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Microwave-assisted synthesis, anti-bacterial and anti-ammator activity of 3-(Benzo[d]thiazol-2-ylimino)-1-((e)-3-(phenyl) acryloyl) indolin-2-one novel Chalcone derivatives

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Abstract
Novel Chalcones is considered as an important chemical for the synthesis of various physiological significance and pharmacological utilized molecules. Traditionally, chalcones are prepared by Claisen-Schmidt condensation. The structures of the newly synthesized compounds (3a-3o) were elucidated by IR, 1H-NMR, Mass spectroscopy. All the synthesized compounds (3a-3o) screened for their anti-bacterial activity and anti-inflammatory. Anti bacterial activity of 3b, 3c, 3i and 3o showed more activity and 3d, 3j, 3m and 3n showed less activity when compare with streptomycin. From anti-inflammatory evaluations, dose level of 50mg/kg of test compounds reported significantly higher activity when compared to dose level of 20 mg/kg. Moreover, compound 3d, 3g, 3j and 3o resulted in similar anti-inflammatory activity when compared with Celecoxib.

Keywords: Chalcones, Claisen-schmidt condensation, Isatin, antibacterial activity, anti-flammatory activity

Introduction
Green chemistry is a new and rapidly emerging field of chemistry. Its growing importance is in utilization of the maximum possible resources in such a way that, there is negligible or minimum production of chemical waste. It is one of the best alternatives for traditional chemical synthesis processes. By applying the green synthesis method, we can not only avoid the use of hazardous, toxic solvents, but also the formation of by-products is avoided. Thus, they are perfectly amenable toautomation for combinatorial synthesis [1]. In 1986, Gedye and Giguere reported for the first time that organic reactions could be conducted very rapidly under microwave irradiation. Schiff bases are aldehyde or ketone-like compounds in which the carbonyl group is replaced by an imine or azomethine group. They are widely used for industrial purposes and also exhibit a broad range of biological activities.

Schiff bases have been reported in their biological properties, such as, antibacterial, antifungal activities [2-5]. Isatin is considered as important class of bioactive compounds exhibiting caspase [6] inhibitor antibacterial and antiproliferative activity [7]. Schiff bases of isatin analogous have anti smallpox [8] and GAL3 receptor antagonist capabilities [9]. Isatin derivatives reported to show antiviral [10], antiinflammatory, analgesic [11], and anticonvulsant activities [12]. Isatin-β-thiosemicarbazone derivatives were found to demonstrate a range of chemotherapeutic activities [13]. Chalcones are abundantly present in nature from ferns to higher plants [14-15]. They are aromatic compounds with an unsaturated side chain and are often cytotoxic *in vitro* [16]. Chalcones have also been reported to be antiinflammatory, analgesic and antipyretic [17].

Some chalcones possess bactericidal, antifungal and insecticidal activity and some of their derivatives are reported to be antimutagenic [18]. Chalcones are 1, 3-diphenyl-2-propene-1-one [19], in which two aromatic rings are linked by a three carbon a, b-unsaturated carbonyl system.

In the present study, we have demonstrated the ability of an unusual class of synthetic molecules containing a pair of basic moieties like Indole and Benzothiazole as different pharmacological active agents. Microwave assisted synthesis for (3a–3o) were employed in solvent- free conditions, the reaction time required was limited to an average of less than 10 min. Pharmacological evaluation of the molecules reveals that compounds 3b, 3c and 3o exhibited antifungal activity nearly similar to the standard.

Materials and Methods

Materials

The all chemicals and reagents used in the present project were of AR and LR grade, procured from Aldrich, Hi-media, Merck, Reach chem, S.D– Fine Chem. Ltd, and Sigma. The techniques employed for the characterization of the synthesized compounds were IR, ^{1}H & ^{13}C-NMR and Mass spectral analysis. 1H NMR spectra were recorded at 500 MHz and 400 MHz and ^{13}C-NMR at 125 MHz, 100 MHz and 75MHz. For ^{1}H-NMR, tetramethylsilane (TMS) was used as internal standard (δ = 0). Low-resolution MS and HRMS data were obtained using ESI ionization. IR spectra were recorded on FT-IR spectrometer (KBr) and reported in reciprocal centimeters (cm-1).

General procedure

Synthesis of 3-(benzo[d]thiazol-2-ylimino)-indolin-2-one (1a-1b): A mixture of 2-Amino-5-nitro-benzothiazole (0.01mol) and corresponding isatin derivative (0.01mol) was prepared in ethanol (10 mL, containing 0.5 mL of acetic acid) in a microwave process vial (30 mL). Then the mixture was subjected to microwave irradiation at 130 W for 10min. By giving a short interval for cooling and to avoid solvent evaporation. After completion of the reaction monitored by TLC by using ethyl acetate/n-hexane, 7:3. Then flask was cooled in ice water. It was then diluted with ice-cold water. The schiff bases formed was filtered, dried and crystallized from Ethanol.

Synthesis of 1-acetyl-3-(benzo[d]thiazol-2-ylimino)-indolin-2-one (2a-2b): The substituted Isatin (1a-1b) (1.0 mmol) was dissolved in DMF (5 ml), and K_2CO_3 (1.3 mmol) was added. The mixture was stirred under room temperature until isatin anion was obtained and hydrogen was removed. Acetyl Chloride (4.0 mmol) was added to the reaction mixture. The reaction was subjected to under microwave irradiation for 15 minutes, at 300 W. Then the reaction mixtures were cooled overnight and the precipitates were formed in ice water. Further it was purified by recrystallization by ethanol.

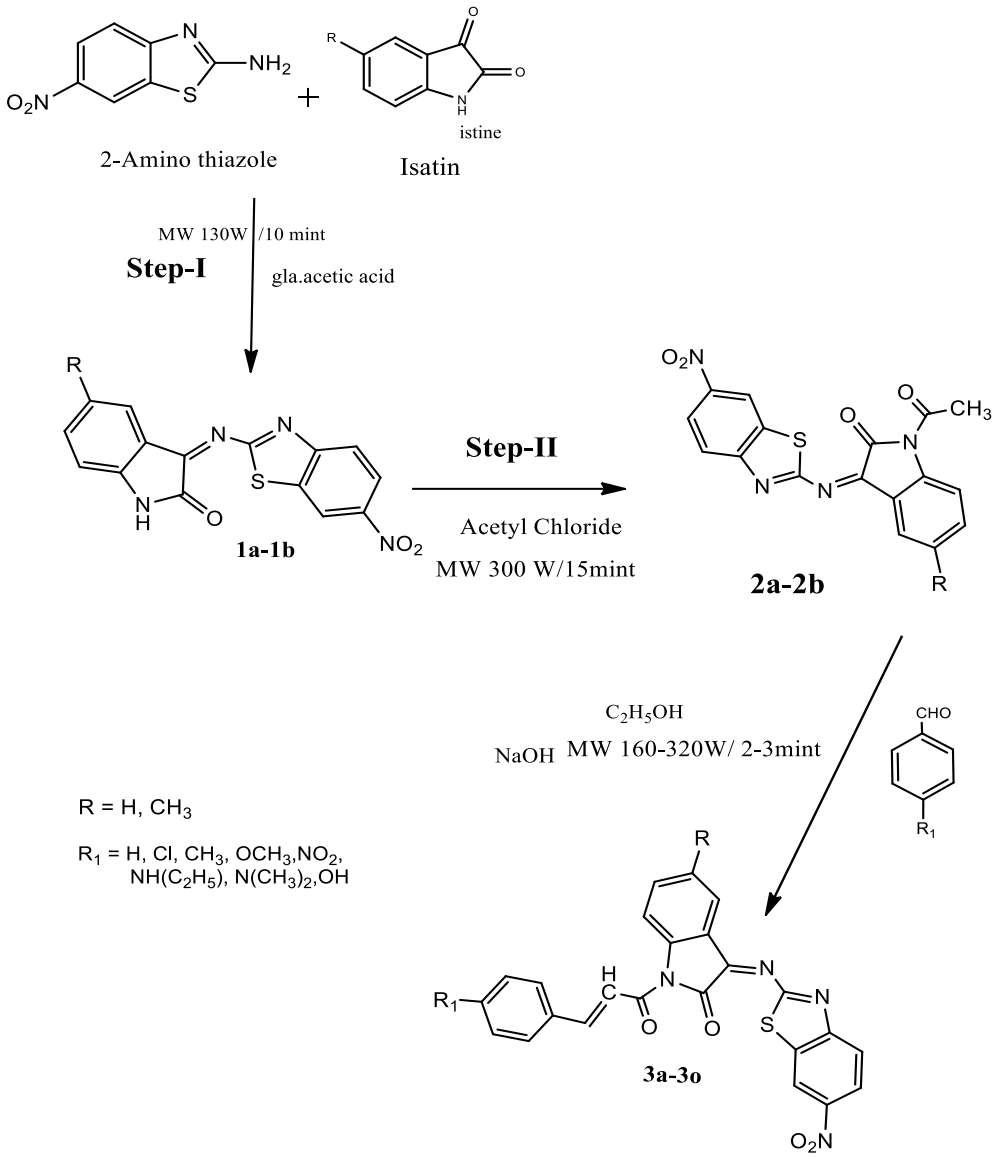
General procedure for the synthesis of 3-(6-nitro-benzo[d]thiazol-2-ylimino)-1-((E)-3-(phenyl) acryloyl) indolin-2-one (3a-3o): An equimolar mixture of compound (2a-2b) (0.01mol) and corresponding Aldehyde derivative (0.01mol) dissolved in minimum amount of rectified spirit and NaOH (40%) were placed in a conical flask. The conical flask was covered with a funnel and then the flask was taken in a domestic microwave oven. The reaction mixture was irradiated under 160-320W microwave irradiation for 60-120 sec. The progress of the reaction was monitored by TLC (n-hexane: ethyl acetate, 7:3) after every 30 sec. The reaction mixture was cooled and the obtained solid was recrystallized from ethyl acetate and n-hexane solvent mixture.

3-(6-nitro-benzo[d]thiazol-2-ylimino)-1-((E)-3-(phenyl) acryloyl) indolin-2-one (3a): Appearance: yellow solid; m.p. 234–2236°C; Mol. formula: $C_{24}H_{14}N4O4S$, Microwave irradiation yield 76%, IR (*ν* cm−1): 3088 (C-H *Str*, Ar), 2905(C–H *Str*, Aliphatic), 1701(C=O *Str*, Indole), 1671(C=O *Str*, Acryloyl), 1586 (CH=CH *Str*), 1539 (C=N *Str*), 1473 (C=C *Str*, Ar), 761 (C-S-C *Str*). ^{1}H-NMR (DMSO) *δδ* ppm: 7.97 (d, 1H, -CO=H), 7.80-7.68 (d, 2H, Ar-H), 7.63-7.53 (d, 2H, Ar-H), 7.52-7.48 (d, 2H, Ar-H), 7.47-7.43 (t, 2H, Ar-H), 7.33 (d, 1H, =CH-Ar), 6.58 (t, 2H, Ar-H), 6.20-6.10 (t, 3H, Ar-H); Mass (ESI-MS): m/z 454.07(M), 455(M + 1, 100%).

3-(6-nitro-benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-chlorophenyl) acryloyl) indolin-2-one (3b): Appearance: white solid; m.p. 251–253°C, Mol. formula: $C_{24}H_{13}ClN4O4SCl$, Microwave irradiation yield 84%, IR (*ν* cm−1): 3096 (C-H *Str*, Ar), 2960(C–H *Str*, Aliphatic), 1710(C=O *Str*, Indole), 1660(C=O *Str*, Acryloyl), 1576 (CH=CH *Str*), 1514 (C=N *Str*), 1434 (C=C *Str*, Ar), 846 (Ar-Cl *Str*), 758 (C-S-C *Str*). ^{1}H-NMR (DMSO) *δδ* ppm: 8.15-8.11 (d, 2H, Ar-H), 8.09-8.05 (d, 2H, Ar-H), 8.01 (d, 1H, -CO=H) 7.94-7.90 (d, 2H, Ar-H), 7.89-7.84 (d, 2H, Ar-H), 7.84 (d, 1H, =CH-Ar), 7.80-7.67 (t, 2H, Ar-H), 7.14-7.09 (t, 2H, Ar-H); Mass (ESI-MS): m/z 488.03(M), 489(M + 1, 100%), 490(M + 2, 30%).

3-(6-nitro-benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-nitrophenyl) acryloyl) indolin-2-one (3c): Appearance: red solid; m.p. 223–225°C Mol. formula: $C_{24}H_{13}N_5O_6S$, Microwave irradiation yield 82%, IR (*ν* cm−1): 3096 (C-H *Str*, Ar), 2951(C–H *Str*, Aliphatic), 1746(C=O *Str*, Indole), 1667(C=O *Str*, Acryloyl), 1554 (CH=CH *Str*), 1514 (C=N *Str*), 1474 (Ar-NO_2 *Str*), 1434 (C=C *Str*, Ar), 799 (C-S-C *Str*). ^{1}H-NMR (DMSO) *δδ* ppm: 8.35 (d, 1H, -CO=H), 8.06-8.04 (d, 2H, Ar-H), 7.94-7.92 (d, 2H, Ar-H), 7.92 (d, 1H, =CH-Ar), 7.82-7.81 (d, 2H, Ar-H), 7.77-7.75 (d, 2H, Ar-H), 7.17-7.14 (t, 2H, Ar-H), 6.88-6.86 (t, 2H, Ar-H); Mass (ESI-MS): m/z 499(M), 500(M + 1, 100%).

3-(6-nitro-benzo[d]thiazol-2-ylimino)-1-((E)-3-(4,4,-dimethl amino phenyl) acryloyl) indolin- 2-one (3d): Appearance: pale green solid; m.p. 235–237°C Mol. formula: $C_{26}H_{19}N_5O_4S$, Microwave irradiation yield 75%, IR (*ν* cm−1): 3086 (C-H *Str*, Ar), 2970,2 905(C–H *Str*, Aliphatic), 1717(C=O *Str*, Indole), 1683(C=O *Str*, Acryloyl), 1555 (CH=CH *Str*), 1520 (C=N *Str*), 1432 (C=C *Str*, Ar), 718 (C-S-C *Str*). ^{1}H-NMR (DMSO) *δδ* ppm: 7.97 (d, 1H, -CO=H), 7.89-7.84 (d, 2H, Ar-H), 7.79-7.78 (d, 2H, Ar-H), 7.69-7.68 (d, 2H, Ar-H), 7.60-7.59 (d, 2H, Ar-H), 7.58-7.51(t, 2H, Ar-H), 7.49-7.48 (t, 2H, Ar-H), 7.14 (d, 1H, =CH-Ar), 2.52-2.50(s, 6H, -$N(CH_3)_2$. Mass (ESI-MS): m/z 498(M), 499(M + 1, 100%).



Scheme-I

3-(6-nitro-benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-methoxyphenyl) acryloyl) indolin-2-one (3e): Appearance: red solid; m.p. 239–240 °C Mol. formula: $C_{25}H_{16}N_4O_5S$, Microwave irradiation yield 73%, IR (ν cm−1): 3018 (C-H *Str*, Ar), 2987, 2898(C–H *Str*, Aliphatic), 1705(C=O *Str*, Indole), 1676(C=O *Str*, Acryloyl), 1540(CH=CH *Str*), 1506 (C=N *Str*), 1459 (C=C *Str*, Ar), 740 (C-S-C *Str*). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 7.97 (d, 1H, -CO=H), 7.80-7.68 (d, 2H, Ar-H), 7.63-7.53 (d, 2H, Ar-H), 7.52-7.48 (d, 2H, Ar-H), 7.47-7.43 (t, 2H, Ar-H), 7.33 (d, 1H, =CH-Ar), 6.58 (t, 2H, Ar-H), 6.20-6.10 (t, 1H, Ar-H); Mass (ESI-MS): m/z 468(M), 469(M + 1, 100%).

Result and Discussion

Chemistry

The present work is based on the Schiff's base reaction between Indole-2,3-dione with 2-aminobenzothiazole to form 3-benzothiazole Isatin derivatives, then it can undergo acylation with acetyl chloride to give a 3-benzothiazole-N-acetyl Isatin derivatives(2a-2b). Finally these derivatives undergo the Claisen condensation reaction with different substituted 3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(phenyl) acryloyl) indolin-2-one Chalcones derivatives.

Antibacterial and Anti-inflammatory Studies

Antibacterial activity: All the compounds (3a–3o) have been screened for Antibacterial activity using cup-plate agar diffusion method by measuring the inhibition zone in mm. Streptomycin (50 µg/mL) was used as a standard drug for antifungal activity. The compounds were screened for antifungal activity against *Salmonella paratyphi*, *P. auregunosa*, *E.Coli*, *P.mirabilis*, *L.bacillus and S.pyrogenus* and in nutrient agar medium.

Anti-Inflammatory

Anti-inflammatory activity of the newly synthesized 3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(phenyl) acryloyl) indolin-2-one was determined by carrageenan induced paw edema assay in rats. Two dose levels (20 mg/kg and 50 mg/kg) of synthesized compounds and Celecoxib (10mg/kg) as standard were administered. The change in the paw volumes were measured before and 1h after carrageenan injection, using the mercury displacement technique with the help of plethysmograph. The percent inhibition of paw edema was calculated from percent inhibition formula.

$$\% \text{ inhibition (I)} = 100[1 - (a - x) / (b - y)]$$

Where

x = mean paw volume of rats before the administration of carrageenan and test compounds or reference compound (test group)

a = mean paw volume of rats after the administration of carrageenan in the test group (drug treated)

b = is the mean paw volume of rats after the administration of carrageenan in the control group

y = mean paw volume of rats before the administration of carrageenan in the control group.

Anti-inflammatory activity of newly synthesized 3-(Benzo [d] thiazol-2-ylimino)-1-((E)-3-(phenyl) acryloyl) indolin-2-one was evaluated by carrageenan induced paw edema bioassay in rats with Celecoxib (20 mg/kg) as reference standard. Percentage inhibitions of the molecules are tabulated in Table 2 and Figure 2.

Table 1: Antibacterial activity by Zone of Inhibition (in mm)

S. No.	Micro Organism	Zone of Inhibition (mm)					
		Salmonella paratyphi	*P. auregunosa*	*E. Coli*	*P. mirabilis*	*L. bacillus*	*S. pyrogenus*
1	3a	19	19	22	20	12	16
4	3b	20	25	22	20	27	17
3	3c	14	20	25	18	25	14
4	3d	21	24	0	12	0	0
5	3e	9	24	13	15	21	11
6	3f	25	15	20	17	0	20
7	3g	12	17	23	17	21	0
8	3h	21	19	23	14	21	10
9	3i	20	27	18	20	20	16
10	3j	10	21	15	19	15	15
11	3k	19	20	18	14	11	12
12	3l	21	18	21	0	21	17
13	3m	19	20	21	16	21	0
14	3n	0	15	21	20	21	22
15	3o	18	0	25	16	25	19
13	Streptomycin	30	32	32	33	28	30

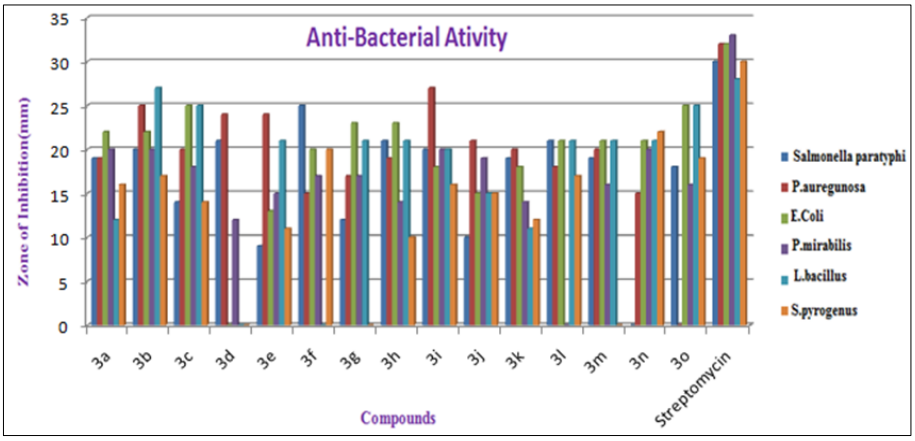


Fig 1: Graphical representation of antibacterial activity of compounds (3a-3o) - Zone of Inhibition (in mm).

Table 2: Anti-Inflammatory activity of compounds (3a-3o) (% inhibition of paw edema)

Compounds	% Inhibition of Paw edema	
	20mg/kg	50mg/kg
3a	30.2	65.2
3b	28.8	33.2
3c	35.2	57.3
3d	44.7	80.6
3e	29.9	69.5
3f	43.8	53.2
3g	48.0	49.6
3h	32.2	72.5
3i	28.9	55.2
3j	38.2	84.9
3k	39.4	65.3
3l	36.9	70.9
3m	43.2	65.3
3n	29.7	59.3
3o	45.6	45.8
Celecoxib	48.9	87.8

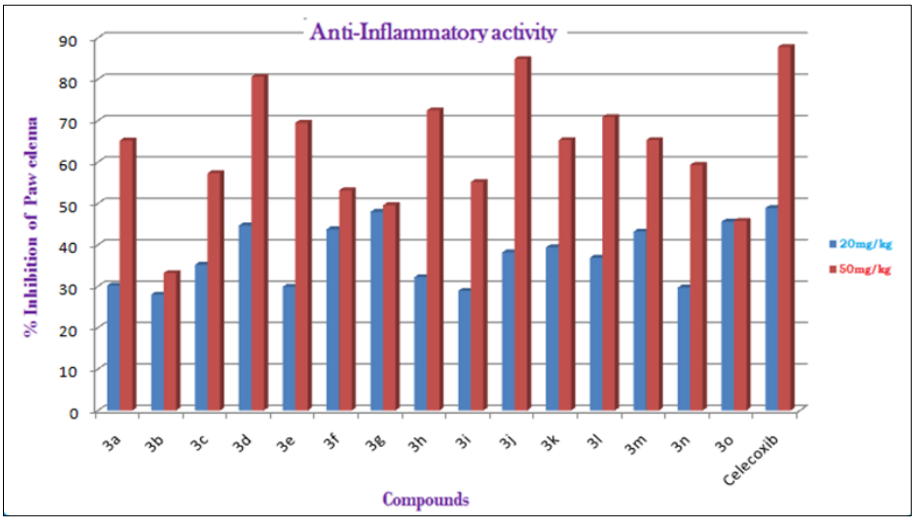


Fig 2: Comparison of Anti-Inflammatory activity of compounds 3a-3o (% inhibition of paw edema)

Most of the synthesized compounds showed significant antibacterial activity. Anti bacterial activity of 3b, 3c, 3i and 3o showed more activity and 3d, 3j, 3m and 3n showed less activity when compare with streptomycin. Anti-inflammatory activity of the newly synthesized compounds (3a-3o) was determined by carrageenan induced paw edema assay in albino rats. Synthesized test compounds with dose level 20 and 50 mg/kg were administered and compared with that of standard drug Celecoxib (20 and 50mg/kg). The paw volumes were measured using the mercury displacement technique with the help of plethysmograph immediately before and 1h after carrageenan injection. From anti-inflammatory evaluations, dose level of 50mg/kg of test compounds reported significantly higher activity when compared to dose level of 20 mg/kg. Moreover, compound 3d, 3g, 3j and 3o resulted in similar anti-inflammatory activity when compared with Celecoxib.

Conclusion

The objective of the present work was to synthesize, purify, characterize and evaluate the biological activity of newly synthesized structural analogs of novel Chalcone derivatives. The yield of the synthesized compound was found to be in the range from 67-86% (Microwave). All these molecules were characterized by FT-IR, ^{1}H-NMR and Mass spectral analysis along with physical data. The synthesized compounds (3a-3o) were also screened for antifungal and anti-inflammatory activity by using slandered protocol.

Author's Contributions

Corresponding author has done all the work, interpreted the data, and written the manuscript.

Reference

1. Sari N, Arslan S, Logoglu E, Sakiyan I. Antibacterial activities of some new amino acid-Schiff bases. G. U. J. Sci. 2003; 16:283-288.
2. Verma M, Pandeya SN, Singh KN, Stabler JP. Anticonvulsant activity of Schiff bases of isatin derivatives. Acta Pharm. 2004; 54:49-56.
3. Domling A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. Chem. Rev. 2006; 106:17-89.
4. Williams DR. Metals, ligands, and cancer. Chem. Rev. 1972; 72:203-213.
5. Campos A, Anacona JR, Campos-Vallette MM, Metal Chem. 1999; 22:283-288.
6. Chu W, Zhang J, Zeng C. Journal of Medicinal Chemistry. 2005; 48:637-647.
7. Chu W, Rothfuss J, Chu Y, Zhoud D, Mach RH. Journal of Medicinal Chemistry. 2009; 52:2188-2191.
8. Chohan Z, Pervez H, Rauf A, Khan A, Supuran CT. Journal of Enzyme Inhibition and Medicinal Chemistry. 2004; 199(5):417-423.
9. Domling A, A Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. Chem. Rev. 2006; 106:17-89.
10. Pirrung CM, Pansare S, Das Sarma KV, Keith KA. Journal of Medicinal Chemistry. 2005; 48(8):3045-3050.
11. Konkel MJ, Lagu B, Boteju LW. Journal of Medicinal Chemistry. 2006; 49(13):3757-3758.
12. Jarrahpour A, Khalili D, De Clark E, Salmi C, Brunel JM. Molecules. 2007; 12(8):1720-1730.
13. Sharaf OA. Bulletin of Faculty of Pharmacy. 1997; 35:79-82.
14. Satyanarayana K, Rao MNA. Indian Drugs. 1993; 30:313-318.
15. Torigoo T, Arisawa M, Iloch S, Fujiu M, Mayuyama HB. Biochem. Biophys. Res. Commun. 1983; 112:833-842.
16. Yılmaz F, Karaali N, Sasmaz S. Bull. Chem. Soc. Ethiop. 2017; 31(2):351-359.
17. Verma M, Pandeya SN, Singh KN, Stables JP. *Acta Pharmaceutica*. 2004; 54(1):49-56.
18. Teitz Y, Ronen D, Vansover A, Stematsky T, Riggs JL. Antiviral Research. 1994; 4:305-314.
19. Star AW, Marby TJ. Phytochemistry. 1971; 10:2812-2817.
20. Dhar DN. the Chemistry of Chalcones and Related Compounds. Wiley, New York, 1981, 213-219.