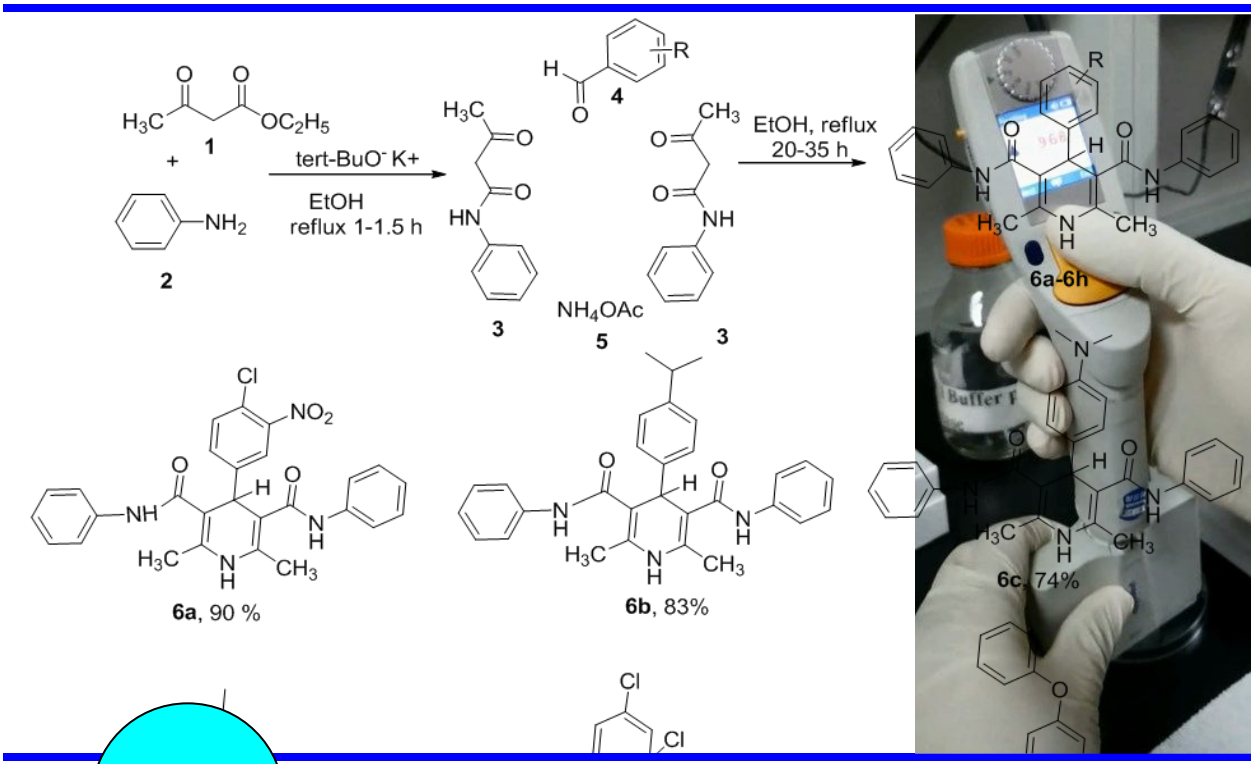

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Synthesis of 4-aryl-2,6-dimethyl-3,5-bis-*N*-(aryl)-carbamoyl-1,4-dihydropyridines as novel skin protecting and anti-aging agents

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Abstract

A series of 4-aryl-2,6-dimethyl-3,5-bis-*N*-(aryl)-carbamoyl-1,4-dihydropyridines **6a-6h** were prepared by using the one-pot three component synthetic method. The target compounds **6a-6h** were synthesized by reacting two molar equivalents of ketone functionality and one mole of aromatic aldehydes in ammonium acetate to obtain the desired products. The structures of newly synthesized compounds were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and elemental analysis. All the synthesized compounds were screened for their elastase inhibition and antioxidant activity. Almost all of the compounds **6a-h** showed good to excellent activities against elastase enzyme more than the reference drug. Compounds **6d** and **6b** at 0.2 ± 0.0 µM and 0.2 ± 0.0 µM were found to most potent derivatives against elastase enzyme. Compound **6a** exhibited prominent free radical scavenging activity. From the results of the biological activity, we infer that some derivatives can serve as lead molecules in pharmacology.

Introduction

The dazzling and fresh appearance of skin does not last for very long. The physiological changes in the skin are inevitable and dermatologists are keenly involved in exploring the potent inhibitors for skin protection. Premature aging occurs mainly due to prolonged exposure of skin to ultraviolet radiations (Kim et al., 2009). Photo-induced skin results in the wrinkle formation and is also linked with oxidative stress and inflammatory response.

The physiological damage to the skin can be either extrinsic or intrinsic and storage of reactive oxygen species (ROS) in human skin can lead to activation of skin disease causing enzymes such as tyrosinase and elastase enzymes (Popoola et al., 2015). Elastase is an enzyme which belongs to the family of chymotrypsin and it is responsible for the cleavage of elastin (Macdonald et al., 1998). Elastin is a protein present in the skin and is responsible for the skin elasticity. Elastin forms the elastic fiber which furnishes elasticity to connective tissues. The abrasion of elastic fibers impedes the elasticity of the skin. Elastase enzyme degrades the elastin, hence inhibition of elastase activity can serve as an efficient way to protect skin aging.

Hantzsch 1,4-dihydropyridines (1,4-DHPs) are widely recognized as Ca^{2+} channel blockers and have emerged as the exquisite class of drugs for the treatment of cardiac-related disorders and hypertension (Spedding and Paoletti, 1992). The DHP heterocyclic ring is a common feature of various bioactive compounds such as vasodilator, bronchodilator (Tanabe et al., 1998), antiatherosclerotic, antitumor, neuroprotective, hepatoprotective (Davis and Davis, 1979) and antidiabetic

agents (Baraldi et al., 1989). 1,4-DHPs are capable of exhibiting extended medicinal utilities including protection of nerve cells, prevent blood aggregation and recently, it has observed that they can also show bioactive effects against Alzheimer's disease (Pastan and Gottesman, 1987). These fascinating bioactive features reveal the promising role of 1,4-DHPs as potent and valuable drug candidates (Sridhar and Perumal, 2005; Kumar and Maurya, 2008).

Based on the sound applications of 1,4-DHPs, herein, we report the one pot-three component synthesis of 4-Aryl-2,6-dimethyl-3,5-bis-*N*-(aryl)-carbamoyl-1,4-dihydropyridines as novel elastase inhibitors and free radical scavenging agents. All the synthesized molecules showed elastase inhibition better than the standard drug.

Materials and Methods

The R_f-values were determined using aluminum precoated silica gel plates Kiesel 60 F254 from Merck (Germany). Melting points of the compounds were measured in open capillaries using Stuart melting point apparatus (SMP3) and are uncorrected. ^{1}H-NMR spectra were determined as DMSO solutions at 300 MHz using a Bruker AM-300 spectrophotometer using TMS as an internal reference. The ^{13}C-NMR spectra were determined at 75 MHz using a Bruker 75 MHz NMR in DMSO-d6 solution using TMS as an internal standard. The elemental analysis was performed on Leco CHNS-932 Elemental Analyzer (Leco Corporation, USA). For the synthesis of compounds, all chemicals were commercially obtained and used without additional purification.

General procedure for the synthesis of *N*-arylacetoacetamides (3)

A mixture of ethyl acetoacetate (**1**, 1.3 g, 10 mmol/L), an aniline (**2**, 10 mmol/L) and a catalytic amount of potassium *tert*-butoxide was taken into a 250 mL round bottom flask and dissolved in 25 mL of ethanol. The reaction mixture was heated under reflux for 1 to 1.5 hours. The product was filtered and washed with small portions of dry ether. Purification was effected by recrystallization from ethanol to obtain colorless crystalline solid.

General procedure for the synthesis of 4-aryl-2,6-dimethyl-3,5-bis-*N*-(aryl)-carbamoyl-1,4-dihydropyridines (6a-6h)

A mixture of *N*-arylacetoacetamide (**3**, 20 mmol/L), an appropriate aldehyde (**4**, 10 mmol/L) and ammonium acetate (**5**, 20 mmol/L) in ethanol (25 mL) was heated under reflux, on a water-bath for 25-35 hours while monitoring the reaction by TLC. Further purification was effected by column chromatography using petroleum ether-chloroform (3:1) as eluent.

4-(4-Chloro-3-nitrophenyl)-2,6-dimethyl-*N*3,*N*5-diphenyl-1,4-dihydropyridine-3,5-dicarboxamide (6a)

Dark orange crystalline solid, m.p.=248-250°C, Yield 93%, R_f=0.44 (n-hexane: Ethyl acetate 6:4), ^{1}H-NMR (DMSO-d_6, 300 MHz); δ (ppm) 10.45 (s, 2H, 2×CO-NH), 9.52 (s, 1H, NH-DHP), 8.28 (s, 1H,=C-OH), 7.84 (d, 1H, Ar-H, *J*= 1.8Hz), 7.64-7.22 (m, 13H, Ar-H), 7.02-6.97 (m, 2H, Ar-H), 5.22 (s, 1H, H4-DHP), 2.10 (s, 6H, 2×-CH_3),^{13}C-NMR (75 MHz DMSO-d6) δ (ppm)167.51 (C=O), 148.51, 147.88, 139.78, 138.99, 133.09, 131.75, 129.23, 128.93, 124.49, 123.43, 122.82, 120.19, 105.33, 41.83, 17.95,Anal. Calcd. for $C_{27}H_{23}ClN_4O_4$: C, 64.48; H, 4.61; N, 11.14; found: C, 64.43; H, 4.59; N, 11.11.

4-(4-Isopropylphenyl)-2,6-dimethyl-*N*3,*N*5-diphenyl-1,4-dihydropyridine-3,5-dicarboxamide (6b)

Dark orange crystalline solid, m.p.=248-250°C, Yield 79%, R_f=0.64 (n-hexane: Ethyl acetate 6:4), ^{1}H-NMR (DMSO-d_6, 300 MHz); δ (ppm) 10.42 (s, 2H, 2×CO-NH), 9.51 (s, 1H, NH-DHP), 8.26(s, 1H,=C-OH), 7.22-7.14 (m, 6H, Ar-H), 7.59-7.43 (m, 8H, Ar-H), 5.21 (s, 1H, H4-DHP), 2.09 (s, 6H, 2×-CH_3), ^{13}C-NMR (75 MHz DMSO-d6) δ (ppm) 167.50, 149.49, 145.32, 141.21, 138.63, 128.91, 128.62, 128.12, 126.31, 121.81, 105.29, 41.37, 32.32, 23.41, 17.91, Anal. Calcd. for $C_{30}H_{31}N_3O_2$: C, 77.39; H, 6.71; N, 9.03; found: C, 77.36; H, 6.65; N, 8.97.

4-(4-(Dimethylamino)phenyl)-2,6-dimethyl-*N*3,*N*5-diphenyl-1,4-dihydropyridine-3,5-dicarboxamide (6c)

Dark orange crystalline solid, m.p.=248-250°C, Yield 83%, R_f=0.71 (n-hexane: Ethyl acetate 6:4), ^{1}H-NMR (DMSO-d_6, 300 MHz); δ (ppm) 10.40 (s, 2H, 2×CO-NH), 9.52 (s, 1H, NH-DHP), 8.26 (s, 1H,=C-OH), 7.62-7.21 (m,10H, Ar-H), 6.62-6.973 (m, 4H, Ar-H), 5.20 (s,1H, H4-DHP), 3.08 (s,6H, 2×N-CH_3), 2.10 (s, 6H, 2×-CH_3),^{13}C-NMR (75 MHz DMSO-d6) δ (ppm) 167.51 (C=O), 148.49, 147.91, 136.81, 133.72, 128.93, 122.61,112.28, 105.31, 41.34, 17.92, Anal. Calcd. for$C_{29}H_{30}N_4O_2$: C, 74.65; H, 6.48; N, 12.01; found: C, 74.61; H, 6.42; N, 11.07.

2,6-Dimethyl-*N*3,*N*5-diphenyl-4-(*p*-tolyl)-1,4-dihydropyridine-3,5-dicarboxamide (6d)

Dark orange crystalline solid, m.p.=248-250°C, Yield 71%, Rf=0.76 (n-hexane: Ethyl acetate 6:4), ^{1}H-NMR (DMSO-d_6, 300 MHz); δ (ppm) 10.43 (s, 2H, 2×CO-NH), 9.51 (s, 1H, NH-DHP), 8.26 (s, 1H,=C-OH)7.65- 7.21 (m, 10H, Ar-H), 7.10 (m, Ar-H), 5.21 (s, 1H, H4-DHP), 2.31 (s, 3H), 2.09 (s, 6H, 2×-CH_3), ^{13}C-NMR (75 MHz DMSO-d6) δ (ppm) 167.49 (C=O), 148.49, 141.81, 137.23, 135.94, 128.95, 128.66, 128.37, 128.18, 127.91, 105.32, 41.36, 21.39, 17.94, Anal. Calcd. For $C_{28}H_{27}N_3O_2$: C, 76.86; H, 6.22; N, 9.60; found: C, 76.82; H, 6.18; N, 9.57.

4-(2,4-Dichlorophenyl)-2,6-dimethyl-*N*3,*N*5-diphenyl-1,4-dihydropyridine-3,5-dicarboxamide (6e)

Dark orange crystalline solid, m.p.=248-250°C, Yield 89%, R_f=0.66 (n-hexane: Ethyl acetate 6:4), ^{1}H-NMR (DMSO-d_6, 300 MHz); δ (ppm) 10.44 (s, 2H, 2×CO-NH), 9.50 (s, 1H, NH-DHP), 8.26, (s, 1H,=C-OH) 7.71-7.15 (m,13H, Ar-H), 5.20 (s, 1H, H4-DHP), 2.09 (s, 6H, 2×-CH_3),^{13}C-NMR (75 MHz DMSO-d6) δ (ppm) 167.51 (C=O), 148.49, 142.12, 136.99, 136.01, 132.03, 131.81, 130.30, 129.09, 128.0, 127.04, 121.67, 121.66, 105.30, 41.32, 17.90, Anal. Calcd. for $C_{27}H_{23}Cl_2N_3O_2$: C, 65.86; H, 4.71; N, 8.53; found: C, 65.81; H, 4.72; N, 7.58.

2,6-Dimethyl-4-(4-phenoxyphenyl)-*N*3,*N*5-diphenyl-1,4-dihydropyridine-3,5-dicarboxamide (6f)

Dark orange crystalline solid, m.p.=248-250°C, Yield 88%, R_f= 0.67 (n-hexane: Ethyl acetate 6:4), ^{1}H-NMR (DMSO-d_6, 300 MHz); δ (ppm) 10.44 (s, 2H, 2×CO-NH), 9.51 (s, 1H, NH-DHP), 8.26, (s, 1H,=C-OH) 7.63-7.16 (m,15H, Ar-H), 5.22 (s, 1H, H4-DHP), 2.10 (s, 6H, 2×-CH_3),^{13}C-NMR (75 MHz DMSO-d6) δ (ppm) 167.51 (C=O), 156.98, 153.87, 149.23, 137.43, 137.55, 128.84, 128.77, 121.34, 136.99, 136.01, 132.03, 131.81, 130.30, 129.09, 128.0, 127.04, 121.67, 121.66, 105.30, 41.32, 17.90,Anal. Calcd. For $C_{33}H_{29}N_3O_3$: C, 76.87; H, 5.67; N, 8.15; found: C, 76.81; H, 5.63; N, 8.09.

4-(3-Chlorophenyl)-2,6-dimethyl-*N*3,*N*5-diphenyl-1,4-dihydropyridine-3,5-dicarboxamide (6g)

Dark orange crystalline solid, m.p.=248-250°C, Yield 84%, R_f=0.81 (n-hexane: Ethyl acetate 6:4), ^{1}H-NMR (DMSO-d_6, 300 MHz); δ (ppm) 10.41 (s, 2H, 2×CO-NH), 9.52 (s, 1H, NH-DHP), 8.25 (s, 1H,=C-OH), 7.64-7.23 (m, 14H, Ar-H), 5.19 (s, 1H, H4-DHP),2.08 (s, 6H, 2×-CH_3), ^{13}C-NMR (75 MHz DMSO-d6) δ (ppm) 167.50 (C=O), 148.49, 143.63, 138.28, 134.29,130.03, 129.89, 129.39, 128.07, 126.23, 125.98, 121.63, 105.31, 41.29, 17.89, Anal. Calcd. For $C_{27}H_{24}ClN_3O_2$ C, 70.81; H, 5.28; N, 9.18; found: C, 70.75; H, 5.21; N, 9.13.

4-(3-Methoxyphenyl)-2,6-dimethyl-*N*3,*N*5-diphenyl-1,4-dihydropyridine-3,5-dicarboxamide (6h)

Dark orange crystalline solid, m.p.=248-250°C, Yield 79%, R_f=0.69 (n-hexane: Ethyl acetate 6:4), ^{1}H-NMR (DMSO-d_6, 300 MHz); δ (ppm) 10.41 (s, 2H, 2×CO-NH), 9.52 (s, 1H, NH-DHP), 8.23 (s, 1H,=C-OH), 7.61-6.82 (m, 14H,Ar-H), 5.21 (s, 1H, H4-DHP), 3.91 (s, 3H, -OCH_3), 2.10 (s, 6H, 2×-CH_3), ^{13}C-NMR (75 MHz DMSO-d6) δ (ppm) 167.51 (C=O), 161.66, 148.49, 142.89, 137.98, 130.04, 128.93, 128.07, 121.88, 119.88, 113.79, 110.91, 105.32, 56.98, 41.35, 17.93, Anal. Calcd. For $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.27; found: C, 74.08; H, 5.96; N, 9.21.

Elastase inhibition activity assay

The elastase inhibitory potency of synthetic compounds was determined by Thongyoo et al., 2009 method with some changes. The quantity of free *p*-nitroaniline, that was hydrolyzed by the action of elastase from the substrate (N-succinyl-Ala-Ala-Ala-p-nitroanilide) was quantified by calculating the absorbance at 410 nm. In general, 0.2 M Tris-HCl buffer (pH 8.0) was prepared and used for preparing substrate (0.8 mM) N-succinyl-Ala-Ala-Ala-p-nitroanilide. After that 130 µL of buffer and 10 µL of compounds was poured in the 96 well microplate and pate was incubated at 25°C for 10 min. After pre-incubation, 10 µL elastase (0.0375 Unit/mL) enzyme was added and the plate was further incubated for 30 min at 25°C. After the final incubation, absorbance was recorded using microplate reader at 410 nm. The assay was performed in triplicate and % of inhibition was calculated using following formula:

$$\text{Elastase inhibition (\%)} = \frac{\text{Ab Control - Ab Sample}}{\text{Ab Control}} \times 100$$

Oleanolic acid was used as the reference drug for elastase.

Free radical scavenging assay

Radical scavenging potency of newly elastase inhibitors was performed by following the already reported protocol of Larik et al., 2016. The assay mixture comprised of 100 µL of DPPH (150 µM), and 20 µL of compounds with increasing doses and the amount of mixture was fixed to 200 µL in each well with DMSO. The assay plate was then incubated at room temperature for 30 min. For comparison, ascorbic acid (Vitamin C) was used as positive control. The absorbance's were recorded at 517 nm using microplate reader (OPTI Max, Tunable). The assay was performed in triplicate and repeated three times.

Results

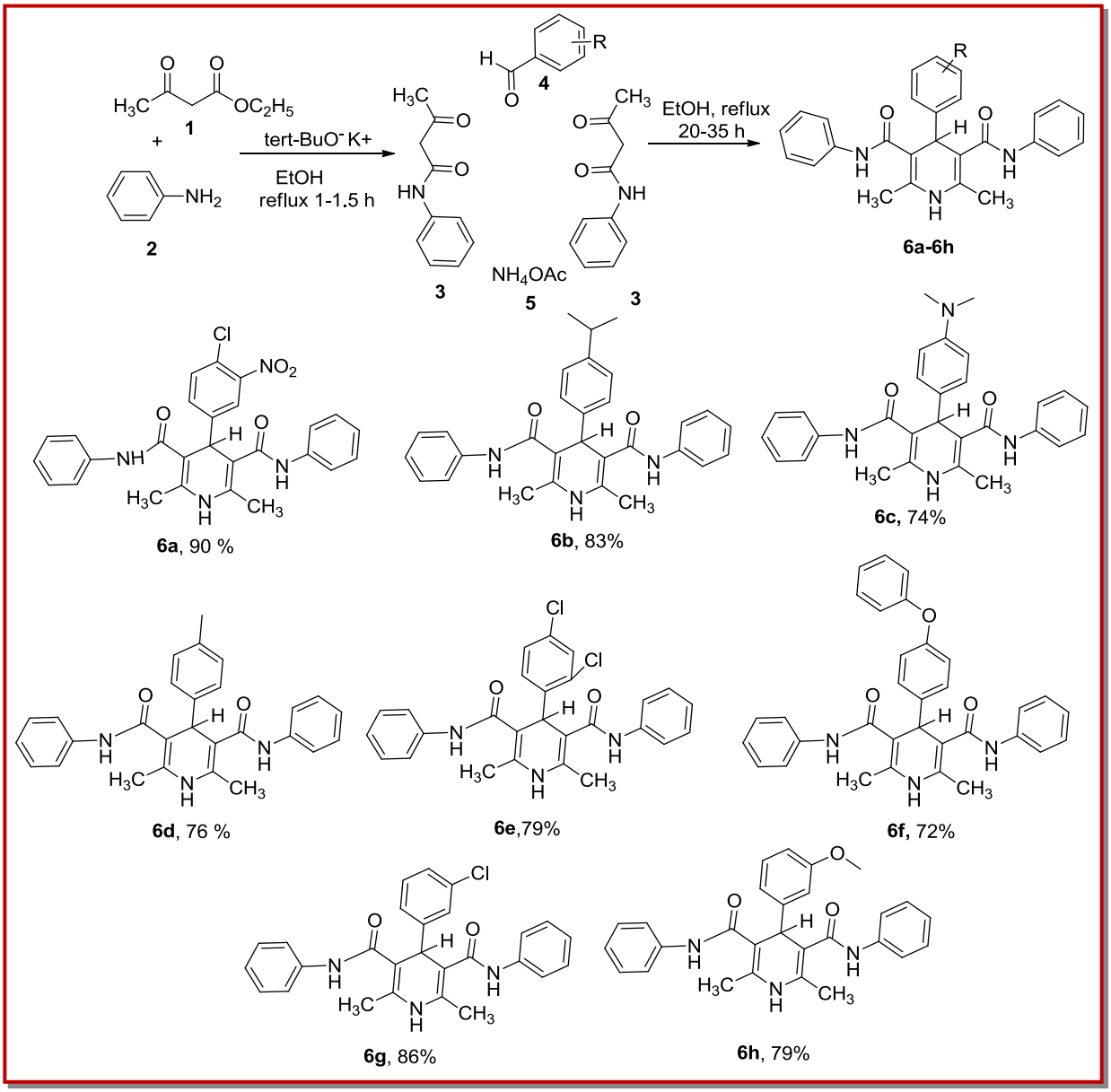
The results of synthesized compounds **6a-6h** are summarized in Table I. The most derivatives in the series were found to **6d** and **6b.** The IC_{50} value of **6d** was 0.2 ±

Table I

Elastase inhibitory activity

Compound	Elastase IC_{50} ± SEM (µM)	%Free radical scavenging (100 µg/mL)
6a	0.9 ± 0.0	95.7
6b	0.2 ± 0.0	11.5
6c	6.3 ± 0.1	12.3
6d	0.2 ± 0.0	39.8
6e	5.1 ± 0.2	9.1
6f	1.2 ± 0.0	6.5
6g	2.05 ± 0.1	15.5
6h	0.4 ± 0.0	15.5
Oleanolic acid	13.5 ± 0.5	-
Vitamin C	-	96.5

Values are expressed as mean ± SEM



Scheme 1: Synthesis of 4-Aryl-2,6-dimethyl-3,5-bis-*N*-(aryl)-carbamoyl-1,4-dihydropyridines

0.0 µM and it was found to possess several-fold better activity than the standard oleanolic acid 13.5 ± 0.5 µM. The compound **6d** showed slightly better inhibition compared to **6b** against the elastase enzyme. The compound **6d** possesses methyl group at para position of aryl ring while compound **6b** bears isopropyl group at para position of aryl ring. The least potential derivatives in the series were found to be compound **6c** and **6e.** The compound **6c** contains *N,N*-dimethyl group at para position that might play the role in its least potential while compound **6e** possess chlorine atom at para position and resulted in its minimum inhibition of the molecule in the series. All the derivatives showed moderate to excellent elastase inhibition activity.

Free radical scavenging

Newly synthesized compounds **6a-6h** were screened for their possible radical scavenging potency. Compound **6a** showed excellent radical scavenging potency in comparison to reference drug vitamin C other compounds did not show significant radical scavenging potency even at high concentration (100 µg/mL).

Discussion

For the synthesis of molecules **(6a-6h)** through a multi-component reaction, first the *N*-arylacetoacetamide **3** was synthesized. Ethyl acetoacetate was treated with

aniline using ethanol as a medium giving intermediate **3** (which was light green in color and was confirmed by mp which was around 98-102°C) under reflux condition. The reaction was carried out using catalytic amount potassium *tert*-butoxide and mechanism was no doubt a nucleophilic substitution reaction. Synthesis of substituted dihydropyridines had been accomplished by adding of compound **3** with different derivatives of aldehydes **4**, and ammonium acetate **5** with the ratio (2:1:1) respectively, using dry distilled ethanol at a temperature around 120-150°C. Usually, 20-35 hours were required for the completion of the reaction. Some by-products were also obtained than the desired products. Hence were purified by column chromatography and preparative TLC (Scheme 1).

The structures of synthesized DHPs were elucidated by NMR studies. The ^{1}H-NMR spectrum for **6a** showed a singlet for 1H of amide linked with unsubstituted benzene moiety at 10.45 ppm whereas secondary amine residing in a heterocycle moiety resonated at 9.52 ppm. Moreover, the characteristics peaks for methyl and tertiary hydrogen in a heterocyclic ring were at 2.10 ppm and 5.22 ppm respectively. All the aromatic regions protons resonated at the aromatic region from 7.85 ppm to 6.97 ppm. The ^{13}C-NMR of **6a** showed carbonyl of amide at 167.51 ppm while rest of ten aromatic carbons and three carbons of a hetero cycling ring showed signals ranging from 148.51 ppm to 41.83 ppm. One carbon for methyl resonated at 17.95 ppm. The other compounds had been confirmed from their respective ^{1}H-NMR and ^{13}C-NMR spectra.

The plethora of literature is available on the significance of 1,4-dihydropyridines as medicinally active lead molecules. This hypothesis and previous experimental finding in the field of medicinal and pharmaceutical chemistry, we envisioned to evaluate the role of 4-aryl-1,4-dihydropyridines as elastase inhibitors and anti-oxidants. The structural modifications on the aryl ring of synthesized molecules resulted in a difference of the biological activity. The electronic perturbing groups such as chlorine, benzyloxy, methyl, isopropyl and *N,N*-dimethyl group showed different activity. The most potent inhibitor **6d**, possessed methyl group at para position of aryl which may be responsible for the enhanced bioactivity. The electron donating groups showed moderate activity and the chlorine atom bearing group showed moderate to excellent inhibition. Interestingly, in case of free radical scavenging activity, compound **6a** was found to potent antioxidant and plausible explanation for this molecule could be that it possess electron pulling groups at aryl ring, such as chlorine atom withdraws electron density from aryl ring through inductive effect while nitro groups withdraw electron density through resonance effect. These newly molecule compound can serve as effective skin protecting and anti-aging agents.

Conclusion

The synthesized compounds 4-aryl-2,6-dimethyl-3,5-bis-*N*-(aryl)-carbamoyl-1,4-dihydropyridines showed significant elastase enzyme inhibition. Compound **6d**, 2,6-dimethyl-*N*3,*N*5-diphenyl-4-(*p*-tolyl)-1,4-dihydropyridine-3,5-dicarboxamide was found to possess remarkable inhibition of elastase, 100-fold better than the standard drug. The compound **6a** displayed most prominent anti-oxidant activity of the series **6a-6h**.

Conflict of Interest

All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work.

References

Baraldi PG, Chiarini A, Budriesi R, Roberti M, Casolari A, Manfredini S, Simoni D, Zanirato V, Varani K, Borea PA. Synthesis and calcium antagonist activity of dialkyl 1, 4-dihydro-2,6-dimethyl-4-(pyrazolyl)-3,5, pyridinedicarboxylates. Drug Des Deliv. 1989; 5: 13-29.

Davis HL, Davis TE. Daunorubicin and adriamycin in cancer treatment: An analysis of their roles and limitations. Cancer Treat Rep. 1979; 63: 809-15.

Kim JH, Byun JC, Hyun CG, Lee NH. Compounds with elastase inhibition and free radical scavenging activities from callistemon lanceolatus. J Med Plants Res. 2009; 3: 914-20.

Kumar A, Maurya RA. Organocatalysed three-component domino synthesis of 1,4-dihydropyridines under solvent free conditions. Tetrahedron 2008; 64: 3477-82.

Larik FA, Saeed A, Channar PA, Ismail H, Dilshad E, Mirza B. New 1-octanoyl-3-aryl thiourea derivatives: Solvent-free synthesis, characterization and multi-target biological activities. Bangladesh J Pharmacol. 2016; 11: 894-902.

MacDonald SJ, Belton DJ, Buckley DM, Spooner JE, Anson MS, Harrison LA, Mills K, Upton RJ, Dowle MD, Smith RA, Molloy CR, Risley C. Syntheses of trans-5-oxo-hexahydropyrrolo [3,2-b] pyrroles and trans-5-oxo-hexahydro-furo [3,2-b] pyrroles (pyrrolidine trans-lactams and trans-lactones): New pharmacophores for elastase inhibition. J Med Chem. 1998; 41: 3919-22.

Pastan I, Gottesman MMN. Multiple-drug resistance in human cancer. N Engl J Med. 1987; 316: 1388-93.

Popoola OK, Marnewick JL, Rautenbach F, Ameer F, Iwuoha EI, Hussein AA. Inhibition of oxidative stress and skin aging-related enzymes by prenylated chalcones and other flavonoids from helichrysum teretifolium. Molecules 2015; 20: 7143-55.

Spedding M, Paoletti R. Classification of calcium channels and the sites of action of drugs modifying channel function. Pharmacol Rev. 1992; 44: 363-76.

Sridhar R, Perumal PT. A new protocol to synthesize 1,4-di-

hydropyridines by using 3,4,5-trifluorobenzeneboronic acid as a catalyst in ionic liquid: Synthesis of novel 4-(3-carboxyl-1H-pyrazol-4-yl)-1,4-dihydropyridines. Tetrahedron 2005; 61: 2465-70.

Tanabe H, Tasaka S, Ohmori H, Gomi N, Sasaki Y, Machida T, Iino M, Kiue A, Naito S, Kuwano M. Newly synthesized dihydropyridine derivatives as modulators of P-glycol-protein-mediated multidrug resistance. Bioorg Med Chem. 1998; 6: 2219-27.

Thongyoo P, Bonomelli C, Leatherbarrow RJ, Tate EW. Potent inhibitors of β-tryptase and human leukocyte elastase based on the MCoT I-II scaffold. J Med Chem. 2009; 52: 6197-200.

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