 171.1 (C-2), 168.5 (C-5), 174.4 (NH*C*O-CH_2N), 57.7 (NHCO*C*H_2N), 36.5 (N(*C*H_3)C_6H_{11}), 27.4 (C-c & C-e of N-methylcyclohexylamine), 30.9 (C-b, C-f of *N*-methylcyclohexylamine), 55.6 (C-a of *N*-methylcyclohexylamine), 23.8 (C-d of *N*-methylcyclohexylamine).	359, 126
19	3067.4 (Aromatic C-H str), 1092.4 (C-O of 1,3,4-oxadiazole nucleus), 1660.5 (C=N of 1,3,4-oxadiazole nucleus), 1602.1 & 1501.9 (Aromatic C-C str), 1303.0 (C-N str tertiary amino group), 1688.2 (C=O str of amide), 3361.5 (N-H str of amide), 2936.8 (Aliphatic C-H str), 1433.9 (C-H def in CH_3), 832.2 (C-H def di-substituted benzene ring).	127.0 (C-2′ & C-6′), 129.5 (C-3′ & C-5′), 137.3 (C-4′), 133.6 (C-1′), 171.3 (C-2), 168.4 (C-5), 174.6 (NH*C*O-CH_2N), 57.7 (NHCO*C*H_2N), 13.2 (*C*H_3CH_2N), 46.3 (CH_3*C*H_2N), 21.5 (*C*$H_3C_6H_5$).	288, 86
20	3068.1 (Aromatic C-H str), 1091.5 (C-O of 1,3,4-oxadiazole nucleus), 1660.6 (C=N of 1,3,4-oxadiazole nucleus), 1603.7 & 1504.2 (Aromatic C-C str), 1303.9 (C-N str tertiary amino group), 1689.8 (C=O str of amide), 3362.5 (N-H str of amide), 2935.6 (Aliphatic C-H str), 1432.0 (C-H def in CH_3), 830.3 (C-H def di-substituted benzene ring).	127.1 (C-2′ & C-6′), 129.4 (C-3′ & C-5′), 137.2 (C-4′), 133.5 (C-1′), 171.1 (C-2), 168.6 (C-5), 174.3 (NH*C*O-CH_2N), 57.9 (NHCO*C*H_2N), 11.8 (*C*$H_3CH_2CH_2$N), 22.3 (CH_3*C*H_2CH_2N), 55.6 (CH_3CH_2*C*H_2N), 21.2 (*C*$H_3C_6H_5$).	316, 114
21	3066.2 (Aromatic C-H str), 1094.6 (C-O of 1,3,4-oxadiazole nucleus), 1660.1 (C=N of 1,3,4-oxadiazole nucleus), 1603.8 & 1501.2 (Aromatic C-C str), 1302.5 (C-N str tertiary amino group), 1687.8 (C=O str of amide), 3364.7 (N-H str of amide), 2933.2 (Aliphatic C-H str), 1432.4 (C-H def in CH_3), 830.5 (C-H def di-substituted benzene ring).	127.0 (C-2′ & C-6′), 129.6 (C-3′ & C-5′), 137.3 (C-4′), 133.7 (C-1′), 171.5 (C-2), 168.2 (C-5), 174.2 (NH*C*O-CH_2N), 57.7 (NHCO*C*H_2N), 13.8 (*C*$H_3CH_2CH_2CH_2$N), 21.2 (CH_3*C*$H_2CH_2CH_2$N), 31.3 (CH_3CH_2*C*H_2CH_2N), 52.6 ($CH_3CH_2CH_2$*C*H_2N), 21.1 (*C*$H_3C_6H_5$).	344, 142

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Table 2. Continued

Compound Code	IR (cm^{-1}) (KBr)	^{13}C-NMR δ (ppm) (DMSO-d_6, TMS)	ESMS (Methanol) m/z Molecular ion peak & Fragment
22	3061.6 (Aromatic C-H str), 1091.5 (C-O of 1,3,4-oxadiazole nucleus), 1659.9 (C=N of 1,3,4-oxadiazole nucleus), 1601.4 & 1502.3 (Aromatic C-C str), 1306.1 (C-N str tertiary amino group), 1690.8 (C=O str of amide), 3371.0 (N-H str of amide), 2933.7 (Aliphatic C-H str), 1433.5 (C-H def in CH_3), 829.6 (C-H def di-substituted benzene ring), 3455.1 (O-H str of alcoholic group), 1162.6 (C-O str of alcoholic group).	127.1 (C-2′ & C-6′), 129.3 (C-3′ & C-5′), 137.6 (C-4′), 133.2 (C-1′), 171.3 (C-2), 168.5 (C-5), 174.7 (NH*C*O-CH_2N), 57.9 (NHCOCH_2N), 62.2 (OHCH_2CH_2N), 56.0 (OHCH_2CH_2N), 21.2 ($CH_3C_6H_5$).	320, 118
23	3059.1 (Aromatic C-H str), 1092.3 (C-O of 1,3,4-oxadiazole nucleus), 1663.8 (C=N of 1,3,4-oxadiazole nucleus), 1598.2 & 1500.3 (Aromatic C-C str), 1302.4 (C-N str tertiary amino group), 1694.3 (C=O str of amide), 3374.9 (N-H str of amide), 2935.3 (Aliphatic C-H str), 1432.2 (C-H def in CH_3), 834.6 (C-H def di-substituted benzene ring).	126.9 (C-2′ & C-6′), 129.4 (C-3′ & C-5′), 137.5 (C-4′), 133.8 (C-1′), 171.4 (C-2), 168.3 (C-5), 174.4 (NH*C*O-CH_2N), 57.8 (NHCOCH_2N), 55.6 (C-a & C-d of morpholine), 71.3 (C-b & C-c of morpholine), 21.0 ($CH_3C_6H_5$).	302, 100
24	3062.8 (Aromatic C-H str), 1088.2 (C-O of 1,3,4-oxadiazole nucleus), 1661.9 (C=N of 1,3,4-oxadiazole nucleus), 1596.9 & 1499.5 (Aromatic C-C str), 1299.7 (C-N str tertiary amino group), 1693.6 (C=O str of amide), 3362.3 (N-H str of amide), 2932.4 (Aliphatic C-H str), 1432.0 (Aliphatic C-H def), 830.6 (C-H def di-substituted benzene ring), 2952.2 (C-H str of cyclohexane).	126.8 (C-2′ & C-6′), 129.6 (C-3′ & C-5′), 137.2 (C-4′), 133.7 (C-1′), 171.7 (C-2), 168.3 (C-5), 174.5 (NH*C*O-CH_2N), 54.8 (NHCOCH_2N), 27.4 (C-c, C-e, C-c′ & C-e′ of dicyclohexylamine), 30.8 (C-b, C-f, C-b′ & C-f′ of dicyclohexylamine), 22.7 (C-d & C-d′ of dicyclohexylamine), 50.9 (C-a & C-a′ of dicyclohexylamine), 21.3 ($CH_3C_6H_5$).	397, 194
25	3063.4 (Aromatic C-H str), 1089.2 (C-O of 1,3,4-oxadiazole nucleus), 1659.1 (C=N of 1,3,4-oxadiazole nucleus), 1601.3 & 1501.1 (Aromatic C-C str), 1302.4 (C-N str tertiary amino group), 1689.9 (C=O str of amide), 3362.5 (N-H str of amide), 2934.3 (C-H str of CH_3), 1432.1 (C-H def in CH_3), 832.6 (C-H def di-substituted benzene ring).	127.2 (C-2′ & C-6′), 129.5 (C-3′ & C-5′), 137.6 (C-4′), 133.4 (C-1′), 171.1 (C-2), 168.2 (C-5), 174.4 (NH*C*O-CH_2N), 57.1 (NHCOCH_2N), 58.6 [N($CH_2C_6H_5$)], 128.5 (C-c, C-e, C-c′ & C-e′ of dibenzylamine), 129.3 (C-b, C-f, C-b′ & C-f′ of dibenzylamine), 127.0 (C-d & C-d′ of dibenzylamine), 136.6 (C-a & C-a′ of dibenzylamine), 21.1 ($CH_3C_6H_5$).	412, 210
26	3063.3 (Aromatic C-H str), 1090.1 (C-O of 1,3,4-oxadiazole nucleus), 1661.4 (C=N of 1,3,4-oxadiazole nucleus), 1599.1 & 1502.2 (Aromatic C-C str), 1302.9 (C-N str tertiary amino group), 1691.5 (C=O str of amide), 3360.3 (N-H str of amide), 745.4 (C-H def disubstituted benzene ring), 2932.5 (Aliphatic C-H str), 1429.8 (C-H def in CH_3), 830.8 (C-H def di-substituted benzene ring).	127.1 (C-2′ & C-6′), 129.2 (C-3′ & C-5′), 137.4 (C-4′), 133.3 (C-1′), 171.4 (C-2), 168.2 (C-5), 174.7 (NH*C*O-CH_2N), 59.5 (NHCOCH_2N), 38.3 [N(CH_3)$CH_2C_6H_5$], 61.2 [N(CH_3)$CH_2C_6H_5$], 128.6 (C-c, C-e of N-methylbenzylamine), 129.2 (C-b, C-f of *N*-methylbenzylamine), 136.4 (C-a of *N*-methylbenzylamine), 127.1 (C-d of of *N*-methylbenzylamine), 21.2 ($CH_3C_6H_5$).	336, 134
27	3061.3 (Aromatic C-H str), 1091.3 (C-O of 1,3,4-oxadiazole nucleus), 1660.4 (C=N of 1,3,4-oxadiazole nucleus), 1599.4 & 1498.8 (Aromatic C-C str), 1302.5 (C-N str tertiary amino group), 1693.1 (C=O str of amide), 3360.9 (N-H str of amide), 2933.6 (C-H str in CH_3), 1432.1 (C-H def in CH_3), 832.2 (C-H def di-substituted benzene ring), 2951.8 (C-H str in cyclohexane).	126.9 (C-2′ & C-6′), 129.4 (C-3′ & C-5′), 137.3 (C-4′), 133.4 (C-1′), 171.3 (C-2), 168.5 (C-5), 174.2 (NH*C*O-CH_2N), 57.9 (NHCOCH_2N), 36.6 (N(CH_3)C_6H_{11}), 27.1 (C-c & C-e of N-methylcyclohexylamine), 30.7 (C-b, C-f of N-methylcyclohexylamine), 55.2 (C-a of *N*-methylcyclohexylamine), 22.8 (C-d of *N*-methylcyclohexylamine), 20.0 ($CH_3C_6H_5$).	328, 126
28	3066.4 (Aromatic C-H str), 1092.0 (C-O of 1,3,4-oxadiazole nucleus), 1658.5 (C=N of 1,3,4-oxadiazole nucleus), 1603.2 & 1502.6 (Aromatic C-C str), 1304.8 (C-N str tertiary amino group), 1689.3 (C=O str of amide), 3361.4 (N-H str of amide), 830.6 (C-H def di-substituted benzene ring), 2932.8 (Aliphatic C-H str), 1433.0 (Aliphatic C-H def), 1242.4 (C-F str).	128.4 (C-2′ & C-6′), 115.8 (C-3′ & C-5′), 162.6 (C-4′), 132.0 (C-1′), 171.8 (C-2), 168.3 (C-5), 174.9 (NH*C*O-CH_2N), 57.6 (NHCOCH_2N), 13.4 (CH_3CH_2N), 46.2 (CH_3CH_2N).	292, 86

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Table 2. Continued

Compound Code	IR (cm^{-1}) (KBr)	^{13}C-NMR δ (ppm) (DMSO-d_6, TMS)	ESMS (Methanol) m/z Molecular ion peak & Fragment
29	3065.4 (Aromatic C-H str), 1092.3 (C-O of 1,3,4-oxadiazole nucleus), 1659.6 (C=N of 1,3,4-oxadiazole nucleus), 1603.5 & 1501.7 (Aromatic C-C str), 1301.5 (C-N str tertiary amino group), 1688.5 (C=O str of amide), 3362.0 (N-H str of amide), 831.5 (C-H def di-substituted benzene ring), 2934.2 (Aliphatic C-H str), 1433.2 (Aliphatic C-H def), 1245.9 (C-F str).	128.5 (C-2′ & C-6′), 115.7 (C-3′ & C-5′), 162.5 (C-4′), 132.2 (C-1′), 171.6 (C-2), 168.5 (C-5), 174.8 (NH*C*O-CH_2N), 57.4 (NHCO*C*H_2N), 11.8 (*C*$H_3CH_2CH_2$N), 22.6 (CH_3*C*H_2CH_2N), 55.9 (CH_3CH_2*C*H_2N).	320, 114
30	3068.2 (Aromatic C-H str), 1094.8 (C-O of 1,3,4-oxadiazole nucleus), 1662.1 (C=N of 1,3,4-oxadiazole nucleus), 1602.4 & 1501.7 (Aromatic C-C str), 1302.4 (C-N str tertiary amino group), 1688.8 (C=O str of amide), 3364.5 (N-H str of amide), 2932.6 (Aliphatic C-H str), 1432.3 (Aliphatic C-H def), 830.6 (C-H def di-substituted benzene ring), 1245.8 (C-F str).	128.3 (C-2′ & C-6′), 115.6 (C-3′ & C-5′), 162.5 (C-4′), 132.1 (C-1′), 171.2 (C-2), 168.5 (C-5), 174.7 (NH*C*O-CH_2N), 57.9 (NHCO*C*H_2N), 14.2 (*C*$H_3CH_2CH_2CH_2$N), 20.9 (CH_3*C*$H_2CH_2CH_2$N), 31.6 (CH_3CH_2*C*H_2CH_2N), 53.4 ($CH_3CH_2CH_2$*C*H_2N).	348, 142
31	3063.5 (Aromatic C-H str), 1092.8 (C-O of 1,3,4-oxadiazole nucleus), 1659.7 (C=N of 1,3,4-oxadiazole nucleus), 1602.4 & 1501.3 (Aromatic C-C str), 1303.2 (C-N str tertiary amino group), 1690.4 (C=O str of amide), 3372.1 (N-H str of amide), 2924.9 (Aliphatic C-H str), 1432.4 (Aliphatic C-H def), 3459.7 (O-H str of alcoholic group), 1163.5 (C-O str of alcoholic group), 829.8 (C-H def di-substituted benzene ring), 1244.2 (C-F str).	128.6 (C-2′ & C-6′), 115.8 (C-3′ & C-5′), 162.8 (C-4′), 132.5 (C-1′), 171.3 (C-2), 168.6 (C-5), 174.4 (NH*C*O-CH_2N), 57.6 (NHCO*C*H_2N), 62.4 (OH*C*H_2CH_2N), 56.7 (OHCH_2*C*H_2N).	324, 118
32	3059.4 (Aromatic C-H str), 1091.7 (C-O of 1,3,4-oxadiazole nucleus), 1662.8 (C=N of 1,3,4-oxadiazole nucleus), 1599.6 & 1498.5 (Aromatic C-C str), 1304.9 (C-N str tertiary amino group), 1696.5 (C=O str of amide), 3372.2 (N-H str of amide), 831.9 (C-H def di-substituted benzene ring), 1245.9 (C-F str).	128.4 (C-2′ & C-6′), 115.9 (C-3′ & C-5′), 162.5 (C-4′), 132.2 (C-1′), 171.6 (C-2), 168.2 (C-5), 174.5 (NH*C*O-CH_2N), 57.3 (NHCO*C*H_2N), 55.7 (C-a & C-d of morpholine), 71.0 (C-b & C-c of morpholine).	306, 100
33	3061.2 (Aromatic C-H str), 1089.2 (C-O of 1,3,4-oxadiazole nucleus), 1662.4 (C=N of 1,3,4-oxadiazole nucleus), 1599.6 & 1498.3 (Aromatic C-C str), 1302.4 (C-N str tertiary amino group), 1692.4 (C=O str of amide), 3362.5 (N-H str of amide), 2953.6 (C-H str of cyclohexane), 833.0 (C-H def di-substituted benzene ring), 1245.9 (C-F str).	126.7 (C-2′ & C-6′), 115.5 (C-3′ & C-5′), 162.1 (C-4′), 132.4 (C-1′), 171.2 (C-2), 168.6 (C-5), 174.3 (NH*C*O-CH_2N), 55.1 (NHCO*C*H_2N), 27.9 (C-c, C-e, C-c′ & C-e′ of dicyclohexylamine), 30.8 (C-b, C-f, C-b′ & C-f′ of dicyclohexylamine), 23.3 (C-d & C-d′ of dicyclohexylamine), 51.4 (C-a & C-a′ of dicyclohexylamine).	400, 194
34	3066.5 (Aromatic C-H str), 1089.1 (C-O of 1,3,4-oxadiazole nucleus), 1658.9 (C=N of 1,3,4-oxadiazole nucleus), 1602.3 & 1501.8 (Aromatic C-C str), 1304.8 (C-N str tertiary amino group), 1689.7 (C=O str of amide), 3360.4 (N-H str of amide), 830.8 (C-H def di-substituted benzene ring), 1246.3 (C-F str).	128.5 (C-2′ & C-6′), 116.0 (C-3′ & C-5′), 162.4 (C-4′), 132.5 (C-1′), 171.8 (C-2), 168.3 (C-5), 174.2 (NH*C*O-CH_2N), 57.0 (NHCO*C*H_2N), 58.5 [N($CH_2C_6H_5$)], 128.4 (C-c, C-e, C-c′ & C-e′ of dibenzylamine), 129.1 (C-b, C-f, C-b′ & C-f′ of dibenzylamine), 127.2 (C-d & C-d′ of dibenzylamine), 136.6 (C-a & C-a′ of dibenzylamine).	416, 210
35	3064.1 (Aromatic C-H str), 1091.6 (C-O of 1,3,4-oxadiazole nucleus), 1664.2 (C=N of 1,3,4-oxadiazole nucleus), 1599.6 & 1499.1 (Aromatic C-C str), 1301.7 (C-N str tertiary amino group), 1692.8 (C=O str of amide), 3361.5 (N-H str of amide), 831.3 (C-H def di-substituted benzene), 2884.4 (Aliphatic C-H str), 1432.6 (Aliphatic C-H def), 746.0 (C-H def mono-substituted benzene ring), 1245.9 (C-F str).	128.6 (C-2′ & C-6′), 115.7 (C-3′ & C-5′), 162.3 (C-4′), 132.4 (C-1′), 171.5 (C-2), 168.2 (C-5), 174.7 (NH*C*O-CH_2N), 59.3 (NHCO*C*H_2N), 38.1 [N(*C*H_3)$CH_2C_6H_5$], 61.2 [N(CH_3)*C*$H_2C_6H_5$], 128.5 (C-c, C-e of *N*-methylbenzylamine), 129.4 (C-b, C-f of *N*-methylbenzylamine), 136.6 (C-a of *N*-methylbenzylamine), 127.2 (C-d of *N*-methylbenzylamine).	340, 134

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Table 2. Continued

Compound Code	IR (cm^{-1}) (KBr)	^{13}C-NMR δ (ppm) (DMSO-d_6, TMS)	ESMS (Methanol) m/z Molecular ion peak & Fragment
36	3062.5 (Aromatic C-H str), 1092.8 (C-O of 1,3,4-oxadiazole nucleus), 1662.7 (C=N of 1,3,4-oxadiazole nucleus), 1601.2 & 1502.3 (Aromatic C-C str), 1303.9 (C-N str tertiary amino group), 1694.1 (C=O str of amide), 3360.8 (N-H str of amide), 833.5 (C-H def di-substituted benzene ring), 2928.4 (C-H str in CH_3), 1432.3 (C-H def in CH_3), 2951.4 (C-H str in cyclohexane), 1245.9 (C-F str).	128.3 (C-2′ & C-6′), 115.9 (C-3′ & C-5′), 162.7 (C-4′), 132.6 (C-1′), 171.4 (C-2), 168.2 (C-5), 174.5 (NH*C*O-CH_2N), 57.6 (NHCOCH_2N), 36.3 (N(CH_3)C_6H_{11}), 27.3 (C-c & C-e of *N*-methylcyclohexylamine), 30.8 (C-b, C-f of *N*-methylcyclohexylamine), 55.4 (C-a of *N*-methylcyclohexylamine), 23.7 (C-d of *N*-methylcyclohexylamine).	332, 126
37	3065.8 (Aromatic C-H str), 1091.6 (C-O of 1,3,4-oxadiazole nucleus), 1659.2 (C=N of 1,3,4-oxadiazole nucleus), 1602.4 & 1503.1 (Aromatic C-C str), 1304.8 (C-N str tertiary amino group), 1689.6 (C=O str of amide), 3362.0 (N-H str of amide), 832.2 (C-H def di-s ubstituted benzene ring), 2934.5 (Aliphatic C-H str), 1431.3 (Aliphatic C-H def), 3448.7 (O-H str of alcoholic group), 1156.0 (C-O str of alcoholic group).	127.5 (C-2′ & C-6′), 115.3 (C-3′ & C-5′), 155.0 (C-4′), 129.6 (C-1′), 171.3 (C-2), 168.4 (C-5), 174.6 (NH*C*O-CH_2N), 57.5 (NHCOCH_2N), 13.6 (CH_3CH_2N), 45.9 (CH_3CH_2N).	290, 86
38	3065.3 (Aromatic C-H str), 1090.2 (C-O of 1,3,4-oxadiazole nucleus), 1658.4 (C=N of 1,3,4-oxadiazole nucleus), 1603.6 & 1502.4 (Aromatic C-C str), 1302.1 (C-N str tertiary amino group), 1688.8 (C=O str of amide), 3360.8 (N-H str of amide), 831.9 (C-H def di-substituted benzene ring), 2932.6 (Aliphatic C-H str), 1434.6 (Aliphatic C-H def), 3446.2 (O-H str of alcoholic group), 1154.5 (C-O str of alcoholic group).	127.2 (C-2′ & C-6′), 115.6 (C-3′ & C-5′), 155.4 (C-4′), 129.5 (C-1′), 171.5 (C-2), 168.6 (C-5), 174.8 (NH*C*O-CH_2N), 57.9 (NHCOCH_2N), 11.9 ($CH_3CH_2CH_2$N), 22.5 ($CH_3CH_2CH_2$N), 55.8 ($CH_3CH_2CH_2$N).	318, 114
39	3067.9 (Aromatic C-H str), 1093.2 (C-O of 1,3,4-oxadiazole nucleus), 1661.3 (C=N of 1,3,4-oxadiazole nucleus), 1601.2 & 1502.8 (Aromatic C-C str), 1301.7 (C-N str tertiary amino group), 1689.1 (C=O str of amide), 3361.3 (N-H str of amide), 831.2 (C-H def di-substituted benzene ring), 2933.5 (Aliphatic C-H str), 1434.1 (Aliphatic C-H def), 3444.6 (O-H str of alcoholic group), 1155.0 (C-O str of alcoholic group).	127.4 (C-2′ & C-6′), 115.3 (C-3′ & C-5′), 155.8 (C-4′), 129.6 (C-1′), 171.4 (C-2), 168.3 (C-5), 174.6 (NH*C*O-CH_2N), 57.8 (NHCOCH_2N), 14.3 ($CH_3CH_2CH_2CH_2$N), 20.7 ($CH_3CH_2CH_2CH_2$N), 31.6 ($CH_3CH_2CH_2CH_2$N), 53.1 ($CH_3CH_2CH_2CH_2$N).	346, 142
40	3062.4 (Aromatic C-H str), 1090.3 (C-O of 1,3,4-oxadiazole nucleus), 1661.5 (C=N of 1,3,4-oxadiazole nucleus), 1601.5 & 1503.1 (Aromatic C-C str), 1304.6 (C-N str tertiary amino group), 1691.8 (C=O str of amide), 3370.2 (N-H str of amide), 833.6 (C-H def di-substituted benzene ring), 2925.6 (Aliphatic C-H str), 1433.7 (Aliphatic C-H def), 3452.9 (O-H str of alcoholic group), 1152.8 (C-O str of alcoholic group).	127.1 (C-2′ & C-6′), 115.5 (C-3′ & C-5′), 155.3 (C-4′), 129.2 (C-1′), 171.1 (C-2), 168.6 (C-5), 174.5 (NH*C*O-CH_2N), 57.9 (NHCOCH_2N), 62.4 (OHCH_2CH_2N), 56.7 (OHCH_2CH_2N).	322, 118
41	3059.2 (Aromatic C-H str), 1090.3 (C-O of 1,3,4-oxadiazole nucleus), 1663.1 (C=N of 1,3,4-oxadiazole nucleus), 1601.4 & 1500.2 (Aromatic C-C str), 1302.8 (C-N str tertiary amino group), 1694.5 (C=O str of amide), 3371.6 (N-H str of amide), 832.8 (C-H def di-substituted benzene ring), 3448.2 (O-H str of alcoholic group), 1155.7 (C-O str of alcoholic group).	127.5 (C-2′ & C-6′), 115.2 (C-3′ & C-5′), 155.6 (C-4′), 129.3 (C-1′), 171.4 (C-2), 168.2 (C-5), 174.1 (NH*C*O-CH_2N), 57.5 (NHCOCH_2N), 55.7 (C-a & C-d of morpholine), 71.1 (C-b & C-c of morpholine).	304, 100
42	3062.4 (Aromatic C-H str), 1088.3 (C-O of 1,3,4-oxadiazole nucleus), 1660.2 (C=N of 1,3,4-oxadiazole nucleus), 1598.6 & 1499.8 (Aromatic C-C str), 1297.6 (C-N str tertiary amino group), 1692.5 (C=O str of amide), 3361.7 (N-H str of amide), 831.1 (C-H def di-substituted benzene ring), 2952.8 (C-H str cyclohexane), 3449.7 (O-H str of alcoholic group), 1153.6 (C-O str of alcoholic group).	127.8 (C-2′ & C-6′), 115.8 (C-3′ & C-5′), 155.7 (C-4′), 129.5 (C-1′), 171.3 (C-2), 168.7 (C-5), 174.8 (NH*C*O-CH_2N), 54.6 (NHCOCH_2N), 27.5 (C-c, C-e, C-c′ & C-e′ of dicyclohexylamine), 31.3 (C-b, C-f, C-b′ & C-f′ of dicyclohexylamine), 23.1 (C-d & C-d′ of dicyclohexylamine), 51.0 (C-a & C-a′ of dicyclohexylamine).	398, 194

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Table 2. Continued

Compound Code	IR (cm^{-1}) (KBr)	^{13}C-NMR δ (ppm) (DMSO-d_6, TMS)	ESMS (Methanol) m/z Molecular ion peak & Fragment
43	3064.2 (Aromatic C-H str), 1090.8 (C-O of 1,3,4-oxadiazole nucleus), 1659.3 (C=N of 1,3,4-oxadiazole nucleus), 1602.4 & 1501.7 (Aromatic C-C str), 1303.6 (C-N str tertiary amino group), 1690.5 (C=O str of amide), 3361.2 (N-H str of amide), 832.4 (C-H def disubstituted benzene ring), 3448.3 (O-H str of alcoholic group), 1155.4 (C-O str of alcoholic group).	127.2 (C-2′ & C-6′), 115.6 (C-3′ & C-5′), 155.2 (C-4′), 129.3 (C-1′), 171.2 (C-2), 168.6 (C-5), 174.7 (NH*C*O-CH_2N), 57.1 (NHCO*C*H_2N), 58.6 [N($CH_2C_6H_5$)], 128.5 (C-c, C-e, C-c′ & C-e′ of dibenzylamine), 129.4 (C-b, C-f, C-b′ & C-f′ of dibenzylamine), 127.2 (C-d & C-d′ of dibenzylamine), 136.9 (C-a & C-a′ of dibenzylamine).	414, 210
44	3063.2 (Aromatic C-H str), 1090.5 (C-O of 1,3,4-oxadiazole nucleus), 1663.2 (C=N of 1,3,4-oxadiazole nucleus), 1599.2 & 1498.1 (Aromatic C-C str), 1301.2 (C-N str tertiary amino group), 1691.4 (C=O str of amide), 3362.0 (N-H str of amide), 831.7 (C-H def disubstituted benzene ring), 2880.2 (Aliphatic C-H str), 1434.3 (Aliphatic C-H def), 746.4 (C-H def mono-substituted benzene ring), 3449.3 (O-H str of alcoholic group), 1153.8 (C-O str of alcoholic group).	127.4 (C-2′ & C-6′), 115.5 (C-3′ & C-5′), 155.8 (C-4′), 129.4 (C-1′), 171.3 (C-2), 168.2 (C-5), 174.1 (NH*C*O-CH_2N), 59.4 (NHCO*C*H_2N), 38.2 [N(*C*H_3)$CH_2C_6H_5$], 61.1 [N(CH_3)*C*$H_2C_6H_5$], 128.6 (C-c, C-e of *N*-methylbenzylamine), 129.4 (C-b, C-f of *N*-methylbenzylamine), 136.5 (C-a of *N*-methylbenzylamine), 127.3 (C-d of of *N*-methylbenzylamine).	338, 134
45	3060.1 (Aromatic C-H str), 1091.3 (C-O of 1,3,4-oxadiazole nucleus), 1661.3 (C=N of 1,3,4-oxadiazole nucleus), 1598.8 & 1499.2 (Aromatic C-C str), 1303.6 (C-N str tertiary amino group), 1692.5 (C=O str of amide), 3362.7 (N-H str of amide), 832.8 (C-H def disubstituted benzene ring), 2926.8 (C-H str in CH_3), 1436.0 (C-H def in CH_3), 3450.8 (O-H str of alcoholic group), 1154.3 (C-O str of alcoholic group), 2954.9 (C-H str in cyclohexane).	127.3 (C-2′ & C-6′), 115.8 (C-3′ & C-5′), 155.9 (C-4′), 129.1 (C-1′), 171.8 (C-2), 168.4 (C-5), 174.9 (NH*C*O-CH_2N), 57.9 (NHCO*C*H_2N), 36.5 (N(*C*H_3)C_6H_{11}), 27.4 (C-c & C-e of *N*-methylcyclohexylamine), 30.7 (C-b, C-f of *N*-methylcyclohexylamine), 55.3 (C-a of *N*-methylcyclohexylamine), 23.6 (C-d of *N*-methylcyclohexylamine).	330, 126

ing again the general consideration that local anesthetic activity usually increases with increasing lipid solubility and the lipophilic portion in the molecule is essential for local anesthetic activity.

An intermediate alkyl chain of a critical length containing an amide bond is present in the title compounds; breaking of this amide bond during metabolism may be responsible for the reversible local anesthetic activity.

Oxadiazole analogues synthesized for their local anesthetic activities contain a tertiary alkylamine portion, commonly considered as the hydrophilic portion of the molecule. With the understanding of the voltage–activated sodium channel and the possible mechanism of action of local anesthetics, it is quite conceivable that the sodium ions produced by protonation of the tertiary amine group are also required for binding to the receptors. Hydrophilic groups present in some of the test compounds in the form of a tertiary alkylamine or as part of a nitrogen heterocycle (morpholine) may be responsible for their significant local anesthetic activity.

On critical observation of synthesized oxadiazole analogues, it has been found that they contain a nitrogen atom attached to a sp^2 carbon atom. The positive mesomeric effect on the sp^2 carbon atom may also be further responsible for their greater affinity for the binding site at the receptor.

In conclusion, 45 novel 1,3,4-oxadiazole analogues were synthesized for their potential local anesthetic activity using rabbit corneal reflex method and guinea pig's wheal derm method. Except very few, all the oxadiazole analogues have exhibited local anesthetic properties. Among all the compounds, the most potent local anesthetic compounds were **19**, **20**, **23**, **28**, **29**, and **35**. One of our major findings is the first-ever reporting of considerable local anesthetic activity in an acetamide system carrying 1,3,4-oxadiazole as a structural unit. In our laboratories, further research work is going to optimize the substitutents around the 1,3,4-oxadiazole nucleus to explore their local anesthetic potential.

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Table 3. Local anesthetic activity of the synthesized oxadiazoles using the rabbit corneal reflex method and the guinea pig wheal derm method.

Compound	Rabbit corneal reflex (Surface anesthesia)			Guinea pig wheal derm (Infiltration anesthesia)		
	Local anesthesia	Onset time (min)	Duration time (min)	Local anesthesia	Onset time (min)	Duration time (min)
1	+	6.66 ± 0.42	25.33 ± 0.42	+	9.33 ± 0.42	33.33 ± 0.33
2	+	7.00 ± 0.44	25.33 ± 0.84	+	9.33 ± 0.66	33.00 ± 0.44
3	+	10.00 ± 0.51	21.66 ± 0.61	+	12.33 ± 0.61	28.66 ± 0.84
4	+	9.00 ± 0.68	24.00 ± 0.51	+	10.33 ± 0.33	28.00 ± 0.51
5	+	8.33 ± 0.33	24.33 ± 0.33	+	9.33 ± 0.66	30.66 ± 0.42
6	+	8.66 ± 0.42	23.00 ± 0.44	+	11.00 ± 0.44	26.33 ± 0.61
7	+	8.33 ± 0.33	23.33 ± 0.66	+	10.33 ± 0.80	26.66 ± 0.84
8	+	9.66 ± 0.61	20.33 ± 0.61	+	12.66 ± 0.42	33.00 ± 0.85
9	+	9.33 ± 0.66	21.33 ± 0.66	+	12.66 ± 0.66	27.66 ± 0.80
10	+	7.00 ± 0.44	24.33 ± 0.33	+	10.00 ± 0.51	31.33 ± 0.66
11	+	7.33 ± 0.44	24.00 ± 0.51	+	10.33 ± 0.61	32.66 ± 0.66
12	+	9.66 ± 0.33	20.66 ± 0.66	+	12.00 ± 0.51	24.66 ± 0.42
13	+	7.33 ± 0.66	23.66 ± 0.61	+	11.33 ± 0.66	28.33 ± 0.33
14	+	7.33 ± 0.66	24.33 ± 0.61	+	10.33 ± 0.33	29.66 ± 0.61
15	+	9.00 ± 0.68	22.33 ± 0.33	+	12.33 ± 0.33	25.00 ± 0.44
16	+	9.00 ± 0.68	22.33 ± 0.61	+	12.00 ± 0.51	25.33 ± 0.66
17	+	10.33 ± 0.33	21.00 ± 0.44	+	14.66 ± 0.42	24.66 ± 0.84
18	-	-	-	-	–	–
19	+	6.33 ± 0.33	27.00 ± 0.68	+	8.33 ± 0.33	37.66 ± 0.33
20	+	6.33 ± 0.33	26.33 ± 0.61	+	9.00 ± 0.85	36.33 ± 0.33
21	+	9.66 ± 0.33	22.00 ± 0.51	+	12.33 ± 0.33	27.00 ± 0.44
22	+	7.66 ± 0.33	23.66 ± 0.61	+	11.33 ± 0.42	27.66 ± 0.61
23	+	6.66 ± 0.42	25.33 ± 0.66	+	8.66 ± 0.42	34.00 ± 0.51
24	+	8.33 ± 0.33	23.33 ± 0.42	+	11.33 ± 0.66	27.33 ± 0.66
25	+	8.66 ± 0.42	23.33 ± 0.66	+	11.66 ± 0.33	27.66 ± 0.33
26	+	10.33 ± 0.33	20.00 ± 0.80	+	14.66 ± 0.42	25.66 ± 0.61
27	–	–	–	+	13.33 ± 0.42	26.33 ± 0.61
28	+	6.33 ± 0.33	26.33 ± 0.61	+	8.33 ± 0.33	37.33 ± 0.42
29	+	6.66 ± 0.42	25.66 ± 0.61	+	9.33 ± 0.42	35.33 ± 0.42
30	+	9.33 ± 0.84	21.33 ± 0.42	+	11.66 ± 0.61	27.66 ± 0.61
31	+	7.33 ± 0.66	24.33 ± 0.33	+	10.66 ± 0.66	29.00 ± 0.68
32	+	6.66 ± 0.42	26.00 ± 0.51	+	9.00 ± 0.44	35.66 ± 0.33
33	+	8.33 ± 0.61	22.66 ± 0.42	+	11.33 ± 0.84	25.66 ± 0.80
34	+	7.66 ± 0.61	24.00 ± 0.51	+	12.33 ± 0.33	28.00 ± 0.51
35	+	9.33 ± 0.84	21.00 ± 0.85	+	12.66 ± 0.42	25.33 ± 0.66
36	+	10.66 ± 0.84	18.00 ± 0.51	+	13.33 ± 0.66	25.00 ± 0.44
37	+	7.00 ± 0.68	24.33 ± 0.33	+	9.33 ± 0.42	32.00 ± 0.73
38	+	6.66 ± 0.66	25.00 ± 0.44	+	9.66 ± 0.33	32.66 ± 0.66
39	+	9.66 ± 0.61	20.66 ± 0.66	+	12.66 ± 0.42	27.00 ± 0.85
40	+	7.33 ± 0.84	24.00 ± 0.89	+	10.33 ± 0.61	28.66 ± 0.42
41	+	6.33 ± 0.33	24.66 ± 0.42	+	9.66 ± 0.80	32.33 ± 0.61
42	+	8.66 ± 0.42	22.33 ± 0.33	+	11.66 ± 0.80	25.66 ± 0.61
43	+	8.33 ± 0.80	22.66 ± 0.42	+	11.66 ± 0.61	26.00 ± 0.73
44	–	–	–	+	13.66 ± 0.33	24.33 ± 0.61
45	–	–	–	–	–	–
Lidocaine	+	5.09 ± 0.02	32.16 ± 0.07	+	8.14 ± 0.05	40.25 ± 0.06

Experimental

Synthesis

All the chemicals and solvents used in this study were purchased from E-Merck (Darmstadt, Germany), Aldrich (Steinheim, Germany), and Himedia (Mumbai, India). Alcohol means aldehyde-free ethanol, wherever mentioned [17]. Melting points were determined by open capillary method and are uncorrected. Elemental analysis was done using an elemental analyzer Heraeus Carlo Erba-1108, data recorded were within a range of ± 0.4% for all final compounds. IR spectra were recorded on a Perkin Elmer IR spectrophotometer (KBr disc) (Perkin Elmer, Beaconsfield, UK), ^{13}C-NMR spectra on a Bruker DRX-300 NMR spectrometer (DMSO-d_6, TMS; Bruker Bioscience, Billerica, MA, USA) and the electrospray mass spectra on a Micromass Quattro II triple-quadrupole mass spectrometer (methanol) (Micromass, Manchester, UK).

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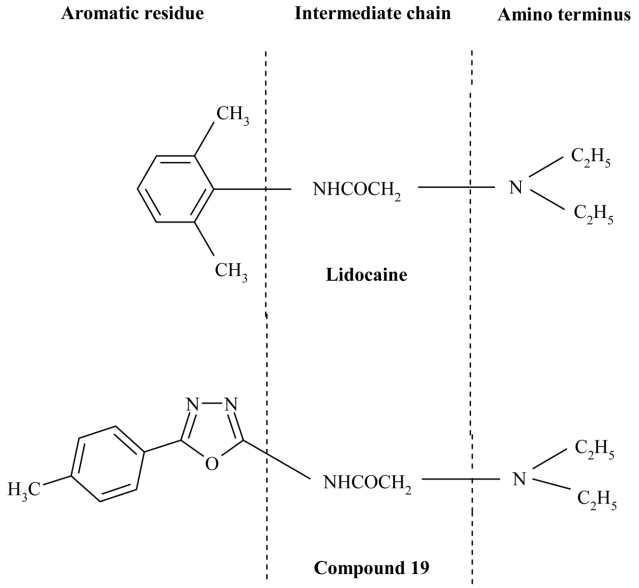

Figure 1. Comparison of structural features of lidocaine and compound **19** as local anesthetic agents.

*General procedure for synthesis of semicarbazones **III***

Required semicarbazones were synthesized according to the reported method [17].

Compounds: **IIIa** yield 78% mp. 230–232°C; **IIIb** 80.5%, 190–192°C; **IIIc** 79%, 200–202°C; **IIId** 76%, 222–224°C; **IIIe** 78%, 234–236°C.

*General procedure for synthesis of 2-amino-5-aryl-1,3,4-oxadiazoles **IV***

Semicarbazone **III** (0.01 mol) and sodium acetate (0.02 mol) were dissolved in 30–40 mL of glacial acetic acid taken in a round-bottomed flask equipped with a separating funnel for the addition of bromine. Bromine (0.7 mL in 5 mL of glacial acetic acid) was added slowly to it, while stirring magnetically. After 30 min of stirring, the solution was poured on crushed ice. The resulting solid was separated, dried, and recrystallized from ethanol [18].

Compounds: **IVa** yield 73%, mp. 202–204°C, IR (KBr, in cm^{-1}), 3081.6 (aromatic C-H), 1092.5 (C-O of oxadiazole nucleus), 1660.7 (C=N of oxadiazole), and 3364.2 (N-H str); **IVb** 76%, 198–200°C, IR (KBr, in cm^{-1}), 3067.3 (aromatic C-H), 1090.6 (C-O of oxadiazole nucleus), 1662.4 (C=N of oxadiazole), and 3367.9 (N-H str); **IVc** 72% 211–213°C, IR (KBr, in cm^{-1}), 3065.0 (aromatic C-H), 1089.1 (C-O of oxadiazole nucleus), 1664.1 (C=N of oxadiazole), and 3365.9 (N-H str.); **IVd** 69%, 236–238°C, IR (KBr, in cm^{-1}), 3072.7 (aromatic C-H), 1092.3 (C-O of oxadiazole nucleus), 1658.3 (C=N of oxadiazole), and 3363.8 (N-H str); **IVe** 70%, 243–245°C, IR (KBr, in cm^{-1}), 3080.4 (aromatic C-H), 1091.8 (C-O of oxadiazole nucleus), 1661.0 (C=N of oxadiazole), and 3365.5 (N-H str).

*General procedure for synthesis of 5-aryl-2-chloroacetamido-1,3,4-oxadiazoles **V***

2-Amino-5-aryl-1,3,4-oxadiazole **IV** (0.1 mol) was taken in a two-necked round-bottomed flask, containing 100 mL dry benzene, fitted with a reflux condenser and a separating funnel. Chloroacetyl chloride (0.1 mol) in dry benzene (40 mL) was placed in a separating funnel and added dropwise while stirring. After total addition of chloroacetyl chloride, the content was refluxed for 3 h. Excess of solvent was distilled off under reduced pressure. The resulting solution was poured on crushed ice. The product was filtered off and washed several times with cold distilled water to free it from chloride. The product was recrystallized with alcohol.

Compounds: **Va** yield 66%, mp. 178–180°C, IR (KBr, in cm^{-1}) 3072.2 (aromatic C-H), 1091.3 (C-O of oxadiazole nucleus), 1659.4 (C=N of oxadiazole), 1686.5 (C=O str of amide), 711.6 (C-Cl str); **Vb** 73%, 172–174°C, IR (KBr, in cm^{-1}) 3062.5 (aromatic C-H), 1092.8 (C-O of oxadiazole nucleus), 1661.0 (C=N of oxadiazole), 1688.1 (C=O str of amide), and 1548.6 and 1356.1 (N=O str in Ar–NO_2); **Vc** 68% 192–194°C, IR (KBr, in cm^{-1}) 3065.1 (aromatic C-H), 1094.7 (C-O of oxadiazole nucleus), 1664.3 (C=N of oxadiazole), 1689.6 (C=O str of amide), and 1434.8 (C-H def); **Vd** 63%, 167–169°C, IR (KBr, in cm^{-1}) 3070.4 (aromatic C-H), 1090.2 (C-O of oxadiazole nucleus), 1658.4 (C=N of oxadiazole), 1685.7 (C=O str of amide), and 1245.2 (C-F str); **Ve** 72%, 186–188°C, IR (KBr, in cm^{-1}) 3073.8 (aromatic C-H), 1093.5 (C-O of oxadiazole nucleus), 1658.6 (C=N of oxadiazole), 1690.3 (C=O str of amide), 3452.7 (O–H str), and 1154.1 (C–O str of the alcoholic group).

*General procedure for synthesis of 2-(substituted)-ethanoylamino-5-(p-substituted)-phenyl-1,3,4-oxadiazole **1–45***

To the solution of 2-chloroacetamide oxadiazole **V** (0.1 mol) in absolute ethanol (50 mL) was added dry pyridine (0.1 mol) and a ethanolic solution of appropriate secondary amines (0.1 mol). The mixture was refluxed for 6 h on a water bath. The excess solvent was removed by distillation under reduced pressure, using a rotatory vacuum evaporator. The crude product obtained on cooling was filtered off and washed several times with cold distilled water to free it from chloride. The product was recrystallized from diethylether. Physical data and spectral data of compounds **1–45** are summarized in Tables 1 and 2, respectively.

Pharmacology

The local anesthetic activity of the test compounds was evaluated by rabbit corneal reflex test [19] (surface anesthesia) and guinea pig wheal derm test [20] (infiltration anesthesia), in which adult albino rabbits and adult guinea pig were used, respectively. Test animals were divided into groups of six (n = 6). The test animals were acclimatized to laboratory conditions for one week before commencement of the experiment. All the animals were housed in clean environment under a 12 h-light-and-12 h-dark cycle. The animals were kept at a temperature of 22°C (± 3°C) and at a relative humidity between 50 to 60%. They were allowed free access to standard dry pellet diet and water *ad libitum*. Lidocaine hydrochloride (xylocaine 2% solution), containing no epinephrine was used as standard. The test compounds were also dissolved in DMSO and pH-adjusted to 7.4 using 0.1 M sodium hydroxide. All the test compounds showed local anesthetic activity at a solution concentration of 2%. No noticeable differentiation in local anesthetic activity was observed at a solution concentration of 0.5 and 1%. The solvent (DMSO) did not show any activity that might have interfered in the interpretation of the results. A acute oral toxicity test was performed for all the synthesized compounds according to the Organization of Economic Co-operation and Develop-

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ment (OECD) guidelines. Statistical analyses were carried out with the single-tailed t-test. A level of $P < 0.001$ was adopted as the test of significance. Procedures employed for the evaluation of local anesthetics were reviewed and approved by the University Animal Ethical Committee.

Acute oral toxicity [21] was performed as per OECD-423 guidelines (acute toxic class method). Swiss albino mice (n = 3) of either sex selected by random sampling technique were used for the study. The animals were kept on fasting for 3 – 4 h, provided only with water *ad libitum* after which the test compounds (suspended in CMC) were administered orally at the dose level of 5 mg/kg and the animals were observed for 3 days. If mortality was observed in 2 to 3 animals, then the dose administered was assigned as toxic dose. If mortality was observed in 1 animal, then the same dose was repeated again to confirm the toxic dose. In the present study, mortality was not observed with a 5 mg/kg dose and the procedure was repeated further for higher doses of 50, 300, and 2000 mg/kg. All the three mice survived with the 2000 mg/kg dose indicating that test compounds are non-toxic to the animals studied and that any amount of dose below 200 mg/kg can be selected for the evaluation of the local anesthetic activity of the test compounds.

Corneal anesthesia in rabbits

Albino rabbits of either sex weighing 2.5 to 3 kg were placed in rabbit holding cages. The test solution (0.25 mL) was instilled into one eye and DMSO was instilled into the other eye, which served as a control. The corneal reflexes were tested every 2 min (time interval) by bristle. Surface anesthesia was regarded complete when the rabbit failed to blink in response to all the six bristle touches. The time of onset and the duration of local anesthesia were recorded.

Infiltration anesthesia in guinea pigs

On the day preceding the experiment, the hair on the back of guinea pigs in an area of approximately 4 to 5 cm in diameter was shaved. This generally produces a certain amount of irritation which disappears overnight. Standard and test solutions (0.25 mL) were injected intracutaneously (i. c.) into the previously shaved backs of guinea pigs. Blockade of the skin contraction around the injected area to pin pricking with a relatively blunt end of a disposable needle was taken as the criterion of sensory anesthesia. The sensitivity to pin-pricking at six different sites within the wheal was tested by the presence or absence of skin-twitching, accompanied by squeaking sound at regular intervals after the administration of the test compounds. The time of onset was calculated as the time from the injection until the animal felt three out of six pricks. The duration of anesthesia was calculated as the time starting from the onset of anesthesia until three out of six pricks were distinctly felt during recovery from the local anesthetic effect.

References

[1] W. Catterall, K. Mackie *in Goodman and Gilman's the pharmacological basis of therapeutics* (Eds.: J. G. Hardman, L. E. Limbird) 10th Ed., McGraw – Hill, Medical Publishing Division, New York, **2002**, pp. 367 – 384.

[2] E. W. Bryness, P. D. McMaster, E. R. Smith, M. R. Blair, *et al.*, *J. Med. Chem.* **1979**, *22*, 1171 – 1176.

[3] D. P. Jindal, M. S. Coumar, B. Singh, M. M. Ismail, *et al.*, *Arzneimittelforschung* **2003**, *53*, 34 – 39.

[4] J. W. Sr. Sowell, A. J. Block, M. E. Derrick, J. J. Freeman, *et al.*, *J. Pharm. Sci.* **1981**, *70*, 537 – 541.

[5] W. O. Foye, C. M. Jan, B. H. Takman, *J. Pharm. Sci.* **1982**, *71*, 680 – 686.

[6] F. A. Omar, N. M. Mhfouz, M. A. Rahman, *Eur. J. Med. Chem.* **1996**, *31*, 819 – 825.

[7] E. Palaska, G. Sahin, P. Kelicen, N. T. Durlu, G. Antinok, *Farmaco* **2002**, *57*, 101 – 107.

[8] K. Raman, K. H. Singh, S. K. Satzman, S. S. Parmar, *J. Pharm. Sci.* **1993**, *82*, 167 – 169.

[9] M. M. Girges, *Arzneimittelforschung* **1994**, *44*, 490 – 495.

[10] M. I. Husain, A. Kumar, R. C. Srivastava, *Curr Sci* **1986**, *55*, 644 – 646.

[11] A. Zarghi, M. Faizi, B. Shafaghi, A. Ahadian, *et al.*, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3126 – 3129.

[12] A. Almasirad, S. A. Tabatabai, M. Faizi, A. Kebriaeizadeh, *et al.*, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6057 – 6059.

[13] M. Harfenist, D. J. Heuser, C. T. Joyner, J. F. Batchelor, H. L. White, *J. Med. Chem.* **1996**, *39*, 1857 – 1863.

[14] M. C. Lu *in Principles of Medicinal Chemistry* (Eds.: W. O. Foye, T. L. Lemke, S. A. Williams), 4th Ed., B.I. Waverly, Pvt. Ltd., New Delhi, **1995**, pp. 312 – 316.

[15] H. P. Rang, M. M. Dale, J. M. Ritter, *Pharmacology*, 4th Ed., Churchill Livingstone, Edinburg, **2001**, pp. 634 – 644.

[16] J. F. Butterworth, G. R. Strichartz, *Anesthesiology* **1990**, *72*, 711 – 734.

[17] *Vogel's Textbook of Practical Organic Chemistry*, 5th Ed., Longman Singapore Publishers, Pvt. Ltd, Singapore, **1996**, pp. 400, 1258.

[18] P. L. Kachroo, R. Gupta, S. C. Gupta, A. K. Gupta, *Natl. Acad. Sci. Lett.* **1990**, *13*, 125 – 126.

[19] A. Quevauviller *in International Encyclopedia of Pharmacology and Therapeutics*, (Ed.: Radouco – Thomas), Vol I, Pergamon Press, Oxford, New York, **1997**, pp. 291 – 318.

[20] E. Bulbring, I. Wajda, *J. Pharmacol. Exp. Ther.* **1945**, *85*, 78 – 84.

[21] D. J. Ecobichon, *The Basis of Toxicology Testing*, CRC Press, New York, **1997**, pp. 43 – 86.

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