Design, Synthesis and Cytotoxic studies of triazole linked hydrazones

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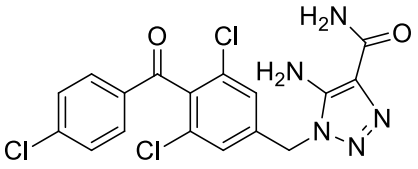
Abstract
Triazoles have been classified as previliged heterocyclic moieties which displayed a broad spectrum of pharmacological and biological properties. This article reports the synthesis of triazole linked derivatives and cytotoxic properties of these derivatives. Among the prepared derivatives 8a-8g, best result were exhibited by 8g.

Introduction

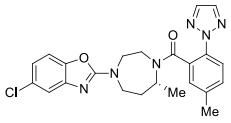
Synthesis and development of new compounds has vastly lagged behind antimicrobials and heart medications [1]. Triazoles belong to heterocyclic compounds containing a 5-membered ring with 2-C as well as 3-N molecules [2]. Azoles has been classified as unique classes of N containing hetero-cycles that displayed numerous organic accomplishments like, anti-bacterial,[3] anti-malarial,[4] anti-fungal,[4] anti-HIV,[5] anti-inflammatory [6] and anti-TB [7] properties. In certain, triazole as well as 1,2,3- triazole, 1,2,4-triazole, benzotriazole, triazolopyrimidine and their products must involve constant awareness in the pharmaceutical chemistry, as well as certain medicines presently in usage was established on tri-azoles particularly 1,2,3-triazole moiety like anti-HIV reagent TSAO, [8] antibiotic Cefatrizine, [9] anti-bacterial reagent Tazobactum [10] and anti-cancer [11] agent CA1 fig 1 [12].



CA1 (anti- cancer agent)

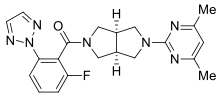
1

Hydrazones, that was manufactured by refluxing acid hydrazides by appropriate carbonyl compounds, display altered use possibilities due to their organic accomplishments, and their metal complex as well as corrosion preventing capacities [13, 14]. Hydrazones must stimulated scholars to manufacture their new products due to their preordained bio-activity as well as efficiency in pharmaceutical interaction [15, 16]. This investigation was an anticipation to discover particular novel as well as further potent antimicrobial as well as antioxidant reagents which competitively impedes side effects as well as improved efficiency to heal pathogenic infections.
Presently, 2H-1,2,3-triazoles was presence useful into numerous fields [17, 18] with their various organic activity as well as single photonic possessions. The procedure, though, cannot be prolonged to the production of 2-side products 1,2,3-triazoles,[19] which correspondingly occur in numerous organically dynamic reagents. For instance, both Suvorexant, a medication for the cure of main sleeplessness [20] as well as Seltorexant, a extremely selective OX2R antagonist,[21] have 2-aryl-side product 1,2,3-triazole moieties (Figure 1).



Suvorexant, MK-4305

2A



Seltorexant, OX2R antagonist

2B

The significance of 2-aryl-side products 1, 2, 3-tri-azoles as pharmaceutical reagents has subsequently encouraged the progress of appropriate manufactured techniques to this discussion of complexes [17, 22-26]. Recent ten years, hydrazone products remained extensively studied as a useful pharma-cophore theme for the scheme of new AEDs [4, 27].

MATERIALS AND METHODS

Infra-red spectrum of the manufactured complexes was noticed on the Burker FT-Infrared spectrometer. Nuclear magnetic resonance was obtained on the Burker FT-Infrared spectrometer typical AV-400 at 400 Mega Hertz. M.p of manufactured complexes was present in glass vessels by used the Gallenkamp equipment. The manufactured complex was distilled by column chromatography as well as re-crystallization process using ethanol as well as di-chloro-benzoic acid as reagents. Thin layer

chromatography take place on precoated Si gel using 60 F254 plates by logical grade solvent such as CH_3OH, dichloro benzoic acid.

Production of 4-amiino-5-(o-chloro-phenyl)-4H-1,2,4-trizole-3-thiol

4-amino-5-(o-chloro-phenyl)-3H-1,2,4-triazole-3-thiol remained manufactured by treating 5-(o-chloro-phenyl)-1,3,4-oxa-diazole-2-thiol (00.10g, 0.0004mol) in the occurrence of Hydrazine mono-hydrate by CH_3CH_2OH as solvent under reflux for 12h. The accomplishment of the process remained scrutinized by Thin layer chromatography. Rough creation afforded in 35% product.

[TLC: P.E/E.A 9:1, Rf = 0.66]

Production of aryl-hydrazones from triazoles derivatives

Consistent tri-azole derivatives (0.7g, 0.002mol) as well as numerous side products RCHO (1.038 g, 0.02mol) remained melted in CH_3OH as well as sonicated for one and half hours. Cool the process mixture at less heat to give unsophisticated solid product. Rudimentary manufactured remained more distilled by re-crystallization.

Hemolytic Assay

3 mL sample remained occupied since human plasma, centrifuged (to separate fluid) for 5min at 1000 multiply by g. Red blood cells was iso-lated melted in phosphate buffer PH 7.4 salts as well as splashed. Synthesized complexes mixture (10mg/mL) remained supplementary (20uL) to 180 uL of erythrocytes (red blood cells) suspension as well as cooled for half hour. Dimethyl sulfoxide (DMSO) taken as a negative control as well as 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid was taken as a positive control. Percentage hemolysis was calculated by using the formula.

Thrombolytic Assay

1 mL sample was taken from human blood, at room temperature that was incubated to pre-weigh for one hour. Subsequently coagulation, the serum remained completely detached as well as all eppendorfs stayed reweighed to control the coagulate bulk. Model (100mL) was added as well as placed at normal human body temperature (37 ^oC) for 180 minutes as well as clot lysis was detected. Dimethyl sulfoxide remained correspondingly additional in a reinforcement containing of tubes that act as a negative thrombo-lytic control while ABTS as positive control. Eppendorfs remained weighed over as well as with a change in bulk later coagulation %age of thrombo-lysis remained intended.

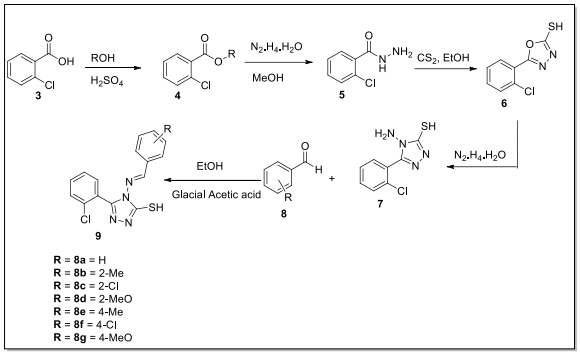


Fig 1. Pathway and reaction conditions for the synthesis of compounds.

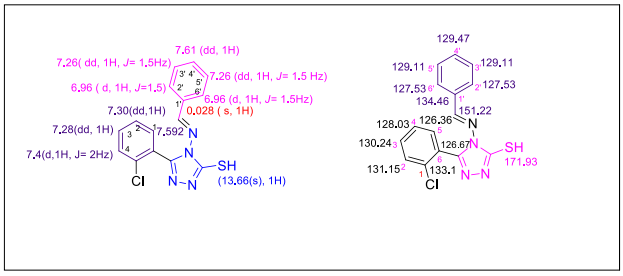


Fig 2. ^{1}H-NMR and ^{13}C-NMR analysis of compounds.

Table 1. Hemolytic, and thrombolytic activity of target compounds 8a-8g.

Sr. #	Derivatives	% age of Hemolysis ± SD	%age of Thrombolysis ± SD
1	8a	5.12 ± 0.02	66.2 ± 0.081
2	8b	4.6 ± 0.045	68.2 ± 0.081
3	8c	0.4 ± 0.004	42.05 ± 0.008
4	8d	1.7 ± 0.016	66.8 ± 0.081
5	8e	0.8 ± 0.012	66.5 ± 0.81
6	8f	2.1 ± 0.003	56.8 ± 0.081
7	8g	0.1 ± 0.007	76.8 ± 0.082
Standard	ABTS	95.9	86

Table 2. Spectral data of compounds 8a- 8g.

Compounds	Melting Point	Yields %	
8a	180 ºC	62	m.p 180 ˚C; IR (KBr): υ 3339 (N-H), 1542 (C = N), 1465 (Ph), 1446 (C = C), 1330 (C–N). 500MHz (1H-NMR, DMSO-*d*6, δ/ppm): 6.96 (d, 2H, Ar-H, *J* = 1.5 Hz), 7.26 (dd, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 7.28 (dd, 1H, Ar-H), 7.45 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.52 (d, 1H, Ar-H, *J* = 1.5 Hz), 8.28, (s, 1H, N = CH), 13.11 (s, 1H, SH). 100 MHz (13C-NMR, DMSO-*d*6, δ/ppm): 126.36, 126.67, 127.53, 128.03, 129.11, 129.47, 130.24, 133.12, 133.15, 134.46 (Ar-C), 151.22, 152.92, 171.93 (N = C). MS *m/z* (ES+) 314.0393
8b	187 ˚C	61	m.p 187 ˚C; IR (KBr): υ 3351 (N-H), 1540 (C = N), 1470 (Ph), 1450 (C = C), 1334 (C–N). 500MHz (1H-NMR, DMSO-*d*6, δ/ppm): 2.38 (s, 3H, CH3), 7.07–7.24 (m, 4H, Ar-H), 7.28 (dd, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 7.45 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.65 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.28 (dd, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 7.95, (s, 1H, N = CH), 13.01 (s, 1H, SH). 100 MHz (13C-NMR, DMSO-*d*6, δ/ppm): 20.06 (CH3), 126.36, 126.64, 126.67, 126.77, 128.03, 128.83,130.24, 130.63, 131.15, 133.12, 133.38, 136.75, (Ar-C), 139.03, 152.92, 171.93 (N = C). MS *m/z* (ES+) 328.0549
8c	192 ºC	62	m.p 192 ˚C; IR (KBr): υ 3354 (N-H), 1542 (C = N), 1473 (Ph), 1451 (C = C), 1339 (C–N). 500MHz (1H-NMR, DMSO-*d*6, δ/ppm): 7.23–7.40 (m, 4H, Ar-H), 7.45 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.65 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.28 (dd, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 8.31, (s, 1H, N = CH), 13.01 (s, 1H, SH). 100 MHz (13C-NMR, DMSO-*d*6, δ/ppm): 20.06 (CH3), 126.36, 127.49, 127.91, 128.03, 129.35, 130.24, 130.84, 131.13, 131.15, 133.12, 133.24 (Ar-C), 143.84, 152.92, 171.93 (N = C). MS *m/z* (ES+) 348.0003
8d	201 ºC	61	m.p 201 ˚C; IR (KBr): υ 3356 (N-H), 1539 (C = N), 1471 (Ph), 1449 (C = C), 1330 (C–N). 500MHz (1H-NMR, DMSO-*d*6, δ/ppm): 3.78 (s, 3H, OMe), 6.82 (d, 1H, Ar-H, *J* = 2.0 Hz), 6.92 (dd, 1H, Ar-H), 7.20 (dd, 1H, Ar-H), 7.24 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.28 (dd, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 7.45 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.65 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.89, (s, 1H, N = CH), 13.11 (s, 1H, SH). 100 MHz (13C-NMR, DMSO-*d*6, δ/ppm): 56.79 (OCH3), 114.01, 121.50, 128.03, 128.47, 128.97, 130.24, 131.15, 160.0 (Ar-C), 139.88, 152.92, 171.93 (N = C). MS *m/z* (ES+) 346.0469
8e	193 ºC	62	m.p 193 ˚C; IR (KBr): υ 3346 (N-H), 1529 (C = N), 1469 (Ph), 1447 (C = C), 1333 (C–N). 500MHz (1H-NMR, DMSO-*d*6, δ/ppm): 2.36 (s, 3H, Me), 6.91 (d, 2H, Ar-H, *J* = 2.0 Hz), 7.11 (d, 2H, Ar-H, *J* = 1.5 Hz), 7.28 (dd, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 7.44 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.58 (d, 1H, Ar-H, *J* = 1.5 Hz), 8.26, (s, 1H, N = CH), 13.31 (s, 1H, SH). 100 MHz (13C-NMR, DMSO-*d*6, δ/ppm): 21.13 (CH3), 126.36, 126.67, 127.84, 128.03, 129.29, 130.24, 131.15, 131.65, 133.12, 139.27 (Ar-C), 151.22, 152.92, 171.93 (N = C). MS *m/z* (ES+) 328.0549
8f	212 ºC	62	m.p 212 ˚C; IR (KBr): υ 3349 (N-H), 1526 (C = N), 1472 (Ph), 1449 (C = C), 1332 (C–N). 500MHz (1H-NMR, DMSO-*d*6, δ/ppm): 6.90 (d, 2H, Ar-H, *J* = 2.0 Hz), 7.32 (d, 2H, Ar-H, *J* = 1.5 Hz), 7.28 (dd, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 7.41 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.57 (d, 1H, Ar-H, *J* = 1.5 Hz), 8.27, (s, 1H, N = CH), 13.21 (s, 1H, SH). 100 MHz (13C-NMR, DMSO-*d*6, δ/ppm): 21.13 (CH3), 126.36, 126.67, 127.84, 128.03, 129.29, 130.24, 131.15, 131.65, 133.12, 139.27 (Ar-C), 151.22, 152.92, 171.93 (N = C). MS *m/z* (ES+) 348.0003
8g	202 ºC	61	m.p 202 ˚C; IR (KBr): υ 3351 (N-H), 1532 (C = N), 1473 (Ph), 1451 (C = C), 1339 (C–N). 500MHz (1H-NMR, DMSO-*d*6, δ/ppm): 6.83 (d, 2H, Ar-H, *J* = 2.0 Hz), 6.88 (d, 2H, Ar-H, *J* = 1.5 Hz), 7.28 (dd, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 7.41 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.57 (d, 1H, Ar-H, *J* = 1.5 Hz), 8.21, (s, 1H, N = CH), 13.21 (s, 1H, SH). 100 MHz (13C-NMR, DMSO-*d*6, δ/ppm): 56.04 (OCH3), 114.52, 126.36, 126.67, 127.11, 128.03, 129.62, 130.24, 131.15, 133.12, 161.03 (Ar-C), 151.22, 152.92, 171.93 (N = C). MS *m/z* (ES+) 346.0045

DISCUSSION

The production of compounds hydrazones 8a-8e remained attained in 60-62% product by relating conservative warming process under reflux for 120 minutes although similar reaction was accepted out in sonication for half hour as well as preferred byproducts remained attained in 60-80% yield in time. Completely the manufactured complexes were characterized by infrared as well as nuclear magnetic resonance.

Spectral analysis of compound

Compound 8f was synthesized; structure was confirmed by ^{1}H, ^{13}C nuclear magnetic resonance, Infrared and by molecular ion peak M^{+} at m/z 348.0003 in MS-E1 spectrum. Different absorption spectra were used to describe various functional groups in IR (KBr): υ 3349 (N-H), 1526 (C = N), 1472 (Ph), 1449 (C = C), 1332 (C–N). 500MHz (1H-NMR, DMSO-*d*6, δ/ppm): 6.90 (d, 2H, Ar-H, *J* = 2.0 Hz), 7.32 (d, 2H, Ar-H, *J* = 1.5 Hz), 7.28 (dd, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 7.41 (d, 1H, Ar-H, *J* = 1.5 Hz), 7.57 (d, 1H, Ar-H, *J* = 1.5 Hz), 8.27, (s, 1H, N = CH), 13.21 (s, 1H, SH). 100 MHz (13C-NMR, DMSO-*d*6, δ/ppm): 21.13 (CH3), 126.36, 126.67, 127.84, 128.03, 129.29, 130.24, 131.15, 131.65, 133.12, 139.27 (Ar-C), 151.22, 152.92, 171.93 (N = C).

Hemolytic activity

The hemolytic activity of new compounds (8a-8g) was tested as well as they were found to induce poor to moderate hemolysis (Table 1 in term of percentage hemolysis). Among these compounds, 8c-8f was found least toxic, while the 8a and 8b were found highly toxic [28, 29].

Thrombolytic activity

All the novel compounds showed moderate clotlysis activity (table 1). Among the synthesized compounds, maximum thrombolytic activity was observed in compound 8g (76.8 ± 0.082) while all other compounds exhibited low clotlysis activity [28, 30, 31].

Conclusion

A series of novel biologically active derivatives has been synthesized and evaluated for their cytotoxic studies. The results displayed these molecules as potent drug candidates for further studies.

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