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Synthesis and Biological Activity of Some Newer Heterocycles

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ABSTRACT

Oxadiazoles are an important class of heterocyclic compounds that are known to possess important pharmacological and antimicrobial properties. chromenes are also known to possess antimicrobial properties. 1, 3, 4-chromeno oxadiazoles, 6-chloro-3- (5-phenyl-1,3,4-oxadiazol-2-yl)-2-(trifluoromethyl)-2H-chromen-2-ol and its derivatives containing synthesis and characterise by spectroscopy. The synthesized compounds were screened for antimicrobial activity found prominent antimicrobial is not.

Key words: Chromeno Oxadiazoles. Oxadizole Chromanooxadizole, Antimicrobial.

I. INTRODUCTION

Different chromeno oxadizole and their derivative were synthesize according to scheme. Their melting point were checked in capillary tube and their structure were conform by NMR, GCMS, IR and UV Spectroscopy.

Synthesis of Ethyl 6-chloro-2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate(3):
A mixture of 5-Chlorosalicyaldehyde (**1**) (1.00 g, 6.4 m mol), Ethyl-4, 4, 4 tri fluro acetoacetate(**2**) (1.424 mL, 6.4 m mol), piperidine(63 µL,0.64mmol) in ethanol (20 mL) was refluxed in an oil bath at93 ^{0}C for 4 hours by stirring under inert nitrogen atmosphere. The progress of the reaction was monitored by TLC using 20 % ethyl acetate- hexane solvent system. The yellow solution turned dark brown. The compound was purified by column chromatography using hexane.

(Yield: 71 %), M.P. (132-135^{0}C)
IR (cm^{-1}): 3,314, 1,700, 1,636, 1,565, 1,460.
^{1}H NMR (107 MHz, Chloroform-d) δ 7.74 (dd, J = 2.0, 1.0 Hz, 1H), 7.56 – 7.25 (m, 2H), 7.00 (d, J =7.5 Hz, 1H), 4.72 – 3.93 (m, 2H), 2.20 (s, 1H), 1.27 (t, J = 5.9 Hz, 3H).
^{13}C NMR (CDCl3, 75 MHz) (δ): 13.9, 62.7, 95.4, 35.1, 116.0, 117.4, 118.7, 122.2, 127.6, 128.6, 133.4,137.9, 151.0, 166.4;
^{19}F-NMR (δ):-87.02 (3F)
HRMS: calc d.Form/z (C13H10ClF3O4 + Na)+: 345.0118; found: 345.0135.

Synthesis of 6-chloro-2-hydroxy-2-(tri fluoro methyl)-2H-chromene-3-carboxylic acid (**4**): The ester compound (**3**) (3.22 g, 0.01 m mol) was dissolved in 20 mL of methanol. NaOH (2 g) dissolved in30 mL water was added slowly to the ester solution. The reaction mixture was refluxed for 4 hours. The reaction progress was monitored by TLC (solvent: 25% ethyl acetate- hexane). After cooling, concentrated HCl (5 mL) was added to give a white crystalline precipitate which was filtered and recrystallized by cold water.

(Yield: 74 %), M.P. (154-158^{0}C)
IR (cm^{-1}): 3314, 1700, 1690, 1636, 1565.
^{1}H NMR (500 MHz, Chloroform-d) (δ): 9.45 (s, 1H), 7.79 (dd, J = 2.0, 1.0 Hz, 1H), 7.72 (d, J = 0.9Hz, 1H), 7.45 (dd, J = 7.5, 2.0 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 2.44 (s, 1H).

^{13}C NMR (125 MHz,) (δ): 168.80 (d, J = 8.6 Hz), 136.17 (d, J = 5.4 Hz), 130.18, 128.81, 127.29,124.50, 122.36, 120.21, 118.07, 117.68, 117.27, 99.03, 98.39.
^{19}FNMR δ: -87.02(3F).
HRMS: calc d.form/z ($C_{11}H_6ClF_3O_4$+ Na)$^+$: 317.611; found: 317.572.

General method for the synthesis of hydrazides (6a-f):-

In 50mL round bottom flask, a mixture of methyl benzoate (**5a-f**) (0.01mol) in 50mL absolute ethanol was added to hydrazine hydrate (99 %) (0.025 mol, 2.5mL) and the reaction mixture was refluxed for3 h. After 2 h of hours, a yellow solid started depositing on the sides of the round bottom flask. After the completion of the reaction, a yellow solid product that was obtained was filtered, washed with cold ethanol, dried and recrystallized from ethanol (yield 90 %)

(**6a**):(Yield: 86 %), M.P. (97-99^{0}C)
^{1}H NMR (500 MHz, Chloroform-d) (δ): 7.76 – 7.69 (m, 2H), 7.45 (s, 1H), 7.42 – 7.34 (m, 2H), 7.34 –7.27 (m, 1H), 4.00 (s, 2H).
^{13}C NMR (125 MHz,) (δ):169.80, 134.20, 131.87, 128.60, 128.34.

(**6b**):(Yield: 64 %), M.P. (86-89^{0}C)
^{1}H NMR (500 MHz, Chloroform-d) (δ): 7.82 – 7.75 (m, 2H), 7.57 – 7.51 (m, 2H), 7.45 (s, 1H), 4.00(s, 2H).
^{13}C NMR (125 MHz,) (δ): 164.70, 136.75, 131.90, 128.70, 128.30.

(**6c**):(Yield: 77 %), M.P. (95-96^{0}C)
^{1}H NMR (500 MHz, Chloroform-d) (δ): 7.71 – 7.65 (m, 2H), 7.44 (s, 1H), 7.00 – 6.94 (m, 2H), 4.00(s, 2H), 3.80 (s, 3H).
^{13}C NMR (125 MHz,) (δ): 165.80, 162.21, 128.82, 125.45, 113.17, 55.35.

(**6d**):(Yield: 66%), M.P. (97-98^{0}C)
^{1}H NMR (500 MHz, Chloroform-d) (δ): 7.88 – 7.81 (m, 2H), 7.45 (s, 1H), 7.30 – 7.21 (m, 2H), 4.00(s, 2H)
^{13}C NMR (125 MHz, Chloroform-d) (δ): 166.83, 165.76, 163.75.

(**6e**):(Yield: 76%), M.P. (99-100^{0}C)
^{1}H NMR (500 MHz, Chloroform-d) (δ): 8.14 (dt, J = 7.4, 5.7 Hz, 1H), 7.63 (s, 1H), 7.12 – 7.01 (m,2H), 4.00 (s, 2H).
^{13}C NMR (125 MHz, Chloroform-d) (δ): 161.88, 113.58 (d, J = 6.5 Hz).

(**6f**):(Yield: 87%), M.P. (94-95^{0}C)
^{1}H NMR (500 MHz, Chloroform-d) (δ): 8.37 – 8.31 (m, 2H), 8.03 – 7.97 (m, 2H), 7.46 (s, 1H), 4.00(s, 2H).
^{13}C NMR (125 MHz, Chloroform-d) (δ): 166.83, 148.41, 134.04, 129.22, 125.51.

General method for the synthesis of chromeno oxadiazoles (7a-f):-

The carboxylic acid (**4**) (0.01mmol) and hydrazide derivative (**6a-f**) (0.01mmol) were refluxed together with $POCl_3$(5mL) for 15h. The progress of the reaction was monitored by TLC (20%ethylacetate-hexane). The yellow colour solution turned orange green. The reaction mixture was cooled by addition of ice cold water and was made basic by adding conc. Na_2CO_3.The resulting solid was filtered. The compound was purified by column chromatography using hexane as the solvent.

(**7a**):(Yield: 44 %), M.P. (166-169^{0}C)
IR cm^{-1}: 3610, 3203, 2690,1977,1873,1717, 1637, 1320,890.
^{1}H NMR (500 MHz, Chloroform-d) (δ): 8.08 (m, 2H), 7.59 (m, 2H), 7.45 (m, 2H), 7.08 (dd, J = 7.5,2.0 Hz, 1H), 6.94 (d, J = 1.0 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 2.21 (s, 1H).

^{13}C NMR (125 MHz, s) (δ): 166.99, 165.23, 139.98, 139.95, 139.94, 131.14, 130.18, 128.87, 127.25,124.89, 124.50, 122.36, 120.21, 118.07, 117.68, 117.27, 104.65.
^{19}F-NMR δ: -87.02 (3F)
HRMS: calcd for m/z (C18H10ClF3N2O3 + Na)$^+$:417.766; found: 416.788

(**7b**):(Yield: 50 %), M.P. (171-173^{0}C)
IR (cm^{-1}): 3586, 3202,1636, 1565, 1334,894
^{1}H NMR (500 MHz, Chloroform-d) (δ): 7.48 – 7.42 (m, 2H), 7.41 – 7.34 (m, 2H), 7.07 (dd, J = 7.4,1.9 Hz, 1H), 6.93 (d, J = 1.1 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 2.21 (s, 1H).

^{13}C NMR (125 MHz,) (δ): 166.98 (d, J = 1.8 Hz), 165.23, 139.94 (d, J = 3.7 Hz), 136.69, 130.18,129.70, 128.81, 128.20, 127.29, 126.02, 122.36, 120.21, 117.68, 117.27.
^{19}F-NMR δ: -87.02

(7c):M.P. (182-183^{0}C)
IR (cm^{-1}): 3587,3059,2308,2157,1503,1443,1321,1293,1227,813
^{1}H NMR (500 MHz, Chloroform-d) (δ): 7.41 – 7.34 (m, 3H), 7.20 – 7.13 (m, 2H), 7.07 (dd, J = 7.5,2.0 Hz, 1H), 6.91 (d, J = 1.1 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 3.80 (s, 3H), 2.21 (s, 1H).

^{13}C NMR (125 MHz) (δ): 166.98 (d, J = 1.8 Hz), 165.23, 162.96, 139.94 (d, J = 3.9 Hz), 130.18,128.81, 127.29, 124.48, 122.36, 120.21, 119.02, 117.68, 117.27, 115.00, 55.35.
^{19}F-NMR δ:- 87.02
HRMS: calcd for m/z ($C_{18}H_9ClF_3N_2O_4$+ Na)$^+$:447.004; found: 447.889

(**7d**):M.P. (162-163^{0}C)
IR (cm^{-1}): 3630, 3173,1634,1487,1346,1326.
^{1}H NMR (500 MHz, Chloroform-d) (δ): 7.55 – 7.47 (m, 2H), 7.38 (dd, J = 2.1, 1.1 Hz, 1H), 7.28 –7.19 (m, 2H), 7.07 (dd, J = 7.5, 2.0 Hz, 1H), 6.93 (d, J = 1.0 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 2.22 (s,1H).
^{13}C NMR (125 MHz,) (δ): 166.98 (d, J = 1.8 Hz), 166.47, 165.23, 164.46, 139.96 (d, J = 5.4 Hz), 130.18, 128.81, 127.29, 124.50, 123.64, 122.36, 120.21, 118.07, 117.68, 117.27, 104.65.
^{19}F-NMR δ: -87.02 (3F),-115.46(IF)
HRMS: calcd. form/z ($C_{18}H_9ClF_4N_2O_3$ + Na)+: 435.12; found: 435.12

(**7e**):M.P. (159-160 ^{0}C)
IR (cm^{-1}): 3631, 3183,1630,1487,1346, 1326.
NMR (500 MHz, Chloroform-d) (δ): 7.53 – 7.44 (m, 1H), 7.38 (dd, J = 2.1, 1.0 Hz, 1H), 7.07 (dd, J =7.5, 2.0 Hz, 1H), 7.01 – 6.94 (m, 2H), 6.92 (d, J = 1.1 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 2.22 (s, 1H).

^{13}C NMR (125 MHz) (δ): 166.98 (d, J = 2.2 Hz), 160.99 (d, J = 12.0 Hz), 139.95 (t, J = 2.6 Hz),130.18, 128.81, 127.29, 124.50, 122.36, 120.21, 118.07, 117.68, 117.27, 106.61, 104.60 (d, J = 13.0Hz).
^{19}F-NMR δ: -87.02(3F),-112.06(1F),-134.13(1F).
HRMS: calcd. form/z ($C_{18}H_8ClF_5N_2O_3$ + Na)$^+$: 452.1118; found: 451.882

(7f):M.P. (165-167^{0}C)
IR (cm–1): 3314, 1636, 1542, 1460, 1335, 1320.
^{1}H NMR (500 MHz, Chloroform-d) (δ): 8.44 – 8.38 (m, 2H), 7.94 – 7.87 (m, 2H), 7.40 (dd, J = 2.0,1.0 Hz, 1H), 7.09 (dd, J = 7.5, 2.0 Hz, 1H), 6.95 (d, J = 1.1 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 2.22 (s,1H).
^{13}C NMR (100 MHz) δ 166.98 (d, J = 1.7 Hz), 165.23, 148.48, 139.96 (d, J = 5.4 Hz), 130.73, 130.19,128.63, 127.29, 125.40, 122.36, 120.21, 117.68, 117.27.
^{19}F-NMR δ: -87.02 (3F)
HRMS: calcd. form/z (C18H9ClF3N3O5 + Na)+: 462.23; found: 462.05

General procedure for testing the anti-bacterial property:

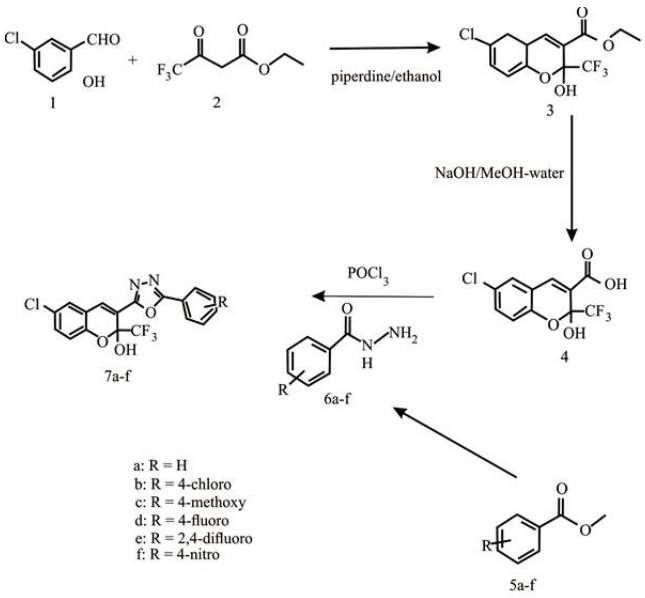
The antibacterial activities of1, 3, 4- chromeno oxadiazoles along with compounds (**3**) and (**4**) were tested against four bacterial strains, namely Staphylococcus aureus and Pseudomonas aeruginosa,which are Gram positive bacteria; and Eschericia coli and Bascillus subtilis,which are Gram negative bacteria, by cup-plate method [6]. Sterilized Nutrient agar medium was sterilized and distributed (100mL each) into two 250 mL conical flasks. They were then allowed to cool to room temperature. Bacterial sub-cultures were grown for a period of 18-24 h, which were added to each of these media and were shaken thoroughly. Thus, the bacterial cultures were uniformly distributed in the respective media. Equal quantities of the agar medium were added in to

sterilized Petri dishes. It was ensured that each 45-50 mL of the medium was present in each Petri dish. The medium was then allowed to solidify. A sterile cork borer, having a diameter of 6 mm, was used to punch the agar media to prepare the cups.

The compounds used in the study were dissolved in DMF to obtain solutions having the required concentrations (50, 100 µg/mL). 1 mL of each solution was then filled into the cups. Then, the Petri dishes were placed in an inverted position and incubated for 24-48 h at 37 ^{0}C in an incubator. Growth inhibition zones developed surrounding each cup after which, their diameters were measured (mm) and compared to standard drugs, Streptomycin and Procaine penicillin.

General procedure for testing the anti-fungal property:

The antifungal activities of1, 3, 4- chromeno oxadiazoles along with compounds (**3**) and (**4**)were tested against two fungi Aspergillus niger and Candida albicans at concentrations of 50 µg/mLand 100 µg/mL by cup-plate method [6].Griseofulvin was chosen as the standard. The potato dextro sugar medium was sterilized and then incubated for 72 h. Fungi were sub cultured and added and uniform distributed by stirring the media. Petri dishes were sterilized and labelled into which the media were poured. They were then allowed to solidify. The plates were then bored to make cups, four of them in each plate. 0.1 mL of the two test dilutions were added to two cups and the two corresponding test dilutions of the standard to the other two cups. After leaving the plates for 2-3 h to allow diffusion to take place, they were incubated at 37 ^{0}C for 24 h. The diameters of the zones of growth inhibition were measured (mm) and compared to the standard.



Scheme 1. Route for the synthesis of 1, 3, 4-chromeno oxadiazoles.

First, 5-chloro salicylaldehyde(**1**) and ethyl tri fluoro aceto acetate (**2**) were reacted by Knoevenagel condensation according to a reported procedure [19],to give an ester, ethyl 6-chloro-2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate (**3**). .The formation of the products was confirmed by comparison of the analytical data in the case of (**3**) with the reported data. The IR spectra of showed absorption bands at 3314 cm-1 for free OH,1700cm^{-1}for CO in ester group. The^{1}H NMR spectra gave triplet at δ1.27 and multiplet at δ 4.72 – 3.93 which shows the presence of 3H and 2H next to the ester group. The ^{19}F NMR spectra exhibited one signalδ-87.02ppm indicating the presence one type of fluorine atoms. The ester was further hydrolyzed to its corresponding carboxylic acid (**4**) using NaOH.Each of the aromatic esters (**5a-f**) was reacted with hydrazine hydrate to obtain the corresponding hydrazides (**6a-f**). Compound (**4**) was reacted with each of the hydrazides with POCl3 to obtain the required 1, 3, 4-oxadiazoles (**7a-e**).The ^{1}NMR of (**7a**) shows a multiplet at δ 8.808, 7.59, and7.45confirming the presence of the aromatic ring attached to oxadiazolering while13C spectra showed peaks at 166.99 and 166.92 indicting the presence of two carbons in the oxadiazolering. The 13Cspectrum of (7c) has a singlet appearing at δ3.808, which indicated the presence of methoxy group in the aromatic ring.

The19F spectra of (**7d**) showed two signals at δ-87.07,-115.46 while ^{19}F spectra of(**7e**) showed three signals atδ -87.07,-112.6 ,-134.13.These results confirms that the fluorine atoms are in different environments in the novel compounds. The IR spectral studies of (**7f**) showed the absorption band at 1542cm^{-1}indicating the N-O asymmetric stretching of NO2group present in aromatic ring.

Table 1. Screening of the compounds for anti-bacterial property.

Compound	Gram positive bacteria				Gram negative bacteria			
	S. aureus		B. subtillus		E. coli		P. aeruginosa	
	50 µg/ mL	100 µg/ mL	50 µg/ mL	100 µg/ mL	50 µg/ mL	100 µg/ mL	50 µg/ mL	100 µg/ mL
3	8	11	7	10	7	11	8	10
4	9	13	8	11	9	12	7	11
7a	10	14	11	15	13	17	12	15
7b	12	16	10	17	11	15	10	15
7c	12	17	11	16	12	15	13	15
7d	13	19	16	20	15	19	14	20
7e	19	25	20	25	19	21	17	19
7f	15	17	14	17	13	17	12	18
Streptomycin					21	26	21	26
Procaine penicillin	22	27	23	28				

The results of the anti-bacterial screening are presented in table 1. From the table, it can be seen that compounds (**3**) and (**4**) exhibited some antibacterial property. However, the activities of the chromeno oxadiazoles (**7a-f**) were significantly higher as compared to compounds (**3**) and (**4**). This shows that the introduction of an oxadiazole moiety increased the anti-bacterial properties substantially.The substituents on the aromatic ring had an effect on the anti-bacterial properties. Compounds (**7a**, **7b**, **7c**,and **7f**) showed moderate anti-bacterial activities against all the four strains. The fluoro substituents showed activities better than the other substituents. This was consistent with the results of a previous study [6]. The 2, 4- difluoro substituent (**7e**) showed the best activity against all the bacterial strains. The activities of (**7e**) were comparable to standard antibiotics, such as streptomycin and procaine penicillin.

Table 2. Screening of the compounds for anti-fungal property

Compound	A. niger		C. albicans	
	50 µg/ mL	100 µg/ mL	50 µg/ mL	100 µg/ mL
3	7	11	10	19
4	7	13	11	17
7a	10	15	9	17
7b	11	16	11	19
7c	11	14	10	16
7d	14	20	16	21
7e	17	26	17	26
7f	14	19	16	22
Griseofulvin	20	35	21	36

The results of the anti-fungal screening are presented in table 2. The results of the antifungal screening were similar to the antibacterial screening. All the compounds showed anti-fungal activity. The antifungal activities of the chromeno oxadiazoles (**7a**-**7f**) were considerably higher than that of compounds, which again indicated that the incorporation of the oxadiazole ring had a positive effect on the anti-fungal properties. The effects of the different substituents on the anti-fungal properties were also studied. The chromeno oxadiazoles that contained a 4-chloro substituent (**7b**) and a 4-nitrogroup (**7f**) showed good anti-fungal properties. However, the chromeno oxadiazoles that contained fluoro substituents showed very good anti-fungal properties. Amongst all the chromeno oxadiazoles,the difluoro compound showed the best anti-fungal activity against both the fungal strains.

II. CONCLUSIONS

Novel 1,3,4- chromeno oxadiazoles were synthesized using a simple multi-step strategy in good yields. The synthesized compounds were well characterized and tested for their antibacterial and antifungal activities. The results were promising as many of these 1,3,4-chromeno oxadiazoles showed good activities. The fluoro-substituted compounds showed the greatest activities. These results give an insight into the structure-property relationships, which are tremendously important for the design of further new antimicrobial compounds.

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