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Synthesis of Novel 3,4-Dihydroquinolin-2(1*H*)-one Guanidines as Potential Antihypertensive Agents

N.R. PAI* and A.B. SAMEL

Department of Chemistry, D.G. Ruparel College, Senapati Bapat Marg, Mahim, Mumbai-400 016, India

*Corresponding author: E-mail: nandini_pai@hotmail.com

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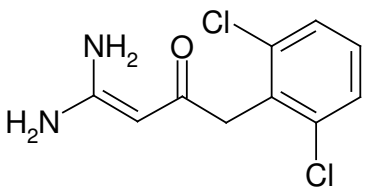
Hydroxy-3,4-dihydroquinolin-2(1*H*)-ones (**4a-c**) were synthesized by intramolecular Friedel Craft alkylation of N-(methoxyphenyl)-3-chloropropionamides (**3a-c**), obtained by acylation of anisidine with chloropropionyl chloride. The hydroxy-3,4-dihydro quinolin-2(1*H*)-ones (**4a-c**) were treated with various dibromo alkanes under phase transfer catalyst conditions at room temperature to give bromoalkyloxy-3,4-dihydroquinolin-2(1*H*)-ones (**5a-l**) which on further reaction with guanidine hydrochloride in dimethyl formamide afforded N-{4-[(2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]alkyl}guanidines (**6a-l**). These compounds were synthesized as potential antihypertensive agents.

Key Words: Antihypertensive agents, Guanidines, 3,4-Dihydroquinolino-2(1*H*)-ones.

INTRODUCTION

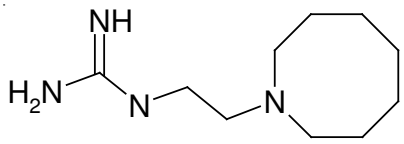
Numerous guanidine derivatives are known which exhibit adrenergic neuron blocking activity and therefore are useful in the treatment of heart and vascular diseases such as hypertension. Guanoxan and, guanabenz act as nitric oxide donors, nitric oxide activates soluble guanylate cyclase (sGC) which leads to relaxation of the muscles and a decrease in the blood pressure[1].

Guanfacine (**I**) lowers both systolic and diastolic blood pressure by activating the central nervous system α_{2a} norepinephrine autoreceptors, which results in reduced peripheral sympathetic outflow and thus a reduction in peripheral sympathetic tone[2].



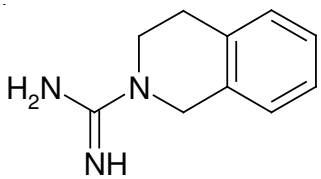
Guanfacine (I)

Guanethidine (**II**) is an antihypertensive drug that reduces the release of catecholamines, such as noradrenaline. Intravenous nerve block (Bier block) using guanethidine has been used to treat chronic pain caused by complex regional pain syndrome[3]. Guanabenz is an α agonist of the α-2 type that is used as an antihypertensive drug. It is used to treat high blood pressure.



Guanethidine (**II**)

The compound 3,4-dihydro-2(1*H*)-isoquinolinecarboxamidine, (Debrisoquin sulfate (**III**) is a potent antihypertensive[4]. A series of 6-cyclic aliphatic amino-7-nitro-3,4-dihydroquinoline-2(1*H*)-ones also showed selective inhibitory activity against platelet aggregation[5]. α-Methylidene-γ-butyrolactone bearing quinolin-2(1*H*)-one and 3,4-dihydroquinolin-2(1*H*)-one derivatives were also found to be vasorelaxing on the KCl-induced vasoconstriction of pig coronary arteries[6].



Debrisoquin (**III**)

Hence it was planned to suitably incorporate the 3,4-dihydroquinolin-2(1*H*)-one moiety anchored to guanidine system by an aliphatic chain and to explore the possibilities of some altered biological action. So the following 3,4-dihydroquinolin-2(1*H*)-one guanidines derivatives were synthesized.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM 300 (300 MHz) instrument using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in parts per million (ppm). Splitting patterns are designated as follows: s- singlet, d- doublet, t- triplet, q- quartet and m- multiplet. Mass spectra (MS) were recorded on Shimadzu LC-MS. The reactions were followed up and the purity of products was carried out on pre-coated TLC plates (Silica gel 60 F254, Merck), visualizing the spots in ultraviolet light.

General method for preparation of N-(methoxyphenyl) -3-chloropropionamides (3a-c)[7]: Anisidine (160 mmol) and sodium carbonate (240 mmol) were added to toluene (20 mL) in a round bottom flask. A solution of 3-chloropropionyl chloride (160 mmol) in toluene (40 mL) was added in 1 h maintaining temperature below 40 ºC, after addition the reaction mixture was heated to 60-65 ºC for 1 h. It was cooled to ambient temperature and 100 mL of 10 % aqueous HCl was added slowly and stirred for 0.5 h. The solid was filtered and washed with water and toluene to get methoxyphenyl-3-chlorolpro-pionamides.

General method for preparation of hydroxy-3,4-dihydroquinolin-2(1*H*)-ones (4a-c)[7]: A round bottom flask was charged with N-(methoxyphenyl)-3-chlorolpropionamide (10 g, 46 mmol) and N,N-dimethyl acetamide (5 mL). Then aluminium chloride (25 g, 184 mmol) was added in lots over 45 min. The temperature was increased to 140-150 ºC. After 2 h the reaction mixture was cooled to 100 ºC and 50 mL toluene was added. The reaction mixture was then cooled further to 15 ºC and chilled water was added stirred further 1 h. The solid obtained was filtered and washed with water and toluene to get compound **4a-c**.

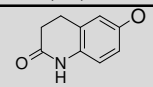
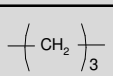
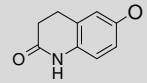
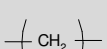
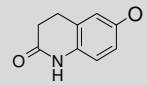
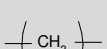
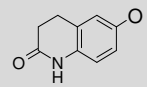
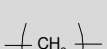
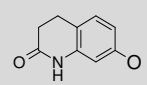
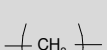
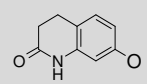
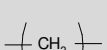
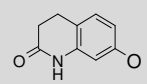
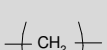
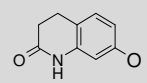
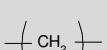
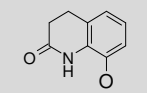
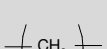
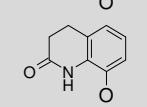
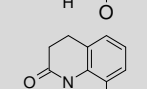
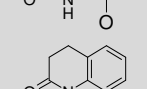
Compound 4a: Yield (82 %), m.p. 238-240 ºC (Lit.[8]); ^{1}H NMR (DMSO-d_6): 2.36 (t, J = 7.5 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 6.50-6.66 (m, 3H), 9.04 (s, 1H), 9.81 (s, 1H); MS m/z: 163.

Compound 4b: Yield (79 %), m.p. 230 ºC; ^{1}H NMR (DMSO-d_6): 2.40 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 6.3 (m, 2H), 6.9 (d, 1H), 9.3 (s, 1H), 10.0 (s, 1H); MS m/z: 163.

Compound 4c: Yield (80 %), m.p. 196 ºC (Lit.[9]); ^{1}H NMR (DMSO-d_6): 2.41 (t, J = 7.5 Hz, 2H), 2.85 (t, J = 7.5 Hz, 2H), 6.74-6.88 (m, 3H), 8.98 (s, 1H), 10.0 (s, 1H); MS m/z: 163.

General method for preparation of bromroalkyloxy-3,4- dihydroquinolin-2(1*H*)-ones (5a-l)[7]: The round bottom flask was charged with **4a-c** (5 g, 30 mmol) in acetone:water mixture (40 mL:2.5 mL). To this mixture was successively added potassium carbonate (5.1 g, 36.7 mmol), PEG-400 (6.1 g) and stirred at ambient temperature for 1 h. The respective dibromo alkane (91.8 mmol) was added at ambient temperature and the stirred for 16 h. The reaction mixture was filtered and washed with acetone. The solvent was removed under reduced pressure. The oily residue obtained was stirred in 100 mL 1:1 mixture of heptane:water. The solid obtained was filtered and washed with water and heptane to get compounds **5a-l** (Table-1).

TABLE-1
DIFFERENT HYDROXY-3,4-DIHYDROQUINOLIN-2(1*H*)-ONE AND ALKYL CHAIN IN COMPOUNDS **5a-l**

Compd.	Hydroxy-3,4-dihydroquinolin-2(1*H*)-one	Chain length	m.p. (ºC)	Yield (%)
5a			112-114[10]	90
5b			139-141[5]	91
5c			110-2	89
5d			107-108[10]	92
5e			112-114	90
5f			110-111[5]	91
5g			122-126[5]	90
5h			107-108	91
5i			110-111	92
5j			125-127	91
5k			76-77	88
5l			72-73	85

Spectral data compounds 5a-l

Compound 5a: IR (KBr, ν_{max}, cm^{-1}): 3195 (NH), 1678 (CONH), 1502 and 1393 (alkyl chain), 1244 and 1033 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 2.16-2.24 (2H, m, -CH_2-), 2.51 (2H, t, J = 7 Hz, -CH_2CO-), 2.62 (2H, t, J = 7 Hz, -CH_2-C-CO-), 3.77 (2H, t, J = 6 Hz, -CH_2Br), 4.05 (2H, t, J = 6 Hz, O-CH_2-), 6.68-6.77 (3H, m, Ar), 9.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 25.0, 30.3, 31.3, 31.8, 65.4, 113.0, 113.1, 114.0, 124.8, 131.9, 153.4, 169.7; MS m/z: 284.

Compound 5b: IR (KBr, ν_{max}, cm^{-1}): 3192 (NH), 1680 (CONH), 1500 and 1390 (alkyl chain), 1241 and 1030 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.89-1.94 (2H, m, -CH_2-), 1.95-

1.98 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.82 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.58 (2H, t, *J* = 6 Hz, -CH_2Br), 4.05 (2H, t, *J* = 6 Hz, O-CH_2-), 6.68-6.77 (3H, m, Ar), 9.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 25.0, 27.8, 30.3, 31.3, 31.8, 65.4, 113.0, 113.1, 114.0, 124.8, 131.9, 153.4, 169.7; MS m/z: 298

Compound 5c: IR (KBr, ν_{max}, cm^{-1}): 3058 (NH), 1668 (CONH), 1504 and 1382 (alkyl chain), 1242 and 1045 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.53-1.56 (2H, m, -CH_2-), 1.67-1.74 (2H, m, -CH_2-), 1.80-1.90 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.80 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.65 (2H, t, *J* = 6 Hz, -CH_2Br), 3.82 (2H, t, *J* = 6 Hz, O-CH_2-), 6.68-6.77 (3H, m, Ar), 9.92 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 24.2, 25.0, 27.8, 30.3, 31.9, 35.0, 67.4, 112.9, 113.9, 115.7, 124.7, 131.6, 153.7, 169.6; MS m/z: 312.

Compound 5d: Yield (92 %), m.p. 107-108 ºC[10]; IR (KBr, ν_{max}, cm^{-1}): 3055 (NH), 1674 (CONH), 1504 and 1398 (alkyl chain), 1244 and 1026 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.40-1.43 (4H, m, -CH_2-), 1.65-1.69 (2H, m, -CH_2-), 1.79-1.85 (2H, m, -CH_2-), 2.39 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.82 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.53 (2H, t, *J* = 6 Hz, -CH_2Br), 3.88 (2H, t, *J* = 6 Hz, O-CH_2-), 6.68-6.76 (3H, m, Ar), 9.91 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 24.6, 25.0, 27.2, 28.5, 30.3, 32.1, 35.0, 67.5, 112.9, 113.9, 115.7, 124.7, 131.6, 153.7, 169.6; MS m/z: 326.

Compound 5e: IR (KBr, ν_{max}, cm^{-1}): 3192 (NH), 1685 (CONH), 1521 and 1375 (alkyl chain), 1257 and 1033 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 2.21-2.25 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.78 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.65 (2H, t, *J* = 6 Hz, -CH_2Br), 3.95 (2H, t, *J* = 6 Hz, O-CH_2-), 6.45 (1H, d, *J* = 2.5 Hz), 6.49 (1H, dd, *J* = 2.5, 8 Hz), 7.04 (1H, d, *J* = 8 Hz), 10.0 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 23.9, 30.6, 31.2, 31.7, 65.2, 101.6, 107.5, 115.7, 128.4, 139.2, 157.5, 170.2; MS m/z: 284.

Compound 5f: IR (KBr, ν_{max}, cm^{-1}): 3033 (NH), 1678 (CONH), 1525 and 1382 (alkyl chain), 1276 and 1060 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.77-1.89 (2H, m, -CH_2-), 1.91-1.98 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.78 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.55 (2H, t, *J* = 6 Hz, -CH_2Br), 3.91 (2H, t, *J* = 6 Hz, O-CH_2-), 6.43 (1H, d, *J* = 2.5 Hz), 6.48 (1H, dd, *J* = 2.5, 8 Hz), 7.04 (1H, d, *J* = 8 Hz), 9.99 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 23.9, 27.3, 29.0, 30.7, 34.7, 66.5, 101.7, 107.4, 115.5, 128.3, 139.1, 157.7, 170.2; MS m/z: 298

Compound 5g: IR (KBr, ν_{max}, cm^{-1}): 3205 (NH), 1690 (CONH), 1514 and 1393 (alkyl chain), 1234 and 1044 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.56-1.65 (2H, m, -CH_2-), 1.66-1.75 (2H, m, -CH_2-), 1.79-1.88 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.78 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.60 (2H, t, *J* = 6 Hz, -CH_2Br), 3.93 (2H, t, *J* = 6 Hz, O-CH_2-), 6.44 (1H, d, *J* = 2.5 Hz), 6.50 (1H, dd, *J* = 2.5, 8 Hz), 7.03 (1H, d, *J* = 8 Hz), 9.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 23.2, 24.0, 27.4, 29.0, 30.7, 34.7, 66.5, 101.7, 107.4, 115.5, 128.3, 139.1, 157.7, 170.3; MS m/z: 312.

Compound 5h: IR (KBr, ν_{max}, cm^{-1}): 3190 (NH), 1677 (CONH), 1530 and 1380 (alkyl chain), 1238 and 1028 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.51-1.63 (4H, m, -CH_2-), 1.65-1.74 (2H, m, -CH_2-), 1.75-1.86 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.78 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.60 (2H, t, *J* = 6 Hz, -CH_2Br), 3.93 (2H, t, *J* = 6 Hz, O-CH_2-), 6.43 (1H, d, *J* = 2.5 Hz), 6.49 (1H, dd, *J* = 2.5, 8 Hz), 7.04 (1H, d, *J* = 8 Hz), 9.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 23.1, 24.2, 27.4, 28.5, 29.0, 30.7, 34.7, 66.5, 101.7, 107.4, 115.4, 128.1, 139.2, 157.6, 170.1; MS m/z: 326.

Compound 5i: IR (KBr, ν_{max}, cm^{-1}): 3209 (NH), 1679 (CONH), 1496 and 1372 (alkyl chain), 1263 and 1028 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.99-2.03 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.85 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.60 (2H, t, *J* = 6 Hz, -CH_2Br), 4.05 (2H, t, *J* = 6 Hz, O-CH_2-), 6.80-6.89 (3H, m, Ar), 8.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 24.8, 29.0, 30.5, 35.1, 67.2, 110.2, 119.6, 122.1, 124.4, 126.8, 145.1, 169.7; MS m/z: 284.

Compound 5j: IR (KBr, ν_{max}, cm^{-1}): 3226 (NH), 1678 (CONH), 1494 and 1371 (alkyl chain), 1269 and 1082 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.79-1.85 (2H, m, -CH_2-), 2.01-2.06 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.85 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.60 (2H, t, *J* = 6 Hz, -CH_2Br), 4.05 (2H, t, *J* = 6 Hz, O-CH_2-), 6.80-6.89 (3H, m, Ar), 8.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 24.8, 27.3, 29.0, 30.5, 35.1, 67.2, 110.2, 119.6, 122.1, 124.4, 126.8, 145.1, 169.7; MS m/z: 298.

Compound 5k: IR (KBr, ν_{max}, cm^{-1}): 3185 (NH), 1684 (CONH), 1522 and 1382 (alkyl chain), 1250 and 1040 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.51-1.56 (2H, m, -CH_2-), 1.74-1.78 (2H, m, -CH_2-), 1.81-1.88 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.85 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.55 (2H, t, *J* = 6 Hz, -CH_2Br), 4.05 (2H, t, *J* = 6 Hz, O-CH_2-), 6.80-6.89 (3H, m, Ar), 8.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 24.2, 24.8, 27.6, 30.5,31.9, 34.9, 67.9, 110.3, 119.6, 122.1, 124.4, 126.7, 145.2, 169.6; MS m/z: 312.

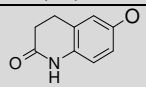
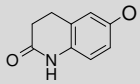
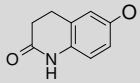
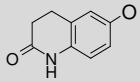
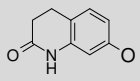
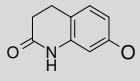
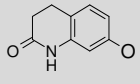
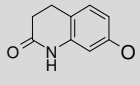
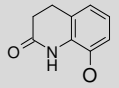
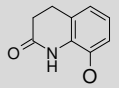
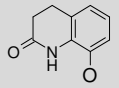
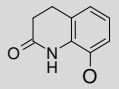
Compound 5l: IR (KBr, ν_{max}, cm^{-1}): 3200 (NH), 1688 (CONH), 1510 and 1381 (alkyl chain), 1235 and 1037 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.32-1.37 (2H, m, -CH_2-), 1.40-1.51 (4H, m, -CH_2-), 1.72-1.77 (2H, m, -CH_2-), 2.44 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.85 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.55 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.96 (2H, t, *J* = 6 Hz, O-CH_2-), 6.74-6.88 (3H, m, Ar), 8.89 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 24.8,25.0, 25.8, 28.3, 28.4, 30.4, 34.9, 68.1, 110.3, 119.6, 122.2, 124.4, 126.6, 145.2, 169.6; MS m/z: 326

General method for preparation of guanidano alkyloxy -3,4-dihydroquinolin-2(1*H*)-one (6a-l): The round bottom flask-1 was charged with **5a-l** (1.5 mmol) and potassium iodide (1.9 mmol) in DMF and heated to 100 ºC for 1 h under nitrogen atmosphere. Another round bottom flask-2 is charged with guanidine hydrochloride (7.7 mmol) and potassium tertiary butoxide (8 mmol) in DMF is stirred at 20 ºC for 1 h under nitrogen atmosphere. The round bottom flask-1 is brought to 20 ºC and its contents are added to flask-2 under nitrogen atmosphere and stirred overnight at room temperature. Then water is added to the reaction mass and pH adjusted to 8 by 1 N HCl. The reaction mass is concentrated to dryness and 5 mL water is added and stirred for 10 min precipitate obtained is filtered and washed with water and heptane to get compounds **6a-l** (Table-2).

Spectral data compounds 6a-l

Compound 6a: IR (KBr, ν_{max}, cm^{-1}): 3342 (NH_2), 3161 (NH), 1678 (CONH), 1508 and 1402 (alkyl chain), 1247 and

TABLE-2
DIFFERENT HYDROXY-3,4-DIHYDROQUINOLIN-2(1*H*)-ONE AND ALKYL CHAIN IN COMPUNDS **6a-l**

Compd.	Hydroxy-3,4-dihydroquinolin-2(1*H*)-one	Chain length	m.p. (ºC)	Yield (%)
6a		$-(CH_2)_3-$	157-159	50
6b		$-(CH_2)_4-$	143-144	51
6c		$-(CH_2)_5-$	114-116	49
6d		$-(CH_2)_6-$	106-107	42
6e		$-(CH_2)_3-$	103-104	53
6f		$-(CH_2)_4-$	95-97	50
6g		$-(CH_2)_5-$	87-89	48
6h		$-(CH_2)_6-$	80-81	51
6i		$-(CH_2)_3-$	114-116	51
6j		$-(CH_2)_4-$	104-106	51
6k		$-(CH_2)_5-$	75-77	48
6l		$-(CH_2)_6-$	67-69	47

1031 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.86-1.90 (2H, m, -CH_2-), 2.38 (2H, t, *J* = 7Hz, -CH_2CO-), 2.81 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.25 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.96 (2H, t, *J* = 6 Hz, O-CH_2-), 6.71-6.79 (3H, m, Ar), 7.17 (3H, bs, -CH_2-NH-C-NH_2),7.93 (1H, s, C=NH), 9.95 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 25.0, 28.2, 30.3, 37.7, 64.9, 113.0, 114.0, 115.7, 124.8, 131.8, 153.5, 157.0, 169.7; MS m/z: 262.

Compound 6b: IR (KBr, ν_{max}, cm^{-1}): 3342 (NH_2), 3138 (NH), 1647 (CONH), 1508 and 1390 (alkyl chain), 1244 and 1020 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.56-1.67 (2H, m, -CH_2-), 1.69-1.75 (2H, m, -CH_2-), 2.38 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.82 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.15 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.91 (2H, t, *J* = 6 Hz, O-CH_2-), 6.70-6.78 (3H, m, Ar), 7.15 (3H,bs, -CH_2-NH-C-NH_2),7.88 (1H, s, C=NH) 9.92 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 25.0, 25.2, 25.8, 30.3, 38.6, 67.2, 112.9, 113.9, 115.7, 124.7, 131.6, 153.7, 157.0, 169.6; MS m/z: 276.

Compound 6c: IR (KBr, ν_{max}, cm^{-1}): 3317 (NH_2), 3157 (NH), 1660 (CONH), 1506 and 1392 (alkyl chain), 1245 and 1047 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.42-1.52 (4H, m, -CH_2-), 1.67-1.71 (2H, m, -CH_2-), 2.39 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.80 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.13 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.89 (2H, t, *J* = 6 Hz, O-CH_2-), 6.69-6.77 (3H, m, Ar), 7.11 (3H,bs, -CH_2-NH-C-NH_2), 7.76 (1H, s, C=NH) 9.93 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 25.5, 25.1, 25.7, 28.6, 30.3, 38.6, 67.5, 112.8, 113.8, 115.7, 124.7, 131.6, 153.8, 156.9, 169.6; MS m/z: 290.

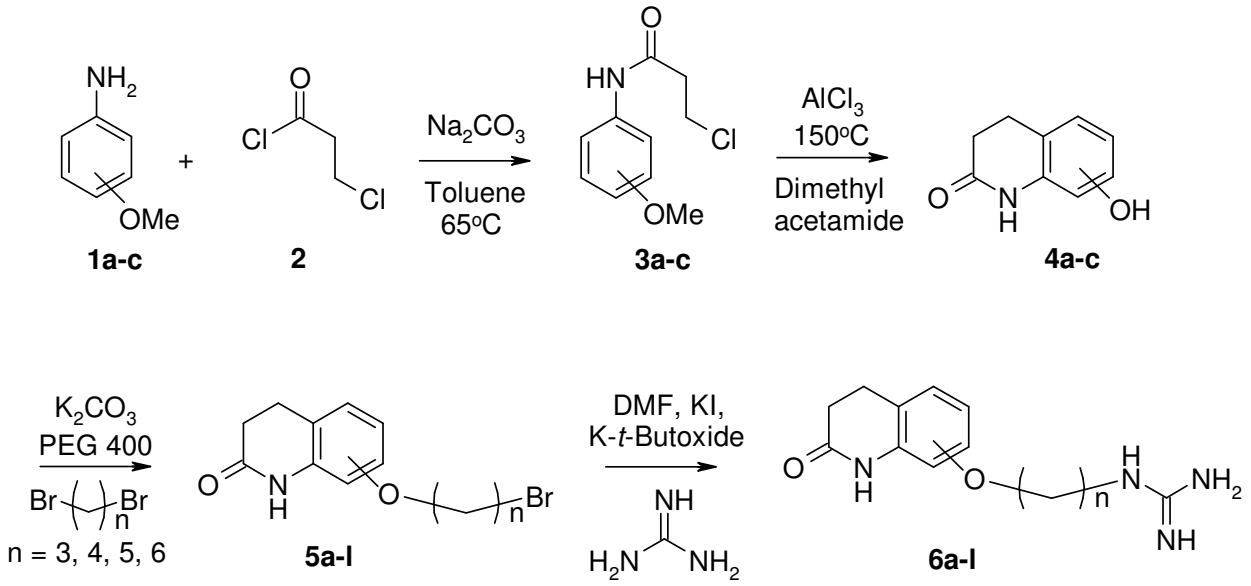
Compound 6d: IR (KBr, ν_{max}, cm^{-1}): 3357 (NH_2), 3190 (NH), 1631 (CONH), 1504 and 1396 (alkyl chain), 1242 and 1033 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.38-1.48 (6H, m, -CH_2-), 1.65-1.69 (2H, m, -CH_2-), 2.39 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.82 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.12 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.89 (2H, t, *J* = 6 Hz, O-CH_2-), 6.70-6.79 (3H, m, Ar), 7.15 (3H, bs, -CH_2-NH-C-NH_2), 7.79 (1H, s, C=NH), 9.95 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 25.0, 25.1, 25.7, 28.3, 28.6, 30.3, 38.6, 67.5, 112.8, 113.9, 115.7, 124.7, 131.5, 153.7, 156.9, 169.7; MS m/z: 304.

Compound 6e: IR (KBr, ν_{max}, cm^{-1}): 3342 (NH_2), 3195 (NH), 1678 (CONH), 1517 and 1377 (alkyl chain), 1261 and 1020 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.89-1.93 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.78 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.26 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.94 (2H, t, *J* = 6 Hz, O-CH_2-), 6.45 (1H, d, *J* = 2.5 Hz), 6.49 (1H, dd, *J* = 2.5, 8 Hz), 6.93 (2H, bs, -CH_2-NH-C-NH_2), 7.05 (1H, d, *J* = 8 Hz), 7.51 (1H, s, -CH_2-NH-C-NH_2), 8.22 (1H, s, C=NH), 10.0 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 23.9, 28.1, 30.7, 34.3, 64.6, 101.6, 107.5, 115.7, 128.3, 139.1, 156.6, 157.5, 170.2; MS m/z: 262.

Compound 6f: IR (KBr, ν_{max}, cm^{-1}): 3340 (NH_2), 3168 (NH), 1655 (CONH), 1504 and 1381 (alkyl chain), 1244 and 1016 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.57-1.64 (2H, m, -CH_2-), 1.67-1.73 (2H, m, -CH_2-), 2.40 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.78 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.15 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.91 (2H, t, *J* = 6 Hz, O-CH_2-), 6.42 (1H, d, *J* = 2.5 Hz), 6.47 (1H, dd, *J* = 2.5, 8 Hz),) 6.93 (2H, bs, -CH_2-NH-C-NH_2), 7.04 (1H, d, *J* = 8 Hz), 7.49 (1H, s, -CH_2-NH-C-NH_2), 8.24 (1H, s, C=NH), 9.99 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 23.9, 25.2, 25.7, 30.7, 34.3, 66.9, 101.7, 107.4, 115.5, 128.3, 139.1, 156.6, 157.7, 170.2; MS m/z: 276.

Compound 6g: IR (KBr, ν_{max}, cm^{-1}): 3342 (NH_2), 3161 (NH), 1657 (CONH), 1506 and 1381 (alkyl chain), 1247 and 1018 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.41-1.46 (2H, m, -CH_2-), 1.47-1.54 (2H, m, -CH_2-), 1.66-1.75 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.78 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.11 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.89 (2H, t, *J* = 6 Hz, O-CH_2-), 6.42 (1H, d, *J* = 2.5 Hz), 6.46 (1H, dd, *J* = 2.5, 8 Hz), 6.93 (2H, bs, -CH_2-NH-C-NH_2), 7.03 (1H, d, *J* = 8 Hz), 7.42 (1H,s, -CH_2-NH-C-NH_2), 8.22 (1H, s, C=NH), 9.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 22.7, 23.9, 28.2, 30.7, 34.3, 38.6, 67.2, 101.6, 107.4, 115.4, 128.3, 139.1, 156.6, 157.8, 170.2; MS m/z: 290.

Compound 6h: IR (KBr, ν_{max}, cm^{-1}): 3345 (NH_2), 3160 (NH), 1660 (CONH), 1508 and 1380 (alkyl chain), 1247 and 1020 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.40-1.47 (4H, m, -CH_2-), 1.48-1.53 (2H, m, -CH_2-), 1.64-1.73 (2H, m, -CH_2-), 2.40 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.77 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.10 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.88 (2H, t, *J* = 6



Scheme-I

Hz, O-CH_2-), 6.41 (1H, d, *J* = 2.5 Hz), 6.46 (1H, dd, *J* = 2.5, 8 Hz), 6.93 (2H, bs, -CH_2-NH-C-NH_2), 7.03 (1H, d, *J* = 8 Hz), 7.42 (1H, s, -CH_2-NH-C-NH_2), 8.21 (1H, s, C=NH), 9.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 22.7, 23.1, 24.2, 27.4, 28.5, 29.0, 30.7, 38.7, 66.5, 101.7, 107.4, 115.4, 128.1, 139.2, 157.6, 170.1; MS m/z: 304.

Compound 6i: IR (KBr, ν_{max}, cm^{-1}): 3348 (NH_2), 3170 (NH), 1645 (CONH), 1495 and 1380 (alkyl chain), 1267 and 1080 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.73-1.77 (2H, m, -CH_2-), 2.41 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.85 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.16 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 4.05 (2H, t, *J* = 6 Hz, O-CH_2-), 6.75-6.92 (3H, m, Ar), 7.11 (3H, bs, -CH_2-NH-C-NH_2), 7.48 (1H, s, C=NH), 8.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 24.8, 29.0, 30.5, 40.2, 67.2, 110.2, 119.6, 122.1, 124.4, 126.8, 145.1, 156.2, 169.7; MS m/z: 262.

Compound 6j: IR (KBr, ν_{max}, cm^{-1}): 3350 (NH_2), 3172 (NH), 1680 (CONH), 1494 and 1388 (alkyl chain), 1265 and 1082 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.66-1.73 (2H, m, -CH_2-), 1.75-1.79 (2H, m, -CH_2-), 2.42 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.87 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.16 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 4.00 (2H, t, *J* = 6 Hz, O-CH_2-), 6.76-6.97 (3H, m, Ar), 7.11 (3H, bs, -CH_2-NH-C-NH_2), 7.48 (1H, s, C=NH), 8.98 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 24.8, 25.1, 25.7, 30.4, 40.5, 67.6, 110.2, 119.6, 122.1, 124.4, 126.7, 145.1, 156.6, 169.6; MS m/z: 276.

Compound 6k: IR (KBr, ν_{max}, cm^{-1}): 3352 (NH_2), 3175 (NH), 1655 (CONH), 1492 and 1388 (alkyl chain), 1260 and 1078 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.37-1.45 (4H, m, -CH_2-), 1.67-1.73 (2H, m, -CH_2-), 2.36 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.78 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.03 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.89 (2H, t, *J* = 6 Hz, O-CH_2-), 6.68-6.84 (3H, m, Ar), 6.90 (3H,bs, -CH_2-NH-C-NH_2), 7.37 (1H, s, C=NH), 8.80 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 22.6, 24.8, 28.0, 34.4, 40.5, 68.0, 110.3, 119.6, 122.2, 124.4, 126.6, 145.1, 156.5, 169.7; MS m/z: 290.

Compound 6l: IR (KBr, ν_{max}, cm^{-1}): 3360 (NH_2), 3172 (NH), 1649 (CONH), 1494 and 1388 (alkyl chain), 1263 and 1083 (Ar-O-CH_2); ^{1}H NMR (DMSO-d_6): 1.32-1.37 (2H, m, -CH_2-), 1.40-1.51 (4H, m, -CH_2-), 1.72-1.77 (2H, m, -CH_2-), 2.44 (2H, t, *J* = 7 Hz, -CH_2CO-), 2.85 (2H, t, *J* = 7 Hz, -CH_2-C-CO-), 3.07 (2H, t, *J* = 6 Hz, -CH_2-NH-C), 3.96 (2H, t, *J* = 6 Hz, O-CH_2-), 6.74-6.88 (3H, m, Ar), 7.12 (3H, bs, -CH_2-NH-C-NH_2), 7.39 (1H, s, C=NH), 8.89 (1H, s, NHCO); ^{13}C NMR (300 MHz; DMSO-d_6): 24.8, 25.0, 25.8, 28.3, 28.4, 30.4, 40.7, 68.1, 110.3, 119.6, 122.2, 124.4, 126.6, 145.2, 156.5, 169.6; MS m/z: 304.

RESULTS AND DISCUSSION

The synthesis involves acylation of anisidine (**1a-c**) with chloropropionyl chloride (**2**) to give N-(methoxyphenyl)-3-chloropropionamide (**3a-c**). Hydroxy-3,4-dihydroquinolin-2(1*H*)-ones (**4a-c**) were then synthesized by intramolecular Friedel Craft alkylation of N-(methoxyphenyl)-3-chloropropionamide (**3a-c**) using lewis acid catalyst like aluminium chloride (3 equivalents) in dimethyl acetamide at 150 ºC, these conditions give demethylation of phenol and ring closure in one pot. The hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**4a-c**) were condensed with various dibromo alkanes in presence of powdered potassium carbonate in acetone water mixture (16:1) under phase transfer catalyst PEG 400 at room temperature to give bromroalkyloxy-3,4-dihydroquinolin-2(1*H*)-ones (**5a-l**). The use of phase transfer conditions facilitates the reaction at room temperature with high yield as side reactions are avoided. The bromroalkyloxy-3,4- dihydroquinolin -2(1*H*)-ones (**5a-l**) on further reaction with guanidine hydrochloride in presence of potassium tertiary butoxide and potassium iodide in dimethyl formamide afforded N-{4-[(2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)oxy]alkyl}guanidine (**6a-l**) (**Scheme-I**).

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