Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(1):19-31

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

An efficient one-pot synthesis and *in-vitro* anti-microbial study of new thiazolidinones, imidazolidinones and thiazinanones based amino alcohols

Shaaban K. Mohamed[*a,b], A. A. Abdelhamid[a], Walid Omara[c,d], Abdel-Aal M. Jaber[e] and Mustafa Albayati[f]

[a]*Chemistry and Environmental Division, Manchester Metropolitan University, Manchester M1 5GD, England.*
[b]*Chemistry Department, Faculty of Science, Minia University, El-Minia, Egypt.*
[c]*School of Molecular Biology, Manchester University, Manchester, England.*
[d]*Faculty of Pharmacy, Minia University, El-Minia, Egypt..*
[e]*Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt.*
[f]*Kirkuk University, College of Science, Department of Chemistry, Kirkuk, Iraq.*

ABSTRACT

*Numbers of thiazoles, thiazolodinones, thiazinanones and imidazolones have been synthesized in a quantitatively yield in an accessible method via one pot reaction technique using the precursor amino alcohols. In vitro antimicrobial properties of the newly synthesized compounds have been scanned and discussed. It showed the thiazole **6e** possessed the highest inhibitory effect against Micrococcus luteus, model Gram-negative bacteria. Thiazolidinone **4a** and thiazole **6a** showed the highest activity against E. coli, model Gram-positive bacteria compared with Ampicillin. All compounds have been characterized by FT-IR, NMR and X-ray.*

Keywords: three components reaction, biological activity, amino alcohols, thiourea, thiazolidinones, thiazine and imidazolones.

INTRODUCTION

Heterocyclic compounds of nitrogen containing five membered ring systems have been described for their biological activity against various micro-organisms [1]. The thiazole ring is an important for main source for moieties of natural products structures and bioactive compounds useful as pharmaceuticals or agrochemical agents [2-6]. Thiazoles play a prominent role in nature. Various pesticides possessing a thiazole nucleus are well known in agriculture. Large numbers of thiazole derivatives have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory [7], anti-tumour [8], anti-hyperlipidemic [9], anti-hypertensive [10] and several other biological properties [11]. Besides, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds [12]. Thus, the thiazole nucleus has been much studied in the field of organic and medicinal chemistry [13].

Imidazoles are well known heterocyclic compounds which are common and have important feature of a variety of medicinal agents [14]. A number of derivatives of imidazoles serve as valuable therapeutic agents [15]. Considerable interest has been created in the chemistry of imidazoles derivatives due to their versatile therapeutic activities like bactericidal [16], antihistaminic [17], antimalarial [18], antidepressant [19], analgesic [20], anti-ulcer [21], antitumor [22], anti-inflammatory [23] etc. Almost every class of imidazole derivatives has been used for different reactions to produce enormous number of heterocycles. Later, in the last three decades many scientists have synthesized various imidazole heterocyclic precursors containing active hydrogen atom on nitrogen and

evaluated in terms of their pharmacological activity [24]. The emergence of powerful and elegant imidazole has stimulated major advances in chemotherapeutic agents of remarkable significance in medicine, biology and pharmacy. Besides this, it is also reported that imidazole compounds are one of the effective antifungal agents [25].

Thiazine is the six member ring system which contains two heteroatoms (N & S) placed in the heterocyclic ring at 1,3 positions. Thiazines are very useful units in the field of medicinal and pharmaceutical chemistry [26]. Several thiazines were synthesized and reported to exhibit ″good to excellent″ levels of antibacterial potency [27]. On the other hand, many of thiazines derivatives are currently of interest due to their therapeutic properties as smooth muscle relaxants and as potassium channel-opening agents [28], which make them potentially useful for the treatment of various diseases.

In light of above facts and further to our study on synthesis of bioactive heterocyclic molecules [29-31] we herein report an efficient synthetic method of new derivatives of thiazole, thiazolidinone, thiazanones and imidazole compounds in addition to studying of their anti-microbial activities.

EXPERIMENTAL SECTION

Chemistry:
All melting points are uncorrected and were recorded on Melt-Temp II melting point apparatus. FT-IR spectra were measured as KBr pellets on a Shimadzu DR-8001 spectrometer. ^{1}H-NMR spectra were recorded on a Varian Gemini at 400 MHz using TMS as an internal reference and DMSO-d6 as a solvent. All compounds were checked for their purity on TLC plates. X-ray was measured on Bruker APEX2, Bruker Kappa APEXII CCD and Oxford Diffraction Xcalibur (Sapphire3, Gemini) area-detector diffractometers cell refinement: Bruker SAINT; program(s) used to solve structure: SHELXS97; program(s) used to refine structure: SHELXL97; molecular graphics: XSEED.

Reaction of phenylisothiocyanate with amino alcohols aminoethanol, **1a**, aminopropanol, **1b,** amino butanol **1c**, amino pentanol **1d** and1-aminopropan-2-ol **1e** at room temperature under solventless conditionafforder the corresponding intermediate thioureas **IIa-e** which directly were reacted with chloroacetyl chloride, bromoethylacetate, ethyl 3-bromopropanoate, and chloro acetone in dixane under reflux for to furnish a quantitative yield ( )of the corresponding thiazolidinones **3a,c,d** and **4a**, thiazinanes **5a,b**, thiazol **6a** and thiazolium chloride **6e** respectively (Scheme 1).

Imidazolidindione **7b** and imidazolones **8b,d** were obtained from reaction of phenylisocyanate with the appropriate amino alcohols **1b,d** in dioxane via formation in situ the corresponding urea **IIIb,d** (Scheme 2) while reaction of phenylisocyanate with 2-aminobutan-1-ol **1f** afforded the corresponding urea carbamate derivative **9**.Reaction of **9** with chloro acetylchloride did not afford the expected imidazolidindione **11.** Reaction of the later with chloro acetylchloride did not give the corresponding imidazolidindione **11**.

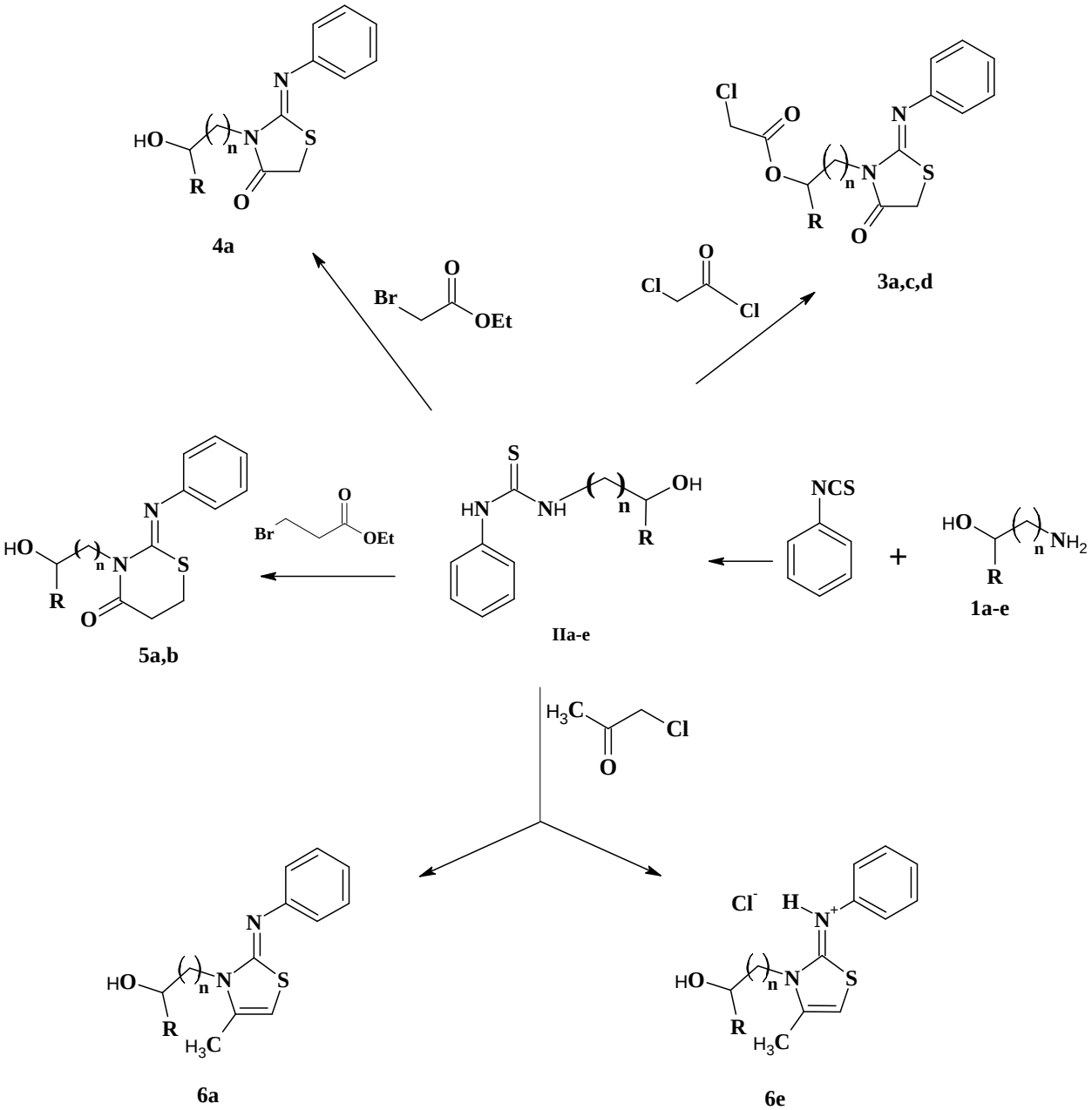
General synthesis of compounds 3a,c,d:
A solution of 0.01 molchloroacetyl chloride in 50ml dioxane was added to a well stirred mixture of 0.01mol phenyl isothiocyanate and 0.01 mol of ethanolamine **1a,** 4-aminobutanol **1c** or 5-aminopentanol **1d.** The reaction mixture wasrefluxedfor 2 hours then left to cool down at room temperature. A mass precipitate was obtained, filtered and washed with cold ethanol. The solid product was crystallized from ethanol to afford the formation of thiazolidinones **3a**, **3c** and **3d** respectively**.**

- ***Chloro-acetic acid 4-(4-oxo-2-phenylimino-thialidin-3-yl)-ethyl ester*** (**3a**): M.p.; 120^{0}C, yield; 99%. This compound was obtained as white crystal (mp= 120 ^{0}C yield = 99%.). IR: spectrum, cm^{-1}: 1600 (C=C), 1646 (C=O cyclic) 1671 (C=O ester), 2923, 2966 (CH-aliphatic), 3056 (CH-aromatic). ^{1}H-NMR spectrum, d, ppm (DMSO) (signals assignment was made based on NOESY and DEPT spectra): 3.48 t (2H, N-$\underline{CH_2}$-CH_2), 3.76 s (2H, S-$\underline{CH_2}$-CO), 4.34 t (4H, O-$\underline{CH_2}$-CH_2, OC-$\underline{CH_2}$-Cl), 7.3 (m, 5H, Ar). ^{13}C NMR spectrum, d, ppm (DMSO-d): 33.5 (N-$\underline{CH_2}$-), 39.9 (S-$\underline{CH_2}$-CO), 48.3 (O-$\underline{CH_2}$-), 64.5 (OC-$\underline{CH_2}$-Cl), 122.0-129 (5CH aromatic), 149 (C aromatic), 163.7 (C=N), 166.6 (C=O cyclic), 171.2 (C=O ester).

- ***Chloro-acetic acid 4-(4-oxo-2-phenylimino-thialidin-3-yl)-butyl ester*** (**3c**): Mp; 90^{0}C, yield; 74%. This compound was obtained as white crystal (Mp= 90^{0}C, yield= 74%). IR: spectrum, cm^{-1}: 1592 (C=C), 1636 (C=O cyclic) 1745 (C=O ester), 2830-2971 (CH-aliphatic), 3025 (CH-aromatic). ^{1}H-NMR spectrum, d, ppm (DMSO) (signals assignment was made based on NOESY and DEPT spectra): 1.65-167 m (4H, CH_2-$\underline{CH_2}$-$\underline{CH_2}$-CH_2), 3.27 t (2H, N-$\underline{CH_2}$-CH_2-CH_2-CH_2), 4.08 s (2H, S-$\underline{CH_2}$-CO), 4.13 t (2H, O-$\underline{CH_2}$-CH_2-CH_2-CH_2), 4.23 s (2H, OC-$\underline{CH_2}$-Cl), 7.2-7.4 (m, 5H, Ar). ^{13}C-NMR spectrum, d, ppm (DMSO-d): 26.2, 26.7 (4H, CH_2-$\underline{CH_2}$-$\underline{CH_2}$-CH_2), 29.4 (2H, N-

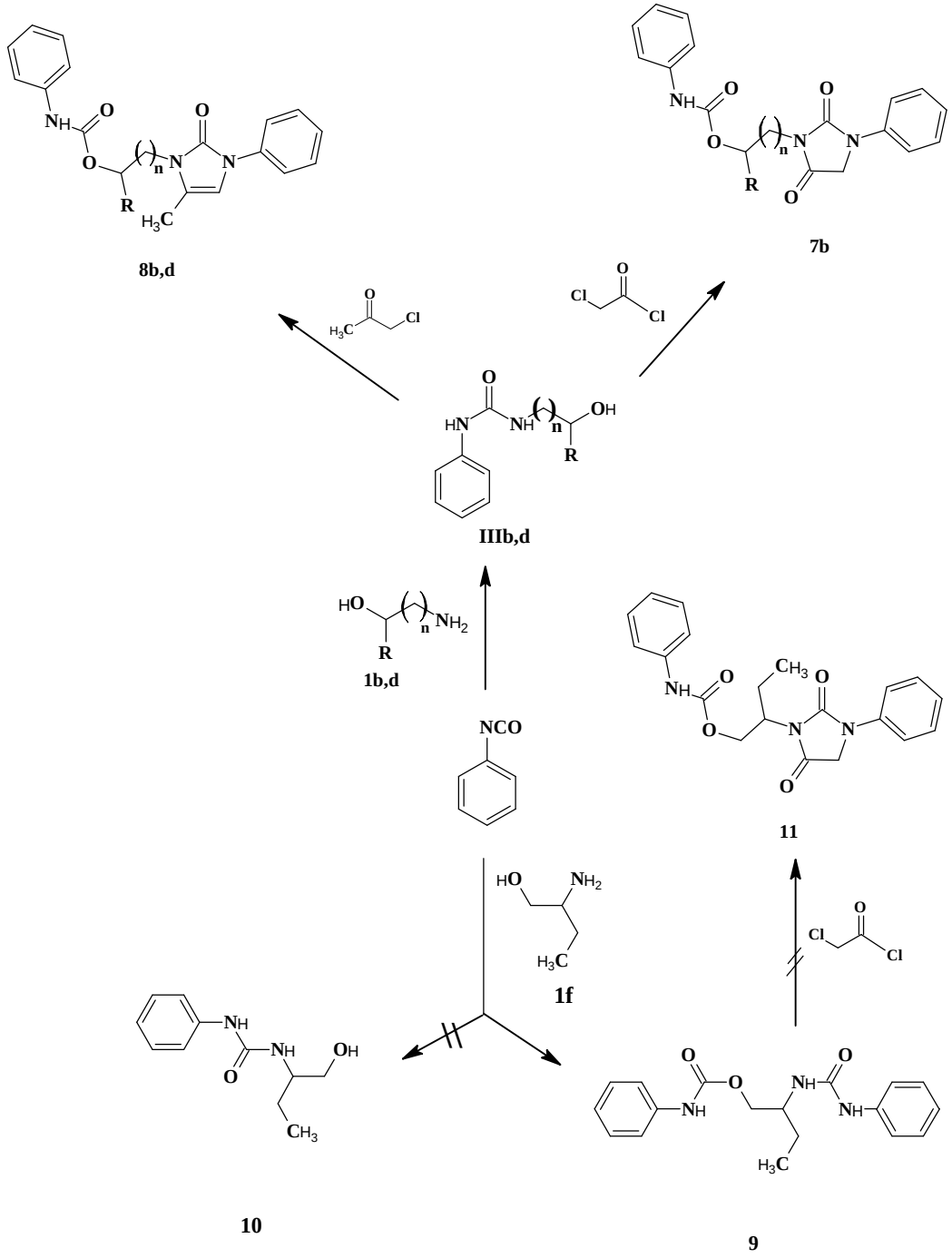
$\underline{CH_2}$-CH_2-CH_2-CH_2), 2H, 40.8 S-$\underline{CH_2}$-CO, 51.1 (2H, O-$\underline{CH_2}$-CH_2-CH_2-CH_2), 65.4 (2H, OC-$\underline{CH_2}$-Cl, 128.0-128.2 (5CH aromatic), 136 (C-aromatic), 152.7(C=N), 167.1(C=O cyclic), 171.0 (C=O ester).

- ***Chloro-acetic acid 5-(4-oxo-2-phenylimino-thiazolidin-3-yl)-pentyl ester* (3d):** This compound was obtained as yellow wax (M.p.; 41^0C, yield; 88%). IR: spectrum, cm^{-1}: 1592 (C=C), 1635 (C=O cyclic), 1764 (C=O ester), 2859-2938 (CH-aliphatic), 3002 (CH-aromatic). ^{1}H-NMR spectrum d, ppm (DMSO) (signals assignment was madebased on NOESY and DEPT spectra): 1.1-1.4 m (8H, OCH_2-$\underline{CH_2}$-CH_2-CH_2-CH_2N), 3.9-4.3 m (6H, O-$\underline{CH_2}$-CH_2-CH_2-CH_2-CH_2-N, CO-CH_2-S, CO-CH_2-Cl), 6.8-7.4 (m, 5H, Ar). ^{13}C-NMR spectrum, d, ppm (DMSO-d): 39-41(4CH_2, OCH_2-$\underline{CH_2}$-CH_2-CH_2-CH_2N), 51(O-CH_2), 65, 66 (2CH_2, CO-$\underline{CH_2}$-S and CO-$\underline{CH_2}$-Cl), 119-129 (5CH, Ar), 136 (C, Ar), 148 ($\underline{C}$=N), 167 (C=O, cyclic), 172 (C=O, ester).



Scheme 1

1,3,4,5,6, 7and 8	R	n
a	H	1
b	H	2
c	H	3
d	H	4
e	CH_3	1



Scheme 2

1, 7and **8**	R	n
b	H	2
d	H	4

Synthesis of (2Z)-3-(2-hydroxyethyl)-2-(phenylimino)-1,3-thiazolidin-4-one (4a):
A solution of 0.01 ethanol amine was added in dropwise to 0.01 mol phenylisocyanate in a round bottomed flask. The obtained solid was dissolved in 50 ml dioxane and followed by addition of 0.01 mol of bromo ethylacetate. The reaction mixture was refluxed for two hours and left to cool at room temperature. The precipitated mass solid was filtered off, dried and recrystallized from ethanol to afford the 85% of the corresponding thiazolidinone **4a**.

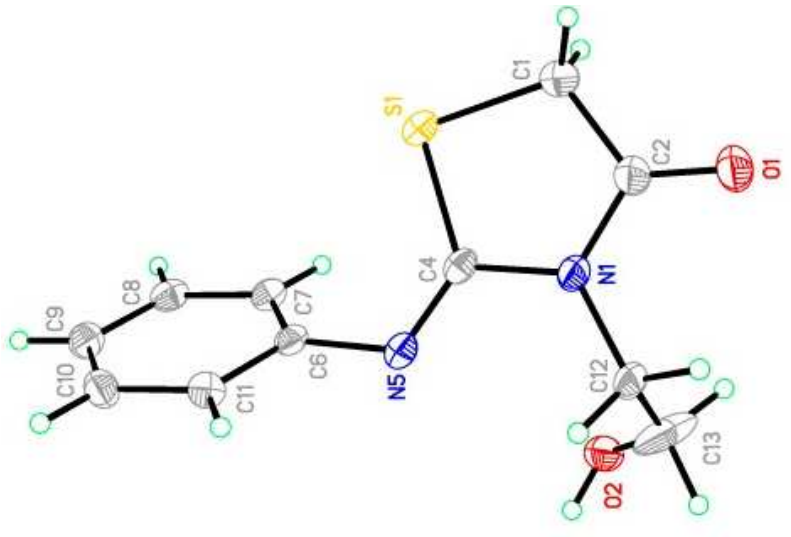


Fig. 1 x-ray structure of 4a

Crystal data

C11H12N2O2S	V = 1093.01 (9) A ° 3
Mr = 236.29	Z = 4
Monoclinic, $P2_1/c$	Mo K_ radiation
a = 11.9612 (6) Å	_ = 0.28 mm_1
b = 6.9478 (3) Å	T = 91 K
c = 13.1554 (6) Å	0.40 _ 0.26 _ 0.11 mm
β = 91.244 (2)º	

Data collection: APEX2 [32]; cell refinement: APEX2 and SAINT [32]; data reduction: SAINT; program(s) used to solve structure: SHELXS97 [33] and TITAN [34]; program(s) used to refine structure: SHELXL97 [33] and TITAN; molecular graphics: SHELXTL [33] and Mercury [35]; software used to prepare material for publication: SHELXL97, enCIFer [36], PLATON [37] and publCIF [38].

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: TK5126). The crystal structure of **4a** showed the thiazole and phenyl rings are inclined at 56.99 (6)º to one another. The thiazole ring is planar with an r.m.s. deviation for the five ring atoms of 0.0274 Å. The presence of the phenylimine substituent is confirmed with the C=N distance to the thiazole ring of 1.2638 (19) Å. The molecule adopts a Z conformation with respect to this bond. The –OH group of the hydroxyethyl substituent is disordered over two positions with relative occupancies 0.517 (4) and 0.483 (4). In the crystal, O—H…O hydrogen bonds, augmented by C—H…N contacts, form dimers with R2 2(11) rings and generate chains along the b axis. Parallel chains are linked in an obverse fashion by weak C—H….S hydrogen bonds. C—H…O hydrogen bonds together with C—H….π contacts further consolidate the structure, stacking molecules along the b axis.

General synthesis of thiazinanones5a,b:
Addition of 0.01 mol Phenyl isothiocyanate to 0.01mol of the appropriate amino alcohols (ethanolamine **1a** or 3-aminopropanol**1b**) resulted in spontaneously formation of the corresponding thiourea derivative in a pure quantitative yield which was dissolved in 50ml dioxane and followed by addition of 0.01 mol ethyl 3-bromopropionate. The reaction mixture was then refluxed with stirring for 2 hours and left to cool down at room temperature. A mass precipitate was obtained, filtered and washed with little cold ethanol. The solid products were crystallized from ethanol to afford the formation of thiazinanones **5a**and**5b**respectively.

- ***3-(2-Hydroxy-ethyl)-2-phenylimino-[1,3]thiazinan-4-one (5a):***

This compound was obtained as white crystal (Mp= 53^0C, yield = 85%). IR: spectrum, cm^{-1}: 1593 (C=C), 1638 (C=O cyclic), 2872-2948 (CH-aliphatic), 3002 (CH-aromatic). 3185-3260(OH alcoholic),^{1}H-NMR spectrum, d, ppm (DMSO) (signals assignment was made based on NOESY and DEPT spectra): 2.85 t (2H, CO-$\underline{CH_2}$-CH_2-S), 3.15 t (2H, S-$\underline{CH_2}$-CH_2-CO), 3.39 t (2H, N-$\underline{CH_2}$-CH_2-O), 3.79 (O-$\underline{CH_2}$-CH_2-N), 7.5 (m, 5H, Ar). ^{13}C-NMR spectrum,d, ppm (DMSO-d): 25 (S-$\underline{CH_2}$-CH_2-CO), 36.1 (CO-$\underline{CH_2}$-CH_2-S), 43.6 (N-$\underline{CH_2}$-CH_2-O), 61.6 (O-$\underline{CH_2}$-CH_2-N), 122-130 (5CH aromatic), 149 (C aromatic), 163(C=N), 175 (C=O).

- ***3-(3-Hydroxy-propyl)-2-phenylimino-[1,3]thiazinan-4-one (5b):***

This compound was obtained as white crystal (Mp= 62^{0}C, yield = 92%). IR: spectrum, cm^{-1}: 1593 (C=C), 1638 (C=O cyclic), 2872-2948 (CH-aliphatic), 3002 (CH-aromatic). 3185-3260(OH alcoholic), ^{1}H-NMR spectrum, d, ppm (DMSO) (signals assignment was made based on NOESY and DEPT spectra): 2.85 t (2H, CO-$\underline{CH_2}$-CH_2-S), 3.15 t (2H, S-$\underline{CH_2}$-CH_2-CO), 3.39 t (2H, N-$\underline{CH_2}$-CH_2-O), 3.79 (O-$\underline{CH_2}$-CH_2-N), 7.5 (m, 5H, Ar). ^{13}C-NMR spectrum, d, ppm (DMSO-d): 25 (S-$\underline{CH_2}$-CH_2-CO), 36.1 (CO-$\underline{CH_2}$-CH_2-S), 43.6 (N-$\underline{CH_2}$-CH_2-O), 61.6 (O-$\underline{CH_2}$-CH_2-N), 122-130 (5CH aromatic), 149 (C aromatic), 163(C=N), 175 (C=O).

Synthesis of thiazoles 6a,e:

A mixture of 0.01 mol aminoethanol **1a** or1-aminopropan-2-ol **1e**, 0.01 mol phenylisothiocyanate and 0.01 mol chloroacetone in 50 ml dioxane was refluxed and monitored by TLC till completion after 2 hours. On cooling, a quantitative solid product was filtered off and dried under vacuum. The crude product was crystallised from ethanol to furnish the corresponding thiazoles **6a** and **6e** respectively.

- ***2-[(2Z)-4-methyl-2-(phenylimino)-1,3-thiazol-3(2H)-yl]ethanol* (6a):**

This compound was obtained as white powder (Mp= 140^{0}C, yield = 91%). IR: spectrum, cm^{-1}: 1592 (C=C), 2838-2937 (CH-aliphatic), 3001 (CH-aromatic). 3277(OH alcoholic),^{1}H-NMR spectrum, d, ppm (DMSO) (signalsassignment was made based on NOESY and DEPT spectra): 2.3 s (3H,$\underline{CH_3}$-C), 2.4 s (OH), 3.7 t (2H, N-$\underline{CH_2}$-CH_2-O), 4.3 t (2H, N-CH_2-$\underline{CH_2}$-O), 6.7 (CH cyclic), 7.3-7.5 (m, 5H, Ar). ^{13}C-NMR spectrum, d, ppm (DMSO-d): 14.6 ($\underline{CH_3}$-C), 49 (N-$\underline{CH_2}$-CH_2-O), 58 (O-$\underline{CH_2}$-CH_2-N), 102 (CH cyclic), 124-130 (5CH aromatic), 140 (C aromatic), 168(C=N).

- ***2-Anilino-3-(2-hydroxypropyl)-4-methyl-1,3-thiazol-3-ium chloride* (6e):**

This compound was obtained as white crystal (Mp= 146^{0}C, yield = 95%).

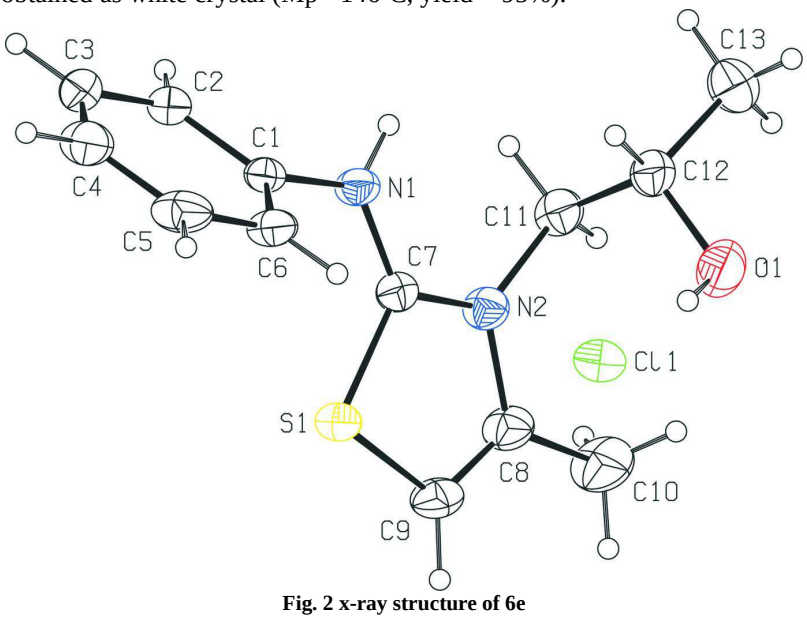


Fig. 2 x-ray structure of 6e

Crystal data:

$C_{13}H_{17}N_2OS^+Cl^-$	V = 1421.21 (8) Å^3
Mr = 284.81	Z = 4
Monoclinic, $P2_1/c$	Mo Kα radiation
a = 11.7570 (4) Å	μ= 0.41 mm^{-1}
b = 12.2477 (4) Å	T = 296 K
c = 10.2954 (3) Å	0.35 x 0.22 x 0.20 mm
β = 106.532 (1)º	

Hydrogen-bond geometry (Å, º):

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1A···Cl1	0.82	2.36	3.1681	169
N1—H1···Cl1^i	0.86	2.34	3.1675	163
C11—H11A···Cl1^i	0.97	2.81	3.6440	144

Symmetry codes: x,-y+1/2, z+1/2

Data collection: APEX2 [39]; cell refinement: SAINT [39]; data reduction: SAINT; program(s) used to solve structure: SHELXS97 [33]; program(s) used to refine structure: SHELXL97 [33]; molecular graphics: ORTEP-3 for Windows [40] and PLATON [37]; software used to prepare material for publication: WinGX [41] and PLATON.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: SU2431). In the title compound, $C13H17N2OS^{+}Cl^{-}$, the thiazolium ring mean plane makes a dihedral angle of 55.46 (9)º with the benzene ring. In the propanol group, the N—C—C– C and N—C—C—O torsion angles are 172.58 (15) and 52.9 (2)º, respectively, and the S—C—C—C torsion angle is 178.99 (18)º. In the crystal, molecules are linked by O— H⋯Cl and N—H⋯Cl hydrogen bonds, forming zigzag chains along {001}. There is also a C—H⋯Cl interaction present.

- **Synthesis of the imidazolidindione (7b):**

A solution of 0.01mol of Phenyl isocyanate was added in dropwise to 0.01mol3-aminopropanol. The instant obtained solid was dissolved in 50 ml dioxane followed by addition of 0.02 mol chloroacetyl chloride. The reaction mixture was refluxed for 2 hours and left to cool down at room temperature. A mass precipitate was obtained, filtered and washed with little of cold ethanol. The solid product was crystallized from ethanol to afford the imidazolidindione **7b**.

- ***3-(2,5-dioxo-3-phenylimidazolidin-1-yl)propyl phenylcarbamate (7b):***This compound was obtained as white powder (Mp= 75^0C, yield = 99%). IR: spectrum, cm^{-1}: 1597 (C=C), 1630 (C=O cyclic), 1705 (C=O ester), 2875-2960 (CH-aliphatic), 3036 (CH-aromatic).^{1}H-NMR spectrum, d, ppm (DMSO) (signals assignment was made based on NOESY and DEPT spectra): 1.8 m (2H, N-CH_2-$\underline{CH_2}$-CH_2-O), 3.1 t (2H, N-$\underline{CH_2}$-CH_2-CH_2-O), 4.0 t (2H, N-CH_2-CH_2-$\underline{CH_2}$-O), 4.1 (CH_2 cyclic), 7.1-7.3 (m, 10H, Ar), 8.0 s (NH). ^{13}C-NMR spectrum, d, ppm (DMSO-d): 27 (N-CH_2-$\underline{CH_2}$-CH_2-O), 36 (O-$\underline{CH_2}$- CH_2-CH_2-N), 40 (N-$\underline{CH_2}$-CH_2-CH_2-O), 52 (CH_2 cyclic, CO-$\underline{CH_2}$-N), 118-129 (10CH aromatic), 138 (2C aromatic), 154(N($\underline{C=O}$)N cyclic), 156(CH_2($\underline{C=O}$)N cyclic),168(NH($\underline{C=O}$)O ester).

Synthesis of imidazolones 8b,d:

A solution of 0.01mol of Phenyl isocyanate was added directly to 0.01mol of the appropriate amino alcohols (3-aminopropanol **1b** or 5-aminopentanol**1d**) followed by adding of 50 ml dioxane and 0.02 mol chloro acetone. The reaction mixture was refluxed and monitored by TLC till completion after 2 hours, then left to cool down at room temperature. A mass precipitate was obtained, filtered, washed with little of cold ethanol andrecrystallized from ethanol to afford the imidazolones**8b,d** respectively.

- ***3-(5-methyl-2-oxo-3-phenyl-2,3-dihydro-1H-imidazol-1-yl)propyl phenylcarbamate (8b):***

This compound was obtained as white powder (Mp= 196^0C, yield = 97%). IR: spectrum, cm^{-1}: 1597 (C=C), 1638 (C=O cyclic), 1704 (C=O ester), 2958-2992 (CH-aliphatic), 3040 (CH-aromatic).^{1}H-NMR spectrum, d, ppm (DMSO) (signals assignment was made based on NOESY and DEPT spectra): 1.7 s (3H,$\underline{CH_3}$-C), 3.4 t (2H, N-$\underline{CH_2}$-CH_2-O), 4.3 t (2H, N-CH_2-$\underline{CH_2}$-O), 6.4 s (CH_2 cyclic), 7.0-7.7 m(10H, Ar), 8.0 s (NH). ^{13}C-NMR spectrum, d, ppm (DMSO-d): 25 ($\underline{CH_3}$-C), 50 (N-$\underline{CH_2}$-CH_2-O), 66 (O-$\underline{CH_2}$-CH_2-N), 100 (CH cyclic), 111 (CH_3-$\underline{C}$), 120-128 (10CH aromatic), 138 (2C aromatic), 145(C=O cyclic), 154(C=O ester).

- ***3-(5-methyl-2-oxo-3-phenyl-2,3-dihydro-1H-imidazol-1-yl)pentyl phenylcarbamate (8d):***

This compound was obtained as white powder (Mp= 126^0C, yield = 92%). IR: spectrum, cm^{-1}: 1597 (C=C), 1634 (C=O cyclic), 1697 (C=O ester), 2861-2935 (CH-aliphatic), 3059 (CH-aromatic). ^{1}H-NMR spectrum, d, ppm (DMSO) (signals assignment was made based on NOESY and DEPT spectra): 1.3 m (2H, OCH_2-CH_2-$\underline{CH_2}$-CH_2-CH_2N), 1.5 m (2H, OCH_2-CH_2-CH_2-$\underline{CH_2}$-CH_2-N), 1.6 m (2H, OCH_2-$\underline{CH_2}$-CH_2-CH_2-CH_2-N), 3.1 t (2H, OCH_2-CH_2-CH_2-CH_2-$\underline{CH_2}$-N), 4.0 t (2H, O$\underline{CH_2}$-CH_2-CH_2-CH_2-CH_2-N), 6.1 s (1H, $\underline{CH}$=C) 7.0-7.6 (m, 10H, Ar), 8.3 s (NH). ^{13}C--NMR spectrum, d, ppm (DMSO-d): 24 (CH_3), 23 (CH_2, OCH_2-CH_2-$\underline{CH_2}$-CH_2-CH_2N), 29.1-29.4 ($2CH_2$, OCH_2-$\underline{CH_2}$-CH_2-$\underline{CH_2}$-CH_2-N), 47 (CH_2, OCH_2-CH_2-CH_2-CH_2-$\underline{CH_2}$-N), 64 (2H, O$\underline{CH_2}$-CH_2-CH_2-CH_2-CH_2-N), 106 ($\underline{CH}$=C), 110 (CH_3-$\underline{C}$), 120-128 (10CH, Ar), 140 (2C, Ar), 150 (C=O, cyclic), 155 (C=O, ester).

Synthesis of urea carbamate (9):

A solution of 0.01mol of Phenyl isocyanate was added in dropwise to 0.01mol 2-aminobutanol**1f.**The obtained solid was dissolved in 50 ml dioxane and added to 0.01 mol chloroacetyl chloride and refluxed for 2 hours. On evaporation of excess solvent under vacuum, mass precipitate was obtained, filtered and washed with little of cold water. The solid products were crystallized from acetone to afford the formation of **9**.

- ***2-[(phenylcarbamoyl)amino]butyl phenylcarbamate (9):*** This compound was obtained as white crystal (Mp= 154^0C, yield = 91%). IR: spectrum, cm^{-1}: 1593 (C=C), 1635 (C=O urea), 1704 (C=O carbamate), 2936-2969 (CH-aliphatic), 3088 (CH-aromatic). ^{1}H-NMR spectrum, d, ppm (DMSO) (signals assignment was made basedon on

NOESY and DEPT spectra): 0.93 t (3H, CH_2-CH_3), 1.5 m (2H, CH-CH_2-CH_3), 3.8 m (1H, CH_2-CH-CH_2), 4.0 d (2H, O-CH_2-CH), 6.1 s (CH-NH-CO), 6.9-7.4 (m, 10H, Ar), 8.4 s (NH-CO-NH-Ph), 9.6 s (O-CO-NH-Ph). ^{13}C-NMR spectrum, d, ppm (DMSO-d): 10.2 (CH_3, CH_3CH_2), 24 (CH_2, CH_3CH_2), 50.2 (CH, CH_2-CH-CH_2), 66.2 (CH_2, O-CH_2-CH), 117-128 (10 CH, Ar), 153, 140 (2C, Ar), 153 (HNCONH, cyclic), 172 (OCONH).

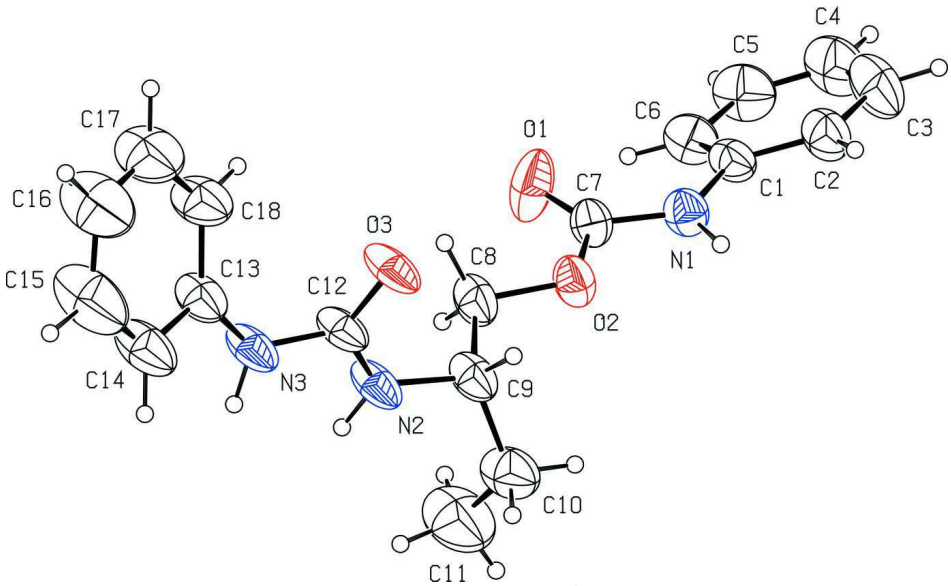


Fig. 3 x-ray structure of 9

Crystal data:

C18H21N3O3	*F*(000) = 696
Mr = 327.38	*D*x = 1.198 Mg m−3
Monoclinic, *Cc*	Cu *Kα* radiation, *λ* = 1.54184 A
Hall symbol: C -2yc	Cell parameters from 838 reflections
a = 10.722 (5) Å	*θ* = 4.0–72.5°
b = 22.297 (3) Å	*μ* = 0.68 mm−1
c = 9.109 (3) Å	*T* = 293 K
β = 123.570 (6)°	Plate, colourless
V = 1814.5 (11) A3	0.14 × 0.12 × 0.07 mm
Z = 4	

Hydrogen-bond geometry (Å, º):

D—H····A	D—H	H····A	D…A	D—H····A
N1—H1*N*····O1^{i}	0.86 (4)	1.97 (4)	2.831 (7)	175(4)
N2—H2*N*····O3^{ii}	0.86 (4)	2.18 (4)	2.920 (6)	145(4)
N3—H3*N*····O3^{ii}	0.86 (6)	2.04 (6)	2.822 (8)	152(4)

Symmetry codes: (i) x -1/2, -y, y+3/2, z -1/2; (ii) x, -y+1, z+1/2
Data collection: CrysAlis PRO [42]; cell refinement: CrysAlis PRO; data reduction: CrysAlis PRO; program(s) used to solve structure: SHELXS97 [33]; program(s) used to refine structure: SHELXL97 [33]; molecular graphics: ORTEP-3 for Windows [40] and PLATON [37]; software used to prepare material for publication: WinGX [41] and PLATON.

Supplementary data and figures for this compound are available from the IUCr electronic archives (Reference: HG5248).

The terminal phenyl rings in the structure make a dihedral angle of 86.3 (5)º. In the crystal, molecules are linked by N—H…..O hydrogen bonds into chains along [001], forming parallel C(4) and R1 2(6) graph-set motifs.

RESULTS AND DISCUSSION

The reaction was proceeded via a nuecluphilic addition of amino group at amino alcohols **1a-e** to the isothiocyanate or isocyanate group to form in situ the corresponding alcoholic intermediates thiourea **II** and urea **III** which in turn reacted with the halogenated active methylene compounds such chloroacetyl chloride, chloroaceton, bromoethylacetate and bromoethylpropanate under reflux via elimination cyclisation reaction mechanism (Schemes

1 and 2). The structure of intermediates **II** and **II** were confirmed by isolation number their derivatives in a solid form in many cases before adding the third reactants and spectrally analyzed separately. Reaction of phenyl isothiocyanate aminoethanol **1a,** aminobutanol **1c** or amino penanol **1d** with chloro acetylacetone afforded the corresponding thiazolidinone derivatives **3a,c,d** respectively. It is noteworthy to confirm that the thiazolidinone chloro ester **3a,c,d** were obtained from a further addition of a second molecule of chloroacetylchloride on their original alcoholic group. IR showed an absorption peaks between 1635-1646 cm^{-1} for the carbonyl group in thiazolidinone ring and another peak at 1671-1764cm^{-1} for the carbonyl of ester. ^{13}C-NMR showed 4CH_2 peaks for **3a**, 6CH_2 for **1c** and 7CH_2 peaks for **1d** in addition to two peaks at 167and 171-172 ppm for (C=O cyclic), (C=O ester) respectively. Aromatic protons have been observed between 6.8-7.4 ppm in ^{1}H-NMR and between 136-149ppm in ^{13}C-NMR in all compounds **1a,c,d**.

When same reaction was carried out with bromoester, the corresponding alcoholic thiazolinone **4a** and thiazinanones**5a,b**was furnished without further addition of bromo ester on the excited alcoholic group. The x-ray analysis confirmed the structure **4a** (fig 1) in which the molecule was stabilized by O—H…O hydrogen bondsgenerating chains along the b axis. Parallel chains are linked in an obverse fashion by weak C—H….S hydrogen bonds. C—H…O hydrogen bonds together with C—H….π contacts further consolidate the structure (Fig. 1).

The FT-IR of **5a,b** showed the alcoholic OH at 3185-3260 cm^{-1} and the cyclic carbonyl group at 1638 cm^{-1}. ^{13}C-NMR spectrum showed four CH_2 peaks at 25, 36, 44 and 62ppm for **5a** and five CH_2peaksat 25, 36.1, 43.6, 53.0 and 61.6 ppm (S-$\underline{CH_2}$-CH_2-CO), (CO-$\underline{CH_2}$-CH_2-S), (N-$\underline{CH_2}$-CH_2-CH_2-O), (O-CH_2-$\underline{CH_2}$-CH_2-N) and (O-$\underline{CH_2}$-CH_2-CH_2-N) respectively for **5b**.A multiplet signal of aromatic protons was assigned at 7.5 ppm in ^{1}H-NMR and at 149 ppm in ^{13}C-NMR for both compounds.

Reaction of chloroacetone with phenyl isothiocyanate and aminoethanol gave the corresponding alcoholic thiazole **6a** and thiazolium chloride **6e** when amino isopropanol was employed. The x-ray diffraction of the mono crystal **6e** confirmed the proposed structure. The crystal data showed that the structure **6e** was stabilized by O— H⋯Cl and N—H⋯Cl hydrogen bonds forming zigzag chains in addition to the interaction bond C—H⋯Cl (Fig. 2).

The alcoholic OH was observed at 3277 cm^{-1} and at 2.4 ppm for **6a**. ^{13}C-NMR showedtwo CH_2 peaks at 49 and 58ppm for (N-$\underline{CH_2}$-CH_2-O), and (O-$\underline{CH_2}$-CH_2-N) respectively. Aromatic protons of **6a** were observed as a broad signal at 7.3-7.5ppm and at 140ppm of the ^{1}H-NMR and ^{13}C-NMR respectively.

On the other hand, reaction of phenylisocyanate with aminopropanol **1b** and chloro acetylchloride in dioxane afforded the corresponding imidazolidindione carbamate **7b** via the intermediate alcoholic urea derivative **IIIb**. Similarly imidazolones **8b,d** were obtained from same reaction technique when chloroacetone was employed. The carbamate structure of **7b** and **8b,d** was formed from an addition of a second molecule of phenylisocyanate on the original alcoholic derivatives of imiazolones.

FT-IR of **7b** and **8b,d** showed a cyclic carbonyl group of imidazole ring between 1630-1638 cm^{-1} and the carbamate carbonyl group at 1697 – 1705 cm^{-1}. Both types of carbonyl groups have also been confirmed bythe^{13}C-NMR spectra at 154-168pmm for the carbonyl of carbamate and for the cyclic ones were at 145 and 150ppm in both structures **8b** and **8d** respectively. and **8**^{1}H-NMR of**7b**showed a singlet peak at 6.2ppm for the cyclic methylene protons and two triplet signals at 3.11 and 4.00ppm $_2$-and for (2H, N-$\underline{CH_2}$-CH_2-CH_2-O) and (2H, N-CH_2--CH_2-$\underline{CH_2}$-O) respectivelyin addition to a multiplet peak at 1.8ppm for the middle methylene protons in the propyl group. The cyclic methylene carbon resonance of 7b was observed in ^{13}C-NMR spectra at 52ppm while the three carbon atoms of the propyl group were recognized at 27, 36 and 40ppm for the underlined CH_2, (N-CH_2-$\underline{CH_2}$-CH_2-O), (O-$\underline{CH_2}$-CH_2-CH_2-N) and (N-$\underline{CH_2}$-CH_2-CH_2-O) respectively.

Reaction of phenyl isocyanate with 2-aminobutanol **1f** and chloroacetyl chloride furnished white crystals of urea carbamate **9** instead of the expected imidazolidindione **11**(Scheme 2). The structure of **9** was confirmed by x-ray analysis which showed that the crystal molecule was stabilized by N—H…..O hydrogen bonds (Fig. 3).The two carbonyl groups were observed from FT-IR spectra at 1635cm^{-1} for the urea one and at 1704cm^{-}1 for the carabamate ones. Same both carbonyl groups were recognized in ^{13}C-NMR spectra at 153 and 172ppm respectively. ^{1}H-NMR of **9** showed one triplet signal for Me group at 0.93ppm and two multiplet peaks at 1.5ppm for the underlined methylene protons (2H, CH-$\underline{CH_2}$-CH_3) and at 3.8ppm for the underlined methine proton (1H, CH_2-$\underline{CH}$-CH_2) in addition to a doublet signal for the methylene protons that adjacent to the carbamate group. Multiplet peak at 6.9-7.4ppm was attributed to the aromatic protons of the two phenyl groups. The four carbons of butyl group were recorded from ^{13}C-NMR spectrumat 10.2ppm for (CH_3, $\underline{CH_3}CH_2$), 24ppm for (CH_2, $CH_3\underline{CH_2}$), 50.2ppm (CH, CH_2-$\underline{CH}$-CH_2) and 66.2ppmfor (CH_2, O-$\underline{CH_2}$-CH).

Anti-microbial:

Methodology

Synthesized compounds were tested for their antibacterial activities using Gram-negative strains represented by *Escherichia coli*, *Salmonella enteric* and *Pseudomonas aeruginosa*; and Gram-positive strains represented by *Staphylococcus aureus, Bacillus subtilis* and *Micrococcus luteus.* (Fig. 4). In addition, antifungal activity was tested using *Candida albicans* and *Candida glabrata*. (Fig. 5).

Synthesized compounds were dissolved in DMF followed by dilution in buffer to obtain final concentrations of 60,000, 30,000 and 15,000 ppm. Final concentration of DMF was less than 2% in the final buffer solutions. Negative control was performed using DMF diluted to similar final concentrations of compound solutions. Ampicillin, as abroad spectrum antibacterial, and Geneticin as antifungal were used for comparison using similar dilutions and final concentrations.

Antimicrobial activity was performed using cup-plate agar diffusion method [43]; in which, plates were prepared by mixing a definite volume of the microbial suspension (inoculums) with sterilized agar media. Then, plates were left to solidify and then wells were prepared using a sterile cork borer. The wells were filled with equal volume of a solution of synthesized compounds and standard drugs. The plates were incubated for 24-48 hrs at 30˚C or 37˚C suitable for each organism. The zones of inhibition were measured in cm as a parameter of antimicrobial activity.

RESULTS

Table 1: Antibacterial activity of compounds measured in cm

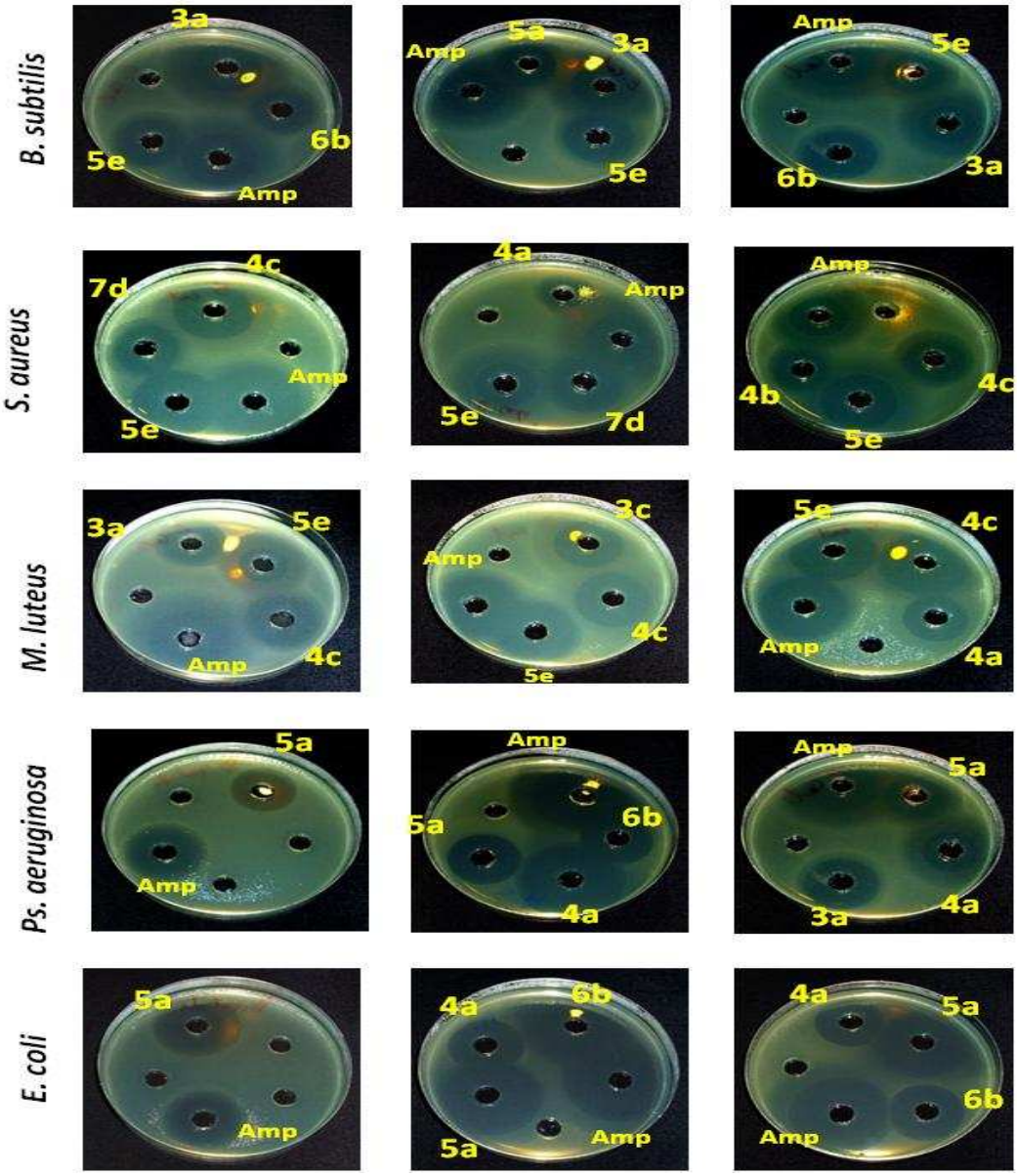
Sample code	3a			3c			3d		
Conc. (ppm) / Organism	60,000	30,000	15,000	60,000	30,000	15,000	60,000	30,000	15,000
Escherichia coli	1.1	0.5	---	0.3	---	---	0.2	---	---
Salmonella enterica	0.7	0.3	---	0.2	---	---	0.3	---	---
Pseudomonas aeruginosa	0.5	0.3	---	0.2	---	---	0.1	---	---
Staphylococcus aureus	0.8	0.5	0.2	0.7	0.4	---	0.8	0.5	0.1
Bacillus subtilis	0.9	0.7	0.2	0.7	0.3	---	0.7	0.3	---
Micrococcus luteus	2.8	2.4	1.8	2.8	2.4	1.9	1.4	1.0	0.7

Sample code	4a			5a			5b		
Conc. (ppm) / Organism	60,000	30,000	15,000	60,000	30,000	15,000	60,000	30,000	15,000
Escherichia coli	2.1	1.6	1.00	0.2	---	---	0.4	---	---
Salmonella enterica	1.5	1.0	0.4	0.3	---	---	0.3	---	---
Pseudomonas aeruginosa	1.2	0.8	0.5	0.2	---	---	0.2	---	---
Staphylococcus aureus	0.5	0.2	---	0.8	0.4	---	0.9	0.6	0.2
Bacillus subtilis	0.7	0.2	---	0.6	0.2	---	0.7	0.4	0.1
Micrococcus luteus	2.2	1.5	1.0	0.4	0.2	---	2.9	2.4	2.1

Sample code	6a			6e			7b		
Conc. (ppm) / Organism	60,000	30,000	15,000	60,000	30,000	15,000	60,000	30,000	15,000
Escherichia coli	2.0	1.6	1.2	0.1	---	---	1.7	1.2	0.5
Salmonella enterica	1.6	1.2	0.6	0.3	---	---	0.9	0.5	0.2
Pseudomonas aeruginosa	1.2	0.8	0.3	0.2	---	---	0.4	0.2	---
Staphylococcus aureus	0.6	0.2	---	1.0	0.7	0.2	0.7	0.4	---
Bacillus subtilis	0.7	0.3	---	0.8	0.4	---	0.8	0.5	0.1
Micrococcus luteus	2.6	2.0	1.3	3.3	2.6	2.0	1.5	1.1	0.6

Sample code	8d			Ampicillin		
Conc. (ppm)	60,000	30,000	15,000	60,000	30,000	15,000

Organism						
Escherichia coli	0.4	---	---	2.2	1.7	1.3
Salmonella enterica	0.3	---	---	1.6	1.1	0.7
Pseudomonas aeruginosa	0.2	---	---	1.5	1.0	0.6
Staphylococcus aureus	0.8	0.4	---	1.2	0.9	0.5
Bacillus subtilis	0.6	0.2	---	1.0	0.8	0.6
Micrococcus luteus	2.4	1.8	1.2	3.5	3.0	2.1



(Fig. 4) Antibacterial activity of labelled compounds on different bacterial strains

Table 2: Antifungal activity of compounds measured in cm

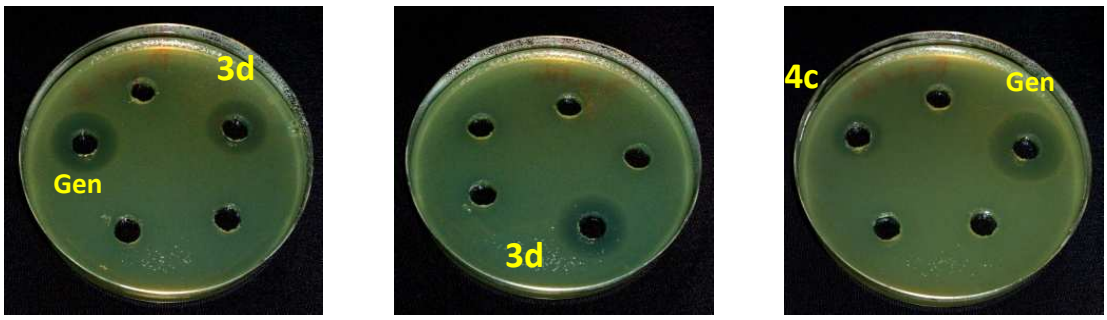
Sample code	3a			3c			3d		
Conc. (ppm) / Organism	60,000	30,000	15,000	60,000	30,000	15,000	60,000	30,000	15,000
Candida albicans	0.7	0.4	---	0.8	0.3	---	0.9	0.6	0.2
Candida glabrata	0.6	0.4	---	0.6	0.2	---	0.7	0.4	---

Sample code	4a			5a			5b		
Conc. (ppm) / Organism	60,000	30,000	15,000	60,000	30,000	15,000	60,000	30,000	15,000
Candida albicans	0.4	0.1	---	0.4	---	---	0.9	0.5	---
Candida glabrata	0.3	---	---	0.3	---	---	0.6	0.2	---

Sample code	6a			6e			7b		
Conc. (ppm) / Organism	60,000	30,000	15,000	60,000	30,000	15,000	60,000	30,000	15,000
Candida albicans	0.3	---	---	0.7	0.3	---	0.6	0.2	---
Candida glabrata	0.7	0.3	---	0.8	0.6	0.2	0.6	0.2	---

Sample code	8d			Geniticin		
Conc. (ppm) / Organism	60,000	30,000	15,000	60,000	30,000	15,000
Candida albicans	0.4	---	---	1.5	1.2	0.8
Candida glabrata	0.8	0.5	---	1.2	0.9	0.5

C. albicans



(Fig. 5) antifungal activity of labelled compounds on *C. albicans*

DISCUSSION

The activity of these compounds was compared to the standard drugs; Ampicillin and Geniticin for antibacterial and antifungal activity respectively. Generally most of them exhibited antibacterial and/or antifungal activity except compound **5a** which showed limited antibacterial activity with nearly no antifungal activity. On the other hand, compounds **4a**, **6a** and **7b** showed broader spectrum than the others with good activity against Gram-positive bacteria, moderate activity against Gram-negative bacteria and weak antifungal activity. Amongst those broad spectrum compounds, **6a** showed the highest. Moderate activity was generally shown against Gram positive bacteria when compared to Ampicillin represented by large inhibition zones against *Micrococcus luteus* and moderate zones against other Gram-positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis*. However, antibacterial activities of all synthesized compounds were less against Gram-negative bacteria as shown on the inhibition zones using *E. coli*, *Pseudomonas aeruginosa* and *Salmonella enterica.*

All compounds at high concentration; 60,000ppm; showed general antibacterial and antifungal activities against all strains tested with inhibition zones ranged from 3.3cm for compound **6e** against *Micrococcus luteus* down to 0.1cm for some compounds mainly against Gram-negative bacteria and Candida species.

Compounds **4a** and **6a** showed the highest activity against *E. coli*, model Gram-negative bacteria with inhibition zones 2.1 to 1.0 and 2.0 to 1.2 cm for their concentrations 60,000 to 15,000 ppm respectively compared with inhibition zones of Ampicillin 2.2 to 1.3 cm for the same concentrations. However, compound **6e** showed the highest activity against *Micrococcus luteus*, model Gram-positive bacteria with inhibition zones 3.3 to 2.0 cm compared with inhibition zones of the standard drug, Ampicilli, 3.5 to 2.1 cm. As antifungal agent, compound **3d** showed the highest activity against *Candida glabrata* and *Candida albicans* with inhibition zones 0.9 and 0.6 for concentration 60,000 ppm compared to the standard drug, Geniticin, 1.2 cm.

REFERENCE

[1] Y-B Yu; H-L Chen; L-Y Wang; X-Z Chen and B Fu, *Molecules***2009**, 14, 4858-4865.
[2] A Rivkin; YS Cho; AE Gabarda; F Yoshimura and SJ Danishefsky,*J. Nat. Prod*. **2004**, *67*, 139–143.
[3] T Ganesh; JK Schilling; RK Palakodety; R Ravindra; N Shanker; S Bane andDGI Kingston,*Tetrahedron* **2003**, *59*, 9979–9984.
[4] PV Plazzi; F Bordi; C Silva; G Morini; A Caretta; E Barocelli and T Vitali,*Eur. J. Med. Chem*. **1995**, *30*, 881–889.
[5] N Bai; YW Sha and G Meng,*Molecules* **2008**, *13*, 943–947.
[6] DJ Hu; SF Liu; TH Huang; HY Tu and AD Zhang,*Molecules***2009**, 14, 1288–1303.
[7] Z Yang; Q Li andX Qian,*Bioorg. Med. Chem*. **2005**, 13, 4864.
[8] GZA Turan-Zitouni; MT Kaplancikli; YP Chevallet andD Kaya,*Eur. J. Med. Chem.* **2005**, *40*, 607.
[9] Z Li; Q Yang and X Qian,*Bioorg. Med. Chem.* **2005**, *13*, 3149.
[10] B Narayana; KK Vijaya-Raj; BV Ashalatha; NS Kumari andBK Sarojini,*Eur. J. Med. Chem.* **2004**, *39*, 867.
[11] PL Vicini; A Geronikaki; M Incerti; B Busonera; G Poni; CA Cabras andP Colla,*Bioorg. Med. Chem.* **2003**, *11*, 4785.
[12] C Sun; SJ Ji and Y Liu,*J. Chin. Chem. Soc*. **2008**, *55*, 292.
[13] S Miwatashi; Y Arikawa; E Kotani;M Miyamoto;K-I Naruo; H Kimura; T Tanaka; S Asahi and S Ohkawa,*J. Med. Chem*. **2005**, *48*, 5966.
[14] M Verma; AK Chaturvedi and SS Parmar,*J. Pharm. Sci*. **1974**, *63*, 1740.
[15] MR Grimmett,*Advances in Heterocyclic Chemistry* **1970**, *27*, 241.
[16] S Jouneau and JP Bazureau,*Tetrahedron Lett*. **1999**, *40*, 8097.
[17] L De Luca,*Curr. Med. Chem*. **2006**, *13*, 1.
[18] M Boiani andM González,*Mini-Rev. Med. Chem*. **2005**, *5*, 409.
[19] JR Feldman and WC Wagner, *J. Org. Chem.*,**1942**, **7**, 31.
[20] A Iro; G Athina; V. Paola and Z.Franca, *ARKIVOC*, **2009**, (VI),89.
[21] H Goker; S Ozden; S Yildiz and D W. Bozkin, *Eur. J. Med. Chem.*, **2005**,40,1062.
[22] S Ozden; H Karatas; S Yildiz and H Goker, *Arch. Pharm. Pharm. Med. Chem.*, **2004**,337,556.
[23] SN Sawhny and BD Sanjay, *Indian J Chem.*, **1987**, 26B, 348.
[24] C Congiu; MT Cocco and V Onnis,*Bioorganic & Medicinal Chemistry Letters.*,**2008**, 18, 989–993.
[25] RV Shingalapur; KM Hosamani; RS Keri, *European Journal of Medicinal Chemistry*, **2009**, 44, 4244–4248.
[26] SK Doifode; MP Wadekar and S Rewatkar,*Orient. J. Chem***., 2011,** 27(3), 1265-1267.
[27] VV Dabholkar and SD Parab,*Heterolett.org*.,**2011**, 1, 176-188.
[28] MH Al-Huniti; MM El-Abadelah; JA Zahra; SS Sabri and A Ingendoh,*Molecules*, **2007**, *12*, 497-503.
[29] SK Mohamed; AA Abdelhamid; AM.Maharramov; ANKhalilov; AV Gurbanov and MA Allahverdiyev, *J. Chem. Pharm. Res*., **2012**, 4(2):955-965.
[30] SK Mohamed; AA Abdelhamid; AM Maharramov; AN Khalilov; FN Nagiyev and MA Allahverdiyev, *J. Chem. Pharm. Res*., **2012**, 4(2):966-971.
[31] SK Mohamed;AA Abdelhamid; AM Maharramov; AN Khalilov, AV Gurbanov and MA Allahverdiev, *J. Chem. Pharm. Res*., **2012**, 4(3):1787-1793.
[32] Bruker, APEX2, SAINT and SADABS. Bruker AXS Inc., Madison, Wisconsin, USA, **2011.**
[33] GM Sheldrick, *Acta Cryst. A64*, **2008**, 112–122.
[34] KA Hunter and J. Simpson, *TITAN2000*, University of Otago, NewZealand, **1999**.
[35] CF Macrae; IJ.Bruno; JA. Chisholm; PR. Edgington; P. McCabe; E. Pidcock; L. Rodriguez-Monge; R. Taylor; J. van de Streek and PA. Wood, *J. Appl. Cryst*., **2008**, 41, 466–470.
[36] FH Allen; O. Johnson; GP Shields; BR Smith and M. Towler, *J.Appl. Cryst*.,2004, 37, 335–338.
[37] AL. Spek, *Acta Cryst. D65*, **2009**, 148–155.
[38] SP. Westrip, *J.Appl. Cryst*., **2010**, 43, 920–925.
[39] Bruker, APEX2, SAINT and SADABS. Bruker AXS Inc., Madison, Wisconsin, USA, **2007**.
[40] LJ. Farrugia, *J. Appl. Cryst*.,**1997**, 30, 565.
[41] LJ. Farrugia, *J. Appl. Cryst.* , **1999,** 32, 837–838.
[42] Oxford Diffraction, *CrysAlis*, **2009**, PRO. Oxford Diffraction Ltd, Yarnton, England.
[43] WW. Davis and TR. Stout, *Applied Microbiology*, **1971**, 22 (4):659-665.