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FULL PAPER

Modification and characterization of subs. triazole on creatinine and studying their antioxidant activity

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In this work, new creatinine derivatives containing (1,2,4-triazole and 5-subs-1,2,4-triazole) ring have been prepared. In the first step, creatinine was reacted with different acid chloride to form 2-subs. amido creatinine 1[a-d]. In the second step, amido creatinine 1[a-d] was reacted with succinoyl chloride to produce imide derivatives 2[a-d]. In the third step, the imide componds prepared were reacted with hydrazine hydrate to give acid hydrazide derivatives 3(a-d). Finally, 1,2,4-triazole derivatives 4-7[a-d] were prepared from the reaction between acid hydrazide with different amide compounds by pellizzari reaction. These new synthesized products have been characterized by FT-IR, ^{1}H-NMR for some of them and were studied regarding the effect of preparing derivatives on antioxidant.

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KEYWORDS

Creatinine; imide; acid hydrazide; 1,2,4-triazole; antioxidant activity.

Introduction

Creatinine is a break product of creatine phosphate in muscle [1]. Creatinine is transferred to the kidneys by blood plasma, eliminating from body by glomerular filtering and partial tubular secretion. The loss of a water molecule from creatine results in the formation of creatinine as a heterocyclic compound [2]. New heterocyclic compounds which contain creatinine were synthesized and antimicrobial activity [3], as well as the activity of GOT and GPT enzymes [4] were studid. Triazole is known as pyrrodiazole, one of the types of organic heterocyclic derivatives, was unsaturated containing five membered ring structure of tow carbon and three nitrogen atoms [5]. 1,2,4-Triazole is one of the very interesting types of compounds which attracted the attention of many chemists and biologists in organic synthesis, pharmaceutical and medicinal field because of their different biological activities like anticancer [6], anti-inflammatory [7], analgesic [8], anti-HIV [9], chronic pain [10], antibacterial [11], antimycobacterial [12], antiviral drugs [13] and antifungal [14]. Amaal S. *et al.* studied the synthesis of new polymers bearing 1,2,4-triazole ring on creatinine with their corrosion protection of stainless steely surfaces [15]. The pellizzari reaction is referred to the synthesis of 1,2,4-triazole derivatives from the reaction of amide and acyl hydrazide; this reaction firstly was prepared by pellizzari in 1911 [16].

Experimental

Materials and instruments

All materials and solvents were used from Fluka and Sigma-Aldrich without purification. Melting points were measured in Gallen Kamp capillary melting point instrument. FT-IR measurements were recorded on Shimadzu model FT-IR-8400 S. ^{1}H-NMR spectra were obtained with Bruker spectrophotometer ultra-shield in 400 MHz and TMS as internal standard in D_2O solution.

Methods

Synthesis of 2-subs-amido creatinine 1[a-d] [17]

The creatinine (0.02 mole) was dissolved in DMF (20 mL) and cooled at (0-5) C^0, and (2-3) drops of triethylamine (TEA) were added. Different acid chlorides [acetyl chloride, benzoyl chloride, 4-nitrobenzoyl chloride and 2-chlorobenzoyl chloride] (0.02 mole) in DMF (20 mL) were slowly added, than staying with strong stirring for (3 hours) at room temperature. The obtained product was filtered, washed with ether and recrystallized from ethanol. The physical properties of synthesized compounds 1[a-d] are shown in Table 1.

Synthesis of imide derivatives 2[a-d] [18]

Creatinine amide 1[a-d] (0.02 mole) were dissolved respectively in DMF (20 mL) and (2-3) drops of triethylamine (TEA) were added. Equimolar of succinyl chloride was added dropwise to the solution, and then it was refluxed for (4-5) hours. The obtained product was filtered, washed with ether and recrystallized from ethanol. The physical properties of the synthesized compounds 2[a-d] are shown in Table 1.

Synthesis of acid hydrazide derivatives 3[a-d] [19]

Hydrazine hydrate (0.01 mole) was added to the solution of (0.01 mole) of imide compounds 2[a-d] in absolut ethanol (25 mL). This mixture was refluxed for (5-6) hours. The obtained product was filtered, washed with ether and recrystallized from ethanol. The physical properties of the synthesized derivatives 3[a-d] are shown in Table 1.

Synthesis of 1,2,4-triazole derivatives 4-7[a-d] [20]

Acid hydrazide derivatives 3[a-d] (0.001 mole) were dissolved in (25 mL) MDF and (0.001 mole) from different amide compounds [formamide, acetamide, benzamide and acrylamide] were added, and then it was refluxed for (5-6) hours. The product was collected and recrystallized from ethanol. The physical properties of synthesized compounds 3[a-d] are shown in Table 2.

Antioxidant activity [21]

DPPH (4 mg) was dissolved in 100 mL of ethanol, and the solution was kept protected from light by covering the test tubes with aluminum foil. Various concentrations of (25, 50, 100) ppm were prepared from some of the prepared compounds. It was prepared by dissolving 1 milligram of the compound and dissolving it with 10 mL of ethanol to prepare 100 ppm, then it was diluted to (50 and 25) ppm. Similar concentrations were prepared. In a test tube, 1 mL of the diluted or normal solution (25, 50, 100) ppm was applied to 1 mL of DPPH solution. The absorbance of each solution was measured at 517 nm using a spectrophotometer after 1 hour of incubation at 37 °C. The following equation was used to determine the potential to scavenge DPPH radicals.

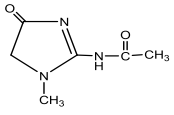
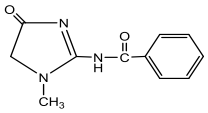
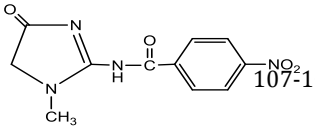
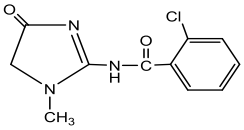
I % = (Absorption blank – Absorption sample) / Absorption blank x 100.

Results and discussion

New 1,2,4-triazole derivatives 4-7[a-d] were prepared from creatinine by its reaction it with different acids chloride to produce 2-

subs-amido creatinine 1[a-d]; then, they were reacted with succinyl chloride to produce 2-imido creatinine derivatives 2[a-d]. Hydrazine hydrate was reacted with imide derivatives 2[a-d] to form acid hydrazide derivatives 3(a-d). Finally, these compounds were reacted with different amides compounds to give 1,2,4-triazole derivatives 4-7[a-d] by pellizzari reaction (Scheme 1). FT-IR spectra of derivatives 1[a-d] were appeared stretching vibrations band to the (C=O) amide at (1647-1652) cm^{-1}, and compounds 2[a-d] appeared band at (1768-1772) cm^{-1} and (1791-1797) cm^{-1} due to the symmetric and asymmetric stretching vibration of (C=O) imide the absorption band at (1800-1805) cm^{-1} due to (C=O) acid chloride[22]. FT-IR spectra of derivatives 3[a-d] resulted in the appearance of two absorption bands at (3242-3265) cm^{-1} and (3363-3419) cm^{-1} due to the stretching vibrations of (-NH_2) group. Table 1 shows the other data of functional groups for compounds 1-3[a-d]. The FT-IR spectra of compounds 4-7[a-d] appeared stretching vibrations band to the (C=N) triazole ring [23] at (1622-1650) cm^{-1} and the other stretching vibration bands for this compounds were shown in Table 2. ^{1}H-NMR spectrum of compounds (4a, 5b, 6c, 6d and 7a) are listed in Table 3. Antioxidant activity based on DPPH stable free radical sweep effect, the antioxidant function of some selective synthesized of some prepared compounds, and ascorbic acid were assessed using the process. The results listed in Table 4 show some of the new prepared derivatives and antioxidant activity against DPPH free radicals and give a good scavenging percentage and compression with ascorbic acid. The reduction ability of DPPH radical was determined by the decrease in absorbance at 517 nm. Further, it is well determined that organic molecules include an electron donating group (NH_2, OCH_3, and OH) that can act as free radical agents and are capable of opposing oxidization. Figure 1 shows that the highest antioxidant activity found in compound (3a, 4b, 5a and 7b) presents the highest scavenging activity on DPPH, whereas the other compounds exhibit moderate because we observed the presence of electron withdrawing groups such as (Cl, NO_2 and Br) on phenyl ring exhibited lowest antioxidant activity [24].

TABLE 1 The physical properties and FT-IR spectral data $cm^{-1}$of synthesized compounds 1-3[a-d]

physical properties					Major FT-IR Absorption Cm^{-1}					
No. of comp.	**Structure of compounds**	**M. P. °C**	**Color**	**Yield%**	***ν* (C-H) Aliph. Asy. Sy.**	**υ (C-H) Arom.**	**υ(C=C) Arom.**	**υ (C=O) (creatinine ring) υ (C=O) aliph. amide**	**υ (C=O) imide**	**Other bands**
1a		175-177	Orange	90	2945 2883	-	-	1718 1652	-	υ (N-H) : 3209
1b		115-117	Orange	92	2987 2891	3037	1602 1546	1718 1647	-	υ (N-H) : 3251
1c		107-109	Yellow	88	2999 2889	3080	1602 1527	1703 1647	-	υ (N-H) : 3289 υ (NO_2) : 1346 1504
1d -		142-144	Yellow	85	2937 2881	3058	1596 1502	1706 1645	-	υ (N-H) : 3255 υ (Cl) : 719

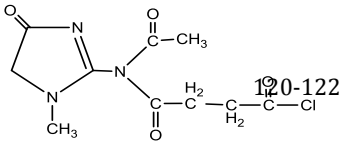
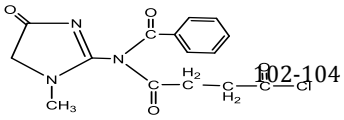
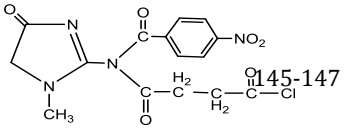
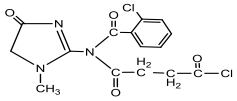
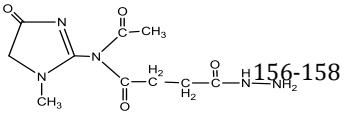
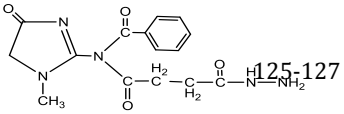
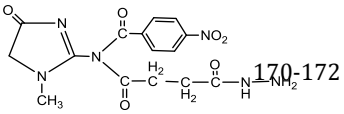
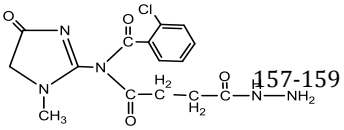
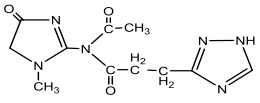
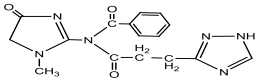
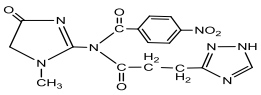
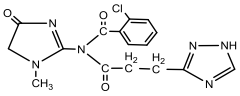
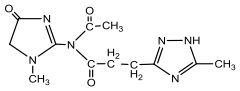
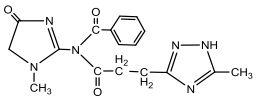
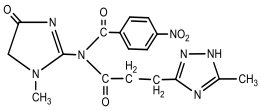
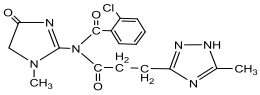
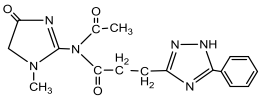
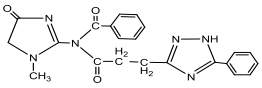
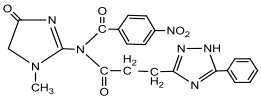
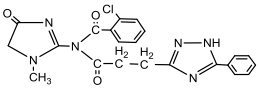
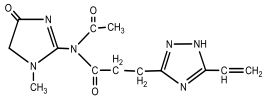
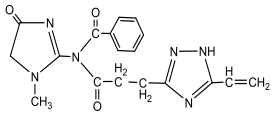
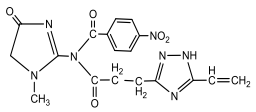
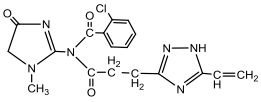
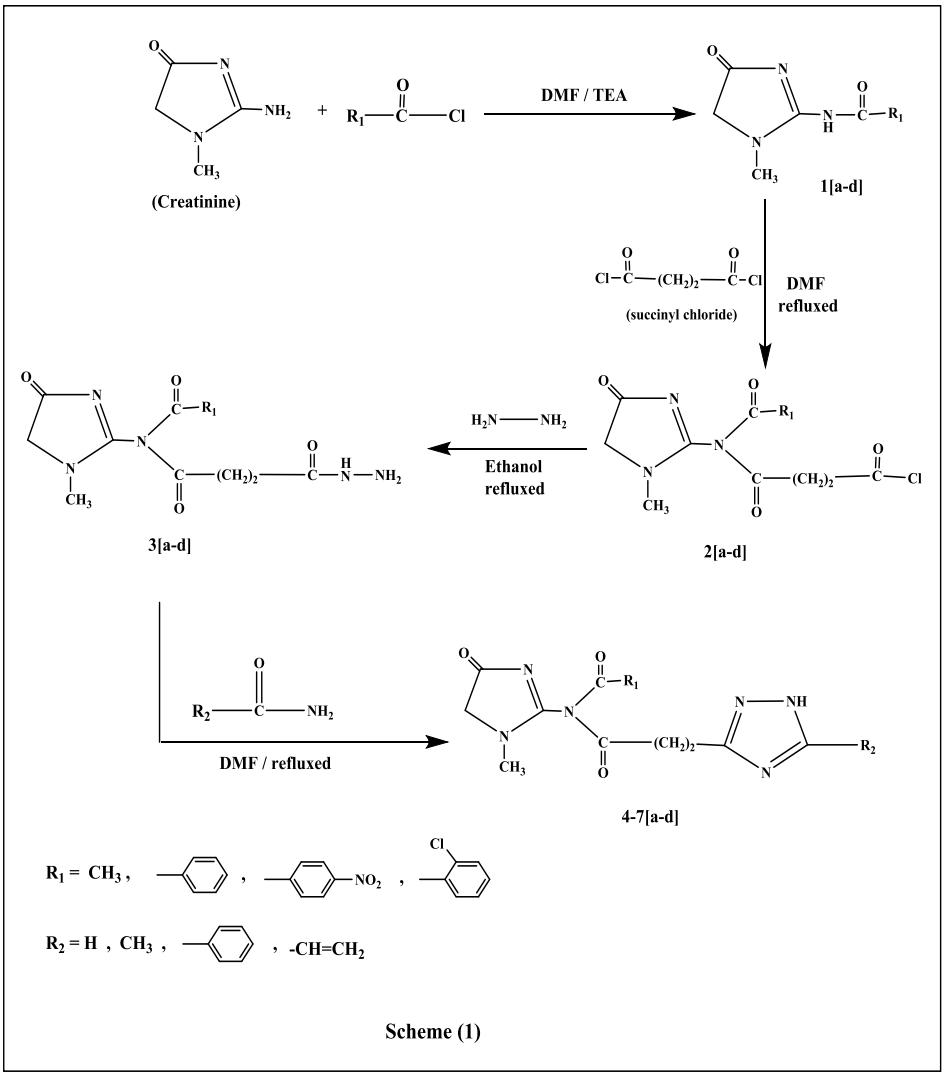
2a		120-122	Brown	80	2960 2870	-	-	1701 -	1797 1768	υ (C=O) : 1800 acid chloride
2b		102-104	Brown	75	2914 2894	3068	1600 1546	1697 -	1797 1772	υ (C=O) : 1805 acid chloride
2c		145-147	Brown	78	2995 2812	3085	1608 1548	1697 -	1797 1770	υ (C=O) : 1803 acid chloride υ (NO_2) : 1365 1546
2d		212-214	Brown	83	2950 2887	3070	1604 1550	1703 -	1795 1770	υ (C=O) : 1800 acid chloride υ (Cl) : 707
3a		156-158	Brown	73	2916 2890	-	-	1697 1665	1797 1772	υ (NH_2) : 3419 3259
3b		125-127	Brown	70	2912 2839	3062	1600 1546	1701 1660	1797 1772	υ (NH_2) : 3392 3242
3c		170-172	Gray	80	2952 2890	3091	1604 1504	1703 1647	1795 1768	υ (NH_2) : 3363 3265 υ (NO_2) : 1342 1546
3d		157-159	Brown	75	2952 2837	3072	1602 1544	1699 1660	1791 1772	υ(NH_2) : 3365 3257 υ (Cl) : 707

TABLE 2 The physical properties and FT-IR spectral data cm^{-1} of synthesized compounds 4-7[a-d]

	physical properties				Major FT-IR Absorption Cm^{-1}					
No. of comp.	**Structure of compounds**	**M. P. °C**	**color**	**Yield %**	**υ (N-H)**	***ν* (C-H) Aliph. Asy. Sy.**	**υ (C-H) Arom.**	**υ (C=O) imide**	**υ (C=O) (creatinine ring)**	**υ (C=N) Triazole ring**	**Other bands**
4a		130-132	Gray	65	3289	2952 2890	-	1797 1770	1699	1622	
4b		173-175	Brown	72	3382	2977 2850	3020	1797 1772	1699	1627	

4c		206-208	Brown	75	3371	2985 2895	3080	1790 1765	1683	1633	υ (NO_2) : 1346 1502
4d		221-223	Gray	68	3348	2977 2880	3090	1790 1770	1710	1645	υ (Cl) :723
5a		172-174	Off white	75	3338	2920 2870	-	1793 1768	1703	1650	
5b		140-142	brown	80	3340	2985 2891	3085	1793 1770	1708	1630	
5c		195-197	Gray	76	3245	2990 2850	3035	1797 1772	1699	1623	υ (NO_2) : 1344 1546
5d		210-212	Brown	86	3240	2995 2880	3056	1795 1770	1718	1649	υ (Cl): 707
6a		182-184	Gray	74	3371	2995 2885	3047	1790 1772	1716	1654	
6b		195-197	Gray	60	3323	2991 2890	3058	1793 1766	1708	1649	
6c		213-215	Brown	70	3330	2977 2880	3070	1790 1770	1716	1649	υ (NO_2) : 1398 1504
6d		180-182	Brown	55	3315	2977 2895	3035	1793 1770	1703	1622	υ (Cl) :719
7a		144-146	Brown	65	3276	2941 2840	-	1799 1766	1714	1633	
7b		176-178	Brown	68	3373	2987 2870	3058	1790 1766	1720	1623	-
7c		188-190	Brown	73	3390	2990 2825	3016	1793 1760	1703	1649	υ (NO_2) : 1348 1541
7d		204-206	Brown	70	3238	2975 2850	3031	1787 1770	1703	1630	υ (Cl): 719



SCHEME 1 Synthesis of 1,2,4-triazole derivatives

TABLE 3 ^{1}H-NMR spectral data (δ ppm) for some compounds

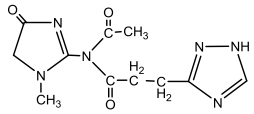
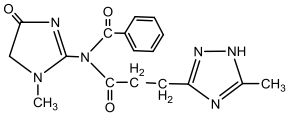
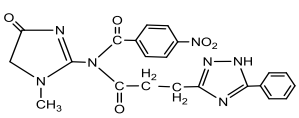
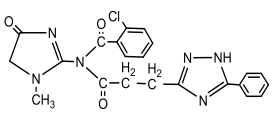
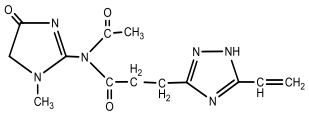
Comp. No.	Compound structure	^{1}H-NMR data of (δ-H) in ppm
4a		2.51 (s,3H, CH_3-CO-N); 2.09-2.49 (t, 4H, CH_2-CH_2); 3.08 (S, 3H, N-CH_3); 7.48 (s, 1H, CH triazol ring); 4.16 (S, 2H, CH_2-CO) and 8.3 (S, 1H, NH triazol ring)
5b		1.09 (s,3H, CH_3); 2.54-2.67 (t, 4H, CH_2-CH_2); 3.10 (S, 3H, N-CH_3); 4.15 (S, 2H, CH_2-CO); 7.74-7.81 (m, 5H, Ar-H) and 8.02 (S, 1H, NH triazol ring)
6c		2.63-2.84 (t, 4H, CH_2-CH_2); 3.02 (S, 3H, N-CH_3); 4.05 (S, 2H, CH_2-CO); 7.83-8.22 (m, 9H, Ar-H) and 8.35 (S, 1H, NH triazol ring)
6d		2.7-2.93 (t, 4H, CH_2-CH_2); 3.22 (S, 3H, N-CH_3); 4.12 (S, 2H, CH_2-CO); 7.11-7.84 (m, 9H, Ar-H) and 8.34 (S, 1H, NH triazol ring)
7a		2.08 (s,3H, CH_3-CO-N); 2.48-2.68 (t, 4H, CH_2-CH_2); 3.17 (S, 3H, N-CH_3); 4.17 (S, 2H, CH_2-CO); 2.77-3.01 (d,t, 3H, CH=CH_2) and 8.2 (S, 1H, NH triazol ring)

TABLE 4 Scavenging % for some of prepare compounds

Comp. No.	Scavenging %		
	25(mg/mL)	50(mg/mL)	100(mg/mL)
3a	43.33	46.45	72.91
3c	32.08	56.04	65.04
4b	44.79	49.79	72.08
4d	27.5	51.66	52.5
5a	65.41	70.62	71.45
5b	40.83	48.54	50.83
6c	18.12	34.37	55.83
6d	46.87	50.83	52.5
7b	61.66	63.33	70
7c	24.79	56.45	59.79
Ascorbic acid	80.95	89.25	93.54

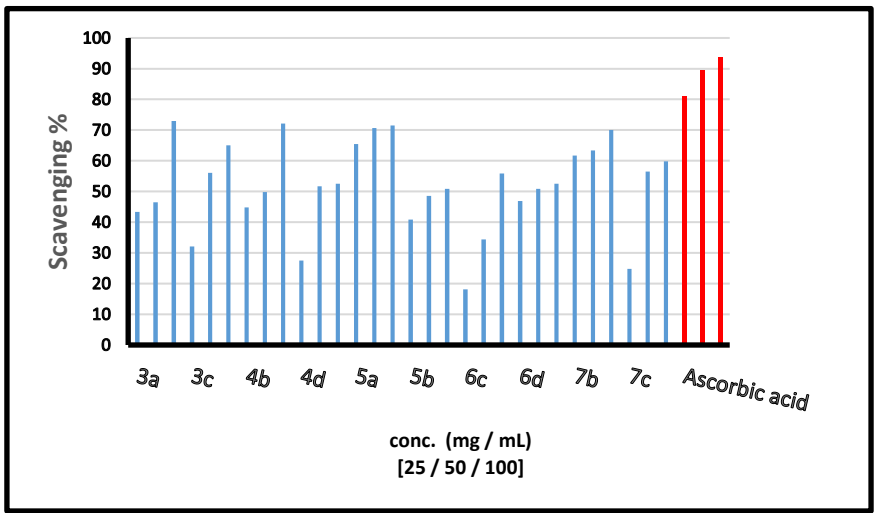


FIGURE 1 shows the scavenging comparison between the prepared compounds and ascorbic acid

Conclusion

The prepared new 1,2,4-triazole derivatives on creatinine were confirmed by using spectroscopic techniques (FT-IR and ^{1}HNMR). The antioxidant activity of the most compounds were strong compressed with ascorbic acid.

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