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COMPARATIVE STUDY OF CONVENTIONAL AND MICROWAVE-ASSISTED SYNTHESIS OF NOVEL 6-(ARYLIDENEAMINO)BENZO[d]OXAZOL-2(3*H*)-ONES WITH POTENTIAL ANTIBACTERIAL ACTIVITY

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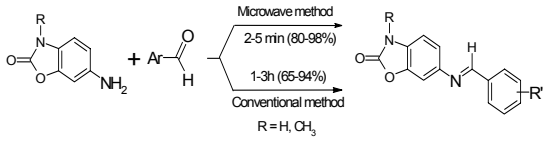
The synthesis and characterization of novel class of Schiff bases derivatives 6-(Benzylideneamino)benzo[d]oxazol-2(3*H*)-ones (**5a-d** and **6a-d**), derived from the condensation reactions of different aromatic aldehydes with 6-amino-2(3*H*)-benzoxazolone and 3-methyl-6-amino-2(3*H*)-benzoxazolone, using conventional and microwave irradiation methods was described. The structure of all newly synthesized compounds has been proven by using various spectral methods such as IR, ^{1}H-NMR and ^{13}C-NMR. The results confirmed that benzoxazolinonic amino group reacted with aromatic aldehydes to form the desired Schiff bases.



INTRODUCTION

Benzoxazolone and its derivatives are an important class of heterocyclic compounds that are known to possess a wide variety of biological properties including antibacterial, anti-HIV, and anti-inflammatory activities among others.[1-10] Thus, development and synthesis of novel compounds derived from this pharmacophore as potential chemotherapeutics, still attracts attention of organic and medicinal chemist,[11-14] and led to the discovery of a number of derivatives endowed with anti-inflammatory, analgesic, antitubercular, antibacterial, antimicrobial, antifungal, anti-HIV, anticonvulsant, normolipemic effects, and nitric oxide synthase (NOS) inhibitory activity have been described in recent years.[15-19] They are present in various natural and non-natural compounds. In industry, they have a wide range of applications such as dyes and pigments with luminescent properties, catalysis, polymer stabilizers,[20,21] corrosion inhibitors,[22] and as ligands in the organometallic compounds.[23,24] The biological activities of Schiff bases have also attracted considerable and growing attention to organic and medicinal researchers for many years, following the discovery of their importance precursors to compounds that are of such pharmaceutical interest. Schiff bases are now well known for their importance and potential applications in various biological fields, such as anticancer,[25] antimicrobial,[26,27] anti-inflammatory,[28-29] antiviral,[30] analgesic,[31] pesticidal,[32] and antioxidant[33,34] agents. Both benzoxazolone and Schiff base compounds are important structures in the medicinal and pharmaceutical fields,[35] and it has been suggested

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that the azomethine linkage might be responsible for the biological activities displayed by Schiff bases.[36]

In view of these observations, and in light of the interesting variety of biological activities seen in compounds containing benzoxazolone moiety and azomethine linkages, we have designed new compounds incorporating the above pharmacophores together in order to prepare compounds, having enhanced antimicrobial activity.

In addition, the development of eco-friendly and economic new processes of organic synthesis, which are efficient and more compatible with the environment demands, has received considerable attention because of growing environmental concerns.[37-39] A decisive contribution has occurred, when in 1986, Gedye *et al.*,[40] and Giguère and Majetich[41] have reported the benefits of irradiation microwave for the syntheses in organic chemistry. In this regard, microwave irradiations have been used extensively and successfully for the synthesis of organic compounds. In comparison with conventional thermal heating, the use of microwave irradiation has become an increasingly valuable tool in organic synthesis, since it is a versatile and facile technique applicable to a large variety of chemical reactions.[42-44] Advantage of this methodology such as enhanced rate of reaction, substantial decrease of reaction time, as well as the increased selectivity and in many cases, improved yields and high purity of the compounds, make it an attractive technique frequently used in developing synthetic methodologies, for applications in the field of drug discovery and drug development research.[45-47] Furthermore, the application of microwave technology for the synthesis of organic compounds in recent years, has opened new perspectives in organic synthesis, and offers advantages over conventional heating because of its efficiency, simplicity and as ecofriendly technique, and has served to support for the development of many reaction procedures which are environmentally friendly.[48-51]

In continuation of our interest in the field of oxygen and nitrogen heterocycles, and as part of our concern in the field of new benzoxazolone-based bioactive compounds,[52,53] we report here a comparative study concerning the synthesis of 2(3*H*)-benzoxazolones Schiff bases under microwave irradiation and conventional heating by direct reaction of 6-amino-2(3*H*)-benzoxazolone with substituted aromatic aldehydes.

Considering all these findings, in this paper we are reporting the synthesis of new benzoxazolinonic Schiff base derivatives differently functionalized on nitrogen in position **3** of the benzoxazolinonic heterocycle and aromatic ring of the aldehyde by conventional and microwave assisted methods, and their characterization through spectral data such as IR, ^{1}H-NMR and ^{13}C-NMR. Therefore, we focused our attention to the synthesis of new compounds containing imine group at position 6 of the 2(3*H*)-benzoxazolone ring (Fig. 1), in order to investigate their chemical and antibacterial activities.

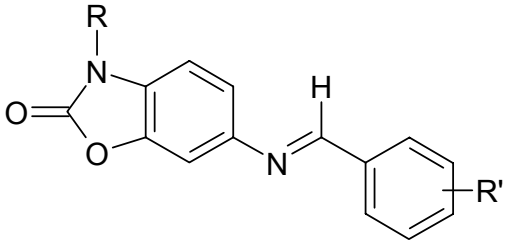


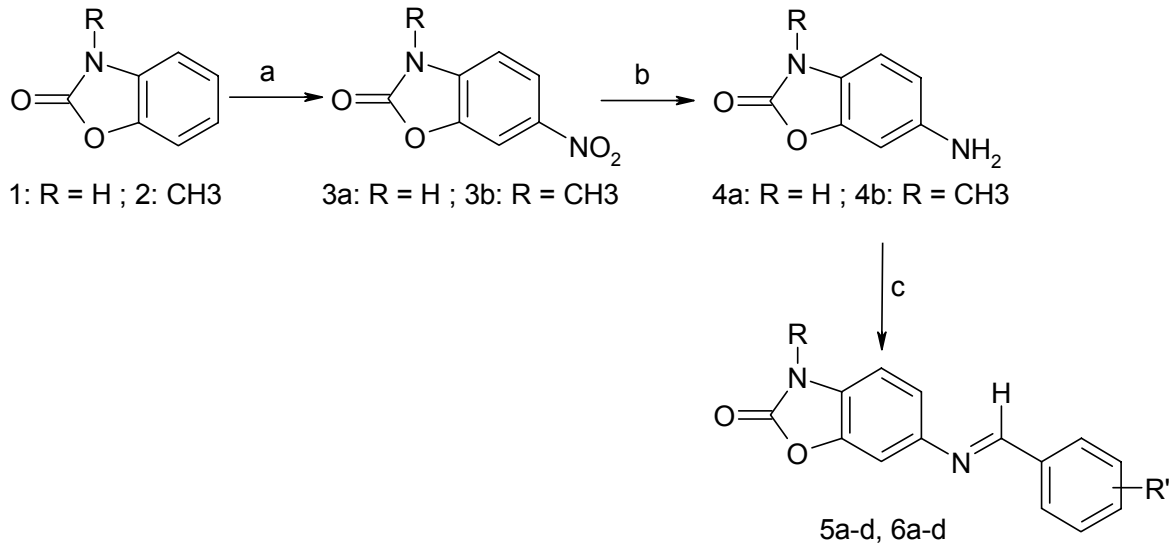
Fig. 1 – Chemical structure of 2(3*H)*-benzoxazolone Schiff base derivatives.

RESULTS AND DISCUSSION

Chemistry

In this study, novel benzoxazolinonic Schiff base derivatives were designed and synthesized via the route outlined in Scheme 1. The key intermediate 2(3*H*)-benzoxazolone (**1)** was obtained by simple reaction between two commercially available compounds 2-aminophenol and urea.[54] This step was followed by N-methylation of the intermediate (**1)** with dimethylsulfate in order to obtain 3-methyl-2(3*H*)-benzoxazolone (**2**). The described method was used,[55] and the reaction product was obtained in a quantitative yield.

According to the reported method,[56] the reaction of compounds **1** and **2** with nitric acid and acetic anhydride produced, 6-nitro-2(3*H*)-benzoxazolone (**3a**, 67%) and 3-methyl-6-nitro-2(3*H*)-benzoxazolone (**3b**, 80%), followed by reduction of the nitro function, afforded the benzoxazolinonic amines intermediates substrates (**4a**, 69%) and (**4b**, 73%) used for the next step without further purification. The structures of compounds **(3a-b)** and **(4a-b)** were confirmed by comparing their spectroscopic and physical data with that in the literature.[57]



Scheme 1 – Reagents and conditions: (a) HNO_3 (68%), acetic anhydride, -5-0°C; (b) $SnCl_2$. $2H_2O$, C_2H_5OH, 3h, reflux; (c) appropriate aldehyde derivative, acetic acid, ethanol, 1-3h, reflux.

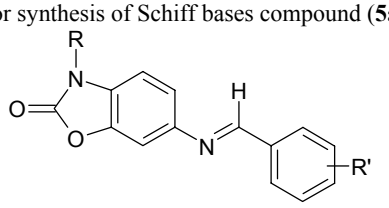
Finally, the new benzoxazolinonic Schiff base compounds (**5a-d)** and (**6a-d)** were synthesized by a series of reactions from 2(3*H*)-benzoxazolone derivatives as shown in Scheme 1. The reactions of 6-amino-2(3*H*)-benzoxazolone (**4a)** and 3-methyl-6-amino-2(3*H*)-benzoxazolone (**4b)** with the corresponding aromatic aldehyde in absolute ethanol for 1-2.5 h at reflux, in the presence of acetic acid as catalyst to obtain the desired benzoxazolinonic Schiff base derivatives in moderate to good yields. In this step, the reaction is the result of the nucleophilic attack of the nitrogen of the amine on the carbonyl of the aldehyde. This leads to the formation of carbon-nitrogen double bond (-CH=N-), and the formation of the desired imine after elimination of a water molecule.

All reactions were carried out by using conventional heating and microwave irradiation, and results were compared in Table 1. Therefore, acetic acid was preferred as solvent for all further conventional heating and microwave-assisted reactions.

All these prepared compounds were characterized for purity by thin layer chromatography (TLC), and their structures were ascertained by proton and carbon-13 nuclear magnetic resonance.

Table 1

Analytical data and comparison of time consumed and yield obtained to complete the reaction, by conventional and microwave methods for synthesis of Schiff bases compound (**5a-d, 6a-d**)



Entry	R	R'	[a]Mp (°C)	[b]Conventional Time (h)	Conventional Yield (%)	[c]Microwave Time (min)	Microwave Yield (%)	[d]Mol. F.
5a	H	H	193-194	2.5	71	2	80	$C_{14}H_{10}N_2O_2$
5b	H	2-OH	262-263	1.0	94	2	95	$C_{14}H_{10}N_2O_3$
5c	H	4-N(CH_3)$_2$	247-248	2.0	83	3	98	$C_{16}H_{15}N_3O_2$
5d	H	3,4,5-(OCH_3)	226-227	1.5	88	5	90	$C_{17}H_{16}N_2O_5$
6a	CH_3	H	180-181	2.0	82	5	85	$C_{15}H_{12}N_2O_2$
6b	CH_3	2-OH	238-239	1.0	91	3	96	$C_{15}H_{12}N_2O_3$
6c	CH3	4-N(CH_3)$_2$	285-288	2.0	65	5	95	$C_{17}H_{17}N_3O_2$
6d	CH_3	3,4,5-(OCH_3)	235-236	1.5	84	5	85	$C_{18}H_{18}N_2O_5$

[a]Melting point; [b,c]Isolated yield after silica chromatography; [d]Molecular formula.

Spectral characterization

Infrared analysis

The infrared spectra (FT-IR) of all the compounds contain a strong intensity absorption band of the azomethine group (-CH=N-) at 1602-1640 cm^{-1}, the presence of aromatic ring has been identified by their characteristic ring vibrations at 1460-1591 cm^{-1}. The presence of a peak in the range 1680-1782 cm^{-1} in all the Schiff bases was assigned to $\nu C{=}O_{oxazolinonic}$ absorption. Comparison of the IR spectral data of the Schiff base derivatives with that of the aldehyde ν(CO) and the primary amine ν(NH) showed the disappearance of $\nu(NH_2)$ and ν(CO), confirming the formation of the desired Schiff base.

NMR analysis

The structure of all synthesized Schiff bases were determined by NMR analysis, based on the analysis of H-H coupling constants as well as chemical shifts. In ^{1}H-NMR spectra, the presence of protons of -CH=N- group was confirmed by one-proton singlet at δ 8.37-8.99 ppm, while the aromatic protons of the Schiff base appear in the appropriate region at δ 6.76-8.34 ppm. The signal appearing as a singlet at δ 11.55-11.86 ppm in the ^{1}H NMR spectra of these imines is assigned to the NH group of N(3)-unsubstituted benzoxazolone. The signals due to the aliphatic protons of the methyl substituent on the N(3)-substituted benzoxazolone derivatives appear in the range δ 3.36-3.47 ppm. The absence of the benzoxazolone N-H signal at δ 11.5-12.4 ppm in the spectrum of the N(3)-substituted derivatives clearly demonstrates the formation of the desired Schiff bases in its deprotonated form.

In order to get further information the ^{13}C-NMR spectra were investigated. The ^{13}C-NMR spectrum of the exhibited signals between δ 159.3 and 170.14 ppm corresponding to the carbon of the -C=N- group. The signals observed at δ 154.30-159.34 ppm are assigned to (C=O) of lactam (oxazolinonic) and the (C-O) of oxazolinonic carbons, respectively. Methyl groups were observed between δ 28.19 and 28.34 ppm. Also, the spectrum showed peaks at 105.83–147.33 ppm corresponding to carbons of the phenyl ring. Details of the experimental protocols used are shown in the experimental section.

EXPERIMENTAL

Material and methods

Melting points were determined on an electrothermal 9200 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr discs with a FT-IR-8300 Shimadzu spectrometer. Both ^{1}H and ^{13}C-NMR spectra were determined on a Brucker AC 200 spectrometer using $CDCl_3$ and d_6-dimethylsulfoxide (DMSO-d_6) solution using tetramethylsilane (TMS) as internal standard, respectively. The chemical shifts are reported in parts per million (δ scale) and all J values are in hertz. Spin multiplicities are given with the following notations: s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Progress of reactions and the purity of the compounds were checked by thin-layer chromatography (TLC) using cyclohexane/ethyl acetate (2:8) as eluent. Column chromatography was performed on silica gel (Kieselgel 60 F-254, 0.20 mm) using cyclohexane and ethyl acetate. The synthesis, physical and analytical properties of compounds: 2(3*H*)-benzoxazolone **(1)** and 3-methyl-2(3*H*)-benzoxazolone **(2)** were previously reported and prepared as cited in the literature, and were in accordance with the literature data.[47-50]

Synthesis of the 6-nitrobenzoxazolone derivatives **(3a-b)**

6-nitro-2(3*H*)-benzoxazolone **3a** (67%) and 3-methyl-6-nitro-2(3*H*)-benzoxazolone **3b** (80%) were prepared according to the reported method and the physical properties (m.p, IR, ^{1}H-NMR) are in accordance with published data.[50]

Synthesis of 6-aminobenzoxazolone derivatives **(4a-b)**

The obtained benzoxazolinonic amines intermediates **4a** (69%) and **4b** (73%) were used for the next step without further purification. The structures of compounds **(4a–b)** were confirmed by comparing their spectroscopic and physical data with the ones in the literature.[50]

General procedure for the synthesis of Schiff bases derivatives obtained from 6-amino-2(3*H*)-benzoxazolone and 6-amino-3-methyl-2(3*H*)-benzoxazolone (5a-d, 6a-d)

A general method has been used for the preparation of all Schiff base ligands.

Conventional method: Substituted aromatic aldehydes derivatives (1 mmol) dissolved in boiling ethanol (10 mL) was mixed with a boiling solution of 6-amino-2(3*H*)-benzoxazolones **(4a-b)** (1 mmol) in the same solvent (5 mL). The resulting mixture was heated on a water bath for 1-2.5 h in the presence of acetic acid as catalyst, and then left to stand overnight at room temperature. The product which formed was filtered off, washed with ethanol, dried, and purified by flash column chromatography using ethyl acetate-cyclohexane (8:2) as eluent.

Microwave method: Compounds **(5a-d)** and **(6a-d)** were synthesized in the similar manner by treating an equimolar mixture of 6-aminobenzoxazolones **(4a-b)** (4 mmol) with substituted aromatic aldehydes (4 mmol) in absolute ethanol (1 mL) in microwave tube. The contents were subjected to microwave irradiation at 200 W for about 2-5 min. Progress of the reaction was monitored by TLC. After the completion of the reaction, solid product was obtained in reaction mixture which was filtered and washed with ethanol, dried, and purified to provide the title compounds as solid crystals.

Schiff bases derivatives 6-(Arylideneamino)benzo[d]oxazol-2(3*H*)-ones (5a-d)

6-(Benzylideneamino)benzo[d]oxazol-2(3H)-one (**5a**)
White powder; mp: 193-194°C. IR (KBr pellets, ν, cm^{-1}): 3050(ν_{N-H}), 1765($\nu_{C=O}$), 1640($\nu_{C=N}$), 1485($\nu_{C=Caromatic}$), 1260(ν_{C-O}). ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): δ 7,04-7,95 (m, 8H, Ar-H), 8,69 (s, 1H, N=CH), 11,7 (s, 1H, N-H). ^{13}C NMR (50 MHz, DMSO-d_6, δ ppm): 159,83(N=C), 154,78(C=O), 146,01, 144,15, 136,20, 131,52, 128.98, 128.75, 118.23, 109.96, 102.43(aromatic carbons).
6-(2-Hydroxybenzylideneamino)benzo[d]oxazol-2(3H)-one (**5b**)
Yellow powder; mp: 262-263°C. IR (KBr pellets, ν, cm^{-1}): 3433(ν_{O-H}), 3040(ν_{N-H}), 1782($\nu_{C=O}$), 1618($\nu_{C=N}$), 1280(ν_{C-O}). ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 6.85-7.75(m, 7H, Ar-H), 8.62(s, 1H, N=CH). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 162.73 (N=C), 160.59 (C=O), 155.07, 144.58, 143.09, 133.55, 132.92, 129.98, 119.81, 119.65, 118.94, 117.03, 110.43, 102.78 (aromatic carbons).
6-(4-(Dimethylamino)benzylideneamino)benzo[d]oxazol-2(3H)-one (**5c**)
Orange powder; mp: 247-248°C. IR (KBr pellets, ν, cm^{-1}): 3300-3500(ν_{N-H});1760(νC=O), 1600($\nu_{C=N}$), 1390($\nu_{C=Caromatic}$), 1200(ν_{C-O}). ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): 3,01 (s, 6H, -CH_3), 6,80-7,70 (m, 7H, Ar-H), 8,44 (s, 1H, N=CH), 11,55 (s, 1H, N-H). ^{13}C NMR (50 MHz, DMSO-d_6, δ ppm): 159,62 (N=C), 155.12 (C=O), 152.79, 147.49, 144.49, 130.65, 128.15, 124.30, 117.96, 111,94, 118.94, 110.18, 102.52 (aromatic carbons);40.00 ($N(CH_3)_2$).
6-(3,4,5-Trimethoxybenzylideneamino)benzo[d]oxazol-2(3H)-one (**5d**)
Beige powder; mp: 226-227°C. IR (KBr pellets, ν, cm^{-1}): 3300-3500(ν_{N-H}), 1760($\nu_{C=O}$), 1618,18($\nu_{C=N}$), 1580($\nu_{C=Caromatic}$), 1234,36(ν_{C-O}). ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): 3.73 (s, 3H, N-CH_3), 3.85 (s, 6H, -CH_3), 7.11-7,26 (m, 5H, Ar-H), 8.58 (s, 1H, N=CH), 11.68 (s, 1H, N-H). ^{13}C NMR (50 MHz, DMSO-d_6, δ ppm): 159.54 (N=C), 154.77 (C=O), 153.31, 146.09, 144.15, 140.43, 131.72, 128.75, 118.03, 109.99, 105.94, 102.43 (aromatic carbons), 60.35 (OCH_3), 56.12 (OCH_3).

Methyl-N-substituted Schiff base derivatives 6-(Arylideneamino)benzo[d]oxazol-2(3H)-ones (6a-d)

3-Méthyl-6-(benzylideneamino)benzo[d]oxazol-2(3H)-one (**6a**)
White powder; mp: 180-181°C. IR (KBr pellets, ν, cm^{-1}): 1780($\nu_{C=O}$);1640($\nu_{C=N}$);1460($\nu_{C=Caromatic}$);1264(ν_{C-O}). ^{1}H NMR (200 MHz, $CDCl_3$/d_6, δ ppm): 3.43 (s, 3H, -CH_3), 6.94-7.93 (m, 8H, Ar-H), 8.48 (s, 1H, N=CH). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 159.80 (N=C), 154.86 (C=O), 147.33, 143.14. 135.95, 131.49, 129.97, 128.78, 117.47, 108.06, 102,84 (aromatic carbons), 28.19 (CH_3).
3-Methyl-6-(2-hydroxybenzylideneamino)benzo[d]oxazol-2(3H)-one (**6b**)
Yellow powder, mp: 238-239°C. IR (KBr pellets, ν, cm^{-1}): 3400-3500($\nu_{O-H,N-H}$), 1778,28($\nu_{C=O}$), 1620($\nu_{C=N}$), 1488($\nu_{C=Caromatic}$), 1282,57(ν_{C-O}). ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): 3.36 (s, 3H, -CH_3), 6.94-7.64 (m, 7H, Ar-H), 8.99 (s, 1H, N=CH). ^{13}C NMR (50 MHz, DMSO-d_6, δ ppm): 162.53 (N=C), 160.26 (C=O), 154.30 (C=O), 143.11, 142.80, 133.26, 132.58, 130.99, 119.48, 119.32, 118.57, 116.71, 109.44, 102.55 (aromatic carbons), 28.34 (CH_3).
3-Methyl-6-(4-(dimethylamino)benzylideneamino)benzo [d]oxazol-2(3H)-one (**6c**)
Yellow powder; mp: 285-288°C, IR (KBr pellets, cm^{-1}): 1750($\nu_{C=O}$), 1616.24($\nu_{C=N}$), 1591.16($\nu_{C=Caromatic}$), 1260, 1180.35(ν_{C-O}). ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): 3.07 (s, 6H, CH_3), 3.40 (s, 3H, N-CH_3), 6.71-7.78 (m, 7H, Ar-H), 8,40 (s, 1H, N=CH). ^{13}C NMR (50 MHz, DMSO-d_6, δ ppm): 161.21(N=C), 154.37(C=O), 154.11, 141.93, 140.67, 131.68, 124.69, 123.43, 122.73, 112.09, 111.22, 109.69 (aromatic carbons), 40.11 (CH_3), 28.23 (CH_3).
3-Methyl-6-(3,4,5-trimethoxybenzylideneamino)benzo[d]oxazol-2(3H)-one (**6d**)
Beige powder; mp: 235-236°C. IR (KBr pellets, ν, cm^{-1}): 1780.96($\nu_{C=O}$), 1614.31($\nu_{C=N}$), 1529.45($\nu_{C=Caromatic}$), 1240(ν_{C-O}). ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 3.42 (s, 3H, N-CH_3), 3.92 (s, 3H, O-CH_3), 3.95 (s, 6H, O-CH_3), 6.94-7.26 (m, 5H, Ar-H), 8.37 (s, 1H, N=CH). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 159.305(N=C), 154.86(C=O), 153.54, 147.26, 143.18, 141.17, 131.41, 129.92, 117.44, 108.07, 105.83, 102,82 (aromatic carbons), 60.97(CH_3), 56.25(CH_3), 28.20 (CH_3).

CONCLUSIONS

In the present work, we have presented the synthesis and characterization of a new set of Schiff bases derivatives, by coupling the benzoxazolinonic pharmacophore and suitably substituted aromatic aldehydes in order to increase their activities. This approach is based on the condensation of a substituted benzaldehyde on the amine group at position 6 of the benzene ring of benzoxazolinone and its methyl-N(3)-substituted derivatives, to prepare new compounds which are highly functionalized, and we expect these compounds as potential candidates for the preparation of a wide range of pharmaceutically active agents. We have established a simple, efficient and selective general method for access to a variety of novel 6-(Benzylideneamino) benzo[d]oxazol-2(3*H*)-ones Schiff bases, starting from readily available substituted 2(3*H*)-benzoxazolones under conventional and microwave-assisted synthesis. In comparison with conventional heating methods, the desired compounds were obtained in shorter times and with good yields. Thus, this work will be very useful for further studies for the preparation of biologically active benzoxazolone Schiff base compounds with simple and convenient method, which may be useful in the synthesis of other analogues derivatives compounds.

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