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$InCl_3$-assisted, synthesis and cytotoxic studies of some novel heteroaryl thiazoles

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ABSTRACT

A series of novel heteroaryl thiazoles (3a-u) was synthesized by the Hantzsch reaction of various α-bromoketones (1a-c) with the heteroaryl thiourea (2a-g) using $InCl_3$ as a catalyst in a shorter reaction time. All the novel thiazole derivatives were characterized and screened for their *in vitro* cytotoxic activity against DAL and EAC cells. Among the 21 compounds screened, the compounds 3b, 3d, 3f, 3h, 3j, 3k, 3m, 3p, 3r, 3t and 3u were found to be the most active against DAL cells with IC_{50} values less than 41.60 µg/mL and the compounds 3d, 3q, 3r and 3t were found to be the most active against EAC cells with IC_{50} values less than 41.60 µg/mL.

Keywords: Thiazole, Isoxazole, Benzothiophene, Benzodioxepine, Indium chloride, Cytotoxicity.

1. INTRODUCTION

Benzothiophene moiety is a prevalent scaffold in a number of naturally occurring and synthetic molecules with attractive biological activities [1]. Davis et al. identified a new benzothiophene containing Rho kinase inhibitor scaffold in an ultra high throughput enzyme activity screen [2]. Benzothiophene derivative strongly inhibited the oxidation of arachidonic acid by recombinant human 5-lipoxygenase and the production of LTB_4 in calcium ionophore-stimulated HWB [3]. Benzothiophene piperidine urea inhibited FAAH by covalently modifying the enzyme's active site serine nucleophile [4]. Benzothiophenyl piperazinyl piperidine derivative showed reduction of hepatic de nova fatty acid synthesis in rats after oral administration [5].

Benzodioxepin derivative possessed cytotoxic activity against human breast cancer cells with IC_{50} = 5.04 ± 1.68 µm nearly equipotent as *5-Flurouracil* [6]. Benzodioxepin derivatives were identified as novel survival motor neuron (SMN) protein modulators [7]. 1,5-Benzodioxepin derivatives displayed high affinity for muscarinic M_1-M_3 receptors [8].

Heterocycles containing an isoxazole ring system are found to exhibit a wide spectrum of biological activities [9]. Isoxazoles displayed high *in vitro* neuroprotective activity against oxidative stress-induced death of neuronal HT22 cells [10]. Isoxazolyl dihydropyridines exhibited inhibition of the multidrug-resistance transporter (MDR-1) [11]. Isoxazole derivatives have shown very potent analgesic activity when compared with standard drug *Pentazocine* [12]. Isoxazolyl pyrazoles exhibited the maximum antinociceptive activity [13].

Thiazole derivatives are known to exhibit various pharmacological properties [14]. Many commercially available drugs (figure 1) including, Riluzole (anticonvulsant), Sulfathiazole (antibacterial) and Zolamine (antihistamine) are derived from thiazole entities. Thiazole derivatives displayed significant anti-inflammatory and antibacterial activities when compared to well known reference drugs *Indomethacin* and *Cefixime* respectively [15]. Thiazole derivatives emerged as the most active antifungal compounds against *Aspergillus flavus* and *Aspergillus fumigatus* [16]. Thiazole chalcones exhibited potential antitumor activity *in vitro* against S180 xenograft in mice [17]. Thiazole derivatives were identified as potent pan inhibitors of Akt kinases [18].

Since the past few decades, the literature has been enriched with progressive finding about the cytotoxic activities of various substituted thiazoles derivatives. Keeping in the view of these observations and in continuation of our research

work on the synthesis of biheterocyclic compounds [19-23], we herein report the synthesis of some novel benzodioxepinthiazoles, isoxazolylthiazoles and benzothiophenylthiazoles which have been found to possess an interesting profile of cytotoxic activities.

2. CHEMISTRY

Synthesis of the thiazole (Scheme 1) was accomplished following the well known Hantzsch's thiazole synthesis involving the reaction of synthons (1a-c) and (2a-g). Various commercial aryl thiourea (2a-g) and commercially available α-bromoketones (1a-c) were cyclised in the presence of 10 mol% $InCl_3$ as a Lewis acid catalyst in refluxing ethanol at 70 ˚C for 2 hours to afford the desired thiazole derivatives (3a-u) in high yield (84-94%). It was hypothesized that a critical choice of metal chloride might efficiently catalyze the Hantzsch's thiazole synthesis by forming a better activated intermediate (Figure 2).

The role of the $InCl_3$ can be postulated in terms of Lewis acidity of the $InCl_3$ leading to its interaction with the carbonyl oxygen of ketone (I) and (III) resulting in its increased polarization leading to increased electrophilicity of the carbocation and thus, promoting condensation step A and cyclisation step B to produce five membered ring (IV), which on dehydration afforded (V). In the absence of $InCl_3$, the product was obtained in a moderate yield (50-60%) after long reaction times (4-6 h).

Though several catalysts such as Ionic liquid [24], acetic acid [25], β-cyclodextrine [26] and ammonium-12-molybdophosphate (AMP) [27] have been employed for Hantzsch's thiazole synthesis, some of these procedures are complicated by harsh reaction conditions, use of harmful organic solvents, low yield and difficulties in the work up procedures. To the best of our knowledge, $InCl_3$ has not been used as a catalyst for Hantzsch's thiazole synthesis and it is now found to be effective than other catalysts investigated.

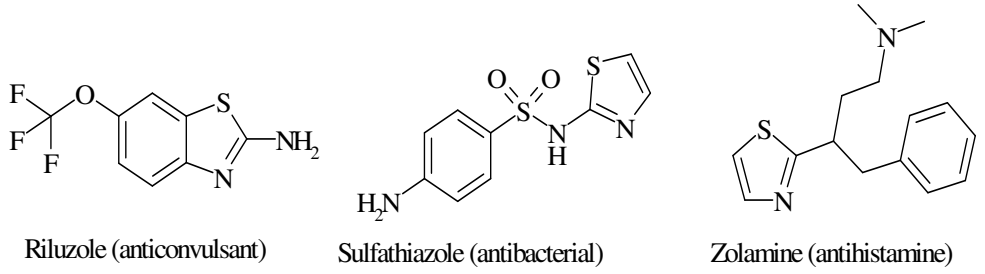
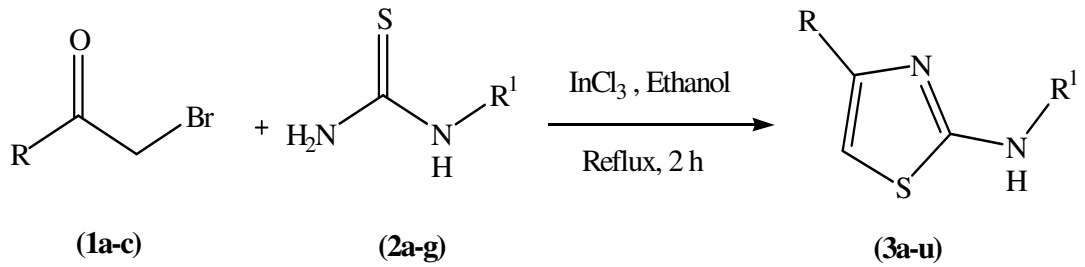
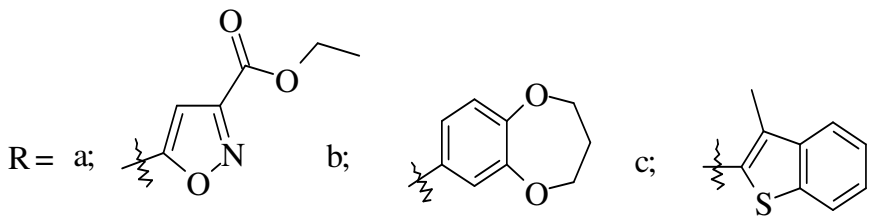


Figure - 1: Some biologically active thiazoles





R^1 = a; (4-F) Phenyl, b; (4-Cl) Phenyl, c; (3-CF_3) Phenyl, d; 2-Pyridyl, e; *p*-Tolyl, f; (2,3-Dimethoxy) Phenyl, g; Benzoyl

Scheme -1: Synthesis of the compounds (3a-u)

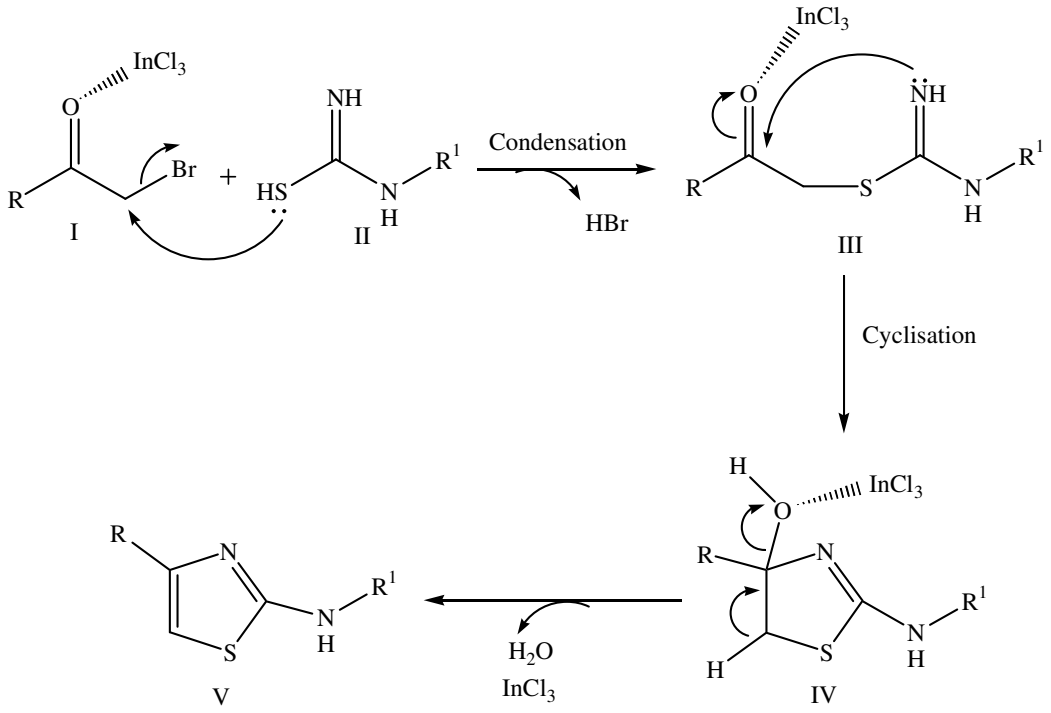


Figure - 2: Plausible mechanism for the synthesis of (3a-u)

3. EXPERIMENTAL

The melting points were determined by open capillary method using electric melting point apparatus and are uncorrected. The IR spectra (KBr disc) were recorded on a Shimadzu-8400S FT-IR Spectrophotometer. ^{1}H NMR spectra were recorded on Bruker 300 MHz (for compounds 3d-u) and 400 MHz (for compounds 3a-c) spectrometer. ^{13}C NMR was recorded on Bruker 400 MHz spectrometer. DMSO-d_6 and $CDCl_3$ were used as a solvents and TMS as an internal standard. The chemical shifts were expressed in δ ppm. The mass spectra were recorded on an Agilent-Single Quartz ESI-MS. The purity of the compounds was checked by TLC. The elemental analyses were carried out using Elemental Vario Micro Cube CHN Rapid Analyzer. All the compounds gave satisfactory elemental analysis.

3.1. General procedure for the synthesis of thiazole derivatives (3a-u).

To a stirring solution of α-bromoketones (1.56 mmol) (1a-c) and phenylthiourea derivatives (1.56 mmol) (2a-g) in ethanol (15 mL) was added $InCl_3$ (10 mol %). The reaction flask was heated at 70 ˚C in an oil bath for 1.5-2 h. The completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated to one fourth volume and poured on to crushed ice. The solid separated was filtered and washed with cold water. The crude product was dried and recrystallised from ethanol.

4. RESULT AND DISCUSSION

The structures of novel thiazole derivatives (3a-u) were established from IR, ^{1}HNMR, ^{13}C NMR and ESI-MS data as illustrated for a representative example. In the IR spectrum of 5-(2-benzoylamino-thiazol-4-yl)-isoxazole-3-carboxylic acid ethyl ester (3g), the amide carbonyl stretching frequency was observed at 1683 cm^{-1} where as the ester carbonyl stretching frequency appeared at 1733 cm^{-1}. The N-H stretching frequency showed a strong band at 3230 cm^{-1}. The ^{1}HNMR spectrum of the compound (3g) exhibited a triplet in the region at δ 1.32 (J = 7.2 Hz) due to methyl protons of ethyl group. A quartet was appeared at δ 4.39 (J = 7.2 Hz) due to methylene protons of ethyl group. A singlet was observed at δ 7.19 due to the presence of aromatic proton. A triplet appeared in the region δ 7.54-7.59 is due to two aromatic protons. A doublet appeared at δ 7.64 (J = 7.2 Hz) is due to one aromatic proton. A doublet appeared at δ 8.12 (J = 8.4 Hz) is due to three aromatic protons. The N-H proton was resonated as a singlet at δ 10.56 which was further confirmed by D_2O exchange experiment. The ^{13}C NMR spectrum of the compound (3g) is given in the experimental section. The mass spectrum (ESI) of 5-(2-*p*-tolylamino-thiazol-4-yl)-isoxazole-3-carboxylic acid ethyl ester (3e) displayed a [M+1] peak at 330.

4.1. Biological activity

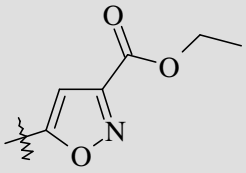
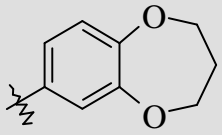
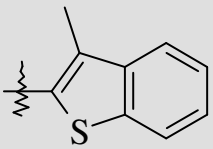
The cytotoxic activity of newly synthesized compounds was examined *in vitro* on Dalton's Ascitic Lymphoma (DAL) and Ehrlich Ascites Carcinoma (EAC) cells using Trypan blue dye exclusion assay [28].

Ascitic fluid withdrawn from the peritoneum of DAL and EAC inoculated mouse was washed with ice cold phosphate buffer saline (PBS) of pH 7.4. Stock cell suspension was adjusted to 1×10^6 cell/0.2 mL by PBS using hemocytometer. The cells were incubated with desired test drug concentration in a final volume of 1 mL for 3 hr at 37 ˚C in a CO_2 incubator with continuous flow of 5% CO_2. *5-Flurorouracil* was used as positive control. After incubation, 0.2 mL of cell line was taken and made upto of final concentration with PBS (0.3 mL), trypan blue (0.5 mL), mixed well and kept aside for 5 min. The total number of dead and living cells counted using a hemocytometer and the percentage viability or cytotoxicity was calculated. All the procedures were done in triplicate manner.

4.1.1. *In Vitro* Cytotoxic Screening

The newly synthesized compounds were evaluated for their *in vitro* cytotoxic activity against Dalton's Ascites Lymphoma (DAL) and Ehrlich Ascites Carcinoma (EAC) cells. *5-Fluorouracil* which is one of the most effective anticancer agents was used as the reference drug in this study. The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of Dalton's Ascites Lymphoma (DAL) and Ehrlich Ascites Carcinoma (EAC) cells. The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability. The IC_{50} of the synthesized compounds compared to the reference drug are shown in (Table 1) and the results are represented graphically in (Figure 3).

Table -1: Results of *in vitro* cytotoxic activity of the synthesized compounds on DAL and EAC cells in IC_{50} (µg/mL)

Compounds	R^1	R	Cancer cell inhibition	
			DAL	EAC
3a	(4-F) Phenyl		56.86	127.9
3b	(4-Cl) Phenyl		28.08	86.78
3c	(3-CF_3) Phenyl		51.45	68.06
3d	2-Pyridyl		17.72	28.73
3e	*p*-Tolyl		105.70	54.70
3f	(2,3-Dimethoxy) Phenyl		26.62	107.60
3g	Benzoyl		102.00	54.25
3h	(4-F) Phenyl		40.07	155.70
3i	(4-Cl) Phenyl		60.04	46.62
3j	(3-CF_3) Phenyl		39.84	102.0
3k	2-Pyridyl		29.87	56.69
3l	*p*-Tolyl		43.55	85.59
3m	(2,3-Dimethoxy) Phenyl		40.84	64.24
3n	Benzoyl		59.83	59.60
3o	(4-F) Phenyl		56.61	43.70
3p	(4-Cl) Phenyl		38.56	59.68
3q	(3-CF_3) Phenyl		73.84	39.88
3r	2-Pyridyl		26.84	30.03
3s	*p*-Tolyl		50.71	59.72
3t	(2,3-Dimethoxy) Phenyl		28.65	40.87
3u	Benzoyl		15.76	50.69
	5-Fluorouracil		41.60	41.60

The investigation of *in vitro* cell cytotoxicity revealed that the most of the tested compounds exhibited good activity against DAL cells. The compounds 3b [R = Isoxazole, R^1 = (4-Cl) phenyl], 3d (R = Isoxazole, R^1 = 2-Pyridyl), 3f [R = Isoxazole, R^1 = (2,3-Dimethoxy) Phenyl], 3h [R = Benzodioxepine, R^1 = (4-F) Phenyl], 3j [R = Benzodioxepine, R^1 = (3-CF_3) Phenyl], 3k [R = Benzodioxepine, R^1 = 2-Pyridyl], 3m [R = Benzodioxepine, R^1 = (2,3-Dimethoxy) Phenyl], 3p [R = Benzothiophene, R^1 = (4-Cl) Phenyl], 3r [R = Benzothiophene, R^1 = 2-Pyridyl], 3t [R = Benzothiophene, R^1 = (2,3-Dimethoxy) Phenyl] and 3u [R = Benzothiophene, R^1 = Benzoyl] displayed excellent activity against DAL cell with IC_{50} value of < 41.60 µg/mL. These derivatives are more potent than *5-Fluorouracil* (positive control). The compounds 3a [R = Isoxazole, R^1 = (4-Cl) Phenyl], 3c [R = Isoxazole, R^1 = (3-CF_3) Phenyl], 3i [R = Benzodioxepine, R^1 = (4-Cl) Phenyl], 3l [R = Benzodioxepine, R^1 = *p*-Tolyl], 3n [R = Benzodioxepine, R^1 = Benzoyl], 3o [R = Benzothiophene, R^1 = (4-F) Phenyl] and 3s [R = Benzothiophene, R^1 = *p*-Tolyl] exhibited moderate activity with IC_{50} values between 43 - 61 µg/mL. The rest of the compounds showed poor activity.

The investigation of *in vitro* cell cytotoxicity revealed that a few of the tested compounds exhibited good activity against EAC cells. The compounds 3d [R = Isoxazole, R^1 = 2-Pyridyl], 3q [R = Benzothiophene, R^1 = (3-CF_3) Phenyl), 3r [R = Benzothiophene, R^1 = 2-Pyridyl] and 3t [R = Benzothiophene, R^1= (2,3-Dimethoxy) Phenyl] displayed excellent activity against EAC cell with IC_{50} value of < 41.60 µg/mL. These derivatives are more potent than *5-Fluorouracil*.

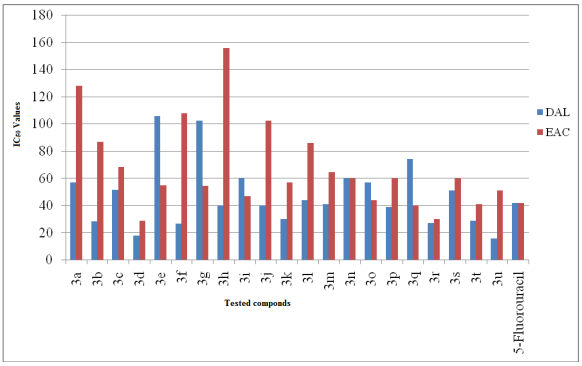


Figure - 3: Graphical representation of *in vitro* cytotoxic activity of the synthesized compounds on DAL and EAC cells in IC_{50} (µg/mL)

The compounds 3e [R = Isoxazole, R^1 = *p*-Tolyl], 3g [R = Isoxazole, R^1 = Benzoyl], 3i [R = Benzodioxepine, R^1 = (4-Cl) Phenyl], 3k [R = Benzodioxepine, R^1 = 2-Pyridyl], 3n [R = Benzodioxepine, R^1 = Benzoyl], 3o [R = Benzothiophene, R^1 = (4-F) Phenyl], 3p [R = Benzothiophene, R^1 = (4-Cl) Phenyl], 3s [R = Benzothiophene, R^1 = *p*-Tolyl] and 3u [R = Benzothiophene, R^1 = Benzoyl] exhibited moderate activity with IC_{50} values between 46 - 60 µg/mL. The rest of the compounds showed poor activity.

4.2. Characterization

4.2.1. 5-[2-(4-Fluoro-phenylamino)-thiazol-4-yl]-isoxazole-3-carboxylic acid methyl ester (3a)

Yield 91%; colorless solid; m.p. 146-148 °C; IR (KBr, cm^{-1}): 1723 (ester C=O), 3220 (N-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.41 (t, 3H, J = 5.4 Hz, CH_3 of ethyl), 4.46 (q, 2H, J = 5.4 Hz, CH_2 of ethyl), 6.94 (s, 1H, Ar-H), 7.07-7.42 (m, 5H, Ar-H) ppm; Anal. Calcd for $C_{15}H_{12}FN_3O_3S$: C, 54.05: H, 3.63: N, 12.61. Found: C, 53.85: H, 3.56: N, 12.50.

4.2.2. 5-[2-(4-Chloro-phenylamino)-thiazol-4-yl]-isoxazole-3-carboxylic acid ethyl ester (3b)

Yield 84%; colorless solid; m.p. 174-176 °C; IR (KBr, cm^{-1}): 1728 (ester C=O), 3226 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, 3H, J = 5.4 Hz, CH_3 of ethyl), 4.44 (q, 2H, J = 7.2 Hz, CH_2 of ethyl), 6.96-7.41 (m, 7H, Ar-H) ppm; Anal. Calcd for $C_{15}H_{12}ClN_3O_3S$: C, 51.51: H, 3.46: N, 12.01. Found: C, 51.38: H, 3.39: N, 11.91.

4.2.3. 5-[2-(3-Trifluoromethyl-phenylamino)-thiazol-4-yl]-isoxazole-3-carboxylic acid ethyl ester (3c)

Yield 87%; colorless solid; m.p. 138-141 °C; IR (KBr, cm^{-1}): 1732 (ester C=O), 3243 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t, 3H, J = 5.4 Hz, CH_3 of ethyl), 4.45 (q, 2H, J = 5.1 Hz, CH_2 of ethyl), 7.07 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.42 (d, 1H, Ar-H, J = 5.7 Hz), 7.53 (t, 1H, J = 6.0 Hz, Ar-H), 7.66-7.74 (m, 2H, Ar-H) ppm; Anal. Calcd for $C_{16}H_{12}F_3N_3O_3S$: C, 50.13: H, 3.16: N, 10.96. Found: C, 50.01: H, 3.02: N, 10.87.

4.2.4. 5-[2-(Pyridin-4-ylamino)-thiazol-4-yl]-isoxazole-3-carboxylic acid ethyl ester (3d)

Yield 89%; colorless solid; m.p. 165-167 °C; IR (KBr, cm^{-1}): 1727 (ester C=O), 3212 (N-H); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.32 (t, 3H, J = 7.2 Hz, CH_3 of ethyl), 4.39 (q, 2H, J = 6.9 Hz, CH_2 of ethyl), 7.19 (s, 1H, Ar-H), 7.54-7.67 (m, 5H, Ar-H), 8.12 (d, 1H, Ar-H), 13.06 (s, 1H, N-H) ppm; Anal. Calcd for $C_{14}H_{12}N_4O_3S$: C, 53.16: H, 3.82: N, 17.71. Found: C, 53.02: H, 3.71: N, 17.58.

4.2.5. 5-(2-p-Tolylamino-thiazol-4-yl)-isoxazole-3-carboxylic acid ethyl ester (3e)

Yield 90%; colorless solid; m.p. 124-127 °C; IR (KBr, cm^{-1}): 1737 (ester C=O), 3334 (N-H); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.32 (t, 3H, J =

6.9 Hz, CH_3 of ethyl), 2.26 (s, 3H, CH_3), 4.39 (q, 2H, J = 7.2 Hz, CH_2 of ethyl), 7.13-7.18 (m, 3H, Ar-H), 7.55 (d, 2H, J = 8.4 Hz, Ar-H), 7.69 (s, 1H, Ar-H), 10.38 (s, 1H, N-H) ppm; ESI-MS: *m/z* [M+1] 330; Anal. Calcd for $C_{16}H_{15}N_3O_3S$: C, 58.35: H, 4.59: N, 12.76. Found: C, 58.22: H, 4.43: N, 12.61.

4.2.6. 5-[2-(2,3-Dimethoxy-phenylamino)-thiazol-4-yl]-isoxazole-3-carboxylic acid ethyl ester (3f)

Yield 86%; violet color solid; m.p. 137-140 ˚C; IR (KBr, cm^{-1}): 1731 (ester C=O), 3234 (N-H); ^1H NMR (300 MHz, DMSO-d_6): δ = 1.32 (s, 3H, J = 6.9 Hz, CH_3 of ethyl), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.35 (q, 2H, J = 7.2 Hz, CH_2 of ethyl), 6.94 (d, 1H, J = 8.7 Hz, Ar-H), 7.07 (s, 1H, Ar-H) 7.18-7.21 (m, 1H, Ar-H), 7.34 (d, 1H, J = 2.1 Hz, Ar-H), 7.67 (s, 1H, Ar-H), 10.31 (s, 1H, N-H) ppm; Anal. Calcd for $C_{17}H_{17}N_3O_5S$: C, 54.39: H, 4.56: N, 11.19. Found: C, 54.23: H, 4.41: N, 11.04.

4.2.7. 5-(2-Benzoylamino-thiazol-4-yl)-isoxazole-3-carboxylic acid ethyl ester (3g)

Yield 93%; colorless solid; m.p; 196-198 ˚C; IR (KBr, cm^{-1}): 1683 (amide C=O), 1733 (ester C=O), 3230 (N-H); ^1H NMR (300 MHz, DMSO-d_6): δ = 1.32 (t, 3H, J = 7.2 Hz, CH_3 of ethyl), 4.39 (q, 2H, J = 7.2 Hz, CH_2 of ethyl), 7.19 (s, 1H, Ar-H), 7.54-7.59 (t, 2H, J = 7.2Hz, Ar-H), 7.64 (d, 1H, J = 7.2Hz, Ar-H), 8.12 (d, 3H, J = 8.4Hz, Ar-H), 10.56 (s, 1H, N-H, D_2O exchangeable) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): 14.58, 62.80, 101.68, 114.68, 128.02, 129.53, 131.66, 133.87, 137.31, 157.30, 160.15, 165.39, 166.59 ppm; Anal. Calcd for $C_{16}H_{13}N_3O_4S$: C, 55.97: H, 3.82: N, 12.24. Found: C, 55. 84: H, 3.70: N, 12.11.

4.2.8. [4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-thiazol-2-yl]-(4-fluoro-phenyl)-amine (3h)

Yield 92%; colorless solid; m.p. 192-194 ˚C; IR (KBr, cm^{-1}): 3192 (N-H); ^1H NMR (300 MHz, DMSO-d_6): δ = 2.10-2.13 (m, 2H, CH_2 of trimethylenedioxy), 4.14-4.15 (m, 4H, 2xOCH_2 of trimethylenedioxy), 6.76-7.51 (m, 7H, Ar-H), 9.49 (s, 1H, Ar-H), 10.07 (s, 1H, N-H) ppm; Anal. Calcd for $C_{18}H_{15}FN_2O_2S$: C, 63.14: H, 4.42: N, 8.18. Found: C, 62.92: H, 4.30: N, 7.97.

4.2.9. [4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-thiazol-2-yl]-(4-chloro-phenyl)-amine (3i)

Yield 89%; colorless solid; m.p. 168-171 ˚C; IR (KBr, cm^{-1}): 3229 (N-H); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.21-2.23 (m, 2H, J = 4.2 Hz, CH_2 of trimethylenedioxy), 4.24-4.28 (m, 4H, 2xOCH_2 of trimethylenedioxy), 6.56 (s, 1H, Ar-H), 7.03 (d, 1H, J = 6.0 Hz, Ar-H), 7.26-7.42 (m, 6H, Ar-H) ppm; Anal. Calcd for $C_{18}H_{15}ClN_2O_2S$: C, 60.25: H, 4.21: N, 7.81. Found: C, 60.17: H, 4.03: N, 7.73.

4.2.10. [4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-thiazol-2-yl]-(3-trifluoromethyl-phenyl)-amine (3j)

Yield 87%; colorless solid; m.p. 181-183 ˚C; IR (KBr, cm^{-1}): 3246 (N-H); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.10-2.13 (m, 2H, CH_2 of trimethylenedioxy), 4.16-4.18 (m, 4H, 2xOCH_2 of trimethylenedioxy), 6.93-7.01 (m, 1H, Ar-H), 7.10 (d, 1H, J = 8.4 Hz, Ar-H), 7.35 (s, 1H, Ar-H), 7.47-7.51 (m, 2H, Ar-H), 7.72 (t, 1H, J = 6.9 Hz, Ar-H), 8.30 (d, 1H, J = 6.6 Hz, Ar-H) ppm; Anal. Calcd for $C_{19}H_{15}F_3N_2O_2S$: C, 58.16: H, 3.85: N, 7.14. Found: C, 58.01: H, 3.68: N, 7.03.

4.2.11. [4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-thiazol-2-yl]-pyridin-2-yl-amine (3k*)*

Yield 90%; colorless solid; m.p. 185-188 ˚C; IR (KBr, cm^{-1}): 3217 (N-H); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.10-2.14 (m, 2H, CH_2 of trimethylenedioxy), 4.13-4.18 (m, 4H, 2xOCH_2 of trimethylenedioxy), 6.92 (d, 1H, J = 8.7 Hz, Ar-H), 7.16-7.23 (m, 3H, Ar-H), 7.47 (t, 2H, J = 1.8Hz, Ar-H), 7.70-7.75 (m, 2H, Ar-H), 10.26 (s, 1H, N-H) ppm; Anal. Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75: H, 4.65: N, 12.91. Found: C, 62.60: H, 4.53: N, 12.78.

4.2.12. [4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-thiazol-2-yl]-p-tolyl-amine (3l)

Yield 90%; colorless solid; m.p. 202-205 ˚C; IR (KBr, cm^{-1}): 3210 (N-H); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.21-2.24 (m, 2H, CH_2 of trimethylenedioxy), 2.38 (s, 3H, CH_3), 4.26-4.29 (m, 4H, 2xOCH_2 of trimethylenedioxy), 6.45 (s, 1H, Ar-H), 7.05 (d, 1H, J = 6.3, Ar-H), 7.26-7.32 (d, 5H, J = 6.3 Hz, Ar-H), 7.38-7.41 (m, 1H, Ar-H), 11.56 (s, 1H, N-H) ppm; Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43: H, 5.36: N, 8.28. Found: C, 67.30: H, 5.21: N, 8.13.

4.2.13. 4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-thiazol-2-yl]-(2,3-dimethoxy-phenyl)-amine (3m)

Yield 92%; violet color solid; m.p. 201-202 ˚C; solid; IR (KBr, cm^{-1}): 3135 (N-H); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.21-2.24 (m, 2H, J = 4.2 Hz, CH_2 of trimethylenedioxy), 3.89 (s, 6H, 2,3-Dimethoxy), 4.25-4.29 (m, 4H, 2xOCH_2 of trimethylenedioxy), 6.45 (s, 1H, Ar-H), 6.89-6.95 (m, 3H, Ar-H), 7.02 (d, 1H, J = 6.0 Hz, Ar-H), 7.32-7.40 (m, 2H, Ar-H), 10.96 (s, 1H, N-H) ppm; Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48: H, 5.24: N, 7.29. Found: C, 62.30: H, 5.16: N, 7.13.

4.2.14. N-[4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-thiazol-2-yl]-benzamide (3n)

Yield 88%; colorless solid; m.p. 162-164 ˚C; IR (KBr, cm^{-1}): 1687 (amide C=O), 3210 (N-H); ^1H NMR (300 MHz, DMSO-d_6): δ = 2.10-2.14 (m, 2H, CH_2 of trimethylenedioxy), 3.83-4.17 (m, 4H, 2xOCH_2 of trimethylenedioxy), 7.01-9.86 (m, 9H, Ar-H), 11.25 (s, 1H, N-H) ppm; Anal. Calcd for $C_{19}H_{16}N_2O_3S$: C, 64.76: H, 4.58: N, 7.95. Found C, 64.62: H, 4.41: N, 7.84.

4.2.15. (4-Fluoro-phenyl)-[4-(3-methyl-benzo[b]thiophen-2-yl)-thiazol-2-yl]-amine (3o)

Yield 91%; yellow color solid; m.p. 131-133 ˚C; IR (KBr, cm^{-1}): 3231 (N-H); ^1H NMR (300 MHz, DMSO-d_6): δ = 2.61 (s, 3H, CH_3), 7.18-7.23 (m, 3H, Ar-H), 7.37-7.42 (m, 2H, Ar-H), 7.72-7.74 (d, 2H, J = 6Hz, Ar-H), 7.81 (d, 1H, J = 7.8 Hz, Ar-H), 7.93 (d, 1H, J = 7.8 Hz, Ar-H), 10.42 (s, 1H, N-H) ppm; Anal. Calcd for $C_{18}H_{13}FN_2S_2$: C, 63.51: H, 3.85: N, 8.23. Found: C, 63.36: H, 3.77: N, 8.10.

4.2.16. (4-Chloro-phenyl)-[4-(3-methyl-benzo[b]thiophen-2-yl)-thiazol-2-yl]-amine (3p)

Yield 85%; colorless solid; m.p. 167-169 ˚C; IR (KBr, cm^{-1}): 3229 (N-H); ^1H NMR (300 MHz, DMSO-d_6): δ = 2.64 (s, 3H, CH_3), 7.29 (s, 1H, Ar-H), 7.36-7.45 (m, 2H, Ar-H), 7.49 (dd, 2H, J = 2.4, 9.0 Hz, Ar-H), 7.57 (d, 1H, J = 8.7 Hz, Ar-H), 7.83 (d, 1H, J = 7.2 Hz, Ar-H), 7.94 (d, 1H, J = 6.9 Hz, Ar-H), 8.32 (d, 1H, J = 2.4 Hz, Ar-H), 10.76 (s, 1H, N-H) ppm; Anal. Calcd for $C_{18}H_{13}ClN_2S_2$: C, 60.58: H, 3.67: N, 7.85. Found: C, 60.47: H, 3.54: N, 7.76.

4.2.17. (3-Trifluoromethyl-phenyl)-[4-(3-Methyl-benzo[b]thiophen-2-yl)-thiazol-2-yl]-amine (3q)

Yield 90%; yellow color solid; m.p. 216-217 ˚C; IR (KBr, cm^{-1}): 3219 (N-H); ^1H NMR (300 MHz, DMSO-d_6): δ = 2.67 (s, 3H, CH_3), 7.14 (t, 3H, J = 3.6 Hz, Ar-H), 7.34-7.44 (m, 2H, Ar-H), 7.58 (d, 2H, J = 8.1 Hz, Ar-H), 7.81 (d, 1H, J = 7.8 Hz, Ar-H), 7.93 (d, 1H, J = 7.8 Hz, Ar-H), 10.27 (s, 1H, N-H) ppm; Anal. Calcd for $C_{19}H_{13}F_3N_2S_2$: C, 58.45: H, 3.36: N, 7.17. Found: C, 58.39: H, 3.20: N, 7.08.

4.2.18. [4-(3-Methyl-benzo[b]thiophen-2-yl)-thiazol-2-yl]-pyridin-2-yl-amine (3r)

Yield 94%; colorless solid; m.p. 155-158 ˚C; IR (KBr, cm^{-1}): 3229 (N-H); ^1H NMR (300 MHz, DMSO-d_6): δ = 2.68 (s, 3H, CH_3), 7.12 (s, 1H, Ar-H), 7.40-7.47 (m, 2H, Ar-H), 7.56 (t, 2H, J = 5.4 Hz, Ar-H), 7.65-7.69 (m, 1H, Ar-H), 7.76 (dd, 1H, J = 2.4, 5.4 Hz, Ar-H), 7.83 (dd, 1H, J = 1.8, 4.8 Hz, Ar-H), 8.25 (d, 2H, J = 5.4 Hz, Ar-H), 12.66 (s, 1H, N-H) ppm; Anal. Calcd for $C_{17}H_{13}N_3S_2$: C, 63.13: H, 4.05: N, 12.66. Found: C, 62.98: H, 3.86: N, 12.45.

4.2.19. [4-(3-Methyl-benzo[b]thiophen-2-yl)-thiazol-2-yl]-p-tolyl-amine (3s)

Yield 90%; colorless solid; m.p. 138-140 ˚C; IR (KBr, cm^{-1}): 3238 (N-H); ^1H NMR (300 MHz, DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 2.61 (s, 3H, CH_3 of benzothiophene), 7.14 (t, 3H, J = 3.9 Hz, Ar-H), 7.34-7.44 (m, 2H, Ar-H), 7.58 (d, 2H, J = 8.4 Hz, Ar-H), 7.81 (d, 1H, J = 7.2 Hz, Ar-H), 7.93 (d, 1H, J = 6.9 Hz, Ar-H), 10.28 (s, 1H, N-H) ppm; Anal. Calcd for $C_{19}H_{16}N_2S_2$: C, 67.82: H, 4.79: N, 8.33. Found: C, 67.69: H, 4.68: N, 8.20.

4.2.20. (2,3-Dimethoxy-phenyl)-[4-(3-methyl-benzo[b]thiophen-2-yl)-thiazol-2-yl]-amine (3t)

Yield 86%; violet color solid; m.p. 185-186 ˚C; IR (KBr, cm^{-1}): 3323 (N-H); ^1H NMR (300 MHz, DMSO-d_6): δ = 2.62 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.93 (d, 1H, J = 8.7 Hz, Ar-H), 7.05 (dd, 1H, J = 2.4, 8.4 Hz, Ar-H), 7.14 (s, 1H, Ar-H), 7.34-7.44 (m, 2H, Ar-H), 7.63 (d, 1H, J = 2.4 Hz, Ar-H), 7.81 (d, 1H, J = 7.5 Hz, Ar-H), 7.91 (d, 1H, J = 7.5 Hz, Ar-H), 10.22 (s, 1H, N-H) ppm; Anal. Calcd for $C_{20}H_{18}N_2O_2S_2$: C, 62.80: H, 4.74: N, 7.32. Found: C, 62.63: H, 4.61: N, 7.23.

4.2.21. N-[4-(3-Methyl-benzo[b]thiophen-2-yl)-thiazol-2-yl]-benzamide (3u)

Yield 86%; colorless solid; m.p. 220-222 ˚C; IR (KBr, cm^{-1}): 3214 (N-H), 1680 (amide C=O); ^1H NMR (300 MHz, DMSO-d_6): δ = 2.61 (s, 3H, CH_3), 7.18-7.23 (m, 3H, Ar-H), 7.37-7.42 (m, 2H, Ar-H), 7.72-7.77 (m, 2H, Ar-H), 7.82 (d, 1H, J = 7.5 Hz, Ar-H), 7.93 (d, 1H, J = 7.8 Hz Ar-H), 10.42 (s, 1H, N-H) ppm; Anal. Calcd for $C_{19}H_{14}N_2OS_2$: C, 65.12: H, 4.03: N, 7.99. Found: C, 64.97: H, 3.89: N, 7.84.

5. CONCLUSION

In summary, a series of novel compounds containing isoxazole, benzodioxepin and benzothiophene core with thiazole moiety have been synthesized and evaluated for their cytotoxic activity against DAL and EAC cell lines. Results showed that the most of these compounds possessed potent cytotoxic activity against DAL and EAC cell lines with IC_{50} values in low micro molar range. Among these, the compound *N*-[4-(3-methyl-benzo[b]thiophen-2-yl)-thiazol-2-yl]-benzamide (3u) is found to be the most cytotoxic compound against DAL cell line with IC_{50} value of 15.76 µg/mL and the compound 5-[2-(pyridin-4-ylamino)-thiazol-4-yl]-isoxazole-3-carboxylic acid ethyl ester (3d) is found to be the most cytotoxic compound against EAC cell line with IC_{50} value of 28.73 µg/mL.

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