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Synthesis and Structural Elucidation of Novel 2,4-Disubstituted 1,3-Oxazole Analogues for Pharmacological Properties

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A series of novel 2,4-disubstituted 1,3-oxazole analogues (**3a-i**) has been designed and synthesized between 1-[3,5-*bis*(trifluoromethyl)-phenyl]-2-bromoethan-1-one and substituted amides by microwave assisted method. 2,4-Disubstituted 1,3-oxazole analogues obtained were at excellent yields and purity of the compound was ascertained by HPLC. The chemical structure of these compounds was elucidated by spectrometric (FT-IR, NMR and LCMS) and elemental analysis. It was observed that, microwave method influenced the better yield and reduction in reaction time when compared to conventional reflux method.

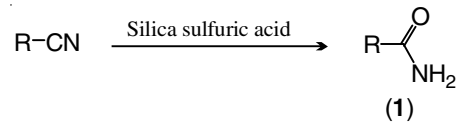
Keywords: Oxazole analogues, Synthesis, Microwave method, Spectrometric analyses, Pharmacological activity.

INTRODUCTION

Five membered substituted heterocyclic ring "1,3-oxazole" is found in many natural products which are known to exhibit pharmacological properties such as antitubercular [1], antimicrobial [2], antiviral [3], antifungal [4,5], anticancer [6], anticholinergic, antihistaminic and MAO-inhibition [7]. Various synthetic strategies are available for the construction of substituted oxazoles [8]. Several synthetic oxazole derivatives have been reported for various pharmacological properties such as antitubercular [9-12], anticancer [13,14], antidepressant [15], anticonvulsant [16], antifungal [17,18] and anti-HIV [19] and antibacterial [20,21] activities.

Fluorinated heterocyclic compounds are known for promising pharmacological properties [22-26]. In continuation of synthetic method [27] for the construction of pharmacologically active heterocyclic compounds [28,29], synthons [30] and study of polymorphism in pharmacologically active compounds [31,32] in the present investigating the design of the title compounds (**3a-i**) is based on the natural product lead compounds (Fig. 1) and their synthetic strategy is described in **Scheme-III**.

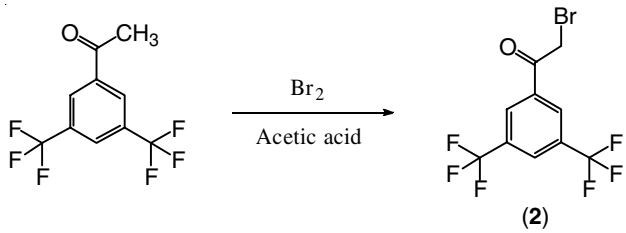
Synthesis of title compounds (**3a-i**) involves consumption of substituted alkyl, aryl and heteroaryl amides (**1**) and 1-[3,5-*bis*(trifluoromethyl)phenyl]-2-bromoethan-1-one (**2**). The substituted alkyl, aryl and heteroaryl amides (**1**) are prepared according to previous report [30] and their synthetic scheme is shown in **Scheme-I**.



(**1**)

Scheme-I: Hydration of nitrile to amide group [Ref. 30]

The synthon, 1-[3,5-*bis*(trifluoromethyl)phenyl]-2-bromoethan-1-one (**2**) is prepared by bromination of 3,5-*bis*(trifluoromethyl)acetophenone in acetic acid medium at room temperature and synthetic scheme is illustrated in **Scheme-II**.



(**2**)

Scheme-II: Preparation of 1-[3,5-*bis*(trifluoromethyl)phenyl]-2-bromoethan-1-one [Ref. 33]

Chemical structure of some of the promising natural product lead compounds for various pharmacological properties are illustrated in Fig. 1.

EXPERIMENTAL

Commercially available chemicals were obtained from Sigma-Aldrich chemical company. Thin layer chromatography

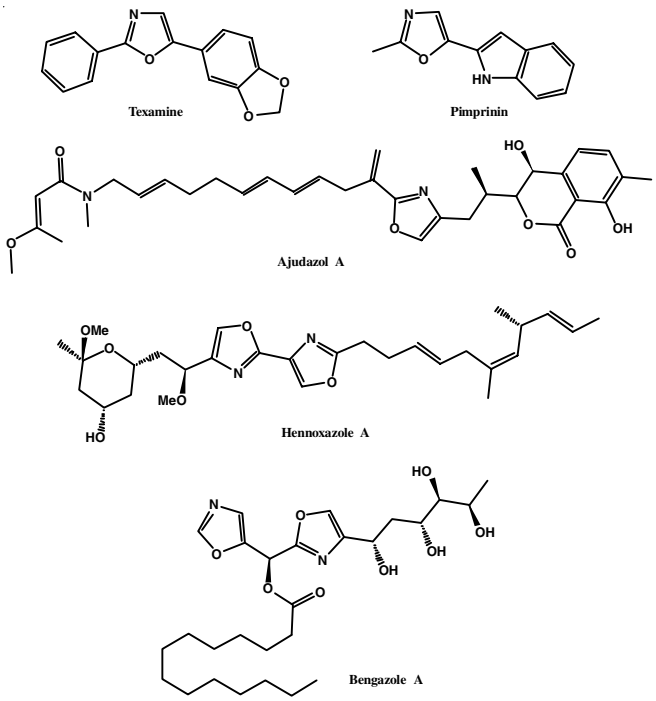


Fig. 1. Natural products containing oxazole nucleus for antimycobacterial (texamine) [Ref. 1], anticholinergic, antihistaminic and MAO-inhibition (pimprinine) [Ref. 7], antimicrobial (ajudazol A) [Ref. 2], antiviral (hennoxazole A) [Ref. 3], antifungal and anthelmintic activity (bengazole A) [Ref. 4,5].

(TLC) was performed on Sigma-Aldrich Silica gel on TLC plates with *n*-hexane and ethyl acetate (3.5:6.5) as solvent system and visualization with iodine chamber. Chemical reactions were monitored on TLC. Melting points were determined on a Buchi melting point B-545 apparatus. The FT-IR spectra were recorded on a Shimadzu FT-IR (IRAFFINITY-1S) spectrometry. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE III 400 MHz instruments in DMSO-d_6 as a solvent. Chemical shifts (δ) were indicated in parts per million downfield from tetramethylsilane and the coupling constants (*J*) are recorded in Hertz. Mass spectra were recorded using LC-MS-Agilent 1100 series with MSD (Ion trap) using 0.1 % aqueous trifluoroacetic acid in acetonitrile system on C18-BDS column. Elemental analysis was performed on Thermo Finnigan FLASH EA 1112 CHN analyzer. c Log P of the compounds was calculated using ChemDraw Professional 16.

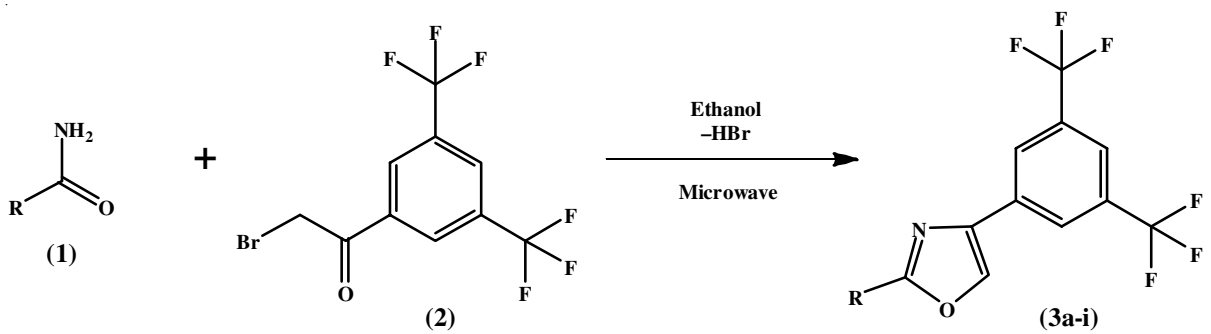
General procedure for the hydration of nitrile to amide group (1): Preparation of substituted alkyl, aryl and heteroaryl amides required for the construction of 4-[3,5-*bis*(trifluoro-methyl)phenyl]-2-substituted oxazoles (**3a-i**) was achieved according to our previous report [30].

Synthetic procedure for the preparation of 1-[3,5-*bis*-(trifluoromethyl)phenyl]-2-bromoethan-1-one (2) [33]: To a stirred solution of 3,5-*bis*(trifluoromethyl)acetophenone (0.5 g, 1.95 mmol) in acetic acid (5 mL) was added drop-wise bromine (0.312 g, 1.95 mmol) in acetic acid. Reaction medium was stirred at room temperature for 5 h. To the resulting mixture, water (5 mL) was added and the mixture was concentrated under reduced pressure. The residue obtained was diluted with ethyl acetate (10 mL), wash the organic layer with water (10 mL), sodium bicarbonate solution (5 mL) and filtered through dried sodium sulphate and evaporated the organic layer to obtain 1-[3,5-*bis*(trifluoromethyl)phenyl]-2-bromoethanone (**2**) as light yellow solid. Purification of the product was achieved by recrystallization method and yield was found at 62 %. m.p: 44-45 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2986, 1689, 1619, 1513, 1475, 1221, 595; ^{1}H NMR: (600 MHz, $CDCl_3$): 8.44 (2H, s), 8.13 (1H, s), 4.48 (2H, s); ^{13}C NMR: ($CDCl_3$, 150 MHz): δ = 188.81, 135.31, 133.06, 132.83, 132.60, 128.99, 127.08, 127.06, 125.42, 123.61, 121.80, 120.00, 29.46; LC-MS: *m/z* = 333 (M^+).

Microwave assisted synthesis of 4-[3,5-*bis*(trifluoro-methyl)phenyl]-2-substituted oxazoles (3a-i) [34]: To a stirred solution of 1-[3,5-*bis*(trifluoromethyl)phenyl]-2-bromoethan-1-one (**2**) (0.5 mmol) in absolute ethanol (10 mL) was added substituted alkyl, aryl and heteroaryl amides (**1**) (0.5 mmol) and exposed to microwaves for 10 min (Table-1). The reaction medium was cooled to room temperature and poured into 12 mL of 10 % sodium acetate solution. The precipitate obtained from the reaction medium was separated by filtration and the crude product was recrystallized from ethanol. The yield of the title compounds was found to be in the range of 86-98 % (Table-2).

4-[3,5-*Bis*(trifluoromethyl)phenyl]-2-vinyloxazole (3a): FT-IR (KBr, ν_{max}, cm^{-1}): 2974, 1614, 1508, 1488, 1217; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.08-8.34 (m, 3H), 7.68 (s, 1H), 6.61 (t, 2H), 5.49 (d, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 165.01, 140.02, 140.16, 135.67, 133.91, 131.92, 130.8, 129.6, 124.98, 124.65, 123.33, 120.40; LC-MS: *m/z* = 308 (M+1); Anal. calcd. (%) for $C_{13}H_7NOF_6$; C, 50.83; H, 2.30; N, 4.56; Found (%): C, 50.80; H, 2.35; N, 4.57.

(4-[3,5-*Bis*(trifluoromethyl)phenyl]oxazol-2-yl)methanol (3b): FT-IR (KBr, ν_{max}, cm^{-1}): 3360, 2981, 1602, 1507, 1461, 1222; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 (s, 1H), 8.08 (s, 2H), 7.70, (s, 1H), 5.39 (s, 2H), 4.80, (s, 1H); ^{13}C NMR



Scheme-III: Synthetic scheme for the construction of 4-[3,5-*bis*(trifluoro-methyl)phenyl]-2-substituted oxazoles [Ref. 34]

TABLE-1
PRELIMINARY SCREENING OF REACTION CONDITIONS FOR THE SYNTHESIS OF REPRESENTATIVE COMPOUND 4-[3,5-*BIS*(TRIFLUOROMETHYL)PHENYL]-2-PHENYLOXAZOLE (**3c**)

Entry	Reaction time (min)		Yield[c]	
	Reflux method[a]	Microwave method[b]	Reflux method	Microwave method
3c	120	10	83	97

[a]To a solution of 1-[3,5-*bis*(trifluoromethyl)phenyl]-2-bromoethan-1-one (**1**) (0.5 mmol) in absolute ethanol (10 mL) was added benzamide (0.5 mmol) and refluxed for 120 min by monitoring reaction progress on the thin layer chromatography.
[b]To a solution of 1-[3,5-*bis*(trifluoromethyl)phenyl]-2-bromoethan-1-one (**1**) (0.5 mmol) in absolute ethanol (10 mL) was added benzamide (0.5 mmol) and the resulting reaction mixture was exposed to microwaves for 10 min. The reaction progress was monitored on the thin layer chromatography by withdrawing samples at every 2 min from reaction vessel.
[c]Yields after purification by recrystallization method using ethanol as suitable solvent.

TABLE-2
PHYSICO-CHEMICAL CONSTANTS OF 4-[3,5-*BIS*(TRIFLUOROMETHYL)PHENYL)-2-SUBSTITUTED OXAZOLES (**3a-i**)

Compd. No.	m.f.	Molar mass	R	Reaction time (min)	Yield (%)[a,b]	m.p. (°C)	c Log P[c]
3a	$C_{13}H_7NOF_6$	307.04	CH_2=CH_2	10	93	133-134	4.4486
3b	$C_{12}H_7NO_2F_6$	311.00	CH_2-OH	10	89	112-113	2.6866
3c	$C_{17}H_9NOF_6$	357.00	C_6H_5	10	97	167-168	5.8226
3d	$C_{18}H_{12}N_2O_2F_6$	402.00	3-NH_2, 4-OCH_3 C_6H_5	10	91	183-184	5.0245
3e	$C_{17}H_7NOCl_2F_6$	424.00	2,6-diCl-C_6H_5	10	98	141-142	6.7514
3f	$C_{17}H_{10}N_2OF_6$	372.00	3-NH_2 C_6H_5	10	90	211-212	4.7756
3g	$C_{17}H_{10}N_2OF_6$	372.00	4-NH_2 C_6H_5	10	86	208-209	4.7756
3h	$C_{17}H_9N_2OClF_6$	406.00	2-NH_2, 5-Cl C_6H_5	10	92	214-215	5.6523
3i	$C_{16}H_9N_3OF_6$	373.00	2-NH_2 Pyridyl	10	94	198-199	4.3538

[a]All of the products were characterized by spectral and physical data; [b]Yields after purification by recrystallization method using ethanol as solvent; [c]c Log P was calculated using ChemDraw Professional 16

(400 MHz, DMSO-d_6): δ = 150.61, 140.11, 133.63, 132.60, 132.52, 131.89, 131.90, 129.81, 129.80, 124.72, 124.71, 123.12, 63.01; LC-MS: *m/z* = 312 (M+1); Anal. calcd. (%) for $C_{12}H_7NO_2F_6$; C, 46.32; H, 2.27; N, 4.50; Found (%): C, 46.33; H, 2.26; N, 4.54.

4-[3,5-*Bis*(trifluoromethyl)phenyl]-2-phenyloxazole (3c): FT-IR (KBr, ν_{max}, cm^{-1}): 2982, 1600, 1505, 1474, 1221; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.32 (s, 1H), 7.63-8.18 (m, 8H); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 159.39, 140.11, 139.92, 133.60, 131.80, 131.79, 130.63, 129.81, 129.80, 129.20, 128.71, 128.11, 127.51, 127.50, 124.71, 124.70; LC-MS: *m/z* = 358 (M+1); Anal. calcd. (%) for $C_{17}H_9NOF_6$; C, 57.15; H, 2.54; N, 3.92; Found (%): C, 57.13; H, 2.55; N, 3.93.

5-(4-[3,5-*Bis*(trifluoromethyl)phenyl]oxazol-2-yl)-2-methoxyaniline (3d): FT-IR (KBr, ν_{max}, cm^{-1}): 2988, 1622, 1504, 1466, 1219; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09-8.33 (m, 3H), 6.89-7.68 (m, 4H), 5.29 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 159.33, 147.43, 140.19, 139.92, 136.8, 133.6, 131.81, 131.80, 129.82, 129.81, 124.71, 124.70, 123.16, 119.21, 115.67, 115.27, 105.9, 55.82; LC-MS: *m/z* = 403 (M+1); Anal. calcd. (%) for $C_{18}H_{12}N_2O_2F_6$; C, 53.74; H, 3.01; N, 6.96; Found (%): C, 53.75; H, 2.98; N, 6.95.

4-[3,5-*Bis*(trifluoromethyl)phenyl]-2-(2,6-dichlorophenyl)oxazole (3e): FT-IR (KBr, ν_{max}, cm^{-1}): 2966, 1608, 1503, 1457, 1223; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09-8.33 (m, 3H), 7.49-7.69 (m, 4H); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 159.33, 140.1, 139.98, 137.39, 133.6, 133.60, 131.81, 131.80, 130.57, 129.81, 129.80, 128.11, 127.42, 124.71, 124.7; LC-MS: *m/z* = 425 (M+1); Anal. calcd. (%) for $C_{17}H_7C_{l2}NOF_6$; C, 47.92; H, 1.66; N, 3.29; Found (%): C, 47.93; H, 1.67; N, 3.29.

3-(4-[3,5-*Bis*(trifluoromethyl)phenyl]oxazol-2-yl)-aniline (3f): FT-IR (KBr, ν_{max}, cm^{-1}): 2976, 1615, 1511, 1481, 1214; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.08-8.33 (m, 3H), 7.69, (s, 1H), 6.74-7.51 (m, 4H), 4.62 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 159.35, 148.90, 140.12, 139.95, 133.67, 131.81, 131.80, 130.13,129.80, 127.71, 126.90, 124.70, 123.11, 118.79, 117.56, 114.22; LC-MS: *m/z* = 373 (M+1); Anal. calcd. (%) for $C_{17}H_{10}N_2OF_6$; C, 54.85; H, 2.71; N, 7.53; Found (%): C, 54.84; H, 2.72; N, 7.54.

4-(4-[3,5-*Bis*(trifluoromethyl)phenyl)oxazol-2-yl)-aniline (3g): FT-IR (KBr, ν_{max}, cm^{-1}): 2977, 1611, 1521, 1479, 1224; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.08-8.33 (m, 3H), 7.69 (s, 1H), 6.59-7.61 (m, 4H), 5.34 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): ν = 159.36, 145.67, 140.10, 133.60, 132.10, 131.81, 131.80, 129.85, 128.39, 124.71, 124.70, 120.60, 115.12; LC-MS: *m/z* = 373 (M+1); Anal. calcd. (%) for $C_{17}H_{10}N_2OF_6$; C, 54.85; H, 2.71; N, 7.53; Found (%): C, 54.86; H, 2.70; N, 7.57.

2-(4-[3,5-*Bis*(trifluoromethyl)phenyl)oxazol-2-yl)-4-chloroaniline (3h): FT-IR (KBr, ν_{max}, cm^{-1}): 2981, 1605, 1518, 1481, 1207; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.08-8.33 (m, 3H), 7.69 (s, 1H), 6.93-7.82 (m, 3H), 5.79 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 159.33, 143.37, 140.10, 139.90, 133.62, 131.81, 131.80, 129.81, 129.80, 129.63, 128.87, 128.32, 124.71, 124.70, 124.56, 123.10, 118.20; LC-MS: *m/z* = 407 (M+1); Anal. calcd. (%) for $C_{17}H_9N_2OF_6Cl$; C, 50.20; H, 2.23; N, 6.89; Found (%): C, 50.22; H, 2.24; N, 6.90.

6-(4-[3,5-*Bis*(trifluoromethyl)phenyl)oxazol-2-yl)pyridin-2-amine (3i): FT-IR (KBr, ν_{max}, cm^{-1}): 2958, 1609, 1511, 1451, 1214; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.08-8.33 (m, 3H), 7.69 (s, 1H), 6.73-7.50 (m, 3H), 6.32 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 159.11, 157.30, 156.68, 140.1, 139.96, 139.57, 133.60, 131.81, 131.80, 129.81, 129.80,

124.71, 124.70, 123.10, 113.67, 105.41; LC-MS: *m/z* = 374; Anal. calcd. (%) for $C_{16}H_9N_3OF_6$; C, 51.49; H, 2.43; N, 11.26; Found (%): C, 51.48; H, 2.42; N, 11.27.

RESULTS AND DISCUSSION

The main synthon require for the construction of proposed title compounds (**3a-i**) is 1-[3,5-*bis*(trifluoromethyl)phenyl]-2-bromoethan-1-one (**2**) and its synthetic scheme is described in **Scheme-II**. The structural elucidation of synthon **2** is achieved by FT-IR, NMR and single crystal X-ray method. Purification of the intermediate **2** was achieved by recrystallization method using aqueous methanol. Yield of the intermediate **1** was 62 %, purity was ascertained by HPLC and it was found to be over 99.4 %. Synthesis of 2,4-disubstituted 1,3-oxazole analogues (**3a-i**) is highlighted in **Scheme-III**. Synthesis of substituted alkyl, aryl and heteroaryl amides was achieved by following our previous report as indicated in **Scheme-I** [30]. Molecular ion peak 333 (M^+) in LC-MS spectra was in compliance with molecular weight of intermediate **2**. In FT-IR spectra of title compound **3b**, a broad peak was observed at 3360 cm^{-1}, which corresponds to hydroxy group. Molecular ion peaks of the title compounds (**3a-i**) were in good agreement with proposed molecular weight according to the LC-MS spectra and elemental analysis results were within ± 0.04 % of the calculated values. c Log P of 2,4-disubstituted 1,3-oxazole analogues (**3a-i**) was calculated using ChemDraw Professional 16 and found to be in the range of 2.6866-6.7514. The compounds **3b** and **3e** were constructed using polar and halogenated non-polar amide and their c Log P was 2.6866 and 6.7514, respectively.

Conclusion

Herein, synthesis and structural elucidation of new series of 4-[3,5-*bis*(trifluoromethyl)phenyl]-2-substituted oxazoles (**3a-i**) has been described. Initially synthesis of representative compound **3c** was started by conventional reflux and microwave method. It was found that microwave method influenced the product yield and reduced the reaction time at 97 % and 10 min, respectively. Remaining compounds **3a**, **3b**, **3d-i** have been synthesized by microwave assisted method and found the product yield in the range of 86-98 %. Functional groups on polar to non-polar aromatic/heteroaromatic amides did not interfere in the construction of 2,4-disubstituted 1,3-oxazole analogues (**3a-i**).

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