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Antioxidant Activity of Some Substituted 1, 2, 4 - Triazo-5-thione Schiff base

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Abstract
Series of Schiff's bases of 3-substituted 1, 2, 4 triazo -5 thione (4a-e) were synthesized from the ester of methyl paraben. The structure of the newly synthesized compounds were confirmed by IR, ^{1}HNMR and Mass spectrum. The bioavailability of all the compound was checked by using customized software. All the compounds were evaluated for its antioxidant activity by hydrogen peroxide scavenging method. The result shows that all the compounds have good bio availability and have significant antioxidant activity. The activity was shown as IC_{50} value which lies between 20 to 60µg/ml
Key words: Triazole, Antioxidant, Bioavailability, Hydrogen peroxide scavenging.

INTRODUCTION

In the past few decades the chemistry of 1, 2, 4-triazole and their fused hetrocyclic derivatives have received considerable attention owing to their synthetic and effective biological importance. For example, a large number of 1, 2, 4-triazole containing ring system have been incorporated into a wide variety of therapeutically interesting derivatives including anti-inflammatory[1], antimicrobial[2], anti-myotic activity such as fluconazole, itraconazole, voriconzole [3] and anti-cancer like alprazolam [4], Etizolam [5]. The thione substituted triazoles are reported for a variety of biological activities such as antibacterial [6)], antifungal [7], antitubercular [8], anti-cancer [9], antihypertensive [10], antiviral [11], antimigrane [12] and antileishmanial [13] activities. A thorough literature survey reveals that Schiff base of varies hetero ring possess diverse type of biological activities [14]. In view of the above mentioned facts we describe herein the synthesis of 3-substituted 1, 2, 4-triazo-5- thione Schiff base and its antioxidant activity. Oral bioavailability was considered to play important role for development of bioactive molecules as therapeutic agents. Therefore a computational study for prediction of 'ADME' properties was performed by using Lipinski's rule of five.

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MATERIALS AND METHODS

Melting points are taken in an open capillary tube using Veego digital melting point apparatus. The purity of the compound was confirmed by TLC using silica gel precoated plates of 0.25 mm thickness with ethyl acetate and petroleum ether (1:1) as eluents. IR spectra were recorded in KBr on Perkin Elmer FTIR spectrometer. The ^{1}HNMR were recorded on Brucker 300 MHz in $CDCl_3$ using TMS as an internal standard.

Synthesis of aryl acid hydrazide (1)

To methyl paraben (0.1M) in 30ml ethanol, hydrazine hydrate (0.1M) was added drop wise with stirring. The resulting mixture was refluxed for 6h. Excess ethanol was distilled and the content was allowed to cool. The formed crystals were filtered, washed

thoroughly with water and dried. Yield 78% m.p. 121°c.

Sythesis of 3-substituted -5 - mercapto - 1, 3, 4 - oxadiazole (2)

To the solution of 1 (0.1M) in 30ml ethanol, KOH (0.1M) in absolute ethanol (50ml) and CS_2 (0.2M) were added and refluxed for 5h, till the evolution of hydrogen sulphide ceased. The reaction mixture was cooled at room temperature and diluted with water. On acidification with dilute hydrochloric acid the required oxadiazole precipitates. It was filtered, washed thoroughly with cold water and recrystallized from ethanol. Yield: 70% m.p : 143°c

Synthesis of 3-substituted 4-amino – 1, 3, 4 - triazo - 5 -thione

The mixture of 2 (0.1M) and hydrazine hydrate (0.1M) in dry pyridine (15ml) were refluxed for about 4h. The reaction mixture after cooling neutralized with dilute hydrochloric acid. The solid obtained was recrystallized with ethanol. White solid, Yield 88%, m.p.155°C; IR (KBr cm^{-1}): 3270 cm^{-1} (NH stretch), 1323cm^{-1} (C=N stretch) 3130 cm^{-1} (aromatic CH stretch), 3434 cm^{-1} (OH stretch), 2586 cm^{-1} (SH stretch), 1284 cm^{-1} (N-N=C stretch) 1622 cm^{-1} (C=C ring stretch). ^{1}HNMR: δ 6.5 – 8.3 (m, 4H, ArH), δ 5.1 (s, 1H, OH), δ 5.46 (s 2H, NH_2) δ 13.1 (s, 1H, SH)

General procedure for the synthesis of Schiff b ase of 3 – su bstituted - 5 - amino - 1, 2, 4 - triazo - 5 - thione.

Equimolar mixture of compound 4 and aromatic aldehyde in 50 ml ethanol were refluxed for 20 minutes. After cooling the product obtained was filtered, dried and recrystallized with methanol.

4a: White solid; Yield 92%; mp: 55°C; R_f : 0.76.
IR (KBr cm^{-1}): 3434 cm^{-1} (OH stretch), 1622 cm^{-1} (C=C stretch) 1323 cm^{-1} (C-N stretch), 1693 (N= C stretch) 1072 cm^{-1} (C-S stretch), 1252 (N-N=C stretch).
^{1}HNMR: δ 6.8-8.4 (m, 9H, 4rH), δ 13.3 (s, 1H, SH). **MS:** m/z 299 (M+1).

4b: White crystals; Yield 85%; mp: 125°C; R_f: 0.71.
IR (KBr cm^{-1}): 3434 cm^{-1} (OH stretch), 1625 (C=C stretch), 1278 cm^{-1} (C-N stretch) 1645 cm^{-1} (N=C stretch), 1077 cm^{-1} (C- S stretch), 1570 cm^{-1} (N-N=C stretch).
^{1}H NMR: δ 6.8-8.4 (m 7H, ArH) δ 13.8 (s, 1H, SH), δ 3-5.5 (s, 2H, OH). **MS** : m/z 314 (M^+).

4c: Pale yellow solid; Yield: 95%; mp:185°C; R_f : 0.9.
IR(KBr cm^{-1}): 3436 cm^{-1} (OH stretch), 1621 cm^{-1} (C=C stretch), 1269 cm^{-1} (C-N stretch), 1615 (N=C stretch), 1120 cm^{-1} (C-S stretch), 1587 cm^{-1} (N-N=C stretch) , 698 cm^{-1} (C-Cl stretch);
^{1}HNMR : δ 6.8 – 9.1 (m,8H, ArH), δ 12.9 (s,1H, SH); **MS**: m/z 334 (M+2).

4d: Yellow solid; Yield: 98% ; mp: 165°C; R_f: 0.85.
IR (KBr cm^{-1}): 3411 cm^{-1} (OH stretch), 1625 cm^{-1} (C=C stretch), 1301 cm^{-1} (C-N stretch), 1635 (N=C stretch), 1077 cm^{-1} (C-S stretch), 1570 cm^{-1} (N-N = N stretch), 1522 cm^{-1} (C-NO_2 stretch);
^{1}H NM R: δ 6.5 – 8.4 (m, 8H, ArH), δ 13.2 (s, 1H, SH) **MS**: m/z 344 (M+2).

4e: Yellow solid; Yield: 46%; mp: 200°C; R_f : 0.82.
IR(KBr cm^{-1}) : 3418 cm^{-1} (OH stretch), 1681 cm^{-1} (C=C stretch), 1311 cm^{-1} (C-N stretch), 1641 cm^{-1} (N=C stretch), 1066 cm^{-1} (C-S stretch), 1575 cm^{-1} (C=N-N stretch), 1534 cm^{-1} (C-NO_2 stretch).

^{1}H NMR: δ 6.5 – 8.4 (m, 8H, ArH), δ 13.2 (s, 1H, SH); **MS:** m/z 344 (M+2).

Bioavailability Studies

Prediction of bioavailability was done by customized software and was tabulated in Table 1.

Antioxidant Activity

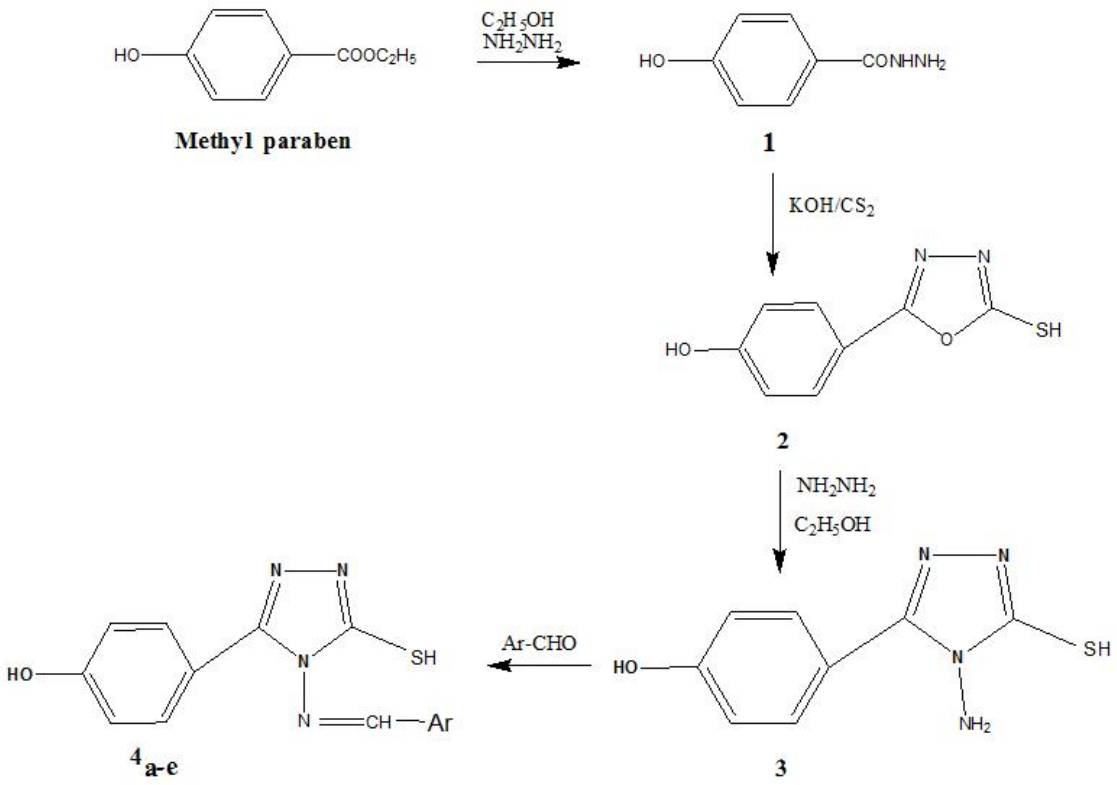
The ability of the entire synthesized compound to scavenge hydrogen peroxide was determined according to the method of Kandikova ponovska [15]. Ascorbic acid was used as a standard. The percentage inhibition of hydrogen peroxide scavenging activity was calculated by using the following formula

$$\% \text{ inhibition} = Ab_{control} - Ab_{test} / Ab_{control}$$

Where, Ab – absorbance

The activity was shown as IC_{50} value (50% inhibitory concentration in µg/ml)

SCHEME-1



RESULTS

As depicted in the scheme, the Schiff base of 3- aryl substituted 4 amino 1, 2, 4 - triazo – 5- thione have been synthesized by multi step reaction. The presence of SH stretching nearby 2500 cm^{-1} and the absence of primary amino stretching confirm presence of these groups. Similarly the ^{1}HNMR spectra of the triazoles **(3)** showed characteristic broad signal at δ 5.8ppm, which were absent in the Schiff base of triazole. These absences establish the conversion of $–NH_2$ into its Schiff base. The IR, ^{1}HNMR and mass spectra supported the structure of various synthesized Schiff base of 1, 2, 4 - triazole. The reports of antioxidant activity of the newly synthesized compounds were shown as IC_{50} value lies between 20-60 µg/ml. The entire compound showed a good hydrogen peroxide scavenging activity. Prediction of bioavailability was carried out by using customized software.

Table1: Bioavailability and Antioxidant Activity of 3-substituted 1, 2, 4 -triazo-5-thione

Lipinski Rule of five				No. of H atom		IC_{50} Value of Antioxidant Activity µg/ml
Compounds	R	log P	M.W	acceptor	donar	
4a	H	3.24	296	8	1	24
4b	3-OH	3.18	312	8	1	20
4c	2-Cl	3.87	330	6	2	60
4d	2-NO_2	3.15	341	7	1	32
4e	3-NO_2	3.18	341	7	1	38

Number violation is less than one indicates that all the synthesized compounds may have a good oral availability according to Lipinski rule of five.

CONCLUSION

The result study reports the successful synthesis and antioxidant activity of new Schiff base and 1, 2, 4 - triazole derivatives. The antioxidant activity revealed that all the tested compounds have good antioxidant activity which may be due to the presence of – SH group in the 5^{th} position. All the compounds also reported to have good oral bioavailability.

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