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Synthesis, Characterization of Derivatives Synthesized by the Condensation of 7-Bromo-9,9-Dimethyl-9H-Fluorene-2-Carboxylic Acid, Benzo[D]Thiazole-2-Amine, 3-Phenoxy-N-Phenylbenzenamine and Pyridine

Abstract

A newly synthesized target molecules of N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide, N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3 phenoxyphenyl)(phenyl)amino)-9H-fluorene-2-carboxamide, and N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl)(phenyl) amino)-9,9-dimethyl-9H-fluorene-2-carboxamide have been synthesized by environment friendly and fast microwave assisted technic and checkedtheir in vitro as potential antimicrobials activity. The synthesized molecules showed the good and scenic antimicrobial and anti-inflammatory activity. This method offers several advantages such as mild reaction condition, high yield, shorter reaction time, and environment friendly, simple experimental procedure.

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Introduction

Heterocyclic compound is one which accomplishes a cyclic structure with at least two different sorts of hetero atoms in the ring. Heterocyclic compounds are very widely distributed in nature and are necessary to life in various ways. A number of derivatives of heterocyclic compounds containing nitrogen and sulphur atom serve as a comical and mutable scaffolds for experimental drug design [1]. Number of heterocyclic nuclei, such as 1,3,4-thiadiazole, benzimidazole, 1,3,5-triazine, and benzothiazole have been recently powwow as antimicrobial agents [2,3]. In fact, benzothiazole derivatives possess a wide variety spectrum of biological applications such as antitumor, schictosomicidal, anti-inflammatory, anticonvulsant, antidiabetic, antipsychotic, diuretic, and antimicrobial activities [4-6].

2-Aminobenzothiazoles show high reactivity. They have beenbroadly used as reactants or reaction intermediates since the NH_2 and endocyclic N functions are suitably situated to enable reactions with common bis electrophilic reagents to form a variety of fused heterocyclic compounds. 2-amino benzothiazole compounds have a wide application and are opined one of an important type of fusedthiazoles. The chemistry of 2-amino benzothiazolecompounds hasmore attention to increasing interest in both synthetic organic chemistry and biological areas [7]. A number of 2-amino benzothiazolederivatives were synthesized by two manners. The first one is Hugersch's method using the reaction of thiourea derivative with bromine in acetic acid. The second one method was using the direct reaction of amine derivatives with potassium thiocyanate and bromine in glacial acetic acid. In 1887 Hoffmann was introduced the cyclizations of 2-amino thiophenol to 2-amino benzothiazole. The formation of 2-anilineobenzothiazole from the reaction of 2-amino thiophenol and phenyl isothiocyanate was noted by Hoffmann.

Some important other methods for synthesize of 2-amino benzothiazole derivativesmentioned by iodobenzenamine and isothiocyanate and catalyze the reaction with copper iodide in the presence of DABCO and toluene as a solvent at 50°C [8]. Tweit, R. C. et al. prepared 2-aminobenzothiazole by the reaction of alkyl isothiocyanate and 2-aminothiol as starting material in the presence of alcohol as a solvent at reflux. Abdul Rauf et al. reported the synthesis of 2-substituted benzothiazoles by the condensation of 2-aminothiophenol with different type of fatty acid chlorides[9]. Benedi*et al.* synthesized 2-substituted-benzothiazoles using by palladium catalyzed intramolecularcycliztion of *o*-bromophenylthioureas and *o*-bromophenylthioamides. Lebedenko reported that heterocyclization of 1-phenyl thiosemicarbazide 1 with polyphosphoric acid in chlorobenzene afforded 2-aminobenzothiazole [10]. The oxidative cyclization of 4-chloro-2-(trifluoromethyl)phenylthiourea with bromine in chloroform followed by basification with $NH_3$to give 6-Chloro-4-(trifluoromethyl)-2-aminobenzothiazole [11-12]. N-(4-nitrobenzothiazol-2-yl)benzamideprepared 1-Benzoyl-3-phenylthiourea was heterocyclized by using a mixture of sodium nitrite and sulphuric acid which has been treatment with 20% H_2SO_4 and NH_2SO_3H led to the formation of 2-amino-4-nitrobenzothiazole [13]. Allen and coworkers have reported that the reaction of *p*-toluidine with sodium thiocyanate in chlorobenzene and in the presence of sulfuric acid gave thiourea. Warming thiourea with sulfuryl chloride at 50◦ C furnished 2-amino-6 methylbenzothiazole [14].

Review of Literature

In this present work, the synthesis of substituted N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide, N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3 phenoxyphenyl)(phenyl)amino)-9H-fluorene-2-carboxamide, and N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl)(phenyl)amino)-9,9-dimethyl-9H-fluorene-2-carboxamide using microwave irradiation was investigated. Microwave-Induced Organic Reaction Enhancement (MORE) chemistry hasgained popularity as a non-conventional and environmental friendly technique for rapid synthesisof researches have described accelerated organic reactions, and a large number of papers have appeared proving the synthetic utility of MORE chemistry in routine organic synthesis [15-23]. Microwave-assisted organic synthesis could help achieve high yields and clean reaction outcomes at short reaction time. Organic solvent free reaction conditions eliminate the toxicity and flammability issues associated with common solvents. Together, solvent free organic syntheses assisted by microwave irradiation have being regarded as environmentally benign methodologies [24]. In continuation of this research, the aim of study is to synthesize some novel compound of benzo thiazole and checked their antimicrobial and anti-inflammatory activity.

number of researchers i.eQiuping, D. et al. obtained 2-N-alkylbenzothiazole using starting material as 2-

Experimental Section

Materials

All compounds and chemicals were purchased from Sigma-Aldrich Chemicals and Merck and used without additional purification. Melting points were determined using an open-ended capillary tube method and are uncorrected. TLC was performed on pre-coated plastic sheets of silica gel G/UV of 0.2 mm thickness (Macherey-Nagel, Germany). The homogeneity and purity of the synthesized compounds was checked by TLC. A FT-IR spectrum was recorded on a Perkin-Elmer 1605 series FT-IR in a KBr disc. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker FT-NMR spectrophotometer using TMS as internal standard.

N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide

A combination reaction of 7-bromo-9,9-dimethyl-9H-fluorene-2-carboxylic acid (0.12mol) and Benzo[d]thiazole-2-amine (20 mL) in the presence of DMSO (65 mL) was assisted by microwave oven for 2-3 minutes at 400 Watts. The obtained mixture was transferred into crushed ice which results in precipitate. The mixture was stirred continuously overnight and filtered it. The crude obtained was dissolved in ethanol (500 ml) and formed slurred, filtered it and then recrystallized from heptane.

The physical and analytical data of $C_{23}H_{17}BrN_2OS$ (448.02) calcu.C, 61.48; H, 3.81; N, 6.23;Found: C, 61.43; H, 3.86; N, 6.70, M.P. 266^{o}C.IR (KBr)ν_{max} in cm^{-1}, 680 cm^{-1} (C—Br), 766 cm^{-1} (C—C), 1244 cm^{-1} (C—N), 1565 cm^{-1} (C=N), 3245 cm^{-1} (—NH), 1544 cm^{-1} (C=C for aromatic compound), 688 cm^{-1} (C—S—C), 3055 cm^{-1} (C—H for aromatic compound).^{1}H NMR ($CDCl_3$) δ in ppm, 9.30 (s, 1H, —NH of thiazol), 7.65-6.85 (m, 10H, Ar—H), 2.34 (m, 6H, CH_3), 9.4 (s, H, NH)^{13}C NMR in $CDCl_3$ ppm 168.63, 153.90, 150.58, 143.78, 139.60, 134.87, 130.44, 126.54, 121.77, 69.33, 57.04, 32.88.GCMS (H^+) m/e 447.02, 382.52, 315.88, 296.40, 246.74, 234.32, 219.31, 212.29, 149.12, 134.20, 111.55, 99.14, 42.12.

N-(benzo[d]thiazol-2-yl)-9, 9-dimethyl-7-((3-phenoxyphenyl)(phenyl)amino) -9H-fluorene-2-carboxamide

A solution of 3-phenoxy-N-phenylbenzenamine (0.04mol), N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide (0.04mol) and toluene (300mL) was condensed and cooled at room temperature. A mixture of Pd(dba)2 (0.43 g), dppf (diphenylphosphinoferrocene) (0.39 g) and sodium t-butoxide (5.40 g) were further added to the solution and it was assisted by microwave oven for 3-4 minutes at 400 Watts and addition of Toluene, then the organic layer was separated out and rinsed off with a saturated solution of sodium chloride and recrystallized from 1:5 ratio of toluene and heptane mixture to furnish product.

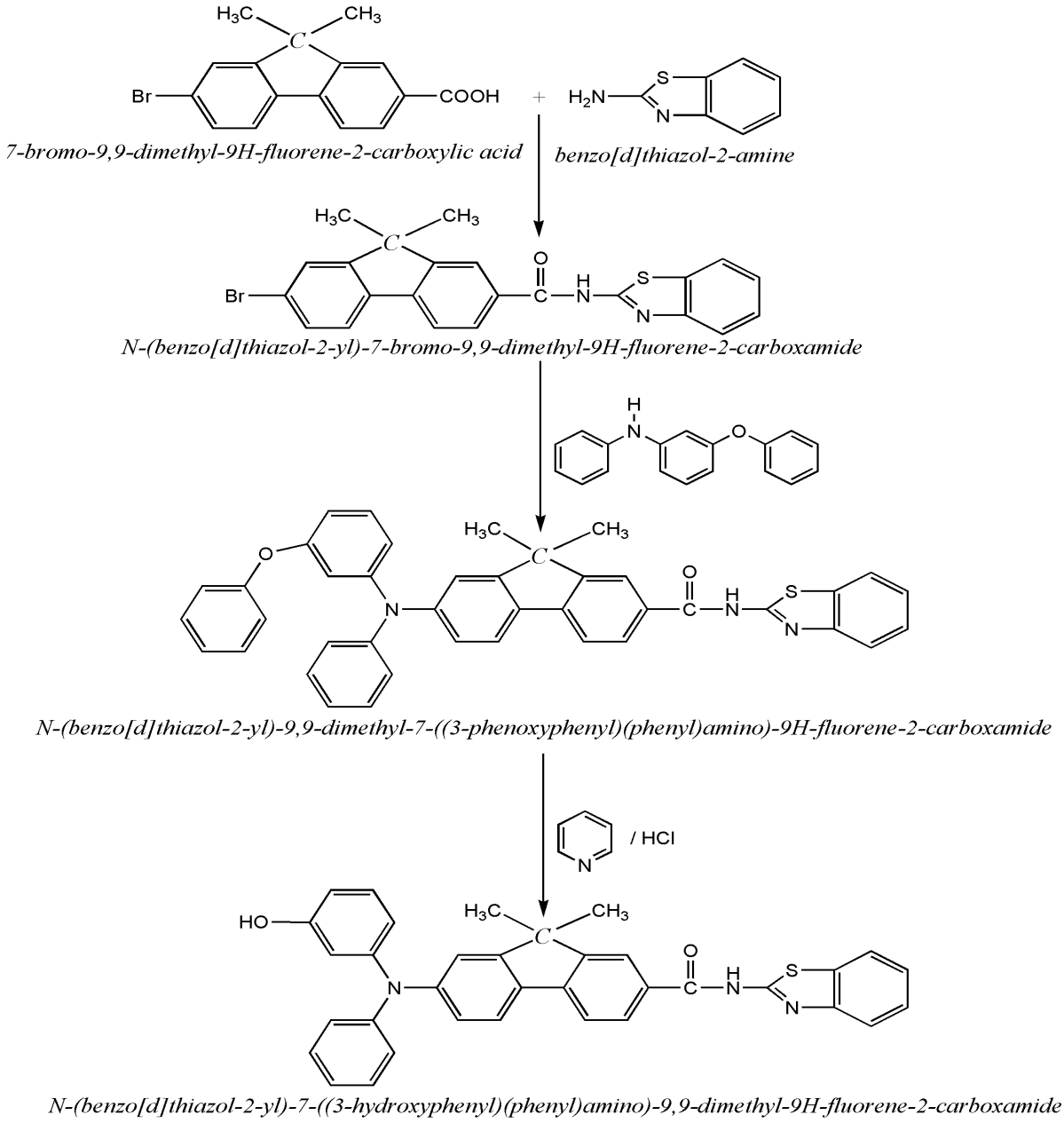
The physical and analytical data of $C_{41}H_{31}N_3O_2S$ (629.21) calcu. C, 78.19; H, 4.96; N, 6.67 Found: C, 78.20; H, 4.94; N, 6.69, M.p. 266^{o}C.IR

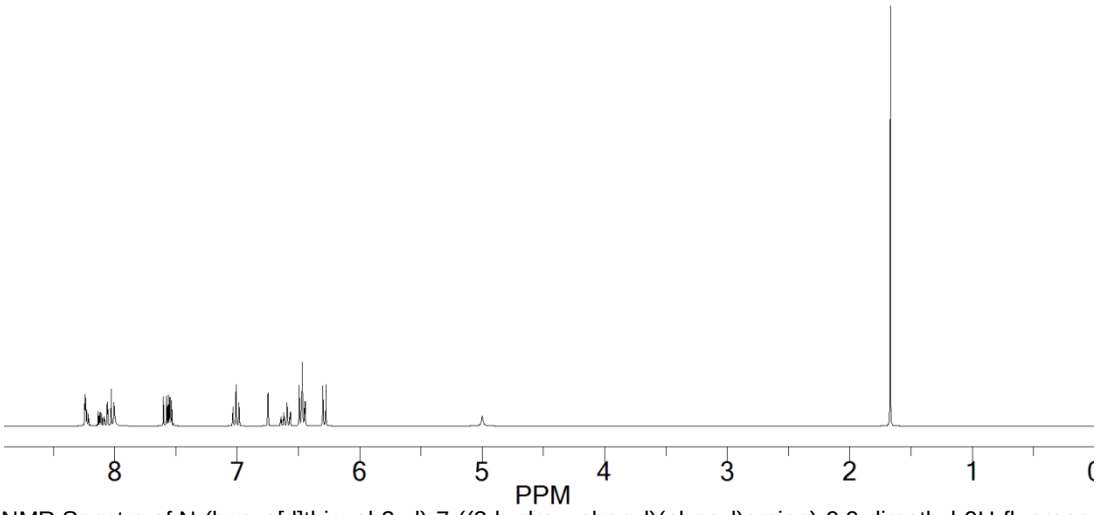
(KBr)ν_{max} in cm $^{-1}$, 685 cm^{-1} (C—S—C), 3044 cm $^{-1}$ (C—H for aromatic compound), 1575 cm $^{-1}$ (C=N), 765 cm $^{-1}$ (C—C), 1245 cm $^{-1}$ (C—N), 1050 cm $^{-1}$ (C—O), 1545 cm $^{-1}$ (C=C for aromatic compound), ^{1}H NMR ($CDCl_3$) δ in ppm, 9.30 (s, 1H, —NH of thiazol), 7.65-6.85 (m, 24H, Ar—H), 2.34 (m, 6H, CH_3).^{13}C NMR in $CDCl_3$ 168.63, 153.90, 150.58, 143.78, 139.60, 134.87, 132.32, 130.44, 129.26, 128.12, 126.54, 125.23, 121.77, 119.34, 116.68, 69.33, 57.04, 32.87.GCMS (H^+) m/e 628.21, 592.06, 488.55, 382.52, 315.88, 296.40, 246.74, 234.32, 219.31, 212.29, 149.12, 134.20, 111.55, 99.14, 42.12.

N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl) (phenyl)amino)-9,9-dimethyl-9H-fluorene-2-carboxamide:

A combination reaction of N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3-phenoxyphenyl) (phenyl)amino)-9H-fluorene-2-carboxamide (0.19 mol) and pyridine hydrochloride (0.74 mol) was assisted by microwave oven for 3-4 seconds. The reaction mixture was then transferred into warm water, continuously stirred for 30 minutes and then filtered. A slurry of the red precipitate and a dilute ammonium hydroxide solution (5 %) was stirred overnight (20 h), filtered, and the residue was recrystallized from toluene.

The analytical data of compound $C_{35}H_{27}N_3O_2S$ (553.18) calcu. C, 75.92; H, 4.92; N, 7.59Found: C, 75.91; H, 4.88; N, 7.62, M.p. 288^{o}C.IR (KBr) ν_{max} in cm $^{-1}$, 765 cm $^{-1}$ (C—C), 1245 cm $^{-1}$ (C—N), 1545 cm $^{-1}$ (C=C for aromatic compound), 685 cm^{-1} (C—S—C), 3044 cm $^{-1}$ (C—H for aromatic compound), 1575 cm^{-1} (C=N), cm-1 3434 (OH). ^{1}H NMR ($CDCl_3$) δ in ppm, 2.35 (m, 6H, CH_3), 7.75-6.75 (m, 19H, Ar—H), 9.30 (s, 1H, —NH of thiazol).^{13}C NMR in $CDCl_3$ 188.63, 169.53, 162.81, 153.90, 150.58, 143.78, 139.60, 134.87, 132.32, 130.44, 129.26, 128.12, 126.54, 125.23, 123.21, 121.77, 119.34, 116.68, 111.24, 88.43, 69.33, 57.04, 32.87.GCMS (H^+) m/e 552.18, 488.06, 409.06, 382.52, 356.88, 344.86, 315.88, 296.40, 246.74, 234.32, 219.31, 212.29, 149.12, 134.20, 111.55, 99.14, 42.12.


H3C
CH3
C
Br
COOH
+
H2N
S
N
7-bromo-9,9-dimethyl-9H-fluorene-2-carboxylic acid
benzo[d]thiazol-2-amine
O
H
N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide
O
N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3-phenoxyphenyl)(phenyl)amino)-9H-fluorene-2-carboxamide
/ HCl
HO
N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl)(phenyl)amino)-9,9-dimethyl-9H-fluorene-2-carboxamide



[1]HNMR Spectra of N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl)(phenyl)amino)-9,9-dimethyl-9H-fluorene-2-carboxamide

Results and Discussion

The target compounds were prepared by standard synthetic procedures in different steps. Initially, N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamidewas synthesized by the combination of 7-bromo-9,9-dimethyl-9H-fluorene-2-carboxylic acid and Benzo[d]thiazole-2-amine in the presence of DMSO was assisted by microwave oven under the above describe manner and used as antimicrobial and anti-inflammatory drugs. Synthesized the N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide compound and proceed the reaction forward to achieve the next target for synthesized the N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3-phenoxy-phenyl)(phenyl)amino)-9H-fluorene-2-carboxamide by the reaction of 3-hydroxydiphenylamine, N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide and toluene by the assisted microwave in the presence of a mixture of Pd(dba)2, dppf (diphenylphosphinoferrocence) and sodium t-butoxide and recrystallized from the mixture of toluene and heptane in 1:5 ratio and used as antimicrobial and anti-inflammatory agent. Next target molecules was prepared from the combination with N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3-phenoxyphenyl)(phenyl)amino)-9H-fluorene-2-carboxamide and pyridine hydrochloride assisted by microwave and recrystallized from toluene and check also the antimicrobial and anti-inflammatory activity of the synthesized target molecules and characterized by different analytical tools.

Antimicrobial Activity

According to the Clinical Laboratory Standards Institute (CLSI) guidelines [23] synthesized moleculessuch as N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide, N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3 phenoxyphenyl) (phenyl)amino)-9H-fluorene-2-carboxamide, and N-(benzo[d]thiazol-2-yl)-7-((3-hydroxy-phenyl) (phenyl)amino)-9,9-dimethyl-9H-fluorene-2-carboxamide was screened against Staphylococcus aureus, Pseudomonas aeruginosa, E. faecalis, Escherichia coliand Candida albicans, Candida parapsilosis, Candida tropicalis, Aspergillusniger for using Norfloxacin (NRF) and Fluconazole as reference drug to determine the antibacterial activity and antifungal activity respectively. The experimental results of antibacterial activity [24-26] and antifungal activity of the synthesized molecules articulated as MIC (mg/mL), are listed in Table 1. The antibacterial activity showed a variable degree of efficacy of the synthesized target molecules against different type stain of bacterial. Results showed in table 1, moleculesN-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide, and N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl)(phenyl)amino)-9,9-dimethyl-9H-fluorene-2-carboxamide are more effective against staphylococcus aureus, E. faecalis, E. Coli and Pseudomonas as reference drug Norfloxacin. The rest compound N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3 phenoxyphenyl)(phenyl)amino)-9H-fluorene-2-carboxamide is equal effective against Staphylococcus aureus like as reference drug and E. faecalis, E. Coli and Pseudomonas aeruginosa showed moderate activity compared to Norfloxacin.As it seen in *Table 1* compounds N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide, N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-(3phenoxyphenyl)(phenyl) amino)-9H-fluorene-2-carboxamide, and N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl)(phenyl) amino)-9,9-dimethyl-9H-fluorene-2-carboxamide have pronounced antifungal activity and exceed that of fluconazole using as a reference drug for antifungal activity. All synthesized compounds are less effective against the Candida albicans and Candida parapsilosis as reference drug. The results suggest that all synthesized compounds may be worth studying further in terms of their antimicrobial activity.

Anti-Inflammatory Activity

In the recent years a number of benzothiazole derivatives have been synthesized and studied to possess anti-inflammatory activity. The activity of newly synthesized target molecules

compared to indomethacin as a reference compound was measured before and 4 hours after carrageenan injection. Percent of the oedema inhibition was calculated as regards saline control group and potency was calculated as regards the percentage of the change of Indomethacin as a reference drug and tested molecules, as shown in Table 2.All the tested compounds showed aappropriate inhibition of oedema size ranging 49.11% for compound N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide, 65.65% for compound N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3 phenoxyphenyl) (phenyl)amino)-9H-fluorene-2-carboxamide, 75.10 % for compound N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl) (phenyl) amino)-9,9-dimethyl-9H-fluorene-2-carboxamideand 79.62% for Indomethacin using as reference drug. In activity relationship point of view, the anti-inflammatory activity of the N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3 phenoxyphenyl)(phenyl)amino)-9H-fluorene-2-carboxamideand N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl)(phenyl)amino)-9,9-dimethyl-9H-fluorene-2-carboxamide was found to be good anti-inflammatory activity.

Conclusion

The penetration of microwave ovens in the pharmaceutical science has becomes very attractive and formedto carry out many transformations of chemicals with greater capacity. At present time, microwave is a major tool for organic synthesis chemistry as the sources of energy and environment friendly [16]. In this present work, we have used microwave for synthesis of targets molecules under the aforesaid described conditions and found the scenic results. The synthesized target molecules have checked and recrystallized under the used of various analytical tools for characterization. The synthesized molecules N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide, N-(benzo[d] thiazol-2-yl)-9,9-dimethyl-7-((3-phenoxyphenyl) (phenyl)amino)-9H-fluorene-2-carboxamide, and N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl)(phenyl) amino)-9,9-dimethyl-9H-fluorene-2-carboxamide have been shown good microbial and anti-inflammatory activity.

Table 1 MIC measures for N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide, N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-(3phenoxyphenyl) (phenyl)amino)-9H-fluorene-2-carboxamide, N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl)(phenyl) amino)-9,9-dimethyl-9H-fluorene-2-carboxamide and reference Drug for antibacterial activity

Compound	MIC					
	S. Aureus	E. faecalis	E. Coli	P. aeruginosa	C. albicans	C. parapsilosis
N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide,	ME	ME	ME	ME	LE	LE
N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3-phenoxy-phenyl)(phenyl)amino)-9H-fluorene-2-carboxamide	SE	MdE	MdE	MdE	LE	LE
N-(benzo[d]thiazol-2-yl)-7-(3-hydroxyphenyl)(phenyl) amino)-9,9-dimethyl-9H-fluorene-2-carboxamide	ME	ME	ME	ME	LE	LE
Norfloxacin	62.5	2.95	4.9	62.5	--	--
Fluconazole	--	--	--	--	250	250

NOTE: ME-More effective, LE-Less effective, SE-Same effective, MdE- Moderate effective.

Table 2: Anti-inflammatory activity of N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide, N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3 phenoxyphenyl) (phenyl)amino)-9H-fluorene-2-carboxamide, N-(benzo[d]thiazol-2-yl)-7-((3-hydroxy-phenyl) (phenyl)amino)-9,9-dimethyl-9H-fluorene-2-carboxamideon carrageen an induced oedema of laboratory mice

Compound	Oedema Volume (ml)			
	Dose (mg/kg)	Zero Min.	4 hour	% Inhibition after 4 hours
Control	Normal saline	29.83±1.23	148.34±2.35	--
N-(benzo[d]thiazol-2-yl)-7-bromo-9,9-dimethyl-9H-fluorene-2-carboxamide,	250 mg/kg	32.23±1.44	75.47±1.22	49.11
N-(benzo[d]thiazol-2-yl)-9,9-dimethyl-7-((3-phenoxy-phenyl)(phenyl) amino) -9H-fluorene-2-carboxamide	250 mg/kg	36.83±1.23	50.94±1.42	65.65
N-(benzo[d]thiazol-2-yl)-7-((3-hydroxyphenyl) (phenyl)amino)-9,9-dimethyl-9H-fluorene-2-carboxamide	250 mg/kg	25.33±1.47	36.93±1.22	70.85
Indomethacin	10 mg/kg	27.83±1.72	30.22±1.57	79.62

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